

21st Edition

HARRISON'S® PRINCIPLES OF INTERNAL MEDICINE

LOSCALZO

FAUCI

KASPER

HAUSER

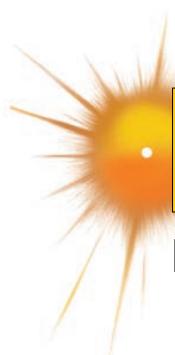
LONGO

JAMESON

VOLUME 1

Mc
Graw
Hill

21st Edition



HARRISON'S®

PRINCIPLES OF

**INTERNAL
MEDICINE**

The title features a stylized sunburst graphic on the left side. The word "HARRISON'S" is in large yellow capital letters, with a registered trademark symbol (®) at the top right. Below it, "PRINCIPLES OF" is in smaller black capital letters. The main title, "INTERNAL MEDICINE", is in large red capital letters.

318 Nephrolithiasis	2368
<i>Gary C. Curhan</i>	
319 Urinary Tract Obstruction	2373
<i>Julian L. Seifert</i>	
320 Interventional Nephrology	2377
<i>Dirk M. Hentschel</i>	

PART 10 Disorders of the Gastrointestinal System

SECTION 1 Disorders of the Alimentary Tract

321 Approach to the Patient with Gastrointestinal Disease	2381
<i>William L. Hasler, Chung Owyang</i>	
322 Gastrointestinal Endoscopy	2387
<i>Louis Michel Wong Kee Song, Mark Topazian</i>	
323 Diseases of the Esophagus	2423
<i>Peter J. Kahrilas, Ikuo Hirano</i>	
324 Peptic Ulcer Disease and Related Disorders	2434
<i>John Del Valle</i>	
325 Disorders of Absorption	2458
<i>Deborah C. Rubin</i>	
326 Inflammatory Bowel Disease	2469
<i>Sonia Friedman, Richard S. Blumberg</i>	
327 Irritable Bowel Syndrome	2490
<i>Chung Owyang</i>	
328 Diverticular Disease and Common Anorectal Disorders	2497
<i>Susan L. Gearhart</i>	
329 Mesenteric Vascular Insufficiency	2506
<i>Maryam Ali Khan, Jaideep Das Gupta, Mahmoud Malas</i>	
330 Acute Intestinal Obstruction	2508
<i>Danny O. Jacobs</i>	
331 Acute Appendicitis and Peritonitis	2513
<i>Danny O. Jacobs</i>	

SECTION 2 Nutrition

332 Nutrient Requirements and Dietary Assessment	2517
<i>Johanna T. Dwyer</i>	
333 Vitamin and Trace Mineral Deficiency and Excess	2523
<i>Paolo M. Suter</i>	
334 Malnutrition and Nutritional Assessment	2534
<i>Gordon L. Jensen</i>	
335 Enteral and Parenteral Nutrition	2539
<i>L. John Hoffer, Bruce R. Bistrian, David F. Driscoll</i>	

SECTION 3 Liver and Biliary Tract Disease

336 Approach to the Patient with Liver Disease	2546
<i>Marc G. Ghany, Jay H. Hoofnagle</i>	
337 Evaluation of Liver Function	2553
<i>Emily D. Bethea, Daniel S. Pratt</i>	
338 The Hyperbilirubinemias	2557
<i>Allan W. Wolkoff</i>	
339 Acute Viral Hepatitis	2562
<i>Jules L. Dienstag</i>	
340 Toxic and Drug-Induced Hepatitis	2584
<i>William M. Lee, Jules L. Dienstag</i>	
341 Chronic Hepatitis	2591
<i>Jules L. Dienstag</i>	

342 Alcohol-Associated Liver Disease	2617
<i>Bernd Schnabl</i>	
343 Nonalcoholic Fatty Liver Diseases and Nonalcoholic Steatohepatitis	2619
<i>Manal F. Abdelmalek, Anna Mae Diehl</i>	
344 Cirrhosis and Its Complications	2624
<i>Alex S. Befeler, Bruce R. Bacon</i>	
345 Liver Transplantation	2633
<i>Raymond T. Chung, Jules L. Dienstag</i>	
346 Diseases of the Gallbladder and Bile Ducts	2641
<i>Norton J. Greenberger, Gustav Paumgartner, Daniel S. Pratt</i>	

SECTION 4 Disorders of the Pancreas

347 Approach to the Patient with Pancreatic Disease	2652
<i>Somashekhar G. Krishna, Darwin L. Conwell, Phil A. Hart</i>	
348 Acute and Chronic Pancreatitis	2657
<i>Phil A. Hart, Darwin L. Conwell, Somashekhar G. Krishna</i>	

PART 11 Immune-Mediated, Inflammatory, and Rheumatologic Disorders

SECTION 1 The Immune System in Health and Disease

349 Introduction to the Immune System	2671
<i>Barton F. Haynes, Kelly A. Soderberg, Anthony S. Fauci</i>	
350 Mechanisms of Regulation and Dysregulation of the Immune System	2701
<i>Barton F. Haynes, Kelly A. Soderberg, Anthony S. Fauci</i>	
351 Primary Immune Deficiency Diseases	2709
<i>Alain Fischer</i>	

SECTION 2 Disorders of Immune-Mediated Injury

352 Urticaria, Angioedema, and Allergic Rhinitis	2719
<i>Katherine L. Tuttle, Joshua A. Boyce</i>	
353 Anaphylaxis	2727
<i>David Hong, Joshua A. Boyce</i>	
354 Mastocytosis	2729
<i>Matthew P. Giannetti, Joshua A. Boyce</i>	
355 Autoimmunity and Autoimmune Diseases	2731
<i>Betty Diamond, Peter E. Lipsky</i>	
356 Systemic Lupus Erythematosus	2736
<i>Bevra Hannahs Hahn, Maureen McMahon</i>	
357 Antiphospholipid Syndrome	2749
<i>Haralampos M. Moutsopoulos, Clio P. Mavragani</i>	
358 Rheumatoid Arthritis	2751
<i>Ankoor Shah, E. William St. Clair</i>	
359 Acute Rheumatic Fever	2766
<i>Joseph Kado, Jonathan Carapetis</i>	
360 Systemic Sclerosis (Scleroderma) and Related Disorders	2771
<i>John Varga</i>	
361 Sjögren's Syndrome	2787
<i>Haralampos M. Moutsopoulos, Clio P. Mavragani</i>	
362 Spondyloarthritis	2790
<i>Joel D. Taurog, Lianne S. Gensler, Nigel Haroon</i>	
363 The Vasculitis Syndromes	2802
<i>Carol A. Langford, Anthony S. Fauci</i>	
364 Behçet Syndrome	2817

Yusuf Yazici

365 Inflammatory Myopathies.....	2819
<i>Steven A. Greenberg, Anthony A. Amato</i>	
366 Relapsing Polychondritis.....	2826
<i>Carol A. Langford</i>	
367 Sarcoidosis.....	2829
<i>Robert P. Baughman, Elyse E. Lower</i>	
368 IgG4-Related Disease.....	2837
<i>John H. Stone</i>	
369 Familial Mediterranean Fever and Other Hereditary Autoinflammatory Diseases.....	2840
<i>Daniel L. Kastner</i>	

SECTION 3 Disorders of the Joints and Adjacent Tissues

370 Approach to Articular and Musculoskeletal Disorders.....	2844
<i>John J. Cush</i>	
371 Osteoarthritis.....	2854
<i>David T. Felson, Tuhina Neogi</i>	
372 Gout and Other Crystal-Associated Arthropathies.....	2862
<i>Hyon K. Choi</i>	
373 Fibromyalgia.....	2868
<i>Leslie J. Crofford</i>	
374 Arthritis Associated with Systemic Disease, and Other Arthritis.....	2871
<i>Carol A. Langford, Brian F. Mandell</i>	
375 Periarticular Disorders of the Extremities.....	2878
<i>Carol A. Langford</i>	

PART 12 Endocrinology and Metabolism

SECTION 1 Endocrinology

376 Approach to the Patient with Endocrine Disorders	2881
<i>J. Larry Jameson</i>	
377 Mechanisms of Hormone Action	2884
<i>J. Larry Jameson</i>	
378 Physiology of Anterior Pituitary Hormones	2891
<i>Shlomo Melmed, J. Larry Jameson</i>	
379 Hypopituitarism	2896
<i>Shlomo Melmed, J. Larry Jameson</i>	
380 Pituitary Tumor Syndromes	2902
<i>Shlomo Melmed, J. Larry Jameson</i>	
381 Disorders of the Neurohypophysis	2918
<i>Gary L. Robertson, Daniel G. Bichet</i>	
382 Thyroid Gland Physiology and Testing.....	2926
<i>J. Larry Jameson, Susan J. Mandel, Anthony P. Weetman</i>	
383 Hypothyroidism.....	2933
<i>J. Larry Jameson, Susan J. Mandel, Anthony P. Weetman</i>	
384 Hyperthyroidism and Other Causes of Thyrotoxicosis	2938
<i>J. Larry Jameson, Susan J. Mandel, Anthony P. Weetman</i>	
385 Thyroid Nodular Disease and Thyroid Cancer.....	2946
<i>J. Larry Jameson, Susan J. Mandel, Anthony P. Weetman</i>	
386 Disorders of the Adrenal Cortex.....	2955
<i>Wiebke Arlt</i>	
387 Pheochromocytoma.....	2976
<i>Hartmut P. H. Neumann</i>	
388 Multiple Endocrine Neoplasia Syndromes.....	2983

R. V. Thakker

389 Autoimmune Polyendocrine Syndromes	2992
<i>Peter A. Gottlieb, Aaron W. Michels</i>	

SECTION 2 Sex- and Gender-Based Medicine

390 Sex Development	2997
<i>Courtney Finlayson, J. Larry Jameson, John C. Achermann</i>	
391 Disorders of the Testes and Male Reproductive System.....	3006
<i>Shalender Bhasin, J. Larry Jameson</i>	
392 Disorders of the Female Reproductive System	3027
<i>Janet E. Hall, Anuja Dokras</i>	
393 Menstrual Disorders and Pelvic Pain	3033
<i>Janet E. Hall, Anuja Dokras</i>	
394 Hirsutism	3039
<i>David A. Ehrmann</i>	
395 Menopause and Postmenopausal Hormone Therapy	3043
<i>JoAnn E. Manson, Shari S. Bassuk</i>	
396 Infertility and Contraception	3050
<i>Anuja Dokras, Janet E. Hall</i>	
397 Sexual Dysfunction	3055
<i>Kevin T. McVay</i>	
398 Women's Health.....	3063
<i>Emily Nosova, Andrea Dunaff</i>	
399 Men's Health	3069
<i>Shalender Bhasin</i>	
400 Lesbian, Gay, Bisexual, and Transgender (LGBT) Health	3078
<i>Baligh R. Yehia, Zachary B. R. McClain</i>	

SECTION 3 Obesity, Diabetes Mellitus, and Metabolic Syndrome

401 Pathobiology of Obesity.....	3080
<i>Stephen O'Rahilly, I. Sadaf Farooqi</i>	
402 Evaluation and Management of Obesity.....	3087
<i>Robert F. Kushner</i>	
403 Diabetes Mellitus: Diagnosis, Classification, and Pathophysiology	3094
<i>Alvin C. Powers, Kevin D. Niswender, Carmella Evans-Molina</i>	
404 Diabetes Mellitus: Management and Therapies.....	3104
<i>Alvin C. Powers, Michael J. Fowler, Michael R. Rickels</i>	
405 Diabetes Mellitus: Complications	3120
<i>Alvin C. Powers, John M. Stafford, Michael R. Rickels</i>	
406 Hypoglycemia	3129
<i>Stephen N. Davis, Philip E. Cryer</i>	
407 Disorders of Lipoprotein Metabolism.....	3135
<i>Daniel J. Rader</i>	
408 The Metabolic Syndrome.....	3150
<i>Robert H. Eckel</i>	

SECTION 4 Disorders of Bone and Mineral Metabolism

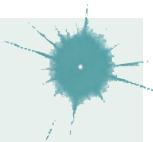
409 Bone and Mineral Metabolism in Health and Disease	3157
<i>F. Richard Bringhurst, Henry M. Kronenberg, Eva S. Liu</i>	
410 Disorders of the Parathyroid Gland and Calcium Homeostasis	3169
<i>John T. Potts, Jr., Harald Jüppner</i>	
411 Osteoporosis.....	3191

Section 1 The Immune System in Health and Disease

349

Introduction to the Immune System

Barton F. Haynes, Kelly A. Soderberg,
Anthony S. Fauci



DEFINITIONS

- **Adaptive immune system**—recently evolved system of immune responses mediated by T and B lymphocytes. Immune responses by these cells are based on specific antigen recognition by clonotypic receptors that are products of genes that rearrange during development and throughout the life of the organism. Additional cells of the adaptive immune system include various types of antigen-presenting cells (APCs).
- **Antibody**—B cell-produced molecules encoded by genes that rearrange during B-cell development consisting of immunoglobulin heavy and light chains that together form the central component of the B-cell receptor (BCR) for antigen. Antibody can exist as B cell-surface antigen-recognition molecules or as secreted molecules in plasma and other body fluids.
- **Antigens**—foreign or self-molecules that are recognized by the adaptive and innate immune systems resulting in immune cell triggering, T-cell activation, and/or B-cell antibody production.
- **Antimicrobial peptides**—small peptides <100 amino acids in length that are produced by cells of the innate immune system and have anti-infectious agent activity.
- **Apoptosis**—the process of *programmed cell death* whereby signaling through various “death receptors” on the surface of cells (e.g., tumor necrosis factor [TNF] receptors, CD95) leads to a signaling cascade that involves activation of the caspase family of molecules and leads to DNA cleavage and cell death. Apoptosis, which does not lead to induction of inordinate inflammation, is to be contrasted with *cell necrosis*, which does lead to induction of inflammatory responses.
- **Autoimmune diseases**—diseases such as systemic lupus erythematosus and rheumatoid arthritis in which cells of the adaptive immune system such as autoreactive T and B cells become overreactive and produce self-reactive T-cell and antibody responses.
- **Autoinflammatory diseases**—hereditary disorders such as hereditary periodic fevers (HPFs) characterized by recurrent episodes of severe inflammation and fever due to mutations in controls of the innate inflammatory response, i.e., the inflammasome (see below and Table 349-5). Patients with HPFs also have rashes, serosal and joint inflammation, and some can have neurologic symptoms. Autoinflammatory diseases are different from autoimmune diseases in that evidence for activation of adaptive immune cells such as autoreactive B cells is not present.
- **Autophagy**—lysosomal degradation pathway mechanism of cells to dispose of intracellular debris and damaged organelles. Autophagy by cells of the innate immune system is used to control intracellular infectious agents such as mycobacteria, in part by initiation of phagosome maturation and enhancing major histocompatibility complex (MHC) class II antigen presentation to CD4 T cells.
- **B-cell receptor for antigen**—complex of surface molecules that rearrange during postnatal B-cell development, made up of surface immunoglobulin (Ig) and associated Ig αβ chain molecules that recognize nominal antigen via Ig heavy- and light-chain variable

regions, and signal the B cell to terminally differentiate to make antigen-specific antibody.

- **B lymphocytes**—bone marrow-derived or bursal-equivalent lymphocytes that express surface immunoglobulin (the BCR for antigen) and secrete specific antibody after interaction with antigen.
- **B regulatory cells**—a population of suppressive B cells that aid in the inhibition of inflammation through the release of cytokines such as interleukin (IL) 10.
- **CD classification of human lymphocyte differentiation antigens**—the development of monoclonal antibody technology led to the discovery of a large number of new leukocyte surface molecules. In 1982, the First International Workshop on Leukocyte Differentiation Antigens was held to establish a nomenclature for cell-surface molecules of human leukocytes. From this and subsequent leukocyte differentiation workshops has come the *cluster of differentiation* (CD) classification of leukocyte antigens.
- **CD4 T cell**—T lymphocyte subset that participates in adaptive immunity and helps B cells make antibody.
- **CD8 T cell**—cytotoxic T lymphocyte subset that destroys tumor cells and cells infected with pathogens.
- **Chemokines**—soluble molecules that direct and determine immune cell movement and circulation pathways.
- **Complement**—cascading series of plasma enzymes and effector proteins that function to lyse pathogens and/or target them to be phagocytized by neutrophils and monocyte/macrophage lineage cells of the reticuloendothelial system.
- **Co-stimulatory molecules**—molecules of APCs (such as B7-1 and B7-2 or CD40) that lead to T-cell activation when bound by ligands on activated T cells (such as CD28 or CD40 ligand).
- **Crystallopathies**—nanoparticle- or microparticle-sized deposits of crystals, misfolded proteins, or airborne particulate matter that can stimulate the inflammasome and initiate inflammation and tissue damage.
- **Cytokines**—soluble proteins that interact with specific cellular receptors that are involved in the regulation of the growth and activation of immune cells and mediate normal or pathologic inflammatory and immune responses.
- **Dendritic cells**—myeloid and/or lymphoid lineage APCs of the adaptive immune system. Immature dendritic cells (DCs), or DC precursors, are key components of the innate immune system by responding to infections with production of high levels of cytokines. DCs are key initiators both of innate immune responses via cytokine production and of adaptive immune responses via presentation of antigen to T lymphocytes.
- **Ig Fc receptors**—receptors found on the surface of certain cells including B cells, natural killer (NK) cells, macrophages, neutrophils, and mast cells. Fc receptors bind to antibodies that have attached to invading pathogen-infected cells. They stimulate cytotoxic cells to destroy microbe-infected cells through a mechanism known as antibody-dependent cell-mediated cytotoxicity (ADCC). Examples of important Fc receptors include CD16 (FcγRIIIa), CD23 (FcεR), CD32 (FcγRII), CD64 (FcγRI), and CD89 (FcαR).
- **Inflammasome**—large cytoplasmic complexes of intracellular proteins that link the sensing of microbial products and cellular stress to the proteolytic activation of IL-1β and IL-18 inflammatory cytokines. Activation of molecules in the inflammasome is a key step in the response of the innate immune system for intracellular recognition of microbial and other danger signals in both health and pathologic states.
- **Innate immune system**—ancient immune recognition system of host cells bearing germline-encoded pattern recognition receptors (PRRs) that recognize pathogens and trigger a variety of mechanisms of pathogen elimination. Cells of the innate immune system include NK cell lymphocytes, monocytes/macrophages, DCs, neutrophils, basophils, eosinophils, tissue mast cells, and epithelial cells.

- **Innate lymphoid cells (ILCs)**—lymphocytes that do not express the type of diversified antigen receptors on T cell and B cells. ILC1s, ILC2s, and ILC3s are tissue resident cells and functionally are analogous to CD4 T_H1, T_H2, and T_H17 cells, respectively.
- **Natural killer (NK) cells**—a type of ILC that kills target cells expressing few or no human leukocyte antigen (HLA) class I molecules, such as malignantly transformed cells and virally infected cells. NK cells express receptors that inhibit killer cell function when self-MHC class I is present. Innate NK cells mirror the functions of CD8 cytotoxic T cells of the adaptive immune system.
- **NK T cells**—innate-like lymphocytes that use an invariant T-cell receptor (TCR)-α chain combined with a limited set of TCR-β chains and coexpress receptors commonly found on NK cells. NK T cells recognize lipid antigens of bacterial, viral, fungal, and protozoal infectious agents.
- **Pathogen-associated molecular patterns (PAMPs)**—invariant molecular structures expressed by large groups of microorganisms that are recognized by host cellular PRRs in the mediation of innate immunity.
- **Pattern recognition receptors (PRR)**—germline-encoded receptors expressed by cells of the innate immune system that recognize PAMPs.
- **Polyreactive antibodies**—low-affinity antibodies produced by B cells that cross-react with multiple antigens and are available at the time of infection to bind and coat invading pathogens and harness innate responses to slow the infection until an adaptive high-affinity protective antibody response can be made.
- **T lymphocytes**—thymus-derived lymphocytes that mediate adaptive cellular immune responses including T helper, T regulatory, and cytotoxic T lymphocyte effector cell functions.
- **T-cell exhaustion**—state of T cells when the persistence of antigen disrupts memory T-cell function, resulting in defects in memory T-cell responses. Most frequently occurs in malignancies and in chronic viral infections such as HIV-1 and hepatitis C.
- **TCR for antigen**—complex of surface molecules that rearrange during postnatal T-cell development made up of clonotypic TCR-α and -β chains that are associated with the CD3 complex composed of invariant γ, δ, ε, ζ, and η chains. TCR-α and -β chains recognize peptide fragments of protein antigen physically bound in APC MHC class I or II molecules, leading to signaling via the CD3 complex to mediate effector functions.
- **T follicular helper T cells (Tfh)**—CD4 T cells regulated by bcl-6 in B-cell follicle germinal centers that produce IL-4 and IL-21 and drive B-cell differentiation and affinity maturation in peripheral lymphoid tissues such as lymph node and spleen.
- **T_H1 T cells**—CD4 helper T-cell subset regulated by transcription factor T-bet that produces interferon (IFN)-γ, IL-2, and TNF-β and participates in cell-mediated immunity.
- **T_H2 T cells**—CD4 helper T-cell subset regulated by transcription factors STAT6 and GATA3 that produces IL-4, IL-5, IL-6, IL-9, IL-10, and IL-13 and regulates antibody and eosinophil responses.
- **T regulatory cells (Treg)**—CD4 and CD8 T cells regulated by the transcription factor Foxp3 that play roles in modulating the immune system to prevent deleterious immune activation. Expression of Foxp3 is a defining Treg marker.
- **T_H9 T cells**—CD4 T cells regulated by the transcription factor PU.1 that secrete IL-9 and enhance inflammation in atopic disease and inflammatory bowel disease as well as mediate antitumor immunity.
- **T_H13 T cells**—T follicular helper cells (Tfh) regulated by the GATA3 transcription factor that produce IL-4, IL-5, and IL-13. T_H13 Tfh induce high-affinity IgE antibody responses that cause anaphylactic reactions to allergens.
- **T_H17 T cells**—CD4 T cells regulated by the transcription factor RORγt that secrete IL-17, IL-22, and IL-26 and play roles in autoimmune inflammatory disorders as well as defend against bacterial and fungal pathogens.
- **Tolerance**—B- and T-cell nonresponsiveness to antigens that results from encounter with foreign or self-antigens by B and T lymphocytes in the absence of expression of APC co-stimulatory

molecules. Tolerance to antigens may be induced and maintained by multiple mechanisms either centrally (B-cell deletion in the thymus for T cells or bone marrow for B cells) or peripherally (by cell deletion or anergy at sites throughout the peripheral immune system).

- **Trained immunity**—the epigenetic, transcriptional, and functional reprogramming of innate immune cells to adapt to previous encounters with pathogens and respond to a second challenge in an altered manner.

INTRODUCTION

The human immune system has evolved over millions of years from both invertebrate and vertebrate organisms to develop sophisticated defense mechanisms that protect the host from microbes and their virulence factors. The normal immune system has three key properties: a highly diverse repertoire of antigen receptors that enables recognition of a nearly infinite range of pathogens; immune memory, to mount rapid recall immune responses; and immunologic tolerance, to avoid immune damage to normal self-tissues. From invertebrates, humans have inherited the *innate immune system*, an ancient defense system that uses germline-encoded proteins to recognize pathogens. Cells of the innate immune system, such as macrophages, DCs, and NK lymphocytes, recognize PAMPs that are highly conserved among many microbes and use a diverse set of PRR molecules. Important components of the recognition of microbes by the innate immune system include recognition by germline-encoded host molecules, recognition of key microbe virulence factors but not recognition of self-molecules, and nonrecognition of benign foreign molecules or microbes. Upon contact with pathogens, cells of the innate immune system may kill pathogens directly or, in concert with DCs, activate a series of events that both slow the infection and recruit the more recently evolved arm of the human immune system, the *adaptive immune system*. In addition, innate immune cells undergo epigenetic, transcriptional, and functional changes that allow adapted (either enhanced or reduced) innate cell responses to repeat encounters with pathogens, called *trained immunity*.

Adaptive immunity is found only in vertebrates and is based on the generation of antigen receptors on T and B lymphocytes by gene rearrangements, such that individual T or B cells express unique antigen receptors on their surface capable of specifically recognizing diverse antigens of infectious agents in the environment. Coupled with specific recognition mechanisms that maintain tolerance (nonreactivity) to self-antigens (**Chap. 350**), T and B lymphocytes bring both *specificity* and *immune memory* to vertebrate host defenses.

This chapter describes the cellular components, key molecules (**Table 349-1**), and mechanisms that make up the innate and adaptive immune systems and describes how adaptive immunity is recruited to the defense of the host by innate immune responses. An appreciation of the cellular and molecular bases of innate and adaptive immune responses is critical to understanding the pathogenesis of inflammatory, autoimmune, infectious, and immunodeficiency diseases, as well as a wide range of diseases associated with inflammation such as atherosclerotic cardiovascular disease and neurodegenerative diseases.

THE INNATE IMMUNE SYSTEM

All multicellular organisms, including humans, have developed the use of surface and intracellular germline-encoded molecules that recognize pathogens. Because of the myriad of human pathogens, host molecules of the human innate immune system sense “danger signals” and either recognize PAMPs, the common molecular structures shared by many pathogens, or recognize host cell molecules produced in response to infection such as heat shock proteins and fragments of the extracellular matrix. PAMPs must be conserved structures vital to pathogen virulence and survival, such as bacterial endotoxin, so that pathogens cannot mutate molecules of PAMPs to evade human innate immune responses. PRRs are host proteins of the innate immune system that recognize PAMPs as host danger signal molecules (**Tables 349-2 and 349-3**). Thus, recognition of pathogen molecules by hematopoietic and

TABLE 349-1 Human Leukocyte Surface Antigens—The CD Classification of Leukocyte Differentiation Antigens

SURFACE ANTIGEN (OTHER NAMES)	FAMILY	MOLECULAR MASS, kDa	DISTRIBUTION	LIGAND(S)	FUNCTION
CD1a (T6, HTA-1)	Ig	49	CD, cortical thymocytes, Langerhans type of DCs	TCR $\gamma\delta$ T cells, NK T cells	CD1 molecules present lipid antigens of intracellular bacteria such as <i>Mycobacterium leprae</i> and <i>M. tuberculosis</i> to TCR $\gamma\delta$ T cells or NK T cells
CD1b	Ig	45	CD, cortical thymocytes, Langerhans type of DCs	TCR $\gamma\delta$ T cells, NK T cells	
CD1c	Ig	43	DC, cortical thymocytes, subset of B cells, Langerhans type of DCs	TCR $\gamma\delta$ T cells, NK T cells	
CD1d	Ig	37	Cortical thymocytes, intestinal epithelium, Langerhans type of DCs	TCR $\gamma\delta$ T cells, NK T cells	
CD2 (T12, LFA-2)	Ig	50	T, NK	CD58, CD48, CD59, CD15	Alternative T-cell activation, T-cell anergy, T-cell cytokine production, T- or NK-mediated cytotoxicity, T-cell apoptosis, cell adhesion
CD3 (T3, Leu-4)	Ig	$\gamma:25-28, \delta:21-28, \epsilon:20-25, \eta:21-22, \zeta:16$	T, NK T	Associates with the TCR	T-cell activation and function; ζ is the signal transduction component of the CD3 complex
CD4 (T4, Leu-3)	Ig	55	T, myeloid	MHC-II, HIV gp120, IL-16, SABP	T-cell selection, T-cell activation, signal transduction with p56/ck, primary receptor for HIV-1
CD7 (3A1, Leu-9)	Ig	40	T, NK	K-12 (CD7L)	T- and NK-cell signal transduction and regulation of IFN- γ , TNF- α production
CD8 (T8, Leu-2)	Ig	34	T, subset of NK	MHC-I	T-cell selection, T-cell activation, signal transduction with p56/ck
CD14 (LPS-receptor)	LRG	53–55	M, G (weak), not by myeloid progenitors	Endotoxin (lipopolysaccharide), lipoteichoic acid, PI	TLR4 mediates with LPS and other PAMP activation of innate immunity
CD16a (Fc γ RIIIa)	Ig	50–80	NK, macrophages, neutrophils	Fc portion of IgG	Mediates phagocytosis and ADCC
CD19 B4	Ig	95	B (except plasma cells), FDC	Not known	Associates with CD21 and CD81 to form a complex involved in signal transduction in B-cell development, activation, and differentiation
CD20 (B1)	Unassigned	33–37	B (except plasma cells)	Not known	Cell signaling, may be important for B-cell activation and proliferation
CD21 (B2, CR2, EBV-R, C3dR)	RCA	145	Mature B, FDC, subset of thymocytes	C3d, C3dg, iC3b, CD23, EBV	Associates with CD19 and CD81 to form a complex involved in signal transduction in B-cell development, activation, and differentiation; Epstein-Barr virus receptor
CD22 (BL-CAM)	Ig	130–140	Mature B	CDw75	Cell adhesion, signaling through association with p72 sky , p53 $/56lyn$, PI3 kinase, SHP1, fLC γ
CD23 (Fc ϵ RII, B6, Leu-20, BLAST-2)	C-type lectin	45	B, M, FDC	IgE, CD21, CD11b, CD11c	Regulates IgE synthesis, cytokine release by monocytes
CD28	Ig	44	T, plasma cells	CD80, CD86	Co-stimulatory for T-cell activation; involved in the decision between T-cell activation and anergy
CD32a (Fc γ RIIIa)	Ig	40	NK, macrophages, neutrophils	Fc portion of IgG	Mediates phagocytosis and ADCC
CD40	TNFR	48–50	B, DC, EC, thymic epithelium, MP, cancers	CD154 (CD40L)	B-cell activation, proliferation, and differentiation; formation of GCs; isotype switching; rescue from apoptosis
CD45 (LCA, T200, B220)	PTP	180, 200, 210, 220	All leukocytes	Galectin-1, CD2, CD3, CD4	T and B activation, thymocyte development, signal transduction, apoptosis
CD45RA	PTP	210, 220	Subset T, medullary thymocytes, “naïve” T	Galectin-1, CD2, CD3, CD4	Isoforms of CD45 containing exon 4 (A), restricted to a subset of T cells
CD45RB	PTP	200, 210, 220	All leukocytes	Galectin-1, CD2, CD3, CD4	Isoforms of CD45 containing exon 5 (B)
CD45RC	PTP	210, 220	Subset T, medullary thymocytes, “naïve” T	Galectin-1, CD2, CD3, CD4	Isoforms of CD45 containing exon 6 (C), restricted to a subset of T cells
CD45RO	PTP	180	Subset T, cortical thymocytes, “memory” T	Galectin-1, CD2, CD3, CD4	Isoforms of CD45 containing no differentially spliced exons, restricted to a subset of T cells
CD64 (Fc γ RI)	Ig	45–55	Macrophages and monocytes	Fc portion of IgG	Mediates phagocytosis and ADCC
CD80 (B7-1, BB1)	Ig	60	Activated B and T, MP, DC	CD28, CD152 (CTLA-4)	Co-regulator of T-cell activation; signaling through CD28 stimulates and through CD152 inhibits T-cell activation
CD86 (B7-2, B70)	Ig	80	Subset B, DC, EC, activated T, thymic epithelium	CD28, CD152 (CTLA-4)	Co-regulator of T-cell activation; signaling through CD28 stimulates and through CD152 inhibits T-cell activation

(Continued)

TABLE 349-1 Human Leukocyte Surface Antigens—The CD Classification of Leukocyte Differentiation Antigens (Continued)

SURFACE ANTIGEN (OTHER NAMES)	FAMILY	MOLECULAR MASS, kDa	DISTRIBUTION	LIGAND(S)	FUNCTION
CD89 (Fc α R)	Ig	55–100	Neutrophils, eosinophils, monocytes, and MP	Fc portion of IgG	Mediates phagocytosis and ADCC of IgA-coated pathogens
CD95 (APO-1, Fas)	TNFR	43	Activated T and B	Fas ligand	Mediates apoptosis
CD112 (nekton-2, PVRL2)	Ig	62	Epithelial cells, endothelial cells, other tissues	DNAM-1 (CD226), TIGIT	T-cell activation (DNAM-1), T-cell inhibition (TIGIT)
CD134 (OX40)	TNFR	48	Activated T	OX40L (CD252)	T-cell survival, cytokine stimulation
CD137 (4-1BB)	TNFR	19	Activated T, DCs, B, NK	CD137L (41BBL)	T-cell co-stimulation
CD155 (PVR)	Ig	50–65	DCs, NK, epithelial cells	TIGIT, CD96, DNAM-1	T-cell inhibition (TIGIT, CD96), T-cell activation (DNAM-1)
CD223 (LAG-3)	Ig	57	NK, B, activated T	MHC class II	T-cell inhibition
CD226 (DNAM-1)	Ig	65	NK, monocytes, T	CD112, CD155	T-cell activation (CD112), T-cell activation (CD155)
CD252 (OX40L)	TNFR	16–25	Antigen-presenting cells, endothelial cells	OX40	T-cell survival, cytokine stimulation
CD272 (BTLA)	Ig	16	Activated T	HVEM	T-cell inhibition
CD274 (PD-L1)	Ig	40	T, NK, myeloid, B, tumor cells	PD-1 (CD279)	Inhibit TCR activation
CD278 (ICOS)	Ig	55–60	Activated T	ICOSL	T-cell activation
CD357 (GITR)	TNFR	41	Activated T, Tregs	GITRL	T-cell activation
CD152 (CTLA-4)	Ig	30–33	Activated T	CD80, CD86	Inhibits T-cell proliferation
CD154 (CD40L)	TNF	33	Activated CD4+ T, subset CD8+, T, NK, M, basophil	CD40	Co-stimulatory for T-cell activation, B-cell proliferation and differentiation
CD279 (PD-1)	Ig	50–55	B, T, TfH	PD-L1 (CD274), PD-L2 (CD273)	Inhibits T-cell proliferation

Abbreviations: ADCC, antibody-dependent cell-mediated cytotoxicity; BTLA, band T lymphocyte attenuators; CTLA, cytotoxic T lymphocyte-associated protein; DC, dendritic cells; DNAM-1, DNAX accessory molecule-1; EBV, Epstein-Barr virus; EC, endothelial cells; ECM, extracellular matrix; Fc γ RIII, low-affinity IgG receptor isoform A; FDC, follicular dendritic cells; G, granulocytes; GC, germinal center; GITR, glucocorticoid-induced TNFR-related protein; GPI, glycosyl phosphatidylinositol; HTA, human thymocyte antigen; HVEM, herpesvirus entry mediator; ICOS, inducible T-cell co-stimulator; Ig, immunoglobulin; IgG, immunoglobulin G; LAG-3, lymphocyte-activation gene 3; LCA, leukocyte common antigen; LPS, lipopolysaccharide; MHC-I, major histocompatibility complex class I; MP, macrophages; Mr, relative molecular mass; NK, natural killer cells; P, platelets; PBT, peripheral blood T cells; PD-1, programmed cell death-1; PI, phosphatidylinositol; PI3K, phosphatidylinositol 3-kinase; PLC, phospholipase C; PTp, protein tyrosine phosphatase; PVR, polio virus receptor; PVRL2, polio virus receptor-related 2; RCA, regulators of complement activation; SABP, seminal actin binding protein; TCR, T-cell receptor; TfH, T follicular helper cells; TIGIT, T cell immunoreceptor with Ig and ITIM domains; TNF, tumor necrosis factor; TNFR, tumor necrosis factor receptor.

Note: For an expanded list of cluster of differentiation (CD) human antigens, see Harrison's Online at <http://www.accessmedicine.com>; and for a full list of CD human antigens from the most recent Human Workshop on Leukocyte Differentiation Antigens (VII), D Mason, P Andre, A Bensussan, et al (eds): *Leucocyte Typing VII*. Oxford: Oxford University Press, 2002.

Source: Compiled from T Kishimoto et al (eds): *Leukocyte Typing VI*. New York: Garland Publishing, 1997; R Brines et al: *Immunol Today* 18:S:1, 1997; and D Mason et al: CD antigens 2002. *Blood* 99:3877, 2002.

nonhematopoietic cell types leads to activation/production of the complement cascade, cytokines, and antimicrobial peptides as effector molecules. In addition, pathogen PAMPs as host danger signal molecules activate DCs to mature and to express molecules on the DC surface that optimize antigen presentation to respond to foreign antigens.

PATTERN RECOGNITION

Major PRR families of proteins include transmembrane proteins, such as the Toll-like receptors (TLRs) and C-type lectin receptors (CLRs), and cytoplasmic proteins, such as the retinoic acid-inducible gene (RIG)-1-like receptors (RLRs) and NOD-like receptors (NLRs) (Table 349-3). A major group of PRR collagenous glycoproteins with C-type lectin domains are termed *collectins* and include the serum protein mannose-binding lectin (MBL). MBL and other collectins, as well as two other protein families—the pentraxins (such as C-reactive protein and serum amyloid P) and macrophage scavenger receptors—all have the property of opsonizing (coating) bacteria for phagocytosis by macrophages and can also activate the complement cascade to lyse bacteria. Integrins are cell-surface adhesion molecules that affect attachment between cells and the extracellular matrix and mediate signal transduction that reflects the chemical composition of the cell environment. For example, integrins signal after cells bind bacterial lipopolysaccharide (LPS) and activate phagocytic cells to ingest pathogens.

There are multiple connections between the innate and adaptive immune systems; these include (1) a plasma protein, LPS-binding protein, that binds and transfers LPS to the macrophage LPS receptor, CD14; (2) a human family of proteins called *Toll-like receptor proteins* (TLRs), some of which are associated with CD14, bind LPS, and signal epithelial cells, DCs, and macrophages to produce cytokines and upregulate cell-surface molecules that signal the initiation of adaptive immune responses (Fig. 349-1, Table 349-3; and (3) families of intracellular microbial sensors called NLRs and RLRs. Proteins in the Toll family can be expressed on macrophages, DCs, and

TABLE 349-2 Major Components of the Innate Immune System

Pattern recognition receptors (PRRs)	Toll-like receptors (TLRs), C-type lectin receptors (CLRs), retinoic acid-inducible gene (RIG)-1-like receptors (RLRs), and NOD-like receptors (NLRs)
Antimicrobial peptides	α -Defensins, β -defensins, cathelin, protegrin, granulysin, histatin, secretory leukoprotease inhibitor, and probiotics
Cells	Macrophages, dendritic cells, innate lymphoid cells (ILC1, ILC2, ILC3), NK cells, lymphoid tissue inducer (LTi) cells, mucosal-associated invariant T (MAIT) cells, NK-T cells, neutrophils, eosinophils, mast cells, basophils, and epithelial cells
Complement components	Classic and alternative complement pathway, and proteins that bind complement components
Cytokines	Autocrine, paracrine, endocrine cytokines that mediate host defense and inflammation, as well as recruit, direct, and regulate adaptive immune responses

Abbreviation: NK, natural killer.

TABLE 349-3 Pattern Recognition Receptors (PRRs) and Their Ligands

PRRs	LOCALIZATION	LIGAND	ORIGIN OF THE LIGAND
TLR			
TLR1	Plasma membrane	Triacyl lipoprotein	Bacteria
TLR2	Plasma membrane	Lipoprotein	Bacteria, viruses, parasite, self
TLR3	Endolysosome	dsRNA	Virus
TLR4	Plasma membrane	LPS	Bacteria, viruses, self
TLR5	Plasma membrane	Flagellin	Bacteria
TLR6	Plasma membrane	Diacyl lipoprotein	Bacteria, viruses
TLR7 (human TLR8)	Endolysosome	ssRNA	Virus, bacteria, self
TLR9	Endolysosome	CpG-DNA	Virus, bacteria, protozoa, self
TLR10	Endolysosome	Unknown	Unknown
TLR11	Plasma membrane	Profilin-like molecule	Protozoa
RLR			
RIG-I	Cytoplasm	Short dsRNA, triphosphate dsRNA	RNA viruses, DNA virus
MDA5	Cytoplasm	Long dsRNA	RNA viruses (Picornaviridae)
LGP2	Cytoplasm	Unknown	RNA viruses
NLR			
NOD1	Cytoplasm	iE-DAP	Bacteria
NOD2	Cytoplasm	MDP	Bacteria
CLR			
Dectin-1	Plasma membrane	β -Glucan	Fungi
Dectin-2	Plasma membrane	β -Glucan	Fungi
MINCLE	Plasma membrane	SAP130	Self, fungi

Abbreviations: CLR, C-type lectin receptors; dsRNA, double-strand RNA; iE-DAP, D-glutamyl-meso-diaminopimelic acid moiety; LGP2, Laboratory of Genetics and Physiology 2 protein encoded by the gene *DHX58*; MDA5, melanoma differentiation-associated protein 5; MDP, MurNAc-L-Ala-D-isoGln, also known as muramyl dipeptide; MINCLE, macrophage-inducible C-type lectin; NLR, NOD-like receptor; NOD, NOTCH protein domain; RIG, retinoic acid-inducible gene; RLR, RIG-like receptors; SAP130, Sin-3 associated protein 130; TLR, Toll-like receptor.

Source: Reproduced with permission from O Takeuchi: Pattern recognition receptors and inflammation. *Cell* 140:805, 2010.

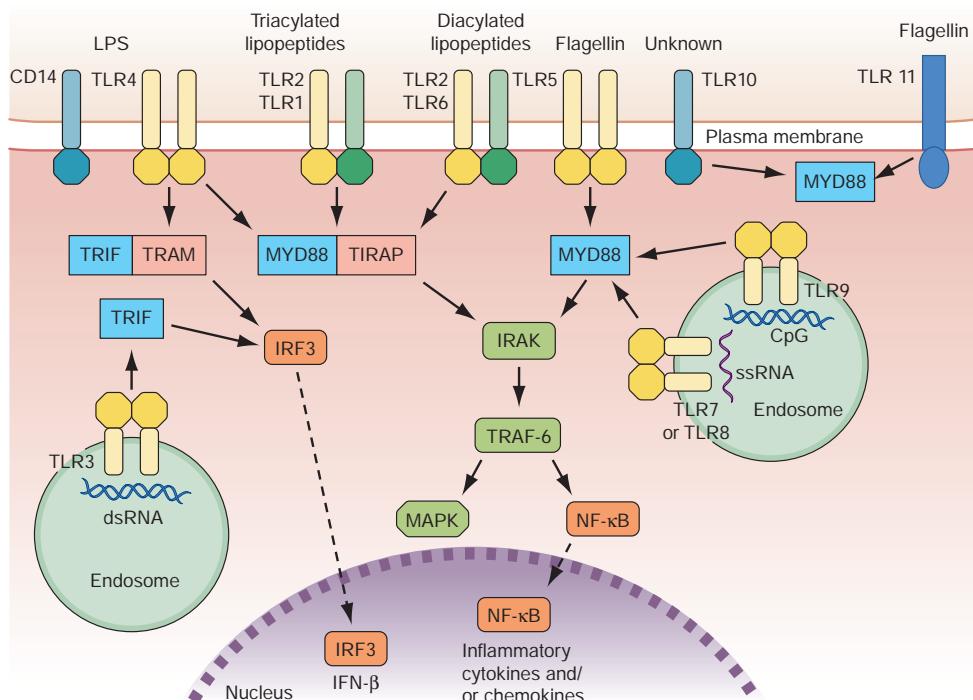


FIGURE 349-1 Overview of major TLR signaling pathways. All TLRs signal through MYD88, with the exception of TLR3. TLR4 and the TLR2 subfamily (TLR1, TLR2, TLR6) also engage TIRAP (Toll-interleukin 1 receptor domain-containing adapter protein). TLR3 signals through TRIF (Toll-interleukin 1 receptor domain-containing adapter-inducing interferon- β). TRIF is also used in conjunction with TRAM (TRIF-related adaptor molecule) in the TLR4-MYD88-independent pathway. Dashed arrows indicate translocation into the nucleus. dsRNA, double-strand RNA; IFN, interferon; IRF3, interferon regulatory factor 3; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinases; NF-κB, nuclear factor-κB; ssRNA, single-strand RNA; TLR, Toll-like receptor. (Reproduced with permission from D Van Duin et al: Triggering TLR signaling in vaccination. *Trends Immunol* 27:49, 2006.)

B cells as well as on a variety of non-hematopoietic cell types, including respiratory epithelial cells. Eleven TLRs have been identified in humans (Table 349-3). Upon ligation, TLRs activate a series of intracellular events that lead to the killing of bacteria- and viral-infected cells as well as to the recruitment and ultimate activation of antigen-specific T and B lymphocytes (Fig. 349-1). Importantly, signaling by massive amounts of LPS through TLR4 leads to the release of high levels of cytokines that mediate LPS-induced shock. Mutations in TLR4 proteins in mice protect from LPS shock, and TLR mutations in humans protect from LPS-induced inflammatory diseases such as LPS-induced asthma.

Two other families of cytoplasmic PRRs are the NLRs and the RLRs. These families, unlike the TLRs, are composed primarily of soluble intracellular proteins that scan host cell cytoplasm for intracellular pathogens (Tables 349-2 and 349-3).

The intracellular microbial sensors, NLRs, after triggering, form large cytoplasmic complexes termed *inflammasomes*, which are aggregates of molecules including NOD-like receptor pyrin (NLRP) proteins (Table 349-4). Inflammasomes activate inflammatory caspases and IL-1 β in the presence of nonbacterial danger signals (cell stress) and bacterial PAMPs. Mutations in inflammasome proteins can lead to chronic inflammation in a group of periodic febrile diseases called *autoinflammatory syndromes*. Polymorphisms in inflammasome components can either protect or enhance risk of infections or autoimmune/autoinflammatory diseases (Table 349-4). Inflammasomes are activated upon sensing of PAMPs. Crystallopathies are diseases caused by tissue crystal deposition such as monosodium urate that can activate the inflammasome and, in the case of urate deposition, can lead to gout with arthritis or renal disease.

EFFECTOR CELLS OF INNATE IMMUNITY

Cells of the innate immune system and their roles in the first line of host defense are listed in Table 349-5. Equally important as their roles in the mediation of innate immune responses are the roles that each cell type plays in recruiting T and B lymphocytes of the adaptive immune system to engage in specific pathogen responses.

Monocytes-Macrophages Monocytes arise from precursor cells within bone marrow (Fig. 349-2) and circulate with a half-life ranging from 1 to 3 days. Monocytes leave the peripheral circulation via capillaries and migration into a vast extravascular cellular pool. Tissue macrophages arise from monocytes that have migrated out of the circulation and by *in situ* proliferation of macrophage precursors in tissue. Common locations where tissue macrophages (and certain of their specialized forms) are found are lymph node, spleen, bone marrow, perivascular connective tissue, serous cavities such as the peritoneum, pleura, skin connective tissue, lung (alveolar macrophages), liver (Kupffer cells), bone (osteoclasts), central nervous system (microglia cells), and synovium (type A lining cells).

In general, monocytes-macrophages are on the first line of defense associated with innate immunity and ingest and destroy microorganisms through the release of toxic products such as hydrogen peroxide (H_2O_2) and nitric oxide (NO). Inflammatory mediators produced by macrophages attract additional effector cells such as neutrophils to the site of infection. Macrophage mediators include prostaglandins; leukotrienes; platelet activating factor; cytokines such as IL-1, TNF- α , IL-6, and IL-12; and chemokines (Tables 349-6 and 349-7).

Although monocytes-macrophages were originally thought to be the major APCs of the immune system, it is now clear that cell types called *dendritic cells* are the most potent and effective APCs in the body (see below). Monocytes-macrophages mediate innate immune effector functions such as destruction of antibody-coated bacteria, tumor cells, or even normal hematopoietic cells in certain types of autoimmune cytopenias. Monocytes-macrophages ingest bacteria or are infected by viruses, and in doing so, they frequently undergo programmed cell death or *apoptosis*. Macrophages that are infected by intracellular infectious agents are recognized by DCs as infected and apoptotic cells and are phagocytosed by DCs. In this manner, DCs “cross-present” infectious agent antigens of macrophages to T cells. Activated macrophages can also mediate antigen-nonspecific lytic activity and eliminate cell

types such as tumor cells in the absence of antibody. This activity is largely mediated by cytokines (i.e., TNF- α and IL-1). Monocytes-macrophages express lineage-specific molecules (e.g., the cell-surface LPS receptor, CD14) as well as surface receptors for a number of molecules, including the Fc region of IgG, activated complement components, and various cytokines (Table 349-6).

Dendritic Cells Human DCs contain several subsets, including myeloid DCs and plasmacytoid DCs. Myeloid DCs can differentiate into either macrophages-monocytes or tissue-specific DCs. In contrast to myeloid DCs, plasmacytoid DCs are inefficient APCs but are potent producers of type I IFN (e.g., IFN- α) in response to viral infections. The maturation of DCs is regulated through cell-to-cell contact and soluble factors, and DCs attract immune effectors through secretion of chemokines. When DCs come in contact with bacterial products, viral proteins, or host proteins released as danger signals from distressed host cells (Fig. 349-2), infectious agent molecules bind to various TLRs and activate DCs to release cytokines and chemokines that drive cells of the innate immune system to become activated to respond to invading organisms, and recruit T and B cells of the adaptive immune system to respond. Plasmacytoid DCs produce antiviral IFN- α that activates NK cell killing of pathogen-infected cells; IFN- α also activates T cells to mature into antipathogen cytotoxic (killer) T cells. Following contact with pathogens, both plasmacytoid and myeloid DCs produce chemokines that attract helper and cytotoxic T cells, B cells, polymorphonuclear cells, and naïve and memory T cells as well as regulatory T cells to ultimately dampen the immune response once the pathogen is controlled. TLR engagement on DCs upregulates MHC class II, B7-1 (CD80), and B7-2 (CD86), which enhance DC-specific antigen presentation and induce cytokine production. Thus, DCs are important bridges between early (innate) and later (adaptive) immunity. DCs also modulate and determine the types of immune responses induced by pathogens via the TLRs expressed on DCs (TLR7–9 on plasmacytoid DCs, TLR4 on monocyteoid DCs) and via the TLR adapter proteins that are induced to associate with TLRs (Fig. 349-1, Table 349-1). In addition, other PRRs, such as C-type lectins, NLRs, and mannose receptors, upon ligation by pathogen products, activate cells of the adaptive immune system and, like TLR stimulation, by a variety of factors, determine the type and quality of the adaptive immune response that is triggered.

Innate Lymphoid Cells ILCs are comprised of ILC1, ILC2, ILC3, lymphoid tissue inducer (LTi), and NK cells. ILC1, ILC2, ILC3, and LTi are primarily tissue resident cells. ILCs develop from a common lymphoid precursor in the bone marrow and then differentiate into one of five ILC types—ILC1, ILC2, ILC3, LTi, or NK cells—based on their development (Fig. 349-3A) and function (Fig. 349-3B). NK cells and ILC1s depend on T-bet transcription factor for their development and function and produce IFN- γ . NK cells are innate analogues to CD8 cytotoxic T cells in that they both mediate granzyme and perforin-based cytotoxic cell activity. ILC1s mirror CD4 T_H1 lymphocytes and react to intracellular pathogens such as viruses and to tumors. ILC2s are the analogues of T_H2 CD4 T cells and are dependent on GATA3 and ROR α factors and produce type 2 cytokines, such as IL-5 and IL-13. ILC2s respond to extracellular parasites and allergens. ILC3s and LTi cells are dependent on transcription factor ROR γ T and produce IL-17. ILC3s are analogues of CD4 T_H17 lymphocytes and attack extracellular pathogens such as bacteria and fungi. LTi cells are critical for the formation of lymph nodes and Peyer's patches in gut during fetal development (Fig. 349-3B).

NK cells express surface receptors for the Fc portion of IgG (FcR) (CD16) and for NCAM-I (CD56), and many NK cells express T lineage markers, particularly CD2, CD7, and CD8, and proliferate in response to IL-2. NK cells arise in both bone marrow and thymic microenvironments. In addition to mediating cytotoxicity to foreign or malignant cells, NK cells also mediate ADCC. ADCC is the binding of an opsonized (antibody-coated) target cell to an Fc receptor-bearing effector cell via the Fc region of antibody, resulting in target cell lysis. NK cell cytotoxicity is the MHC-unrestricted, non-antibody-mediated

TABLE 349-4 Mutations in Innate Inflammasome Molecules Associated with Clinical Disease

Inherited Inflammasomopathies				
MUTATED GENE	DISEASE	INHERITED PATTERN AND EFFECT	PHENOTYPE	PREDOMINANT EFFECTOR CELLS
<i>NLRP1</i>	NLRP1-associated autoinflammation with arthritis and dyskeratosis	Autosomal dominant GoF	Hyperkeratotic ulcerative skin lesions, fever, arthritis, ANA	Keratinocytes
<i>NLRP3</i>	Cryopyrin-associated periodic syndromes (CAPS)	Autosomal dominant GoF	Spectrum from cold-induced urticaria and fever to CNS inflammation and bone overgrowth	Monocytes, granulocytes (neutrophils), chondrocytes
<i>NLRC4</i>	Autoinflammatory infantile fever with enterocolitis (AIFEC)	Autosomal dominant GoF	Recurrent MAS, enterocolitis, cold-induced fever and urticaria, CNS inflammation	Monocytes/macrophages
<i>MEFV</i>	Familial Mediterranean fever (FMF)	Autosomal recessive LoF or gene-dosage-dependent autosomal dominant GoF	Fever, serositis, rash, SAA amyloidosis	Neutrophils, monocytes, serosal and synovial fibroblasts

Genetic Polymorphisms in Inflammasome Components and Human Infectious Diseases

INFECTIOUS AGENT/DISEASE	GENE	VARIANT ID	EFFECT ON INFLAMMASOME ACTIVATION	ASSOCIATION
<i>Candida albicans</i> (recurrent vulvovaginal candidiasis)	<i>NLRP3</i>	rs74163773	Increased	Risk
<i>Chlamydia trachomatis</i>	<i>NLRP3</i>	rs12065526	Unknown	Risk
HCV	<i>NLRP3</i>	rs1539019; rs35829419	Unknown; increased	Protection
HIV-1	<i>NLRP3</i>	rs10754558	Increased	Protection
	<i>IFI16</i>	rs1417806	Increased	Protection
HPV	<i>NLRP1</i>	rs11651270	Increased	Protection
	<i>NLRP3</i>	rs10754558	Increased	Protection
HSV-2	<i>IFI16</i>	rs2276404	Increased	Protection
HTLV	<i>NLRP3</i>	rs10754558	Increased	Protection
Microbial infection in lungs	<i>NLRC4</i>	rs212704	Decreased	Risk
<i>Mycobacterium leprae</i>	<i>NLRP1</i>	rs2670660, rs12150220 rs2137722	Increased (Haplotype)	Protection
<i>Mycobacterium tuberculosis</i>	<i>NLRP3</i>	rs10754558 rs10754558 <i>CARD8</i> <i>NLRC4</i>	Increased Increased Unknown Decreased	Protection Risk Risk Protection
<i>Plasmodium vivax</i>	<i>NLRP1</i>	rs12150220	Increased	Risk
Renal parenchymal infections	<i>NLRP3</i>	rs4612666	Increased	Protection
<i>Streptococcus pneumoniae</i>	<i>NLRP1</i>	rs11651270	Increased	Risk
	<i>CARD8</i>	rs2043211	Increased	
<i>Trypanosoma cruzi</i>	<i>NLRP1</i>	rs11691270	Increased	Risk
	<i>CASP1</i>	rs501192	Unknown	Risk

Genetic Polymorphisms in Inflammasome Components and Autoimmune in Polygenic Autoinflammatory Diseases

Addison disease	<i>NLRP1</i>	rs12150220	Increased	Risk
Ankylosing spondylitis	<i>NLRP3</i>	rs4612666	Increased	Risk
	<i>MEFV</i>	rs224204	Unknown	Risk
	<i>CARD8</i>	rs2043211	Increased	Protection
Autoimmune thyroiditis	<i>NLRP1</i>	rs12150220, rs2670660	Increased	Risk
	<i>AIM2</i>	rs855873	Unknown	Risk
Behcet disease	<i>AIM2</i>	rs855873	Unknown	Risk
	<i>IFI16</i>	rs6940	Decreased	
Celiac disease	<i>NLRP3</i>	rs35829419	Increased	Protection; risk
IBD: Crohn's disease (CD) and ulcerative colitis (UC)	<i>NLRP3</i>	rs35829419 rs10754558 rs10925019 rs4925648 rs4353135, rs55646866; rs4266924, rs672995, rs10733113	Increased Increased Increased Unknown Unknown Decreased; unknown	Risk (men) Protection Risk Risk Risk Risk

(Continued)

TABLE 349-4 Mutations in Innate Inflammasome Molecules Associated with Clinical Disease (Continued)

INFECTIOUS AGENT/DISEASE	GENE	VARIANT ID	EFFECT ON INFLAMMASOME ACTIVATION	ASSOCIATION
IBD: Crohn's disease (CD) and ulcerative colitis (UC) (Cont.)	MEFV	rs182674, rs224217, rs224225, rs224224, rs224223, rs224222	Unknown	Risk
	CARD8	rs2043211	Increased	Risk
		rs1972619	Unknown	Protection Risk
HS purpura	MEFV	rs3743930	Unknown	Risk
Kawasaki disease	NLRP1	rs11651270, rs8079034, rs3744717, rs11078571, rs16954813, rs8079727	Increased (haplotype)	Risk
Multiple sclerosis	NLRP3	rs3806265, rs10754557	Unknown	Risk
	NLRC4	rs35829419 rs479333	Increased Decreased	Risk Protection
PFAPA	CARD8	rs140826611	Unknown	Risk
Psoriasis	NLRP1	rs8079034	Unknown	Risk
	NLRP3	rs3806265, rs10754557	Unknown	Risk
		rs10733113	Unknown	Risk
	CARD8	rs2043211	Increased	Risk
	AIM2	rs2276405	Unknown	Protection
Psoriatic JIA	NLRP3	rs4353135	Decreased	Risk
		rs3806265	Unknown	Risk
	MEFV	rs224204	Unknown	Risk
Rheumatoid arthritis	NLRP1	rs878329	Unknown	Risk
	NLRP3	rs35829419 rs10754558	Increased Increased	Risk Risk
		rs10159239, rs4925648, rs4925659	Unknown	Risk
	CASP5	rs9651713	Unknown	Risk
SLE	NLRP1	rs12150220, rs2670660	Increased	Risk
Systemic sclerosis	NLRP1	rs8182352	Unknown	Risk
Type 1 diabetes	NLRP1	rs12150220 rs2670660, rs11651270	Increased Increased	Risk Protection
	NLRP3	rs10754558	Increased	Protection
Vitiligo	NLRP1	rs12150220 rs2670660 rs8182352 rs6502867 rs1008588	Increased Increased Unknown Unknown Unknown	Risk Risk Risk Risk Risk

Note: Mutated gene and respective syndrome name are reported for inflammasomopathies, as well as inheritance pattern and effect of mutations, clinical phenotype, and predominant disease effector cells. Inflammasome variants previously associated with infectious agents and/or diseases are briefly resumed from literature (<https://www.ncbi.nlm.nih.gov/pubmed>). Significantly associated polymorphisms were grouped according to the infectious agent/disease, Infectious agent or disease (in alphabetical order), gene name (gene), identification number of polymorphism (ID), resulting effect on inflammasome activation ("increased," "decreased," or "unknown"), cohort origin (cohort) and eventually specifications (severity, etc.), sample size (n), and type (case/control or cases only), association result ("risk" or "protection"), and respective references are reported.

Abbreviations: ANA, antinuclear antibodies; CNS, central nervous system; GoF, gain-of-function; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HPV, human papillomavirus; HS, Henoch-Schönlein; HSV, herpes simplex virus; HTLV, human T-lymphotropic virus; IBD, inflammatory bowel disease; JIA, juvenile idiopathic arthritis; LoF, loss-of-function; MAS, macrophage activation syndrome; PFAPA, periodic fever with aphthous stomatitis, pharyngitis, and cervical adenitis; SAA, serum amyloid A; SLE, systemic lupus erythematosus.

Source: Reproduced with permission from FP Fernandes et al: Inflammasome genetics and complex diseases: A comprehensive review. Eur J Hum Genet 28:1307, 2020.

killing of target cells, which are usually malignant cell types, transplanted foreign cells, or virus-infected cells. Thus, NK cell cytotoxicity may play an important role in immune surveillance and destruction of malignant and virus-infected host cells. NK cell hyporesponsiveness is also observed in patients with *Chédiak-Higashi syndrome*, an autosomal recessive disease associated with fusion of cytoplasmic granules and defective degranulation of neutrophil lysosomes.

NK cells have a variety of surface receptors that have inhibitory or activating functions and belong to two structural families. These families include the immunoglobulin superfamily and the lectin-like type II transmembrane proteins. NK immunoglobulin superfamily receptors include the killer cell immunoglobulin-like activating or

inhibitory receptors (KIRs), many of which have been shown to have HLA class I ligands. The KIRs are made up proteins with either two (KIR2D) or three (KIR3D) extracellular immunoglobulin domains (D). Moreover, their nomenclature designates their function as either inhibitory KIRs with a long (L) cytoplasmic tail and immunoreceptor tyrosine-based inhibitory motif (ITIM) (KIRDL) or activating KIRs with a short (S) cytoplasmic tail (KIRDS). NK cell inactivation by KIRs is a central mechanism to prevent damage to normal host cells. Genetic studies have demonstrated the association of KIRs with viral infection outcome and autoimmune disease (Table 349-8).

In addition to the KIRs, a second set of immunoglobulin superfamily receptors includes the natural cytotoxicity receptors (NCRs), which

TABLE 349-5 Cells of the Innate Immune System and Their Major Roles in Triggering Adaptive Immunity

CELL TYPE	MAJOR ROLE IN INNATE IMMUNITY	MAJOR ROLE IN ADAPTIVE IMMUNITY
Macrophages	Phagocytose and kill bacteria; produce antimicrobial peptides; bind LPS; produce inflammatory cytokines	Produce IL-1 and TNF- α to upregulate lymphocyte adhesion molecules and chemokines to attract antigen-specific lymphocyte. Produce IL-12 to recruit T _H 1 T helper cell responses; upregulate co-stimulatory and MHC molecules to facilitate T and B lymphocyte recognition and activation. Macrophages and dendritic cells, after LPS signaling, upregulate co-stimulatory molecules B7-1 (CD80) and B7-2 (CD86) that are required for activation of pathogen-specific T cells. There are also Toll-like proteins on B cells and dendritic cells that, after LPS ligation, induce CD80 and CD86 on these cells for T-cell antigen presentation.
Plasmacytoid dendritic cells (DCs) of lymphoid lineage	Produce large amounts of interferon- α (IFN- α), which has antitumor and antiviral activity, and are found in T-cell zones of lymphoid organs; they circulate in blood	IFN- α is a potent activator of macrophage and mature DCs to phagocytose invading pathogens and present pathogen antigens to T and B cells.
Myeloid DCs are of two types: interstitial and Langerhans-derived	Interstitial DCs are strong producers of IL-12 and IL-10 and are located in T-cell zones of lymphoid organs, circulate in blood, and are present in the interstices of the lung, heart, and kidney; Langerhans DCs are strong producers of IL-12; are located in T-cell zones of lymph nodes, skin epithelia, and the thymic medulla; and circulate in blood	Interstitial DCs are potent activators of macrophage and mature DCs to phagocytose invading pathogens and present pathogen antigens to T and B cells.
ILC1 cells	Weakly cytotoxic, dependent on T-bet transcription factor, first line of defense against viruses and bacteria	Produce IFN- γ to recruit CD4 T _H 1 T cells
ILC2 cells	Mediate innate responses to parasites/helminths, repair damaged tissues by producing amphiregulin	Produce IL-4, IL-5, IL-13; recruit CD4 T _H 2 T cells
ILC3 cells	Innate immune response to extracellular bacteria and gut microbiome	Produce IL-22, IL-17, GM-CSF, lymphotoxin; recruit CD4 T _H 17 T cells
Lymphoid tissue inducer (LTi) cells	Critical for formation of secondary lymphoid tissue during embryogenesis	Produce lymphotoxin for lymph node and Peyer's patch development in which adaptive immune responses occur
Natural killer (NK) cells	Kill foreign and host cells that have low levels of MHC+ self-peptides. Express NK receptors that inhibit NK function in the presence of high expression of self-MHC.	Produce TNF- α and IFN- γ , which recruit T _H 1 helper T-cell responses
NK-T cells	Lymphocytes with both T-cell and NK surface markers that recognize lipid antigens of intracellular bacteria such as <i>Mycobacterium tuberculosis</i> by CD1 molecules and kill host cells infected with intracellular bacteria	Produce IL-4 to recruit T _H 2 helper T-cell responses, IgG1 and IgE production
Neutrophils	Phagocytose and kill bacteria, produce antimicrobial peptides	Produce nitric oxide synthase and nitric oxide, which inhibit apoptosis in lymphocytes and can prolong adaptive immune responses
Eosinophils	Kill invading parasites	Produce IL-5, which recruits Ig-specific antibody responses
Mast cells and basophils	Release TNF- α , IL-6, and IFN- γ in response to a variety of bacterial PAMPs	Produce IL-4, which recruits T _H 2 helper T cell responses, and recruit IgG1- and IgE-specific antibody responses
Epithelial cells	Produce antimicrobial peptides; tissue-specific epithelia produce mediator of local innate immunity; e.g., lung epithelial cells produce surfactant proteins (proteins within the collectin family) that bind and promote clearance of lung-invading microbes	Produces TGF- β , which triggers IgA-specific antibody responses

Abbreviations: GM-CSF, granulocyte-macrophage colony-stimulating factor; IL-4, IL-5, IL-6, IL-10, and IL-12, interleukin 4, 5, 6, 10, and 12, respectively; ILC, innate lymphoid cell; MHC, major histocompatibility complex; LPS, lipopolysaccharide; PAMP, pathogen-associated molecular patterns; TGF, transforming growth factor; T_H, helper T cell; TNF- α , tumor necrosis factor-alpha.

Source: Adapted from R Medzhitov, CA Janeway: Curr Opin Immunol 9:4, 1997. Copyright 1997.

include NKp46, NKp30, and NKp44. These receptors help to mediate NK cell activation against target cells. The ligands to which NCRs bind on target cells have been recently recognized to be comprised of molecules of pathogens such as influenza, cytomegalovirus, and malaria as well as host molecules expressed on tumor cells.

NK cell signaling is, therefore, a highly coordinated series of inhibiting and activating signals that prevent NK cells from responding to uninfected, nonmalignant self-cells; however, they are activated to attack malignant and virally infected cells (Fig. 349-4). Recent evidence suggests that NK cells, although not possessing rearranging immune recognition genes, may be able to mediate recall for NK cell responses to viruses and for immune responses such as contact hypersensitivity.

Some NK cells express CD3 and invariant TCR- α chains and are termed *NK T cells*. TCRs of NK T cells recognize lipid molecules of intracellular bacteria when presented in the context of CD1 molecules on APCs. Upon activation, NK T cells secrete effector cytokines such as IL-4 and IFN- γ . This mode of recognition of intracellular bacteria such as *Listeria monocytogenes* and *Mycobacterium*

tuberculosis by NK T cells leads to induction of activation of DCs and is thought to be an important innate defense mechanism against these organisms.

The receptors for the Fc portion of IgG (FcγRs) are present on NK cells, B cells, macrophages, neutrophils, and mast cells and mediate interactions of IgG with antibody-coated target cells, such as virally infected cells. Antibody-NK interaction via antibody Fc and NK cell FcR links the adaptive and innate immune systems and regulates the mediation of IgG antibody effector functions such as ADCC. There are both activation and inhibitory FcγRs. Activation FcγRs, such as FcγRI (CD64), FcγRIIa (CD32a), and FcγRIIIa (CD16a), are characterized by the presence of an immunoreceptor tyrosine-based activating motif (ITAM) sequence, whereas inhibitory FcγRs, such as FcγRIIb (CD32b), contain an ITIM sequence. There is evidence that dysregulation in IgG-FcγR interactions plays roles in arthritis, multiple sclerosis, and systemic lupus erythematosus.

Neutrophils, Eosinophils, and Basophils Granulocytes are present in nearly all forms of inflammation and are amplifiers and

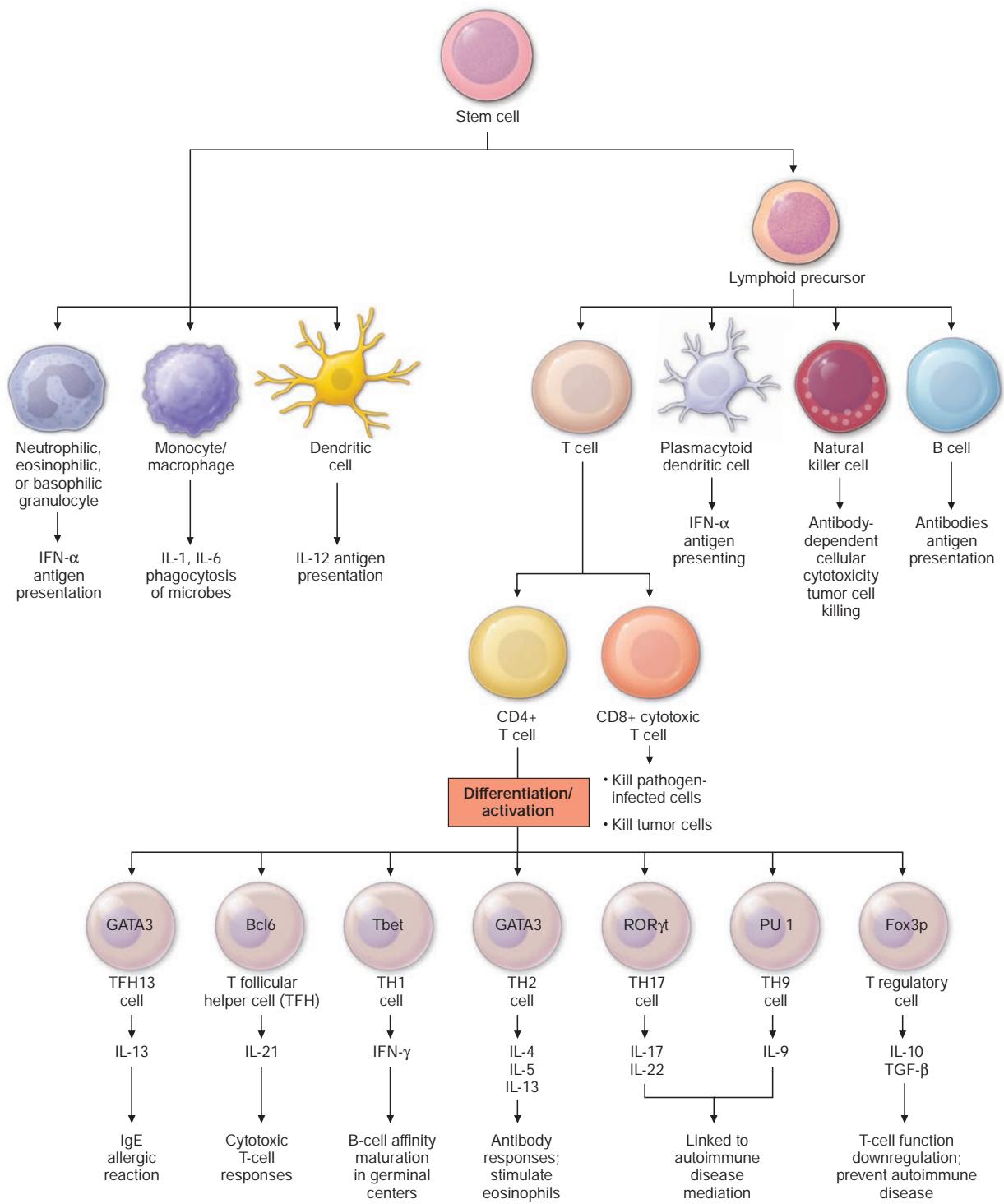


FIGURE 349-2 Model of immune effector cell development. Hematopoietic stem cells differentiate into T cells, antigen-presenting dendritic cells, natural killer cells, macrophages, granulocytes, or B cells. Foreign antigen is processed by dendritic cells, macrophages, and B cells, and peptide fragments of foreign antigen are presented to CD4+ and/or CD8+ T cells. CD8+ T-cell activation leads to induction of cytotoxic T lymphocyte (CTL) or killer T-cell generation, as well as induction of cytokine-producing CD8+ cytotoxic T cells. Granulocytes (neutrophils, eosinophils, or basophils) are effector cells of the innate immune system and mediate anti-infectious agent activity by cytokine production, infectious agent killing, or both. T_H1 CD4+ T cells play an important role in defense against intracellular microbes and help in the generation of CD8+ cytotoxic T cells. T_H2 CD4+ T cells producing interferon (IFN) γ or interleukin (IL) 4, IL-5, or IL-13 regulate Ig class switching and determine the type of antibody produced. T_H17 cells secrete IL-17 and IL-22; T_H9 cells secrete IL-9, and Tfh13 cells secrete IL-4, IL-5, and IL-13. T_H17 and T_H9 CD4 T cells are linked to mediation of autoimmune disease, and Tfh13 cells are linked to IgE-mediated anaphylaxis. CD4+ T regulatory cells produce IL-10 and transforming growth factor (TGF)- β and downregulate T- and B-cell responses once the microbe has been eliminated. Each of the types of CD4+ T cells are regulated by different transcription factors, and the key transcription factors are shown in the circles above each CD4+ T-cell type.

TABLE 349-6 Cytokines and Cytokine Receptors

CYTOKINE	RECEPTOR	CELL SOURCE	CELL TARGET	BIOLOGIC ACTIVITY
IL-1 α , β	Type I IL-1 r , type II IL-1 r	Monocytes/macrophages, B cells, fibroblasts, most epithelial cells including thymic epithelium, endothelial cells	All cells	Upregulates adhesion molecule expression, neutrophil and macrophage emigration, mimics shock, fever, upregulates hepatic acute-phase protein production, facilitates hematopoiesis
IL-2	IL-2r α , β , common γ	T cells	T cells, B cells, NK cells, monocytes-macrophages	Promotes T-cell activation and proliferation, B-cell growth, NK-cell proliferation and activation, enhanced monocyte/macrophage cytolytic activity
IL-3	IL-3r, common β	T cells, NK cells, mast cells	Monocytes-macrophages, mast cells, eosinophils, bone marrow progenitors	Stimulates hematopoietic progenitors
IL-4	IL-4r α , common γ	T cells, mast cells, basophils	T cells, B cells, NK cells, monocytes-macrophages, neutrophils, eosinophils, endothelial cells, fibroblasts	Stimulates T H_2 helper T-cell differentiation and proliferation; stimulates B-cell Ig class switch to IgG1 and IgE anti-inflammatory action on T cells, monocytes; produced by T follicular helper cells in B-cell germinal centers that stimulate B-cell maturation.
IL-5	IL-5r α , common γ	T cells, mast cells, eosinophils	Eosinophils, basophils, murine B cells	Regulates eosinophil migration and activation
IL-6	IL-6r, gp130	Monocytes-macrophages, B cells, fibroblasts, most epithelium including thymic epithelium, endothelial cells	T cells, B cells, epithelial cells, hepatocytes, monocytes-macrophages	Induces acute-phase protein production, T- and B-cell differentiation and growth, myeloma cell growth, and osteoclast growth and activation
IL-7	IL-7r α , common γ	Bone marrow, thymic epithelial cells	T cells, B cells, bone marrow cells	Differentiates B-, T-, and NK-cell precursors, activates T and NK cells
IL-8	CXCR1, CXCR2	Monocytes-macrophages, T cells, neutrophils, fibroblasts, endothelial cells, epithelial cells	Neutrophils, T cells, monocytes-macrophages, endothelial cells, basophils	Induces neutrophil, monocyte, and T-cell migration, induces neutrophil adherence to endothelial cells and histamine release from basophils, and stimulates angiogenesis; suppresses proliferation of hepatic precursors
IL-9	IL-9r α , common γ	T cells	Bone marrow progenitors, B cells, T cells, mast cells	Induces mast cell proliferation and function, synergizes with IL-4 in IgG and IgE production and T-cell growth, activation, and differentiation
IL-10	IL-10r	Monocytes-macrophages, T cells, B cells, keratinocytes, mast cells	Monocytes-macrophages, T cells, B cells, NK cells, mast cells	Inhibits macrophage proinflammatory cytokine production, downregulates cytokine class II antigen and B7-1 and B7-2 expression, inhibits differentiation of T H_1 helper T cells, inhibits NK cell function, stimulates mast cell proliferation and function, B-cell activation, and differentiation
IL-11	IL-11r α , gp130	Bone marrow stromal cells	Megakaryocytes, B cells, hepatocytes	Induces megakaryocyte colony formation and maturation, enhances antibody responses, stimulates acute-phase protein production
IL-12 (35-kDa and 40-kDa subunits)	IL-12r	Activated macrophages, dendritic cells, neutrophils	T cells, NK cells	Induces T H_1 T helper cell formation and lymphokine-activated killer cell formation; increases CD8+ CTL cytolytic activity: ↓IL-17, ↑IFN- γ
IL-13	IL-13r/IL-4r α	T cells (T H_2)	Monocytes-macrophages, B cells, endothelial cells, keratinocytes	Upregulates VCAM-1 and C-C chemokine expression on endothelial cells and B-cell activation and differentiation, and inhibits macrophage proinflammatory cytokine production
IL-14	Unknown	T cells	Normal and malignant B cells	Induces B-cell proliferation, inhibits antibody secretion, and expands selected B-cell subgroups
IL-15	IL-15r α , common γ , IL2r β	Monocytes-macrophages, epithelial cells, fibroblasts	T cells, NK cells	Promotes T-cell activation and proliferation, angiogenesis, and NK cells
IL-16	CD4	Mast cells, eosinophils, CD8+ T cells, respiratory epithelium	CD4+ T cells, monocytes-macrophages, eosinophils	Promotes chemoattraction of CD4+ T cells, monocytes, and eosinophils; inhibits HIV-1 replication; inhibits T-cell activation through CD3/T-cell receptor
IL-17	IL-17r	CD4+ T cells	Fibroblasts, endothelium, epithelium, macrophages	Enhances cytokine/chemokine secretion; promotes delayed-type reactions
IL-18	IL-18r (IL-1R-related protein)	Keratinocytes, macrophages	T cells, B cells, NK cells	Upregulates IFN- γ production, enhances NK cell cytotoxicity
IL-21	IL- δ chain/IL-21R	CD4 T cells	NK cells	Downregulates NK cell-activating molecules, NKG2D/DAP10; produced by T follicular helper cells in B-cell germinal centers that stimulate B-cell maturation.
IL-22	IL-22 R1/IL-10R2	DC, T cells	Epithelial cells	Innate responses against bacterial pathogens; promotes hepatocyte survival
IL-23	IL-12Rb1/IL23R	Macrophages, other cell types	T cells	Opposite effects of IL-12 (↑IL-17, ↑IFN- γ)
IL-24	IL-20R1/IL-20R2 IL-22R1/IL-20R2	Macrophages, T H_2 cells	Nonhematopoietic cells such as fibroblasts	Promotes wound healing

(Continued)

TABLE 349-6 Cytokines and Cytokine Receptors (Continued)

CYTOKINE	RECEPTOR	CELL SOURCE	CELL TARGET	BIOLOGIC ACTIVITY
IL-25 (also called IL-17E)	IL-17RB	CD4 T cells, mast cells	Fibroblasts, endothelium, epithelium, macrophages	Proinflammatory; induces cytokine production
IL-26	IL-20R1/IL-10R2	T _H 1, T _H 17 T cells, synovial cells	Epithelial cells	Proinflammatory; induces cytokine production
IL-27	gp130 ^t wsx-1	Myeloid cells such as macrophages and DCs	T cells	Collaborates with other cytokines to activate T-cell differentiation
IL-28A (IFN-λ2)	IFN-λ receptor 1, IL-28Ra, IL-10Rβ	Myeloid lineage cells; epithelial cells	Epithelial cells	Enhanced clearance of viral infections
IL-28B (IFN-λ3)	IFN-λ receptor 1, IL-28Ra, IL-10Rβ	Myeloid lineage cells; epithelial cells	Epithelial cells	Enhanced clearance of viral infections
IL-29 (IFN-λ1)	IFN-λ receptor 1, IL-28Ra, IL-10Rβ	Myeloid lineage cells; epithelial cells	Epithelial cells	Enhanced clearance of viral infections
IL-30 (p28 of IL-27)	IL-27Ra; gp130+wsx-1	Activated macrophages and DCs; epithelial malignancies	Monocytes	Anti-inflammatory cytokines; upregulation of breast and prostate cancer metastasis
IL-31	IL-31RA/oncostatin MRβ	Eosinophils, CD4 T cells	Epithelial cells, monocytes	Pruritis, proinflammatory
IL-32 (NK4)	?	Monocytes, T cells, NK cells, epithelial cells	Monocytes, macrophages, bone marrow stroma	Angiogenesis, IL-2 production in bone marrow, proinflammatory
IL-33 (NF-HEV; IL-1 F11)	ST-2	Endothelial cells, epithelial cells, fibroblasts, mucosal epithelium	T cells, mast cells eosinophils, basophils, ILC2s	Alarmin cytokine, proinflammatory
IL-34 (C16orf77)	CSF-1R, PTP-E, CD138	Neurons, Treg, myeloid cells		Anti-inflammatory myeloid cell proliferation
IL-35	IL-12Rβ2/IL-12RB2, gp130/gp130, IL-12Rb2/gp130	Tregs, Bregs	Macrophages, T cells	Prevents T _H 1 and T _H 17 proliferation; induced Treg/Breg proliferation/anti-inflammatory
IL-36α IL36β IL36γ IL36RA (IL-1 F5)	IL-36R	Keratocytes Mucosal epithelial cells Monocytes-macrophages Langerhans cells CD4 T cells	Epithelial cells, macrophages, DCs, T cells, B cells, plasma cells	T _H responses, proinflammatory
IL-38 IL-10 F10	IL-1R, IL-36R, IL-1RA PL1	Epithelial cells, B cells	Epithelial cells, macrophages, DCs, T cells, B cells, plasma cells	Blocks IL-36; anti-inflammatory
IL-39	?	Macrophages, DCs, B cells	Neutrophils	Proinflammatory
IL-40	?	B cells, bone marrow/stroma	B cells	Involved in IgA production, B-cell homeostasis and development
IFN-α	Type I interferon receptor	All cells	All cells	Promotes antiviral activity; stimulates T-cell, macrophage, and NK-cell activity; direct antitumor effects; upregulates MHC class I antigen expression; used therapeutically in viral and autoimmune conditions
IFN-β	Type I interferon receptor	All cells	All cells	Antiviral activity; stimulates T-cell, macrophage, and NK-cell activity; direct antitumor effects; upregulates MHC class I antigen expression; used therapeutically in viral and autoimmune conditions
IFN-γ	Type II interferon receptor	T cells, NK cells	All cells	Regulates macrophage and NK-cell activations; stimulates immunoglobulin secretion by B cells; induction of class II histocompatibility antigens; T _H 1 T-cell differentiation
TNF-α	TNFR1, TNFR2	Monocytes-macrophages, mast cells, basophils, eosinophils, NK cells, B cells, T cells, keratinocytes, fibroblasts, thymic epithelial cells	All cells except erythrocytes	Fever, anorexia, shock, capillary leak syndrome, enhanced leukocyte cytotoxicity, enhanced NK-cell function, acute phase protein synthesis, proinflammatory cytokine induction
TNF-β	TNFR1, TNFR2	T cells, B cells	All cells except erythrocytes	Cell cytotoxicity, lymph node and spleen development
LT-β	LTβR	T cells	All cells except erythrocytes	Cell cytotoxicity, normal lymph node development
G-CSF	G-CSFr; gp130	Monocytes-macrophages, fibroblasts, endothelial cells, thymic epithelial cells, stromal cells	Myeloid cells, endothelial cells	Regulates myelopoiesis; enhances survival and function of neutrophils; clinical use in reversing neutropenia after cytotoxic chemotherapy
GM-CSF	GM-CSFr, common β	T cells, monocytes-macrophages, fibroblasts, endothelial cells, thymic epithelial cells	Monocytes-macrophages, neutrophils, eosinophils, fibroblasts, endothelial cells	Regulates myelopoiesis; enhances macrophage bactericidal and tumorcidal activity; mediator of dendritic cell maturation and function; upregulates NK-cell function; clinical use in reversing neutropenia after cytotoxic chemotherapy
M-CSF	M-CSFr (<i>c-fms</i> protooncogene)	Fibroblasts, endothelial cells, monocytes-macrophages, T cells, B cells, epithelial cells including thymic epithelium	Monocytes-macrophages	Regulates monocyte-macrophage production and function

(Continued)

TABLE 349-6 Cytokines and Cytokine Receptors (Continued)

CYTOKINE	RECEPTOR	CELL SOURCE	CELL TARGET	BIOLOGIC ACTIVITY
LIF	LIFR- α ; gp130	Activated T cells, bone marrow stromal cells, thymic epithelium	Megakaryocytes, monocytes, hepatocytes, possibly lymphocyte subpopulations	Induces hepatic acute-phase protein production; stimulates macrophage differentiation; promotes growth of myeloma cells and hematopoietic progenitors; stimulates thrombopoiesis
OSM	OSMr; LIFr; gp130	Activated monocytes-macrophages and T cells, bone marrow stromal cells, some breast carcinoma cell lines, myeloma cells	Neurons, hepatocytes, monocytes-macrophages, adipocytes, alveolar epithelial cells, embryonic stem cells, melanocytes, endothelial cells, fibroblasts, myeloma cells	Induces hepatic acute-phase protein production; stimulates macrophage differentiation; promotes growth of myeloma cells and hematopoietic progenitors; stimulates thrombopoiesis; stimulates growth of Kaposi's sarcoma cells
SCF	SCFr (<i>c-kit</i> protooncogene)	Bone marrow stromal cells and fibroblasts	Embryonic stem cells, myeloid and lymphoid precursors, mast cells	Stimulates hematopoietic progenitor cell growth, mast cell growth; promotes embryonic stem cell migration
TGF- β (3 isoforms)	Type I, II, III TGF- β receptor	Most cell types	Most cell types	Downregulates T-cell, macrophage, and granulocyte responses; stimulates synthesis of matrix proteins; stimulates angiogenesis
Lymphotactin/SCM-1	XCR1	NK cells, mast cells, double-negative thymocytes, activated CD8+ T cells	T cells, NK cells	Chemoattractant for lymphocytes; only known chemokine of C class
MCP-1	CCR2	Fibroblasts, smooth-muscle cells, activated PBMCs	Monocytes-macrophages, NK cells, memory T cells, basophils	Chemoattractant for monocytes, activated memory T cells, and NK cells; induces granule release from CD8+ T cells and NK cells; potent histamine-releasing factor for basophils; suppresses proliferation of hematopoietic precursors; regulates monocyte protease production
MCP-2	CCR1, CCR2	Fibroblasts, activated PBMCs	Monocytes-macrophages, T cells, eosinophils, basophils, NK cells	Chemoattractant for monocytes, memory and naïve T cells, eosinophils, ?NK cells; activates basophils and eosinophils; regulates monocyte protease production
MCP-3	CCR1, CCR2	Fibroblasts, activated PBMCs	Monocytes-macrophages, T cells, eosinophils, basophils, NK cells, dendritic cells	Chemoattractant for monocytes, memory and naïve T cells, dendritic cells, eosinophils, ?NK cells; activates basophils and eosinophils; regulates monocyte protease production
MCP-4	CCR2, CCR3	Lung, colon, small intestinal epithelial cells, activated endothelial cells	Monocytes-macrophages, T cells, eosinophils, basophils	Chemoattractant for monocytes, T cells, eosinophils, and basophils
Eotaxin	CCR3	Pulmonary epithelial cells, heart	Eosinophils, basophils	Potent chemoattractant for eosinophils and basophils; induces allergic airways disease; acts in concert with IL-5 to activate eosinophils; antibodies to eotaxin inhibit airway inflammation
TARC	CCR4	Thymus, dendritic cells, activated T cells	T cells, NK cells	Chemoattractant for T and NK cells
MDC	CCR4	Monocytes-macrophages, dendritic cells, thymus	Activated T cells	Chemoattractant for activated T cells; inhibits infection with T-cell tropic HIV-1
MIP-1 α	CCR1, CCR5	Monocytes-macrophages, T cells	Monocytes-macrophages, T cells, dendritic cells, NK cells, eosinophils, basophils	Chemoattractant for monocytes, T cells, dendritic cells, and NK cells, and weak chemoattractant for eosinophils and basophils; activates NK-cell function; suppresses proliferation of hematopoietic precursors; necessary for myocarditis associated with coxsackievirus infection; inhibits infection with monocytotropic HIV-1
MIP-1 β	CCR5	Monocytes-macrophages, T cells	Monocytes-macrophages, T cells, NK cells, dendritic cells	Chemoattractant for monocytes, T cells, and NK cells; activates NK-cell function; inhibits infection with monocytotropic HIV-1
RANTES	CCR1, CCR2, CCR5	Monocytes-macrophages, T cells, fibroblasts, eosinophils	Monocytes-macrophages, T cells, NK cells, dendritic cells, eosinophils, basophils	Chemoattractant for monocytes-macrophages, CD4+, CD45R0+ T cells, CD8+ T cells, NK cells, eosinophils, and basophils; induces histamine release from basophils; inhibits infections with monocytotropic HIV-1
LARC/MIP-3 α /Exodus-1	CCR6	Dendritic cells, fetal liver cells, activated T cells	T cells, B cells	Chemoattractant for lymphocytes
ELC/MIP-3 β	CCR7	Thymus, lymph node, appendix	Activated T cells and B cells	Chemoattractant for B and T cells; receptor upregulated on EBV-infected B cells and HSV-infected T cells
I-309/TCA-3	CCR8	Activated T cells	Monocytes-macrophages, T cells	Chemoattractant for monocytes; prevents glucocorticoid-induced apoptosis in some T-cell lines
SLC/TCA-4/Exodus-2	CCR7	Thymic epithelial cells, lymph node, appendix, and spleen	T cells	Chemoattractant for T lymphocytes; inhibits hematopoiesis
DC-CK1/PARC	Unknown	Dendritic cells in secondary lymphoid tissues	Naive T cells	May have a role in induction of immune responses

(Continued)

TABLE 349-6 Cytokines and Cytokine Receptors (Continued)

CYTOKINE	RECEPTOR	CELL SOURCE	CELL TARGET	BIOLOGIC ACTIVITY
TECK	CCR9	Dendritic cells, thymus, liver, small intestine	T cells, monocytes-macrophages, dendritic cells	Thymic dendritic cell-derived cytokine, possibly involved in T-cell development
GRO- α /MGSA	CXCR2	Activated granulocytes, monocyte-macrophages, and epithelial cells	Neutrophils, epithelial cells, ?endothelial cells	Neutrophil chemoattractant and activator; mitogenic for some melanoma cell lines; suppresses proliferation of hematopoietic precursors; angiogenic activity
GRO- β /MIP-2 α	CXCR2	Activated granulocytes and monocyte-macrophages	Neutrophils and ?endothelial cells	Neutrophil chemoattractant and activator; angiogenic activity
NAP-2	CXCR2	Platelets	Neutrophils, basophils	Derived from platelet basic protein; neutrophil chemoattractant and activator
IP-10	CXCR3	Monocytes-macrophages, T cells, fibroblasts, endothelial cells, epithelial cells	Activated T cells, tumor-infiltrating lymphocytes, ?endothelial cells, ?NK cells	IFN- γ -inducible protein that is a chemoattractant for T cells; suppresses proliferation of hematopoietic precursors
MIG	CXCR3	Monocytes-macrophages, T cells, fibroblasts	Activated T cells, tumor-infiltrating lymphocytes	IFN- γ -inducible protein that is a chemoattractant for T cells; suppresses proliferation of hematopoietic precursors
SDF-1	CXCR4	Fibroblasts	T cells, dendritic cells, ?basophils, ?endothelial cells	Low-potency, high-efficacy T-cell chemoattractant; required for B lymphocyte development; prevents infection of CD4+, CXCR4+ cells by T-cell tropic HIV-1
Fractalkine	CX3CR1	Activated endothelial cells	NK cells, T cells, monocytes-macrophages	Cell-surface chemokine/mucin hybrid molecule that functions as a chemoattractant, leukocyte activator, and cell adhesion molecule
PF-4	Unknown	Platelets, megakaryocytes	Fibroblasts, endothelial cells	Chemoattractant for fibroblasts; suppresses proliferation of hematopoietic precursors; inhibits endothelial cell proliferation and angiogenesis

Abbreviations: B7-1, CD80; B7-2, CD86; Breg, regulatory B cells; CCR, CC-type chemokine receptor; CXCR, CXC-type chemokine receptor; DC, dendritic cell; DC-CK, dendritic cell chemoattractant; EBV, Epstein-Barr virus; ELC, EB11 ligand chemokine (MIP-1b); G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; GRP, growth-related peptide; HSV, herpes simplex virus; IFN, interferon; Ig, immunoglobulin; IL, interleukin; IP-10, IFN- γ -inducible protein-10; LARC, liver- and activation-regulated chemokine; LIF, leukemia inhibitory factor; MCP, monocyte chemotactic protein; M-CSF, macrophage colony-stimulating factor; MDC, macrophage-derived chemokine; MGSA, melanoma growth-stimulating activity; MHC, major histocompatibility complex; MIG, monokine induced by IFN- γ ; MIP, macrophage inflammatory protein; NAP, neutrophil-activating protein; NK, natural killer; OSM, oncostatin M; PAF, pulmonary- and activation-regulated chemokine; PBMC, peripheral blood mononuclear cells; PF, platelet factor; RANTES, regulated on activation, normally T cell-expressed and -secreted; SCF, stem cell factor; SDF, stromal cell-derived factor; SLC, secondary lymphoid tissue chemokine; TARC, thymus- and activation-regulated chemokine; TCA, T-cell activation protein; TECK, thymus-expressed chemokine; TGF, transforming growth factor; T_H1 and T_H2, helper T cell subsets; TNF, tumor necrosis factor; Treg, regulatory T cells; VCAM, vascular cell adhesion molecule.

Sources: Data from JS Sundy et al: Appendix B, in *Inflammation, Basic Principles and Clinical Correlates*, 3rd ed, J Gallin, R Snyderman (eds). Philadelphia, Lippincott Williams and Wilkins, 1999; J Ye et al: *Frontiers in Pharmacology* 11; HM Lazear et al: *Immunity* 43: 15, 2015; J Catalan-Dibene et al: *J Interferon and Cytokine Research* 38: 423, 2018.

effectors of innate immune responses (Fig. 349-2). Unchecked accumulation and activation of granulocytes can lead to host tissue damage, as seen in neutrophil- and eosinophil-mediated *systemic necrotizing vasculitis*. Granulocytes are derived from stem cells in bone marrow. Each type of granulocyte (neutrophil, eosinophil, or basophil) is derived from a different subclass of progenitor cell that is stimulated to proliferate by colony-stimulating factors (Table 349-6). During terminal maturation of granulocytes, class-specific nuclear morphology and cytoplasmic granules appear that allow for histologic identification of granulocyte type.

Neutrophils express Fc receptor IIIa for IgG (CD16a) as well as receptors for activated complement components (C3b or CD35). Upon interaction of neutrophils with antibody-coated (opsonized) bacteria or immune complexes, azurophilic granules (containing myeloperoxidase, lysozyme, elastase, and other enzymes) and specific granules (containing lactoferrin, lysozyme, collagenase, and other enzymes) are released, and microbicidal superoxide radicals (O_2^-) are generated at the neutrophil surface. The generation of superoxide leads to inflammation by direct injury to tissue and by alteration of macromolecules such as collagen and DNA.

Eosinophils are potent cytotoxic effector cells for various parasitic organisms. In *Nippostrongylus brasiliensis* helminth infection, eosinophils are important cytotoxic effector cells for removal of these parasites. Key to regulation of eosinophil cytotoxicity to *N. brasiliensis* worms are antigen-specific T helper cells that produce IL-4, thus providing an example of regulation of innate immune responses by adaptive immunity antigen-specific T cells. Intracytoplasmic contents of eosinophils, such as major basic protein, eosinophil cationic protein, and eosinophil-derived neurotoxin, are capable of directly damaging

tissues and may be responsible in part for the organ system dysfunction in the *hypereosinophilic syndromes* (Chap. 64). Because the eosinophil granule contains anti-inflammatory types of enzymes (histaminase, arylsulfatase, phospholipase D), eosinophils may homeostatically downregulate or terminate ongoing inflammatory responses.

Basophils and tissue mast cells are potent reservoirs of cytokines such as IL-4 and can respond to bacteria and viruses with antipathogen cytokine production through multiple TLRs expressed on their surface. Mast cells and basophils can also mediate immunity through the binding of antipathogen antibodies. This is a particularly important host defense mechanism against parasitic diseases. Basophils express high-affinity surface receptors for IgE (Fc ϵ RII) (CD23) and, upon cross-linking of basophil-bound IgE by antigen, can release histamine, eosinophil chemotactic factor of anaphylaxis, and neutral protease—all mediators of allergic immediate (anaphylaxis) hypersensitivity responses. In addition, basophils express surface receptors for activated complement components (C3a, C5a), through which mediator release can be directly affected. Thus, basophils, like most cells of the immune system, can be activated in the service of host defense against pathogens, or they can be activated for mediation release and cause pathogenic responses in allergic and inflammatory diseases. **For further discussion of tissue mast cells, see Chap. 354.**

The Complement System The complement system, an important soluble component of the innate immune system, is a series of plasma enzymes, regulatory proteins, and proteins that are activated in a cascading fashion, resulting in cell lysis. There are four pathways of the complement system: the classic activation pathway activated by antigen/antibody immune complexes, the MBL (a serum collectin) activation

TABLE 349-7 CC, CXC₁, CX₃, C₁, and XC Families of Chemokines and Chemokine Receptors

CHEMOKINE RECEPTOR	CHEMOKINE LIGANDS	CELL TYPES	DISEASE CONNECTION
CCR1	CCL3 (MIP-1 α), CCL5 (RANTES), CCL7 (MCP-3), CCL14 (HCC1)	T cells, monocytes, eosinophils, basophils	Rheumatoid arthritis, multiple sclerosis
CCR2	CCL2 (MCP-1), CCL8 (MCP-2), CCL7 (MCP-3), CCL13 (MCP-4), CCL16 (HCC4)	Monocytes, dendritic cells (immature), memory T cells	Atherosclerosis, rheumatoid arthritis, multiple sclerosis, resistance to intracellular pathogens, type 2 diabetes mellitus
CCR3	CCL11 (eotaxin), CCL13 (eotaxin-2), CCL7 (MCP-3), CCL5 (RANTES), CCL8 (MCP-2), CCL13 (MCP-4)	Eosinophils, basophils, mast cells, T _H 2, platelets	Allergic asthma and rhinitis
CCR4	CCL17 (TARC), CCL22 (MDC)	T cells (T _H 2), dendritic cells (mature), basophils, macrophages, platelets	Parasitic infection, graft rejection, T-cell homing to skin
CCR5	CCL3 (MIP-1 α), CCL4 (MIP-1 α), CCL5 (RANTES), CCL11 (eotaxin), CCL14 (HCC1), CCL16 (HCC4)	T cells, monocytes	HIV-1 co-receptor (T cell-tropic strains), transplant rejection
CCR6	CCL20 (MIP-3 α , LARC)	T cells (T regulatory and memory), B cells, dendritic cells	Mucosal humoral immunity, allergic asthma, intestinal T-cell homing
CCR7	CCL19 (ELC), CCL21 (SLC)	T cells, dendritic cells (mature)	Transport of T cells and dendritic cells to lymph nodes, antigen presentation, and cellular immunity
CCR8	CCL1 (1309)	T cells (T _H 2), monocytes, dendritic cells	Dendritic cell migration to lymph node, type 2 cellular immunity, granuloma formation
CCR9	CCL25 (TECK)	T cells, IgA+ plasma cells	Homing of T cells and IgA+ plasma cells to the intestine, inflammatory bowel disease
CCR10	CCL27 (CTACK), CCL28 (MEC)	T cells	T-cell homing to intestine and skin
CXCR1	CXCL8 (interleukin-8), CXCL6 (GCP2)	Neutrophils, monocytes	Inflammatory lung disease, COPD
CXCR2	CXCL8, CXCL1 (GRO α), CXCL2 (GRO α), CXCL3 (GRO α), CXCL5 (ENA-78), CXCL6	Neutrophils, monocytes, microvascular endothelial cells	Inflammatory lung disease, COPD, angiogenic for tumor growth
CXCR3-A	CXCL9 (MIG), CXCL10 (IP-10), CXCL11 (I-TAC)	Type 1 helper cells, mast cells, mesangial cells	Inflammatory skin disease, multiple sclerosis, transplant rejection
CXCR3-B	CXCL4 (PF4), CXCL9 (MIG), CXCL10 (IP-10), CXCL11 (I-TAC)	Microvascular endothelial cells, neoplastic cells	Angiostatic for tumor growth
CXCR4	CXCL12 (SDF-1)	Widely expressed	HIV-1 co-receptor (T cell-tropic), tumor metastases, hematopoiesis
CXCR5	CXCL13 (BCA-1)	B cells, follicular helper T cells	Formation of B-cell follicles
CXCR6	CXCL16 (SR-PSOX)	CD8+ T cells, natural killer cells, and memory CD4+ T cells	Inflammatory liver disease, atherosclerosis (CXCL16)
CX ₃ CR1	CX3CL1 (fractalkine)	Macrophages, endothelial cells, smooth-muscle cells	Atherosclerosis
XCR1	XCL1 (lymphotactin), XCL2	T cells, natural killer cells	Rheumatoid arthritis, IgA nephropathy, tumor response

Abbreviations: BCA-1, B-cell chemoattractant 1; COPD, chronic obstructive pulmonary disease; CTACK, cutaneous T cell-attracting chemokine; ELC, Epstein-Barr I1-ligand chemokine; ENA, epithelial cell-derived neutrophil-activating peptide; GCP, granulocyte chemotactic protein; GRO, growth-regulated oncogene; HCC, hemofiltrate chemokine; IP-10, interferon inducible 10; I-TAC, interferon-inducible T-cell alpha chemoattractant; LARC, liver- and activation-regulated chemokine; MCP, monocyte chemoattractant protein; MDC, macrophage-derived chemokine; MEC, mammary-enriched chemokine; MIG, monokine induced by interferon- γ ; MIP, macrophage inflammatory protein; PF, platelet factor; SDF, stromal cell-derived factor; SLC, secondary lymphoid-tissue chemokine; SR-PSOX, scavenger receptor for phosphatidylserine-containing oxidized lipids; TARC, thymus- and activation-regulated chemokine; TECK, thymus-expressed chemokine; T_H2, type 2 helper T cells.

Source: From IF Charo, RM Ransohoff: The many roles of chemokines and chemokine receptors in inflammation. N Engl J Med 354:610, 2006. Copyright © (2006) Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

pathway activated by microbes with terminal mannose groups, the alternative activation pathway activated by microbes or tumor cells, and the terminal pathway that is common to the first three pathways and leads to the membrane attack complex that lyses cells (Fig. 349-5). The series of enzymes of the complement system are serine proteases.

Activation of the classic complement pathway via immune complex binding to C1q links the innate and adaptive immune systems via specific antibody in the immune complex. The alternative complement activation pathway is antibody-independent and is activated by binding of C3 directly to pathogens and “altered self” such as tumor cells. In the renal glomerular inflammatory disease *IgA nephropathy*, IgA activates the alternative complement pathway and causes glomerular damage and decreased renal function. Activation of the classic complement pathway via C1, C4, and C2 and activation of the alternative pathway via factor D, C3, and factor B both lead to cleavage and activation of C3. C3 activation fragments, when bound to target surfaces such as bacteria and other foreign antigens, are critical for opsonization (coating by antibody and complement) in preparation for phagocytosis. The MBL pathway substitutes MBL-associated serine proteases (MASPs) 1

and 2 for C1q, C1r, and C1s to activate C4. The MBL activation pathway is activated by mannose on the surface of bacteria and viruses.

The three pathways of complement activation all converge on the final common terminal pathway. C3 cleavage by each pathway results in activation of C5, C6, C7, C8, and C9, resulting in the membrane attack complex that physically inserts into the membranes of target cells or bacteria and lyses them.

Thus, complement activation is a critical component of innate immunity for responding to microbial infection. The functional consequences of complement activation by the three initiating pathways and the terminal pathway are shown in Fig. 349-5. In general, the cleavage products of complement components facilitate microbe or damaged cell clearance (C1q, C4, C3), promote activation and enhancement of inflammation (anaphylatoxins, C3a, C5a), and promote microbe or opsonized cell lysis (membrane attack complex). Deficiencies of early complement components C1, C4, or C2 can be associated with autoimmune disorders or with encapsulated bacterial infections like *Streptococcus pneumoniae*. Deficiencies of late complement components (C5-C9) are associated with increased *Neisseria* infections.

Cytokines are soluble proteins produced by a wide variety of cell types (Tables 349-6 and 349-7). They are critical for both normal innate and adaptive immune responses, and their expression may be perturbed in most immune, inflammatory, and infectious disease states.

Cytokines are involved in the regulation of the growth, development, and activation of immune system cells and in the mediation of the inflammatory response. In general, cytokines are characterized by considerable redundancy; different cytokines have similar functions. In addition, many cytokines are pleiotropic in that they are capable of

acting on many different cell types. This pleiotropism results from the expression on multiple cell types of receptors for the same cytokine (see below), leading to the formation of “cytokine networks.” The action of cytokines may be (1) autocrine when the target cell is the same cell that secretes the cytokine, (2) paracrine when the target cell is nearby, and (3) endocrine when the cytokine is secreted into the circulation and acts distal to the source.

Cytokines have been named based on presumed targets or based on presumed functions. Those cytokines that are thought to primarily target leukocytes have been named IL-1, -2, -3, etc. Many cytokines that

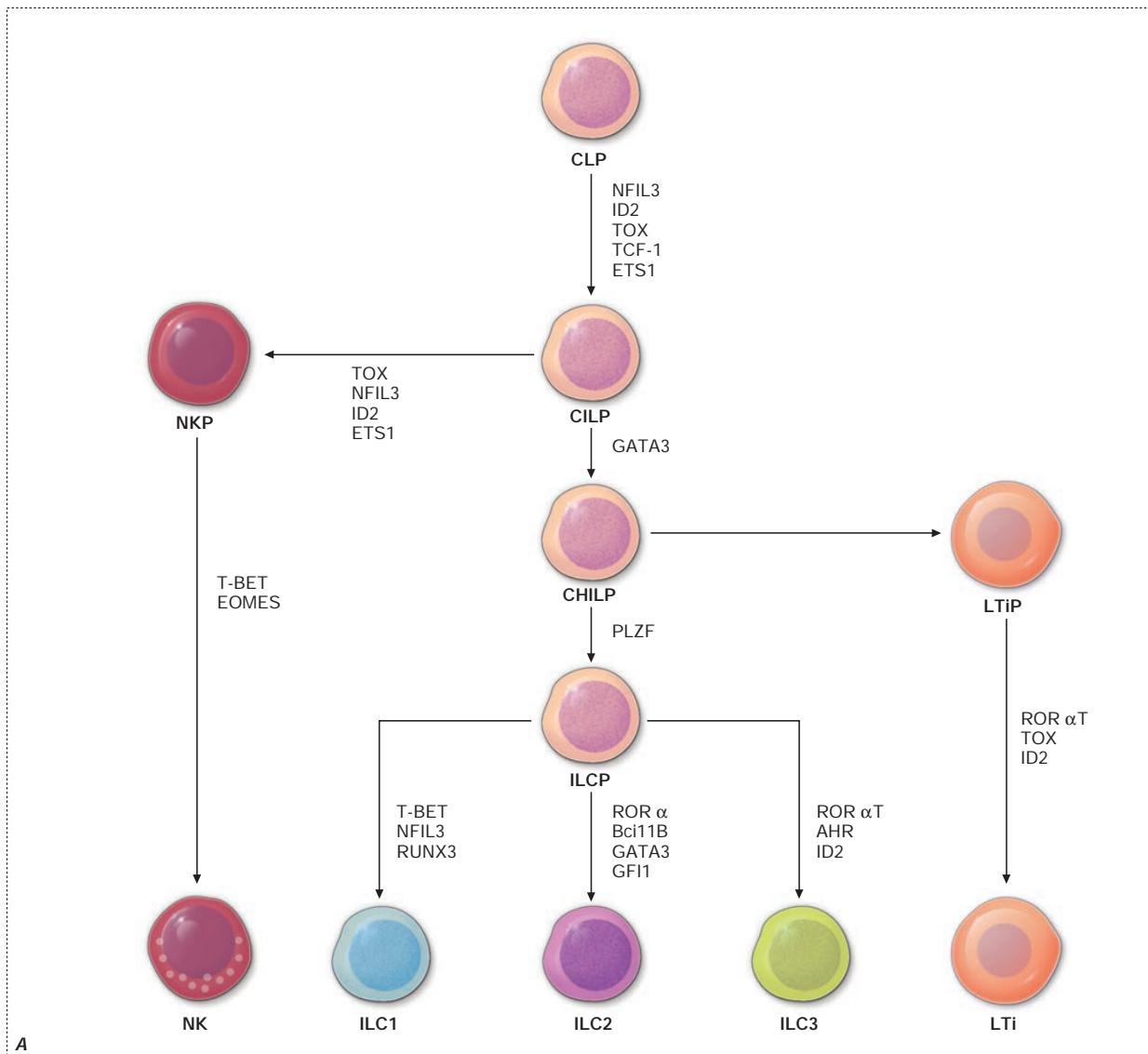


FIGURE 349-3 Development and function of innate lymphoid cells (ILCs). **A.** ILC development, mainly based on mouse ILC differentiation paths, is schematized. ILCs develop from common innate lymphoid progenitors (CILPs), which themselves differentiate from common lymphoid progenitors (CLPs). CILPs can differentiate into natural killer (NK) cell precursor (NKP) cells or into common helper innate lymphoid progenitors (CHILPs), which themselves give rise to lymphoid tissue inducer progenitors (LTiPs) and innate lymphoid cell precursors (ILCPs). LTiPs differentiate into lymphoid tissue inducers (LTis) and ILCPs into ILC1, ILC2, or ILC3. Each stage of differentiation is dependent on the expression of the indicated transcription factors: NFIL3 (nuclear factor IL-3 induced), Id2 (inhibitor of DNA binding 2), TOX (thymocyte selection-associated high mobility group box protein), TCF-1 (T-cell factor 1), ETS1 (avian erythroblastosis virus E26 homolog-1), GATA3 (GATA binding protein 3), PLZF (promyelocytic leukemia zinc finger), T-bet (T-box transcription factor), Eomes (eomesodermin), RUNX3 (runt-related transcription factor 3), ROR α (RAR-related orphan receptor α), Bcl11b (B cell lymphoma/leukemia 11B), Gfi1 (growth factor independent 1), ROR γ t (RAR-related orphan receptor γ t), and AHR (Aryl hydrocarbon receptor). It has been shown in humans that ILC1 subsets may originate from precursors other than ILCPs, but the identity of these precursors remains unknown at this time. **B.** Some of the most well-known immune functions of each ILC subset are shown. NK cells and ILC1s react to intracellular pathogens, such as viruses, and to tumors; ILC2s respond to large extracellular parasites and allergens; ILC3s combat extracellular microbes, such as bacteria and fungi; and Lutes are involved in the formation of secondary lymphoid structures. For each ILC subset, effector molecules that can be produced upon activation are indicated: AREG, amphiregulin; RANK, receptor activation of nuclear factor κ B; RANK-L, RANK-ligand. (Reproduced with permission from E Vivier et al: Innate lymphoid cells: 10 years on. *Cell* 174:1054, 2018.)

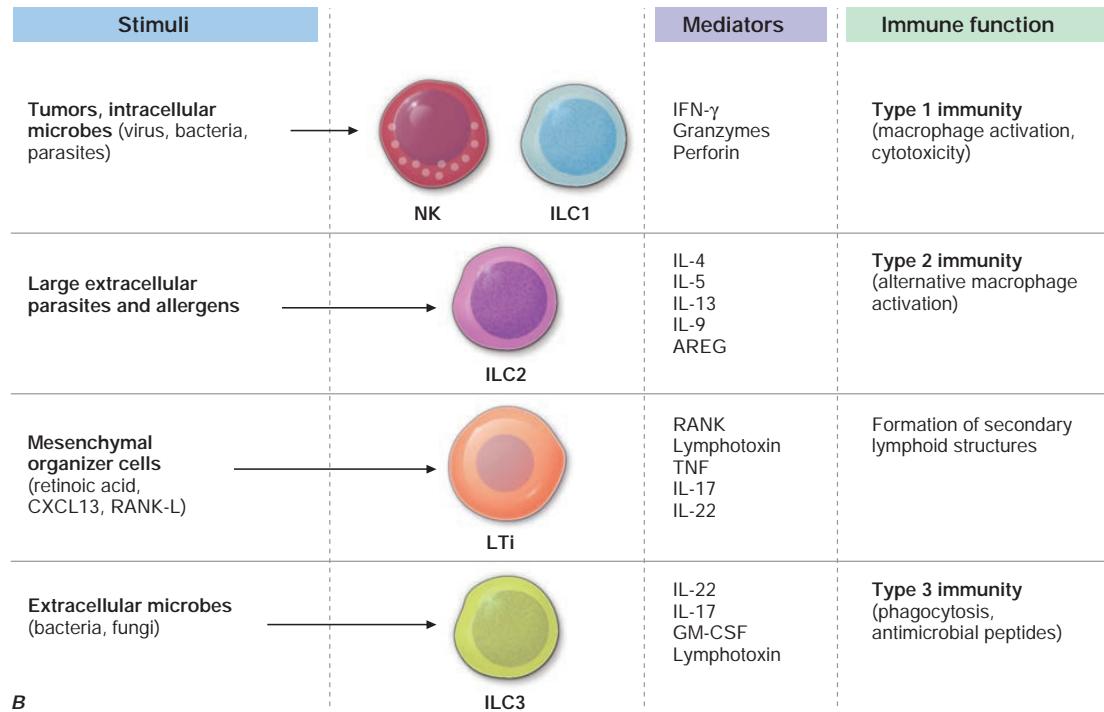


FIGURE 349-3 (Continued)

were originally described as having a certain function have retained those names (e.g., granulocyte colony-stimulating factor [G-CSF]). Cytokines belong in general to three major structural families: the hematopoietin family; the TNF, IL-1, platelet-derived growth factor (PDGF), and transforming growth factor (TGF) β families; and

the CXC and C-C chemokine families. Chemokines are cytokines that regulate cell movement and trafficking; they act through G protein-coupled receptors and have a distinctive three-dimensional structure. IL-8 is the only chemokine that early on was named an IL (Table 349-6).

TABLE 349-8 Association of KIRs with Disease

DISEASE	KIR ASSOCIATION	OBSERVATION
Psoriatic arthritis	KIR2DS1/KIR2DS2; HLA-Cw group homozygosity	Susceptibility
Spondylarthritides	Increased KIR3DL2 expression Interaction of HLA-B27 homodimers with KIR3DL1/KIR3DL2; independent of peptide	May contribute to disease pathology May contribute to disease pathogenesis
Ankylosing spondylitis	KIR3DL1/3DS1; HLA-B27 genotypes	Susceptibility
Rheumatoid vasculitis	KIR2DS2; HLA-Cw*03 Increased KIR2L1/2DS2 in patients with extraarticular manifestations	Susceptibility Clinical manifestations may have different genetic backgrounds with respect to KIR genotype
Rheumatoid arthritis	Decreased KIR2DS1/3DS1 in patients without bone erosions KIR2DS4; HLA-Cw4	Susceptibility Susceptibility
Scleroderma	KIR2DS2+/KIR2DL2-	Susceptibility
Behçet's disease	Altered KIR3DL1 expression	Associated with severe eye disease
Psoriasis vulgaris	2DS1; HLA-Cw*06 2DS1; 2DL5; haplotype B	Susceptibility Susceptibility
IDDM	KIR2DS2; HLA-C1	Susceptibility
Type 1 diabetes	KIR2DS2; HLA-C1 and no HLA-C2, no HLA-Bw4	Increased disease progression
Preeclampsia	KIR2DL1 with fewer KIR2DS (mother); HLA-C2 (fetus)	Increased disease progression
AIDS	KIR3DS1; HLA-Bw4Ile80 KIR3DS1 homozygous; no HLA-Bw4Ile80	Decreased disease progression Increased disease progression
HCV infection	KIR2DL3 homozygous; HLA-C1 homozygous	Decreased disease progression
Cervical neoplasia (HPV induced)	KIR3DS1; HLA-C1 homozygous and no HLA-Bw4	Increased disease progression
Malignant melanoma	KIR2DL2 and/or KIR2DL3; HLA-C1	Increased disease progression

Abbreviations: HCV, hepatitis C virus; HLA, human leukocyte antigen; HPV, human papillomavirus; IDDM, insulin-dependent diabetes mellitus; KIR, killer cell immunoglobulin-like receptor.

Source: Reproduced with permission from R Diaz-Pena et al: KIR genes and their role in spondyloarthropathies. *Adv Exp Med Biol* 649:286, 2009.

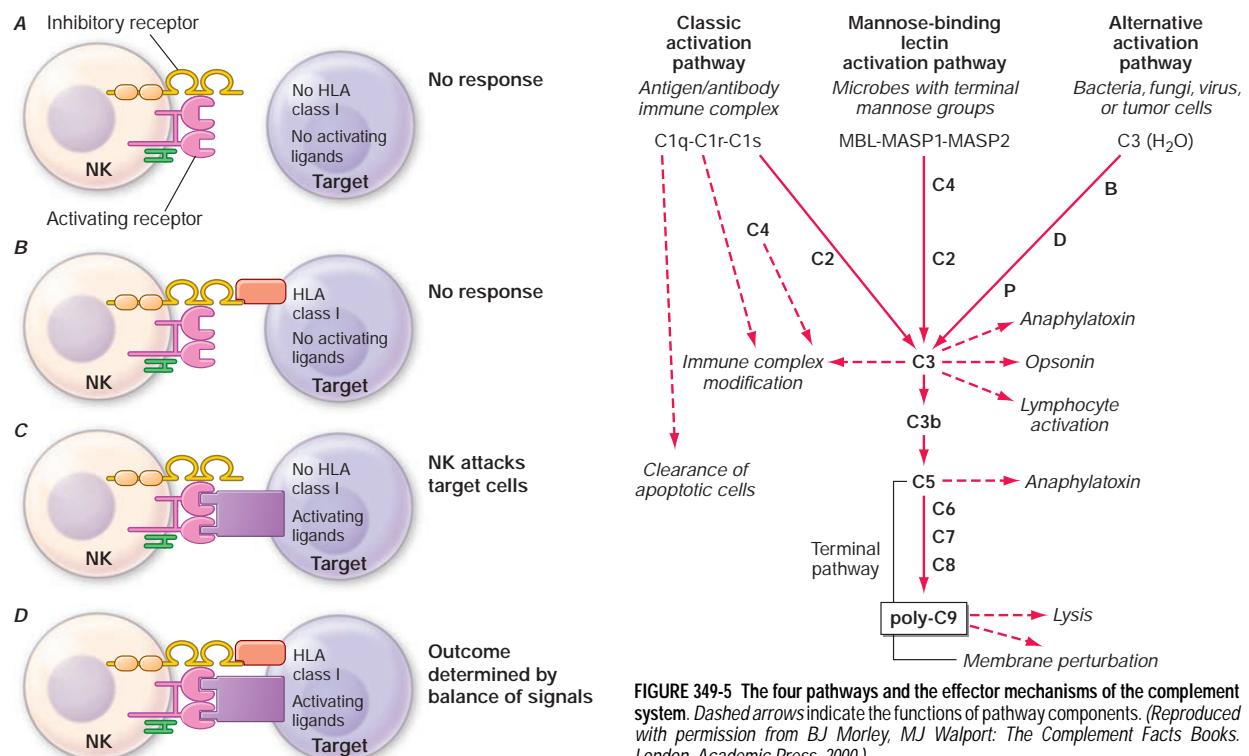


FIGURE 349-4 Encounters between natural killer (NK) cells: Potential targets and possible outcomes. The amount of activating and inhibitory receptors on the NK cells and the amount of ligands on the target cell, as well as the qualitative differences in the signals transduced, determine the extent of the NK response. **A**, When target cells have no HLA class I or activating ligands, NK cells cannot kill target cells. **B**, When target cells bear self-HLA, NK cells cannot kill targets. **C**, When target cells are pathogen-infected and have downregulated HLA and express activating ligands, NK cells kill target cells. **D**, When NK cells encounter targets with both self-HLA and activating receptors, then the level of target killing is determined by the balance of inhibitory and activating signals to the NK cell. HLA, human leukocyte antigen. (Republished with permission of Annual Review of Immunology, from NK Cell Recognition, L Lanier 23:225,2005; permission conveyed through Copyright Clearance Center, Inc.)

In general, cytokines exert their effects by influencing gene activation that results in cellular activation, growth, differentiation, functional cell-surface molecule expression, and cellular effector function. In this regard, cytokines can have dramatic effects on the regulation of immune responses and the pathogenesis of a variety of diseases. Indeed, T cells have been categorized on the basis of the pattern of cytokines that they secrete, which results in either humoral immune response ($T_{H}2$) or cell-mediated immune response ($T_{H}1$). A third type of T helper cell is the $T_{H}17$ cell that contributes to host defense against extracellular bacteria and fungi, particularly at mucosal sites (Fig. 349-2).

Cytokine receptors can be grouped into five general families based on similarities in their extracellular amino acid sequences and conserved structural domains. The **immunoglobulin (Ig) superfamily** represents a large number of cell-surface and secreted proteins. The IL-1 receptors (type 1, type 2) are examples of cytokine receptors with extracellular Ig domains.

The hallmark of the **hematopoietic growth factor (type 1) receptor** family is that the extracellular regions of each receptor contain two conserved motifs. One motif, located at the N terminus, is rich in cysteine residues. The other motif is located at the C terminus proximal to the transmembrane region and comprises five amino acid residues, tryptophan-serine-X-tryptophan-serine (WSXWS). This family can be grouped on the basis of the number of receptor subunits they have and on the utilization of shared subunits. A number of cytokine receptors, i.e., IL-6, IL-11, IL-12, and leukemia inhibitory factor, are paired with

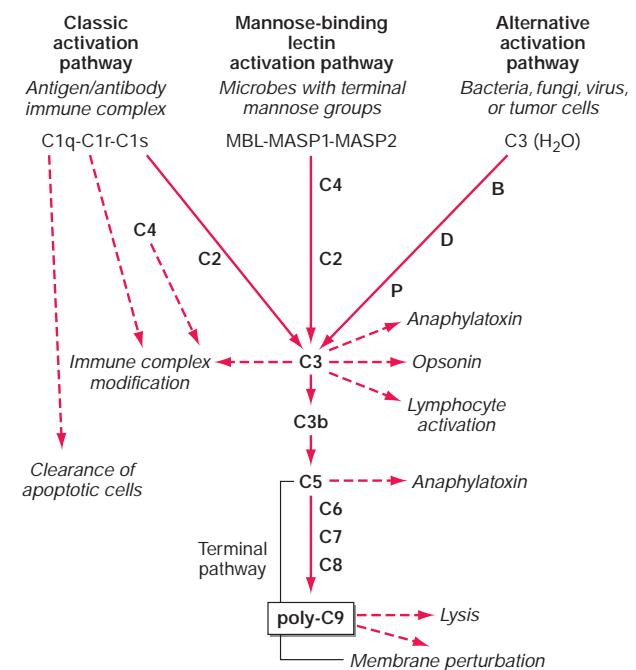


FIGURE 349-5 The four pathways and the effector mechanisms of the complement system. Dashed arrows indicate the functions of pathway components. (Reproduced with permission from BJ Morley, MJ Walport: *The Complement Facts Books*. London, Academic Press, 2000.)

gp130. There is also a common 150-kDa subunit shared by IL-3, IL-5, and granulocyte-macrophage colony-stimulating factor (GM-CSF) receptors. The gamma chain (γ_c) of the IL-2 receptor is common to the IL-2, IL-4, IL-7, IL-9, and IL-15 receptors. Thus, the specific cytokine receptor is responsible for ligand-specific binding, whereas the subunits such as gp130, the 150-kDa subunit, and γ_c are important in signal transduction. The γ_c gene is on the X chromosome, and mutations in the γ_c protein result in the **X-linked form of severe combined immune deficiency syndrome (X-SCID)** (Chap. 351).

The members of the **interferon (type II) receptor** family include the receptors for IFN- γ and - β , which share a similar 210-amino-acid binding domain with conserved cysteine pairs at both the amino and carboxy termini. The members of the **TNF (type III) receptor family** share a common binding domain composed of repeated cysteine-rich regions. Members of this family include the p55 and p75 receptors for TNF (TNF-R1 and TNF-R2, respectively); CD40 antigen, which is an important B-cell surface marker involved in immunoglobulin isotype switching; fas/Apo-1, whose triggering induces apoptosis; CD27 and CD30, which are found on activated T cells and B cells; and nerve growth factor receptor.

The common motif for the **seven transmembrane helix family** was originally found in receptors linked to GTP-binding proteins. This family includes receptors for chemokines (Table 349-7), β -adrenergic receptors, and retinal rhodopsin. It is important to note that two members of the chemokine receptor family, CXC chemokine receptor type 4 (CXCR4) and β chemokine receptor type 5 (CCR5), have been found to serve as the two major co-receptors for binding and entry of HIV-1 into CD4-expressing host cells (Chap. 202).

Significant advances have been made in defining the signaling pathways through which cytokines exert their intracellular effects. The Janus family of protein tyrosine kinases (JAK) is a critical element involved in signaling via the hematopoietin receptors. Four JAK kinases, JAK1, JAK2, JAK3, and Tyk2, preferentially bind different cytokine receptor subunits. Cytokine binding to its receptor brings the cytokine receptor subunits into apposition and allows a pair of JAKs to transphosphorylate and activate one another. The JAKs then phosphorylate the receptor on the tyrosine residues and allow

signaling molecules to bind to the receptor, whereby the signaling molecules become phosphorylated. Signaling molecules bind the receptor because they have domains (SH2, or src homology 2 domains) that can bind phosphorylated tyrosine residues. There are a number of these important signaling molecules that bind the receptor, such as the adapter molecule SHC, which can couple the receptor to the activation of the mitogen-activated protein kinase pathway. In addition, an important class of substrate of the JAKs is the signal transducers and activators of transcription (STAT) family of transcription factors. STATs have SH2 domains that enable them to bind to phosphorylated receptors, where they are then phosphorylated by the JAKs. It appears that different STATs have specificity for different receptor subunits. The STATs then dissociate from the receptor and translocate to the nucleus, bind to DNA motifs that they recognize, and regulate gene expression. The STATs preferentially bind DNA motifs that are slightly different from one another and thereby control transcription of specific genes. The importance of this pathway is particularly relevant to lymphoid development. Mutations of JAK3 itself also result in a disorder identical to X-SCID; however, because JAK3 is found on chromosome 19 and not on the X chromosome, JAK3 deficiency occurs in boys and girls (**Chap. 351**).

THE ADAPTIVE IMMUNE SYSTEM

Adaptive immunity is characterized by antigen-specific responses to a foreign antigen or pathogen. A key feature of adaptive immunity is that following the initial contact with antigen (*immunologic priming*), subsequent antigen exposure leads to more rapid and vigorous immune responses (*immunologic memory*). The adaptive immune system consists of dual limbs of cellular and humoral immunity. The principal effectors of cellular immunity are T lymphocytes, whereas the principal effectors of humoral immunity are B lymphocytes. Both B and T lymphocytes derive from a common stem cell (**Fig. 349-6**).

The proportion and distribution of immunocompetent cells in various tissues reflect cell traffic, homing patterns, and functional capabilities. Bone marrow is the major site of maturation of B cells, monocytes-macrophages, DCs, and granulocytes and contains pluripotent stem cells that, under the influence of various colony-stimulating factors, can give rise to all hematopoietic cell types. T-cell precursors also arise from hematopoietic stem cells and home to the thymus for maturation. Mature T lymphocytes, B lymphocytes, monocytes, and DCs enter the circulation and home to peripheral lymphoid organs (lymph nodes, spleen) and mucosal surface-associated lymphoid tissue (gut, genitourinary, and respiratory tracts) as well as the skin and mucous membranes and await activation by foreign antigen.

T Cells The pool of effector T cells is established in the thymus early in life and is maintained throughout life both by new T-cell production in the thymus and by antigen-driven expansion of virgin peripheral T cells into “memory”

T cells that reside in peripheral lymphoid organs. The thymus exports ~2% of the total number of thymocytes per day throughout life, with the total number of daily thymic emigrants decreasing by ~3% per year during the first four decades of life.

Mature T lymphocytes constitute 70–80% of normal peripheral blood lymphocytes (only 2% of the total-body lymphocytes are contained in peripheral blood), 90% of thoracic duct lymphocytes, 30–40% of lymph node cells, and 20–30% of spleen lymphoid cells. In lymph nodes, T cells occupy deep paracortical areas around B-cell germinal centers, and in the spleen, they are located in periarteriolar areas of white pulp (**Chap. 66**). T cells are the primary effectors of cell-mediated immunity, with subsets of T cells maturing into CD8+ cytotoxic T cells capable of lysis of virus-infected or foreign cells (short-lived effector T cells) and CD4+ T cells capable of T-cell help for CD8+ T-cell and B-cell development. Two populations of long-lived memory T cells are triggered by infections: effector memory and central memory T cells. Effector memory T cells reside in nonlymphoid organs and respond rapidly to repeated pathogenic infections with cytokine production and cytotoxic functions to kill virus-infected

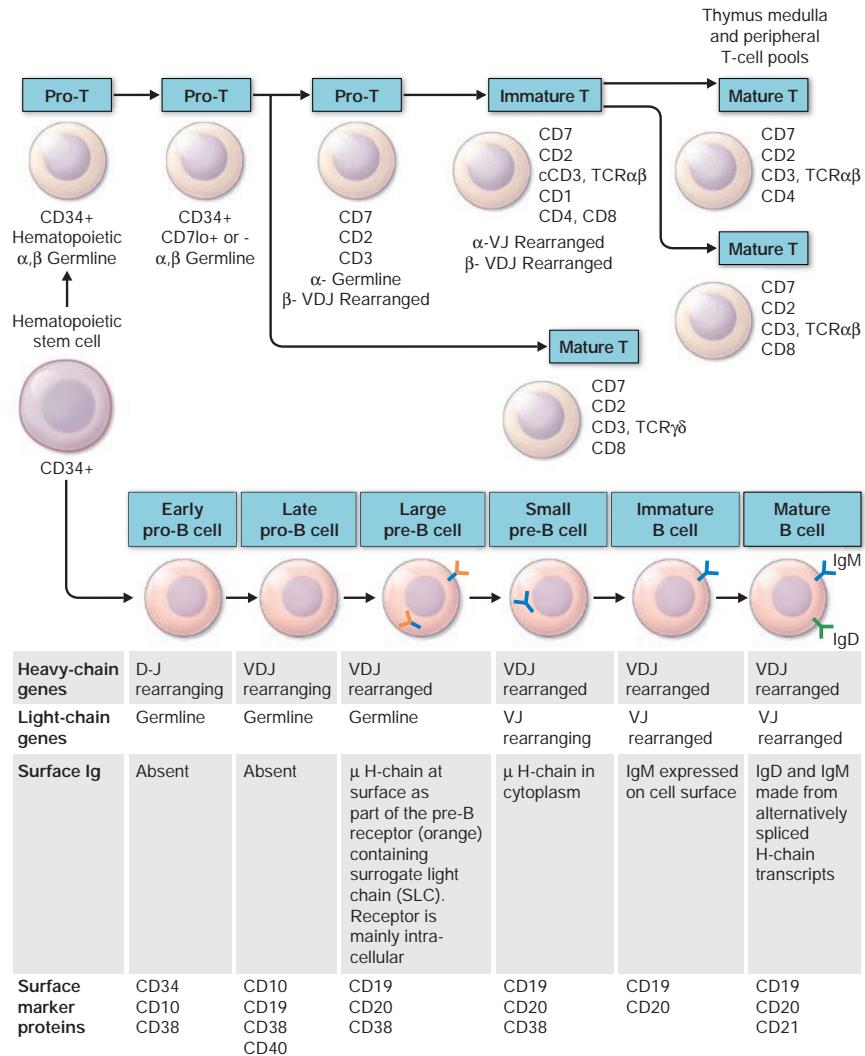


FIGURE 349-6 Development stages of T and B cells. Elements of the developing T- and B-cell receptor for antigen are shown schematically. The classification into the various stages of B-cell development is primarily defined by rearrangement of the immunoglobulin (Ig) heavy (H) and light (L) chain genes and by the absence or presence of specific surface markers. The classification of stages of T-cell development is primarily defined by cell-surface marker protein expression (sCD3, surface CD3 expression; cCD3, cytoplasmic CD3 expression; TCR, T-cell receptor). For B-cell development, the pre-B-cell receptor is shown as a blue-orange B-cell receptor. (From Janeway's Immunobiology, 9th ed by Kenneth Murphy and Casey Weaver. Copyright © 2017 by Garland Science, Taylor & Francis Group, LLC. Used by permission of W. W. Norton & Company, Inc.)

cells. Central memory T cells home to lymphoid organs where they replenish long- and short-lived and effector memory T cells as needed.

In general, CD4+ T cells are the primary regulatory cells of T and B lymphocyte and monocyte function by the production of cytokines and by direct cell contact (Fig. 349-2). In addition, T cells regulate erythroid cell maturation in bone marrow and, through cell contact (CD40 ligand), have an important role in activation of B cells and induction of Ig isotype switching. Considerable evidence now exists that colonization of the gut by commensal bacteria (the gut microbiome) is responsible for expansion of the peripheral CD4+ T-cell compartment in normal children and adults.

Human T cells express cell-surface proteins that mark stages of intra-thymic T-cell maturation or identify specific functional subpopulations of mature T cells. Many of these molecules mediate or participate in important T-cell functions (Table 349-1, Fig. 349-6, **Chap. 350**).

The earliest identifiable T-cell precursors in bone marrow are CD34+ pro-T cells (i.e., cells in which TCR genes are neither rearranged nor expressed). In the thymus, CD34+ T-cell precursors begin cytoplasmic (c) synthesis of components of the CD3 complex of TCR-associated molecules (Fig. 349-6). Within T-cell precursors, TCR for antigen gene rearrangement yields two T-cell lineages, expressing either TCR- $\alpha\beta$ chains or TCR- $\gamma\delta$ chains. T cells expressing the TCR- $\alpha\beta$ chains constitute the majority of peripheral T cells in blood, lymph node, and spleen and terminally differentiate into either CD4+ or CD8+ cells. Cells expressing TCR- $\gamma\delta$ chains circulate as a minor population in blood; their functions, although not fully understood, have been postulated to be those of immune surveillance at epithelial surfaces and cellular defenses against mycobacterial organisms and other intracellular bacteria through recognition of bacterial lipids.

In the thymus, the recognition of self-peptides on thymic epithelial cells, thymic macrophages, and DCs plays an important role in shaping

T-cell repertoire. As immature cortical thymocytes begin to express surface TCR for antigen, thymocytes with TCRs capable of interacting with self-peptides in the context of self-MHC antigens with low affinity are activated and survive (positive selection). Thymocytes with TCRs that are incapable of binding to self-MHC antigens or bind with high affinity die of attrition (no selection) or by apoptosis (negative selection). Thymocytes that are positively selected undergo maturation into CD4 or CD8 single positive T cells, and then migrate to the thymus medulla where they interact with self-peptide-self-MHC molecules, where they can again undergo selection. The purpose of negative and positive thymocyte selection is to eliminate potential pathogenic auto-reactive T cells, and at the same time, select a repertoire of mature T cells capable of recognizing foreign antigens.

Mature TCR $\alpha\beta$ thymocytes that are positively selected are functional MHC class II-restricted CD4+ T cells (Fig. 349-2), or they are CD8+ T cells destined to become CD8+ MHC class I-restricted cytotoxic T cells. *MHC class I or class II restriction* means that T cells recognize antigen peptide fragments only when they are presented in the antigen-recognition site of a class I or class II MHC molecule, respectively. After thymocyte maturation and selection, CD4 and CD8 thymocytes leave the thymus and migrate to the peripheral immune system. The thymus can continue to be a contributor to the peripheral immune system well into adult life, both normally and when the peripheral T-cell pool is damaged, such as occurs in AIDS and cancer chemotherapy.

MOLECULAR BASIS OF T-CELL RECOGNITION OF ANTIGEN The TCR for antigen is a complex of molecules consisting of an antigen-binding heterodimer of either $\alpha\beta$ or $\gamma\delta$ chains noncovalently linked with five CD3 subunits (γ , δ , ϵ , ζ , and η) (Fig. 349-7). The CD3 ζ chains are either disulfide-linked homodimers (CD3- $\zeta\zeta$) or disulfide-linked heterodimers composed of one ζ chain and one η chain. TCR- $\alpha\beta$ or TCR- $\gamma\delta$ molecules must be associated with CD3 molecules to be

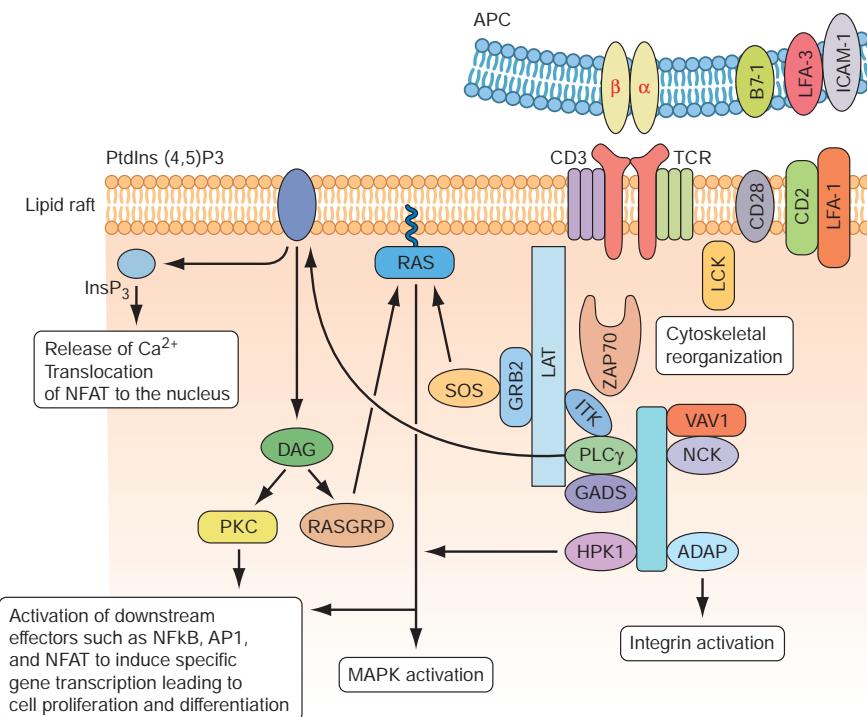


FIGURE 349-7 Signaling through the T-cell receptor. Activation signals are mediated via immunoreceptor tyrosine-based activation (ITAM) sequences in LAT and CD3 chains (blue bars) that bind to enzymes and transduce activation signals to the nucleus via the indicated intracellular activation pathways. Ligation of the T-cell receptor (TCR) by MHC complexed with antigen results in sequential activation of LCK and γ -chain-associated protein kinase of 70 kDa (ZAP70). ZAP70 phosphorylates several downstream targets, including LAT (linker for activation of T cells) and SLP76 (SCR homology 2 [SH2] domain-containing leukocyte protein of 76 kDa). SLP76 is recruited to membrane-bound LAT through its constitutive interaction with GADS (GRB2-related adaptor protein). Together, SLP76 and LAT nucleate a multimolecular signaling complex, which induces a host of downstream responses, including calcium flux, mitogen-activated protein kinase (MAPK) activation, integrin activation, and cytoskeletal reorganization. APC, antigen-presenting cell; NFAT, nuclear factor of activated T cells. (Reproduced with permission from GA Koretzky, F Abtahian, MA Silverman. SLP76 and SLP65: complex regulation of signalling in lymphocytes and beyond. *Nat Rev Immunol* 6:67, 2006.)

inserted into the T-cell surface membrane, TCR- α being paired with TCR- β and TCR- γ being paired with TCR- δ . Molecules of the CD3 complex mediate transduction of T-cell activation signals via TCRs, whereas TCR- α and - β or - γ and - δ molecules combine to form the TCR antigen-binding site.

The α , β , γ , and δ TCR for antigen molecules have amino acid sequence homology and structural similarities to immunoglobulin heavy and light chains and are members of the *immunoglobulin gene superfamily* of molecules. The genes encoding TCR molecules are encoded as clusters of gene segments that rearrange during T-cell maturation. This creates an efficient and compact mechanism for housing the diversity requirements of antigen receptor molecules. The TCR- α chain is on chromosome 14 and consists of a series of V (variable), J (joining), and C (constant) regions. The TCR- β chain is on chromosome 7 and consists of multiple V, D (diversity), J, and C TCR- β loci. The TCR- γ chain is on chromosome 7, and the TCR- δ chain is in the middle of the TCR- α locus on chromosome 14. Thus, molecules of the TCR for antigen have constant (framework) and variable regions, and the gene segments encoding the α , β , γ , and δ chains of these molecules are recombined and selected in the thymus, culminating in synthesis of the completed molecule. In both T- and B-cell precursors (see below), DNA rearrangements of antigen receptor genes involve the same enzymes, recombinase activating gene RAG1 and RAG2, both DNA-dependent protein kinases.

TCR diversity is created by the different V, D, and J segments that are possible for each receptor chain by the many permutations of V, D, and J segment combinations, by “N-region diversification” due to the addition of nucleotides at the junction of rearranged gene segments, and by the pairing of individual chains to form a TCR dimer. As T cells mature in the thymus, the repertoire of antigen-reactive T cells is modified by selection processes that eliminate many autoreactive T cells, enhance the proliferation of cells that function appropriately with self-MHC molecules and antigen, and allow T cells with nonproductive TCR rearrangements to die.

TCR- $\alpha\beta$ cells do not recognize native protein or carbohydrate antigens. Instead, T cells recognize only short (~9–13 amino acids) peptide fragments derived from protein antigens taken up or produced in APCs. Foreign antigens may be taken up by endocytosis into acidified intracellular vesicles or by phagocytosis and degraded into small peptides that associate with MHC class II molecules (exogenous antigen-presentation pathway). Other foreign antigens arise endogenously in the cytosol (such as from replicating viruses) and are broken down into small peptides that associate with MHC class I molecules (endogenous antigen-presenting pathway). Thus, APCs proteolytically degrade foreign proteins and display peptide fragments embedded in the MHC class I or II antigen-recognition site on the MHC molecule surface, where foreign peptide fragments are available to bind to TCR- $\alpha\beta$ or TCR- $\gamma\delta$ chains of reactive T cells. CD4 molecules act as adhesives and, by direct binding to MHC class II (DR, DQ, or DP) molecules, stabilize the interaction of TCR with peptide antigen (Fig. 349-7). Similarly, CD8 molecules also act as adhesives to stabilize the TCR-antigen interaction by direct CD8 molecule binding to MHC class I (A, B, or C) molecules.

Antigens that arise in the cytosol and are processed via the endogenous antigen-presentation pathway are cleaved into small peptides by a complex of proteases called the *proteasome*. From the proteasome, antigen peptide fragments are transported from the cytosol into the lumen of the endoplasmic reticulum by a heterodimeric complex termed *transporters associated with antigen processing* or TAP proteins. There, MHC class I molecules in the endoplasmic reticulum membrane physically associate with processed cytosolic peptides. Following peptide association with class I molecules, peptide-class I complexes are exported to the Golgi apparatus, and then to the cell surface, for recognition by CD8+ T cells.

Antigens taken up from the extracellular space via endocytosis into intracellular acidified vesicles are degraded by vesicle proteases into peptide fragments. Intracellular vesicles containing MHC class II molecules fuse with peptide-containing vesicles, thus allowing peptide fragments to physically bind to MHC class II molecules. Peptide-MHC class II complexes are then transported to the cell surface for recognition by CD4+ T cells.

Whereas it is generally agreed that the TCR- $\alpha\beta$ receptor recognizes peptide antigens in the context of MHC class I or class II molecules, lipids in the cell wall of intracellular bacteria such as *M. tuberculosis* can also be presented to a wide variety of T cells, including subsets of TCR- $\gamma\delta$ T cells, and a subset of CD8+ TCR- $\alpha\beta$ T cells. Importantly, bacterial lipid antigens are not presented in the context of MHC class I or II molecules, but rather are presented in the context of MHC-related CD1 molecules. Some $\gamma\delta$ T cells that recognize lipid antigens via CD1 molecules have very restricted TCR usage, do not need antigen priming to respond to bacterial lipids, and may be a form of innate rather than acquired immunity to intracellular bacteria.

Just as foreign antigens are degraded and their peptide fragments presented in the context of MHC class I or class II molecules on APCs, endogenous self-proteins also are degraded, and self-peptide fragments are presented to T cells in the context of MHC class I or class II molecules on APCs. In peripheral lymphoid organs, there are T cells that are capable of recognizing self-protein fragments but normally are *anergic* or *tolerant*, i.e., nonresponsive to self-antigenic stimulation, due to lack of self-antigen upregulating APC *co-stimulatory molecules* such as B7-1 (CD80) and B7-2 (CD86) (see below and Chap. 350).

Once engagement of mature T-cell TCR by foreign peptide occurs in the context of self-MHC class I or class II molecules, binding of non-antigen-specific adhesion ligand pairs such as CD54-CD11/CD18 and CD58-CD2 stabilizes MHC peptide-TCR binding, and the expression of these adhesion molecules is upregulated (Fig. 349-6). Once antigen ligation of the TCR occurs, the T-cell membrane is partitioned into *lipid membrane microdomains*, or *lipid rafts*, that coalesce the key signaling molecules TCR/CD3 complex, CD28, CD2, LAT (linker for activation of T cells), intracellular activated (dephosphorylated) src family protein tyrosine kinases (PTKs), and the key CD3 ζ -associated protein-70 (ZAP-70) PTK (Fig. 349-7). Importantly, during T-cell activation, the CD45 molecule, with protein tyrosine phosphatase activity, is partitioned away from the TCR complex to allow activating phosphorylation events to occur. The coalescence of signaling molecules of activated T lymphocytes in *microdomains* has suggested that T cell-APC interactions can be considered *immunologic synapses*, analogous in function to neuronal synapses.

After TCR-MHC binding is stabilized, activation signals are transmitted through the cell to the nucleus and lead to the expression of gene products important in mediating the wide diversity of T-cell functions such as the secretion of IL-2. The TCR does not have intrinsic signaling activity but is linked to a variety of signaling pathways via ITAMs expressed on the various CD3 chains that bind to proteins that mediate signal transduction. Each of the pathways results in the activation of particular transcription factors that control the expression of cytokine and cytokine receptor genes. Thus, antigen-MHC binding to the TCR induces the activation of the src family of PTKs, Fyn and Lck (Lck is associated with CD4 or CD8 co-stimulatory molecules); phosphorylation of CD3 ζ chain; activation of the related tyrosine kinases ZAP-70 and Syk; and downstream activation of the calcium-dependent calcineurin pathway, the ras pathway, and the protein kinase C pathway. Each of these pathways leads to activation of specific families of transcription factors (including *NF-AT*, *fos* and *jun*, and *rel/NF-B*) that form heteromultimers capable of inducing expression of IL-2, IL-2 receptor, IL-4, TNF- α , and other T-cell mediators.

In addition to the signals delivered to the T cell from the TCR complex and CD4 and CD8, molecules on the T cell, such as CD28 and inducible co-stimulator (ICOS), and molecules on DCs, such as B7-1 (CD80) and B7-2 (CD86), also deliver important co-stimulatory signals that upregulate T-cell cytokine production and are essential for T-cell activation. If signaling through CD28 or ICOS does not occur, or if CD28 is blocked, the T cell becomes anergic rather than activated (see “Immune Tolerance and Autoimmunity” below and Chap. 350). CTLA-4 (CD152) is similar to CD28 in its ability to bind CD80 and CD86. Unlike CD28, CTLA-4 transmits an inhibitory signal to T cells, acting as an off switch.

T-CELL EXHAUSTION IN VIRAL INFECTIONS AND CANCER In chronic viral infections such as HIV-1, hepatitis C virus, and hepatitis B virus and in chronic malignancies, the persistence of antigen disrupts memory

T-cell function, resulting in defects in memory T-cell responses. This has been defined as *T-cell exhaustion* and is associated with T-cell programmed cell death protein 1 (PD-1) (CD279) expression. Exhausted T cells have compromised proliferation and lose the ability to produce effector molecules, like IL-2, TNF- α , and IFN- γ . PD-1 downregulates T-cell responses and is associated with T-cell exhaustion and disease progression. For this reason, inhibition of T-cell PD-1 activity to enhance effector T-cell function is being explored as a target for immunotherapy in both viral infections and certain malignancies (Chap. 350).

T-CELL SUPERANTIGENS Conventional antigens bind to MHC class I or II molecules in the groove of the $\alpha\beta$ heterodimer and bind to T cells via the V regions of the TCR- α and - β chains. In contrast, superantigens bind directly to the lateral portion of the TCR- β chain and MHC class II β chain and stimulate T cells based solely on the V β gene segment used independent of the D, J, and V α sequences present. *Superantigens* are protein molecules capable of activating up to 20% of the peripheral T-cell pool, whereas conventional antigens activate <1 in 10,000 T cells. T-cell superantigens include staphylococcal enterotoxins and other bacterial products. Superantigen stimulation of human peripheral T cells occurs in the clinical setting of *staphylococcal toxic shock syndrome*, leading to massive overproduction of T-cell cytokines that leads to hypotension and shock (Chap. 147).

B CELLS Mature B cells constitute 5–10% of human peripheral blood lymphocytes, 20–30% of lymph node cells, 50% of splenic lymphocytes, and ~10% of bone marrow lymphocytes. B cells express on their surface intramembrane immunoglobulin (Ig) molecules that function as BCRs for antigen in a complex of Ig-associated α and β

signaling molecules with properties similar to those described in T cells (Fig. 349-8). Unlike T cells, which recognize only processed peptide fragments of conventional antigens embedded in the notches of MHC class I and class II antigens of APCs, B cells are capable of recognizing and proliferating to whole unprocessed native antigens via antigen binding to B-cell surface Ig (sIg) receptors. B cells also express surface receptors for the Fc region of IgG molecules (CD32) as well as receptors for activated complement components (C3d or CD21, C3b or CD35). The primary function of B cells is to produce antibodies. B cells also serve as APCs and are highly efficient at antigen processing. Their antigen-presenting function is enhanced by a variety of cytokines. Mature B cells are derived from bone marrow precursor cells that arise continuously throughout life (Fig. 349-6).

B lymphocyte development can be separated into antigen-independent and antigen-dependent phases. Antigen-independent B-cell development occurs in primary lymphoid organs and includes all stages of B-cell maturation up to the slg $+$ mature B cell. Antigen-dependent B-cell maturation is driven by the interaction of antigen with the mature B-cell sIg, leading to memory B-cell induction, Ig class switching, and plasma cell formation. Antigen-dependent stages of B-cell maturation occur in secondary lymphoid organs, including lymph node, spleen, and gut Peyer's patches. In contrast to the T-cell repertoire that is generated intrathymically before contact with foreign antigen, the repertoire of B cells expressing diverse antigen-reactive sites is modified by further alteration of Ig genes after stimulation by antigen—a process called *somatic hypermutation*—that occurs in lymph node germinal centers.

During B-cell development, diversity of the antigen-binding variable region of Ig is generated by an ordered set of Ig gene rearrangements

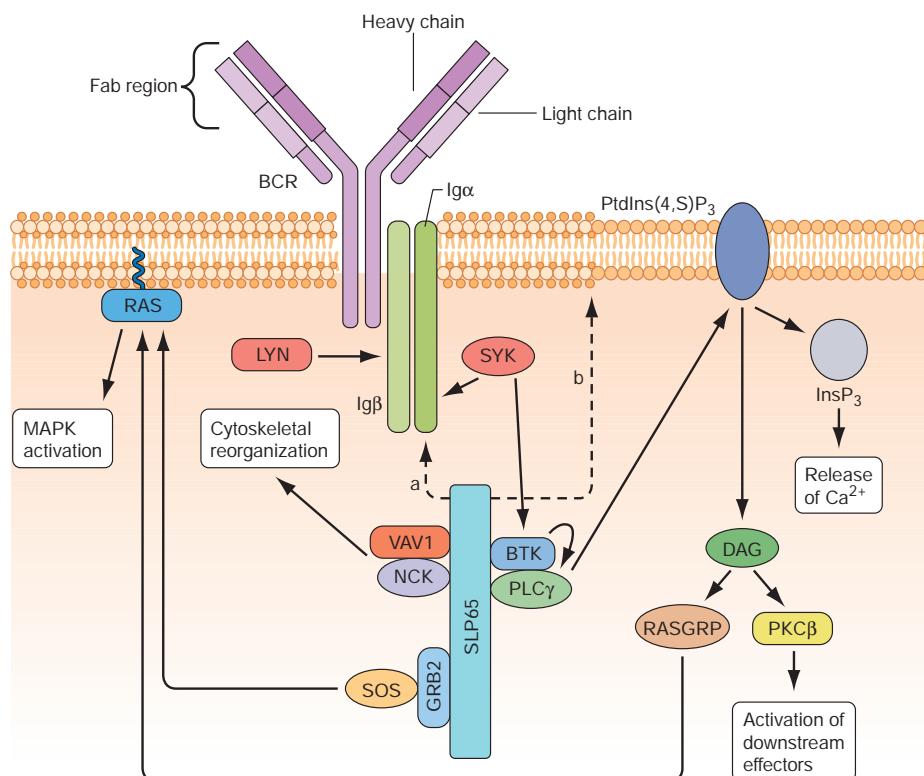


FIGURE 349-8 B-cell receptor (BCR) activation results in the sequential activation of protein tyrosine kinases, which results in the formation of a signaling complex and activation of downstream pathways as shown. Whereas SLP65 is recruited to the membrane through GADS and LAT, the mechanism of SLP65 recruitment is unclear. Studies have indicated two mechanisms: (a) direct binding by the SH2 domain of SLP65 to immunoglobulin (Ig) of the BCR complex or (b) membrane recruitment through a leucine zipper in the amino terminus of SLP65 and an unknown binding partner. ADAP, adhesion- and degranulation-promoting adaptor protein; AP1, activator protein 1; BTK, Bruton's tyrosine kinase; DAG, diacylglycerol; GRB2, growth factor receptor-bound protein 2; HPK1, hematopoietic progenitor kinase 1; InsP₃, inositol-1,4,5-trisphosphate; ITK, interleukin-2-inducible T-cell kinase; NCK, noncatalytic region of tyrosine kinase; NF-B, nuclear factor B; PKC, protein kinase C; PLC, phospholipase C; PtdIns(4,5)P₂, phosphatidylinositol-4,5-bisphosphate; RASGRP, RAS guanyl-releasing protein; SOS, son of sevenless homologue; SYK, spleen tyrosine kinase. (Reproduced with permission from GA Koretzky, F Abtahian, MA Silverman. SLP65 and SLP65: complex regulation of signalling in lymphocytes and beyond. *Nat Rev Immunol* 6:67, 2006.)

that are similar to the rearrangements undergone by TCR α , β , γ , and δ genes. For the heavy chain, there is first a rearrangement of D segments to J segments, followed by a second rearrangement between a V gene segment and the newly formed D-J sequence; the C segment is aligned to the V-D-J complex to yield a functional Ig heavy chain gene (V-D-J-C). During later stages, a functional κ or γ light chain gene is generated by rearrangement of a V segment to a J segment, ultimately yielding an intact Ig molecule composed of heavy and light chains.

The process of Ig gene rearrangement is regulated and results in a single antibody specificity produced by each B cell, with each Ig molecule comprising one type of heavy chain and one type of light chain. Although each B cell contains two copies of Ig light and heavy chain genes, only one gene of each type is productively rearranged and expressed in each B cell, a process termed *allelic exclusion*.

There are ~300 V_{κ} genes and 5 J_{κ} genes, resulting in the pairing of V_{κ} and J_{κ} genes to create >1500 different kappa light chain combinations. There are ~70 V_{λ} genes and 4 J_{λ} genes for >280 different lambda light chain combinations. The number of distinct light chains that can be generated is increased by somatic mutations within the V and J genes, thus creating large numbers of possible specificities from a limited amount of germline genetic information. As noted above, in heavy chain Ig gene rearrangement, the VH domain is created by the joining of three types of germline genes called V_H , D_H , and J_H , thus allowing for even greater diversity in the variable region of heavy chains than of light chains.

The most immature B-cell precursors (early pro-B cells) lack cytoplasmic Ig (cIg) and slg (Fig. 349-6). The large pre-B cell is marked by the acquisition of the surface pre-BCR composed of μ heavy (H) chains and a pre-B light chain, termed *V pre-B*. *V pre-B* is a surrogate light chain receptor encoded by the non-rearranged *V pre-B* and the $\gamma 5$ light-chain locus (the pre-BCR). Pro- and pre-B cells are driven to proliferate and mature by signals from bone marrow stroma—in particular, IL-7. Light chain rearrangement occurs in the small pre-B-cell stage such that the full BCR is expressed at the immature B-cell stage. Immature B cells have rearranged Ig light chain genes and express slgM. As immature B cells develop into mature B cells, slgD is expressed as well as slgM. At this point, B lineage development in bone marrow is complete, and B cells exit into the peripheral circulation and migrate to secondary lymphoid organs to encounter specific antigens.

Random rearrangements of Ig genes occasionally generate self-reactive antibodies, and mechanisms must be in place to correct these mistakes. One such mechanism is BCR editing, whereby autoreactive BCRs are mutated to not react with self-antigens. If receptor editing is unsuccessful in eliminating autoreactive B cells, then autoreactive B cells undergo negative selection in the bone marrow through induction of apoptosis after BCR engagement of self-antigen.

After leaving the bone marrow, B cells populate peripheral B-cell sites, such as lymph node and spleen, and await contact with foreign antigens that react with each B cell's clonotypic receptor. Antigen-driven B-cell activation occurs through the BCR, and a process known as *somatic hypermutation* takes place whereby point mutations in rearranged H- and L-genes give rise to mutant slg molecules, some of which bind antigen better than the original slg molecules. Somatic hypermutation, therefore, is a process whereby memory B cells in peripheral lymph organs have the best binding or the highest-affinity antibodies. This overall process of generating the best antibodies is called *affinity maturation of antibody*.

Lymphocytes that synthesize IgG, IgA, and IgE are derived from slgM+, slgD+ mature B cells. Ig class switching occurs in lymph node and other peripheral lymphoid tissue germinal centers. CD40 on B cells and CD40 ligand on T cells constitute a critical co-stimulatory receptor-ligand pair of immune-stimulatory molecules. Pairs of CD40+ B cells and CD40 ligand+ T cells bind and drive B-cell Ig class switching via T cell-produced cytokines such as IL-4 and TGF- β . IL-1, -2, -4, -5, and -6 synergize to drive mature B cells to proliferate and differentiate into Ig-secreting cells.

Humoral Mediators of Adaptive Immunity: Immunoglobulins

Immunoglobulins are the products of differentiated B cells and mediate the humoral arm of the immune response. The primary functions of antibodies are to bind specifically to antigen and bring about the inactivation or removal of the offending toxin, microbe, parasite, or other foreign substance from the body. The structural basis of Ig molecule function and Ig gene organization has provided insight into the role of antibodies in normal protective immunity, pathologic immune-mediated damage by immune complexes, and autoantibody formation against host determinants.

All immunoglobulins have the basic structure of two heavy and two light chains (Fig. 349-8). Immunoglobulin isotype (i.e., G, M, A, D, E) is determined by the type of Ig heavy chain present. IgG and IgA isotypes can be divided further into subclasses (G1, G2, G3, G4, and A1, A2) based on specific antigenic determinants on Ig heavy chains. The characteristics of human immunoglobulins are outlined in Table 349-9. The four chains are covalently linked by disulfide bonds. Each chain is made up of a V region and C regions (also called *domains*), themselves made up of units of ~110 amino acids. Light chains have one variable (V_L) and one constant (C_L) unit; heavy chains have one variable unit (V_H) and three or four constant (C_H) units, depending on isotype. As the name suggests, the constant, or C, regions of Ig molecules are made up of homologous sequences and share the same primary structure as all other Ig chains of the

TABLE 349-9 Physical, Chemical, and Biologic Properties of Human Immunoglobulins

PROPERTY	IgG	IgA	IgM	IgD	IgE
Usual molecular form	Monomer	Monomer, dimer	Pentamer, hexamer	Monomer	Monomer
Other chains	None	J chain, SC	J chain	None	None
Subclasses	G1, G2, G3, G4	A1, A2	None	None	None
Heavy chain allotypes	Gm (=30)	No A1, A2m (2)	None	None	None
Molecular mass, kDa	150	160, 400	950, 1150	175	190
Serum level in average adult, mg/mL	9.5–12.5	1.5–2.6	0.7–1.7	0.04	0.0003
Percentage of total serum Ig	75–85	7–15	5–10	0.3	0.019
Serum half-life, days	23	6	5	3	2.5
Synthesis rate, mg/kg per day	33	65	7	0.4	0.016
Antibody valence	2	2, 4	10, 12	2	2
Classical complement activation	+(G1, 2?, 3)	–	++	–	–
Alternate complement activation	+(G4)	+	–	+	–
Binding cells via Fc	Macrophages, neutrophils, large granular lymphocytes	Lymphocytes	Lymphocytes	None	Mast cells, basophils, B cells
Biologic properties	Placental transfer, secondary antibody for most antipathogen responses	Secretory immunoglobulin	Primary antibody responses	Marker for mature B cells	Allergy, antiparasite responses

Source: Reproduced with permission from L Carayannopoulos, JD Capra, in WE Paul (ed): *Fundamental Immunology*, 3rd ed. New York, Raven, 1993.

same isotype and subclass. Constant regions are involved in biologic functions of Ig molecules. The C_H2 domain of IgG and the C_H4 units of IgM are involved with the binding of the C1q portion of C1 during complement activation. The C_H region at the carboxy-terminal end of the IgG molecule, the Fc region, binds to surface Fc receptors (CD16, CD32, CD64) of macrophages, DCs, NK cells, B cells, neutrophils, and eosinophils. The Fc of IgA binds to FcaR (CD89), and the Fc of IgE binds to FceR (CD23).

Variable regions (V_L and V_H) constitute the antibody-binding (Fab) region of the molecule. Within the V_L and V_H regions are hypervariable regions (extreme sequence variability) that constitute the antigen-binding site unique to each Ig molecule. The idioype is defined as the specific region of the Fab portion of the Ig molecule to which antigen binds. Antibodies against the idioype portion of an antibody molecule are called *anti-idioype antibodies*. The formation of such antibodies in vivo during a normal B-cell antibody response may generate a negative (or "off") signal to B cells to terminate antibody production.

IgG constitutes ~75–85% of total serum immunoglobulin. The four IgG subclasses are numbered in order of their level in serum, IgG1 being found in greatest amounts and IgG4 the least. IgG subclasses have clinical relevance in their varying ability to bind macrophage and neutrophil Fc receptors and to activate complement (Table 349-9). Moreover, selective deficiencies of certain IgG subclasses give rise to clinical syndromes in which the patient is inordinately susceptible to bacterial infections. IgG antibodies are frequently the predominant antibody made after rechallenge of the host with antigen (secondary antibody response).

IgM antibodies normally circulate as a 950-kDa pentamer with 160-kDa bivalent monomers joined by a molecule called the *J chain*, a 15-kDa nonimmunoglobulin molecule that also effects polymerization of IgA molecules. IgM is the first immunoglobulin to appear in the immune response (primary antibody response) and is the initial type of antibody made by neonates. Membrane IgM in the monomeric form also functions as a major antigen receptor on the surface of mature B cells (Table 349-9). IgM is an important component of immune complexes in autoimmune diseases. For example, IgM antibodies against IgG molecules (rheumatoid factors) are present in high titers in *rheumatoid arthritis*, other collagen diseases, and some infectious diseases (*subacute bacterial endocarditis*).

IgA constitutes only 7–15% of total serum immunoglobulin but is the predominant class of immunoglobulin in secretions. IgA in secretions (tears, saliva, nasal secretions, gastrointestinal tract fluid, and human milk) is in the form of secretory IgA (sIgA), a polymer consisting of two IgA monomers, a joining molecule, again termed the J chain, and a glycoprotein called the *secretory protein*. Of the two IgA subclasses, IgA1 is primarily found in serum, whereas IgA2 is more prevalent in secretions. IgA fixes complement via the alternative complement pathway and has potent antiviral activity in humans by prevention of virus binding to respiratory and gastrointestinal epithelial cells.

IgD is found in minute quantities in serum and, together with IgM, is a major receptor for antigen on the naïve B-cell surface. IgE, which is present in serum in very low concentrations, is the major class of immunoglobulin involved in arming mast cells and basophils by binding to these cells via the Fc region. Antigen cross-linking of IgE molecules on basophil and mast cell surfaces results in release of mediators of the immediate hypersensitivity (allergic) response (Table 349-9).

CELLULAR INTERACTIONS IN REGULATION OF NORMAL IMMUNE RESPONSES

The net result of activation of the humoral (B-cell) and cellular (T-cell) arms of the adaptive immune system by foreign antigen is the elimination of antigen directly by specific effector T cells or in concert with specific antibody.

The expression of adaptive immune cell function is the result of a complex series of immunoregulatory events that occur in phases. Both T and B lymphocytes mediate immune functions, and each of these cell types, when given appropriate signals, passes through stages, from activation and induction through proliferation, differentiation, and ultimately effector functions. The effector function expressed may

be at the end point of a response, such as secretion of antibody by a differentiated plasma cell, or it might serve a regulatory function that modulates other functions, such as is seen with CD4+ and CD8+ T lymphocytes that modulate both differentiation of B cells and activation of CD8+ cytotoxic T cells.

CD4 helper T cells can be subdivided on the basis of cytokines produced (Fig. 349-2). Activated T_H1-type helper T cells secrete IL-2, IFN-γ, IL-3, TNF-α, GM-CSF, and TNF-β, whereas activated T_H2-type helper T cells secrete IL-3, -4, -5, -6, -10, and -13. T_H1 CD4+ T cells, through elaboration of IFN-γ, have a central role in mediating intracellular killing by a variety of pathogens. T_H1 CD4+ T cells also provide T-cell help for generation of cytotoxic T cells and some types of opsonizing antibody, and they generally respond to antigens that lead to delayed hypersensitivity types of immune responses for many intracellular viruses and bacteria (such as HIV-1 or *M. tuberculosis*). In contrast, T_H2 cells have a primary role in regulatory humoral immunity and isotype switching. T_H2 cells, through production of IL-4 and IL-10, have a regulatory role in limiting proinflammatory responses mediated by T_H1 cells (Fig. 349-2). In addition, T_H2 CD4+ T cells provide help to B cells for specific Ig production and respond to antigens that require high antibody levels for foreign antigen elimination (extracellular encapsulated bacteria such as *S. pneumoniae* and certain parasite infections). Additional subsets of the CD4 T_H cells have been described, one of which is termed T_H17, that secrete cytokines IL-17, -22, and -26. T_H17 cells have been shown to play a role in autoimmune inflammatory disorders in addition to defense against extracellular bacteria and fungi, particularly at mucosal surfaces. T_H9 cells are defined by their secretion of IL-9 and have been shown to play a role in atopic disease, inflammatory bowel disease, and antitumor immunity. Moreover, the Tfh subset of helper T cells is crucial for providing the necessary signals to B cells in germinal centers to undergo affinity maturation. A subset of Tfh cells called Tfh13 cells secrete IL-4, IL-5, and IL-13 in response to allergens and mediate anaphylaxis reactions (Fig. 349-2). In summary, the type of T-cell response generated in an immune response is determined by the microbe PAMPs presented to the DCs, the TLRs on the DCs that become activated, the types of DCs that are activated, and the cytokines that are produced (Table 349-6). Commonly, myeloid DCs produce IL-12 and activate T_H1 T-cell responses that result in IFN-γ and cytotoxic T-cell induction, and plasmacytoid DCs produce IFN-α and lead to T_H2 responses that result in IL-4 production and enhanced antibody responses.

As shown in Fig. 349-2, upon activation by DCs, T-cell subsets that produce IL-2, IL-3, IFN-γ, and/or IL-4, -5, -6, -10, and -13 are generated and exert positive and negative influences on effector T and B cells. For B cells, trophic effects are mediated by a variety of cytokines, particularly T cell-derived IL-3, -4, -5, and -6, that act at sequential stages of B-cell maturation, resulting in B-cell proliferation, differentiation, and ultimately antibody secretion. For cytotoxic T cells, trophic factors include inducer T-cell secretion of IL-2, IFN-γ, and IL-12.

Important types of immunomodulatory T cells that control immune responses are *CD4+ and CD8+ T regulatory cells*. These cells express the α chain of the IL-2 receptor (CD25), produce IL-10, and suppress both T- and B-cell responses. T regulatory cells (Tregs) are induced by immature DCs and play key roles in maintaining tolerance to self-antigens. Loss of Treg cells is the cause of organ-specific autoimmune disease in mice such as autoimmune thyroiditis, adrenalitis, and oophoritis (see "Immune Tolerance and Autoimmunity" below, Chap. 350). Tregs also play key roles in controlling the magnitude and duration of immune responses to microbes. Normally, after the initial immune response to a microbe has eliminated the invader, Tregs are activated to suppress the antimicrobe response and prevent host injury. Some microbes have adapted to induce Treg activation at the site of infection to promote parasite infection and survival. In *Leishmania* infection, the parasite induces Treg accumulation at skin infection sites that dampens anti-*Leishmania* T-cell responses and prevents parasite elimination. Although B cells recognize native antigen via B-cell surface Ig receptors, B cells require T-cell help to produce high-affinity antibody of multiple isotypes that are the most effective in eliminating foreign antigen. In B cell germinal centers, the CD4 T cells that promote B cell maturation and affinity maturation are termed T follicular

helper (Tfh) cells. T cell–B cell interactions that lead to high-affinity antibody production require (1) processing of native antigen by B cells and expression of peptide fragments on the B-cell surface for presentation to T_H cells, (2) the ligation of B cells by both the TCR complex and the CD40 ligand, (3) induction of the process termed *antibody isotype switching* in antigen-specific B-cell clones, and (4) induction of the process of affinity maturation of antibody in the germinal centers of B-cell follicles of lymph node and spleen.

Naïve B cells express cell-surface IgD and IgM, and initial contact of naïve B cells with antigen is via binding of native antigen to B-cell surface IgM. T-cell cytokines, released following T_H2 cell contact with B cells or by a “bystander” effect, induce changes in Ig gene conformation that promote recombination of Ig genes. These events then result in the switching of expression of heavy chain exons in a triggered B cell, leading to the secretion of IgG, IgA, or, in some cases, IgE antibody with the same V region antigen specificity as the original IgM antibody, for response to a wide variety of extracellular bacteria, protozoa, and helminths. CD40 ligand expression by activated T cells is critical for induction of B-cell antibody isotype switching and for B-cell responsiveness to cytokines. Patients with mutations in T-cell CD40 ligand have B cells that are unable to undergo isotype switching, resulting in lack of memory B-cell generation and the immunodeficiency syndrome of *X-linked hyper-IgM syndrome* (Chaps. 350 and 351).

IMMUNE TOLERANCE AND AUTOIMMUNITY

Immune tolerance is defined as the absence of activation of pathogenic autoreactivity to self-antigens. *Autoimmune diseases* are syndromes caused by the activation of T or B cells or both, with no evidence of other causes such as infections or malignancies (Chaps. 350 and 355). Immune tolerance and autoimmunity are present normally in health; when abnormal, they represent extremes from the normal state. For example, low levels of autoreactivity of T and B cells with self-antigens in the periphery are critical to T- and B-cell survival. Similarly, low levels of autoreactivity and thymocyte recognition of self-antigens in the thymus are the mechanisms whereby normal T cells are positively selected to survive and leave the thymus to respond to foreign microbes in the periphery and T cells highly reactive to self-antigens are negatively selected and die to prevent overly self-reactive T cells from migrating to the periphery (central tolerance). However, not all self-antigens are expressed in the thymus to delete highly self-reactive T cells, and there are mechanisms for induction of tolerance in peripheral T cells as well. Unlike the presentation of microbial antigens by mature DCs, the presentation of self-antigens by immature DCs neither activates nor matures the DCs to express high levels of co-stimulatory molecules such as B7-1 (CD80) or B7-2 (CD86). When peripheral T cells are stimulated by DCs expressing self-antigens in the context of HLA molecules, sufficient stimulation of T cells occurs to keep them alive, but otherwise, they remain anergic, or nonresponsive, until T cells contact a DC with high levels of co-stimulatory molecules expressing microbial antigens and become activated to respond to the microbe. If B cells have high self-reactive BCRs, they normally undergo either deletion in the bone marrow or receptor editing to express a less autoreactive receptor. Although many autoimmune diseases are characterized by abnormal or pathogenic autoantibody production (Table 349-10), most autoimmune diseases are caused by a combination of excess T- and B-cell reactivity.

Multiple factors contribute to the genesis of autoimmune disease syndromes, including genetic susceptibility (e.g., HLAB27 with ankylosing spondylitis), environmental immune stimulants such as drugs (e.g., procainamide and phenytoin [Dilantin] with drug-induced systemic lupus erythematosus), infectious agent triggers (such as Epstein-Barr virus and autoantibody production against red blood cells and platelets), and loss of T regulatory cells (leading to thyroiditis, adrenalitis, and oophoritis).

Immunity at Mucosal Surfaces Mucosa covering the respiratory, digestive, and urogenital tracts; the eye conjunctiva; the inner ear; and the ducts of all exocrine glands contain cells of the innate and adaptive mucosal immune system that protect these surfaces against pathogens. In the healthy adult, mucosa-associated lymphoid tissue (MALT)

contains 80% of all immune cells within the body and constitutes the largest mammalian lymphoid organ system.

MALT has three main functions: (1) to protect the mucous membranes from invasive pathogens; (2) to prevent uptake of foreign antigens from food, commensal organisms, and airborne pathogens and particulate matter; and (3) to prevent pathologic immune responses from foreign antigens if they do cross the mucosal barriers of the body.

MALT is a compartmentalized system of immune cells that functions independently from systemic immune organs. Whereas the systemic immune organs are essentially sterile under normal conditions and respond vigorously to pathogens, MALT immune cells are continuously bathed in foreign proteins and commensal bacteria, and they must select those pathogenic antigens that must be eliminated. MALT contains anatomically defined foci of immune cells in the intestine, tonsil, appendix, and peribronchial areas that are inductive sites for mucosal immune responses. From these sites, immune T and B cells migrate to effector sites in mucosal parenchyma and exocrine glands where mucosal immune cells eliminate pathogen-infected cells. In addition to mucosal immune responses, all mucosal sites have strong mechanical and chemical barriers and cleansing functions to repel pathogens.

Key components of MALT include specialized epithelial cells called “membrane” or “M” cells that take up antigens and deliver them to DCs or other APCs. Effector cells in MALT include B cells producing antipathogen neutralizing antibodies of secretory IgA as well as IgG isotype, T cells producing similar cytokines as in systemic immune system response, and T helper and cytotoxic T cells that respond to pathogen-infected cells.

Secretory IgA is produced in amounts of >50 mg/kg of body weight per 24 h and functions to inhibit bacterial adhesion, inhibit macromolecular absorption in the gut, neutralize viruses, and enhance antigen elimination in tissue through binding to IgA and receptor-mediated transport of immune complexes through epithelial cells.

Recent studies have demonstrated the importance of commensal gut and other mucosal bacteria to the health of the human immune system. Normal commensal flora induces anti-inflammatory events in the gut and protects epithelial cells from pathogens through TLRs and other PRR signaling. When the gut is depleted of normal commensal flora, the immune system becomes abnormal, with loss of T_H1 T-cell function. Restoration of the normal gut flora can reestablish the balance in T helper cell ratios characteristic of the normal immune system. Diet also has an impact on the gut microbiome. Altered microbiome composition has been etiologically related to obesity, insulin resistance, and diabetes. When the gut barrier is intact, either antigens do not transverse the gut epithelium or, when pathogens are present, a self-limited, protective MALT immune response eliminates the pathogen (Fig. 349-8). However, when the gut barrier breaks down, immune responses to commensal flora antigens can cause inflammatory bowel diseases such as *Crohn's disease* and, perhaps, *ulcerative colitis* (Chap. 326). Uncontrolled MALT immune responses to food antigens, such as gluten, can cause *celiac disease* (Chap. 326).

THE CELLULAR AND MOLECULAR CONTROL OF PROGRAMMED CELL DEATH

The process of apoptosis (programmed cell death) plays a crucial role in regulating normal immune responses to antigen. In general, a wide variety of stimuli trigger one of several apoptotic pathways to eliminate microbe-infected cells, eliminate cells with damaged DNA, or eliminate activated immune cells that are no longer needed (Fig. 349-9). The largest known family of “death receptors” is the TNF receptor (TNF-R) family (TNF-R1, TNF-R2, Fas [CD95], death receptor 3 [DR3], death receptor 4 [DR4; TNF-related apoptosis-including ligand receptor 1, or TRAIL-R1], and death receptor 5 [DR5, TRAIL-R2]); their ligands are all in the TNF-α family. Binding of ligands to these death receptors leads to a signaling cascade that involves activation of the caspase family of molecules that leads to DNA cleavage and cell death. Two other pathways of programmed cell death involve nuclear p53 in the elimination of cells with abnormal DNA and mitochondrial cytochrome c to induce cell death in damaged cells (Fig. 349-9). A number of human diseases have now been described that result from, or are

TABLE 349-10 Recombinant or Purified Autoantigens Recognized by Autoantibodies Associated with Human Autoimmune Disorders

AUTOANTIGEN	AUTOIMMUNE DISEASES	AUTOANTIGEN	AUTOIMMUNE DISEASES		
Cell- or Organ-Specific Autoimmunity					
Acetylcholine receptor	Myasthenia gravis	Aminoacyl-tRNA synthetase (several)	Polymyositis, dermatomyositis		
Actin	Chronic active hepatitis, primary biliary cirrhosis	Cardiolipin	Systemic lupus erythematosus, antiphospholipid syndrome		
Adenine nucleotide translator (ANT)	Dilated cardiomyopathy, myocarditis	Carbonic anhydrase II	Systemic lupus erythematosus, Sjögren's syndrome, systemic sclerosis		
β-Adrenoreceptor	Dilated cardiomyopathy	Collagen (multiple types)	Rheumatoid arthritis, systemic lupus erythematosus, progressive systemic sclerosis		
Aromatic L-amino acid decarboxylase	Autoimmune polyendocrine syndrome type 1 (APS-1)	Centromere-associated proteins	Systemic sclerosis		
Asialoglycoprotein receptor	Autoimmune hepatitis	DNA-dependent nucleoside-stimulated ATPase	Dermatomyositis		
Bactericidal/permeability-increasing protein (Bpi)	Cystic fibrosis vasculitides	Fibrillarin	Scleroderma		
Calcium-sensing receptor	Acquired hypoparathyroidism	Fibronectin	Systemic lupus erythematosus, rheumatoid arthritis, morphea		
Cholesterol side-chain cleavage enzyme (CYP11a)	Autoimmune polyglandular syndrome-1	Glucose-6-phosphate isomerase	Rheumatoid arthritis		
Collagen type IV-α3-chain	Goodpasture's syndrome	β2-Glycoprotein I (B2-GPI)	Primary antiphospholipid syndrome		
Cytochrome P450 2D6 (CYP2D6)	Autoimmune hepatitis	Golgin (95, 97, 160, 180) Heat shock protein	Sjögren's syndrome, systemic lupus erythematosus, rheumatoid arthritis, various immune-related disorders		
Desmin	Crohn's disease, coronary artery disease	Hemidesmosomal protein 180	Bullous pemphigoid, herpes gestationis, cicatricial pemphigoid		
Desmoglein 1	Pemphigus foliaceus	Histone H2A-H2B-DNA	Systemic lupus erythematosus		
Desmoglein 3	Pemphigus vulgaris	IgE receptor	Chronic idiopathic urticaria		
F-actin	Autoimmune hepatitis	Keratin	Rheumatoid arthritis		
GM gangliosides	Guillain-Barré syndrome	Ku-DNA-protein kinase	Systemic lupus erythematosus		
Glutamate decarboxylase (GAD65)	Type 1 diabetes, stiff-person syndrome	Ku-nucleoprotein La phosphoprotein (La 55-B)	Connective tissue syndrome Sjögren's syndrome		
Glutamate receptor (GLUR)	Rasmussen encephalitis	Myeloperoxidase	Necrotizing and crescentic glomerulonephritis, systemic vasculitis		
H/K ATPase	Autoimmune gastritis	Proteinase 3 (PR3)	Granulomatosis with polyangiitis (Wegener's), Churg-Strauss syndrome		
17-α-Hydroxylase (CYP17)	Autoimmune polyglandular syndrome-1	RNA polymerase I-III (RNP)	Systemic sclerosis, systemic lupus erythematosus		
21-Hydroxylase (CYP21)	Addison's disease	Signal recognition protein (SRP54)	Polymyositis		
IA-2 (ICA512)	Type 1 diabetes	Topoisomerase-1 (Scl-70)	Scleroderma, Raynaud's syndrome		
Insulin	Type 1 diabetes, insulin hypoglycemic syndrome (Hirata's disease)	Tublin	Chronic liver disease, visceral leishmaniasis		
Insulin receptor	Type B insulin resistance, acanthosis, systemic lupus erythematosus	Vimentin	Systemic autoimmune disease		
Intrinsic factor type 1	Pernicious anemia	Plasma Protein and Cytokine Autoimmunity			
Leukocyte function-associated antigen (LFA-1)	Treatment-resistant Lyme arthritis	C1 inhibitor	Autoimmune C1 deficiency		
Myelin-associated glycoprotein (MAG)	Polyneuropathy	C1q	Systemic lupus erythematosus, membrane proliferative glomerulonephritis		
Myelin-basic protein	Multiple sclerosis, demyelinating diseases	Cytokines (IL-1α, IL-1β, IL-6, TNF-α, IFN-γ IL17A, IL-17F, GM-CSF)	IL-1α, IL-1β: rheumatoid arthritis, systemic sclerosis, systemic lupus erythematosus; IL-6: bacterial infections; IFN-γ: bacterial infections, varicella-zoster virus reactivation; IL-17A, IL-17F: chronic mucocutaneous candidiasis; GM-CSF: pulmonary alveolar proteinosis, fungal infections		
Myelin oligodendrocyte glycoprotein (MOG)	Multiple sclerosis	Factor II, factor V, factor VII, factor VIII, factor IX, factor X, factor XI, thrombin vWF	Prolonged coagulation time		
Myosin	Rheumatic fever	Glycoprotein IIb/IIIa and Ib/IX	Autoimmune thrombocytopenia purpura		
p-80-Collin	Atopic dermatitis	IgA	Immunodeficiency associated with systemic lupus erythematosus, pernicious anemia, thyroiditis, Sjögren's syndrome, and chronic active hepatitis		
Pyruvate dehydrogenase complex-E2 (PDC-E2)	Primary biliary cirrhosis	Oxidized LDL (OxLDL)	Atherosclerosis		
Sodium iodide symporter (NIS)	Graves' disease, autoimmune hypothyroidism	Cancer and Paraneoplastic Autoimmunity			
SOX-10	Vitiligo	Amphiphysin	Neuropathy, small-cell lung cancer		
Thyroid and eye muscle shared protein	Thyroid-associated ophthalmopathy	Cyclin B1	Hepatocellular carcinoma		
Thyroglobulin	Autoimmune thyroiditis				
Thyroid peroxidase	Autoimmune Hashimoto's thyroiditis				
Thyrotropin receptor	Graves' disease				
Tissue transglutaminase	Celiac disease				
Transcription coactivator p75	Atopic dermatitis				
Tryptophan hydroxylase	Autoimmune polyglandular syndrome-1				
Tyrosinase	Vitiligo, metastatic melanoma				
Tyrosine hydroxylase	Autoimmune polyglandular syndrome-1				
Systemic Autoimmunity					
ACTH	ACTH deficiency				
Aminoacyl-tRNA histidyl synthetase	Myositis, dermatomyositis				

(Continued)

TABLE 349-10 Recombinant or Purified Autoantigens Recognized by Autoantibodies Associated with Human Autoimmune Disorders (Continued)

AUTOANTIGEN	AUTOIMMUNE DISEASES	AUTOANTIGEN	AUTOIMMUNE DISEASES
Cancer and Paraneoplastic Autoimmunity (continued)			
DNA topoisomerase II	Liver cancer	p62 (IGF-II mRNA-binding protein)	Hepatocellular carcinoma (China)
Desmoplakin	Paraneoplastic pemphigus	Recoverin	Cancer-associated retinopathy
Gephyrin	Paraneoplastic stiff-person syndrome	Ri protein	Paraneoplastic opsoclonus myoclonus ataxia
Hu proteins	Paraneoplastic encephalomyelitis	BIV spectrin	Lower motor neuron syndrome
Neuronal nicotinic acetylcholine receptor	Subacute autonomic neuropathy, cancer	Synaptotagmin	Lambert-Eaton myasthenic syndrome
p53	Cancer, systemic lupus erythematosus	Voltage-gated calcium channels	Lambert-Eaton myasthenic syndrome
		Yo protein	Paraneoplastic cerebellar degeneration

Source: From A Lernmark et al: J Clin Invest 108:1091, 2001; Cappelano G et al: Am J Clin Exp Immunol 1:136, 2012; C-L Ku et al: Hum Genet 139:783, 2020.

associated with mutated apoptosis genes. These include mutations in the Fas and Fas ligand genes in autoimmune and lymphoproliferation syndromes, and multiple associations of mutations in genes in the apoptotic pathway with malignant syndromes (Chap. 350).

MECHANISMS OF IMMUNE-MEDIATED DAMAGE TO MICROBES OR HOST TISSUES

Several responses by the host innate and adaptive immune systems to foreign microbes culminate in rapid and efficient elimination of

microbes. In these scenarios, the classic weapons of the adaptive immune system (T cells, B cells) interface with cells (macrophages, DCs, NK cells, neutrophils, eosinophils, basophils) and soluble products (microbial peptides, pentraxins, complement and coagulation systems) of the innate immune system (Chaps. 64 and 352).

There are five general phases of host defenses: (1) migration of leukocytes to sites of antigen localization; (2) antigen-nonspecific recognition of pathogens by macrophages and other cells and systems of the innate immune system; (3) specific recognition of foreign

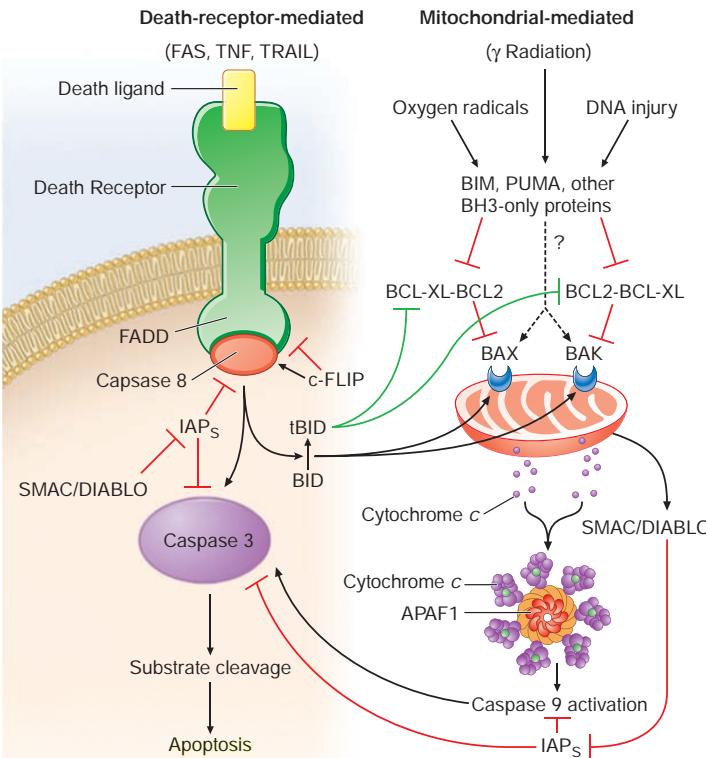


FIGURE 349-9 Pathways of cellular apoptosis. There are two major pathways of apoptosis: the death-receptor pathway, which is mediated by activation of death receptors, and the BCL2-regulated mitochondrial pathway, which is mediated by noxious stimuli that ultimately lead to mitochondrial injury. Ligation of death receptors recruits the adaptor protein FAS-associated death domain (FADD). FADD in turn recruits caspase 8, which ultimately activates caspase 3, the key "executioner" caspase. Cellular FLICE-inhibitory protein (c-FLIP) can either inhibit or potentiate binding of FADD and caspase 8, depending on its concentration. In the intrinsic pathway, proapoptotic BH3 proteins are activated by noxious stimuli, which interact with and inhibit antiapoptotic BCL2 or BCL-XL. Thus, BAX and BAK are free to induce mitochondrial permeabilization with release of cytochrome c, which ultimately results in the activation of caspase 9 through the apoptosome. Caspase 9 then activates caspase 3. SMAC/DIABLO is also released after mitochondrial permeabilization and acts to block the action of inhibitors of apoptosis protein (IAPs), which inhibit caspase activation. There is potential cross-talk between the two pathways, which is mediated by the truncated form of BID (tBID) that is produced by caspase 8-mediated BID cleavage: tBID acts to inhibit the BCL2-BCL-XL pathway and to activate BAX and BAK. There is debate (indicated by the question mark) as to whether proapoptotic BH3 molecules (e.g., BIM and PUMA) act directly on BAX and BAK to induce mitochondrial permeability or whether they act only on BCL2-BCL-XL. APAF1, apoptotic protease-activating factor 1; BH3, BCL homologue; TNF, tumor necrosis factor; TRAIL, TNF-related apoptosis-inducing ligand. (From RS Hotchkiss et al: Cell death in disease: mechanisms and emerging therapeutic concepts. N Engl J Med 361:1570, 2009. Copyright © (2009) Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.)

antigens mediated by T and B lymphocytes; (4) amplification of the inflammatory response with recruitment of specific and nonspecific effector cells by complement components, cytokines, kinins, arachidonic acid metabolites, and mast cell–basophil products; and (5) macrophage, neutrophil, and lymphocyte participation in destruction of antigen with ultimate removal of antigen particles by phagocytosis (by macrophages or neutrophils) or by direct cytotoxic mechanisms (involving macrophages, neutrophils, DCs, and lymphocytes). Under normal circumstances, orderly progression of host defenses through these phases results in a well-controlled immune and inflammatory response that protects the host from the offending antigen. However, dysfunction of any of the host defense systems can damage host tissue and produce clinical disease. Furthermore, for certain pathogens or antigens, the normal immune response itself might contribute substantially to the tissue damage. For example, the immune and inflammatory response in the brain to certain pathogens such as *M. tuberculosis* may be responsible for much of the morbidity rate of this disease in that organ system (Chap. 178). In addition, the morbidity rate associated with certain pneumonias such as that caused by *Pneumocystis jiroveci* may be associated more with inflammatory infiltrates than with the tissue-destructive effects of the microorganism itself (Chap. 220).

Molecular Basis of Lymphocyte–Endothelial Cell Interactions The control of lymphocyte circulatory patterns between the bloodstream and peripheral lymphoid organs operates at the level of lymphocyte–endothelial cell interactions to control the specificity of lymphocyte subset entry into organs. Similarly, lymphocyte–endothelial cell interactions regulate the entry of lymphocytes into inflamed tissue. Adhesion molecule expression on lymphocytes and endothelial cells regulates the retention and subsequent egress of lymphocytes within tissue sites of antigenic stimulation, delaying cell exit from tissue and preventing reentry into the circulating lymphocyte pool (Fig. 349-10). All types of lymphocyte migration begin with lymphocyte attachment to specialized regions of vessels, termed *high endothelial venules* (HEVs). An important concept is that adhesion molecules do not generally bind their ligand until a conformational change (ligand activation) occurs in the adhesion molecule that allows ligand binding. Induction of a conformation-dependent determinant on an adhesion molecule can be accomplished by cytokines or via ligation of other adhesion molecules on the cell.

The first stage of lymphocyte–endothelial cell interactions, *attachment and rolling*, occurs when lymphocytes leave the stream of flowing blood cells in a postcapillary venule and roll along venule endothelial

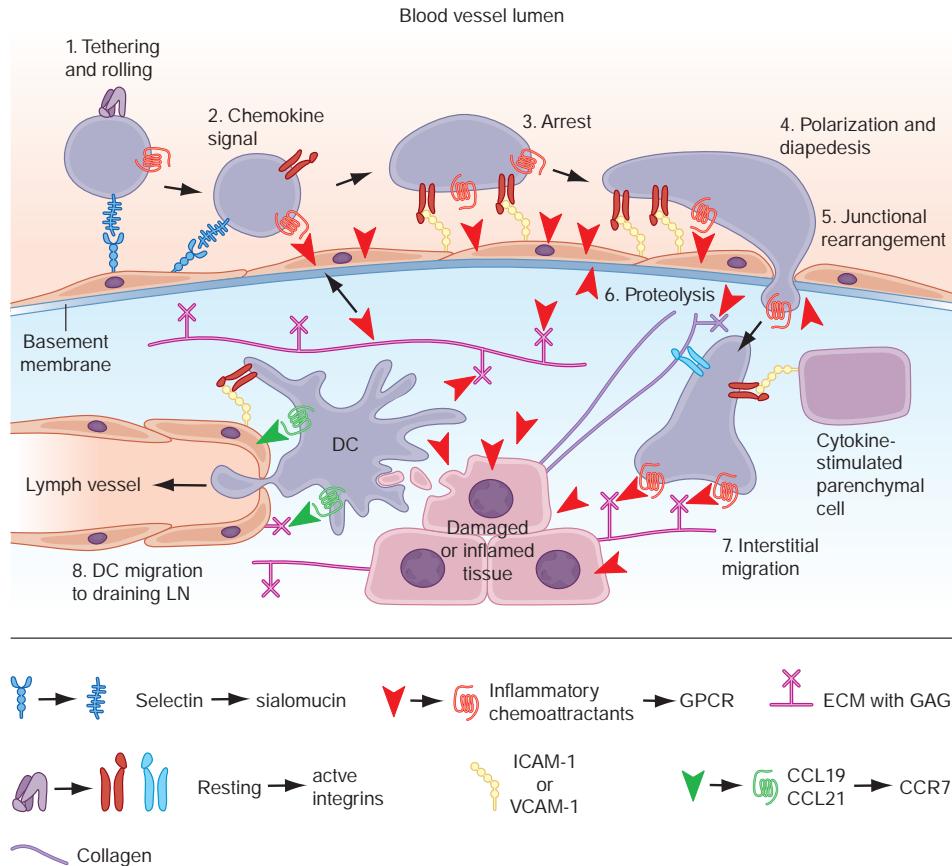


FIGURE 349-10 Key migration steps of immune cells at sites of inflammation. Inflammation due to tissue damage or infection induces the release of cytokines (not shown) and inflammatory chemoattractants (red arrowheads) from distressed stromal cells and “professional” sentinels, such as mast cells and macrophages (not shown). The inflammatory signals induce upregulation of endothelial selectins and immunoglobulin “superfamily” members, particularly ICAM-1 and/or VCAM-1. Chemoattractants, particularly chemokines, are produced by or translocated across venular endothelial cells (red arrow) and are displayed in the lumen to rolling leukocytes. Those leukocytes that express the appropriate set of trafficking molecules undergo a multistep adhesion cascade (steps 1–3) and then polarize and move by diapedesis across the venular wall (steps 4 and 5). Diapedesis involves transient disassembly of endothelial junctions and penetration through the underlying basement membrane (step 6). Once in the extravascular (interstitial) space, the migrating cell uses different integrins to gain “footholds” on collagen fibers and other ECM molecules, such as laminin and fibronectin, and on inflammation-induced ICAM-1 on the surface of parenchymal cells (step 7). The migrating cell receives guidance cues from distinct sets of chemoattractants, particularly chemokines, which may be immobilized on glycosaminoglycans (GAG) that “decorate” many ECM molecules and stromal cells. Inflammatory signals also induce tissue dendritic cells (DCs) to undergo maturation. Once DCs process material from damaged tissues and invading pathogens, they upregulate CCR7, which allows them to enter draining lymph vessels that express the CCR7 ligand CCL21 (and CCL19). In lymph nodes (LNs), these antigen-loaded mature DCs activate naïve T cells and expand pools of effector lymphocytes, which enter the blood and migrate back to the site of inflammation. T cells in tissue also use this CCR7-dependent route to migrate from peripheral sites to draining lymph nodes through afferent lymphatics. (Reproduced with permission from AD Luster et al: Immune cell migration in inflammation: present and future therapeutic targets. *Nat Immunol* 6:1182, 2005.)

cells (Fig. 349-10). Lymphocyte rolling is mediated by the l-selectin molecule (LECAM-1, LAM-1, CD62L) and slows cell transit time through venules, allowing time for activation of adherent cells.

The second stage of lymphocyte–endothelial cell interactions, *firm adhesion with activation-dependent stable arrest*, requires stimulation of lymphocytes by chemoattractants or by endothelial cell–derived cytokines. Cytokines thought to participate in adherent cell activation include members of the IL-8 family, platelet-activation factor, leukotriene B₄, and C5a. In addition, HEVs express chemokines, SLC (CCL21) and ELC (CCL19), which participate in this process. Following activation by chemoattractants, lymphocytes shed l-selectin from the cell surface and upregulate cell CD11b/18 (MAC-1) or CD11a/18 (LFA-1) molecules, resulting in firm attachment of lymphocytes to HEVs.

Lymphocyte homing to peripheral lymph nodes involves adhesion of l-selectin to glycoprotein HEV ligands collectively referred to as *peripheral node addressin (PNAd)*, whereas homing of lymphocytes to intestine Peyer's patches primarily involves adhesion of the α4β7 integrin to mucosal addressin cell adhesion molecule-1 (MAdCAM-1) on the Peyer's patch HEVs. However, for migration to mucosal Peyer's patch lymphoid aggregates, naïve lymphocytes primarily use l-selectin, whereas memory lymphocytes use α4β7 integrin. α4β1 integrin (CD49d/CD29, VLA-4)–VCAM-1 interactions are important in the initial interaction of memory lymphocytes with HEVs of multiple organs in sites of inflammation (Table 349-11).

The third stage of leukocyte emigration in HEVs is *sticking and arrest*. Sticking of the lymphocyte to endothelial cells and arrest at the site of sticking are mediated predominantly by ligation of α1β2 integrin LFA-1 to the integrin ligand ICAM-1 on HEVs. Whereas the first three stages of lymphocyte attachment to HEVs take only a few seconds,

the fourth stage of lymphocyte emigration, *transendothelial migration*, takes ~10 min. Although the molecular mechanisms that control lymphocyte transendothelial migration are not fully characterized, the HEV CD44 molecule and molecules of the HEV glycocalyx (extracellular matrix) are thought to play important regulatory roles in this process (Fig. 349-10). Finally, expression of matrix metalloproteases capable of digesting the subendothelial basement membrane, rich in nonfibrillar collagen, appears to be required for the penetration of lymphoid cells into the extravascular sites.

Abnormal induction of HEV formation and use of the molecules discussed above have been implicated in the induction and maintenance of inflammation in a number of chronic inflammatory diseases. In animal models of type 1 diabetes mellitus, MAdCAM-1 and GlyCAM-1 have been shown to be highly expressed on HEVs in inflamed pancreatic islets, and treatment of these animals with inhibitors of l-selectin and α4 integrin function blocked the development of type 1 diabetes mellitus (Chap. 403). A similar role for abnormal induction of the adhesion molecules of lymphocyte emigration has been suggested in *rheumatoid arthritis* (Chap. 358), *Hashimoto's thyroiditis* (Chap. 382), *Graves' disease* (Chap. 382), *multiple sclerosis* (Chap. 444), *Crohn's disease* (Chap. 326), and *ulcerative colitis* (Chap. 326).

Immune-Complex Formation Clearance of antigen by immune-complex formation between antigen, complement, and antibody is a highly effective mechanism of host defense. However, depending on the level of immune complexes formed and their physicochemical properties, immune complexes may or may not result in host and foreign cell damage. After antigen exposure, certain types of soluble antigen-antibody complexes freely circulate and, if not cleared

TABLE 349-11 Trafficking Molecules Involved in Inflammatory Disease Processes

		PROPOSED LEUKOCYTE RECEPTORS FOR ENDOTHELIAL TRAFFIC SIGNALS		
DISEASE	KEY EFFECTOR CELL	L-SELECTIN, LIGAND	G PROTEIN-COUPLED RECEPTOR	INTEGRIN ^a
Acute Inflammation				
Myocardial infarction	Neutrophil	PSGL-1	CXCR1, CXCR2, PAFR, BLT1	LFA-1, Mac-1
Stroke	Neutrophil	l-Selectin, PSGL-1	CXCR1, CXCR2, PAFR, BLT1	LFA-1, Mac-1
Ischemia-reperfusion	Neutrophil	PSGL-1	CXCR1, CXCR2, PAFR, BLT1	LFA-1, Mac-1
T_H1 Inflammation				
Atherosclerosis	Monocyte T _H 1	PSGL-1 PSGL-1	CCR1, CCR2, BLT1, CXCR2, CX3CR1 CXCR3, CCR5	VLA-4 VLA-4
Multiple sclerosis	T _H 1 Monocyte	PSGL-1 (?) PSGL-1 (?)	CXCR3, CXCR6 CCR2, CCR1	VLA-4, LFA-1 VLA-4, LFA-1
Rheumatoid arthritis	Monocyte T _H 1 Neutrophil	PSGL-1 PSGL-1 l-Selectin, PSGL-1	CCR1, CCR2 CXCR3, CXCR6 CXCR2, BLT1	VLA-1, VLA-2, VLA-4, LFA-1 VLA-1, VLA-2, VLA-4, LFA-1 LFA-1 ^b
Psoriasis	Skin-homing T _H 1	CLA	CCR4, CCR10, CXCR3	VLA-4 ^c , LFA-1
Crohn's disease	Gut-homing T _H 1	PSGL-1	CCR9, CXCR3	α4, β7, LFA-1
Type 1 diabetes	T _H 1 CD8	PSGL-1 (?) l-Selectin (?), PSGL-1 (?)	CCR4, CCR5 CXCR3	VLA-4, LFA-1 VLA-4, LFA-1
Allograft rejection	CD8 B cell	PSGL-1 l-Selectin, PSGL-1	CXCR3, CX3CR1, BLT1 CXCR5, CXCR4	VLA-4, LFA-1 VLA-4, LFA-1
Hepatitis	CD8	PSGL-1	CXCR3, CCR5, CXCR6	VLA-4
Lupus	T _H 1 Plasmacytoid DC B cell	None l-Selectin, CLA CLA (?)	CXCR6 CCR7, CXCR3, ChemR23 CXCR5, CXCR4	VLA-4 ^d LFA-1, Mac-1 LFA-1
T_H2 Inflammation				
Asthma	T _H 2 Eosinophil Mast cells	PSGL-1 PSGL-1 PSGL-1	CCR4, CCR8, BLT1 CCR3, PAFR, BLT1 CCR2, CCR3, BLT1	LFA-1 VLA-4, LFA-1 VLA-4, LFA-1
Atopic dermatitis	Skin-homing T _H 2	CLA	CCR4, CCR10	VLA-4, LFA-1

^aVarious β₁ integrins have been linked in different ways in basal lamina and interstitial migration of distinct cell types and inflammatory settings. ^bIn some settings, Mac-1 has been linked to transmigration. ^cCD44 can act in concert with VLA-4 in particular models of leukocyte arrest. ^dT_H2 cells require VAP-1 to traffic to inflamed liver.

Source: Reproduced with permission from AD Luster et al: Immune cell migration in inflammation: present and future therapeutic targets. Nat Immunol 6:1182, 2005.

TABLE 349-12 Complement Deficiencies and Associated Diseases

COMPONENT	ASSOCIATED DISEASES
Classic Pathway	
C1q, C1r, C1s, C4	Immune-complex syndromes, ^a pyogenic infections
C2	Immune-complex syndromes, ^a few with pyogenic infections
C1 inhibitor	Rare immune-complex disease, few with pyogenic infections
C3 and Alternative Pathway C3	
C3	Immune-complex syndromes, ^a pyogenic infections
D	Pyogenic infections
Properdin	<i>Neisseria</i> infections
I	Pyogenic infections
H	Hemolytic-uremic syndrome
Membrane Attack Complex	
C5, C6, C7, C8	Recurrent <i>Neisseria</i> infections, immune-complex disease
C9	Rare <i>Neisseria</i> infections

^aImmune-complex syndromes include systemic lupus erythematosus (SLE) and SLE-like syndromes, glomerulonephritis, and vasculitis syndromes.

Source: After JA Schifferli, DK Peters: Lancet 322:957, 1983. Copyright 1983.

by the reticuloendothelial system, can be deposited in blood vessel walls and in other tissues such as renal glomeruli and cause *vasculitis* or *glomerulonephritis* syndromes (**Chaps. 314 and 363**). Deficiencies of early complement components are associated with inefficient clearance of immune complexes and immune complex-mediated tissue damage in autoimmune syndromes, whereas deficiencies of the later complement components are associated with susceptibility to recurrent *Neisseria* infections (**Table 349-12**).

Immediate-Type Hypersensitivity Helper T cells that drive antiallergen IgE responses are usually T_H2-type inducer T cells that secrete IL-4, IL-5, IL-6, and IL-10. A subset of Tfh, Tfh13, cells have been identified that produce IL-4, IL-5, and IL-13, which play a key role in responses to allergens that induce IgE and mediate anaphylaxis. Mast cells and basophils have high-affinity receptors for the Fc portion of IgE (FcRI), and cell-bound antiallergen IgE effectively “arms” basophils and mast cells. Mediator release is triggered by antigen (allergen) interaction with Fc receptor-bound IgE, and the mediators released are responsible for the pathophysiologic changes of *allergic diseases*. Mediators released from mast cells and basophils can be divided into three broad functional types: (1) those that increase vascular permeability and contract smooth muscle (histamine, platelet-activating factor, SRS-A, BK-A), (2) those that are chemotactic for or activate other inflammatory cells (ECF-A, NCF, leukotriene B₄), and (3) those that modulate the release of other mediators (BK-A, platelet-activating factor) (**Chap. 352**).

Cytotoxic Reactions of Antibody In this type of immunologic injury, complement-fixing (C1-binding) antibodies against normal or foreign cells or tissues (IgM, IgG1, IgG2, IgG3) bind complement via the classic pathway and initiate a sequence of events similar to that initiated by immune-complex deposition, resulting in cell lysis or tissue injury. Examples of antibody-mediated cytotoxic reactions include red cell lysis in *transfusion reactions*, *Goodpasture's syndrome* with anti-glomerular basement membrane antibody formation, and *pemphigus vulgaris* with anti-epidermal antibodies inducing blistering skin disease.

Delayed-Type Hypersensitivity Reactions Inflammatory reactions initiated by mononuclear leukocytes and not by antibody alone have been termed *delayed-type hypersensitivity reactions*. The term *delayed* has been used to contrast a secondary cellular response that appears 48–72 h after antigen exposure with an *immediate* hypersensitivity response generally seen within 12 h of antigen challenge and initiated by basophil mediator release or preformed antibody.

For example, in an individual previously infected with *M. tuberculosis* organisms, intradermal placement of tuberculin purified protein derivative as a skin test challenge results in an indurated area of skin at 48–72 h, indicating previous exposure to tuberculosis.

The cellular events that result in classic delayed-type hypersensitivity responses are centered on T cells (predominantly, although not exclusively, IFN-γ, IL-2, and TNF-α-secreting T_H1-type helper T cells) and macrophages. Recently, NK cells have been suggested to play a major role in the form of delayed hypersensitivity that occurs following skin contact with immunogens. First, local immune and inflammatory responses at the site of foreign antigen upregulate endothelial cell adhesion molecule expression, promoting the accumulation of lymphocytes at the tissue site. In the scheme outlined in Fig. 349-2, antigen is processed by DCs and presented to small numbers of CD4+ T cells expressing a TCR specific for the antigen. IL-12 produced by APCs induces T cells to produce IFN-γ (T_H1 response). Macrophages frequently undergo epithelioid cell transformation and fuse to form multinucleated giant cells in response to IFN-γ. This type of mononuclear cell infiltrate is termed *granulomatous inflammation*. Examples of diseases in which delayed-type hypersensitivity plays a major role are fungal infections (*histoplasmosis*; **Chap. 212**), mycobacterial infections (*tuberculosis*, *leprosy*; **Chaps. 178 and 179**), chlamydial infections (*lymphogranuloma venereum*; **Chap. 189**), helminth infections (*schistosomiasis*; **Chap. 234**), reactions to toxins (*berylliosis*; **Chap. 289**), and hypersensitivity reactions to organic dusts (*hypersensitivity pneumonitis*; **Chap. 288**). In addition, delayed-type hypersensitivity responses play important roles in tissue damage in autoimmune diseases such as *rheumatoid arthritis*, *temporal arteritis*, and granulomatosis with polyangiitis (GPA) (**Chaps. 358 and 363**).

Autophagy Autophagy is a process that involves a lysosomal degradation pathway mechanism of cells to dispose of intracellular debris and damaged organelles. Autophagy by cells of the innate immune system is used to control intracellular infectious agents such as *M. tuberculosis*, in part by initiation of phagosome maturation and enhancing MHC class II antigen presentation to CD4 T cells.

CLINICAL EVALUATION OF IMMUNE FUNCTION

Clinical assessment of immunity requires investigation of the four major components of the immune system that participate in host defense and in the pathogenesis of autoimmune diseases: (1) humoral immunity (B cells); (2) cell-mediated immunity (T cells, monocytes); (3) phagocytic cells of the reticuloendothelial system (macrophages), as well as polymorphonuclear leukocytes; and (4) complement. Clinical problems that require an evaluation of immunity include chronic infections, recurrent infections, unusual infecting agents, and certain autoimmune syndromes. The type of clinical syndrome under evaluation can provide information regarding possible immune defects (**Chap. 351**). Defects in cellular immunity generally result in viral, mycobacterial, and fungal infections. An extreme example of deficiency in cellular immunity is AIDS (**Chap. 197**). Antibody deficiencies result in recurrent bacterial infections, frequently with organisms such as *S. pneumoniae* and *Haemophilus influenzae* (**Chap. 351**). Disorders of phagocyte function are frequently manifested by recurrent skin infections, often due to *Staphylococcus aureus* (**Chap. 64**). Finally, deficiencies of early and late complement components are associated with autoimmune phenomena and recurrent *Neisseria* infections (Table 349-12). **For further discussion of useful initial screening tests of immune function, see Chap. 351.**

IMMUNOTHERAPY

Many therapies for autoimmune and inflammatory diseases involve the use of nonspecific immune-modulating or immunosuppressive agents such as glucocorticoids or cytotoxic drugs. The goal of development of new treatments for immune-mediated diseases is to design ways to specifically interrupt pathologic immune responses, leaving nonpathologic immune responses intact (**Chap. 350**). Novel ways to interrupt pathologic immune responses that are under investigation include the use of anti-inflammatory cytokines or specific cytokine inhibitors as

anti-inflammatory agents, the use of monoclonal antibodies against T or B lymphocytes as therapeutic agents, the use of intravenous Ig for certain infections and immune complex-mediated diseases, the use of specific cytokines to reconstitute components of the immune system, and bone marrow transplantation to replace the pathogenic immune system with a more normal immune system (**Chaps. 64, 202, 350, and 351**). CTLA-4 inhibitors such as ipilimumab and tremelimumab and anti-PD-1 antibodies such as nivolumab have been shown to reverse CD8 T-cell exhaustion in melanoma and other solid tumors and induce immune cell control of tumor growth (**Chap. 350**). A new technique that engineers autologous T cells to express antibody receptors that target leukemic cells, termed *chimeric antigen receptor T cells* (CAR T cells), has been approved by the U.S. Food and Drug Administration (FDA) for the treatment of certain types of leukemias and lymphomas (**Chap. 350**).

Cell-based therapies have been studied for many years, including ex vivo activation of NK cells for reinfusion into patients with malignancies, and DC therapy of ex vivo priming of DCs for enhanced presentation of cancer antigens, with reinfusion of primed DCs into the patient. One such strategy for DC therapy has been approved by the FDA for treatment of advanced prostate cancer.

Cytokines and Cytokine Inhibitors Several TNF inhibitors are used as biological therapies in the treatment of rheumatoid arthritis; these include monoclonal antibodies, TNF-R Fc fusion proteins, and Fab fragments. Use of anti-TNF- α antibody therapies such as adalimumab, infliximab, and golimumab has resulted in clinical improvement in patients with these diseases and has opened the way for targeting TNF- α to treat other severe forms of autoimmune and/or inflammatory disease (**Chap. 350**). Blockage of TNF- α has been effective in *rheumatoid arthritis*, *psoriasis*, *Crohn's disease*, and *ankylosing spondylitis*. Other cytokine inhibitors are recombinant soluble TNF- α receptor (R) fused to human Ig and anakinra (soluble *IL-1 receptor antagonist*, or IL-1ra). The treatment of autoinflammatory syndromes (Table 349-5) with recombinant IL-1 receptor antagonist can prevent symptoms in these syndromes, because the overproduction of IL-1 β is a hallmark of these diseases.

TNF- α -Fc fusion protein (etanercept) and IL-1ra act to inhibit the activity of pathogenic cytokines in rheumatoid arthritis, i.e., TNF- α and IL-1, respectively. Similarly, anti-IL-6, IFN- β , and IL-11 act to inhibit pathogenic proinflammatory cytokines. Anti-IL-6 (tocilizumab) inhibits IL-6 activity, whereas IFN- β and IL-11 decrease IL-1 and TNF- α production (**Chap. 350**). Of particular note has been the successful use of IFN- γ in the treatment of the phagocytic cell defect in *chronic granulomatous disease* (**Chap. 64**).

T_H17 CD4 T cells have been implicated in the pathogenesis of psoriasis, ulcerative colitis, and other autoimmune diseases. Monoclonal antibodies have now been developed that target cytokines (IL-12, IL-23) that induce T_H17 T-cell differentiation and are licensed by the FDA for treatment of psoriasis. Monoclonal antibodies that directly target IL-17 have also recently been licensed for psoriasis and psoriatic arthritis treatment. Monoclonal antibodies against cytokines and immunoregulatory molecules are now mainstays of cancer and autoimmune disease therapy (**Chap. 350**).

Intravenous Immunoglobulin (IVIg) IVIg has been used successfully to block reticuloendothelial cell function and immune complex clearance in various immune cytopenias such as immune thrombocytopenia (**Chap. 115**). In addition, IVIg is useful for prevention of tissue damage in certain inflammatory syndromes such as Kawasaki disease (**Chap. 363**) and as Ig replacement therapy for certain types of immunoglobulin deficiencies (**Chap. 351**). In addition, controlled clinical trials support the use of IVIg in selected patients with graft-versus-host disease, multiple sclerosis, myasthenia gravis, Guillain-Barré syndrome, and chronic demyelinating polyneuropathy.

Stem Cell Transplantation Hematopoietic stem cell transplantation (SCT) is now being comprehensively studied to treat several autoimmune diseases including systemic lupus erythematosus, multiple sclerosis, and scleroderma. The goal of immune reconstitution in

autoimmune disease syndromes is to replace a dysfunctional immune system with a normally reactive immune cell repertoire. Preliminary results in patients with scleroderma and lupus have showed encouraging results. Controlled clinical trials in these three diseases are now being launched in the United States and Europe to compare the toxicity and efficacy of conventional immunosuppression therapy with that of myeloablative autologous SCT. Recently, SCT was used in the setting of HIV-1 infection. HIV-1 infection of CD4+ T cells requires the presence of surface CD4 receptor and the chemokine receptor 5 (CCR5) co-receptor. Studies have demonstrated that patients who are homozygous for a 32-bp deletion in the CCR5 allele do not express CD4+ T-cell CCR5 and thus are resistant to HIV-1 infection with HIV-1 strains that use this co-receptor. Stem cells from a homozygous CCR5 delta32 donor were transplanted to an HIV-1-infected patient following standard conditioning for such transplants, and the patient has maintained long-term control of the virus without antiretrovirals. Thus, a number of recent insights into immune system function have spawned a new field of interventional immunotherapy and have enhanced the prospect for development of more specific and nontoxic therapies for immune and inflammatory diseases (**Chap. 350**).

FURTHER READING

- Altan-Bonnet G, Mukherjee R: Cytokine-mediated communication: A quantitative appraisal of immune complexity. *Nat Rev Immunol* 19:205, 2020.
- Dupage M, Bluestone JA: Harnessing the plasticity of CD4+T cells to treat immune-mediated disease. *Nat Rev Immunol* 3:149, 2016.
- McLean KC, Mandal M: It takes three receptors to raise a B cell. *Trends Immunol* 41:629, 2020.
- Mulay SR, Anders HJ: Crystallopathies. *N Engl J Med* 374:25, 2016.
- Netea MG et al: Defining trained immunity and its role in health and disease. *Nat Rev Immunol* 20:375, 2020.
- Pelluccio DG et al: Thymic development of unconventional T cells: How NKT, cells MAIT cells and $\gamma\delta$ T cells emerge. *Nat Rev Immunol* 20:756, 2020.
- Puleendran B: Immunology taught by vaccines. *Science* 366:1074, 2019.
- Ratner D et al: Bacterial secretion systems and regulation of inflammasome activation. *J Leuk Bio* 101:165, 2017.
- Vivier E et al: Innate lymphoid cells: 10 years on. *Cell* 174:1054, 2018.
- Yang F et al: The diverse biological functions of neutrophils, beyond the defense against infections. *Inflammation* 40:311, 2017.

350

Mechanisms of Regulation and Dysregulation of the Immune System

Barton F. Haynes, Kelly A. Soderberg,
Anthony S. Fauci

DEFINITIONS

Anergy—A reversible tolerance mechanism in which the T or B cell is in an unresponsive state following an antigen encounter but remains alive.

Chimeric antigen receptor T cells (CAR T)—Synthetic hybrid receptors created by recombinant techniques that combine an extracellular domain, usually derived from an antibody single-chain variable fragment (scFv), with intracellular signaling domains from activating co-stimulatory molecules (from endogenous T-cell receptors

[TCRs], CD28, or 4-1BB) that allow for retargeting of T cells to antigens on malignant cells.

Checkpoint inhibition therapy—A form of cancer immunotherapy whereby antibodies against T-cell or antigen-presenting cell regulators of immune cell inhibition are used to activate cytotoxic T cells to kill tumor cells.

Co-stimulation of T cells—A secondary signal that T cells require for activation following presentation of peptide antigen by major histocompatibility complex (MHC) molecules to TCRs on either CD4 or CD8 T cells. A prime mediator of co-stimulation is the T cell CD28 molecule binding to B7-1 (CD80, CD86) on antigen-presenting cells.

Cytokines—Soluble proteins that interact with specific cellular receptors that are involved in the regulation of the growth and activation of immune cells and mediate normal and pathologic inflammatory and immune responses.

Immune homeostasis—Balanced protective immunity that does not overreact to pathogens and harm the host, and immunity that is not deficient and does not predispose the host to harmful infections or malignancies.

Immunoediting—Process of immunity selecting clones of cancer cells with reduced immunogenicities resulting in tumor escape.

Natural killer cells—Lymphocytes with cytotoxic potential for host cells with non-self-antigens, such as cells infected with pathogens or tumor cells expressing tumor-specific neoantigens.

T-cell exhaustion—State of T cells when the persistence of antigen disrupts memory T-cell function, resulting in defects in memory T-cell responses. Most frequently occurs in malignancies and in chronic viral infections such as HIV-1 and hepatitis C.

T regulatory cells (Tregs)—CD4 and CD8 T cells regulated by the transcription factor FOXP3 that play roles in downmodulating B- and T-cell responses in peripheral lymphoid tissues to prevent deleterious immune activation that can lead to autoimmune diseases.

Tumor-infiltrating lymphocytes—Lymphocytes that infiltrate tumors that may be in the exhausted state and upon which checkpoint inhibition therapy works.

Tumor neoantigens—Molecules in malignant cells that develop mutations that create non-self-antigens that are recognized by host T cells as non-self and against which tumor-infiltrating CD4 and CD8 T cells respond to reject the tumor.

INTRODUCTION

Immune homeostasis is the maintenance of a balance between immunity that protects the host and dysregulated immunity that predisposes the host to harmful infections, autoimmunity, or malignancies. Overactivity of innate and adaptive immunity leads to autoimmunity and/or inflammatory diseases. Underactivity of immune responses can lead to both immune deficiency and autoimmunity. Disruption of immune homeostasis contributes either directly or indirectly to many forms of disease. Thus, a major goal of immunotherapy is to either maintain immune homeostasis or reestablish immune balance in diseases of immune dysregulation.

This is an important time in the study of the biology of the immune system. The development of high-throughput genome sequencing, full genome transcriptome analysis, proteomics, metabolomics, and the realization of the importance of the human microbiome to immune system homeostasis have provided remarkable opportunities for development of new treatments for immune-mediated and malignant diseases. The emerging concept is that the immune system itself can be manipulated to be used as a therapeutic intervention for cancer and also can be safely manipulated for control of autoimmune disease. Moreover, new data are emerging that immune dysregulation is involved in the pathogenesis of diseases not traditionally thought of as immune-related, such as neurodegenerative diseases and atherosclerotic cardiovascular disease, and that the normal process of aging is associated with inflammatory processes.

Thus, a new frontier of medicine is to understand basic regulatory mechanisms of the innate and adaptive immune system with the goal of learning specific rules of immune system regulation, such that

eventually the immune system can be “tuned” to safely stay in the zone of immune homeostasis and, at the same time, effectively protect against emerging and reemerging infectious diseases or eliminate malignancies as they arise. Moreover, when inflammatory or autoimmune diseases arise, effective strategies of immune regulation can be developed to safely treat them.

Thus, this chapter builds on [Chap. 349, Introduction to the Immune System](#), to discuss T- and B-cell immunoregulation, to highlight recent successes in translating basic immunologic research into treatments of various hematopoietic and solid tumors, and to discuss mechanisms of immune dysregulation in autoimmunity and aging.

MECHANISMS OF REGULATION OF T-CELL ACTIVATION

Key roles of T cells are to respond to and eliminate cells bearing foreign antigens and to ignore cells expressing self-antigens. To respond to foreign antigens, stimulating cells must deliver an activating co-stimulatory signal in addition to TCR ligation. To avoid responding to cells bearing self-antigens, T cells must also maintain immune tolerance. Central T-cell tolerance is maintained by autoreactive T-cell deletion in the thymus, while peripheral tolerance is maintained by regulatory T cells (Treg), T-cell anergy, and peripheral clonal deletion (see section below, Mechanisms of Immune Dysregulation in Autoimmune Disease). Thus, T-cell activation is an integral component of the adaptive immune response to pathogens as well as to tumor neoantigens.

Two stimulatory signals are required for T-cell activation. One T-cell signal is delivered by antigen peptide presented in the context of MHC ([Chap. 349](#)). However, in the absence of a co-stimulating signal, the T cell will not be activated by peptide MHC alone but rather will become anergic or unresponsive. A second co-stimulatory signal is needed for T-cell activation, resulting in cytoskeletal remodeling, production of cytokines, and cell survival and differentiation. In addition to the TCR/CD3 complex ([Chap. 349](#)), T cells express a complex array of co-stimulatory as well as inhibitory molecules that bind to their respective receptors on the surface of antigen-presenting cells (APCs) and orchestrate both initiation and control of T-cell activation to maintain immune homeostasis ([Fig. 350-1, and see Chap. 349, Table 349-1](#)). Of these, CD28, cytotoxic T lymphocyte antigen 4 (CTLA-4), and programmed cell death protein 1 (PD-1) and their ligands were among the first to be recognized to be central to control of T-cell activation.

The CD28 molecule is a member of the immunoglobulin (Ig) superfamily and is the original member of a subfamily of co-stimulatory or inhibitory molecules on the surface of T cells that includes CTLA-4, inducible T-cell costimulator (ICOS), PD-1, T-cell immunoreceptor with Ig and ITIM domains (TIGIT), and B- and T-cell attenuator (BTLA) ([Fig. 350-1](#)). CD28 stimulates intracellular signaling through AKT and PI3 kinase, resulting in induction of NF- κ B, AP-1, and NFAT, which are all critical for T-cell activation and differentiation ([Chap. 349, Fig. 349-7](#)). CTLA-4 and PD-1 are CD28 subfamily members that control T-cell activation by inhibiting the stimulating activity of CD28 and other T-cell co-stimulatory molecules.

CTLA-4 is a key negative regulator of T-cell activation that down-modulates the T-cell response to antigen by interaction with its ligands, B7-1 and B7-2, to control unchecked T-cell proliferation. CTLA-4 is upregulated following TCR engagement with MHC/peptide, thus dampening TCR signaling by competing with CD28 binding to B7 ligands (B7-1 [CD80] and B7-2 [CD86]) on APCs by virtue of higher affinity of CTLA-4 for B7 ligands. In this manner, T cells respond to foreign antigen but are prevented from damaging host tissues due to overexuberant responses ([Fig. 350-2A](#)). CTLA-4 thus mediates its dampening effect on T-cell activation by competing with T-cell CD28 binding to B7 receptors, as well as through the suppressive effect of CTLA-4+ Tregs. The human *CTLA4* gene is just one of several genes in which monogenetic mutations are associated with decreased Treg function and autoimmune syndromes ([Table 350-1](#)).

PD-1 is also a major inhibitory molecule of T-cell activation by interaction with its ligands PD-L1 and PD-L2 on APCs ([Fig. 350-1](#)).

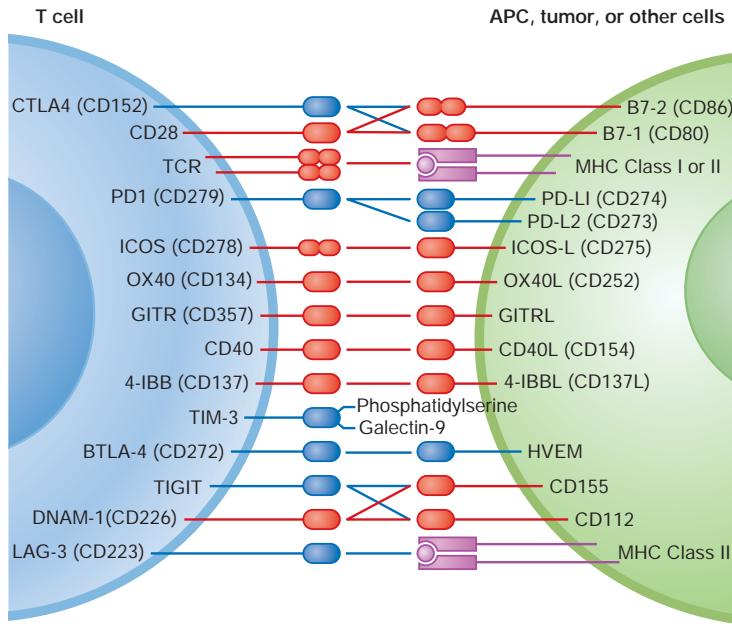


FIGURE 350-1 Regulatory stimulating or inhibiting molecules on T cells or antigen-presenting cells (APCs), tumor cells, or other cells.

While initially thought to be a cell death receptor, PD-1 is rapidly expressed upon activation of T and B cells and is also a marker of T follicular helper CD4+ T cells in B-cell germinal centers. PD-1 acts to dampen T-cell activation by dephosphorylation of CD28 via the Src homology region 2-containing protein tyrosine phosphatase 2 (SHP2).

Although a marker of immune cell activation, PD-1 is also a marker for exhausted T cells. T-cell exhaustion is an important mechanism of maintaining immune homeostasis and preventing host tissue T-cell damage, but also leads to immune dysfunction in the setting of chronic antigenic stimulation such as occurs in chronic viral diseases (HIV-1, hepatitis C) and in cancer. Chronic viral diseases and tumors lead to transcriptional and metabolic signatures that define the exhausted T-cell state. T-cell exhaustion has been a major roadblock to overcome for successful cancer immunotherapy.

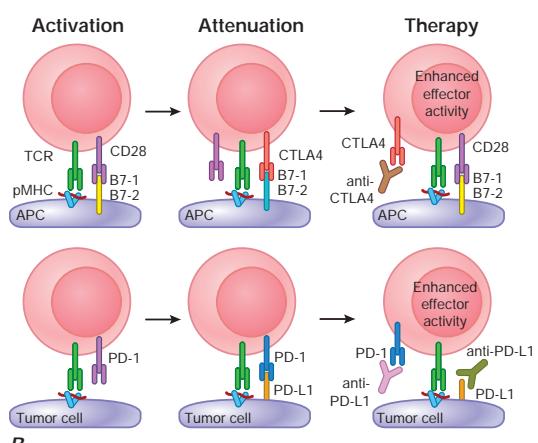
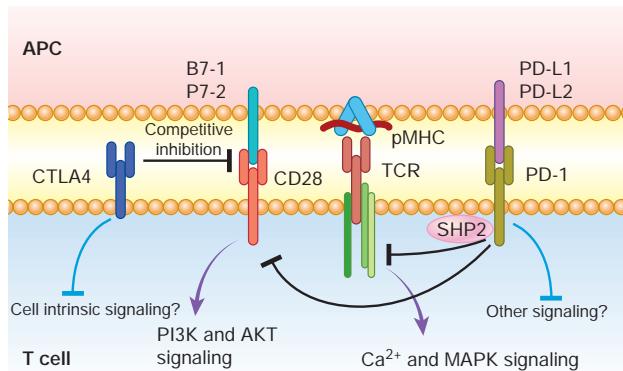
CHECKPOINT INHIBITION THERAPY FOR CANCER

The field of immune checkpoint therapy has joined surgery, radiation, chemotherapy, and targeted therapy as a mainstay for cancer therapy. There are now an extensive number of therapeutic monoclonal antibodies approved by the U.S. Food and Drug Administration (FDA), initially starting with melanoma in 2011–2014 and now available for a wide range of malignancies including kidney, lung, liver, head and neck, and gastric tumors (Table 350-2). Both CTLA-4 and PD-1 blockade have proved remarkably successful in treating a number of tumors, but only in a fraction of patients. Because each receptor-ligand pair regulates distinct T-cell inhibitory pathways, combination therapy using anti-PD-1 and anti-CTLA-4 antibodies has been especially useful and has induced significant tumor regression in ~50% of melanoma patients. What is different in the use of checkpoint inhibitor antibodies is that the therapy is not targeted to the tumor per se, but rather is targeted to immunoregulatory molecules on host T cells. Moreover, therapy is not targeted to specific molecules on tumors, but rather is targeted to release exhausted tumor-infiltrating T cells (TILs) to be activated to kill tumor cells by removing immune regulatory inhibition.

CTLA-4 induces tumor rejection by a number of mechanisms. First, anti-CTLA-4 antibody mediates direct blockade of CTLA-4 competition with CD28 for B7-1 and B7-2 co-stimulatory ligands, thus allowing CD28-mediated T-cell activation (Fig. 350-2B). Tumor

cells do not express B7 molecules; thus, CTLA-4 blockade likely occurs in tumor-draining lymph nodes where exhausted T cells interact with APCs presenting tumor neoantigens to T cells. A second mechanism of CTLA-4 blockade-induced tumor rejection is depletion or reduction in suppressive effects of Tregs. Suppressive effect of Tregs include secretion of immunosuppressive cytokines such as transforming growth factor (TGF)- β or interleukin (IL) 10 or by direct inhibition of T-cell proliferation and/or cytolytic activity. A third potential mechanism of anti-CTLA-4 antibody are restricted primarily to tumor neoantigen-specific CD8 T cells within the tumor microenvironment and not to T cells in lymph nodes or spleen.

PD-1 blockade by PD-1 antibody also induces tumor regression by reversing T-cell exhaustion, leading to enhanced T-cell killing



A

FIGURE 350-2 Molecular mechanisms of CTLA-4 and PD-1 attenuation of T-cell activation and schematic of the molecular mechanisms of action of CTLA-4 and PD-1. **A.** Schematic of the molecular interactions and downstream signaling induced by ligation of CTLA-4 and PD-1 by their respective ligands. The possibility of additional downstream cell-intrinsic signaling mechanisms is highlighted for both CTLA-4 and PD-1. **B.** The stepwise progression of T-cell activation, attenuation by normal regulatory mechanisms, and release of such negative regulation by therapeutic intervention using anti-CTLA-4 or anti-PD-1 antibodies is outlined. (Reprinted from SC Wei et al: Fundamental mechanisms of immune checkpoint blockade therapy. *Cancer Discov* 8:1069, 2018, with permission from AACR.)

TABLE 350-1 Monogenetic Mutations That Lead to Immune Dysregulation and Autoimmunity

MUTATIONS AND FUNCTIONAL DEFICITS	DISEASES OR SYNDROME
RAG1, RAG2: lymphopenia with recombinase deficiency	Severe combined immune deficiency (Omenn's syndrome) with autoreactive T cells
Fas, FasL, CASP10: apoptosis defects	Autoimmune lymphoproliferative disease
AIRE, deletion chromosome 22q11.2; decrease in central tolerance	Ch. 22q11.2: DiGeorge's syndrome with autoimmune T cells AIRE: autoimmunity, polyneuropathy, candidiasis, ectodermal dysplasia (APECED syndrome)
FOXP3, CD25, CTLA-4, LRBA: decrease in peripheral immune tolerance with decrease in Treg function	FOXP3: IPEX syndrome (immune dysregulation, polyendocrinopathy, enteropathy, X-linked) CD25: enteropathy, dermatitis, autoimmunity, susceptibility to infections CTLA-4: associated with multiple autoimmune syndromes LRBA: infant with enteritis; hypogammaglobulinemia, autoimmune cytopenias
STAT-1, STAT-3: modulation of type 1 interferons	STAT-1 deficiency: decreased IFN- γ , susceptible to TB STAT-1 gain of function: chronic mucocutaneous candidiasis with autoimmune diseases STAT-3 deficiency: hyper-IgE syndrome (Job's syndrome) STAT-3 gain of function: lymphopenia, autoimmune cytopenias, diabetes, enteropathy
C1q, C1r/s, C2, C4; complement deficiencies	Systemic lupus erythematosus (SLE)
Fc RII, Fc RIII, C-reactive protein, complement receptor for C3b (ITGAM or complement receptor 3), COPA, tripeptidyl peptidase; lack of removal of cell debris	Fc II, Fc III, CRP, complement receptor for C3b: systemic lupus erythematosus COPA: autoimmune lung, renal, joint disease Tripeptidyl peptidase II: susceptibility to bacterial, viral, and fungal pathogens
Phosphoinositide-3-kinase delta (PI3K), phospho-lipase C 2, protein kinase C (PKC) deficiency, protein kinase C (PKC) deficiency: hyperactivation of lymphocytes	PI3K: lymphoproliferation, respiratory infections, hypogammaglobulinemia Phospholipase C 2: cold urticaria, antibody deficiency, autoimmunity PKC: early-onset SLE with decreased B-cell apoptosis, autoantibody-mediated renal disease and lymphoproliferation
Activation-induced cytidine deaminase (AID): class-impaired B-cell development	Hyper IgM syndrome type 2, low IgA, IgG, recurrent bacterial switch recombination; infections, autoimmune cytopenias, SLE

Abbreviations: APECED, autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy; AIRE, autoimmunity regulator; COPA, gene encodes the non-clathrin-coated vesicular coat protein; COP-alpha: CTLA-4, cytotoxic T lymphocyte associated protein-4; Fc γ R, Fc γ receptor; FOXP3, forkhead box P3; IFN, interferon; ITGAM, integrin alpha M; LRBA, lipopolysaccharide (LPS)-responsive and beige-like anchor protein; RAG, recombinase activating gene; STAT, signal transducer and activator of transcription; TB, tuberculosis; Treg, T regulatory cell.

Source: B Grimbacher et al: The crossroads of autoimmunity and immunodeficiency: Lessons from polygenic traits and monogenic defects. *J Allergy Clin Immunol* 137:3, 2016.

of tumor cells. Optimal PD-1 antibody-mediated checkpoint inhibition is seen when infiltrating CD8 T cells are present in the tumor microenvironment and reversal of the exhausted T-cell state can occur *in situ*. PD-1 blockade can also act by reversal of metabolic reprogramming of exhausted T cells, leading to enhanced cytolytic T-cell effector function. Antibodies to the primary PD-1 receptor, PD-L1, are also sufficient to induce reversal of T-cell exhaustion and induce tumor killing and are approved by the FDA for treatment of non-small-cell lung cancer (Table 350-2). PD-L1 is induced on tumor cells by T_H1 cytokines, which may explain anti-PD-L1 efficacy since T_H1 cytokines drive cytotoxic T-cell responses (Chap. 349). Efficacy of anti-PD-L1 may also be due in part to mediation of antibody-dependent cellular cytotoxicity (ADCC) killing of tumor cells (Chap. 349).

Tumor cells express neoantigens that are targets for T-cell recognition in the tumor microenvironment. Immune pressure within the tumor microenvironment can select for tumor cells that present few or mutated neoantigens and thus escape ongoing antitumor immunity. Moreover, a low number of tumor-infiltrating lymphocytes, tumor microenvironment production of immunosuppressive indoleamine 2,3-dioxygenase (IDO), and tumor infiltration with either myeloid-derived suppressor cells or Tregs can also limit checkpoint blockade therapy.

Other strategies for improving the immunoregulation of antitumor responses include combinations of anti-PD-1, anti-CTLA-4, or anti-PD-L1 antibodies with other checkpoint inhibitors (see Chap. 349, Table 349-1, and Fig. 350-1). For example, engagement of the ICOS pathway enhances the efficacy of CTLA-4 blockade in animal models of cancer immunotherapy. T-cell immunoglobulin and mucin-domain containing-3 (TIM-3), TIGIT, or lymphocyte-activation gene 3 (LAG-3) inhibition has been suggested to enhance checkpoint inhibition and augment CD8 tumor cell killing. A new transcription factor, thymocyte-selection-associated high mobility box (TOX), has been defined as a key controller of CD8 T-cell exhaustion. Thus, TOX inhibition could synergize with checkpoint inhibition therapy to reverse the T-cell exhaustion state. Finally, the combination of checkpoint inhibition with other cancer treatments including chemotherapy, radiation, tumor signaling pathway inhibitors, and epigenetic modulators is being tested.

Anti-PD-L1 antibodies also mediate antitumor effects by ADCC, which utilizes natural killer (NK) effector cells (Chap. 349). Indeed, a number of checkpoint inhibitor molecules have been found to be expressed on NK cells including CTLA-4, PD-1, LAG-3, TIGIT, and TIM-3 (Fig. 350-1; see also Chap. 349, Table 349-1). A new field of work is to target NK cells with existing checkpoint inhibitors and with antibodies against an NK-specific inhibitory molecule, NKG2A, that are designed to release NK cells to kill tumor cells. One such anti-NKG2A antibody, monalizumab, has entered human clinical trials. NK cells also express natural cytotoxicity-activating receptors including NKP30, NKP44, and NKP46 receptors (Chap. 349). Engagement of natural cytotoxicity-activating receptors in concert with the NK Fc RIII (CD16) and antibody against a tumor antigen also can enhance NK cell targeting of tumor antigens and is in preclinical development.

CHIMERIC ANTIGEN RECEPTOR T CELLS

Chimeric antigen receptor (CAR) T cells are synthetic hybrid receptors created by recombinant techniques that combine an extracellular domain, usually derived from an antibody single-chain variable fragment (scFv), with intracellular signaling domains from activating co-stimulatory molecules (from endogenous TCRs, CD28, or 4-1BB) that allow for retargeting of T cells to antigens on malignant cells (Fig. 350-3). A CAR T cell targeting the CD19 molecule on malignant B cells provided the first and most promising therapeutic results in the treatment of B-cell malignancies, with complete response rates of 70–90%. CAR T cells targeting the NY-ESO antigen on sarcoma cells have induced remissions in patients with synovial cell sarcoma. CAR T cells targeting B-cell maturation antigen (BCMA) on myeloma cells have also induced clinical responses. The CAR T-cell strategy is being developed for targeting solid tumors and modified as universal CAR T cells to overcome the need for MHC matching with T CAR recipients. One such strategy is to modify T cells to release cytokine, express co-stimulatory ligands, or secrete checkpoint-blocking single-chain variable fragment (scFvs). The next generation of CAR T cells are known as T cells redirected for universal cytokine-mediated killing (TRUCKs). Cytokine-secreting tumor-specific T cells could harness

TABLE 350-2 Summary of the Tumor Types for Which Immune Checkpoint Blockade Therapies Are Approved by the U.S. Food and Drug Administration (FDA)

TUMOR TYPE	THERAPEUTIC AGENT	TARGET	FDA APPROVAL YEAR
Melanoma	Ipilimumab	CTLA-4	2011
Melanoma	Nivolumab	PD-1	2014
Melanoma	Pembrolizumab	PD-1	2014
Non-small-cell lung cancer	Nivolumab	PD-1	2015
Non-small-cell lung cancer	Pembrolizumab	PD-1	2015
Melanoma (<i>BRAF</i> wild-type)	Ipilimumab + nivolumab	CTLA-4 + PD-1	2015
Melanoma (adjuvant)	Ipilimumab	CTLA-4	2015
Renal cell carcinoma	Nivolumab	PD-1	2015
Hodgkin's lymphoma	Nivolumab	PD-1	2016
Urothelial carcinoma	Atezolizumab	PD-L1	2016
Head and neck squamous cell carcinoma	Nivolumab	PD-1	2016
Head and neck squamous cell carcinoma	Pembrolizumab	PD-1	2016
Melanoma (any <i>BRAF</i> status)	Ipilimumab + nivolumab	CTLA-4 + PD-1	2016
Non-small-cell lung cancer	Atezolizumab	PD-L1	2016
Hodgkin's lymphoma	Pembrolizumab	PD-1	2017
Merkel cell carcinoma	Avelumab	PD-L1	2017
Urothelial carcinoma	Avelumab	PD-L1	2017
Urothelial carcinoma	Durvalumab	PD-L1	2017
Urothelial carcinoma	Nivolumab	PD-1	2017
Urothelial carcinoma	Pembrolizumab	PD-1	2017
MSI-high or MMR-deficient solid tumors of any histology	Pembrolizumab	PD-1	2017
MSI-high, MMR-deficient metastatic colorectal cancer	Nivolumab	PD-1	2017
Pediatric melanoma	Ipilimumab	CTLA-4	2017
Hepatocellular carcinoma	Nivolumab	PD-1	2017
Gastric and gastroesophageal carcinoma	Pembrolizumab	PD-1	2017
Non-small-cell lung cancer	Durvalumab	PD-L1	2018
Renal cell carcinoma	Ipilimumab + nivolumab	CTLA-4 + PD-1	2018

Note: A summary of the tumor indications, therapeutic agents, and year of FDA approval for immune checkpoint blockade therapies. FDA approval includes regular approval and accelerated approval granted as of May 2018. Ipilimumab is an anti-CTLA-4 antibody. Nivolumab and pembrolizumab are anti-PD-1 antibodies. Atezolizumab, avelumab, and durvalumab are anti-PD-L1 antibodies. Tumor type reflects the indications for which treatment has been approved. Only the first FDA approval granted for each broad tissue type or indication for each therapeutic agent is noted. In cases where multiple therapies received approval for the same tumor type in the same year, agents are listed alphabetically.

Abbreviations: BRAF, v-raf murine sarcoma viral oncogene, homolog B1; MMR, mismatch repair; MSI, microsatellite instability.

Source: Reprinted from SC Wei et al: Fundamental mechanisms of immune checkpoint blockade therapy. *Cancer Discov* 8:1069, 2018, with permission from AACR.

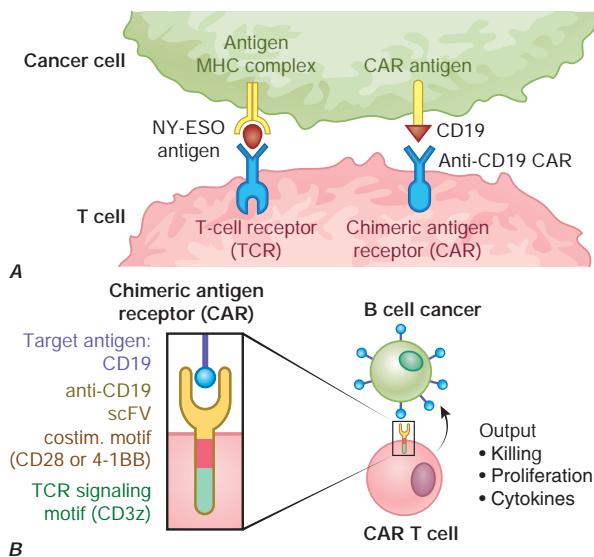


FIGURE 350-3 Platforms for redirecting T cells to cancer. A T-cell receptors (TCRs; e.g., anti-NY-ESO1) or chimeric antigen receptors (CARs; e.g., anti-CD19 CAR). **B**, CAR structure includes an extracellular antigen recognition domain fused to intracellular TCR signaling domains (CD3z) and co-stimulatory domains (e.g., CD28 or 4-1BB). (Reproduced with permission from WA Lim, CH June: The principles of engineering immune cells to treat cancer. *Cell* 168:724, 2017.)

the adjuvant effect of recombinant cytokines by local delivery to the tumor to decrease cytokine side effects of excess inflammation, termed **cytokine release syndrome**, that can be seen with CAR T-cell therapy.

MECHANISMS OF IMMUNE DYSREGULATION IN AUTOIMMUNE DISEASE

Autoimmune diseases occur in ~5% of people and are caused by immune dysregulation from breakdowns in immune tolerance. A complex array of immune checkpoints are involved in the maintenance of immune homeostasis and, when mutated, can result in autoimmune syndromes (Tables 350-1 and 350-3). Central tolerance for deletion of autoreactive T cells or modification of their TCRs occurs in the thymus, and for B cells with self-reactive B-cell receptors, central deletion occurs in bone marrow. Peripheral tolerance occurs in lymph nodes, spleen, and tissue-associated lymphoid tissue such as gastrointestinal tract Peyer's patches. The sites and modes of peripheral tolerance are varied and reflect the complex cellular and cytokine interactions that occur in mediation of T- and B-cell adaptive immunity (Chap. 349). While B- and T-cell deletion can occur in the periphery, tolerance can also occur with cell inactivation termed **anergy**, a state of immune responsiveness following contact with antigen. T- and B-cell responses are also dampened in the periphery by Tregs producing TGF-β and IL-10. The result of immune dysregulation in autoimmune disease is the production of a myriad of antibodies against self-antigens (autoantibodies), many of which are pathogenic for the clinical manifestations of the autoimmune disease (see Chap. 349, Table 349-10).

TABLE 350-3 Immune Tolerance Checkpoints in T- and B-Cell Immunity

CENTRAL TOLERANCE	PERIPHERAL TOLERANCE
THYMUS	PERIPHERAL LYMPHOID TISSUES
- TCR editing by V(D)J	- B and T cell anergy and inhibitory signaling (CTLA-4, PD-1 and other checkpoint molecules)
- Thymic negative selection	- TCR or BCR induction of BIM
- T cell anergy and inhibitory signaling	- T cell competition for IL-2, IL-7, IL-15 and peptide-MHC
- T regulatory cell differentiation	- B cell competition for survival cytokine BAFF
	- T cell growth dependence on CD28 ligands and other co-stimulatory molecules
	- Elimination of antigen-bearing dendritic cells by activated T cells producing perforin or FasL
	- Suppression of T and B cell responses by T regulatory cells and TGF β , IL-10
	- T cell death by FasL
	- Regulation of T follicular helper cell differentiation and function
BONE MARROW	- B cell growth dependence on BCR ligands
- Immature B cell maturation arrest	- B cell growth dependence on TCR ligands
- BCR editing by V(D)J recombination	- B cell death by FasL on T cells
- Immature B cell deletion	- BCR modulation of plasma cell differentiation
	- BCR-induced death of germinal center B cells
	- Germinal center B cell dependence on T follicular helper cells (CD40L, IL-21)

Abbreviations: BAFF, B cell activating factor; BCR, B cell receptor; BIM, Bcl-2-like protein 11; Fas; TGF β = T cell growth factor beta; FasL = Fas ligand that binds to the death receptor; MHC, major histocompatibility complex; TCR, T cell receptor; V(D)J, variable, diversity, joining regions of antibody V region.

Source: Adapted from CG Goodnow: Multistep pathogenesis of autoimmune disease. *Cell* 130:25, 2007.

Tregs are CD4 and CD8 T cells that downmodulate B- and T-cell responses in peripheral lymphoid tissues to prevent autoimmune diseases, and the transcriptional regulator FOXP3 is centrally involved in the establishment of the Treg phenotype. Mutations in genes that lead to loss of Tregs or their function result in autoimmune and inflammatory syndromes (Table 350-1). Mutations in FOXP3 lead to an X-linked syndrome characterized by immune dysregulation, polyendocrinopathy, and enteropathy (IPEX). Similarly, mutations in the CD25 (IL-2 receptor γ) molecule expressed on Tregs lead to enteropathy, dermatitis, other manifestations of autoimmunity, and susceptibility to infections. Mutations in the checkpoint inhibitor T-cell molecule CTLA-4—also expressed on Tregs—leads to loss of Treg function and results in multiple autoimmune syndromes in humans depending on the CTLA-4 mutation. In mice, knockout of the *ctla4* gene leads to massive uncontrolled lymphoproliferation and early death. Finally, mutations in the lipopolysaccharide (lipopolysaccharide-responsive and beige-like anchor [LRBA]) protein cause a syndrome in infants characterized by enteritis, hypogammaglobulinemia, and autoimmune cytopenias.

Chronic viral infections can perturb Treg number and function. In HIV-1 infection, chronic antigenic stimulation leads to shifts in the B-cell repertoire toward an autoimmune permissive state, with increased numbers of autoreactive B cells and decreased CD4+ Tregs leading to serum autoantibodies or clinical manifestations of autoimmune disease in ~50% of untreated HIV-1-infected individuals.

In addition to checkpoint inhibition for cancer immunotherapy, monoclonal antibodies can be used for immune modulation to correct dysregulated immunity in autoimmune diseases to restore normal levels of immunoregulatory tolerance control. Monoclonal therapies have been developed and successfully used for the treatment of autoimmune and inflammatory diseases (Table 350-4). Some of the monoclonal antibodies such as anti-CD20 (rituximab) have also been used for the treatment of B-cell malignancies. CTLA-4-Fc has been developed to prevent CD28-induced T-cell activation, resulting in immune suppression for rheumatoid arthritis (RA) and transplantation. TNF- α has been shown to play a central role in RA pathogenesis, and anti-TNF- α antibodies have been successful in treatment of RA and are approved for other autoimmune syndromes including other forms of arthritis, inflammatory bowel disease, and psoriasis. Antibodies against β integrin block the migration of β 7+ T cells to the gastrointestinal tract and are used to treat inflammatory bowel disease (IBD). The T_H17 cytokine IL-17 has been found to be overproduced in psoriasis, and monoclonal anti-IL-17 antibody therapy for psoriasis is now approved by the FDA (Chap. 57).

Tregs are therapeutic candidates for restoring immune tolerance in autoimmune and autoinflammatory diseases, with the prospect of reducing or replacing immunosuppressive drugs. Like CAR T cells, Treg therapy involves expanding autologous Treg cells in vitro and reinfusing them into individuals with autoimmune or inflammatory diseases. To make Treg therapy more targeted for suppression of antigen-specific immune responses, CAR T technology is being used to redirect Tregs to pathogenic T and B cells. Treg cellular therapy is in human clinical trials for the treatment of graft-versus-host disease in the setting of transplantation and for prevention of progression of type 1 diabetes mellitus (Chap. 404).

IMMUNE DYSREGULATION IN AGING

Aging of the immune system in humans is characterized by decline in both innate and adaptive immunity. Aging is also paradoxically associated with a state of chronic inflammation, termed “inflammaging,” with an increased risk of autoimmune disease. Aging is associated with reduced NK cell function, reduced monocyte/macrophage immune cell expression of toll-like receptors, reduced chemotaxis and phagocytosis, and reduced MHC expression and signaling. Other phagocytic cells such as polymorphonuclear cells are similarly dysfunctional. Dendritic cells in aged individuals are present in reduced numbers with impaired antigen-presenting function and signaling. Adaptive immunity is similarly impaired with decreased antibody repertoire breadth, decrease in number of B cells, and decrease in B-cell responses to specific antigens. Similarly, T-cell responses to antigen are decreased, such as to seasonal influenza vaccination.

Aging is characterized by accumulation of senescent cells in many tissues that secrete inflammatory cytokines, chemokines, and other inflammatory mediators. The best example of the role of enhanced cytokine production in the “inflammaging” syndrome is in thymic atrophy, which is a major event contributing to age-associated immune system decline. During life, the thymus decreases in size and naïve T-cell output decreases; beginning with puberty, thymocytes progressively decrease in number, such that after ~50 years of age, ~90% of thymocytes have been replaced by adipocytes in the thymus perivascular space. Thymic adipocytes produce leukemia inhibitory factor, oncostatin M, IL-6, and stem cell factor (SCF). Administration of these cytokines to young mice induces thymic atrophy, demonstrating that these thymosuppressive cytokines actively induce thymocyte loss. Adipocytes in other sites also produce inflammatory cytokines, contributing to tissue senescence. Finally, respiratory failure due to SARS-CoV-1, Middle Eastern respiratory syndrome, or SARS-CoV-2 infection is associated with a cytokine release syndrome with IL-6 overproduction, which occurs most frequently in older individuals.

TABLE 350-4 Monoclonal Antibodies Approved for Clinical Use in Autoimmune Disease, Some of Which Are Also Used in Malignancies^a

TARGET MOLECULE	FUNCTION	FDA-APPROVED mAbs, TRAPS, AND BISPECIFIC mAbs	AUTOIMMUNE/INFLAMMATORY	MALIGNANCY	OTHER/COMMENTS
CD52	Marker of T and B lymphocyte subsets	Alemtuzumab (Lemtrada)	Multiple sclerosis	Chronic lymphocytic leukemia	Trade name changed from Campath-1H (cancer) to Lemtrada (multiple sclerosis) Humanized IgG1k
CD25	Alpha-chain of the IL-2 receptor	Basiliximab (Simulect)	Multiple sclerosis		Basiliximab: chimeric mouse/human IgG1k
		Daclizumab (Zenapax)	Transplant rejection		Daclizumab: humanized IgG1
CD20	Participates in B-cell differentiation	Obinutuzumab (Gazyva) Ibritumomab tiuxetan (Zevalin)	Rheumatoid arthritis	B-cell malignancies	Obinutuzumab is the first approved glycoengineered IgG1 mAb with enhanced ADCC
		Tositumomab (Bexxar) ^a Ofatumumab (Arzerra) Rituximab (Rituxan)			Rituximab is chimeric mouse/human IgG1k Ibritumomab tiuxetan and tositumomab are radioconjugates that can be used when tumors stop responding to the anti-CD20 mAbs
					Ibritumomab and tositumomab are mouse IgG2a
CD80/CD86	Provide co-stimulatory signals necessary for T-cell activation and survival; ligand trap prevents activation of CD28 immune checkpoint resulting in immune suppression	Belatacept (Nulojix) Abatacept (Orencia) (both CTLA-4-Fc fusion proteins)	Rheumatoid arthritis Transplant rejection		
TNF- α	Inflammatory cytokine that drives multiple autoimmune diseases ^a	Adalimumab (Humira) Certolizumab pegol (Cimzia) Golimumab (Simponi) Infliximab (Remicade) Etanercept (Enbrel) There are more than 20 anti-TNF biosimilars in various stages of development. Already approved are infliximab biosimilars (Remsima, Inflectra, Flixabi), etanercept biosimilars (Erelzi, Benepali), and adalimumab biosimilars (Amjevita). This field will change very rapidly as many dossiers are now under regulatory scrutiny. Biosimilars are given a suffix, e.g., etanercept-szzs (Erelzi)	Crohn's disease, ulcerative colitis, RA, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, plaque psoriasis, hidradenitis suppurativa, uveitis		Not all TNF blockers are approved for all indications Drugs in italics are biosimilars: adalimumab, infliximab, inflectra, <i>adalimumab-atto</i> are IgG1 mAbs; <i>certolizumab pegol</i> is a pegylated Fab fragment; etanercept is a soluble Fc-TNF receptor trap that binds TNF (there is one biosimilar). At least four biosimilar TNF blockers have been approved in the EU (two each for infliximab and etanercept)
VEGF	Cytokine that stimulates vasculogenesis and angiogenesis. Overproduced in some inflammatory disorders and tumors to induce increased blood supply.	Bevacizumab (Avastin) Ramucirumab (Cyramza) Aflibercept (Eylea/Zaltrap) Ranibizumab (Lucentis)	Age-related macular degeneration, macular edema, diabetic macular edema, diabetic retinopathy	Colorectal cancer, nonsquamous NSCLC, breast cancer, glioblastoma, renal cell carcinoma, gastric cancer or gastroesophageal junction adenocarcinoma	Bevacizumab and ramucirumab are IgG1 mAbs for cancer therapy (ramucirumab was derived from phage display); ranibizumab is a Fab fragment (single arm binder). It has a short half-life if administered intravenously, but it is stable when locally injected into the eye. Aflibercept is a ligand trap with optical (Eylea) and cancer (Zaltrap) applications.
IL-4 receptor alpha subunit	Receptor that mediates IL-4 and IL-13-induced inflammation	Dupilumab (Dupixent)	Atopic dermatitis (eczema), steroid-dependent asthma		
IgE	Binds to mast cells, basophils, and other cells that express Fc-epsilon receptor and induces release of inflammatory cytokines	Omalizumab (Xolair)	Asthma		IgG1 mAb also used off-label to treat IgE-related conditions (allergic rhinitis, drug allergies, other)

(Continued)

TABLE 350-4 Monoclonal Antibodies Approved for Clinical Use in Autoimmune Disease, Some of Which Are Also Used in Malignancies^a (Continued)

TARGET MOLECULE	FUNCTION	FDA-APPROVED mAbs, TRAPS, AND BISPECIFIC mAbs	AUTOIMMUNE/INFLAMMATORY	MALIGNANCY	OTHER/COMMENTS
Alpha-4 integrin	Alpha-4 integrin facilitates exit of inflammatory cells from blood into intestine or across the blood-brain barrier	Vedolizumab (Entyvio) Natalizumab (Tysabri)	Multiple sclerosis, Crohn's disease, and ulcerative colitis		IgG4 natalizumab therapy has been associated with PML caused by John Cunningham virus in immunocompromised patients. IgG1k vedolizumab may not be associated with PML.
Complement C5	Inhibits complement cascade	Eculizumab (Solaris)	Prevents destruction of red blood cells by activated complement (paroxysmal nocturnal hemoglobinuria)		IgG2/4 mAb; most expensive drug in the world (\$409,500 annually)
P40 subunit of IL-12 and IL-23	Mutations in cryopyrin lead to overproduction of IL-1 and inflammatory disease; IL-1 also drives other inflammatory diseases	Canakinumab (Ilaris) Rilonacept (Arcalyst) ^a	Rare inflammatory syndromes, active juvenile arthritis, gouty arthritis		Canakinumab is an IgG1k mAb; rilonacept is an IL-1 trap designed from the IL-1R fused with human mAb Fc region.
IL-6	Overexpression of IL-6 is associated with multiple malignancies	Siltuximab (Sylvant)		Pseudo-malignancy: Castleman's disease (similar to lymphoma)	Murine/human chimeric IgG1k
IL-6R (IL-6 receptor)	Current approvals based on role of IL-6 in promoting inflammatory autoimmune disease	Tocilizumab (Actemra)	Rheumatoid arthritis, polyarticular juvenile arthritis, juvenile idiopathic arthritis		Human/mouse chimeric mAb with initial approval for efficacy in RA after failure of TNF blocker
BAFF (tumor necrosis factor superfamily member 13b)	Role in proliferation and differentiation of B cells	Belimumab (Benlysta)	Systemic lupus erythematosus		IgG1-γ/λ
SLAMF7/CD319	SLAMF7 triggers the activation and differentiation of a wide variety of immune cells (innate and adaptive immune response) perhaps primarily mediated by natural killer cells and myeloma cells	Elotuzumab (Empliciti)		Multiple myeloma	This IgG1k mAb is thought to activate SLAMF7 receptor and to have a secondary mechanism of mediating ADCC vs multiple myeloma cells
IL-5	Induces differentiation and survival of eosinophils	Reslizumab (Cinquir) Mepolizumab (Nucala)	Asthma		Both IgG1k mAbs
IL-17A	Inflammatory cytokine	Ixekizumab (Taltz) Secukinumab (Cosentyx)	Plaque psoriasis, ankylosing spondylitis		Ixekizumab is an IgG4; secukinumab is an IgG1k

^aApproved for use in United States only.

Note: An actively updated summary of MAb approvals can be found at www.antibodysociety.org. mAbs can be murine, chimeric (human Fc region), humanized, or human; traps are derived from receptors and compete with natural receptor for binding target; bispecific mAbs are engineered to bind to two different targets simultaneously (usually to bring immune cell into contact with target cell, thereby triggering target cell killing). Antibody-drug conjugate (X): toxin or radioisotope attached to mAb to increase efficacy. Agents approved for use in the United States only are noted; others are approved in both United States and United Kingdom.

Abbreviations: ADCC, antibody-dependent cell-mediated cytotoxicity; BAFF, B-cell activating factor; CTLA-4, cytotoxic T-cell lymphocyte-associated protein-4; EU, European Union; Ig, immunoglobulin; FDA, U.S. Food and Drug Administration; IL, interleukin; mAb, monoclonal antibody; NSCLC, non-small-cell lung cancer; PML, progressive multifocal leukoencephalopathy; RA, rheumatoid arthritis; SLAMF7, signaling lymphocytic activation molecule family member 7; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor.

Source: Republished with permission of Royal College of Physicians, from Developments in therapy with monoclonal antibodies and related proteins, HM Shepard et al, 17:220, 2017; permission conveyed through Copyright Clearance Center, Inc.

FURTHER READING

- Ferreira LMR et al: Next-generation regulatory T cell therapy. *Nat Rev Drug Discov* 18:749, 2019.
 Goodnow CG: Multistep pathogenesis of autoimmune disease. *Cell* 130:25, 2020.
 Lim WA, June CH: The principles of engineering immune cells to treat cancer. *Cell* 168:724, 2017.
 Schildberg FA et al: Coinhibitory pathways in the B7-CD28 ligand-receptor family. *Immunity* 44:955, 2016.

Sharma P, Allison JP: The future of immune checkpoint therapy. *Science* 348:5661, 2015.

Sharma P, Allison JP: Dissecting the mechanisms of immune checkpoint therapy. *Nature Rev Immunol* 20:75, 2020.

Sharpe A, Pauken KE: The diverse functions of the PD-1 pathway. *Nat Rev Immunol* 18:153, 2018.

Wei SC et al: Fundamental mechanisms of immune checkpoint blockade therapy. *Cancer Discov* 8:1069, 2018.

351

Primary Immune Deficiency Diseases

Alain Fischer

Immunity is intrinsic to life and an important tool in the fight for survival against pathogenic microorganisms. The human immune system can be divided into two major components: the innate immune system and the adaptive immune system (Chap. 349). The innate immune system provides the rapid triggering of inflammatory responses based on the recognition (at the cell surface or within cells) of either molecules expressed by microorganisms or molecules that serve as “danger signals” released by cells under attack. These receptor/ligand interactions trigger signaling events that ultimately lead to inflammation. Virtually all cell lineages (not just immune cells) are involved in innate immune responses; however, myeloid cells (i.e., neutrophils and macrophages) play a major role because of their phagocytic capacity. The adaptive immune system operates by clonal recognition of antigens followed by a dramatic expansion of antigen-reactive cells and execution of an immune effector program. Most of the effector cells die off rapidly, whereas memory cells persist. Although both T and B lymphocytes recognize distinct chemical moieties and execute distinct adaptive immune responses, the latter is largely dependent on the former in generating long-lived humoral immunity. Adaptive responses utilize components of the innate immune system; for example, the antigen-presentation capabilities of dendritic cells help to determine the type of effector response. Not surprisingly, immune responses are controlled by a series of regulatory mechanisms.

Hundreds of gene products have been characterized as effectors or mediators of the immune system (Chap. 349). Whenever the expression or function of one of these products is genetically impaired (provided the function is nonredundant), a primary immunodeficiency (PID) occurs.

PIDs are genetic diseases with primarily Mendelian inheritance. More than 450 conditions have now been described, and deleterious mutations in ~420 genes have been identified. The overall prevalence of PIDs has been estimated in various countries at 5–10 per 100,000 individuals; however, given the difficulty in diagnosing these rare and complex diseases, this figure is probably an underestimate. PIDs can involve all possible aspects of immune responses, from innate through adaptive, cell differentiation, and effector function and regulation. For the sake of clarity, PIDs should be classified according to (1) the arm of the immune system that is defective and (2) the mechanism of the defect (when known). Table 351-1 classifies the most prevalent PIDs according to this manner of classification; however, one should bear in mind that the classification of PIDs sometimes involves arbitrary decisions because of overlap and, in some cases, lack of data.

The consequences of PIDs vary widely as a function of the molecules that are defective. This concept translates into multiple levels of vulnerability to infection by pathogenic and opportunistic microorganisms, ranging from extremely broad (as in severe combined immunodeficiency [SCID]) to narrowly restricted to a single microorganism (as in Mendelian susceptibility to mycobacterial disease [MSMD]). The locations of the sites of infection and the causal microorganisms involved will thus help physicians arrive at proper diagnoses. PIDs can also lead to immunopathologic responses such as allergy (as in Wiskott-Aldrich syndrome [WAS]), lymphoproliferation, and autoimmunity. A combination of recurrent infections, inflammation, and autoimmunity can be observed in a number of PIDs, thus creating obvious therapeutic challenges. Finally, some PIDs increase the risk of cancer, notably but not exclusively lymphocytic cancers, for example, lymphoma.

DIAGNOSIS OF PRIMARY IMMUNODEFICIENCIES

The most frequent symptom prompting the diagnosis of a PID is the presence of recurrent or unusually severe infections. As mentioned above, recurrent allergic or autoimmune manifestations may also alert

TABLE 351-1 Classification of Primary Immune Deficiency Diseases

Deficiencies of the Innate Immune System

- Phagocytic cells:
 - Impaired production: severe congenital neutropenia (SCN)
 - Asplenia
 - Impaired adhesion: leukocyte adhesion deficiency (LAD)
 - Impaired killing: chronic granulomatous disease (CGD)
- Innate immunity receptors and signal transduction:
 - Defects in Toll-like receptor signaling
 - Mendelian susceptibility to mycobacterial disease
- Complement deficiencies:
 - Classical, alternative, and lectin pathways
 - Lytic phase

Deficiencies of the Adaptive Immune System

• T lymphocytes:	Severe combined immune deficiencies (SCIDs) DiGeorge's syndrome Combined immunodeficiencies Hyper-IgE syndrome (autosomal dominant) DOCK8 deficiency CD40 ligand deficiency Wiskott-Aldrich syndrome Ataxia-telangiectasia and other DNA repair deficiencies
• B lymphocytes:	XL and AR agammaglobulinemia Hyper-IgM syndrome Common variable immunodeficiency (CVID) IgA deficiency

Regulatory Defects

• Innate immunity	Autoinflammatory syndromes (outside the scope of this chapter) Severe colitis Hemophagocytic lymphohistiocytosis (HLH) Autoimmune lymphoproliferation syndrome (ALPS)
• Adaptive immunity	Autoimmunity and inflammatory diseases (IPEX, APECED)

Abbreviations: APECED, autoimmune polyendocrinopathy candidiasis ectodermal dysplasia; AR, autosomal recessive; IPEX, immunodysregulation polyendocrinopathy enteropathy X-linked syndrome; XL, X-linked.

the physician to a possible diagnosis of PID. In such cases, a detailed account of the subject's personal and family medical history should be obtained. It is of the utmost importance to gather as much medical information as possible on relatives and up to several generations of ancestors. In addition to the obvious focus on primary symptoms, the clinical examination should evaluate the size of lymphoid organs and, when appropriate, look for the characteristic signs of a number of complex syndromes that may be associated with a PID.

The performance of laboratory tests should be guided to some extent by the clinical findings. Infections of the respiratory tract (bronchi, sinuses) mostly suggest a defective antibody response. In general, invasive bacterial infections can result from complement deficiencies, signaling defects of innate immune responses, asplenia, or defective antibody responses. Viral infections, recurrent *Candida* infections, and opportunistic infections are generally suggestive of impaired T-cell immunity. Skin infections and deep-seated abscesses primarily reflect innate immune defects (such as chronic granulomatous disease); however, they may also appear in the autosomal dominant hyper-IgE syndrome. Table 351-2 summarizes the laboratory tests that are most frequently used to diagnose a PID. More specific tests (notably genetic tests) are then used to make a definitive diagnosis. Genomic tools now allow us to more efficiently track genetic defects through usage of gene panel resequencing and/or whole exome/genome sequencing.



TABLE 351-2 Tests Most Frequently Used to Diagnose a Primary Immune Deficiency (PID)

TEST	INFORMATION	PID DISEASE
Blood cell counts and cell morphology	Neutrophil counts ^a Lymphocyte counts ^a Eosinophilia Howell-Jolly bodies	↓ Severe congenital neutropenia, ↑ LAD T-cell ID WAS, hyper-IgE syndrome Asplenia
Chest x-ray	Thymic shadow Costochondral junctions	SCID, DiGeorge's syndrome Adenosine deaminase deficiency
Bone x-ray	Metaphyseal ends	Cartilage hair hypoplasia
Immunoglobulin serum levels	IgG, IgA, IgM IgE	B-cell ID Hyper-IgE syndrome, WAS, T-cell ID
Lymphocyte phenotype	T, B lymphocyte counts	T-cell ID, agammaglobulinemia
Dihydrorhodamine fluorescence (DHR) assay Nitroblue tetrazolium (NBT) assay	Reactive oxygen species production by PMNs	Chronic granulomatous disease
CH50, AP50	Classic and alternative complement pathways	Complement deficiencies
Ultrasonography of the abdomen	Spleen size	Asplenia

^aNormal counts vary with age. For example, the lymphocyte count is between 3000 and 9000/ μ L of blood below the age of 3 months and between 1500 and 2500/ μ L in adults.

Abbreviations: ID, immunodeficiency; LAD, leukocyte adhesion deficiency; PMNs, polymorphonuclear leukocytes; SCID, severe combined immunodeficiency; WAS, Wiskott-Aldrich syndrome.

The PIDs discussed below have been grouped together according to the affected cells and the mechanisms involved (Table 351-1, Fig. 351-1).

PRIMARY IMMUNODEFICIENCIES OF THE INNATE IMMUNE SYSTEM

PIDs of the innate immune system are relatively rare and account for ~10% of all PIDs.

SEVERE CONGENITAL NEUTROPEНИA

Severe congenital neutropenia (SCN) consists of a group of inherited diseases that are characterized by severely impaired neutrophil counts (<500 polymorphonuclear leukocytes [PMN]/ μ L of blood). The condition is usually manifested from birth. SCN may also be cyclic (with a 3-week periodicity), and other neutropenia syndromes can also be intermittent. Although the most frequent inheritance pattern for SCN is autosomal dominant, autosomal recessive and X-linked recessive conditions also exist. Bacterial infections at the interface between the body and the external milieu (e.g., the orifices, wounds, and the respiratory tract) are common manifestations. Bacterial infections can rapidly progress through soft tissue and are followed by dissemination in the bloodstream. Severe visceral fungal infections can also ensue. The absence of pus is a hallmark of this condition.

Diagnosis of SCN requires examination of the bone marrow. Most SCNs are associated with a block in granulopoiesis at the promyelocytic stage (Fig. 351-1). SCN has multiple etiologies, and to date, mutations in 21 different genes have been identified. Most of these mutations result in isolated SCN, whereas others are syndromic (Chap. 64). The most frequent forms of SCN are caused by the premature cell death of granulocyte precursors, as observed in deficiencies of GFI1, HAX1, and elastase 2 (*ELANE*), with the latter accounting for 50% of SCN sufferers. Certain *ELANE* mutations cause cyclic neutropenia syndrome. A gain-of-function mutation in the *WASP* gene (see the

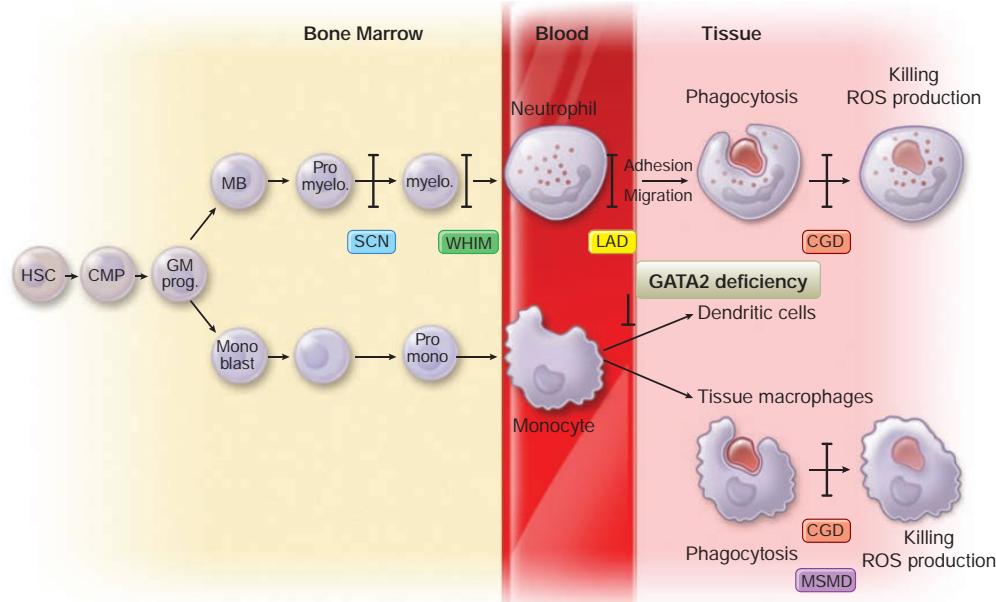


FIGURE 351-1 Differentiation of phagocytic cells and related primary immunodeficiencies (PIDs). Hematopoietic stem cells (HSCs) differentiate into common myeloid progenitors (CMPs) and then granulocyte-monocyte progenitors (GM prog.), which, in turn, differentiate into neutrophils (MB: myeloblasts; Promyelo: promyelocytes; myelo: myelocytes) or monocytes (monoblasts and promonocytes). Upon activation, neutrophils adhere to the vascular endothelium, transmigrate, and phagocytose the targets. Reactive oxygen species (ROS) are delivered to the microorganism-containing phagosomes. Macrophages in tissues kill using the same mechanism. Following activation by interferon γ (not shown here), macrophages can be armed to kill intracellular pathogens such as mycobacteria. For sake of simplicity, not all cell differentiation stages are shown. The abbreviations for PIDs are contained in boxes placed at corresponding stages of the pathway. CGD, chronic granulomatous disease; GATA2, zinc finger transcription factor; LAD, leukocyte adhesion deficiencies; MSMD, Mendelian susceptibility to mycobacterial disease; SCN, severe congenital neutropenia; WHIM, warts, hypogammaglobulinemia, infections, and myelokathexis.

section “Wiskott-Aldrich Syndrome” below) causes X-linked SCN, which is also associated with monocytopenia.

As mentioned above, SCN exposes the patient to life-threatening, disseminated bacterial and fungal infections. Treatment requires careful hygiene measures, notably in infants. Later in life, special oral and dental care is essential, along with the prevention of bacterial infection by prophylactic administration of trimethoprim/sulfamethoxazole. Subcutaneous injection of the cytokine granulocyte colony-stimulating factor (G-CSF) usually improves neutrophil development and thus prevents infection in most SCN diseases. However, there are two caveats: (1) a few cases of SCN with *ELANE* mutation are refractory to G-CSF and may require curative treatment via allogeneic hematopoietic stem cell transplantation (HSCT); and (2) a subset of G-CSF-treated patients carrying *ELANE* mutations are at a greater risk of developing acute myelogenous leukemia associated (in most cases) with somatic gain-of-function mutations of the G-CSF receptor gene.

A few SCN conditions are associated with additional immune defects involving leukocyte migration as observed in the warts, hypogammaglobulinemia, infections, and myelokathexis (WHIM) syndrome (gain-of-function mutation of the chemokine *CXCR4*) or in moesin deficiency.

ASPLENIA

Primary failure of the development of a spleen is an extremely rare disease that can be either syndromic (in Ivemark syndrome) or isolated with an autosomal dominant expression; in the latter case, mutations in the ribosomal protein SA were recently found. Due to the absence of natural filtration of microbes in the blood, asplenia predisposes affected individuals to fulminant infections by encapsulated bacteria. Although most infections occur in the first years of life, cases may also arise in adulthood. The diagnosis is confirmed by abdominal ultrasonography and the detection of Howell-Jolly bodies in red blood cells. Effective prophylactic measures (twice-daily oral penicillin and appropriate vaccination programs) usually prevent fatal outcomes.

GATA2 DEFICIENCY

Recently, an immunodeficiency combining monocytopenia and dendritic and lymphoid (B and natural killer [NK]) cell deficiency (DCML), also called monocytopenia with nontuberculous mycobacterial infections (mono-MAC), has been described as a consequence of a dominant mutation in the gene *GATA2*, a transcription factor involved in hematopoiesis. This condition also predisposes to lymphedema, myelodysplasia, and acute myeloid leukemia. Infections (bacterial and viral) are life-threatening, thus indicating, together with the malignant risk, HSCT.

LEUKOCYTE ADHESION DEFICIENCY

Leukocyte adhesion deficiency (LAD) consists of three autosomal recessive conditions (LAD I, II, and III) (Chap. 64). The most frequent condition (LAD I) is caused by mutations in the $\beta 2$ integrin gene; following leukocyte activation, $\beta 2$ integrins mediate adhesion to inflamed endothelium expressing cognate ligands. LAD III results from a defect in a regulatory protein (kindlin, also known as Fermt 3) involved in activating the ligand affinity of $\beta 2$ integrins. The extremely rare LAD II condition is the end result of a defect in selectin-mediated leukocyte rolling that occurs prior to $\beta 2$ integrin binding. There is a primary defect in fucose transporter such that oligosaccharide selectin ligands are missing in this syndromic condition.

Given that neutrophils are not able to reach infected tissues, LAD renders the individual susceptible to bacterial and fungal infections in a way that is similar to that of patients with SCN. LAD also causes impaired wound healing and delayed loss of the umbilical cord. A diagnosis can be suspected in cases of pus-free skin/tissue infections and massive hyperleukocytosis ($>30,000/\mu\text{L}$) in the blood (mostly granulocytes). Patients with LAD III also develop bleeding because the $\beta 2$ integrin in platelets is not functional. Use of immunofluorescence and functional assays to detect $\beta 2$ integrin can help form a diagnosis. Severe forms of LAD may require HSCT, although gene therapy is also now being considered. Neutrophil-specific granule deficiency (a very

rare condition caused by a mutation in the gene for transcription factor C/EBP α) results in a condition that is clinically similar to LAD. Infrequent additional leukocyte motility defects have also been reported.

CHRONIC GRANULOMATOUS DISEASES

Chronic granulomatous diseases (CGDs) are characterized by impaired phagocytic killing of microorganisms by neutrophils and macrophages (Chap. 64). The incidence is ~1 per 200,000 live births. About 70% of cases are associated with X-linked recessive inheritance versus autosomal inheritance in the remaining 30%. CGD causes deep-tissue bacterial and fungal abscesses in macrophage-rich organs such as the lymph nodes, liver, and lungs. Recurrent skin infections (such as folliculitis) are common and can prompt an early diagnosis of CGD. The infectious agents are typically catalase-positive bacteria (such as *Staphylococcus aureus* and *Serratia marcescens*) but also include *Burkholderia cepacia*, pathogenic mycobacteria (in certain regions of the world), and fungi (mainly filamentous molds, such as *Aspergillus*).

CGD is caused by defective production of reactive oxygen species (ROS) in the phagolysosome membrane following phagocytosis of microorganisms. It results from the lack of a component of NADPH oxidase (gp91phox or p22phox) or of the associated adapter/activating proteins (p47phox, p67phox, or p40phox) that mediate the transport of electrons into the phagolysosome for creating ROS by interaction with O_2^- . Under normal circumstances, these ROS either directly kill engulfed microorganisms or enable the rise in pH needed to activate the phagosomal proteases that contribute to microbial killing. Diagnosis of CGD is based on assays of ROS production in neutrophils and monocytes (Table 351-2). As its name suggests, CGD is also a granulomatous disease. Macrophage-rich granulomas can often arise in the liver, spleen, and other organs. These are sterile granulomas that cause disease by obstruction (bladder, pylorus, etc.) or protracted inflammation (colitis, restrictive lung disease).

The management of infections in patients with CGD can be a complex process. The treatment of bacterial infections is generally based on combination therapy with antibiotics that are able to penetrate into cells. The treatment of fungal infections requires aggressive, long-term use of antifungals. Inflammatory/granulomatous lesions are usually steroid-sensitive, but often become glucocorticoid-dependent; liver abscesses are best managed by administering antibiotics together with glucocorticoids.

The treatment of CGD mostly relies on preventing infections. It has been unambiguously demonstrated that prophylactic usage of trimethoprim/sulfamethoxazole is both well tolerated and highly effective in reducing the risk of bacterial infection. Daily administration of azole derivatives (notably itraconazole) also reduces the frequency of fungal complications. It has long been suggested that interferon γ administration is helpful, although medical experts continue to disagree over this controversial issue. Patients may do reasonably well for some time with prophylaxis and careful management. However, patients are at high risk lifelong of severe and persistent fungal infections and/or chronic inflammatory complications, leading to consideration of performing HSCT. Due to an increase in reported successes, HSCT is now an established curative approach for CGD; however, the risk-versus-benefit ratio must be carefully assessed on a case-by-case basis. Gene therapy approaches are also being evaluated.

MENDELIAN SUSCEPTIBILITY TO MYCOBACTERIAL DISEASE

This group of diseases is characterized by a defect in the interleukin-12 (IL-12)-interferon (IFN) γ axis (including IL-12p40, IL-12 receptor [R_1] β_1 and β_2 , IFN- γ R, and R $_s$, TYK2, STAT1, IRF8, and ISG515 deficiencies), which ultimately leads to impaired IFN- γ -dependent macrophage activation. Both recessive and dominant inheritance modes have been observed. The hallmark of this PID is a specific and relatively narrow vulnerability to tuberculous and nontuberculous mycobacteria. The most severe phenotype (as observed in complete IFN- γ receptor deficiency) is characterized by disseminated infection that can be fatal even when aggressive and appropriate antimycobacterial therapy is applied. In addition to mycobacterial infections, MSMD

patients (and particularly those with an IL-12/IL-12R deficiency) are prone to developing *Salmonella* infections. Although MSMDs are very rare, they should be considered in any patient with persistent mycobacterial infection. Treatment with IFN- γ may efficiently bypass an IL-12/IL-12R deficiency. HSCT is a therapeutic option for the most severe cases.

TOLL-LIKE RECEPTOR (TLR) PATHWAY DEFICIENCIES

In a certain group of patients with early-onset, invasive *Streptococcus pneumoniae* infections or (less frequently) *Staphylococcus aureus* or other pyogenic infections, conventional screening for PIDs does not identify the cause of the defect in host defense. It has been established that these patients carry recessive mutations in genes that encode essential adaptor molecules (IRAK4 and MYD88) involved in the signaling pathways of the majority of known TLRs (Chap. 349). Remarkably, susceptibility to infection appears to decrease after the first few years of life—perhaps an indication that adaptive immunity (once triggered by an initial microbial challenge) is then able to prevent recurrent infections.

Certain TLRs (TLR-3, -7, -8, and -9) are involved in the recognition of RNA and DNA and usually become engaged during viral infections. Very specific susceptibility to herpes simplex encephalitis has been described in patients with a deficiency in Unc93b (a molecule associated with TLR-3, -7, -8, and -9 required for correct subcellular localization), TLR-3, or associated signaling molecules TRIF, TBK1, and TRAF3, resulting in defective type I IFN production. The fact that no other TLR deficiencies have been found—despite extensive screening of patients with unexplained, recurrent infections—strongly suggests that these receptors are functionally redundant. Hypomorphic mutations in NEMO/IKK- γ (a member of the NF- κ B complex, which is activated downstream of TLR receptors) lead to a complex, variable immunodeficiency and a number of associated features. Susceptibility to both invasive, pyogenic infections and mycobacteria may be observed in this particular setting.

Rare cases of predisposition to severe viral infections (influenza, live measles vaccine) have been found in patients with genetic defects in IFN type I receptor and signaling pathways.

COMPLEMENT DEFICIENCY

The complement system is composed of a complex cascade of plasma proteins (Chap. 349) that leads to the deposition of C3b fragments on the surface of particles and the formation of immune complexes that can culminate in the activation of a lytic complex at the bacterial surface. C3 cleavage can be mediated via three pathways: the classic, alternate, and lectin pathways. C3b coats particles as part of the opsonization process that facilitates phagocytosis following binding to cognate receptors. A deficiency in any component of the classic pathway (C1q, C1r, C1s, C4, and C2) can predispose an individual to bacterial infections that are tissue-invasive or that occur in the respiratory tract. Likewise, a C3 deficiency or a deficiency in factor I (a protein that regulates C3 consumption, thus leading to a C3 deficiency due to its absence) also results in the same type of vulnerability to infection. It has recently been reported that a very rare deficiency in ficolin-3 predisposes affected individuals to bacterial infections. Deficiencies in the alternative pathway (factors D and properdin) are associated with the occurrence of invasive *Neisseria* infections.

Lastly, deficiencies of any complement component involved in the lytic phase (C5, C6, C7, C8, and, to a lesser extent, C9) predispose affected individuals to systemic infection by *Neisseria*. This is explained by the critical role of complement in the lysis of the thick cell wall possessed by this class of bacteria.

Diagnosis of a complement deficiency relies primarily on testing the status of the classic and alternate pathway via functional assays, that is, the CH50 and AP50 tests, respectively. When either pathway is profoundly impaired, determination of the status of the relevant components in that pathway enables a precise diagnosis. Appropriate vaccinations and daily administration of oral penicillin are efficient means of preventing recurrent infections. It is noteworthy that several complement deficiencies (in the classic pathway and the lytic phase) may also predispose affected individuals to autoimmune diseases (notably systemic lupus erythematosus; Chap. 356).

PRIMARY IMMUNODEFICIENCIES OF THE ADAPTIVE IMMUNE SYSTEM

T LYMPHOCYTE DEFICIENCIES (TABLE 351-1, FIGS. 351-2 AND 351-3)

Given the central role of T lymphocytes in adaptive immune responses (Chap. 349), PIDs involving T cells generally have severe pathologic consequences; this explains the poor overall prognosis and the need for early diagnosis and the early intervention with appropriate therapy. Several differentiation pathways of T-cell effectors have been described, one or all of which may be affected by a given PID (Fig. 351-2). Follicular helper CD4+ T cells in germinal centers are required for T-dependent antibody production, including the generation of

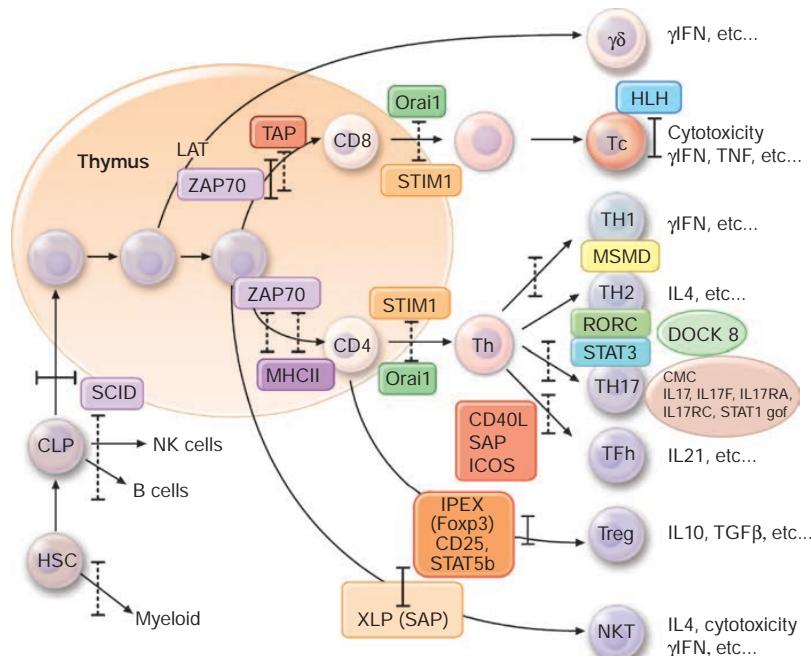


FIGURE 351-2 T-cell differentiation, effector pathways, and related primary immunodeficiencies (PIDs). Hematopoietic stem cells (HSCs) differentiate into common lymphoid progenitors (CLPs), which, in turn, give rise to the T-cell precursors that migrate to the thymus. The development of CD4+ and CD8+ T cells is shown. Known T-cell effector pathways are indicated, that is, $\gamma\delta$ cells, cytotoxic T cells (Tc), T_H1, T_H2, T_H17, TFH (follicular helper) CD4 effector T cells, regulatory T cells (Treg), and natural killer T cells (NKTs); abbreviations for PIDs are contained in boxes. Vertical bars indicate a complete deficiency; broken bars a partial deficiency. DOCK8, autosomal recessive form of hyper-IgE syndrome; HLH, hemophagocytic lymphohistiocytosis; IL17F, IL17RA, STAT1 (gof: gain of function), CMC (chronic mucocutaneous candidiasis), CD40L, ICOS, SAP deficiencies; IPEX, immunodysregulation polyendocrinopathy enteropathy X-linked syndrome; LAT, linker for activation of T cells; MHCII, major histocompatibility complex class II deficiency; MSMD, Mendelian susceptibility to mycobacterial disease; Orai1, STIM1 deficiencies; RORC, RAR related orphan receptor C; SCID, severe combined immunodeficiency; STAT3, autosomal dominant form of hyper-IgE syndrome; TAP, TAP1 and TAP2 deficiencies; XLP, X-linked proliferative syndromes; ZAP70, zeta-associated protein deficiency.

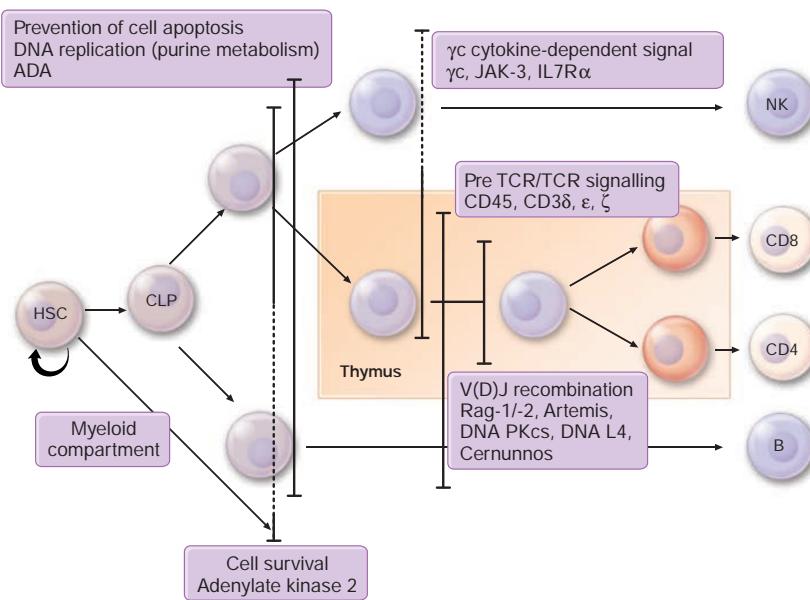


FIGURE 351-3 T-cell differentiation and severe combined immunodeficiencies (SCIDs). The vertical bars indicate the five mechanisms currently known to lead to SCID. The names of deficient proteins are indicated in the boxes adjacent to the vertical bars. A broken line means that deficiency is partial or involves only some of the indicated immunodeficiencies. ADA, adenosine deaminase deficiency; CLPs, common lymphoid progenitors; DNAL4, DNA ligase 4; HSCs, hematopoietic stem cells; NKs, natural killer cells; TCR, T-cell receptor.

Ig class-switched, high-affinity antibodies. CD4+ T_H1 cells provide cytokine-dependent (mostly IFN- γ -dependent) help to macrophages for intracellular killing of various microorganisms, including mycobacteria and *Salmonella*. CD4+ T_H2 cells produce IL-4, IL-5, and IL-13 and thus recruit and activate eosinophils and other cells required to fight helminth infections. CD4+ T_H17 cells produce IL-17 and IL-22 cytokines that recruit neutrophils to the skin and lungs to fight bacterial and fungal infections. Cytotoxic CD8+ T cells can kill infected cells, notably in the context of viral infections. In addition, certain T-cell deficiencies predispose affected individuals to *Pneumocystis jiroveci* lung infections early in life and to chronic gut/biliary duct/liver infections by *Cryptosporidium* and related genera later on in life. Lastly, naturally occurring or induced regulatory T cells are essential for controlling inflammation (notably reactivity to commensal bacteria in the gut) and autoimmunity. The role of other T-cell subsets with limited T-cell receptor (TCR) diversity (such as γδTCR T cells or natural killer T [NKT] cells) in PIDs is less well known; however, these subsets can be defective in certain PIDs, and this finding can sometimes contribute to the diagnosis (e.g., NKT-cell deficiency in X-linked proliferative syndrome [XLP]). T-cell deficiencies account for ~20% of all cases of PID.

Severe Combined Immunodeficiencies SCIDs constitute a group of rare PIDs characterized by a profound block in T-cell development and thus the complete absence of these cells. The developmental block is always the consequence of an intrinsic deficiency. The incidence of SCID is estimated to be 1 in 50,000 live births. Given the severity of the T-cell deficiency, clinical consequences occur early in life (usually within 3–6 months of birth). The most frequent clinical manifestations are recurrent oral candidiasis, failure to thrive, and protracted diarrhea and/or acute interstitial pneumonitis caused by *P. jiroveci* (although the latter can also be observed in the first year of life in children with B-cell deficiencies). Severe viral infections or invasive bacterial infections can also occur. Patients may also experience complications related to infections caused by live vaccines (notably bacille Calmette-Guérin [BCG]) that may lead not only to local and regional infection but also to disseminated infection manifested by fever, splenomegaly, and skin and lytic bone lesions. A scaly skin eruption can be observed in a context of maternal T-cell engraftment (see below).

A diagnosis of SCID can be suspected based on the patient's clinical history and, possibly, a family history of deaths in very young children (suggestive of either X-linked or recessive inheritance). Lymphocytopenia is strongly suggestive of SCID in >90% of cases (Table 351-2). The absence of a thymic shadow on a chest x-ray can also be suggestive of SCID. An accurate diagnosis relies on precise determination of the number of circulating T, B, and NK lymphocytes and their subsets. T-cell lymphopenia may be masked in some patients by the presence of maternal T cells (derived from maternal-fetal blood transfers) that cannot be eliminated. Although counts are usually low (<500/ μ L of blood), higher maternal T-cell counts may, under some circumstances, initially mask the presence of SCID. Thus, screening for maternal cells by using adequate genetic markers should be performed whenever necessary. Inheritance pattern analysis and lymphocyte phenotyping can discriminate between various forms of SCID and provide guidance in the choice of accurate molecular diagnostic tests (see below). To date, five distinct causative mechanisms for SCID (Fig. 351-3) have been identified. T-cell quantification of receptor excision circles

(TREC) by using the Guthrie card is a reliable diagnostic test for newborn screening. It is now operational in the United States and several other countries worldwide. Its more widespread use will lead to the provision of therapy (see below) to uninfected patients resulting in a maximal chance of cure.

SEVERE COMBINED IMMUNODEFICIENCY CAUSED BY A CYTOKINE-SIGNALING DEFICIENCY The most frequent SCID phenotype (accounting for 30–40% of all cases) is the absence of both T and NK cells. This outcome results from a deficiency in either the common γ chain (γ c) receptor that is shared by several cytokine receptors (the IL-2, -4, -7, -9, -15, and -21 receptors) or Jak-associated kinase (JAK) 3 that binds to the cytoplasmic portion of the γ c chain receptor and induces signal transduction following cytokine binding. The former form of SCID (γ c deficiency) has an X-linked inheritance mode, while the second is autosomal recessive. A lack of the IL-7R α chain (which, together with γ c, forms the IL-7 receptor) induces a selective T-cell deficiency.

PURINE METABOLISM DEFICIENCY Ten to 20% of SCID patients exhibit a deficiency in adenosine deaminase (ADA), an enzyme of purine metabolism that deaminates adenosine (ado) and deoxyadenosine (dAdo). An ADA deficiency results in the accumulation of ado and dAdo metabolites that induce premature cell death of lymphocyte progenitors. The condition results in the absence of B and NK lymphocytes as well as T cells. The clinical expression of complete ADA deficiency typically occurs very early in life. Since ADA is a ubiquitous enzyme, its deficiency can also cause bone dysplasia with abnormal costochondral junctions and metaphyses (found in 50% of cases) and neurologic defects. The very rare purine nucleoside phosphorylase (PNP) deficiency causes a profound although incomplete T-cell deficiency that is often associated with severe neurologic impairments.

DEFECTIVE REARRANGEMENTS OF T- AND B-CELL RECEPTORS A series of SCID conditions are characterized by a selective deficiency in T and B lymphocytes with autosomal recessive inheritance. These conditions account for 20–30% of SCID cases and result from mutations in genes encoding proteins that mediate the recombination of V(D)J gene elements in T- and B-cell antigen receptor genes (required for the

generation of diversity in antigen recognition). The main deficiencies involve RAG1, RAG2, DNA-dependent protein kinase, and Artemis. A less severe (albeit variable) immunologic phenotype can result from other deficiencies in the same pathway, that is, DNA ligase 4 and Cernunnos deficiencies. Given that these latter factors are involved in DNA repair, these deficiencies may also cause developmental defects.

DEFECTIVE (PRE-)T-CELL RECEPTOR SIGNALING IN THE THYMUS A selective T-cell defect can be caused by a series of rare deficiencies in molecules involved in signaling via the pre-TCR or the TCR. These include deficiencies in CD3 subunits associated with the (pre-)TCR (i.e., CD3 δ , ϵ , and ζ) and CD45.

RETICULAR DYSGENESIS Reticular dysgenesis is an extremely rare form of SCID that causes T and NK deficiencies with severe neutropenia and sensorineural deafness. It results from an adenylate kinase 2 deficiency. RAC-2 gain of function can cause the same immunologic phenotype.

Patients with SCID require appropriate care with aggressive anti-infective therapies, immunoglobulin replacement, and (when necessary) parenteral nutrition support. In most cases, curative treatment relies on HSCT. Today, HSCT provides a very high curative potential for SCID patients who are otherwise in reasonably good condition. Gene therapy has been found to be successful for cases of X-linked SCID (γ c deficiency) and SCID caused by an ADA deficiency. Lastly, a third option for the treatment of ADA deficiency consists of enzyme substitution with a pegylated enzyme.

Thymic Defects A profound T-cell defect can also result from faulty development of the thymus, as is most often observed in rare cases of DiGeorge's syndrome—a relatively common condition leading to a constellation of developmental defects. In ~1% of such cases, the thymus is completely absent, leading to virtually no mature T cells. However, expansion of oligoclonal T cells can occur and is associated with skin lesions. Diagnosis (using immunofluorescence *in situ* hybridization) is based on the identification of a hemizygous deletion in the long arm of chromosome 22. To recover the capability for T-cell differentiation, these cases require a thymic graft. CHARGE (coloboma of the eye, heart anomaly, choanal atresia, retardation, genital, and ear anomalies) syndrome (CHD7 deficiency) is a less frequent cause of impaired thymus development. Lastly, the very rare "nude" defect is characterized by the absence of both hair and the thymus.

Omenn Syndrome *Omenn syndrome* consists of a subset of T-cell deficiencies that present with a unique phenotype, including early-onset erythroderma, alopecia, hepatosplenomegaly, and failure to thrive. These patients usually display T-cell lymphocytosis, eosinophilia, and low B-cell counts. It has been found that the T cells of these patients exhibit a low TCR heterogeneity. This peculiar syndrome is the consequence of hypomorphic mutations in genes usually associated with SCID, that is, *RAG1*, *RAG2*, or (less frequently) *ARTEMIS* or *IL-7Ra*. The impaired homeostasis of differentiating T cells thus causes this immune system-associated disease. These patients are very fragile, requiring simultaneous anti-infective therapy, nutritional support, and immunosuppression. HSCT provides a curative approach.

Functional T-Cell Defects (Fig. 351-2) A subset of T-cell PIDs with autosomal inheritance is characterized by partially preserved T-cell differentiation but defective activation resulting in abnormal effector function. There are many causes of these defects, but all lead to susceptibility to viral and opportunistic infections, chronic diarrhea, and failure to thrive, with onset during childhood often associated with autoimmune manifestations. Careful phenotyping and *in vitro* functional assays are required to identify these diseases, the best characterized of which are the following.

ZETA-ASSOCIATED PROTEIN 70 (ZAP70) DEFICIENCY Zeta-associated protein 70 (ZAP70) is recruited to the TCR following antigen recognition. A ZAP70 deficiency leads typically to an almost complete absence of CD8+ T cells; CD4+ T cells are present but cannot be activated *in vitro* by TCR stimulation.

CALCIUM SIGNALING DEFECTS A small number of patients have been reported who exhibit a profound defect in *in vitro* T- and B-cell

activation as a result of defective antigen receptor-mediated Ca^{2+} influx. This defect is caused by a mutation in the calcium channel gene (*ORAI1*) or its activator (*STIM-1*). It is noteworthy that these patients are also prone to autoimmune manifestations (blood cytopenias) and exhibit a nonprogressive muscle disease.

HUMAN LEUKOCYTE ANTIGEN (HLA) CLASS II DEFICIENCY Defective expression of HLA class II molecules is the hallmark of a group of four recessive genetic defects all of which affect molecules (RFX5, RFXAP, RFXANK, and CIITA) involved in the transactivation of the genes coding for HLA class II. As a result, low but variable CD4+ T-cell counts are observed in addition to defective antigen-specific T- and B-cell responses. These patients are particularly susceptible to herpesvirus, adenovirus, and enterovirus infections and chronic gut/liver *Cryptosporidium* infections.

HLA CLASS I DEFICIENCY Defective expression of molecules involved in antigen presentation by HLA class I molecules (i.e., TAP-1, TAP-2, and Tapasin) leads to reduced CD8+ T-cell counts, loss of HLA class I antigen expression, and a particular phenotype consisting of chronic obstructive pulmonary disease and severe vasculitis.

OTHER DEFECTS A variety of other T-cell PIDs have been described, some of which are associated with a precise molecular defect (e.g., IL-2-inducible T-cell kinase [ITK] deficiency; CD27, CD70, IL-21, and IL-21 receptor deficiencies; CARD11 deficiency; MALT1 deficiency; BCL10 deficiency; DOCK2 deficiency; RORC deficiency; RLTPR deficiency). These conditions are also characterized by profound vulnerability to infections, such as severe Epstein-Barr virus (EBV)-induced B-cell proliferation and autoimmune disorders. Milder phenotypes are associated with CD8 and CD3 γ deficiencies. Combined immunodeficiency associated with anhidrotic ectoderm dysplasia is the consequence of defects in the NF- κ B signaling pathway (X-linked IKK γ deficiency and gain-of-function IKB β).

HSCT is indicated for most of these diseases, although the prognosis is worse than in SCID because many patients are chronically infected at the time of diagnosis. Fairly aggressive immunosuppression and myeloablation may be necessary to achieve engraftment of allogeneic stem cells.

T-Cell Primary Immunodeficiencies with DNA Repair Defects This is a group of PIDs characterized by a combination of T- and B-cell defects of variable intensity, together with a number of nonimmunologic features resulting from DNA fragility. The autosomal recessive disorder *ataxia-telangiectasia* (AT) is the most frequently encountered condition in this group. It has an incidence of 1:40,000 live births and causes B-cell defects (low IgA, IgG2 deficiency, and low antibody production), which often require immunoglobulin replacement. AT is associated with a progressive T-cell immunodeficiency. As the name suggests, the hallmark features of AT are telangiectasia and cerebellar ataxia. The latter manifestations may not be detectable before the age of 3–4 years, so that AT should be considered in young children with IgA deficiency and recurrent and problematic infections. Diagnosis is based on a cytogenetic analysis showing excessive chromosomal rearrangements (mostly affecting chromosomes 7 and 14) in lymphocytes. AT is caused by a mutation in the gene encoding the ATM protein—a kinase that plays an important role in the detection and repair of DNA lesions (or cell death if the lesions are too numerous) by triggering several different pathways. Overall, AT is a progressive disease that carries a very high risk of lymphoma, leukemia, and (during adulthood) carcinomas. A variant of AT ("AT-like disease") is caused by mutation in the *MRE11* gene.

Nijmegen breakage syndrome (NBS) is a less common condition that also results from chromosome instability (with the same cytogenetic abnormalities as in AT). NBS is characterized by a severe T- and B-cell combined immune deficiency with autosomal recessive inheritance. Individuals with NBS exhibit microcephaly and a bird-like face but have neither ataxia nor telangiectasia. The risk of malignancies is very high. NBS results from a deficiency in nibrin (NBS1, a protein associated with MRE11 and Rad50 that is involved in checking DNA lesions) caused by hypomorphic mutations.

Severe forms of *dyskeratosis congenita* (also known as Hoyeraal-Hreidarsson syndrome) combine a progressive immunodeficiency that can also include an absence of B and NK lymphocytes, progressive bone marrow failure, microcephaly, in utero growth retardation, and gastrointestinal disease. The disease can be X-linked or, more rarely, autosomal recessive. It is caused by the mutation of genes encoding telomere maintenance proteins, including dyskerin (DKC1).

Finally, *immunodeficiency with centromeric and facial anomalies* (ICF) is a complex syndrome of autosomal recessive inheritance that variably combines a mild T-cell immune deficiency with a more severe B-cell immune deficiency, coarse face, digestive disease, and mild mental retardation. A diagnostic feature is the detection by cytogenetic analysis of multiradial aspects in multiple chromosomes (most frequently 1, 9, and 16) corresponding to an abnormal DNA structure secondary to defective DNA methylation. It is the consequence of a deficiency in most cases in the DNA methyltransferase DNMT3B, ZBTB24, CDCA7, or HELLS.

T-Cell Primary Immunodeficiencies with Hyper-IgE Several T-cell PIDs are associated with elevated serum IgE levels (as in Omenn syndrome). A condition sometimes referred to as *autosomal recessive hyper-IgE syndrome* is notably characterized by recurrent bacterial infections in the skin and respiratory tract and severe skin and mucosal infections by pox viruses and human papillomaviruses, together with severe allergic manifestations. T and B lymphocyte counts are low. Mutations in the *DOCK8* gene have been found in many of these patients. This condition is an indication for HSCT.

A very rare, related condition with autosomal recessive inheritance that causes a similar susceptibility to infection with various microbes (see above), including mycobacteria, reportedly results from a deficiency in Tyk-2, a JAK family kinase involved in the signaling of many different cytokine receptors.

Autosomal Dominant Hyper-IgE Syndrome This unique condition, the *autosomal dominant hyper-IgE syndrome*, is usually diagnosed by the combination of recurrent skin and lung infections that can be complicated by pneumatoceles. Infections are caused by pyogenic bacteria and fungi. Several other manifestations characterize hyper-IgE syndrome, including facial dysmorphia, defective loss of primary teeth, hyperextensibility, scoliosis, and osteoporosis. Elevated serum IgE levels are typical of this syndrome. Defective T_H17 effector responses have been shown to account at least in part for the specific patterns of susceptibility to particular microbes. This condition is caused by a heterozygous (dominant) mutation in the gene encoding the transcription factor STAT3 that is required in a number of signaling pathways following binding of cytokine to cytokine receptors (such as that of IL-6 and the IL-6 receptor). It also results in partially defective antibody production because of defective IL-21 receptor signaling. Hence, immunoglobulin substitution can be considered as prophylaxis of bacterial infections.

Most recently, a recessive condition that mimics immunologic aspects of hyper-IgE syndrome has been ascribed to ZNF341 deficiency.

Cartilage Hair Hypoplasia The autosomal recessive *cartilage hair hypoplasia* (CHH) disease is characterized by short-limb dwarfism, metaphyseal dysostosis, and sparse hair, together with a combined T- and B-cell PID of extremely variable intensity (ranging from quasi-SCID to no clinically significant immune defects). The condition can predispose to erythroblastopenia, autoimmunity, and tumors. It is caused by mutations in the *RMRP* gene for a noncoding ribosome-associated RNA. Schimke immuno-osseous dysplasia is another autosomal recessive condition variably associating combined immunodeficiency, bone disease, and more importantly severe nephropathy.

CD40 Ligand and CD40 Deficiencies *Hyper-IgM syndrome* (HIGM) is a well-known PID that is usually classified as a B-cell immune deficiency (see Fig. 351-4 and below). It results from defective

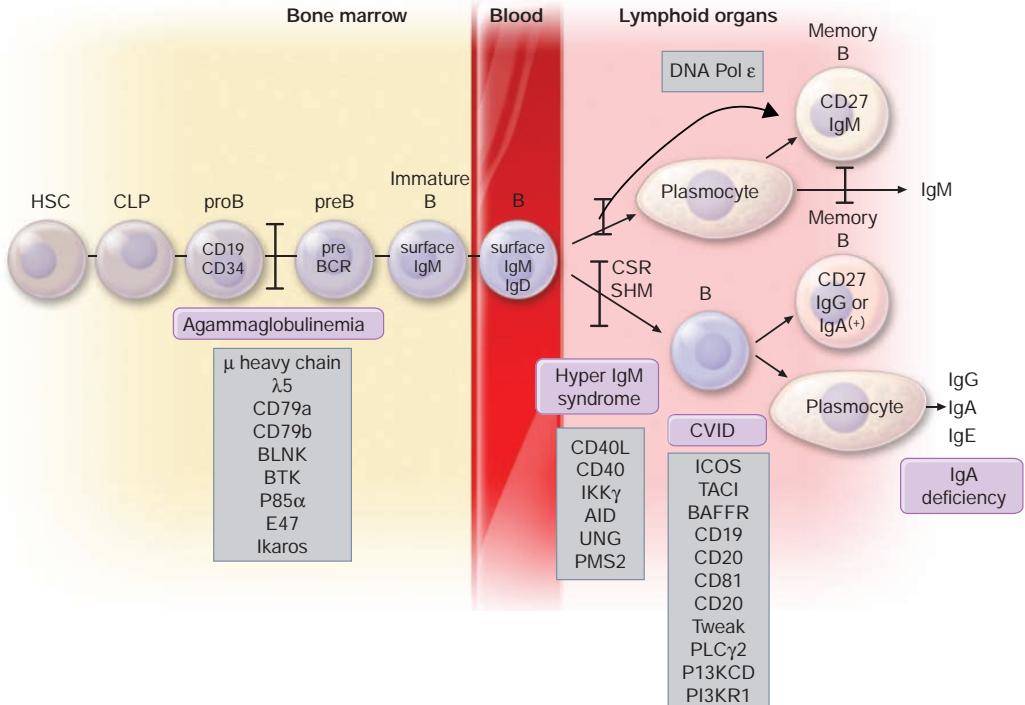


FIGURE 351-4 B-cell differentiation and related primary immunodeficiencies (PIDs). Hematopoietic stem cells (HSCs) differentiate into common lymphoid progenitors (CLPs), which give rise to pre-B cells. The B-cell differentiation pathway goes through the pre-B-cell stage (expression of the μ heavy chain and surrogate light chain), the immature B-cell stage (expression of surface IgM), and the mature B-cell stage (expression of surface IgM and IgD). The main phenotypic characteristics of these cells are indicated. In lymphoid organs, B cells can differentiate into plasma cells and produce IgM or undergo (in germinal centers) Ig class switch recombination (CSR) and somatic mutation of the variable region of V genes (SHM) that enable selection of high-affinity antibodies. These B cells produce antibodies of various isotypes and generate memory B cells. PIDs are indicated in the purple boxes. CVID, common variable immunodeficiency.

2716 immunoglobulin class switch recombination (CSR) in germinal centers and leads to profound deficiency in production of IgG, IgA, and IgE (although IgM production is maintained). Approximately half of HIGM sufferers are also prone to opportunistic infections, for example, interstitial pneumonitis caused by *P. jiroveci* (in young children), protracted diarrhea and cholangitis caused by *Cryptosporidium*, and infection of the brain with *Toxoplasma gondii*.

In the majority of cases, this condition has an X-linked inheritance and is caused by a deficiency in CD40 ligand (L). CD40L induces signaling events in B cells that are necessary for both CSR and adequate activation of other CD40-expressing cells that are involved in innate immune responses against the above-mentioned microorganisms. More rarely, the condition is caused by a deficiency in CD40 itself. The poorer prognosis of CD40L and CD40 deficiencies (relative to most other HIGM conditions) implies that (1) thorough investigations have to be performed in all cases of HIGM and (2) potentially curative HSCT should be discussed on a case-by-case basis for this group of patients.

Wiskott-Aldrich Syndrome WAS is a complex, recessive, X-linked disease with an incidence of ~1 in 200,000 live births. It is caused by mutations in the *WASP* gene that affect not only T lymphocytes but also the other lymphocyte subsets, dendritic cells, and platelets. WAS is typically characterized by the following clinical manifestations: recurrent bacterial infections, eczema, and bleeding caused by thrombocytopenia. However, these manifestations are highly variable—mostly as a consequence of the many different *WASP* mutations that have been observed. Null mutations predispose affected individuals to invasive and bronchopulmonary infections, viral infections, severe eczema, and autoimmune manifestations. The latter include autoantibody-mediated blood cytopenia, glomerulonephritis, skin and visceral vasculitis (including brain vasculitis), erythema nodosum, and arthritis. Another possible consequence of WAS is lymphoma, which may be virally induced (e.g., by EBV or Kaposi's sarcoma–associated herpesvirus). Thrombocytopenia can be severe and compounded by the peripheral destruction of platelets associated with autoimmune disorders. Hypomorphic mutations usually lead to milder outcomes that are generally limited to thrombocytopenia. It is noteworthy that even patients with “isolated” X-linked thrombocytopenia can develop severe autoimmune disease or lymphoma later in life. The immunologic workup is not very informative; there can be a relative CD8+ T-cell deficiency, frequently accompanied by low serum IgM levels and decreased antigen-specific antibody responses. A typical feature is reduced-sized platelets on a blood smear. Diagnosis is based on intracellular immunofluorescence analysis of WAS protein (WASp) expression in blood cells. WASp regulates the actin cytoskeleton and thus plays an important role in many lymphocyte functions, including cell adhesion and migration and the formation of synapses between antigen-presenting and target cells. Predisposition to autoimmune disorders is in part related to defective regulatory T cells. The treatment of WAS should match the severity of disease expression. Prophylactic antibiotics, immunoglobulin G (IgG) supplementation, and careful topical treatment of eczema are indicated. Although splenectomy improves platelet count in a majority of cases, this intervention is associated with a significant risk of infection (both before and after HSCT). Allogeneic HSCT is curative, with good results overall. Gene therapy trials have been performed. A similar condition has been reported in a girl with a deficiency in the Wiskott-Aldrich interacting protein (WIP).

A few other complex PIDs are worth mentioning. *Sp110* deficiency causes a T-cell PID with liver venoocclusive disease and hypogammaglobulinemia. *Chronic mucocutaneous candidiasis* (CMC) is a heterogeneous disease, considering the different inheritance patterns that have been observed. In some cases, chronic candidiasis is associated with late-onset bronchopulmonary infections, bronchiectasis, and brain aneurysms. Moderate forms of CMC are related to autoimmunity and AIRE deficiency (see below). In this setting, predisposition to *Candida* infection is associated with the detection of autoantibodies to T_{H17} cytokines. Recently, deficiencies in IL-17A, IL-17F, and IL-17 receptor A and C and in the associated protein Act1, and above all,

gain-of-function mutations in *STAT1* have been found to be associated with CMC. In all cases, CMC is related to defective T_{H17} function. Innate immunodeficiency in CARD9 also predisposes to chronic invasive fungal infection.

B LYMPHOCYTE DEFICIENCIES (TABLE 351-1, FIG. 351-4)

Deficiencies that predominantly affect B lymphocytes are the most frequent PIDs and account for 60–70% of all cases. B lymphocytes make antibodies. Pentameric IgMs are found in the vascular compartment and are also secreted at mucosal surfaces. IgG antibodies diffuse freely into extravascular spaces, whereas IgA antibodies are produced and secreted predominantly from mucosa-associated lymphoid tissues. Although Ig isotypes have distinct effector functions, including Fc receptor-mediated and (indirectly) C_3 receptor-dependent phagocytosis of microorganisms, they share the ability to recognize and neutralize a given pathogen. Defective antibody production therefore allows the establishment of invasive, pyogenic bacterial infections as well as recurrent sinus and pulmonary infections (mostly caused by *S. pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, and, less frequently, gram-negative bacteria). If left untreated, recurrent bronchial infections lead to bronchiectasis and, ultimately, cor pulmonale and death. Parasitic infections such as caused by *Giardia lamblia* and bacterial infections caused by *Helicobacter* and *Campylobacter* of the gut are also observed. A complete lack of antibody production (namely agammaglobulinemia) can also predispose affected individuals to severe, chronic, disseminated enteroviral infections causing meningoencephalitis, hepatitis, and a dermatomyositis-like disease.

Even with the most profound of B-cell deficiencies, infections rarely occur before the age of 6 months; this is because of transient protection provided by the transplacental passage of immunoglobulins during the last trimester of pregnancy. Conversely, a genetically nonimmunodeficient child born to a mother with hypogammaglobulinemia is, in the absence of maternal Ig substitution, usually prone to severe bacterial infections in utero and for several months after birth.

Diagnosis of B-cell PIDs relies on the determination of serum Ig levels (Table 351-2). Determination of antibody production following immunization with tetanus toxoid vaccine or nonconjugated pneumococcal polysaccharide antigens can also help diagnose more subtle deficiencies. Another useful test is B-cell phenotype determination in switched $\mu-\delta-$ CD27+ and nonswitched memory B cells ($\mu+\delta-$ CD27+). In agammaglobulinemic patients, examination of bone marrow B-cell precursors (Fig. 351-4) can help obtain a precise diagnosis and guide the choice of genetic tests.

Agammaglobulinemia Agammaglobulinemia is characterized by a profound defect in B-cell development (<1% of the normal B-cell blood count). In most patients, very low residual Ig isotypes can be detected in the serum. In 85% of cases, agammaglobulinemia is caused by a mutation in the *BTK* gene that is located on the X chromosome. The *BTK* gene product is a kinase that participates in (pre) B-cell receptor signaling. When the kinase is defective, there is a block (albeit a leaky one) at the pre-B to B-cell stage (Fig. 351-4). Detection of *BTK* by intracellular immunofluorescence of monocytes, and lack thereof in patients with X-linked agammaglobulinemia (XLA), is a useful diagnostic test. Not all of the mutations in *BTK* result in agammaglobulinemia, since some patients have a milder form of hypogammaglobulinemia and low but detectable B-cell counts. These cases should not be confused with common variable immunodeficiency (CVID, see below). About 10% of agammaglobulinemia cases are caused by alterations in genes encoding elements of the pre-B-cell receptor, i.e., the μ heavy chain, the $\lambda 5$ surrogate light chain, Ig α or Ig β , the scaffold protein BLNK, the p85 α subunit of phosphatidylinositol 3 phosphate kinase (P13K), the E47, and the Ikaros transcription factors. In 5% of cases, the defect is unknown. It is noteworthy that agammaglobulinemia can be observed in patients with ICF syndrome, despite the presence of normal peripheral B-cell counts. Lastly, agammaglobulinemia can be a manifestation of a myelodysplastic syndrome (associated or not with neutropenia). Treatment of agammaglobulinemic patients is based on immunoglobulin replacement (see below). Profound

hypogammaglobulinemia is also observed in adults, in association with thymoma.

Hyper-IgM (HIGM) Syndromes HIGM is a rare B-cell PID characterized by defective Ig CSR. It results in very low serum levels of IgG and IgA and elevated or normal serum IgM levels. The clinical severity is similar to that seen in agammaglobulinemia, although chronic lung disease and sinusitis are less frequent and enteroviral infections are uncommon. As discussed above, a diagnosis of HIGM involves screening for an X-linked CD40L deficiency and an autosomal recessive CD40 deficiency, which affect both B and T cells. In 50% of cases affecting only B cells, these isolated HIGM syndromes result from mutations in the gene encoding activation-induced deaminase, the protein that induces CSR in B-cell germinal centers. These patients usually have enlarged lymphoid organs. In the other 50% of cases, the etiology is unknown (except for rare UNG and PMS2 deficiencies). Furthermore, IgM-mediated autoimmunity and lymphomas can occur in HIGM syndrome. It is noteworthy that HIGM can result from fetal rubella syndrome or can be a predominant immunologic feature of other PIDs, such as the immunodeficiency associated with ectodermic anhydrotic hypoplasia X-linked NEMO deficiency and the combined T- and B-cell PIDs caused by DNA repair defects such as AT and Cernunnos deficiency.

Common Variable Immunodeficiency CVID is an ill-defined condition characterized by low serum levels of one or more Ig isotypes. Its prevalence is estimated to be 1 in 20,000. The condition is recognized predominantly in adults, although clinical manifestations can occur earlier in life. Hypogammaglobulinemia is associated with at least partially defective antibody production in response to vaccine antigens. B lymphocyte counts are often normal but can be low. Besides infections, CVID patients may develop lymphoproliferation (splenomegaly), granulomatous lesions, colitis, antibody-mediated autoimmune disease, and lymphomas that define disease prognosis. A family history is found in 10% of cases. A clear-cut dominant inheritance pattern is found in some families, whereas recessive inheritance is observed more rarely. In most cases, no molecular cause can be identified. A small number of patients in Germany were found to carry mutations in the ICOS gene encoding a T-cell membrane protein that contributes to B-cell activation and survival. In 10% of patients with CVID, monoallelic or biallelic mutations of the gene encoding TACI (a member of the tumor necrosis factor [TNF] receptor family that is expressed on B cells) have been found. In fact, heterozygous TACI mutations correspond to a genetic susceptibility factor, since similar heterozygous mutations are found in 1% of controls. NFkB1 transcription factor mutations have been found in a small fraction of patients with CVID. The B-cell activating factor (BAFF) receptor was found to be defective in a kindred with CVID, although not all individuals carrying the mutation have CVID. A group of patients with hypogammaglobulinemia and lymphoproliferation was shown to exhibit dominant gain-of-function mutations in the PIK3CD gene encoding the p110 δ form of PI3 kinase or in the PI3KR1 gene encoding the regulatory p85 α subunit of PI3 kinase. Rare cases of hypogammaglobulinemia were found to be associated with CD19, CD20, CD21, and CD81 deficiencies. These patients have B cells that can be identified by typing for other B-cell markers.

A diagnosis of CVID should be made after excluding the presence of hypomorphic mutations associated with agammaglobulinemia or more subtle T-cell defects; this is particularly the case in children. It is possible that many cases of CVID result from a constellation of factors, rather than a single genetic defect. Hypogammaglobulinemia can be associated with neutropenia and lymphopenia in the WHIM syndrome caused by a dominant gain-of-function mutation of CXCR4, resulting in cell retention in the bone marrow.

Selective Ig Isotype Deficiencies IgA deficiency and CVID represent polar ends of a clinical spectrum due to the same underlying gene defect(s) in a large subset of these patients. IgA deficiency is the most common PID; it can be found in 1 in every 600 individuals. It is asymptomatic in most cases; however, individuals may present

with increased numbers of acute and chronic respiratory infections that may lead to bronchiectasis. In addition, over their lifetime, these patients experience an increased susceptibility to drug allergies, atopic disorders, and autoimmune diseases. Symptomatic IgA deficiency is probably related to CVID, since it can be found in relatives of patients with CVID. Furthermore, IgA deficiency may progress to CVID. It is thus important to assess serum Ig levels in IgA-deficient patients (especially when infections occur frequently) in order to detect changes that should prompt the initiation of immunoglobulin replacement. Selective IgG2 (+G4) deficiency (which in some cases may be associated with IgA deficiency) can also result in recurrent sinopulmonary infections and should thus be specifically sought in this clinical setting. These conditions are ill-defined and often transient during childhood. A pathophysiologic explanation has not been found.

Selective Antibody Deficiency to Polysaccharide Antigens

Some patients with normal serum Ig levels are prone to *S. pneumoniae* and *H. influenzae* infections of the respiratory tract. Defective production of antibodies against polysaccharide antigens (such as those in the *S. pneumoniae* cell wall) can be observed and is probably causative. This condition may correspond to a defect in marginal zone B cells, a B-cell subpopulation involved in T-independent antibody responses.

Immunoglobulin Replacement IgG antibodies have a half-life of 21–28 days. Thus, injection of plasma-derived polyclonal IgG containing a myriad of high-affinity antibodies can provide protection against disease-causing microorganisms in patients with defective IgG antibody production. This form of therapy should not be based on laboratory data alone (i.e., IgG and/or antibody deficiency) but should be guided by the occurrence or not of infections; otherwise, patients might be subjected to unjustified IgG infusions. Immunoglobulin replacement can be performed by IV or subcutaneous routes. In the former case, injections have to be repeated every 3–4 weeks, with a residual target level above 800 mg/mL in patients who had very low IgG levels prior to therapy. Subcutaneous injections are typically performed once a week, although the frequency can be adjusted on a case-by-case basis. A trough level above 800 mg/mL is desirable. Whatever the mode of administration, the main goal is to reduce the frequency of the respiratory tract infections and prevent chronic lung and sinus disease. The two routes appear to be equally safe and efficacious, and so the choice should be left to the preference of the patient.

In patients with chronic lung disease, chest physical therapy with good pulmonary toilet and the use of antibiotics, notably azithromycin, are also needed. Immunoglobulin replacement is well tolerated by most patients, although the selection of the best-tolerated Ig preparation may be necessary in certain cases. Since IgG preparations contain a small proportion of IgAs, caution should be taken in patients with residual antibody production capacity and a complete IgA deficiency, as these subjects may develop anti-IgA antibodies that can trigger anaphylactic shock. These patients should be treated with IgA-free IgG preparations. Immunoglobulin replacement is a lifelong therapy; its rationale and procedures have to be fully understood and mastered by the patient and his or her family in order to guarantee the strict observance required for efficacy.

PRIMARY IMMUNODEFICIENCIES AFFECTING REGULATORY PATHWAYS (TABLE 351-1)

An increasing number of PIDs have been found to cause homeostatic dysregulation of the immune system, either alone or in association with increased vulnerability to infections. Defects of this type affecting the innate immune system and autoinflammatory syndromes will not be covered in this chapter. However, three specific entities (hemophagocytic lymphohistiocytosis [HLH], lymphoproliferation, and autoimmunity) will be described below.

HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

HLH is characterized by an unremitting activation of CD8+ T lymphocytes and macrophages that leads to organ damage (notably in the

2718 liver, bone marrow, and central nervous system). This syndrome results from a broad set of inherited diseases, most of which impair T and NK lymphocyte cytotoxicity. The manifestations of HLH are often induced by a viral infection. EBV is the most frequent trigger. In severe forms of HLH, disease onset may start during the first year of life or even (in rare cases) at birth.

Diagnosis relies on the identification of the characteristic symptoms of HLH (fever, hepatosplenomegaly, edema, neurologic diseases, blood cytopenia, increased liver enzymes, hypofibrinogenemia, high triglyceride [hyperferritinemia] levels, elevated markers of T-cell activation, and hemophagocytic features in the bone marrow or cerebrospinal fluid). Functional assays of postactivation cytotoxic granule exocytosis (CD107 fluorescence at the cell membrane) can suggest genetically determined HLH. The conditions can be classified into three subsets:

1. Familial HLH with autosomal recessive inheritance, including perforin deficiency (30% of cases) that can be recognized by assessing intracellular perforin expression; Munc13-4 deficiency (30% of cases); syntaxin 11 deficiency (10% of cases); Munc18-2 deficiency (20% of cases); and a few residual cases that lack a known molecular defect.
2. HLH with partial albinism. Three conditions combine HLH and abnormal pigmentation, where hair examination can help in the diagnosis: Chédiak-Higashi syndrome, Griscelli syndrome, and Hermansky-Pudlak syndrome type II. Chédiak-Higashi syndrome is also characterized by the presence of giant lysosomes within leukocytes (**Chap. 64**), in addition to a primary neurologic disorder with slow progression of symptoms over time.
3. XLP is characterized in most patients by the induction of HLH following EBV infection, while other patients develop progressive hypogammaglobulinemia similar to what is observed in CVID and/or certain lymphomas. XLP is caused by a mutation in the *SH2D1A* gene that encodes the adaptor protein SAP (associated with a SLAM family receptor). Several immunologic abnormalities have been described, including low 2B4-mediated NK cell cytotoxicity, impaired differentiation of NKT cells, defective antigen-induced T-cell death, and defective T-cell helper activity for B cells. A related disorder (XLP2) has recently been described. It is also X-linked and induces HLH (frequently after EBV infection), although the clinical manifestation may be less pronounced. The condition is associated with a deficiency of the antiapoptotic molecule XIAP. The pathophysiology of XLP2 remains unclear; however, it may be related to control of inflammation in macrophages as there is a functional link between XIAP and NLRC4, an inflammasome component, in which gain of function can also induce HLH. XLP2 is also frequently associated with colitis.

HLH is a life-threatening complication. The treatment of this condition requires aggressive immunosuppression with either the cytotoxic agent etoposide or anti-T-cell antibodies; specific therapy targeting IFN- γ , which is critical in causing HLH, is an additional option to consider. Once remission has been achieved, HSCT should be performed, since it provides the only curative form of therapy. Of note, acquired forms of HLH are more commonly observed in adults as a complication of infection, malignancies or autoimmune diseases or sometimes on its own.

AUTOIMMUNE LYMPHOPROLIFERATIVE SYNDROME

Autoimmune lymphoproliferative syndrome (ALPS) is characterized by nonmalignant T and B lymphoproliferation causing splenomegaly and enlarged lymph nodes; 70% of patients also display autoimmune manifestations such as autoimmune cytopenias, Guillain-Barré syndrome, uveitis, and hepatitis (**Chaps. 66 and 349**). A hallmark of ALPS is the presence of CD4–CD8– TCR $\alpha\beta$ T cells (2–50%) in the blood of affected individuals. Hypergammaglobulinemia involving IgG and IgA is also frequently observed. The syndrome is caused by

a defect in Fas-mediated apoptosis of lymphocytes, which can thus accumulate and mediate autoimmunity. Furthermore, ALPS can lead to malignancies.

Most patients carry a heterozygous mutation in the gene encoding Fas that is characterized by dominant inheritance and variable penetrance, depending on the nature of the mutation. A rare and severe form of the disease with early onset can be observed in patients carrying a biallelic mutation of Fas, which profoundly impairs the protein's expression and/or function. Fas-ligand, caspase 10, caspase 8, and somatic neuroblastoma RAS viral oncogene homologue (NRAS) and KRAS mutations have also been reported in a few cases of ALPS. Many cases of ALPS have not been precisely delineated at the molecular level. A B cell–predominant ALPS has recently been found associated with a protein kinase C δ gene mutation. Treatment of ALPS is essentially based on the use of proapoptotic drugs, which need to be carefully administered in order to avoid toxicity.

COLITIS, AUTOIMMUNITY, AND PRIMARY IMMUNODEFICIENCIES

Several PIDs (most of which are T cell-related) can cause severe gut inflammation. The prototypic example is *immunodysregulation polyendocrinopathy enteropathy X-linked syndrome* (IPEX), characterized by a widespread inflammatory enteropathy, food intolerance, skin rashes, autoimmune cytopenias, and diabetes. The syndrome is caused by loss-of-function mutations in the gene encoding the transcription factor FOXP3, which is required for the acquisition of effector function by regulatory T cells. In most cases of IPEX, CD4+CD25+ regulatory T cells are absent from the blood. This condition has a poor prognosis and requires aggressive immunosuppression. The only possible curative approach is allogeneic HSCT. IPEX-like syndromes that lack a FOXP3 mutation have also been described. In some cases, CD25 (IL-2 receptor α subunit) and CD122 (IL-2 receptor β subunit) deficiencies have been found. Defective IL-2 receptor expression also impairs regulatory cell expansion/function. This functional T-cell deficiency means that IL-2 receptor-deficient patients are also at increased risk of opportunistic infections. It is noteworthy that abnormalities in regulatory T cells have been described in other PID settings, such as in Omenn syndrome, STAT5b deficiency, STIM1 (Ca flux) deficiency, and WAS; these abnormalities may account (at least in part) for the occurrence of inflammation and autoimmunity. The autoimmune features observed in a small fraction of patients with DiGeorge's syndrome may have the same cause. Severe, early-onset inflammatory gut disease has been described in patients with a deficiency in the IL-10 receptor or IL-10.

Dominant mutations in genes encoding the regulatory molecule CTLA-4, recessive mutations in the gene encoding LRBA (a molecule involved in recycling of CTLA-4), as well as dominant gain-of-function mutation of STAT3 cause a multifaceted lymphoproliferative and autoimmune syndrome, frequently involving inflammatory bowel disease that can be associated with hypogammaglobulinemia. Molecular diagnosis is required before adapted targeted therapies are undertaken.

A distinct autoimmune entity is observed in *autoimmune polyendocrinopathy candidiasis ectodermal dysplasia* (APECED) syndrome, which is characterized by autosomal recessive inheritance. It consists of multiple autoimmune manifestations that can affect solid organs in general and endocrine glands in particular. Mild, chronic *Candida* infection is often associated with this syndrome. The condition is due to mutations in the autoimmune regulator (AIRE) gene and results in impaired thymic expression of self-antigens by medullary epithelial cells and impaired negative selection of self-reactive T cells that leads to autoimmune manifestations.

A combination of hypogammaglobulinemia, autoantibody production, cold-induced urticaria or skin granulomas, or autoinflammation has been reported and has been termed *PLC γ 2-associated antibody deficiency and immune dysregulation* (PLAID or APLAID).

CONCLUSION

The variety and complexity of the clinical manifestations of the many different PIDs strongly indicate that it is important to raise awareness of these diseases. Indeed, early diagnosis is essential for establishing an appropriate therapeutic regimen. Hence, patients with suspected PIDs must always be referred to experienced clinical centers that are able to perform appropriate molecular and genetic tests. A precise molecular diagnosis is not only necessary for initiating the most suitable treatment, but is also important for genetic counseling and prenatal diagnosis.

One pitfall that may hamper diagnosis is the high variability that is associated with many PIDs. Variable disease expression can result from the differing consequences of various mutations associated with a given condition, as exemplified by WAS and, to a lesser extent, XLA. There can also be effects of modifier genes (as also suspected in XLA) and environmental factors such as EBV infection that can be the main trigger of disease in XLP conditions. Furthermore, it has recently been established that somatic mutations in an affected gene can attenuate the phenotype of a number of T-cell PIDs. This has been described for ADA deficiency, X-linked SCID, RAG deficiencies, NF- κ B essential modulator (NEMO) deficiency, and, most frequently, WAS. In contrast, somatic mutations can create disease states analogous to PID, as reported for ALPS. Lastly, cytokine-neutralizing autoantibodies can mimic a PID, as shown for IFN- γ .

Many aspects of the pathophysiology of PIDs are still unknown, and the disease-causing gene mutations have not been identified in all cases (as illustrated by CVID and IgA deficiency). However, our medical understanding of PIDs has now reached the stage where scientifically based approaches to the diagnosis and treatment of these diseases can be implemented. A genetic diagnosis has become a milestone step in the care of PID patients.

FURTHER READING

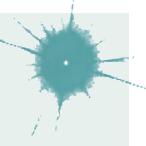
- Abolhassani H et al: Current genetic landscape in common variable immune deficiency. *Blood* 135:656, 2020.
- Casanova JL et al: Guidelines for genetic studies in single patients: Lessons from primary immunodeficiencies. *J Exp Med* 211:2137, 2014.
- Fischer A, Hacein-Bey-Abina S: Gene therapy for severe combined immunodeficiencies and beyond. *J Exp Med* 217:e20190607, 2020.
- Holland SM: Chronic granulomatous disease. *Hematol Oncol Clin North Am* 27:89, viii, 2013.
- Kwan A et al: Newborn screening for severe combined immunodeficiency in 11 screening programs in the United States. *JAMA* 312:729, 2014.
- Notarangelo LD: Functional T cell immunodeficiencies (with T cells present). *Annu Rev Immunol* 31:195, 2013.
- Ochs HD et al (eds): *Primary Immunodeficiencies: A Molecular and Genetic Approach*. New York, Oxford University Press, 2013.
- Picard C, Fischer A: Contribution of high-throughput DNA sequencing to the study of primary immunodeficiencies. *Eur J Immunol* 44:2854, 2014.
- Tangye SG et al: Human inborn errors of immunity: 2019 update on the classification from the International Union of Immunological Societies Expert Committee. *J Clin Immunol* 40:24, 2020.

Section 2 Disorders of Immune-Mediated Injury

352

Urticaria, Angioedema, and Allergic Rhinitis

Katherine L. Tuttle, Joshua A. Boyce



INTRODUCTION

The term *atopy* implies a tendency to manifest asthma, rhinitis, urticaria, food allergy, and atopic dermatitis alone or in combination, in association with the presence of allergen-specific IgE. However, individuals without an atopic background may also develop hypersensitivity reactions, particularly urticaria and anaphylaxis, associated with the presence of IgE. Since mast cells are key effector cells in allergic rhinitis and asthma, and the dominant effector in urticaria, anaphylaxis, and systemic mastocytosis, mast cell developmental biology, activation pathway, product profile, and target tissues will be considered in the introduction to these clinical disorders. Dysregulation of mast cell development seen in mastocytosis will be covered in a separate chapter.

The binding of IgE to human mast cells and basophils, a process termed *sensitization*, prepares these cells for subsequent antigen-specific activation. The high-affinity Fc receptor for IgE, designated Fc ϵ RI, is composed of one α , one β , and two disulfide-linked γ chains, which together cross the plasma membrane seven times. The α chain is responsible for IgE binding, and the β and γ chains provide for signal transduction that follows the aggregation of the sensitized tetrameric receptors by polymeric antigen. The binding of IgE stabilizes the α chain at the plasma membrane, thus increasing the density of Fc ϵ RI receptors at the cell surface while sensitizing the cell for effector responses. This accounts for the correlation between serum IgE levels and the numbers of Fc ϵ RI receptors detected on circulating basophils. Signal transduction is initiated through the action of a Src family-related tyrosine kinase termed Lyn that is constitutively associated with the β chain. Lyn transphosphorylates the canonical immunoreceptor tyrosine-based activation motifs (ITAMs) of the β and γ chains of the receptor, resulting in recruitment of more active Lyn to the β chain and of Syk tyrosine kinase. The phosphorylated tyrosines in the ITAMs function as binding sites for the tandem src homology two (SH2) domains within Syk. Syk activates not only phospholipase Cy, which associates with the linker of activated T cells at the plasma membrane, but also phosphatidylinositol 3-kinase to provide phosphatidylinositol-3,4,5-trisphosphate, which allows membrane targeting of the Tec family kinase Btk and its activation by Lyn. In addition, the Src family tyrosine kinase Fyn becomes activated after aggregation of IgE receptors and phosphorylates the adapter protein Gab2 that enhances activation of phosphatidylinositol 3-kinase. Indeed, this additional input is essential for mast cell activation, but it can be partially inhibited by Lyn, indicating that the extent of mast cell activation is in part regulated by the interplay between these Src family kinases. Activated phospholipase Cy cleaves phospholipid membrane substrates to provide inositol-1,4,5-trisphosphate (IP₃) and 1,2-diacylglycerols (1,2-DAGs) to mobilize intracellular calcium and activate protein kinase C, respectively. The subsequent opening of calcium-regulated activated channels provides the sustained elevations of intracellular calcium required to recruit the mitogen-activated protein kinases ERK, JNK, and p38 (serine/threonine kinases), which provide cascades to augment arachidonic acid release and to mediate nuclear translocation of transcription factors for various cytokines. The calcium ion-dependent activation of phospholipases cleaves membrane phospholipids to generate lysophospholipids, which, like 1,2-DAG, may facilitate the fusion of the secretory granule perigranular membrane with the cell membrane, a step that releases the membrane-free granules containing the preformed mast cell mediators.

The secretory granule of the human mast cell has a crystalline structure. IgE-dependent cell activation results in solubilization and

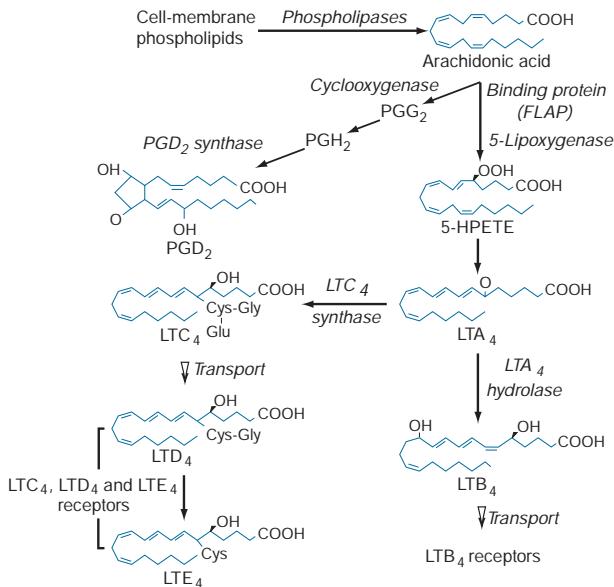


FIGURE 352-1 Pathways for biosynthesis and release of membrane-derived lipid mediators from mast cells. In the 5-lipoxygenase pathway, leukotriene A₄ (LTA₄) is the intermediate from which the terminal-pathway enzymes generate the distinct final products, leukotriene C₄ (LTC₄) and leukotriene B₄ (LTB₄), which leave the cell by separate saturable transport systems. Gamma glutamyl transpeptidase and a dipeptidase then cleave glutamic acid and glycine from LTC₄ to form LTD₄ and LTE₄, respectively. The major mast cell product of the cyclooxygenase system is PGD₂.

swelling of the granule contents within the first minute of receptor perturbation; this reaction is followed by the ordering of intermediate filaments about the swollen granule, movement of the granule toward the cell surface, and fusion of the perigranular membrane with that of other granules and with the plasmalemma to form extracellular channels for mediator release while maintaining cell viability.

In addition to exocytosis, aggregation of FcεRI initiates two additional pathways for generation of bioactive products, namely, lipid mediators, chemokines, and cytokines. Cytokines elaborated by mast cells include tumor necrosis factor α (TNF-α), interleukin (IL) 1, IL-6, IL-4, IL-5, IL-13, and granulocyte-macrophage colony-stimulating factor (GM-CSF).

Lipid mediator generation (Fig. 352-1) involves translocation of calcium ion-dependent cytosolic phospholipase A₂ to the outer nuclear membrane, with subsequent release of arachidonic acid for metabolic processing by the distinct prostanoid and leukotriene pathways. The constitutive prostaglandin endoperoxide synthase-1 (PGHS-1/cyclooxygenase-1) and the de novo inducible PGHS-2 (cyclooxygenase-2) convert released arachidonic acid to the sequential intermediates, prostaglandins G₂ and H₂. The glutathione-dependent hematopoietic prostaglandin D₂ (PGD₂) synthase then converts PGH₂ to PGD₂, the predominant mast cell prostanoid. The PGD₂ receptor DP₁ is expressed by platelets, natural killer cells, dendritic cells, and epithelial cells, whereas DP₂ is expressed by T_H2 lymphocytes, innate lymphoid type 2 cells, eosinophils, and basophils. Mast cells also generate thromboxane A₂ (TXA₂), a short lived but powerful mediator that induces bronchoconstriction and platelet activation through the T prostanoid (TP) receptor.

For leukotriene biosynthesis, the released arachidonic acid is metabolized by 5-lipoxygenase (5-LO) in the presence of an integral nuclear membrane protein, 5-LO activating protein (FLAP). The calcium ion-dependent translocation of 5-LO to the nuclear membrane converts the arachidonic acid to the sequential intermediates, 5-hydroperoxyeicosatetraenoic acid (5-HETE) and leukotriene (LT) A₄. LTA₄ is conjugated with reduced glutathione by LTC₄ synthase, an integral nuclear membrane protein homologous to FLAP. Intracellular LTC₄ is released by a carrier-specific export step for extracellular

metabolism to the additional cysteinyl leukotrienes, LTD₄ and LTE₄, by the sequential removal of glutamic acid and glycine. Alternatively, cytosolic LTA₄ hydrolase converts some LTA₄ to the dihydroxy leukotriene LTB₄, which also undergoes specific export. Two receptors for LTB₄, BLT₁ and BLT₂, mediate chemotaxis of human neutrophils. Two receptors for the cysteinyl leukotrienes, CysLT₁ and CysLT₂, are present on smooth muscle of the airways and the microvasculature and on hematopoietic cells such as macrophages, eosinophils, and mast cells. Whereas the CysLT₁ receptor has a preference for LTD₄ and is blocked by the receptor antagonists in clinical use, the CysLT₂ receptor is equally responsive to LTD₄ and LTC₄, is unaffected by these antagonists, and is a negative regulator of the function of the CysLT₁ receptor. LTD₄, acting at CysLT₁ receptors, is the most potent known bronchoconstrictor, whereas LTE₄ induces a vascular leak and mediates the recruitment of eosinophils to the bronchial mucosa. Recently, GPR99, initially identified as a receptor for α-ketoglutarate, was identified as an LTE₄ receptor. The lysophospholipid formed during the release of arachidonic acid from 1-*O*-alkyl-2-acyl-sn-glyceryl-3-phosphorylcholine can be acetylated in the second position to form platelet-activating factor (PAF). Serum levels of PAF correlated positively with the severity of anaphylaxis to peanut in a recent study, whereas the levels of PAF acetyl hydrolase (a PAF-degrading enzyme) were inversely related to the same outcome.

Human mast cells express receptors for anaphylatoxin, C5a and C3a, toll-like receptors, receptors for epithelial alarmins thymic stromal lymphopoietin (TSLP) and IL-33, and a newly recognized Mas-related G protein-coupled receptor (MRGPX2), all which activate mast cells in an IgE-dependent manner. MRGPX2 is a target of many small-molecule drugs with a central tetrahydroisoquinoline motif, such as ciprofloxacin and rocuronium, which may explain the observed episodes of anaphylaxis to these medications without evidence of IgE-mediated hypersensitivity.

Unlike most other cells of bone marrow origin, mast cells circulate as committed progenitors lacking their characteristic secretory granules. These committed progenitors express *c-kit*, the receptor for stem cell factor (SCF). Unlike most other lineages, they retain and increase *c-kit* expression with maturation. The SCF interaction with *c-kit* is an absolute requirement for the development of both constitutive connective tissue and skin mast cells and for the accumulation of mast cells at mucosal surfaces during T_H2-type immune responses. Several T cell-derived cytokines (IL-3, IL-4, IL-5, and IL-9) can potentiate SCF-dependent mast cell proliferation and/or survival in vitro in mice and humans. Indeed, mast cells are absent from the intestinal mucosa in clinical T-cell deficiencies but are present in the submucosa. Historical mast cell classification has been based on the immunodetection of secretory granule neutral proteases. Mast cells in the lung parenchyma and intestinal mucosa selectively express tryptase, and those in the intestinal and airway submucosa, perivascular spaces, skin, lymph nodes, and breast parenchyma express tryptase, chymase, and carboxypeptidase A (CPA). Selective environmental cues, such as T_H2 inflammation, can lead to different protease expression; in the mucosal epithelium of severe asthmatics and apical epithelium of nasal polyps, mast cells can express tryptase and CPA without chymase. The secretory granules of mast cells selectively positive for tryptase exhibit closed scrolls with a periodicity suggestive of a crystalline structure by electron microscopy, whereas the secretory granules of mast cells with multiple proteases are scroll-poor, with an amorphous or lattice-like appearance. In addition to immunodetection of proteases, expression profiling through single-cell RNA sequencing methods has further elucidated different mast cell populations.

Mast cells are distributed at cutaneous and mucosal surfaces and in submucosal tissues about venules and could influence the entry of foreign substances by their rapid response capability (Fig. 352-2). Upon stimulus-specific activation and secretory granule exocytosis, histamine and acid hydrolases are solubilized, whereas the neutral proteases, which are cationic, remain largely bound to the anionic proteoglycans, heparin and chondroitin sulfate E, with which they function as a complex. Histamine and the various lipid mediators (PGD₂,

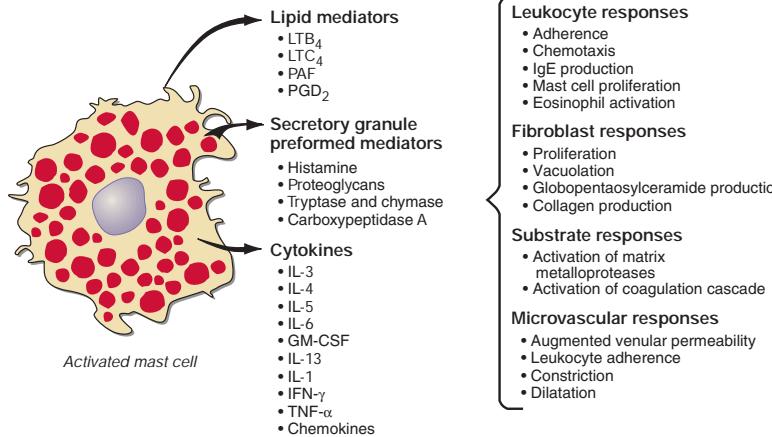


FIGURE 352-2 Bioactive mediators of three categories generated by IgE-dependent activation of murine mast cells can elicit common but sequential target cell effects leading to acute and sustained inflammatory responses. GM-CSF, granulocyte-macrophage colony-stimulating factor; IL, interleukin; IFN, interferon; LT, leukotriene; PAF, platelet-activating factor; PGD₂, prostaglandin D₂; TNF, tumor necrosis factor.

LTC₄/D₄/E₄, PAF) alter venular permeability, thereby allowing influx of plasma proteins such as complement and immunoglobulins, whereas LTB₄ mediates leukocyte–endothelial cell adhesion and subsequent directed migration (chemotaxis). The accumulation of leukocytes and plasma opsonins facilitates defense of the microenvironment. The inflammatory response can also be detrimental, as in asthma, where the smooth-muscle constrictor activity of the cysteinyl leukotrienes is evident and much more potent than that of histamine.

The cellular component of the mast cell-mediated inflammatory response is augmented and sustained by cytokines and chemokines. IgE-dependent activation of human skin mast cells *in situ* elicits TNF- α production and release, which in turn induces endothelial cell responses favoring leukocyte adhesion. Similarly, activation of purified human lung mast cells or cord blood–derived cultured mast cells *in vitro* results in substantial production of proinflammatory (TNF- α) and immunomodulatory cytokines (IL-4, IL-5, IL-13) and chemokines. Bronchial biopsy specimens from patients with asthma reveal that mast cells are immunohistochemically positive for IL-4 and IL-5, but that the predominant localization of IL-4, IL-5, and GM-CSF is to T cells, defined as T_H2 by this profile. IL-4 modulates the T-cell phenotype to the T_H2 subtype, determines the isotype switch to IgE (as does IL-13), and upregulates Fc ϵ R_I-mediated expression of cytokines by mast cells based on *in vitro* studies.

An immediate and late cellular phase of allergic inflammation can be induced in the skin, nose, or lung of some allergic humans with local allergen challenge. The immediate phase in the nose involves pruritus and watery discharge; in the lung, it involves bronchospasm and mucus secretion; and in the skin, it involves a wheal-and-flare response with pruritus. Diminished nasal patency, reduced pulmonary function, or erythema with swelling at the skin site in a late-phase response at 6–8 h is associated with biopsy findings of infiltrating and activated T_H2 cells, eosinophils, basophils, and some neutrophils. The progression from early mast cell activation to late cellular infiltration has been used as an experimental surrogate of rhinitis or asthma. However, in asthma, there is an intrinsic hyperreactivity of the airways independent of the associated inflammation. Moreover, early- and late-phase responses (at least in the lung) are far more sensitive to blockade of IgE-dependent mast cell activation (or actions of histamine and cysteinyl leukotrienes) than are spontaneous or virally induced asthma exacerbations.

Consideration of the mechanism of immediate-type hypersensitivity diseases in the human has focused largely on the IgE-dependent recognition of otherwise innocuous substances. A region of chromosome 5 (5q23-31) contains genes implicated in the control of IgE levels including IL-4 and IL-13, as well as IL-3 and IL-9, which are involved in mucosal mast cell hyperplasia, and IL-5 and GM-CSF, which are

Leukocyte responses

- Adherence
- Chemotaxis
- IgE production
- Mast cell proliferation
- Eosinophil activation

Fibroblast responses

- Proliferation
- Vacuolation
- Glucopentaosylceramide production
- Collagen production

Substrate responses

- Activation of matrix metalloproteases
- Activation of coagulation cascade

Microvascular responses

- Augmented venular permeability
- Leukocyte adherence
- Constriction
- Dilatation

central to eosinophil development and their enhanced tissue viability. Genes with linkage to the specific IgE response to particular allergens include those encoding the major histocompatibility complex (MHC) and certain chains of the T-cell receptor (TCR- $\alpha\delta$). The complexity of atopy and the associated diseases includes susceptibility, severity, and therapeutic responses, each of which is among the separate variables modulated by both innate and adaptive immune stimuli.

The induction of allergic disease requires sensitization of a predisposed individual to a specific allergen. The greatest propensity for the development of atopic allergy occurs in childhood and early adolescence. The allergen is processed by antigen-presenting cells of the monocytic lineage (particularly dendritic cells) located throughout the body at epithelial surfaces that contact the outside environment, such as the nose, lungs, eyes, skin, and intestine. These antigen-presenting cells present the epitope-bearing peptides via their MHC to T helper cells and their subsets. The T-cell response depends both on cognate recognition and on the cytokine microenvironment provided by the antigen-presenting dendritic cells, with IL-4 directing a T_H2 subset, interferon (IFN) γ a T_H1 profile, and IL-6 with transforming growth factor β (TGF- β) a T_H17 subset. Allergens can induce an epithelial alarmin response, with expression of IL-25, TSLP, and IL-33, which stimulate group 2 innate lymphoid cells, which can generate large quantities of IL-5 and IL-13. Allergens also contain pattern recognition ligands that facilitate the immune response by direct initiation of cytokine generation from innate cell types such as basophils, mast cells, eosinophils, and others. The T_H2 response is associated with activation of specific B cells that can also present allergens or that transform into plasma cells for antibody production. Synthesis and release into the plasma of allergen-specific IgE results in sensitization of Fc ϵ R_I-bearing cells such as mast cells and basophils, which become activated on exposure to the specific allergen. In certain diseases, including those associated with atopy, the monocyte and eosinophil populations can express a trimeric Fc ϵ R_I, which lacks the β chain, and yet respond to its aggregation.

URTICARIA AND ANGIOEDEMA

DEFINITION

Urticaria and angioedema represent the same pathophysiologic process occurring at different levels of the skin. Urticaria involves dilation of vascular structures in the superficial dermis, while angioedema originates from the deeper dermis and subcutaneous tissues. Not surprisingly, they often appear together, with roughly 40% of patients reporting both, and affect >20% of the population at some time during their life span. Urticaria can occur on any area of the body

as well-circumscribed wheals with erythematous raised serpiginous borders and blanched centers that may coalesce to become giant wheals. Urticular lesions last for <24 h, are intensely pruritic, frequently migrate around the body, and leave no bruising or scarring. Angioedema is marked by dramatic swelling with more pain than pruritus and minimal erythema, which may develop with a pruritic prodrome and takes hours to days to resolve. Acute urticaria and/or angioedema are episodes that occur for <6 weeks' duration, whereas attacks persisting for >6 weeks are designated chronic.

PREDISPOSING FACTORS AND ETIOLOGY

Acute or chronic urticaria and/or angioedema can occur at any point in the life span with the third to fifth decades the most common for chronic disease. Women are affected more often than men with a slight predominance for those with a history of atopy. Acute urticaria is most often the result of exposure to a food, environmental, or drug allergen or viral infection, while chronic urticaria is often idiopathic. More than two-thirds of new-onset urticaria cases are ultimately diagnosed as acute.

The classification of urticaria-angioedema presented in **Table 352-1** focuses on the different mechanisms for eliciting clinical disease and can be useful for differential diagnosis.

Additional etiologies include physical stimuli such as cold, heat, solar UV radiation, exercise, and mechanical irritation. The physical urticarias can be distinguished by the precipitating event and other aspects of the clinical presentation. *Dermatographism*, which occurs in 2–5% of the population, is defined by the appearance of a linear wheal with surrounding erythema at the site of a brisk stroke with a firm object (**Fig. 352-3**). Dermatographism has a prevalence that peaks in the second to third decades. It is not influenced by atopy and has a duration generally of <5 years. *Pressure urticaria*, which often accompanies chronic idiopathic urticaria, presents in response to a sustained stimulus such as a shoulder strap or belt, running (feet), or manual labor (hands). *Cholinergic urticaria* is distinctive in that the pruritic wheals are of small size (1–2 mm) and are surrounded by a large area of erythema; attacks are precipitated by fever, a hot bath or shower, or exercise and are presumptively attributed to a rise in core body temperature. *Exercise-induced anaphylaxis* can be precipitated by exertion alone or can be dependent on food ingestion prior to exercise. There is an association with the presence of IgE specific for α -5 gliadin, a component of wheat. The clinical presentation can be limited to flushing, erythema, and pruritic urticaria but may progress to angioedema of the



FIGURE 352-3 Dermographic urticarial lesion induced by stroking the forearm lightly with the edge of a tongue blade. The photograph, taken after 10 min, demonstrates a prominent wheal-and-flare reaction in the shape of a hashtag. (Photograph provided by Katherine N. Cahill, MD, Harvard Medical School.)

face, oropharynx, larynx, or intestine and/or to vascular collapse; it is distinguished from cholinergic urticaria by presenting with wheals of conventional size and by not occurring with passive heating. *Solar urticaria* is subdivided into six groups by the response to specific portions of the light spectrum. *Cold urticaria* is local at body areas exposed to low ambient temperature or cold objects but can progress to vascular collapse with immersion in cold water (swimming). *Vibratory urticaria and angioedema* may occur after years of occupational exposure or can be idiopathic; it may be accompanied by cholinergic urticaria. In rare cases, variants of cold and vibratory urticaria are inherited and syndromic conditions, with mutations in the NLRP3 component of inflammasome leading to familial cold autoinflammatory syndrome, and mutations in the mast cell mechanoreceptor ADGRE2 associated with familial vibratory urticaria. Other rare forms of physical allergy, always defined by stimulus-specific elicitation, include *local heat urticaria*, *aquagenic urticaria* from contact with water of any temperature (sometimes associated with polycythemia vera), and *contact urticaria* from direct interaction with some chemical substance (such as latex).

Isolated Angioedema Angioedema without urticaria can be idiopathic or due to the generation of bradykinin in the setting of C1 inhibitor (C1INH) deficiency that may be inborn as an autosomal dominant mutation or may be acquired through the appearance of an autoantibody in the setting of malignancy or autoimmune disease. The angiotensin-converting enzyme (ACE) inhibitors can provoke a similar clinical presentation in 0.2–0.7% of exposed patients due to delayed degradation of bradykinin. Black race, organ transplant, female gender, smoking, and increasing age are known risk factors for ACE inhibitor-related angioedema.

CLINICAL PRESENTATION AND PATHOPHYSIOLOGY

Urticular eruptions are distinctly pruritic, may involve any area of the body from the scalp to the soles of the feet, and appear in crops of 12- to 36-h duration, with old lesions fading as new ones appear. Most of the physical urticarias (cold, cholinergic, dermatographism) are an exception, with individual lesions lasting <2 h. Neither urticaria nor angioedema lesions are symmetric or dependent in distribution. The most common sites for angioedema are often periorbital and perioral. Angioedema of the upper respiratory tract may be life-threatening due to transient laryngeal obstruction, whereas gastrointestinal involvement may present with abdominal colic, with or without nausea and vomiting, and can result in unnecessary surgical intervention. No residual scarring occurs with either urticaria or angioedema unless there is an underlying vasculitic process.

The pathology is characterized by edema of the superficial dermis in urticaria and of the subcutaneous tissue and deep dermis in angioedema. Collagen bundles in affected areas are widely separated, and the venules are sometimes dilated. Any perivenular infiltrate consists of lymphocytes, monocytes, eosinophils, and neutrophils that are present in varying combination and numbers.

The best evidence for IgE and mast cell involvement in urticaria and angioedema is *cold urticaria*. Cryoglobulins or cold agglutinins are present in up to 5% of these patients. Ice cube placement on the

TABLE 352-1 Classification of Urticaria and/or Angioedema

ACUTE	CHRONIC
Drug reactions	Idiopathic—subset with autoimmune component
Including (but not limited to): antimicrobials, nonsteroidal anti-inflammatory drugs (NSAIDs), contrast media, angiotensin-converting enzyme (ACE) inhibitors, etc.	Collagen vascular disease—urticular vasculitis and other small vessel vasculitis
Food reactions	Physical stimuli
Inhalation or contact with environmental allergens	Dermographism
Transfusion reactions	Cholinergic urticaria
Stinging and biting insects	Vibration, cold, pressure, water (aquagenic)
Toxin (scombroid)	Sun (solar)
Infections—viral, bacterial, parasitic	Mastocytosis (cutaneous or systemic)
	Hereditary
	Hereditary angioedema (HAE)
	C3b inhibitor deficiency
	CIAS1-associated periodic fever syndromes (familial cold urticaria, Muckle-Wells syndrome)
	Schnitzler's syndrome
	Hypereosinophilic syndrome
	Gleich's syndrome

volar forearm precipitates urticaria or angioedema within minutes of the challenge. Histologic studies reveal marked mast cell degranulation with associated edema of the dermis and subcutaneous tissues. Elevated levels of histamine have been found in the plasma of venous effluent and in the fluid of suction blisters at experimentally induced lesional sites in patients with cold urticaria, dermographism, pressure urticaria, vibratory angioedema, light urticaria, and heat urticaria. By ultrastructural analysis, the pattern of mast cell degranulation in cold urticaria resembles an IgE-mediated response with solubilization of granule contents, fusion of the perigranular and cell membranes, and discharge of granule contents, whereas in a dermatographic lesion, there is additional superimposed zonal (piecemeal) degranulation. Elevations of plasma histamine levels with biopsy-proven mast cell degranulation have also been demonstrated with generalized attacks of *cholinergic urticaria*.

Up to 45% of patients with chronic urticaria have an autoimmune cause for their disease including autoantibodies to IgE or to the α chain of Fc ϵ RI. In some patients, autologous serum injected into their own skin can induce a wheal-and-flare reaction involving mast cell activation. The presence of these antibodies can also be recognized by their capacity to release histamine or induce activation markers such as CD63 or CD203 on basophils. An association with antibodies to microsomal peroxidase and/or thyroglobulin has been observed with both clinically significant Hashimoto's thyroiditis as well as a euthyroid state.

The urticaria and angioedema associated with classic serum sickness or with hypocomplementemic cutaneous necrotizing angiitis (urticular vasculitis) are believed to be immune-complex-mediated diseases.

Isolated Angioedema Hereditary angioedema (HAE) is a fully penetrant, autosomal dominant disease due to a mutation in the *SERPING1* gene leading to a deficiency of C1INH (type 1) in ~85% of patients or to a dysfunctional protein (type 2) in the remainder affecting 1:30,000–80,000 in the general population. A third, less common type of HAE has been described in which C1INH function is normal, and the causal lesion is a mutant form of factor XII, which leads to generation of excessive bradykinin. C1INH deficiency can also develop in a sporadic acquired form as a result of excessive consumption of C1INH due either to formation of immune complexes or to the generation of an autoantibody directed to C1INH in the setting of lymphoproliferative or autoimmune disease. C1INH blocks the catalytic function of activated factor XII (Hageman factor) and of kallikrein, as well as the C1r/C1s components of C1, with the common result of degrading bradykinin. During clinical attacks of angioedema, C1INH function or levels fall, patients develop elevated plasma levels of bradykinin leading to angioedema, and excessive activation of C1 results in a decline in C4 and C2 levels.

The use of ACE inhibitors results in impaired bradykinin degradation, which explains the idiosyncratic angioedema that can occur in ACE inhibitor-exposed patients with a normal C1INH. Bradykinin-mediated angioedema, whether caused by ACE inhibitors or by C1INH deficiency, is noteworthy for the conspicuous absence of concomitant urticaria or pruritus, the frequent involvement of the gastrointestinal tract, and the duration of symptoms >24 h.

DIAGNOSIS

The classification of urticaria and angioedema as presented in Table 352-1 in terms of duration can facilitate identification of possible mechanisms. History alone of self-limited episodes can be sufficient to make a diagnosis in the setting of acute disease triggered by drug, environmental, or food allergen with history-directed confirmatory skin testing or assay for serum allergen-specific IgE. Direct reproduction of the lesion in physical urticarias is particularly valuable because it so often establishes the cause of the lesion. In chronic urticaria/angioedema, initial diagnostic testing should be guided by history and physical exam. Practice guidelines provide clinicians two options if history and physical exam are unrevealing: no laboratory testing or limited testing, which includes complete blood count with assessment for

eosinophilia, erythrocyte sedimentation rate, and thyroid-stimulating hormone level. The vast majority of chronic urticaria is associated with no laboratory abnormality. Urticular lesions that last longer than 36 h, result in scarring, and are reported as painful and not pruritic warrant biopsy to evaluate for cellular infiltration, nuclear debris, and fibrinoid necrosis of the venules consistent with urticarial vasculitis. Chronic angioedema without urticaria warrants assessment of complement levels. Concomitant flushing and hyperpigmented papules that urticate with stroking in the absence of angioedema raise the question of mastocytosis. An appropriate travel history should trigger an evaluation for parasites.

The diagnosis of HAE is suggested not only by family history but also by the lack of pruritus and of urticarial lesions, the prominence of recurrent gastrointestinal attacks of colic, and episodes of laryngeal edema. Laboratory diagnosis depends on demonstrating a deficiency of C1INH antigen (type 1) or a nonfunctional protein (type 2) by a catalytic inhibition assay. C4 and C2 are chronically depleted and fall further during attacks due to the activation of additional C1. Patients with the acquired forms of C1INH deficiency have the same clinical manifestations but differ in the lack of a familial element. Furthermore, their sera exhibit a reduction of C1 function and C1q protein as well as C1INH, C4, and C2. Lastly, type 3 HAE is associated with normal levels of complement proteins and a factor XII gene mutation.

TREATMENT

Urticaria and Angioedema

For most forms of urticaria, H₁ antihistamines effectively attenuate both urtication and pruritus; long-acting, nonsedating agents, such as loratadine, desloratadine, and fexofenadine, or low-sedating agents, such as cetirizine or levocetirizine, generally are used first and can be increased to up to four times daily dosing. Earlier generation antihistamines, such as chlorpheniramine or diphenhydramine, are sedating, and they induce psychomotor impairment, including reduced eye-hand coordination and machine operating skills. Their anticholinergic (muscarinic) effects include visual disturbance, urinary retention, and constipation. Clinical practice guidelines indicate that the addition of an H₂ antagonist such as ranitidine or famotidine in conventional dosages and a CysLT₁ receptor antagonist, such as montelukast 10 mg daily or zafirlukast 20 mg twice a day, may add benefit when H₁ antihistamines are inadequate. For chronic urticaria that has failed to respond to the above combinations, monoclonal anti-IgE antibodies such as omalizumab are now the next line of therapy. Older agents with antihistamine properties such as doxepin, cyproheptadine, and hydroxyzine have proven effective when H₁ antihistamines fail but are less effective than omalizumab and are sedating.

Topical glucocorticoids are of no value, and systemic glucocorticoids are generally avoided in idiopathic, allergen-induced, or physical urticarias due to their long-term toxicity. Systemic glucocorticoids are useful in the management of patients with pressure urticaria, vasculitic urticaria (especially with eosinophil prominence), idiopathic angioedema with or without urticaria, or chronic urticaria that responds poorly to conventional treatment and should be considered in any patient with debilitating disease. With persistent vasculitic urticaria, hydroxychloroquine, dapsone, or colchicine may be added to the regimen before or along with systemic glucocorticoids. Cyclosporine is efficacious for patients with chronic idiopathic urticaria that is severe and poorly responsive to other modalities and/or when glucocorticoids are a requirement.

BRADYKININ-MEDIATED ANGIOEDEMA

Infusion of plasma-derived C1INH protein and lanadelumab, a monoclonal antiplasma kallikrein antibody, is approved for prophylaxis of HAE attacks. Administration of plasma-derived or recombinant C1INH protein, a bradykinin 2 receptor antagonist (icatibant), or a kallikrein inhibitor (ecallantide) may be used for treatment of an acute attack of HAE. Older, less expensive

preventative options include attenuated androgens, which stimulate production by the normal gene of an amount of functional C1INH. The antifibrinolytic agent ϵ -aminocaproic acid may be used for preoperative prophylaxis but is contraindicated in patients with thrombotic tendencies or arterial atherosclerosis. Fresh frozen plasma infusion can be used for acute attacks in a setting that lacks access to newer modalities. Published studies are conflicting on the efficacy of bradykinin 2 receptor antagonists and C1INH protein in the treatment of ACE inhibitor-induced angioedema. Treatment of the underlying autoimmune disease or malignancy is indicated for acquired C1INH deficiency.

ALLERGIC RHINITIS

DEFINITION

Rhinitis is characterized by sneezing; rhinorrhea; obstruction of the nasal passages; conjunctival, nasal, and pharyngeal itching; and lacrimation and can be classified as allergic or nonallergic. A clinical history of rhinitis symptoms occurring in a temporal relationship to allergen exposure and documentation of sensitization to an environmental allergen are required for a diagnosis of allergic rhinitis. Although commonly seasonal due to elicitation by airborne pollens, it can be perennial in an environment of chronic exposure to house dust mites, animal danders, or insect (cockroach) products. The overall prevalence in North America has increased in the past 20 years and is 10–30%, with the peak prevalence of >30% occurring in the fifth decade.

PREDISPOSING FACTORS AND ETIOLOGY

Allergic rhinitis generally occurs in atopic individuals, often in association with atopic dermatitis, food allergy, urticaria, and/or asthma ([Chap. 287](#)). Up to 50% of patients with allergic rhinitis manifest asthma, whereas 70–80% of individuals with asthma and 80% of individuals with chronic bilateral sinusitis experience allergic rhinitis. Female sex, particulate air pollution exposure, and maternal tobacco smoking increase the risk of developing allergic rhinitis.

Wind-pollinated trees, grasses, and weeds produce sufficient quantities of pollen suitable for wide distribution by air currents to elicit seasonal allergic rhinitis. The dates of pollination of these species historically varied little from year to year in a particular locale but may be quite different in another climate. In the temperate areas of North America, trees typically pollinate from March through May, grasses in June and early July, and weeds from mid-August to early October. Molds, which are widespread in nature because they occur in soil or decaying organic matter, propagate spores in a pattern that depends on climatic conditions. Climate change is impacting these patterns with early tree pollination and prolonged ragweed season with the delay of the first frost. In laboratory studies, exposure to high carbon dioxide concentrations increases pollen production in ragweed and timothy grass. Perennial allergic rhinitis occurs in response to allergens that are present throughout the year, including animal dander, cockroach-derived proteins, mold spores, or dust mites such as *Dermatophagooides farinae* and *Dermatophagooides pteronyssinus*. Dust mites are scavengers of human skin and excrete cysteine protease allergens in their feces.

PATHOPHYSIOLOGY AND MANIFESTATIONS

Episodic rhinorrhea, sneezing, obstruction of the nasal passages with lacrimation, and pruritus of the conjunctiva, nasal mucosa, and oropharynx are the hallmarks of allergic rhinitis. The nasal mucosa is pale and boggy, the conjunctiva congested and edematous, and the pharynx generally unremarkable. Swelling of the turbinates and mucous membranes with obstruction of the sinus ostia and eustachian tubes precipitates secondary infections of the sinuses and middle ear, respectively. A growing number of patients with seasonal allergic rhinitis demonstrate pollen-associated food allergen syndrome characterized by oropharyngeal pruritus and/or mild swelling following the ingestion of plant-based foods in the same plant family as a tree, grass, or weed, which contain cross-reacting allergens.

The nose presents a large mucosal surface area through the folds of the turbinates and serves to adjust the temperature and moisture content of inhaled air and to filter out particulate materials >10 μm in size by impingement in a mucous blanket; ciliary action moves the entrapped particles toward the pharynx. Entrapment of pollen and digestion of the outer coat by mucosal enzymes such as lysozymes release protein allergens. The initial interaction occurs between the allergen and intraepithelial mast cells and then proceeds to involve deeper perivascular mast cells, both of which are sensitized with specific IgE. During the symptomatic season when the mucosae are already swollen and hyperemic, there is enhanced adverse reactivity to the seasonal pollen as well as irritants such as tobacco smoke and fragrances. Biopsy specimens of nasal mucosa during seasonal rhinitis show submucosal edema with infiltration by eosinophils, along with some basophils and neutrophils.

The mucosal surface fluid contains IgA and IgE, which apparently arrives by diffusion from plasma cells in proximity to mucosal surfaces. IgE fixes to mucosal and submucosal mast cells, and the intensity of the clinical response to inhaled allergens is quantitatively related to the naturally occurring pollen dose. In sensitive individuals, the introduction of allergen into the nose is associated with sneezing, nasal obstruction, and discharge, and the fluid contains histamine, PGD₂, and leukotrienes. Thus, the mast cells of the nasal mucosa and submucosa generate and release mediators through IgE-dependent reactions that are capable of producing tissue edema and eosinophilic infiltration.

DIAGNOSIS

The diagnosis of seasonal allergic rhinitis depends largely on an accurate history of occurrence coincident with the pollination of the offending weeds, grasses, or trees. The continuous character of perennial allergic rhinitis due to contamination of the home or place of work makes historic analysis difficult, but there may be variability in symptoms that can be related to exposure to animal dander, dust mite and/or cockroach allergens, fungal spores, or work-related allergens such as latex. Patients with perennial rhinitis commonly develop the problem in adult life and manifest nasal congestion and a postnasal discharge, often associated with thickening of the sinus membranes demonstrated by radiography. Perennial nonallergic rhinitis with eosinophilia syndrome (NARES) occurs in the middle decades of life and is characterized by nasal obstruction, anosmia, chronic sinusitis, and prominent eosinophilic nasal discharge in the absence of allergen sensitization. The term *vasomotor rhinitis* or *perennial nonallergic rhinitis* designates a condition of enhanced reactivity of the nasopharynx in which a symptom complex resembling perennial allergic rhinitis occurs with nonspecific stimuli, including chemical odors, temperature and humidity variations, and position changes but occurs without tissue eosinophilia or an allergic etiology. Other entities to be excluded are structural abnormalities of the nasopharynx; exposure to irritants; gustatory rhinitis associated with cholinergic activation that occurs while eating or ingesting alcohol; hypothyroidism; upper respiratory tract infection; pregnancy with prominent nasal mucosal edema; prolonged topical use of α -adrenergic agents in the form of nasal sprays (rhinitis medicamentosa); and the use of certain systemic agents such as β -adrenergic antagonists, ACE inhibitors, direct vasodilators (hydralazine), α_1 -adrenergic receptor antagonists, estrogens, progesterone, nonsteroidal anti-inflammatory drugs, gabapentin, phosphodiesterase-5 inhibitors, and psychotropics (risperidone, chlorpromazine, amitriptyline).

The nasal secretions of allergic patients are rich in eosinophils, and a modest peripheral eosinophilia can be observed. Local or systemic neutrophilia implies infection. Total serum IgE is frequently elevated, but the demonstration of immunologic specificity for IgE is critical to an etiologic diagnosis. A skin test by the intracutaneous route (puncture or prick) with the allergens of interest provides a rapid and reliable approach to identifying allergen-specific IgE that has sensitized cutaneous mast cells. A positive intracutaneous skin test with 1:10–1:20 weight/volume of extract has a high predictive value for the presence of allergy. An intradermal test with a 1:500–1:1000 dilution of

0.05 mL may follow if indicated by history when the intracutaneous test is negative, but while more sensitive, it is less reliable due to the reactivity of some asymptomatic individuals at the test dose.

Newer methodology for detecting total IgE, including the development of enzyme-linked immunosorbent assays (ELISAs) employing anti-IgE bound to either a solid-phase or a liquid-phase particle, provides rapid and cost-effective determinations. Measurements of specific anti-IgE in serum are obtained by its binding to an allergen and quantitation by subsequent uptake of labeled anti-IgE. As compared to the skin test, the assay of specific IgE in serum is less sensitive but has high specificity.

TREATMENT

Allergic Rhinitis

Although allergen avoidance is the most cost-effective means of managing allergic rhinitis, only in the case of animal dander and possibly dust mites is it feasible. Treatment with pharmacologic agents represents the standard initial approach to seasonal or perennial allergic rhinitis. Oral long-acting H₁ antihistamines, such as fexofenadine, loratadine, desloratadine, cetirizine, and levoceftirizine, are effective for nasopharyngeal itching, sneezing, and watery rhinorrhea and for such ocular manifestations as itching, tearing, and erythema, but they are less efficacious for the nasal congestion. They reduce nasal and ocular symptoms by about one-third. These antihistamines are less lipophilic and more H₁ selective, thus minimizing their ability to cross the blood-brain barrier and therefore diminishing their sedating and anticholinergic effect; they do not differ appreciably in efficacy for relief of rhinitis and/or sneezing.

Intranasal high-potency glucocorticoids are the most effective drugs available for the relief of established rhinitis, seasonal or perennial, and are effective in relieving nasal congestion as well as ocular symptoms. They provide efficacy with substantially reduced side effects as compared with this same class of agent administered orally. Their most frequent side effect is local irritation, with fungal overgrowth being a rare occurrence. The currently available intranasal glucocorticoids—beclomethasone, flunisolide, triamcinolone, budesonide, fluticasone propionate, fluticasone furoate, ciclesonide, and mometasone furoate—are equally effective for nasal symptom relief, including nasal congestion; these agents all achieve up to 70% overall symptom relief with some variation in the time period for onset of benefit. The nasal antihistamines azelastine and olopatadine may benefit individuals with nonallergic vasomotor rhinitis as well as have additive benefit to intranasal steroids in allergic rhinitis, but they have an adverse effect of dysgeusia (taste perversion) in some patients. Alternative nasal decongestants include α-adrenergic agents such as phenylephrine or oxymetazoline; however, the duration of their efficacy is limited because of rebound rhinitis (i.e., 7- to 14-day use can lead to rhinitis medicamentosa) and such systemic responses as hypertension. Oral α-adrenergic agonist decongestants containing pseudoephedrine can improve management of nasal congestion, generally in combination with an antihistamine. These pseudoephedrine combination products can cause insomnia and are precluded from use in patients with narrow-angle glaucoma, urinary retention, severe hypertension, marked coronary artery disease, or a first-trimester pregnancy. The CysLT₁ antagonist montelukast is approved for treatment of both seasonal and perennial rhinitis. However, it is less effective than H₁ antihistamines and nasal glucocorticoids, and reports of neuropsychiatric events have led to increased U.S. Food and Drug Administration precautions. Cromolyn sodium nasal spray inhibits mast cell degranulation and can be used prophylactically on a continuous basis during the season or as needed before a known exposure. Topical ipratropium is an anticholinergic agent effective in reducing rhinorrhea, including that of patients with perennial nonallergic symptoms, and it can be additionally efficacious when combined with intranasal glucocorticoids. For concomitant allergic

conjunctivitis, topical treatment with cromolyn sodium is effective in treating mild allergic symptoms, and topical antihistamines such as olopatadine, azelastine, ketotifen, or epinastine administered to the eye provide rapid relief of itching and redness and are more effective than oral antihistamines.

Immunotherapy Immunotherapy consists of repeated exposure to the allergen(s) considered to be specifically responsible for the symptom complex. Two forms of immunotherapy, subcutaneous (SCIT) and sublingual (SLIT), are currently available. Randomized, controlled studies of ragweed, grass, dust mite, and cat dander allergens administered via SCIT for treatment of allergic rhinitis have demonstrated significant improved symptom control over medications alone with the advantage of providing a durable benefit, as well as a reduction in asthma symptoms, medication use, and bronchial hyperreactivity in allergic asthma. Clinical practice guidelines recommend a duration of SCIT is 3–5 years, with discontinuation being based on minimal symptoms over two consecutive seasons of exposure to the allergen. Clinical benefit appears related to the administration of a high dose of relevant allergen, gradually uptitrating concentration and advancing from weekly to monthly intervals. SCIT injections occur in a licensed treatment site; 2–3% of SCIT patients experience a systemic reaction, including anaphylaxis, over a 12-month period. The majority of these reactions occur soon after injection, and thus, patients should remain at the treatment site for at least 30 min after allergen administration so that any systemic reactions can be managed. Local reactions with erythema and induration are not uncommon and may persist for 1–3 days. SLIT is prepared as a tablet to be dissolved under the tongue at home after the first dose. The efficacy of SLIT is comparable to SCIT but only for the three allergen formulations currently available: dust mite, timothy/northern grasses, and short ragweed. Systemic reactions are less frequent with SLIT, but transient oral pruritus is common. Immunotherapy is contraindicated in patients with significant cardiovascular disease or unstable asthma. Severe cases of anaphylaxis have occurred after allergen immunotherapy when patients were taking a β-adrenergic blocking agent. Thus, immunotherapy should be conducted with caution in any patient requiring β-adrenergic blocking therapy due to the difficulty in managing an anaphylactic complication.

Immunotherapy should be reserved for clearly documented seasonal or perennial rhinitis that is clinically related to defined allergen exposure with confirmation by the presence of allergen-specific IgE through skin or in vitro specific IgE testing. The response to immunotherapy is associated with a complex of cellular and humoral effects that includes a modulation in T lymphocyte cytokine production and allergen-specific IgG₄ expansion. Systemic treatment with omalizumab, an anti-IgE monoclonal antibody, is efficacious for allergic rhinitis and can be used with immunotherapy to enhance safety and efficacy. However, current approval is only for treatment of patients with persistent allergic asthma not controlled by inhaled glucocorticoid therapy or chronic idiopathic urticaria not controlled by oral H₁ antihistamines.

A sequence for the management of allergic or perennial rhinitis based on an allergen-specific diagnosis and stepwise management as required for symptom control would include the following: (1) identification of the offending allergen(s) by history with confirmation of the presence of allergen-specific IgE by skin test and/or serum assay; (2) avoidance of the offending allergen; and (3) medical management in a stepwise fashion (Fig. 352-4). Mild intermittent symptoms of allergic rhinitis are treated with oral antihistamines, oral CysLT₁ receptor antagonists, intranasal antihistamines, or intranasal cromolyn. Moderate to more severe allergic rhinitis is managed with intranasal glucocorticoids plus oral antihistamines, oral CysLT₁ receptor antagonists, or antihistamine-decongestant combinations. Persistent or seasonal allergic rhinitis, rhinoconjunctivitis, or asthma that remains uncontrolled with maximal medical therapy merit consideration of allergen-specific immunotherapy.

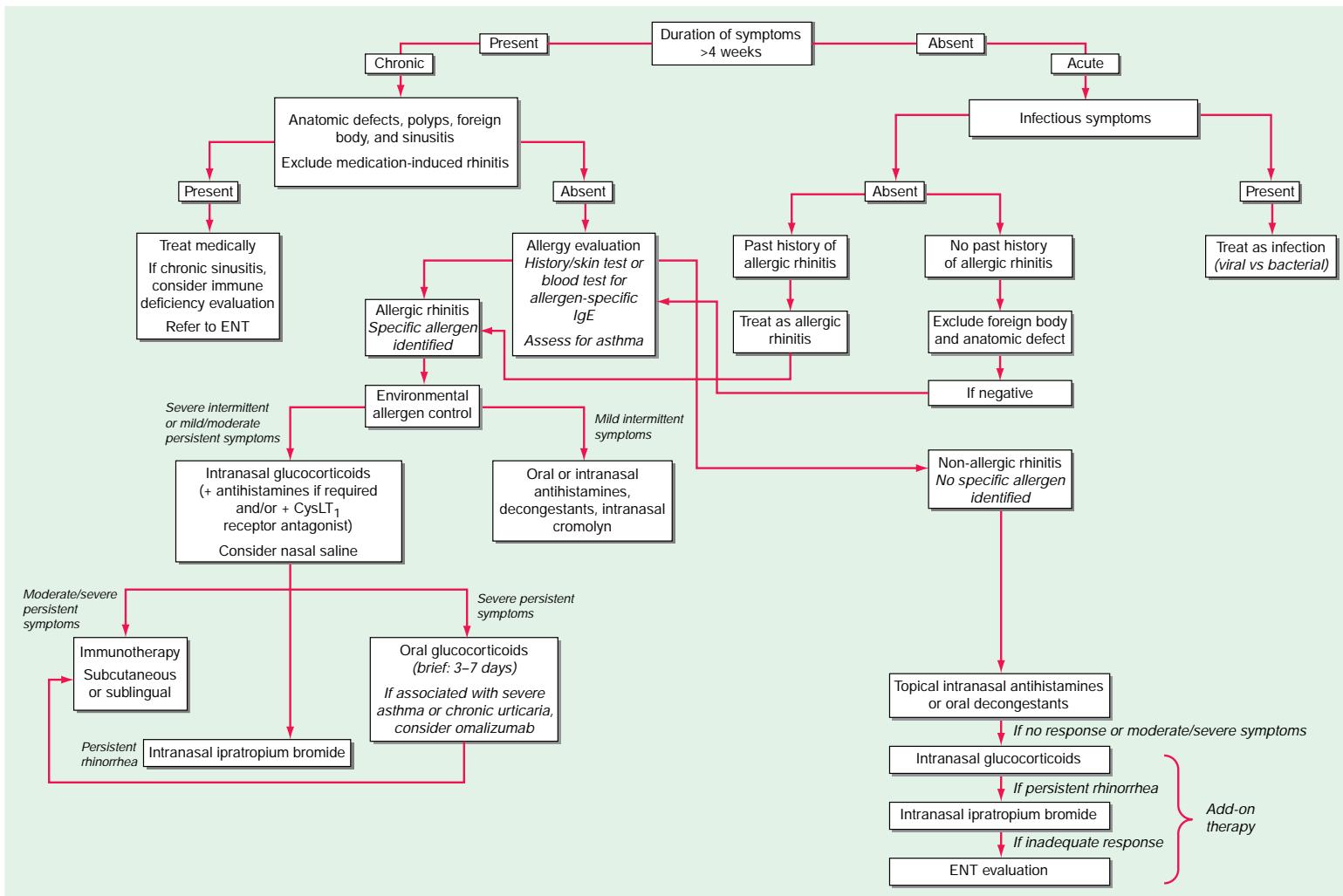


FIGURE 352-4 Algorithm for the diagnosis and management of rhinitis. Persistent is defined as >4 days per week for >4 weeks. Moderate/severe is defined as abnormal sleep, impaired daily activities (school, work, sport, leisure), and/or troublesome symptoms. CysLT, cysteinyl leukotriene; ENT, ear, nose, and throat; IgE, immunoglobulin E.

FURTHER READING

- Bernstein DI et al: Allergic rhinitis: Mechanisms and treatment. *Immunol Allergy Clin North Am* 36:261, 2016.
- Cho SH et al: Chronic rhinosinusitis without nasal polyps. *J Allergy Clin Immunol Pract* 4:575, 2016.
- Cicardi M et al: Classification, diagnosis, and approach to treatment for angioedema: Consensus report from the Hereditary Angioedema International Working Group. *Allergy* 69:602, 2014.
- Corren J et al: Allergic and nonallergic rhinitis, in *Middleton's Allergy: Principles and Practice*, 8th ed. NF Adkinson et al (eds). Philadelphia, Saunders, 2014, pp 664–685.
- Jutel M et al: International consensus on allergen immunotherapy II: Mechanisms, standardization, and pharmacoeconomics. *J Allergy Clin Immunol* 137:358, 2016.
- Maurer M et al: Omalizumab for the treatment of chronic idiopathic or spontaneous urticaria. *N Engl J Med* 368:924, 2013.
- Saini SS: Urticaria and angioedema, in *Middleton's Allergy: Principles and Practice*, 8th ed. NF Adkinson et al (eds). Philadelphia, Saunders, 2014, pp 575–587.

of the collagen fibers and the glandular elements; vascular congestion and eosinophilic infiltration also are present. Patients dying of vascular collapse without antecedent hypoxia from respiratory insufficiency have visceral congestion with a presumptive loss of intravascular fluid volume. The associated electrocardiographic abnormalities, with or without infarction, in some patients may reflect a primary cardiac event mediated by mast cells (which are prominent near the coronary vessels) or may be secondary to a critical reduction in blood volume.

Gastrointestinal manifestations represent another severe presentation of anaphylaxis and include nausea, vomiting, crampy abdominal pain, and/or fecal incontinence. Angioedema of the bowel wall may also cause sufficient intravascular volume depletion to precipitate cardiovascular collapse.

Cutaneous manifestations are among the most common presentations of anaphylaxis (>90% of cases). Symptoms include urticarial eruptions, flushing with diffuse erythema, and/or a feeling of generalized warmth. Urticarial eruptions are intensely pruritic and may be localized or disseminated. They may coalesce to form giant hives but seldom persist beyond 48 h.

PATHOPHYSIOLOGY

Many of the important early mediators of anaphylaxis are derived from mast cells, basophils, and eosinophils. Mast cells and basophils contain preformed granules composed of histamine, proteases (tryptase, chymase), proteoglycans (heparin, chondroitin sulfate), and tumor necrosis factor- α , which are rapidly released into surrounding tissue upon cell activation, a process known as degranulation. Mast cells, basophils, and eosinophils are also sources of arachidonic acid-derived products, which include cysteinyl leukotrienes, prostaglandins, and platelet-activating factor (PAF). Histamine release results in flushing, urticaria, pruritus, and, in high concentrations, hypotension and tachycardia. Cysteinyl leukotrienes and prostaglandin D₂ cause bronchoconstriction and increased microvascular permeability. Prostaglandin D₂ causes cutaneous flushing and attracts eosinophils and basophils to the site of mast cell activation. Serum PAF levels correlate with anaphylaxis severity and are inversely proportional to the constitutive level of PAF acetylhydrolase, which is necessary for PAF inactivation. Tryptase and chymase can activate complement and coagulation pathways. Activation of these pathways results in production of the anaphylotoxins, C3a and C5a, and activation of the kallikrein-kinin system, which regulates blood pressure and vascular permeability. The actions of these anaphylactic mediators are likely additive or synergistic at the target tissues.

PREDISPOSING FACTORS AND MECHANISMS

Because the most dangerous manifestations of anaphylaxis involve the cardiovascular and/or respiratory systems, preexisting asthma and underlying cardiovascular disease could lead to more rapid decompensation from anaphylaxis. Atopy is not generally thought to be a risk factor for anaphylaxis from drug reactions or Hymenoptera stings, but it is associated with radiocontrast sensitivity, exercise-induced anaphylaxis, idiopathic anaphylaxis, and allergy to foods or latex. Severe Hymenoptera-induced anaphylaxis (generally with prominent hypotension) can be a presenting feature of underlying systemic mastocytosis. Hymenoptera allergy is also more likely in patients whose occupations (i.e., beekeepers, trash haulers, and landscape workers) place them in regular proximity to stinging insects. Most commonly, allergen-induced cross-linking of IgE-bound Fc ϵ RI receptors on mast cells and basophils initiates the signal transduction events leading to hypersensitivity syndromes, including anaphylaxis. The generation of allergen-specific IgE is the end result of sensitization via the adaptive immune system. While the mechanisms underlying sensitization are beyond the scope of this chapter, environmental factors, innate immune responses, and cytokines are among the many variables leading to antigen-specific IgE production by B cells and plasma cells. IgE-mediated drug allergies are most common with antibiotics and certain chemotherapy drugs, though theoretically, they can occur with almost any medication. As is the case with environmental allergies, repeated exposure to the allergy-causing antigen is an important risk factor to keep in mind when evaluating patients with anaphylaxis. In

353 Anaphylaxis

David Hong, Joshua A. Boyce



BACKGROUND

Anaphylaxis is a potentially life-threatening systemic allergic reaction involving one or more organ systems that typically occurs within seconds to minutes of exposure to the anaphylactic trigger, most often a drug, food, or Hymenoptera sting. The term *anaphylaxis* was first described in 1902 by Charles Richet and Paul Portier who attempted to immunize dogs against sea anemone toxin in the same way Pasteur was able to vaccinate individuals against the smallpox virus. To their surprise, repeated administration of small, sublethal doses of sea anemone toxin reliably induced acute-onset death when readministered 2–3 weeks after initial “vaccination” to the toxin. The phenomenon was termed ana (anti)-phylaxis (“protection or guarding”) because vaccination with anemone toxin resulted in the opposite intended immune effect. Charles Richet was awarded the Nobel Prize in Physiology or Medicine in 1913 for this work, which led to further insights into hypersensitivity and mast cell biology.

CLINICAL MANIFESTATIONS

While 80–90% of anaphylactic episodes are uniphasic, about 10–20% of cases are biphasic, in which anaphylactic symptoms return about an hour or longer after resolution of initial symptoms. Anaphylactic reactions are particularly dangerous when hypotension or hypoxia occurs, leading potentially to cardiovascular collapse or respiratory failure, respectively. There may be upper or lower airway obstruction or both. Laryngeal edema may be experienced as a “lump” in the throat, hoarseness, or stridor, whereas bronchial obstruction is associated with a feeling of tightness in the chest and/or audible wheezing. Patients with underlying asthma are predisposed to severe involvement of the lower airways and increased mortality associated with anaphylaxis. In fatal cases with clinical bronchial obstruction, the lungs show marked hyperinflation on gross and microscopic examination. The microscopic findings in the bronchi, however, are limited to luminal secretions, peribronchial congestion, submucosal edema, and eosinophilic infiltration, and the acute emphysema is attributed to intractable bronchospasm that subsides with death. Angioedema resulting in death by mechanical obstruction occurs in the epiglottis and larynx; however, the process also is evident in the hypopharynx and to some extent in the trachea. On microscopic examination, there is wide separation

the case of allergy to carboplatin, the incidence of hypersensitivity is 27% in patients who have had ≥7 lifetime infusions and as high as 46% in patients who have had ≥15 lifetime infusions. Similarly, patients with cystic fibrosis have a relatively high incidence of allergic reactions to IV antibiotics that they receive periodically for intermittent “clean-outs” to maintain airway clearance. Drugs can also function as haptens that form immunogenic conjugates with host proteins. The conjugating hapten may be the parent compound, a nonenzymatically derived storage product, or a metabolite formed in the host. Recombinant biologics can also induce the formation of IgE against the proteins or against glycosylated structures that serve as immunogens. Outbreaks of anaphylaxis to the epidermal growth factor receptor (EGFR) antibody cetuximab have been reported in association with elevated titers of serum IgE to alpha-1,3-galactose (alpha-gal), an oligosaccharide found in nonprimate mammals. Cetuximab is derived from a mouse cell line expressing a transferase that tags the Fab' portion of the cetuximab heavy chain with alpha-gal. Interestingly, patients with a history of multiple bites from *Amblyomma americanum* ticks commonly found in the Carolinas, Arkansas, and Tennessee are more likely to have anti-alpha-gal IgE as compared with control patients living outside those states. Some individuals who become sensitized to alpha-gal can develop episodes of delayed-onset anaphylaxis to meat from beef, lamb, and pork.

Non-IgE-mediated mast cell activation secondary to certain drugs is clinically indistinguishable from classical IgE-mediated hypersensitivity reactions, but it can occur with first known exposure since there is no prior need for mast cell sensitization by IgE. MRGPRX2, a G protein-coupled receptor that is highly expressed in skin mast cells, has been shown in mouse models and in vitro studies using human cells to induce mast cell activation and mediator release secondary to neuromuscular blocking drugs (NMBDs), quinolones, and icatibant. These findings are clinically significant since NMBDs are a relatively common cause of perioperative anaphylaxis and in other settings requiring endotracheal intubation and quinolones are a commonly used antibiotic family. Icatibant, a bradykinin-2 receptor antagonist administered by subcutaneous injection for the treatment of acute attacks of hereditary angioedema, is known to frequently result in local injection site reactions. Another example of non-IgE-mediated anaphylaxis is demonstrated with paclitaxel, a chemotherapy agent most commonly used in combination with carboplatin to treat ovarian cancer. It is derived from yew tree bark and needles that require polyethoxylated castor oil (Cremophor) to be solubilized into aqueous solution. Cremophor has been shown in vitro to activate the complement cascade, resulting in complement-dependent histamine release from mast cells and basophils. A version of paclitaxel that is solubilized by being bound to albumin nanoparticles, Abraxane, has a far lower rate of hypersensitivity, especially for patients who have had infusion reactions to Cremophor-solubilized paclitaxel. Reactions to radiocontrast and vancomycin are other examples of non-IgE-mediated hypersensitivity. Opiates and nonsteroidal anti-inflammatory drugs (NSAIDs) are other drug categories that can have similar adverse reactions.

DIAGNOSIS

The diagnosis of an anaphylactic reaction depends primarily on a history revealing the onset of symptoms and signs within seconds to minutes after the putative trigger is encountered. An exception is delayed anaphylaxis to meats in alpha-gal-sensitized patients. Every attempt to identify the specific cause or causes should be made to minimize the risk of recurrent anaphylaxis. If a particular drug or food is suspected, skin or serum-specific IgE testing can be useful to confirm clinical suspicions. If a specific trigger cannot be identified by history or testing, a workup of underlying baseline atopic diatheses may be useful to identify risk factors that could play a potential contributory role. In the acute setting, laboratory biomarkers of mast cell degranulation may be useful to document the severity of an anaphylactic episode. The most obvious serum biomarker to assay, histamine, has an extremely short half-life with a measurable time-window that expires <1 h from the onset of anaphylaxis. A more practical and useful biomarker is serum tryptase, which peaks 60–90 min after the onset of anaphylaxis and

can be measured as long as 5 h after the onset of anaphylaxis. It may be useful to follow-up an elevated tryptase measurement in the acute setting with another measurement when the patient is clinically stable to establish a baseline reference. An elevated baseline tryptase level may warrant further workup for mastocytosis, especially if the presenting reaction occurred in the setting of Hymenoptera sting.

TREATMENT

Early recognition of an anaphylactic reaction and appropriate intervention are critically important because severe, even fatal, complications can occur within minutes after symptoms first appear. The treatment of first choice is intramuscular administration of 0.3–0.5 mL of 1:1000 (1 mg/mL) epinephrine, with repeated doses at 5- to 20-min intervals as needed for a severe reaction. The failure to use epinephrine within the first 20 min of symptoms is a risk factor for poor clinical outcomes in various studies of anaphylaxis. Another important variable that may affect anaphylaxis survival is body posture, as an upright or sitting posture may lead to “empty ventricle syndrome” in which there is insufficient venous return to the heart from sudden-onset hypotension secondary to intravascular volume depletion. Epinephrine can further accelerate empty ventricle syndrome due to its chronotropic effects. For this reason, it is recommended that patients who suffer from anaphylaxis be placed in the supine position before receiving epinephrine. IV fluids and vasopressor agents may be administered in the acute medical setting if intractable hypotension occurs. Epinephrine provides both α- and β-adrenergic effects, resulting in vasoconstriction, bronchial smooth-muscle relaxation, and attenuation of enhanced venular permeability. Beta blockers may attenuate this response; therefore, an alternative antihypertensive may be considered in patients at high risk of needing emergency epinephrine. Oxygen alone via a nasal catheter or with nebulized albuterol may be helpful; however, either endotracheal intubation or a tracheostomy is mandatory for oxygen delivery if progressive hypoxia develops. Ancillary agents such as antihistamines, glucocorticoids, and bronchodilators are also useful therapeutics to treat urticaria/angioedema and bronchospasm once the patient is hemodynamically stable.

PREVENTION

Avoidance The simplest, most straightforward approach to the long-term management of a patient with a history of anaphylaxis is strict avoidance of known anaphylactic triggers and education on acute management, specifically, instructing the patient on proper use and indications for use of self-administered epinephrine. Lifelong avoidance is not easy if the trigger is an occupational exposure, Hymenoptera sting, a common food (i.e., peanut), or a drug representing the sole or best therapeutic option for the patient. Special management options may exist for these patients.

Venom Immunotherapy Patients with only large local reactions to Hymenoptera stings are unlikely to have anaphylaxis with subsequent stings. However, patients of any age who have had documented anaphylaxis should be formally evaluated and started on venom immunotherapy (VIT) if skin or serologic IgE testing confirms the history. Immunotherapy is a means of “tolerizing” patients to allergen by means of serial subcutaneous administration of escalating doses of extract containing relevant allergen until a target maintenance dose is achieved. As in the case of Richet’s unfortunate dogs, anaphylaxis can sometimes occur during the course of administering immunotherapy extracts, so formulating extracts and administering them is typically done under the care of a specialist familiar with this type of treatment. In the case of Hymenoptera allergy, patients receive VIT extracts containing actual Hymenoptera venom with a maintenance dose equivalent to 2–5 stings. The recommended duration of treatment is 3–5 years; however, some patients who have experienced severe respiratory or cardiovascular anaphylaxis are put on lifelong therapy.

Preventative Tolerance Induction IgE sensitization to foods occurs most frequently in infants and young children, especially those

354

Mastocytosis

Matthew P. Giannetti, Joshua A. Boyce



with atopic dermatitis, and is a risk factor for anaphylaxis (although detection of specific IgE through skin or serum testing has relatively poor predictive value). While most allergy to egg, milk, soy, and/or wheat resolves spontaneously during childhood, ~80% of children with peanut allergy remain sensitive for life. A sharp rise in the prevalence of peanut allergy was also observed in the late 1990s to early 2000s, especially in countries with Western diets where the average age of peanut introduction was age ≥ 3 years. Curiously, in cultures where peanut was introduced much earlier into children's diets, the prevalence of peanut allergy remained low. The landmark Learning Early About Peanut Allergy (LEAP) study demonstrated that early introduction of peanut protein to the diet of high-risk infants (4–11 months of age with atopic dermatitis and/or egg allergy) prevented the development of most (80% or more) peanut allergy compared with children who did not consume peanuts (avoidance group), even when IgE sensitization (based on positive skin test) had already developed at the time of study entry. While the induction of tolerance at an early age seems to be key to preventing clinical reactivity later in life, it is not yet clear if this principle holds true for other foods commonly associated with hypersensitivity reactions.

Desensitization For patients who have experienced anaphylaxis from drug allergy and whose treatment regimen requires the administration of the offending drug, desensitization may be a short-term treatment option to prevent reactions. Desensitization elicits a temporary state of tolerance to the drug in sensitized, clinically reactive patients. While it has been a proven technique for penicillin-allergic patients for decades, desensitization has more recently been proven to be effective for certain chemotherapy agents, especially platin-based chemotherapy agents that can induce IgE-mediated sensitization with repeated exposures. The exact mechanisms underlying desensitization are not fully understood; however, temporary tolerance can be achieved through the serial administration of gradually escalating doses of drug, starting from extremely low doses, over the course of hours. So long as the patient continues to receive the drug in question at regular intervals based on drug half-life, a "desensitized" state can also be maintained until the drug is no longer needed. While drug desensitization certainly works for IgE-mediated reactions, it has been performed in cases of non-IgE-mediated anaphylaxis from Cremophor-solubilized paclitaxel as described earlier in this chapter. Desensitization has also been shown by multiple groups to prevent non-IgE-mediated reactions from a variety of biologic agents, various chemotherapy drugs, and NSAIDs. Given the complexity and variety of possible drug reactions, the decision to desensitize, challenge, or avoid should be made in conjunction with an allergy specialist for complete evaluation and proper risk stratification of the different possible approaches to take.

FURTHER READING

- Brennan PJ et al: Hypersensitivity reactions to mAbs: 105 desensitizations in 23 patients, from evaluation to treatment. *J Allergy Clin Immunol* 124:1259, 2009.
- Castells MC et al: Hypersensitivity reactions to chemotherapy: Outcomes and safety of rapid desensitization in 413 cases. *J Allergy Clin Immunol* 122:574, 2008.
- Chung CH et al: Cetuximab-induced anaphylaxis and IgE specific for galactose-alpha-1,3-galactose. *N Engl J Med* 358:1109, 2008.
- Du Toit G et al: LEAP Study Team. Randomized trial of peanut consumption in infants at risk for peanut allergy. *N Engl J Med* 373:803, 2015.
- Du Toit G et al: Immune Tolerance Network LEAP-On Study Team. Effect of avoidance on peanut allergy after early peanut consumption. *N Engl J Med* 374:1435, 2016.
- Lieberman P et al: Anaphylaxis—A practice parameter update 2015. *Ann Allergy Asthma Immunol* 115:341, 2015.
- McNeil BD et al: Identification of a mast cell-specific receptor crucial for pseudoallergic drug reactions. *Nature* 519:237, 2015.

DEFINITION AND EPIDEMIOLOGY

Mastocytosis is defined by accumulation of clonally expanded mast cells in tissues such as skin, bone marrow, liver, spleen, and gut. Diagnostically, mast cell expansion is most readily identified in skin and/or bone marrow. Mastocytosis occurs at any age and has a slight preponderance in males. The prevalence of mastocytosis is estimated at ~ 1 in 10,000 people. Most forms of the disease are characterized by somatic gain-of-function mutations in the stem cell factor receptor (*KIT*) gene. Familial occurrence is rare, and atopy is not increased compared with the general population.

CLASSIFICATION AND PATHOPHYSIOLOGY

A consensus classification for mastocytosis recognizes cutaneous mastocytosis with variants, five systemic forms, and the rarest variant, mast cell sarcoma (Table 354-1).

Cutaneous mastocytosis is the most common diagnosis in children and indicates disease limited to skin with absence of pathologic infiltrates in internal organs. It is usually diagnosed within the first year of life with demonstration of fixed, maculopapular, polymorphic, and hyperpigmented lesions (maculopapular cutaneous mastocytosis [MPCM], formerly known as urticaria pigmentosa), mastocytoma(s), or diffuse cutaneous mastocytosis. Although mast cell accumulation is limited to the skin, children often have systemic symptoms. Systemic mastocytosis (SM) refers to involvement of a noncutaneous site (usually bone marrow). There are five distinct variants of SM. *Indolent systemic mastocytosis* (ISM) accounts for the majority of adult patients. ISM is diagnosed when there is no evidence of an associated hematologic disorder, mast cell leukemia, or organ dysfunction due to mast cell infiltration. ISM is associated with a normal life expectancy. *Smoldering systemic mastocytosis* (SSM) is characterized by high mast cell burden as evidenced by a bone marrow infiltration of $>30\%$ and a baseline serum tryptase >200 ng/mL (B findings), but absence of *systemic mastocytosis associated with clonal hematologic non-mast cell lineage disease* (SM-AHNMD) or *aggressive systemic mastocytosis* (ASM) (Table 354-2). In SM-AHNMD, the prognosis is determined by the nature of the associated disorder, which can range from dysmyelopoiesis to leukemias usually of myeloid origin. In ASM, mast cell infiltration/proliferation occurs in multiple organs such as liver, spleen, gut, bone, and bone marrow resulting in one or more C findings and a poor prognosis (Table 354-2). *Mast cell leukemia* (MCL) is the rarest form of SM and is invariably fatal at present; the peripheral blood contains circulating, metachromatically staining, atypical mast cells. An aleukemic form of MCL is recognized without circulating mast cells when the percentage of high-grade immature mast cells in bone

TABLE 354-1 Classification of Mastocytosis

Cutaneous mastocytosis (CM)
Maculopapular cutaneous mastocytosis (MPCM)
Solitary mastocytoma of skin
Diffuse cutaneous mastocytosis
Indolent systemic mastocytosis (ISM)
Smoldering systemic mastocytosis
Systemic mastocytosis with an associated clonal hematologic non-mast cell lineage disease (SM-AHNMD)
Aggressive systemic mastocytosis (ASM)
Mast cell leukemia (MCL)
Mast cell sarcoma (MCS)

Source: Modified from H-P Horny et al: Mastocytosis. In: WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, revised 4th ed. SH Swerdlow et al (eds). Lyon, France, IARC Press, 2017, pp 61–69.

TABLE 354-2 B and C Findings for Diagnosis of SSM and ASM

B Findings (2 or more in the absence of any C findings are required for a diagnosis of SSM):
1. MC infiltration in bone marrow biopsy of >30% and a basal serum tryptase level >200 ng/mL
2. Hypercellular bone marrow with signs of dysmyelopoiesis but without cytopenias meeting C criteria or WHO criteria for an MDS or MPN
3. Palpable hepatomegaly, palpable splenomegaly, or lymphadenopathy (on CT or ultrasound: >2 cm) without impaired liver function or hypersplenism
C Findings (1 or more required for a diagnosis of ASM). C findings should be reasonably attributable to high tissue mast cell infiltration.
1. Cytopenia(s): ANC <1000/ μ L or Hb <10 g/dL or PLT <100,000/ μ L
2. Hepatomegaly with ascites and impaired liver function
3. Palpable splenomegaly with associated hypersplenism
4. Malabsorption with hypoalbuminemia and weight loss
5. Skeletal lesions: large area(s) of osteolysis with pathologic fractures (presence of osteoporosis alone without osteolytic lesions does not satisfy this criterion)

Abbreviations: ANC, absolute neutrophil count; ASM, aggressive systemic mastocytosis; CT, computed tomography; Hb, hemoglobin; MC, mast cells; MDS, myelodysplastic syndromes; MPN, myeloproliferative disorders; PLT, platelets; SSM, smoldering systemic mastocytosis; WHO, World Health Organization.

marrow smears exceeds 20% in a nonspicular area. Mast cell sarcoma is a rare solid mast cell tumor with malignant invasive features.

Somatic activating mutations in the *KIT* gene are characteristic of mastocytosis. *KIT* D816V is most commonly observed, although other mutations have been reported. *KIT* mutations are found in mast cells and sometimes in multiple other cell lineages in patients with mastocytosis. *KIT* mutations are observed in patients with all forms of SM but are also present in some children with cutaneous mastocytosis in lesional skin, as might be anticipated because mast cells are of bone marrow lineage. Additional mutations in genes such as *TET2*, *SRSF2*, *ASXL1*, and *RUNX1* known to be associated with other hematologic neoplastic disorders can be detected in patients, usually with advanced (non-ISM) forms of SM. The prognosis for patients with cutaneous mastocytosis and for almost all patients with ISM is a normal life expectancy, whereas that for patients with SM-AHNMD is determined by the non-mast cell component. ASM and MCL have a poor prognosis, while patients with SSM have an intermediate prognosis. Progression from ISM to a more advanced form is rare (~5% overall); however, patients should be monitored for emergence of hematologic disease and end-organ manifestations of ASM. In infants and children with cutaneous manifestations, namely, maculopapular cutaneous mastocytosis, mastocytoma(s), or bullous lesions, visceral involvement is usually lacking, and spontaneous resolution is common prior to adolescence. Polymorphic maculopapular cutaneous mastocytosis usually resolves spontaneously. Progression from cutaneous mastocytosis (CM) to ISM may occur in ~10% of children, especially in those with high mast cell burden (diffuse cutaneous mastocytosis) or hematologic abnormalities and those who present with smaller uniform lesions with diameters measuring <2 cm (monomorphic cutaneous mastocytosis).

CLINICAL MANIFESTATIONS

The clinical manifestations of SM are due to the release of bioactive substances acting at both local and distal sites, tissue infiltration by mast cells, and the tissue response to the cellular infiltrate. The pharmacologically induced manifestations are intermittent flushing, tachycardia and vascular collapse, gastric distress, crampy lower abdominal pain, and diarrhea. The increased local mast cell burden in the skin (MPCM), bone marrow, and gastrointestinal tract may be a direct cause of pruritus, bone pain, and malabsorption, respectively. Mast cell-mediated fibrotic changes may occur in liver, spleen, and bone marrow but not in gastrointestinal tissue or skin.

The cutaneous lesions of MPCM are reddish-brown macules, papules, or plaques that respond to trauma with urtication and erythema (Darier's sign). Two distinct forms of MPCM are recognized: polymorphic MPCM and monomorphic MPCM. Children with CM may present with MPCM, mastocytomas, or diffuse cutaneous mastocytosis

(DCM). Mastocytomas are generally solitary elevated lesions that are yellow, brown, or red in color. Their size may vary from a few millimeters to several centimeters. Rubbing or irritation of the mastocytoma lesion may lead to systemic symptoms such as flushing and urticaria. Children with DCM present without distinct lesions, but rather a generalized thickening of skin and "peau d'orange" appearance due to diffuse mast cell infiltration. DCM may be associated with bullae formation and more severe systemic symptoms, including upper gastrointestinal irritation and vascular collapse in the first few years of life. Maculopapular skin lesions of mastocytosis may be present in patients with adult-onset systemic disease. The apparent incidence of cutaneous lesions is ≥80% in patients with ISM and <50% in those with SM-AHNMD or ASM. In the upper gastrointestinal tract, gastritis and peptic ulcer are significant problems. In the lower intestinal tract, the occurrence of diarrhea and abdominal pain is attributed to increased motility due to mast cell mediators; this problem can be aggravated by malabsorption, which can also cause secondary nutritional insufficiency and osteomalacia. The periportal fibrosis associated with mast cell infiltration may lead to portal hypertension and ascites. In some patients, anaphylaxis with rapid and life-threatening vascular collapse may occur. Anaphylaxis is most commonly induced by Hymenoptera stings, and patients often have evidence of venom-specific IgE. The neuropsychiatric disturbances are clinically most evident as impaired recent memory, decreased attention span, and "migraine-like" headaches. Patients may experience exacerbation of a specific clinical sign or symptom variably with alcohol ingestion, temperature changes, stress, use of mast cell-interactive opioids, or ingestion of nonsteroidal anti-inflammatory drugs (NSAIDs).

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Cutaneous mastocytosis is diagnosed by observing the characteristic lesions of MPCM or mastocytoma(s). A skin biopsy may be obtained to confirm these subvariants of CM, whereas patients with suspected DCM and bullous mastocytosis require a skin biopsy to confirm the diagnosis. Although the diagnosis of SM is generally suspected based on clinical history, physical examination findings, and laboratory procedures, it can only be confirmed with a tissue diagnosis. The diagnosis of SM necessitates a bone marrow biopsy to meet the criteria of one major plus one minor or three minor findings (Table 354-3). The major criterion requires mast cell aggregates, often in paratrabecular and perivascular locations with associated lymphocytes and eosinophils. Minor criteria include abnormal "spindled" mast cell morphology, aberrant mast cell membrane immunophenotype (CD25 and/or CD2), or a codon 816 mutation in an extracutaneous tissue. A basal serum total tryptase level is a noninvasive approach to consider before bone marrow biopsy. The pro-β and α forms of tryptase are elevated in more than one-half of patients with SM and provide a minor criterion; the fully processed ("mature") β form is increased in patients undergoing an anaphylactic reaction. A rare histopathologic subvariant called *well-differentiated systemic mastocytosis* (WDSM) is characterized by clusters of mature-appearing, fully granulated and round mast cells, lack of aberrant CD25 and CD2 expression, and lack of D816V *KIT* mutation in most patients. These patients often have a history of

TABLE 354-3 Diagnostic Criteria for Systemic Mastocytosis^a

Major:
Multifocal dense infiltrates of mast cells (>15 mast cells per aggregate) in bone marrow or other extracutaneous tissues
Minor:
Abnormal mast cell morphology (spindle shape, bi- or multilobed or eccentric nucleus, hypogranulated cytoplasm)
Aberrant mast cell surface phenotype with expression of CD25 (IL-2 receptor alpha chain) and/or CD2
Detection of codon 816 mutation in peripheral blood cells, bone marrow cells, or an extracutaneous lesional tissue
Total serum tryptase >20 ng/mL

^aDiagnosis requires either the major criterion and one minor criterion or three minor criteria.

childhood-onset cutaneous disease, and their mast cells may display aberrant CD30 expression and other markers of clonality such as atypical (non-D816V) *KIT* mutations. Additional studies directed at the presentation include a bone densitometry, bone scan, or skeletal survey; computed tomography scan or endoscopy; and a neuropsychiatric evaluation. Osteoporosis is increased in mastocytosis and may lead to pathologic fractures.

Some patients presenting with recurrent mast cell activation symptoms (particularly anaphylaxis with hypotensive syncope) have been found to have underlying mastocytosis. A subset of these patients may be found to have evidence of a clonal hematologic process such as the D816V *KIT* mutation or aberrant mast cells displaying CD25, but lack other diagnostic criteria for SM. Such patients are termed to have *monoclonal mast cell activation syndrome*.

The differential diagnosis requires the exclusion of other disorders. A 24-h urine assessment of 5-hydroxy-indoleacetic acid and metanephrines should exclude a carcinoid tumor and pheochromocytoma, respectively. Hereditary α -tryptasemia may be characterized by symptoms of mast cell activation in addition to multisystem involvement and elevated baseline serum tryptase. These patients have autosomal dominant inheritance of α -tryptase gene duplications at the TPSAB1 locus. Most patients with recurrent IgE-induced or idiopathic anaphylaxis present with urticaria, angioedema, and/or bronchospasm, which are not typical manifestations of anaphylaxis in SM.

TREATMENT

Mastocytosis

The management of SM is symptom control using a stepwise symptom/sign-directed approach. Medications include an H₁ antihistamine for flushing and pruritus, an H₂ antihistamine or proton pump inhibitor for gastric acid hypersecretion, oral cromolyn sodium for diarrhea and abdominal pain, and occasionally aspirin (in those who are known to be tolerant of NSAIDs) for severe flushing to block biosynthesis of prostaglandin D₂. Systemic glucocorticoids appear to alleviate malabsorption. Mast cell cytoreductive therapy consisting of midostaurin, avapritinib, IFN- α , or cladribine is generally reserved for advanced, nonindolent variants of SM. Midostaurin and avapritinib are small-molecule tyrosine kinase inhibitors with activity against both mutated *KIT* D816V and wild-type *KIT* and should be considered as a first-line therapy for these disease variants. The efficacy of cytoreductive therapy in mastocytosis is variable, perhaps because of side effects that limit dosages. Imatinib is not effective in most cases as the D816V *KIT* mutation mediates resistance. Combination chemotherapy is appropriate for the frank leukemias. Stem cell transplantation has been shown to be effective in a small subset of patients with advanced mastocytosis. A self-injectable epinephrine prescription is recommended for most patients due to increased incidence of anaphylaxis. Patients with a history of systemic Hymenoptera venom reaction should be evaluated for venom-specific IgE and placed on lifelong venom immunotherapy if positive.

FURTHER READING

- Akin C: *Mastocytosis: A Comprehensive Guide*. New York, Springer International Publishing, 2020.
- Hartmann K et al: Cutaneous manifestations in patients with mastocytosis: Consensus report of the European Competence Network on Mastocytosis; the American Academy of Allergy, Asthma & Immunology; and the European Academy of Allergology and Clinical Immunology. *J Allergy Clin Immunol* 137:35, 2016.
- Horny H-P et al: Mastocytosis (mast cell disease). In: *WHO Classification of Tumours. Pathology & Genetics. Tumours of Haematopoietic and Lymphoid Tissues*. SH Swerdlow et al (eds). Lyon, France, IARC Press, 2008, pp 54–63.
- Theoharides TC et al: Mast cells, mastocytosis, and related disorders. *N Engl J Med* 373:163, 2015.

Ustun C et al: Consensus opinion on allogeneic hematopoietic cell transplantation in advanced systemic mastocytosis. *Biol Blood Marrow Transplant* 22:1348, 2016.

Valent P et al: European Competence Network on Mastocytosis. Proposed diagnostic algorithm for patients with suspected mastocytosis: A proposal of the European Competence Network on Mastocytosis. *Allergy* 69:1267, 2014.

Valent P et al: Mastocytosis: 2016 updated WHO classification and novel emerging treatment concepts. *Blood* 11:1420, 2017.

355

Autoimmunity and Autoimmune Diseases

Betty Diamond, Peter E. Lipsky



One of the central features of the immune system is the capacity to mount an inflammatory response to potentially harmful foreign materials while avoiding damage to self-tissues. Whereas recognition of self plays an important role in shaping the repertoires of immune receptors on both T and B cells and in clearing apoptotic and other tissue debris from sites throughout the body, the development of potentially harmful immune responses to self-antigens is, in general, prohibited. The essential feature of an *autoimmune disease* is that tissue injury is caused by the immunologic reaction of the organism against its own tissues. *Autoimmunity*, on the other hand, refers merely to the presence of antibodies or T lymphocytes that react with self-antigens and does not necessarily imply that the self-reactivity has pathogenic consequences. Autoimmunity is present in all individuals and increases with age; however, autoimmune disease occurs only in those individuals in whom the breakdown of one or more of the basic mechanisms regulating immune tolerance results in self-reactivity that can cause tissue damage.

Polyreactive autoantibodies that recognize many host antigens are present throughout life. These antibodies are usually of the IgM heavy chain isotype and are encoded by nonmutated germline immunoglobulin variable region genes. These antibodies are essential, as they remove apoptotic debris through non-inflammatory pathways. Expression of these autoantibodies may be increased after some inciting events. When autoimmunity is induced by an inciting event, such as infection or tissue damage from trauma or ischemia, the autoreactivity is generally self-limited. When such autoimmunity does persist, however, pathology may or may not result. Moreover, even in the presence of organ pathology, it may be difficult to determine whether the damage is mediated by autoreactivity or an ongoing pathologic process related to the inciting trigger. Individuals with autoimmune disease may have numerous autoantibodies, only some or even none of which may be pathogenic. For example, patients with systemic sclerosis may have a wide array of antinuclear antibodies that are important in disease classification but are not clearly pathogenic; in contrast, patients with pemphigus may also exhibit a wide array of autoantibodies, one of which (antibody to desmoglein 1 and 3) is known to be pathogenic.

MECHANISMS OF AUTOIMMUNITY

Since Ehrlich first postulated the existence of mechanisms to prevent the generation of self-reactivity in the early 1900s, there has been a progressive increase in understanding of this prohibition in parallel with a progressive increase in understanding of the immune system. Burnet's clonal selection theory included the idea that interaction of lymphoid cells with their specific antigens during fetal or early postnatal life would lead to deletion of such "forbidden clones." This idea was refuted, however, when it was shown that autoimmune diseases could be induced in experimental animals by simple immunization

TABLE 355-1 Mechanisms Preventing Autoimmunity

1. Sequestration of self-antigens
2. Generation and maintenance of tolerance
 - a. Central deletion of autoreactive lymphocytes
 - b. Peripheral anergy of autoreactive lymphocytes
 - c. Receptor replacement in autoreactive lymphocytes
3. Regulatory mechanisms
 - a. Regulatory T cells
 - b. Regulatory B cells
 - c. Regulatory mesenchymal cells
 - d. Regulatory cytokines
 - e. Idiotype network

procedures, that autoantigen-binding cells could be demonstrated easily in the circulation of normal individuals, and that self-limited autoimmune phenomena frequently developed after tissue damage from infection or trauma. These observations indicated that clones of cells capable of responding to autoantigens were present in the repertoire of antigen-reactive cells in normal adults and suggested that mechanisms in addition to clonal deletion were responsible for preventing their activation.

Currently, three general processes are thought to be involved in the maintenance of selective unresponsiveness to autoantigens (**Table 355-1**): (1) sequestration of self-antigens, rendering them inaccessible to the immune system; (2) specific unresponsiveness (tolerance or anergy) of relevant T or B cells; and (3) limitation of potential reactivity by regulatory mechanisms. Derangements of these normal processes may predispose to the development of autoimmunity (**Table 355-2**). In general, induction of autoimmunity requires both an exogenous trigger, such as bacterial or viral infection or cigarette smoking or a perturbation of the microbiome, and the presence of endogenous abnormalities in the cells of the immune system. A number of exogenous triggers have been identified. For example, microbial superantigens, such as staphylococcal protein A and staphylococcal enterotoxins, are substances that can stimulate a broad range of T and B cells through specific interactions with selected families of immune receptors, irrespective of their antigen specificity. If autoantigen-reactive T and/or B cells express these receptors, autoimmunity may be induced by stimulation with these substances. Alternatively, molecular mimicry or cross-reactivity between a microbial product and a

self-antigen may lead to activation of autoreactive lymphocytes. One of the best examples of autoreactivity and autoimmune disease resulting from molecular mimicry is rheumatic fever, in which antibodies to the M protein of streptococci cross-react with myosin, laminin, and other matrix proteins as well as with neuronal antigens. Deposition of these autoantibodies in the heart initiates an inflammatory response, whereas their penetration into the brain can result in Sydenham's chorea. Molecular mimicry between microbial proteins and host tissues has been reported in type 1 diabetes mellitus, rheumatoid arthritis, systemic lupus erythematosus (SLE), celiac disease, and multiple sclerosis. It is presumed that infectious agents may be able to overcome self-tolerance because they possess *pathogen-associated molecular patterns* (PAMPs). These molecules (e.g., bacterial endotoxin, RNA, or DNA) exert adjuvant-like effects on the immune system by interacting with *Toll-like receptors* (TLRs) and other *pattern recognition receptors* (PRRs) that increase the immunogenicity and immunostimulatory capacity of the microbial material. The adjuvants activate dendritic cells, which in turn stimulate the activation of previously quiescent lymphocytes that recognize both microbial antigens and self-antigens. Alternatively, PAMPs can activate PRRs on tissue epithelial cells, which then activate dendritic cells. Cellular and tissue damage can result in release of *damage-associated molecular patterns* (DAMPs), including DNA, RNA nucleosomes, and other tissue debris, which may activate cells of the inflammatory and immune systems through engagement of the same array of PRRs. This pathway may lead to autoimmune disease in individuals who have impairments in mechanisms for clearance of tissue debris.

Although previous work focused on the role of pathogenic microorganisms in triggering autoimmunity, more recent studies have focused on the role of the microbiome, the collection of nonpathogenic microorganisms that reside on various body surfaces. It has become clear that the interaction between specific constituents of these microbiota and the immune system can shape the nature of the immune response to either favor or discourage immune/inflammatory responses. Thus, some genera within the microbiome may favor a nonresponsive state dominated by regulatory T cells, whereas others may favor the development of T effector cells and a proinflammatory state. Gender bias in autoimmune conditions may also be favored by differences in the dominant organisms within the microbiome.

Endogenous derangements of the immune system also contribute to the loss of immunologic tolerance to self-antigens and the development of autoimmunity (**Table 355-2**). Some autoantigens reside in immunologically privileged sites, such as the brain or the anterior chamber of the eye. These sites are characterized by the inability of engrafted tissue to elicit immune responses. Immunologic privilege results from a number of events, including the limited entry of proteins from those sites into lymphatics, the local production of immunosuppressive cytokines such as transforming growth factor β , and the local expression of molecules (including Fas ligand and PD-1 ligand) that can induce apoptosis or quiescence of activated T cells. Lymphoid cells remain in a state of immunologic ignorance (neither activated nor energized) with regard to proteins expressed uniquely in immunologically privileged sites. If the privileged site is damaged by trauma or inflammation or if T cells are activated elsewhere, proteins expressed at this site can become immunogenic and be the targets of immunologic assault. In multiple sclerosis and sympathetic ophthalmia, for example, antigens uniquely expressed in the brain and eye, respectively, become the target of activated T cells.

Alterations in antigen presentation may also contribute to autoimmunity. Peptide determinants (*epitopes*) of a self-antigen that are not routinely presented to lymphocytes may be recognized as a result of altered proteolytic processing of the molecule and the ensuing presentation of novel peptides (*cryptic epitopes*). When B cells rather than dendritic cells present self-antigen, they may also present cryptic epitopes that can activate autoreactive T cells. These cryptic epitopes will not previously have been available to affect the silencing of autoreactive lymphocytes. Furthermore, once there is immunologic recognition of one protein component of a multimolecular complex, reactivity may be induced to other components of the complex after

TABLE 355-2 Mechanisms of Autoimmunity

- I. Exogenous
 - A. Molecular mimicry
 - B. Superantigenic stimulation
 - C. Microbial and tissue damage-associated adjuvanticity
- II. Endogenous
 - A. Altered antigen presentation
 1. Loss of immunologic privilege
 2. Presentation of novel or cryptic epitopes (epitope spreading)
 3. Alteration of self-antigen
 4. Enhanced function of antigen-presenting cells
 - a. Costimulatory molecule expression
 - b. Cytokine production
 - B. Increased T-cell help
 1. Cytokine production
 2. Costimulatory molecules
 - C. Increased B-cell function
 1. B-cell activating factor
 2. Costimulatory molecules
 - D. Apoptotic defects or defects in clearance of apoptotic material
 - E. Cytokine imbalance
 - F. Altered immunoregulation

internalization and presentation of all molecules within the complex (epitope spreading). Finally, inflammation, environmental agents, drug exposure, or normal senescence may cause a posttranslational alteration in proteins, resulting in the generation of immune responses that cross-react with normal self-proteins. For example, the induction and/or release of protein arginine deiminase enzymes results in the conversion of arginine residues to citrullines in a variety of proteins, thereby altering their capacity to induce immune responses. Production of antibodies to citrullinated proteins has been observed in rheumatoid arthritis and chronic lung disease as well as in normal smokers. These antibodies can contribute to organ pathology. Alterations in the availability and presentation of autoantigens may be important components of immunoreactivity in certain models of organ-specific autoimmune diseases. In addition, these factors may be relevant to an understanding of the pathogenesis of various drug-induced autoimmune conditions. However, the diversity of autoreactivity manifesting in non-organ-specific systemic autoimmune diseases suggests that these conditions may result from a more general activation of the immune system rather than from an alteration in individual self-antigens.

Many autoimmune diseases are characterized by the presence of antibodies that react with antigens present in apoptotic material. Defects in the clearance of apoptotic material have been shown to elicit autoimmunity and autoimmune disease in a number of animal models. Moreover, such defects have been found in patients with SLE. Apoptotic debris that is not cleared quickly by the immune system can function as endogenous ligands for a number of PRRs on dendritic cells and B cells. Under such circumstances, dendritic cells and/or B cells are activated, and an immune response to apoptotic debris can develop. In addition, the presence of uncleared extracellular apoptotic material within germinal centers of secondary lymphoid organs in patients with SLE may facilitate the direct activation of autoimmune B-cell clones. Similarly, cellular contents, including nuclear material, released from neutrophils undergoing a form of cell death referred to as NETosis, may be particularly immunogenic.

Deficiency in C1q, likewise, can predispose or exacerbate autoimmunity. C1q assists in the clearance of apoptotic debris and NETotic material binding to IgM autoantibodies and to inhibitory receptors on monocytes and dendritic cells. If C1q is not present, a mechanism of immune suppression is lost. Moreover, if antibodies have undergone class switch recombination to IgG, the apoptotic debris containing immune complexes will engage activating Fc receptors on myeloid cells to induce an inflammatory response. Studies in a number of experimental models have suggested that intense stimulation of T lymphocytes can produce nonspecific signals that directly lead to polyclonal B-cell activation with the formation of multiple autoantibodies and bypass the need for antigen-specific helper T cells. For example, antinuclear, antierythrocyte, and antilymphocyte antibodies are produced during the chronic graft-versus-host reaction. In addition, autoimmune hemolytic anemia and immune complex-mediated glomerulonephritis can be induced in this manner. Direct stimulation of B lymphocytes can also lead to the production of autoantibodies. Thus, the administration of polyclonal B-cell activators, such as bacterial endotoxin, to normal mice leads to the production of a number of autoantibodies, including those to DNA and IgG (rheumatoid factor). A variety of genetic modifications resulting in hyperresponsiveness of B cells also can lead to the production of autoantibodies and, in animals of appropriate genetic background, a lupus-like syndrome. Moreover, excess B-cell activating factor (BAFF), a B-cell survival-promoting cytokine, can impair B-cell tolerance, cause T cell-independent B-cell activation, and lead to the development of autoimmunity. SLE can also be induced in mice through exuberant dendritic cell activation, through a redundancy of TLR7 and transposition to the Y chromosome (as in BXSB-Yaa mice), or through exposure to CpG, a ligand for TLR9. The ensuing induction of inflammatory mediators can cause a switch from the production of nonpathogenic IgM autoantibodies to the production of pathogenic IgG autoantibodies in the absence of antigen-specific T-cell help. Aberrant selection of the B- or T-cell repertoire at the time of antigen receptor expression can also predispose to autoimmunity. For example, B-cell immunodeficiency caused by

an absence of the B-cell receptor-associated kinase (Bruton's tyrosine kinase) leads to X-linked agammaglobulinemia. This syndrome is characterized by reduced B-cell numbers. This leads to high levels of BAFF, which alter B-cell selection and result in greater survival of autoreactive B cells. Likewise, negative selection of autoreactive T cells in the thymus requires expression of the autoimmune regulator (*AIRE*) gene that enables the expression of tissue-specific proteins in thymic medullary epithelial cells. Peptides from these proteins are expressed in the context of major histocompatibility complex (MHC) molecules and mediate the central deletion of autoreactive T cells. The absence of *AIRE* gene expression leads to a failure of negative selection of autoreactive cells, autoantibody production, and severe inflammatory destruction of multiple organs. Individuals deficient in *AIRE* gene expression develop autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED).

Primary alterations in the activity of T and/or B cells, cytokine imbalances, or defective immunoregulatory circuits may also contribute to the emergence of autoimmunity. Diminished production of tumor necrosis factor (TNF) and interleukin (IL) 10 has been reported to be associated with the development of autoimmunity. Overproduction or therapeutic administration of type 1 interferon has also been associated with autoimmunity. Overexpression of costimulatory molecules on T cells similarly can lead to autoantibody production.

Autoimmunity may also result from an abnormality of immunoregulatory mechanisms. Observations made in both human autoimmune disease and animal models suggest that defects in the generation and expression of regulatory T-cell (Treg) activity may allow the production of autoimmunity. It has been appreciated that the IPEX (immunodysregulation, polyendocrinopathy, enteropathy X-linked) syndrome results from the failure to express the *FOXP3* gene, which encodes a molecule critical in the differentiation of Tregs. Administration of normal Tregs or of factors derived from them can prevent the development of autoimmune disease in rodent models of autoimmunity, and allogeneic stem cell transplantation ameliorates human IPEX. Abnormalities in the function of Tregs have been noted in a number of human autoimmune diseases, including rheumatoid arthritis and SLE, although it remains uncertain whether these functional abnormalities are causative or are secondary to inflammation. One of the mechanisms by which Tregs control immune/inflammatory responses is by the production of the cytokine IL-10. In this regard, children with a deficiency in the expression of IL-10 or the IL-10 receptor develop inflammatory bowel disease that mimics Crohn's disease and that can be cured by allogeneic stem cell transplantation. Furthermore, recent data indicate that B cells may also exert regulatory function, largely through the production of IL-10. Deficiency of IL-10-producing regulatory B cells can prolong the course of multiple sclerosis in an animal model, and such cells are thought to be functionally diminished in human SLE. Finally, myeloid cells can inhibit immune responses. Depending on the microenvironment and cytokine stimulation, macrophages can functionally differentiate into classical M1 or inflammatory macrophages with enhanced microbicidal and cytotoxic activities or alternatively activated or M2 macrophages with anti-inflammatory and reparative capabilities. Abnormalities in this balance have been noted to contribute to animal models of autoimmunity and to human disease where a switch from M2-like to M1-like macrophages seems to be involved in development of disease activity in SLE. Importantly, C1q helps maintain macrophages in a quiescent state. Of note, dendritic cells also begin as tolerogenic cells but become immunogenic with activation. This pathway to autoimmunity has become important with the widespread use of checkpoint inhibitor therapy for cancer, which leads to autoimmune symptoms in up to one-third of recipients.

It should be apparent that no single mechanism can explain all the varied manifestations of autoimmunity or autoimmune disease. Furthermore, genetic evaluation has shown that convergence of a number of abnormalities is most often required for the induction of an autoimmune disease. Additional factors that appear to be important determinants in the induction of autoimmunity include age, sex (many autoimmune diseases are far more common in women), exposure to infectious agents, and environmental contacts. How these disparate

2734 factors affect the capacity to develop self-reactivity is currently being investigated intensively.

GENETIC CONSIDERATIONS

Evidence in humans that there are susceptibility genes for autoimmunity comes from family studies and especially from studies of twins. Studies in type 1 diabetes mellitus, rheumatoid arthritis, multiple sclerosis, and SLE have shown ~15–30% disease concordance in monozygotic twins, whereas the figure is <5% for dizygotic twins. The occurrence of different autoimmune diseases within the same family has suggested that certain susceptibility genes may predispose to a variety of autoimmune diseases. Many hundreds of genetic polymorphisms associated with one or more autoimmune diseases have been identified to date. As predicted, some genes are associated with multiple autoimmune diseases, whereas others are specifically associated with only one autoimmune condition. Moreover, recent genetic evidence suggests that clusters of genetic risk factors can commonly be found in groups of autoimmune diseases. For example, one group of genetic risk factors is most frequently associated with Crohn's disease, psoriasis, and multiple sclerosis, whereas a second is most strongly associated with celiac disease, rheumatoid arthritis, and SLE. These results imply that autoimmune diseases with widely different clinical presentations and patterns of organ involvement may involve similar immunopathogenic pathways or endophenotypes. For example, the same allele of the gene encoding PTPN22 is associated with multiple autoimmune diseases. Its product is a phosphatase expressed by a variety of hematopoietic cells that downregulates antigen receptor-mediated stimulation of T and B cells. The risk allele is associated with type 1 diabetes mellitus, rheumatoid arthritis, and SLE in some populations. In recent years, genome-wide association studies have demonstrated a variety of other genes that are involved in human autoimmune diseases. Importantly, the genetic contribution to autoimmune disease differs somewhat in people of different ancestries. Most genes individually confer a relatively low risk for autoimmune diseases and are found in normal individuals but, in aggregate, are associated with substantial risk of disease. In addition, most polymorphisms associated with autoimmune diseases are in noncoding regions of DNA, implying that protein expression levels rather than altered function might convey most genetic risk for autoimmune diseases. Abnormalities in epigenetics or the mechanisms, such as cellular metabolism, controlling and influencing gene expression have also been implicated in contributing to autoimmune diseases. No single gene or epigenetic modification has been identified that is essential for autoimmune diseases. In addition to this evidence from humans, certain inbred mouse strains reproducibly

develop specific spontaneous or experimentally induced autoimmune diseases, whereas others do not. These findings have now led to a search for genes that might be protective.

The strongest consistent association for susceptibility to autoimmune disease is with particular MHC alleles. It has been suggested that the association of MHC genotype with autoimmune disease relates to differences in the ability of different allelic variations of MHC molecules to present autoantigenic peptides to autoreactive T cells. An alternative hypothesis involves the role of MHC alleles in shaping the T-cell receptor repertoire during T-cell ontogeny in the thymus. In addition, specific MHC gene products may themselves be the source of peptides that can be recognized by T cells. Cross-reactivity between such MHC peptides and peptides derived from proteins produced by common microbes may trigger autoimmunity by molecular mimicry. Finally, there appears to be a contribution from non-MHC genes encoded within the MHC locus. However, MHC genotype alone does not determine the development of autoimmunity. Identical twins are far more likely to develop the same autoimmune disease than MHC-identical nontwin siblings. Studies of the genetics of type 1 diabetes mellitus, SLE, rheumatoid arthritis, and multiple sclerosis in humans and mice have identified several independently segregating disease susceptibility loci in addition to the MHC. Genes that encode molecules of the innate immune response are also involved in autoimmunity. In humans, inherited homozygous deficiency of the early proteins of the classic pathway of complement (C1q, C4, or C2) as well as genes involved in the type 1 interferon pathway are very strongly associated with the development of SLE.

IMMUNOPATHOGENIC MECHANISMS IN AUTOIMMUNE DISEASES

The mechanisms of tissue injury in autoimmune diseases can be divided into antibody-mediated and cell-mediated processes. Representative examples are listed in **Table 355-3**.

The pathogenicity of autoantibodies can be mediated through several mechanisms, including opsonization of soluble factors or cells, activation of an inflammatory cascade via the complement system, and interference with the physiologic function of soluble molecules or cells or immune complex-mediated activation of cells through engagement of activating Fc receptors.

In autoimmune thrombocytopenic purpura, opsonization of platelets targets them for elimination by phagocytes. Likewise, in autoimmune hemolytic anemia, binding of immunoglobulin to red cell membranes leads to phagocytosis and lysis of the opsonized cell. Goodpasture's syndrome, a disease characterized by lung hemorrhage and

TABLE 355-3 Mechanisms of Tissue Damage in Autoimmune Disease

EFFECTOR	MECHANISM	TARGET	DISEASE
Autoantibody	Blocking or inactivation	α Chain of the nicotinic acetylcholine receptor	Myasthenia gravis
		Phospholipid- β -glycoprotein I complex	Antiphospholipid syndrome
		Insulin receptor	Insulin-resistant diabetes mellitus
	Stimulation	Intrinsic factor	Pernicious anemia
		TSH receptor (LATS)	Graves' disease
		Proteinase-3 (ANCA)	Granulomatosis with polyangiitis
		Epidermal cadherin	Pemphigus vulgaris
		Desmoglein 3	
	Complement activation	α , Chain of collagen IV	Goodpasture's syndrome
	Immune complex formation	Double-stranded DNA	Systemic lupus erythematosus
T cells		Immunoglobulin	Rheumatoid arthritis
	Opsonization	Platelet GpIIb:IIIa	Autoimmune thrombocytopenic purpura
		Rh antigens, I antigen	Autoimmune hemolytic anemia
	Antibody-dependent cellular cytotoxicity	Thyroid peroxidase, thyroglobulin	Hashimoto's thyroiditis
T cells	Cytokine production		Rheumatoid arthritis, multiple sclerosis, type 1 diabetes mellitus
	Cellular cytotoxicity		Type 1 diabetes mellitus

Abbreviations: ANCA, antineutrophil cytoplasmic antibody; LATS, long-acting thyroid stimulator; TSH, thyroid-stimulating hormone.

severe glomerulonephritis, represents an example of antibody binding leading to local activation of complement and neutrophil accumulation and activation. The autoantibody in this disease binds to the α_3 chain of type IV collagen in the basement membrane. In SLE, activation of the complement cascade at sites of immunoglobulin deposition in renal glomeruli is considered to be a major mechanism of renal damage. Moreover, the DNA- and RNA-containing immune complexes in SLE activate TLR9 and TLR7, respectively, in plasmacytoid dendritic cells and promote the production of type I interferon and proinflammatory cytokines conducive to amplification of the autoimmune response.

Autoantibodies can also interfere with normal physiologic functions of cells or soluble factors. Autoantibodies to hormone receptors can lead to stimulation of cells or to inhibition of cell function through interference with receptor signaling. For example, long-acting thyroid stimulators—autoantibodies that bind to the receptor for thyroid-stimulating hormone (TSH)—are present in Graves' disease and function as agonists, causing the thyroid to respond as if there were an excess of TSH. Alternatively, antibodies to the insulin receptor can cause insulin-resistant diabetes mellitus through receptor blockade. In myasthenia gravis, autoantibodies to the acetylcholine receptor can be detected in 85–90% of patients and are responsible for muscle weakness. The exact location of the antigenic epitope, the valence and affinity of the antibody, and perhaps other characteristics determine whether activation or blockade results from antibody binding.

Antiphospholipid antibodies are associated with thromboembolic events in primary and secondary antiphospholipid syndrome and have also been associated with fetal loss. The major antibody is directed to the phospholipid- β_2 -glycoprotein I complex and appears to exert a procoagulant effect. In pemphigus vulgaris, autoantibodies bind to desmoglein 1 and 3, components of the epidermal cell desmosome, and play a role in the induction of the disease. These antibodies exert their pathologic effect by disrupting cell-cell junctions through stimulation of the production of epithelial proteases, with consequent blister formation. Cytoplasmic antineutrophil cytoplasmic antibody (c-ANCA), found in granulomatosis with polyangiitis, is an antibody to an intracellular antigen, the 29-kDa serine protease (proteinase-3). In vitro experiments have shown that IgG anti-c-ANCA causes cellular activation and degranulation of primed neutrophils.

It is important to note that autoantibodies of a given specificity may cause disease only in genetically susceptible hosts, as has been shown in experimental models of myasthenia gravis, SLE, rheumatic fever, and rheumatoid arthritis. Furthermore, once organ damage is initiated, new inflammatory cascades are initiated that can sustain and amplify the autoimmune process. Finally, some autoantibodies seem to be markers for disease but have, as yet, no known pathogenic potential.

In many autoimmune diseases, myeloid cells play an essential role as effector cells of inflammation. M1-like macrophages activated by cytokines, such as type 2 interferon, immune complexes through activating Fc receptors, or surface or intracellular TLRs can produce a number of inflammatory cytokines, including IL-1, TNF, and IL-6, that contribute to tissue inflammation.

AUTOIMMUNE DISEASES

Manifestations of autoimmunity are found in a large number of pathologic conditions. However, their presence does not necessarily imply that the pathologic process is an autoimmune disease. A number of attempts to establish formal criteria for the classification of diseases as autoimmune have been made, but none is universally accepted. One set of criteria is shown in **Table 355-4**; however, this scheme should be viewed merely as a guide in consideration of the problem.

To classify a disease as autoimmune, it is necessary to demonstrate that the immune response to a self-antigen causes the observed pathology. Initially, the detection of antibodies to the affected tissue in the serum of patients suffering from various diseases was taken as evidence that these diseases had an autoimmune basis. However, such autoantibodies can also be found when tissue damage is caused by trauma or infection and, in these cases, are secondary to tissue damage. Thus, autoimmunity must be shown to be pathogenic before a disease is categorized as autoimmune.

TABLE 355-4 Human Autoimmune Disease: Presumptive Evidence for Immunologic Pathogenesis

Major Criteria

1. Presence of autoantibodies or evidence of cellular reactivity to self
2. Documentation of relevant autoantibody or lymphocytic infiltrate in the pathologic lesion
3. Demonstration that relevant autoantibody or T cells can cause tissue pathology
 - a. Transplacental transmission
 - b. Adaptive transfer into animals
 - c. In vitro impact on cellular function

Supportive Evidence

1. Reasonable animal model
2. Beneficial effect from immunosuppressive agents
3. Association with other evidence of autoimmunity
4. No evidence of infection or other obvious cause

To confirm autoantibody pathogenicity, it may be possible to transfer disease to experimental animals by the administration of autoantibodies from a patient leading to the development of pathology in the recipient that is similar to that seen in the patient. This scenario has been documented, for example, in Graves' disease. Some autoimmune diseases can be transferred from mother to fetus and are observed in the newborn babies. The symptoms of the disease in the newborn usually disappear as the levels of maternal antibody decrease. An exception, however, is congenital heart block, in which damage to the developing conducting system of the heart follows in utero transfer of anti-Ro antibody from the mother to the fetus. This antibody transfer can result in a permanent developmental defect in the heart.

In most situations, the critical factors that determine when the development of autoimmunity results in autoimmune disease have not been delineated. The relationship of autoimmunity to the development of autoimmune disease may be associated with the fine specificity of the antibodies and their isotype or T cells or their specific effector capabilities. In many circumstances, a mechanistic understanding of the pathogenic potential of autoantibodies has not been established. In some autoimmune diseases, biased production of cytokines by helper T (T_H) cells may play a role in pathogenesis. In this regard, T cells can differentiate into specialized effector cells that predominantly produce interferon γ (T_{H1}), IL-4 (T_{H2}), or IL-17 (T_{H17}) or that provide help to B cells (T follicular helper [T_{FH}]) (**Chap. 349**). T_{H1} cells facilitate macrophage activation and classic cell-mediated immunity, whereas T_{H2} cells are thought to have regulatory functions and are involved in the resolution of normal immune responses as well as in the development of responses to a variety of parasites. T_{H17} cells produce a number of inflammatory cytokines, including IL-17 and IL-22, and seem to be prominently involved in host resistance to certain fungal infections. Tfh cells help B cells by constitutively producing IL-21. In a number of autoimmune diseases, such as rheumatoid arthritis, multiple sclerosis, type 1 diabetes mellitus, ankylosing spondylitis, and Crohn's disease, there appears to be biased differentiation of T_{H1} and T_{H17} cells, with resultant organ damage. Studies suggest an accentuated differentiation of T_{H17} cells associated with animal models of inflammatory arthritis, whereas increased differentiation of Tfh cells has been associated with SLE. Importantly, genetically determined or environmentally induced features of the target organ may determine susceptibility of the target organ to autoantibodies or autoreactive T cell-mediated damage.

ORGAN-SPECIFIC VERSUS SYSTEMIC AUTOIMMUNE DISEASES

The spectrum of autoimmune diseases ranges from conditions specifically affecting a single organ to systemic disorders that involve many organs (**Table 355-5**). Hashimoto's autoimmune thyroiditis is an example of an organ-specific autoimmune disease (**Chap. 382**). In this disorder, a specific lesion in the thyroid is associated with infiltration of mononuclear cells and damage to follicular cells. Antibody to thyroid constituents can be demonstrated in nearly all cases. Other

TABLE 355-5 Diseases on the Autoimmune Spectrum

Organ Specific	
Graves' disease	Vitiligo
Hashimoto's thyroiditis	Autoimmune hemolytic anemia
Autoimmune polyglandular syndrome	Autoimmune thrombocytopenic purpura
Type 1 diabetes mellitus	Pernicious anemia
Insulin-resistant diabetes mellitus	Myasthenia gravis
Immune-mediated infertility	Multiple sclerosis
Autoimmune Addison's disease	Guillain-Barré syndrome
Pemphigus vulgaris	Stiff-man syndrome
Pemphigus foliaceus	Acute rheumatic fever
Dermatitis herpetiformis	Sympathetic ophthalmia
Autoimmune alopecia	Goodpasture's syndrome
Primary biliary cirrhosis	
Organ Nonspecific (Systemic)	
Systemic lupus erythematosus	Granulomatosis with polyangiitis
Rheumatoid arthritis	Antiphospholipid syndrome
Systemic necrotizing vasculitis	Sjögren's syndrome

organ- or tissue-specific autoimmune disorders include pemphigus vulgaris, autoimmune hemolytic anemia, idiopathic thrombocytopenic purpura, Goodpasture's syndrome, myasthenia gravis, and sympathetic ophthalmia. One important feature of some organ-specific autoimmune diseases is the tendency for overlap, such that an individual with one specific syndrome is more likely to develop a second syndrome. For example, there is a high incidence of pernicious anemia in individuals with autoimmune thyroiditis. More striking is the tendency for individuals with an organ-specific autoimmune disease to develop multiple other manifestations of autoimmunity without the development of associated organ pathology. Thus, as many as 50% of individuals with pernicious anemia have non-cross-reacting antibodies to thyroid constituents, whereas patients with myasthenia gravis may develop antinuclear antibodies, antithyroid antibodies, rheumatoid factor, antilymphocyte antibodies, and polyclonal hypergammaglobulinemia. Part of the explanation may relate to the genetic elements shared by individuals with these different diseases.

Systemic autoimmune diseases differ from organ-specific diseases in that pathologic lesions are found in multiple diverse organs and tissues. The hallmark of these conditions is the demonstration of associated relevant autoimmune manifestations that are likely to have an etiologic role in organ pathology. SLE represents the prototype of these disorders because of its abundant autoimmune manifestations that characteristically involve the kidneys, joints, skin, serosal surfaces, blood vessels, and central nervous system (**Chap. 356**). The disease is associated with a vast array of autoantibodies whose production appears to be a part of a generalized hyperreactivity of the humoral immune system. Other features of SLE include generalized B-cell hyperresponsiveness and polyclonal hypergammaglobulinemia. Current evidence suggests that both hypo- and hyperresponsiveness to antigen can lead to survival and activation of autoreactive B cells in SLE. The autoantibodies in SLE are thought to arise as part of an accentuated T cell-dependent B-cell response since most pathogenic anti-DNA autoantibodies exhibit evidence of extensive somatic hypermutation.

TREATMENT

Autoimmune Diseases

Treatment of autoimmune diseases can focus on suppressing the induction of autoimmunity, restoring normal regulatory mechanisms, or inhibiting the effector mechanisms. To decrease the number or function of autoreactive cells, immunosuppressive or ablative therapies are most commonly used. In recent years, cytokine blockade has been demonstrated to be effective in preventing

immune activation in some diseases or in inhibiting the extensive inflammatory effector mechanisms characteristic of these diseases. New therapies have also been developed to target lymphoid cells more specifically by blocking a costimulatory signal needed for T- or B-cell activation, by blocking the migratory capacity of lymphocytes, or by eliminating the effector T cells or B cells. The efficacy of these therapies in some diseases—e.g., SLE (belimumab), rheumatoid arthritis (TNF neutralization, IL-6 receptor blockade, CD28 competition, B-cell depletion, IL-1 neutralization), psoriasis (IL-12/23 depletion, TNF neutralization), and inflammatory bowel disease (TNF neutralization, IL-12/23 neutralization)—has been demonstrated. Small molecules that block cytokine signaling pathways by blocking the Janus kinase (JAK) family of kinases have also entered the clinic. Biologicals that delete B cells have demonstrated efficacy in a number of autoimmune diseases characterized by pathogenic effector T cells, highlighting the importance of B cells as antigen-presenting cells. Finally, there is renewed interest in cellular therapies in autoimmune diseases, including hematopoietic stem cell reconstitutions and treatment with immunosuppressive mesenchymal stem cells. Therapies that prevent target organ damage or support target organ function also remain important in the management of autoimmune disease.

FURTHER READING

- Caielli S et al: Oxidized mitochondrial nucleoids release by neutrophils drive type I interferon production in human lupus. *J Exp Med* 5:697, 2016.
- Jackson SW et al: B cells take the front seat: Dysregulated B cell signals orchestrate loss of tolerance and autoantibody production. *Curr Opin Immunol* 33:70, 2015.
- Teruel M, Alacron-Riquelme ME: Genetics of systemic lupus erythematosus and Sjögren's syndrome: An update. *Curr Opin Rheumatol* 28:506, 2016.
- Tsokos GC et al: New insights into the immunopathogenesis of systemic lupus erythematosus. *Nat Rev Rheumatol* 22:716, 2016.
- Ueno H: T follicular helper cells in human autoimmunity. *Curr Opin Immunol* 43:24, 2016.
- Yin Y et al: Normalization of CD4+ T cell metabolism reverses lupus. *Science Transl Med* 7:274, 2015.

356 Systemic Lupus Erythematosus

Bevra Hannahs Hahn, Maureen McMahon



DEFINITION AND PREVALENCE

Systemic lupus erythematosus (SLE) is an autoimmune disease in which organs and cells undergo damage initially mediated by tissue-binding autoantibodies and immune complexes. In most patients, autoantibodies are present for a few years before the first clinical symptom appears. Ninety percent of patients are women of child-bearing years; people of all genders, ages, and ethnic groups are susceptible. The prevalence of SLE in the United States is 81–144 per 100,000. Prevalence is higher in all nonwhite races/ethnicities compared to whites, with the highest prevalence in African-American and Afro-Caribbean women and the lowest in white men. SLE is 5.5–6.5 times more prevalent in women than in men.

PATHOGENESIS AND ETIOLOGY

The proposed pathogenic mechanisms of SLE are illustrated in **Fig. 356-1**. The abnormal immune responses underlying SLE may be summarized as leading to production of increased quantities and

PREDISPOSING FACTORS

GENES

High hazard ratios (6):

- Deficiencies of C1q, C2, C4 (rare)
- TREX1 mutations affecting DNA degradation (rare)



Affecting Ag presentation or persistence, e.g., phagocytosis of immune complexes
HLA-DRB1 (*1501, *0301), DR3, DQA2, CR2, FCGR2A/B

Enhance innate immunity, including production of IFNs
TNFAIP3, IRF5/TNPO3, IRF7/PHRF1, ITGAM, ICAMs

Alter adaptive immunity B and/or T cell signaling
BANK1, STAT4, MSH5, IZKF3, TCF7

GENES FOR LUPUS NEPHRITIS

HLA-DR3, STAT4, APOL1 (African Americans),
FCGR3A, ITGAM, IRF5, IRF7, TNFSF4 (Ox40L), DNase1

ENVIRONMENT/MICROENVIRONMENT

Ultraviolet light, smoking, crystalline silica, ?EBV infection, femaleness



EPIGENETICS

Hypomethylation of DNA: In CD4+T, B and monocytes

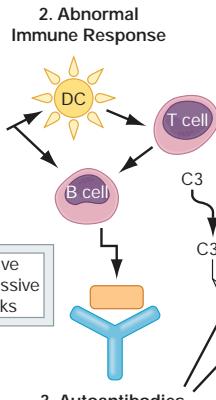
Some affect IFN production

Histone modifications: Some increase expression of predisposing genes and/or IFN production

MicroRNA affecting gene expression

Mir-21, -146A, -155, -569, -30A, Let-7a

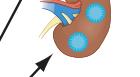
2. Abnormal Immune Response



4. Inflammation



C3
C3a



Chr. inflam.
Chr. oxid.

Rash
Nephritis
Arthritis
Leukopenia
CNS dz
Carditis
Clotting
Etc.

5. Damage



Renal failure
Artherosclerosis
Pulm fibrosis
Stroke
Damage from Rx
Etc.

FIGURE 356-1 Pathogenesis of systemic lupus erythematosus (SLE). Pathogenesis is related in large part to production of increased quantities and immunogenic forms of nucleic acids and other self-antigens, which drive autoimmune-inducing activation of innate immunity, autoantibodies, and T cells. Interactions between genes, environment, and epigenetic changes drive increased autophagy, antigen (Ag) presentation, neutrophil NETosis, autoantibody formation with increased plasma cells, and production of pathogenic effector T cells in T₁, T₁₇, and Tf₁ subsets, and in B-cell subsets with ineffective regulatory networks. Genes confirmed in more than one genome-wide association analysis in multiple racial groups that increase susceptibility to SLE or lupus nephritis (HR > 1.5) are listed (reviewed in Deng Y, Tsao B: Genetics of Human SLE, in *Dubois Lupus Erythematosus and Related Syndromes*, 9th ed. DJ Wallace, BH Hahn [eds]. Philadelphia, Elsevier, 2019, pp 54-69; and Teruel M, Alarcon-Riquelme ME: The genetic basis of systemic lupus erythematosus: What are the risk factors and what have we learned. *J Autoimmun* 74:161, 2016. Epigenetics are reviewed in Richardson B: The interaction between environmental triggers and epigenetics in autoimmunity. *Clin Immunol* 192:1, 2018; and Scherzer CD et al: Epigenetic programming underpins B cell dysfunction in human SLE. *Nat Immunol* 20:1071, 2019. Environmental triggers are reviewed in Gulati G, Brunner HI: Environmental triggers in systemic lupus erythematosus. *Semin Arthritis Rheum* 47:710, 2018). These result in abnormal immune responses that generate pathogenic autoantibodies and immune complexes that deposit in tissue, activate complement, induce cytokine and chemokine release causing inflammation, and over time lead to irreversible organ damage (reviewed in Arazi A et al: The immune cell landscape in kidneys of patients with lupus nephritis. *Nat Rev Immunol* 20:902, 2019; and Hahn BH: Pathogenesis of SLE, in *Dubois Lupus Erythematosus and Related Syndromes*, 9th ed. DJ Wallace, BH Hahn [eds]. Philadelphia, Elsevier, 2019; and Anders HJ, Rovin B: A pathophysiology-based approach to diagnosis and treatment of lupus nephritis. *Kidney Int* 90:493, 2016). C1q, complement system; C3, complement component; CNS, central nervous system; DC, dendritic cell; EBV, Epstein-Barr virus; HLA, human leukocyte antigen; FcR, immunoglobulin Fc-binding receptor; IL, interleukin; MCP, monocyte chemoattractant protein; PTPN, phosphotyrosine phosphatase; UV, ultraviolet.

immunogenic forms of nucleic acids, their accompanying proteins, and other self-antigens, with resultant stimulation of large quantities of autoantibodies. Autoantibodies of SLE are described in Fig. 356-1 and **Table 356-1**.

SLE autoimmunity may begin with activation of innate immunity, partly through binding of DNA, RNA, and proteins by Toll-like receptors in plasmacytoid dendritic cells (pDCs) and monocytes/macrophages. The pDCs (and other cells) produce interferon (IFN) α. Upregulation of genes induced by IFNs (particularly IFN-α) is a genetic “signature” in whole blood, peripheral blood cells, skin lesions, synovium, and kidneys in 50–80% of SLE patients and is particularly associated with active disease. Activated macrophages produce inflammatory cytokines/chemokines such as interleukin (IL) 12, tumor necrosis factor α (TNF-α), and the B-cell maturation/survival factor BLys/BAFF. Furthermore, lupus phagocytic cells have reduced capacity to clear immune complexes, apoptotic cells, and their autoantigen-containing (e.g., DNA/RNA/Ro/La and phospholipid) surface blebs. The result is persistence of large quantities of autoantigens. Neutrophils release immunogenic DNA/protein-containing neutrophil extracellular traps (NETs), and natural killer (NK) cells have reduced ability to kill auto-reactive T and B cells or to produce the transforming growth factor β (TGF-β) needed for development of regulatory T cells.

The activated innate immune system interacts with various subsets of the B and T cells of adaptive immunity. SLE peripheral B cells have increased numbers of naïve activated B cells and double-negative B cells (DN2: CD27-CD11c+T-BET+CXCR5-), which are precursors

of autoantibody-secreting cells. Both subsets have abnormal epigenetic modifications with more open chromatin than normal B cells and thus are subject to hyperactivation via their B-cell receptors, Toll-like receptor 7 (TLR7), and cytokines such as IL-21. Therefore, SLE B cells are poised to react to their environment with increased autoantibody secretion. Central B cells (germinal center, follicular B cells) also produce autoantibodies. DN2 and isotype-switched memory B cells differentiate into both short-lived (in periphery) and long-lived (in bone marrow) plasma cells that secrete autoantibodies and are elevated in patients with active SLE. B cells not only present antigens, but they also secrete IL-6 and IL-10, which promote autoreactive B-cell survival (as does estrogen). Some B and T lymphocyte subsets have altered metabolism (abnormal mitochondrial electron transport, membrane potential, and oxidative stress), increased glucose utilization, increased pyruvate production, activation of mechanistic target of rapamycin (mTOR), and increased autophagy. Helper T cells are easily activated and driven into either differentiation, activation, or apoptosis. In SLE patients, after peptides bind the T-cell receptor (TCR), T-cell signaling is abnormal, beginning with complexing of TCR with the common chain FcRγ rather than the usual CD3ζ. This results in abnormal elevations of phosphorylated Syk, the P13K/mTORC pathway, CaMKIV, PP2A, and calcineurin, with resultant increased calcium influx. Rho-associated protein kinases (ROCK) pathways are also elevated, probably via cytokine receptors, with increases in STAT3 and therefore in IL-17. The net result is underproduction of IL-2 (needed for survival of T lymphocytes and for generation of regulatory T cells) and elevation

TABLE 356-1 Autoantibodies in Serum or Plasma in Systemic Lupus Erythematosus (SLE)

ANTIBODY	PREVALENCE, %	ANTIGEN RECOGNIZED	CLINICAL UTILITY
Antinuclear antibodies	98	Multiple nuclear	Best screening test; repeated negative tests by immunofluorescence make SLE unlikely. Immunofluorescence is best standard test: titers of 1:80 or higher may separate clinically significant tests from false positives. Has good sensitivity but poor specificity for SLE.
Anti-dsDNA	70	DNA (double-stranded)	High titers are SLE-specific and in some patients correlate with disease activity, nephritis, vasculitis. <i>Critchidia</i> immunofluorescence is more specific for SLE than ELISA methods.
Anti-C1q	33	Collagen-like determinants on complement component C1q	Present in 63% of lupus nephritis, associated with active lupus nephritis especially when anti-dsDNA is also present. Correlates with activity of nephritis. Not specific for SLE.
Anti-Sm	25	Protein complexed to 6 species of nuclear U1 RNA	Specific for SLE; no definite clinical correlations; most patients also have anti-RNP; more common in blacks and Asians than whites
Anti-RNP	40	Protein complexed to U1 RNA	Not specific for SLE; high titers associated with syndromes that have overlap features of several rheumatic syndromes including SLE; more common in blacks than whites; correlates with high IFN-induced gene signature
Anti-Ro (SS-A)	30	Protein complexed to hY RNA, primarily 60 kDa and 52 kDa	Not specific for SLE; associated with sicca syndrome, predisposes to subacute cutaneous lupus and neonatal lupus with congenital heart block.
Anti-La (SS-B)	10	47-kDa protein complexed to hY RNA	Usually associated with anti-Ro.
Antihistone	70	Histones associated with DNA (in nucleosome, chromatin)	More frequent in drug-induced lupus than in SLE.
Antiphospholipid	50	Phospholipids, β_2 -glycoprotein 1 (β_2 G1) cofactor, prothrombin	Three tests available—ELISAs for cardiolipin and β_2 G1, sensitive prothrombin time (DRVVT) for lupus anticoagulant; predisposes to clotting, fetal loss, thrombocytopenia.
Antierythrocyte	60	Erythrocyte membrane	Measured as direct Coombs test; a small proportion develops overt hemolysis.
Antiplatelet	30	Surface and altered cytoplasmic antigens on platelets	Associated with thrombocytopenia, but sensitivity and specificity are not good; this is not a useful clinical test.
Antineuronal (includes antiglutamate receptor 2)	60	Neuronal and lymphocyte surface antigens	In some series, a positive test in CSF correlates with active CNS lupus.
Antiribosomal P	20	Protein in ribosomes	In some series, a positive test in serum correlates with depression or psychosis due to CNS lupus.

Abbreviations: CNS, central nervous system; CSF, cerebrospinal fluid; DRVVT, dilute Russell viper venom time; ELISA, enzyme-linked immunosorbent assay.

of IL-17. These changes push the adaptive immune system toward generation of helper T cells ($T_{H}1$, Tfh , $T_{H}17$) and away from downregulating regulatory T cells. Several of these B- and T-cell pathways are targets of therapeutic interventions in current clinical trials.

Tissue damage begins with deposition of autoantibodies and/or immune complexes, followed by destruction mediated by complement activation and release of cytokines/chemokines. Nonimmune tissue-fixed cells also are activated with resultant inflammation and damage, such as basal cells of the dermis, synovial fibroblasts, renal mesangial cells, podocytes and tubular epithelium, and endothelial cells throughout the body. Meanwhile, the initial immune attack is attracting into the target tissues additional B and T cells, monocytes/macrophages, dendritic cells, and plasma cells. Inflammation also causes release of vasoactive peptides, oxidative damage, and release of growth factors and fibrosing factors. Sclerosis/fibrosis with irreversible tissue damage can occur in multiple tissues including kidneys, lungs, blood vessels, and skin. Each of these processes depends on the individual's genetic background, environmental influences, and epigenetics.

SLE is usually a multigenic disease. Rare single-gene defects confer high hazard ratios (HRs) for SLE (HR 5–25), including homozygous deficiencies of early components of complement (C1q,r,s; C2; C4) and a mutation in *TREX1* (encoding a DNase) on the X chromosome. In most genetically susceptible individuals, normal alleles, mutations, and/or copy numbers of multiple ancestral genes each contribute a small amount to abnormal immune/inflammation/tissue damage responses; if enough predisposing variations are present, disease results. Approximately 90 genes with normal single nucleotide polymorphisms (SNPs; or mutations or altered copy numbers) increase risk for SLE and/or clinical subsets of SLE and/or irreversible organ damage. They have been identified in recent genome-wide or immunochip association studies in different ancestries. Individually, they

confer an HR for SLE of 1.4–3 and, even in combination, account for only 28% of disease susceptibility, suggesting that environmental exposures and epigenetics play major roles. Examples are listed in Fig. 356-1, showing those with HR ≥ 1.4 and listing them according to their major known functions. Approximately 50% of known predisposing genes influence IFN production or function—the most characteristic increased gene expression pattern of SLE patients. Multiple genes affect final responses: for example, a gene effect in the promoter for *IRF5* that increases IFN production is associated with SLE in all ancestries, but a haplotype containing *IRF5* and transportin 3 (*TNPO3*), which probably further increases IFN responses, is present only in European ancestries. Some polymorphisms influence clinical manifestations; these are listed in Fig. 356-1. Some genes relate to end-organ dysfunction rather than SLE, such as *MYH9/APOL1* associating with end-stage renal disease (ESRD) in all ancestries, whereas *APOL1/G2* associates with ESRD (but not SLE) only in African Americans. Such combinations probably account for lupus nephritis being more common and more severe in African Americans than in other races. Some gene effects are in promoter regions (e.g., *MYH9/APOL* and *IL-10*), and others are conferred by copy numbers (e.g., *C4A*, *TLR7*). In addition, multiple epigenetic changes characterize SLE, including hypomethylation of DNA-encoding genes, promoter regions, and/or transcription factors in CD4+ T cells, B cells, and monocytes, e.g., genes that control production of type 1 IFNs. In contrast, some DNA regions in SLE B cells are hypermethylated. There are also histone modifications in SLE DNA. Some of these changes are mediated by microRNAs associated with SLE, including some that control DNA methyltransferases (DNMTs; such as miR-146a), which control methylation of DNA in CD4+ T cells and resultant IFN production. Some gene polymorphisms contribute to several autoimmune diseases, such as *STAT4* and *CTLA4*. Most of these genetic effects influence immune responses to the external and internal environment;

when such responses are abnormal or prolonged, autoimmune disease is favored.

Female sex is permissive for SLE with evidence for hormone effects, genes on the X chromosome, and epigenetic differences between genders playing a role. Females of many mammalian species make higher antibody responses than males. Women exposed to estrogen-containing oral contraceptives or hormone replacement have an increased risk of developing SLE (HR 1.2–2). Estradiol binds to receptors on T and B lymphocytes, increasing activation and survival of those cells, especially autoreactive subsets, thus favoring prolonged immune responses. Genes on the X chromosome that influence SLE, such as *TREXI*, may play a role in gender predisposition, possibly because some genes on the second X in females are not silent. People with XYY karyotype (Klinefelter's syndrome) have a significantly increased risk for SLE.

Several environmental stimuli may influence SLE (Fig. 356-1). Exposure to ultraviolet light causes flares of SLE in ~70% of patients, possibly by increasing apoptosis in skin cells or by altering DNA and intracellular proteins to make them antigenic. Some infections and lupus-inducing drugs activate autoreactive T and B cells; if such cells are not appropriately regulated, prolonged autoantibody production occurs. Most SLE patients have autoantibodies for 3 years or more before the first symptoms of disease, suggesting that regulation controls the degree of autoimmunity for years before quantities and qualities of autoantibodies, activated innate immunity, pathogenic B and T cells, and activated tissue-fixed cells cause clinical disease. Epstein-Barr virus (EBV) may be one infectious agent that can trigger SLE in susceptible individuals. Children and adults with SLE are more likely to be infected by EBV than age-, sex-, and ethnicity-matched controls. EBV contains amino acid sequences that mimic sequences on human spliceosomes (RNA/protein antigens) often recognized by autoantibodies in people with SLE. Current tobacco smoking increases risk for SLE (HR 1.5). Prolonged occupational exposure to crystalline silica (e.g., inhalation of soap powder dust or soil in farming activities) increases risk (HR 4.3) in African-American women. Exposure to pesticides during childhood, both in residential use and in farming, increases the risk of SLE. Long-term exposure to air pollution also increases the risk of SLE. Thus, interplay between genetic susceptibility, environment, gender, race, and abnormal immune responses results in autoimmunity (**Chap. 355**).

PATHOLOGY

In SLE, biopsies of affected skin show deposition of Ig at the dermal-epidermal junction (DEJ), injury to basal keratinocytes, and inflammation dominated by T lymphocytes in the DEJ and around blood vessels and dermal appendages. Clinically unaffected skin may also show Ig deposition at the DEJ. Lupus skin lesions are characterized by expression of IFN-regulated cytokines and chemokines and by IFN-producing pDCs and keratinocytes. These patterns are not specific for dermatologic SLE; however, they are highly suggestive.

In renal biopsies, the pattern and severity of injury are important in diagnosis and in selecting the best therapy. Most recent clinical studies of lupus nephritis have used the International Society of Nephrology (ISN) and the Renal Pathology Society (RPS) classification (**Table 356-2**). In the ISN/RPS classification, the addition of "A" for active and "C" for chronic changes gives physicians information regarding the potential reversibility of disease. The system focuses on glomerular disease, although the presence of tubular interstitial and vascular disease, as well as the chronicity score in both glomeruli and interstitium, is important in predicting clinical outcomes. In general, class III and IV disease, as well as class V accompanied by III or IV disease, should be treated with aggressive immunosuppression if possible because there is a high risk for ESRD if patients are untreated or undertreated. In contrast, treatment for lupus nephritis is not recommended in patients with class I or II disease or with extensive irreversible changes (class VI). In the 2019 European League of Rheumatism/American College of Rheumatology (EULAR/ACR) criteria for classification of SLE, a diagnosis can be established on the basis of class III or class IV renal histology in the presence of antinuclear autoantibodies, without meeting additional criteria (**Tables 356-3 and 356-4**).

TABLE 356-2 Classification of Lupus Nephritis (International Society of Nephrology and Renal Pathology Society)

Class I: Minimal Mesangial Lupus Nephritis

Normal glomeruli by light microscopy, but mesangial immune deposits by immunofluorescence.

Class II: Mesangial Proliferative Lupus Nephritis

Purely mesangial hypercellularity of any degree or mesangial matrix expansion by light microscopy, with mesangial immune deposits. A few isolated subepithelial or subendothelial deposits may be visible by immunofluorescence or electron microscopy, but not by light microscopy.

Class III: Focal Lupus Nephritis

Active or inactive focal, segmental or global endo- or extracapillary glomerulonephritis involving 50% of all glomeruli, typically with focal subendothelial immune deposits, with or without mesangial alterations.

Class III (A): Active lesions—focal proliferative lupus nephritis

Class III (A/C): Active and chronic lesions—focal proliferative and sclerosing lupus nephritis

Class III (C): Chronic inactive lesions with glomerular scars—focal sclerosing lupus nephritis

Class IV: Diffuse Lupus Nephritis

Active or inactive diffuse, segmental or global endo- or extracapillary glomerulonephritis involving 50% of all glomeruli, typically with diffuse subendothelial immune deposits, with or without mesangial alterations. This class is divided into diffuse segmental (IV-S) lupus nephritis when 50% of the involved glomeruli have segmental lesions, and diffuse global (IV-G) lupus nephritis when 50% of the involved glomeruli have global lesions. Segmental is defined as a glomerular lesion that involves less than one-half of the glomerular tuft. This class includes cases with diffuse wire loop deposits but with little or no glomerular proliferation.

Class IV-S (A): Active lesions—diffuse segmental proliferative lupus nephritis

Class IV-G (A): Active lesions—diffuse global proliferative lupus nephritis

Class IV-S (A/C): Active and chronic lesions—diffuse segmental proliferative and sclerosing lupus nephritis

Class IV-G (A/C): Active and chronic lesions—diffuse global proliferative and sclerosing lupus nephritis

Class IV-S (C): Chronic inactive lesions with scars—diffuse segmental sclerosing lupus nephritis

Class IV-G (C): Chronic inactive lesions with scars—diffuse global sclerosing lupus nephritis

Class V: Membranous Lupus Nephritis

Global or segmental subepithelial immune deposits or their morphologic sequelae by light microscopy and by immunofluorescence or electron microscopy, with or without mesangial alterations. Class V lupus nephritis may occur in combination with class III or IV, in which case both will be diagnosed. Class V lupus nephritis may show advanced sclerosis.

Class VI: Advanced Sclerotic Lupus Nephritis

90% of glomeruli globally sclerosed without residual activity.

Note: Indicate and grade (mild, moderate, severe) tubular atrophy, interstitial inflammation and fibrosis, and severity of arteriosclerosis or other vascular lesions.

Source: Reproduced with permission from JJ Weening et al: The classification of glomerulonephritis in systemic lupus erythematosus revisited. Kidney Int 65:521, 2004.

Histologic abnormalities in blood vessels may also determine therapy. Patterns of vasculitis are not specific for SLE but may indicate active disease: leukocytoclastic vasculitis is most common (**Chap. 363**).

Lymph node biopsies are usually performed to rule out infection or malignancies. In SLE, they show nonspecific diffuse chronic inflammation.

DIAGNOSIS

The diagnosis of SLE is based on characteristic clinical features and autoantibodies. Two classification systems are currently in use: the 2012 Systemic Lupus International Collaborating Clinics (SLICC) criteria and the 2019 EULAR/ACR classification in which clinical manifestations are weighted. Both are shown in Tables 356-3 and 356-4. The SLICC criteria are easier for evaluating an individual patient, but the EULAR/ACR are more current and will probably be used for

TABLE 356-3 Systemic Lupus International Collaborating Clinic Criteria for Classification of Systemic Lupus Erythematosus

CLINICAL MANIFESTATIONS	IMMUNOLOGIC MANIFESTATIONS
Skin	ANA > reference negative value
Acute, subacute cutaneous LE (photosensitive, malar, maculopapular, bullous)	Anti-dsDNA > reference, if by ELISA 2x reference
Chronic cutaneous LE (discoid lupus, panniculitis, lichen planus-like, hypertrophic verrucous, chillblains)	Anti-Sm
Oral or nasal ulcers	Antiphospholipid (any of lupus anticoagulant, false-positive RPR, anticardiolipin, anti-β ₂ -glycoprotein 1)
Nonscarring alopecia	Low serum complement (C3, C4, or CH50)
Synovitis involving 2 joints	Positive direct Coombs test
Serositis (pleurisy, pericarditis)	
Renal	
Prot/Cr 0.5	
RBC casts	
Biopsy ^a	
Neurologic	
Seizures, psychosis, mononeuritis, myelitis, peripheral or cranial neuropathies, acute confusional state	
Hemolytic anemia	
Leukopenia (<4000/µL) or lymphopenia (<1000/µL)	
Thrombocytopenia (<100,000/µL)	

^aRenal biopsy read as systemic lupus qualifies for classification as SLE if any lupus autoantibodies are present, even if total criteria are fewer than 4.

Interpretation: Presence of any four criteria (must have at least 1 in each category) qualifies patient to be classified as having SLE with 93% specificity and 92% sensitivity. American College of Rheumatology is developing new criteria for SLE. For update, see website Rheumatology.org.

Abbreviations: ANA, antinuclear antibody; Cr, creatinine; ELISA, enzyme-linked immunosorbent assay; LE, lupus erythematosus; Prot, protein; RBC, red blood cell; RPR, rapid plasma reagent.

Source: M Petri et al: Arthritis Rheum 64:2677, 2012. Because these criteria are relatively new, some currently ongoing clinical studies use prior American College of Rheumatology Criteria; see EM Tan et al: Arthritis Rheum 25:1271, 1982; update MC Hochberg: Arthritis Rheum 40:1725, 1997.

most clinical studies in SLE for the next several years. An algorithm for diagnosis and initial therapy is shown in Fig. 356-2. The criteria are intended for diagnosis of SLE in subjects included in studies; the authors use them in individual patients for estimating the probability that a disease is SLE. In the SLICC criteria, any combination of four or more well-documented criteria at any time during an individual's history, with at least one in the clinical and one in the immunologic category, makes it likely that the patient has SLE (specificity 97%, sensitivity 84%). For EULAR/ACR criteria, a subject must have a positive ANA ($\geq 1:80$ by immunofluorescence) and a score of 10 (specificity 97%, sensitivity 93%). In many patients, criteria accrue over time. Anti-nuclear antibodies (ANAs) are positive in >98% of patients during the course of disease; repeated negative tests by immunofluorescent methods suggest that the diagnosis is not SLE, unless other autoantibodies are present (Fig. 356-2). High-titer IgG antibodies to double-stranded DNA and antibodies to the Sm antigen are both specific for SLE and, therefore, favor the diagnosis in the presence of compatible clinical manifestations. The presence of multiple autoantibodies in an individual without clinical symptoms should not be considered diagnostic for SLE, although such persons are at increased risk.

INTERPRETATION OF CLINICAL MANIFESTATIONS

When a diagnosis of SLE is made, it is important to establish the severity and potential reversibility of the illness and to estimate the possible consequences of various therapeutic interventions. In the following paragraphs, descriptions of some disease manifestations begin with relatively mild problems and progress to those that are more life-threatening.

OVERVIEW AND SYSTEMIC MANIFESTATIONS

At its onset, SLE may involve one or several organ systems; over time, additional manifestations may occur (Tables 356-3, 356-4, and 356-5). Most of the autoantibodies characteristic of each person are present at the time clinical manifestations appear (Tables 356-1, 356-3, and 356-4). Severity of SLE varies from mild and intermittent to severe and fulminant. Systemic symptoms, particularly fatigue and myalgias/arthralgias, are present most of the time. Severe systemic illness requiring high-dose glucocorticoid therapy can occur with fever, prostration, weight loss, and anemia with or without other organ-targeted manifestations. Approximately 85% of patients have either continuing active disease (on current treatment) or one or more flares of active disease annually. Permanent complete remissions (absence of symptoms with no treatment) occur in <5%. Recommended treatment target is remission on therapy (no clinical manifestations; abnormal laboratory tests permitted) or induction of low lupus disease activity. See "Management of Systemic Lupus Erythematosus," below, for more detail.

MUSCULOSKELETAL MANIFESTATIONS

Most people with SLE have intermittent polyarthritis, varying from mild to disabling. Polyarthritis is characterized by soft tissue swelling and tenderness in joints and/or tendons, most commonly in hands, wrists, and knees. Joint deformities (hands and feet) develop in only 10% and are often reducible. Erosions on joint x-rays are rare but can be identified by ultrasound in 10–50% of patients; individuals with erosions may fulfill criteria for both RA and SLE ("rhupus"). If pain persists in a single joint, such as knee, shoulder, or hip, a diagnosis of ischemic necrosis of bone (INB) should be considered, particularly if there are no other manifestations of active SLE. INB prevalence is increased in SLE, especially in patients treated with systemic glucocorticoids. Myositis with clinical muscle weakness, elevated creatine kinase levels, positive magnetic resonance imaging (MRI) scan, and muscle necrosis and inflammation on biopsy can occur, although most patients have myalgias without frank myositis. Glucocorticoid therapies (commonly) and antimarial therapies (rarely) can cause muscle weakness; these adverse effects must be distinguished from active inflammatory disease.

CUTANEOUS MANIFESTATIONS

Lupus dermatitis can be classified as acute, subacute, or chronic, and there are many different types of lesions encompassed within these groups. Discoid lupus erythematosus (DLE) is the most common chronic dermatitis in lupus; lesions are roughly circular with slightly raised, scaly, hyperpigmented erythematous rims and depigmented, atrophic centers in which all dermal appendages are permanently destroyed. Lesions can be disfiguring, particularly on the face and scalp. Only 5% of people with DLE have SLE (although half have positive ANA); however, among individuals with SLE, as many as 20% have DLE. The most common acute SLE rash is a photosensitive, slightly raised, occasionally scaly erythema on the face (particularly the cheeks and nose—the "butterfly" rash), ears, chin, V region of the neck and chest, upper back, and extensor surfaces of the arms. Worsening of this rash often accompanies flare of systemic disease. Subacute cutaneous lupus erythematosus (SCLE) consists of scaly red patches, similar to psoriasis, or circular, flat, red-rimmed ("annular") lesions. Patients with these manifestations are exquisitely photosensitive; most have antibodies to Ro (SS-A). Other SLE rashes include recurring urticaria, lichen planus-like dermatitis, bullae, and panniculitis ("lupus profundus"). Rashes can be minor or severe; they may be the major disease manifestation. Small ulcerations on the oral or nasal mucosa are common in SLE; the lesions resemble aphthous ulcers and may or may not be painful.

RENAL MANIFESTATIONS

Nephritis is usually the most serious manifestation of SLE, particularly because nephritis and infection are the leading causes of mortality in the first decade of disease. Because nephritis is asymptomatic in most lupus patients, urinalysis should be ordered in any person suspected of having SLE. The classification of lupus nephritis is primarily histologic (see "Pathology," above, and Table 356-2). Renal biopsy

TABLE 356-4 2019 EULAR/ACR Classification Criteria for Systemic Lupus Erythematosus (SLE)

	<i>Positive ANA (titer at least 1:80) is obligatory entry criterion, followed by additive weighted criteria in 7 clinical and 3 immunologic domains. Accumulating ≥10 points classifies as SLE. All manifestations must be attributable to SLE.</i>		
DOMAIN	CRITERIA	CLINICAL CRITERIA	
		% OF PATIENTS WITH FEATURE ^a	WEIGHT
Constitutional, 80%	Fever	50	2
Hematologic, 50%	Leukopenia	30	3
	Thrombocytopenia	20	4
	Autoimmune hemolytic anemia	10	4
Neuropsychiatric, 75%	Delirium	5	2
	Psychosis	7	3
	Seizure	11	5
Mucocutaneous, 80%	Nonscarring alopecia	15	2
	Oral ulcers	45	2
	Subcutaneous or discoid lupus	30	4
	Acute cutaneous lupus	70	6
Serosal, 50%	Pleural or pericardial effusion	50	5
	Acute pericarditis	35	6
Musculoskeletal, 95%	Joint involvement	90	6
Renal, 50%	Proteinuria >0.5 g/24 h	50	4
	Renal biopsy class II or V LN	25% of LN	8
	Renal biopsy class III or IV LN	60% of LN	10
IMMUNOLOGIC CRITERIA			
DOMAIN	CRITERIA	% OF PATIENTS WITH FEATURE ^a	WEIGHT
Antiphospholipids	+ Anticardiolipin, anti-β ₂ -glycoprotein, or lupus anticoagulant (LAC)	40	2
Complements	Low C3 or C4	35	3
	Low C3 and C4	30	4
SLE-specific antibodies	Anti-dsDNA or anti-Smith antibodies	40	6

^aPercentage of SLE patients exhibiting the criterion at any time during disease. Estimated from data provided in pertinent chapters in Wallace DJ, Hahn BH (eds): *Dubois' Lupus Erythematosus and Related Syndromes*, 9th ed. Philadelphia, Elsevier, 2019.

Abbreviations: ACR, American College of Rheumatology; ANA, antinuclear antibody; EULAR, European Union League Against Rheumatism; LN, lupus nephritis.

is recommended for every SLE patient with any clinical evidence of nephritis; results are used to plan current therapies and their duration. Patients with dangerous proliferative forms of glomerular damage (ISN III and IV) usually have microscopic hematuria and proteinuria (>500 mg per 24 h); approximately one-half develop nephrotic syndrome, and most develop hypertension. Overall, in the United States, ~20% of individuals with lupus diffuse proliferative glomerulonephritis (DGN) die or develop ESRD within 10 years of diagnosis. Such individuals require aggressive control of SLE and of the complications of renal disease and of therapy unless damage is irreversible (Fig. 356-2, **Table 356-6**). African Americans, Hispanics, and Asians/Pacific Islanders are more likely to develop nephritis than Caucasians. African Americans are more likely to develop ESRD than are whites, even with the most current therapies. Approximately 20% of SLE patients with proteinuria (usually nephrotic) have membranous glomerular changes without proliferative changes on renal biopsy. Their outcome is better than for those with DPGN, but patients with class V and nephrotic range proteinuria should be treated in the same way as those with classes III or IV proliferative disease. Lupus nephritis is usually an ongoing disease, with flares requiring re-treatment or increased treatment over many years. For most people with lupus nephritis, accelerated atherosclerosis becomes important after several years of disease; attention must be given to control of systemic inflammation, blood pressure, hyperlipidemia, and hyperglycemia.

NERVOUS SYSTEM MANIFESTATIONS

There are many central nervous system (CNS) and peripheral nervous system manifestations of SLE; in some patients, these are the

major cause of morbidity and mortality. It is useful to approach this diagnostically by asking first whether the symptoms result from SLE or another condition (such as infection in immunosuppressed individuals or side effects of therapies). If symptoms are related to SLE, it should be determined whether they are caused by a diffuse process (requiring immunosuppression) or vascular occlusive disease (requiring anticoagulation). The most common manifestation of diffuse CNS lupus is cognitive dysfunction, including difficulties with memory and reasoning. Headaches are also common. When excruciating, they often indicate SLE flare; when milder, they are difficult to distinguish from migraine or tension headaches. Seizures of any type may be caused by lupus; treatment often requires both antiseizure and immunosuppressive therapies. Psychosis can be the dominant manifestation of SLE; it must be distinguished from glucocorticoid-induced psychosis. The latter usually occurs in the first weeks of glucocorticoid therapy, at daily doses of ≥40 mg of prednisone or equivalent; psychosis resolves over several days after glucocorticoids are decreased or stopped. Myopathy is often disabling; rapid initiation of immunosuppressive therapy including high-dose glucocorticoids is standard of care.

VASCULAR OCCLUSIONS INCLUDING STROKE AND MYOCARDIAL INFARCTIONS

The prevalence of transient ischemic attacks, strokes, and myocardial infarctions is increased in patients with SLE. These vascular events are increased in, but not exclusive to, SLE patients with antibodies to phospholipids (antiphospholipid antibodies) (**Chap. 357**). Ischemia in the brain can be caused by focal occlusion (either noninflammatory or associated with vasculitis) or by embolization from carotid artery

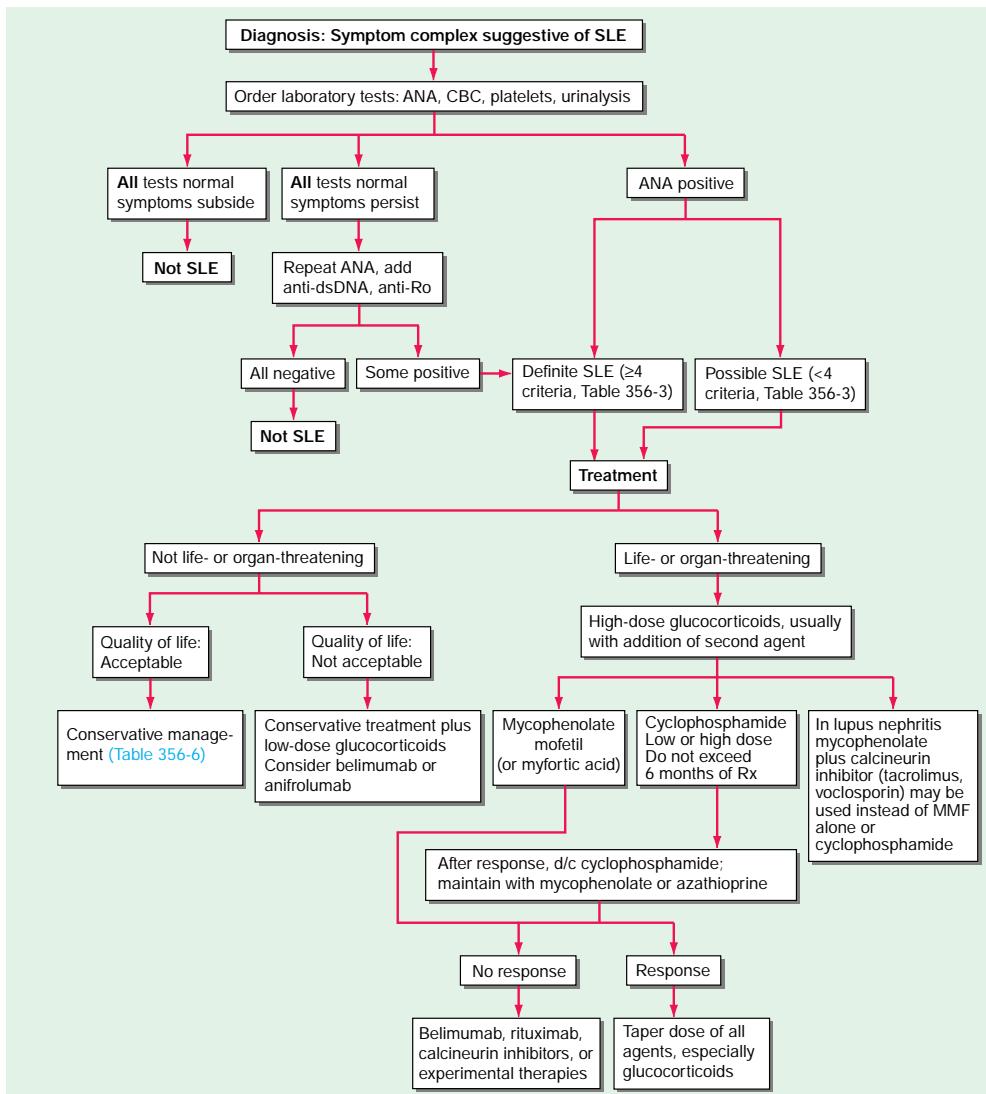


FIGURE 356-2 Algorithm for diagnosis and initial therapy of systemic lupus erythematosus (SLE). For guidelines on management of lupus and lupus nephritis, see Fanouriakis A et al: 2019 Update of the EULAR/ACR recommendations for the management of systemic lupus erythematosus. *Ann Rheum Dis* 78:736, 2019; Hahn BH et al: American College of Rheumatology guidelines for screening, treatment, and management of lupus nephritis. *Arthritis Care Res (Hoboken)* 64:797, 2012; Tunnicliffe DJ et al: Immunosuppressive treatment for proliferative lupus nephritis. *Cochrane Database Syst Rev* 29:CD002922, 2018. For belimumab, see Stohl W: Inhibition of B cell activating factor (BAFF) in the management of systemic lupus erythematosus (SLE). *Expert Rev Clin Immunol* 13:163, 2017 and Furie R et al: Two-year, randomized, controlled trial of belimumab in lupus nephritis. *New Eng J Med* 383:1117, 2020. For rituximab, and other current experimental therapies, see Davis LS, Reimold AM: Research and therapeutics—traditional and emerging therapies in systemic lupus erythematosus. *Rheumatology (Oxford)* 56(Suppl 1):1100, 2017. For tacrolimus and triple therapy, see Liu Z et al: Multitarget therapy for induction treatment of lupus nephritis: A randomized trial. *Ann Intern Med* 162:18, 2015. For voclosporin see Rovin BH et al: Efficacy and safety of voclosporin versus placebo for lupus nephritis: a double-blind, randomised, multicentre, placebo-controlled, phase 3 trial. *Lancet* published May 7, 2021. For Anifrolumab see Morand EF et al: Trial of anifrolumab in active systemic lupus erythematosus. *N Eng J Med* 382:211, 2020. ANA, antinuclear antibodies; CBC, complete blood count; MMF, mycophenolate mofetil; Rx, therapy; SLE, systemic lupus erythematosus.

plaques or from vegetations of Libman-Sacks endocarditis. Appropriate tests for antiphospholipid antibodies (see below) and for sources of emboli should be ordered in such patients to estimate the need for, intensity of, and duration of anti-inflammatory and/or anticoagulant therapies. When it is most likely that a cerebral event results from clotting, long-term anticoagulation is the therapy of choice. Two processes can occur at once—vasculitis plus bland vascular occlusions—in which case it is appropriate to treat with anticoagulation plus immunosuppression.

In SLE, myocardial infarctions are primarily manifestations of accelerated atherosclerosis. The increased risk for vascular events is three- to tenfold overall and is highest in women aged < 49 years compared to age-matched controls. Characteristics associated with increased

risk for atherosclerosis include male gender, older age, hypertension, dyslipidemia, diabetes, dysfunctional proinflammatory high-density lipoproteins, high disease activity, high glucocorticoid dose, and high serum homocysteine and leptin. Statin therapies reduce levels of low-density lipoproteins (LDL) in SLE patients; significant reduction of all-cause mortality by statins has been shown in SLE patients with renal transplants and in an epidemiologic study of a large number of patients in Taiwan.

PULMONARY MANIFESTATIONS

The most common pulmonary manifestation of SLE is pleuritis with or without pleural effusion. This manifestation, when mild, may respond to treatment with nonsteroidal anti-inflammatory drugs (NSAIDs);

TABLE 356-5 Clinical Manifestations of SLE and Prevalence over the Entire Course of Disease^a

MANIFESTATION	PREVALENCE, %
Systemic: Fatigue, malaise, fever, anorexia, weight loss	95
Musculoskeletal	
Arthralgias/myalgias	95
Polyarthritis	60
Hand deformities	10
Myopathy/myositis	25/5
Ischemic necrosis of bone	15
Cutaneous	80
Photosensitivity	70
Malar rash	50
Oral ulcers	40
Alopecia	40
Discoid rash	20
Vasculitis rash	20
Other (e.g., urticaria, subacute cutaneous lupus)	15
Hematologic	85
Anemia (chronic disease)	70
Leukopenia (<4000/ μ L)	65
Lymphopenia (<1500/ μ L)	50
Thrombocytopenia (<100,000/ μ L)	15
Lymphadenopathy	15
Splenomegaly	15
Hemolytic anemia	10
Neurologic	60
Cognitive disorder	50
Mood disorder	40
Depression	25
Headache	25
Seizures	20
Mono-, polyneuropathy	15
Stroke, TIA	10
Acute confusional state or movement disorder	2–5
Aseptic meningitis, myelopathy	<1
Cardiopulmonary	60
Pleurisy, pericarditis, effusions	30–50
Myocarditis, endocarditis	10
Lupus pneumonitis	10
Coronary artery disease	10
Interstitial fibrosis	5
Pulmonary hypertension, ARDS, hemorrhage	<5
Shrinking lung syndrome	<5
Renal	30–50
Proteinuria 500 mg/24 h, cellular casts	30–60
Nephrotic syndrome	25
End-stage renal disease	5–10
Gastrointestinal	40
Nonspecific (nausea, mild pain, diarrhea)	30
Abnormal liver enzymes	40
Vasculitis	5
Thrombosis	15
Venous	10
Arterial	5
Ocular	15
Sicca syndrome	15
Conjunctivitis, episcleritis	10
Vasculitis	5

^aNumbers indicate percentage of patients who have the manifestation at some time during the course of illness.

Abbreviations: ARDS, acute respiratory distress syndrome; SLE, systemic lupus erythematosus; TIA, transient ischemic attack.

when more severe, patients require a brief course of glucocorticoid therapy. Pulmonary infiltrates also occur as a manifestation of active SLE and are difficult to distinguish from infection on imaging studies. Life-threatening pulmonary manifestations include interstitial inflammation leading to fibrosis (histologic pattern mimics usual diffuse interstitial pneumonitis), shrinking lung syndrome, and intra-alveolar hemorrhage; all of these probably require early aggressive immunosuppressive therapy as well as supportive care. Pulmonary arterial hypertension occurs in a small proportion of SLE patients and should be treated in the same way as idiopathic pulmonary hypertension.

CARDIAC MANIFESTATIONS

Pericarditis is the most frequent cardiac manifestation; it usually responds to anti-inflammatory therapy and infrequently leads to tamponade. More serious cardiac manifestations are myocarditis and fibrinous endocarditis of Libman-Sacks. Myocardial inflammation can be associated with left ventricular dysfunction and heart failure. Overall, lupus patients have a 2.7-fold higher risk of developing heart failure compared with the general population. Arrhythmias are frequent. Endocardial involvement can lead to valvular insufficiencies, most commonly of the mitral or aortic valves, or to embolic events. It has not been proven that glucocorticoid or other immunosuppressive therapies lead to improvement of lupus myocarditis or endocarditis, but it is usual practice to administer trial of high-dose steroids along with appropriate supportive therapy for heart failure, arrhythmia, or embolic events. As discussed above, patients with SLE are at increased risk for myocardial infarction, usually due to accelerated atherosclerosis, which probably results from immune attack, chronic inflammation, and/or chronic oxidative damage to arteries.

HEMATOLOGIC MANIFESTATIONS

The most frequent hematologic manifestation of SLE is anemia, usually normochromic normocytic, reflecting chronic illness and consequent impaired utilization of iron. Hemolysis can be rapid in onset and severe, requiring high-dose glucocorticoid therapy. Leukopenia is also common and almost always consists of lymphopenia, not granulocytopenia; lymphopenia rarely predisposes to infections and by itself usually does not require therapy. Thrombocytopenia may be a recurring problem. If platelet counts are >40,000/ μ L and abnormal bleeding is absent, therapy may not be required. High-dose glucocorticoid therapy (e.g., 1 mg/kg per day of prednisone or equivalent) is usually effective for the first few episodes of severe thrombocytopenia. Recurring or prolonged hemolytic anemia or thrombocytopenia, or disease requiring an unacceptably high dose of daily glucocorticoids, should be treated with additional strategies such as rituximab, platelet growth factors, and/or splenectomy (see “Management of Systemic Lupus Erythematosus” below).

GASTROINTESTINAL MANIFESTATIONS

Nausea, sometimes with vomiting, and diarrhea can be manifestations of an SLE flare. Diffuse abdominal pain can be caused by autoimmune peritonitis and/or intestinal vasculitis. Increases in serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are common when SLE is active. These manifestations usually improve promptly during systemic glucocorticoid therapy. Vasculitis involving the intestine can be life-threatening; perforations, ischemia, bleeding, and sepsis are frequent complications. Aggressive immunosuppressive therapy with high-dose glucocorticoids is recommended for short-term control; evidence of recurrence is an indication for additional immunosuppression.

OCULAR MANIFESTATIONS

Sicca syndrome (Sjögren's syndrome; **Chap. 361**) and nonspecific conjunctivitis are common in SLE and rarely threaten vision. In contrast, retinal vasculitis and optic neuritis are serious manifestations: blindness can develop over days to weeks. Aggressive immunosuppression is recommended, although there are no controlled trials to prove effectiveness. Complications of systemic and intraorbital glucocorticoid therapy include cataracts (common) and glaucoma.

TABLE 356-6 Medications for the Management of SLE

MEDICATION	DOSE RANGE	DRUG INTERACTIONS	SERIOUS OR COMMON ADVERSE EFFECTS
NSAIDs, salicylates (Ecotrin ^a and St. Joseph's aspirin ^a approved by FDA for use in SLE)	Doses toward upper limit of recommended range usually required	A2R/ACE inhibitors, glucocorticoids, fluconazole, methotrexate, thiazides	NSAIDs: Higher incidence of aseptic meningitis, elevated liver enzymes, decreased renal function, vasculitis of skin; entire class, especially COX-2-specific inhibitors, may increase risk for myocardial infarction Salicylates: ototoxicity, tinnitus Both: GI events and symptoms, allergic reactions, dermatitis, dizziness, acute renal failure, edema, hypertension
Topical glucocorticoids	Mid potency for face; mid to high potency for other areas	None known	Atrophy of skin, contact dermatitis, folliculitis, hypopigmentation, infection
Topical sunscreens	SPF 15 at least; 30+ preferred	None known	Contact dermatitis
Hydroxychloroquine ^a (quinacrine can be added or substituted)	200–400 mg qd (100 mg qd); do not exceed 5.0 mg/kg actual weight	Contraindicated use with QT-prolonging agents (e.g., donepezil, amiodarone) and with aurothioglucose. Caution with cyclosporine, cimetidine, digoxin, ampicillin, lanthanum, antacids, kaolin.	Retinal damage, agranulocytosis, aplastic anemia, ataxia, cardiomyopathy, dizziness, myopathy, ototoxicity, peripheral neuropathy, pigmentation of skin, seizures, thrombocytopenia; quinacrine usually causes diffuse yellow skin coloration
DHEA (dehydroepiandrosterone)	200 mg qd	Unclear	Acne, menstrual irregularities, high serum levels of testosterone
Methotrexate (for dermatitis, arthritis)	10–25 mg once a week, PO or SC, with folic acid; decrease dose if CrCl <60 mL/min	Acitretin, leflunomide, NSAIDs and salicylates, penicillins, probenecid, sulfonamides, trimethoprim. Caution with interventions that can suppress bone marrow or cause liver toxicity.	Anemia, bone marrow suppression, leukopenia, thrombocytopenia, hepatotoxicity, nephrotoxicity, infections, neurotoxicity, pulmonary fibrosis, pneumonitis, severe dermatitis, seizures, pseudolymphoma
Glucocorticoids, oral ^a (several specific brands are approved by FDA for use in SLE)	Prednisone, prednisolone: 0.5–1 mg/kg per day for severe SLE 0.07–0.3 mg/kg per day or qod for milder disease. Taper to 7.5 mg daily or less if possible.	A2R/ACE antagonists, antiarrhythmics class III, cyclosporine, NSAIDs and salicylates, phenothiazines, phenytoins, quinolones, rifampin, risperidone, thiazides, sulfonylureas, warfarin	Infection, VZV infection, hypertension, hyperglycemia, hypokalemia, acne, allergic reactions, anxiety, aseptic necrosis of bone, cushingoid changes, CHF, fragile skin, insomnia, menstrual irregularities, mood swings, osteoporosis, psychosis
Methylprednisolone sodium succinate, IV ^a (FDA approved for lupus nephritis)	For severe disease, 0.5–1 g IV qd × 3 days	As for oral glucocorticoids	As for oral glucocorticoids (if used repeatedly); anaphylaxis
Cyclophosphamide ^b IV	Low dose (for whites of northern European backgrounds): 500 mg every 2 weeks for 6 doses, then begin maintenance with MMF or AZA. High dose: 7–25 mg/kg every month × 6; consider mesna administration with dose	Allopurinol, bone marrow suppressants, colony-stimulating factors, doxorubicin, rituximab, succinylcholine, zidovudine	Infection, VZV infection, bone marrow suppression, leukopenia, anemia, thrombocytopenia, hemorrhagic cystitis (less with IV), carcinoma of the bladder, alopecia, nausea, diarrhea, malaise, malignancy, ovarian and testicular failure. Ovarian failure is probably not a problem with low dose.
Oral cyclophosphamide	1.5–3 mg/kg per day; decrease dose for CrCl <25 mL/min		
Mycophenolate mofetil (MMF) ^a or mycophenolic acid (MPA)	MMF: 2–3 g/d PO total given bid for induction therapy, 1–2 g/d total given bid for maintenance therapy; max 1 g bid if CrCl <25 mL/min. Begin with low dose and increase every 1–2 weeks to minimize GI side effects. Start treatment at 0.5 g bid. If used with calcineurin inhibitor, target dose of mycophenolate is 1 g bid. MPA: 360–1080 mg bid; caution if CrCl <25 mL/min	Acyclovir, antacids, azathioprine, bile acid-binding resins, ganciclovir, iron, salts, probenecid, oral contraceptives	Infection, leukopenia, anemia, thrombocytopenia, lymphoma, lymphoproliferative disorders, malignancy, alopecia, cough, diarrhea, fever, GI symptoms, headache, hypertension, hypercholesterolemia, hypokalemia, insomnia, peripheral edema, elevated liver enzymes, tremor, rash. Limited data suggest Asians should begin treatment with doses not exceeding 2 g daily to reduce adverse events.
Azathioprine (AZA) ^b	2–3 mg/kg per day PO for induction; 1–2 mg/kg per day for maintenance; decrease frequency of dose if CrCl <50 mL/min	ACE inhibitors, allopurinol, bone marrow suppressants, interferons, mycophenolate mofetil, rituximab, warfarin, zidovudine	Infection, VZV infection, bone marrow suppression, leukopenia, anemia, thrombocytopenia, pancreatitis, hepatotoxicity, malignancy, alopecia, fever, flulike illness, GI symptoms
Belimumab	10 mg/kg IV weeks 0, 2, and 4, then monthly or subcutaneous 200 mg each week	IVIg, live vaccines (contraindicated), tofacitinib	Infusion reactions, allergy, infections, headache and diffuse body aching
Rituximab (for patients resistant to above therapies)	375 mg/m ² every week × 4 or 1 g every 2 weeks × 2	IVIg, live vaccines (contraindicated), infliximab, cisplatin (renal failure), tofacitinib	Infection (including PML), infusion reactions, headache, arrhythmias, allergic responses

(Continued)

TABLE 356-6 Medications for the Management of SLE (Continued)

MEDICATION	DOSE RANGE	DRUG INTERACTIONS	SERIOUS OR COMMON ADVERSE EFFECTS
Tacrolimus	Trough blood level should not exceed 5.5 ng/mL to minimize toxicity. Begin dose at 1 mg bid	Increases risk for QT interval prolongation (e.g., hydroxychloroquine); interferes with drugs using CYP3A pathway; caution with fluconazole, ritonavir, voriconazole, clotrimazole, metronidazole, omeprazole, fentanyl, ketoconazole, caspofungin, amiodarone. Do not ingest grapefruit or pomegranate juice while taking tacrolimus.	Infection, nephrotoxicity, neural toxicity
Voclosporin with MMF	Three 7.9 mg capsules bid, do not use if GFR <45 mL/min	Do not use with strong CYP3A4 inhibitors/inducers Do not use with cyclosporine	Infection, hypertension, hyperkalemia, decrease GFR, tremor May cause fetal harm.
Anifrolumab	300 mg i.v. every 4 weeks	Do not use with other biologics Reduce dose if eGFR is less than 60 mL/min/1.73 m ² BSA	Infection, herpes zoster, bronchitis, infusion reactions, anaphylaxis

^aIndicates medication is approved for use in SLE by the U.S. Food and Drug Administration. ^bIndicates the medication has been used with glucocorticoids in the trials showing efficacy.

Abbreviations: A2R, angiotensin II receptor; ACE, angiotensin-converting enzyme; CHF, congestive heart failure; CrCl, creatinine clearance; FDA, U.S. Food and Drug Administration; GI, gastrointestinal; IVIg, intravenous immunoglobulin; NSAIDs, nonsteroidal anti-inflammatory drugs; PML, progressive multifocal leukoencephalopathy; SLE, systemic lupus erythematosus; SPF, sun protection factor; VZV, varicella-zoster virus.

LABORATORY TESTS

Laboratory tests serve (1) to establish or rule out the diagnosis; (2) to follow the course of disease and, in particular, to suggest that a flare is occurring or organ damage is developing; and (3) to identify adverse effects of therapies.

TESTS FOR AUTOANTIBODIES (TABLES 356-1 AND 356-3)

Diagnostically, the most important autoantibodies are ANA because the test is positive in >95% of patients, usually at the onset of symptoms. A few patients develop ANA within 1 year of symptom onset; repeated testing may thus be useful. ANA tests using immunofluorescent methods are more reliable than enzyme-linked immunosorbent assays (ELISAs) and/or bead assays, which have less specificity. ANA-negative lupus exists but is rare in adults and is usually associated with other autoantibodies (anti-Ro or anti-DNA). High-titer IgG antibodies to double-stranded DNA (dsDNA) (but not to single-stranded DNA) are specific for SLE. ELISA and immunofluorescent reactions of sera with the dsDNA in the flagellate *Critchidia luciliiae* have ~60% sensitivity for SLE. Titers of anti-dsDNA vary over time. In some patients, increases in quantities of anti-dsDNA herald a flare, particularly of nephritis or vasculitis, and especially when associated with declining levels of C3 or C4 complement. Antibodies to Sm are also specific for SLE and assist in diagnosis; anti-Sm antibodies do not usually correlate with disease activity or clinical manifestations. Antiphospholipid antibodies are not specific for SLE, but their presence fulfills one classification criterion, and they identify patients at increased risk for venous or arterial clotting, thrombocytopenia, and fetal loss. There are three widely accepted tests that measure different antibodies (anticardiolipin, anti-β₂-glycoprotein, and the lupus anticoagulant). ELISA is used for anticardiolipin and anti-β₂-glycoprotein (both internationally standardized with good reproducibility); a sensitive phospholipid-based activated prothrombin time such as the dilute Russell venom viper test is used to identify the lupus anticoagulant. The higher the titers of IgG anticardiolipin (>40 IU is considered high), and the greater the number of different antiphospholipid antibodies that are detected, the greater is the risk for a clinical episode of clotting. Quantities of antiphospholipid antibodies may vary markedly over time; repeated testing is justified if clinical manifestations of the antiphospholipid syndrome (APS) appear ([Chap. 357](#)). To classify a patient as having APS, with or without SLE, by international criteria requires the presence of one or more clotting episodes and/or repeated fetal losses plus at least two positive tests for antiphospholipid antibodies, at least 12 weeks apart; however, many patients with APS do not meet these stringent criteria, which are intended for inclusion of patients into studies.

An additional autoantibody test with predictive value (not used for diagnosis) detects anti-Ro/SS-A, which indicates increased risk for neonatal lupus, sicca syndrome, and SCLE. Women with child-bearing

potential and SLE should be screened for antiphospholipid antibodies and anti-Ro, because both antibodies have the potential to cause fetal harm.

Antibodies to C1q are not specific or sensitive for SLE; however, they are highly associated with active lupus nephritis and may fluctuate as the activity of nephritis changes.

STANDARD TESTS FOR DIAGNOSIS

Screening tests for complete blood count, platelet count, and urinalysis may detect abnormalities that contribute to the diagnosis and influence management decisions.

TESTS FOR FOLLOWING DISEASE COURSE

It is useful to follow tests that indicate the status of organ involvement known to be present during SLE flares. These might include urinalysis for hematuria and proteinuria, hemoglobin levels, platelet counts, and serum levels of creatinine or albumin. There is great interest in identification of additional markers of disease activity. Candidates include levels of anti-DNA and anti-C1q antibodies, several components of complement (C3 is most widely available), activated complement products (an assay is commercially available that measures binding to the C4d receptor on erythrocytes and B cells), IFN-inducible gene expression in peripheral blood cells, serum levels of BLyS (B lymphocyte stimulator, also called BAFF), and urinary levels of TNF-like weak inducer of apoptosis (TWEAK), neutrophil gelatinase-associated lipocalin (NGAL), or monocyte chemoattractant protein 1 (MCP-1). None is uniformly agreed upon as a reliable indicator of flare or of response to therapeutic interventions. It is likely that a panel of multiple proteins and nuclear products (and possibly levels of selected miRNAs and methylation profiles of DNA) will be developed to predict both impending flare and response to recently instituted therapies. Increased quantities of plasma cells, and increased expression of their gene signatures in whole blood, are associated with active disease and flares, but measurements are not commercially available. For now, the physician should determine for each patient whether certain available laboratory test changes predict flare (falling complement, rising anti-DNA, increased proteinuria, worsening anemia, etc.). If so, altering therapy in response to these changes may be advisable (30 mg of prednisone daily for 2 weeks has been shown to prevent flares in patients with rising anti-DNA plus falling complement). In addition, given the increased prevalence of atherosclerosis in SLE, it is advisable to follow the recommendations of the National Cholesterol Education Program for testing and treatment, including scoring of SLE as an independent risk factor, similar to diabetes mellitus.

MANAGEMENT OF SYSTEMIC LUPUS ERYTHEMATOSUS

There is no cure for SLE, and complete sustained remissions are rare. There is an international effort to encourage practitioners and patients to aim for low-level disease activity (LLDAS), meaning mild symptoms

on the lowest possible doses of medications. LLDAS scoring uses Systemic Lupus Erythematosus Disease Activity Score-2K (SLEDAI-2K; Touma Z et al, *Lupus* 19:49, 2010). SLEDAI-2K is a widely used measure of SLE disease activity; scores >3 reflect clinically active disease. For example, active arthritis scores 4 points, rash 2 points, pleurisy 2 points, proteinuria 4 points, vasculitis 8 points, low complement 2 points, and leukopenia 1 point. LLDAS is defined currently as (1) a SLEDAI-2K score ≤4; (2) no new lupus disease activity compared with the previous visit; (3) physician's global assessment ≤1 (scale 0–3); (4) current prednisone dose ≤7.5 mg daily; and (5) well-tolerated stable doses of antimalarials and/or immunosuppressives. LLDAS can be achieved in 50–80% of patients and, if sustained for 2 or more years (possible in ~30%), associates with significantly less accrual of damage and better quality of life. Therefore, the physician should plan to induce improvement of acute flares and then maintain improvements with strategies that suppress symptoms to an acceptable level and prevent organ damage. Chronic prednisone doses should be tapered to the lowest doses possible (ideally ≤7.5 mg). Therapeutic choices depend on (1) whether disease manifestations are life-threatening or likely to cause organ damage, justifying aggressive therapies; (2) whether manifestations are potentially reversible; and (3) the best approaches to preventing complications of disease and its treatments. Therapies, doses, and adverse effects are listed in Table 356-6.

CONSERVATIVE THERAPIES FOR MANAGEMENT OF NON-LIFE-THREATENING DISEASE

Among patients with fatigue, pain, and autoantibodies indicative of SLE but without major organ involvement, management can be directed to suppression of symptoms. Analgesics and antimalarials are mainstays. NSAIDs are useful analgesics/anti-inflammatories, particularly for arthritis/arthralgias. However, two major issues indicate caution in using NSAIDs. First, SLE patients compared with the general population are at increased risk for NSAID-induced aseptic meningitis, elevated serum transaminases, hypertension, and renal dysfunction. Second, all NSAIDs, particularly those that inhibit cyclooxygenase-2 specifically, may increase risk for myocardial infarction. Acetaminophen to control pain may be a good strategy, but NSAIDs are more effective in some patients. The relative hazards of NSAIDs compared with low-dose glucocorticoid therapy have not been established. Antimalarials (hydroxychloroquine, chloroquine, and quinacrine) often reduce disease symptoms. Withdrawal of hydroxychloroquine results in increased numbers of disease flares. Hydroxychloroquine prolongs survival and reduces accrual of tissue damage, including renal damage. Some experts recommend a hydroxychloroquine blood level of ≥750 ng/mL to optimize responses in active SLE; after achieving response, doses should be reduced. Because of potential retinal toxicity (occurring in 6% of patients after cumulative doses of 1000 g, ~5 years of continuing therapy), patients receiving antimalarials should undergo ophthalmologic examinations annually. One clinical trial showed that administration of dehydroepiandrosterone reduced activity of mild disease. If quality of life is inadequate despite these conservative measures, treatment with low doses of systemic glucocorticoids may be necessary. Belimumab (anti-Baff) and anifrolumab (anti-IFN type 1 receptor) are biologics that are each effective for patients with persistent disease activity and fatigue despite standard therapies; SLE patients most likely to respond to belimumab have robust clinical activity (SLEDAI-2K score of ≥10), positive anti-DNA, and low serum complement. See above under "Management of Systemic Lupus Erythematosus" for more details regarding SLEDAI-2K. Lupus dermatitis should be managed with topical sunscreens, anti-malarials, topical glucocorticoids, and/or tacrolimus and, if severe or unresponsive, systemic glucocorticoids with or without mycophenolate mofetil, azathioprine, methotrexate, or belimumab. Anifrolumab has been highly effective in patients with lupus dermatitis.

LIFE-THREATENING SLE: PROLIFERATIVE FORMS OF LUPUS NEPHRITIS

Guidelines for management of lupus nephritis have been published: see Tables 356-3 and 356-6 and Figure 356-2. The mainstay of treatment

for any inflammatory life-threatening or organ-threatening manifestations of SLE is systemic glucocorticoids (0.5–1 mg/kg per day PO or 500–1000 mg of methylprednisolone sodium succinate IV daily for 3 days followed by 0.5–1 mg/kg of daily prednisone or equivalent). Evidence that glucocorticoid therapy is life-saving comes from retrospective studies from the predialysis era; survival was significantly better in people with DPGN treated with high-dose daily glucocorticoids (40–60 mg of prednisone daily for 4–6 months) versus lower doses. Currently, high doses are recommended for much shorter periods; recent trials of interventions for severe SLE use 4–6 weeks of 0.5–1 mg/kg per day of prednisone or equivalent. Thereafter, doses are tapered as rapidly as the clinical situation permits, usually to a maintenance dose ≤7.5 mg of prednisone or equivalent per day. Many patients with an episode of severe SLE require many years of maintenance therapy with low-dose glucocorticoids. Frequent attempts to gradually reduce the glucocorticoid requirement are recommended because virtually everyone develops important adverse effects (Table 356-6). High-quality clinical studies regarding initiating therapy for severe, active SLE with IV pulses of high-dose glucocorticoids are not available. The use of IV pulses of glucocorticoids must be tempered by safety considerations, such as the presence of conditions adversely affected by glucocorticoids (e.g., infection, hyperglycemia, hypertension, osteoporosis). One open trial showed high response rates in patients with lupus nephritis treated with mycophenolate mofetil plus rituximab, without maintenance daily glucocorticoids; how widely this can be used is unclear.

Cytotoxic/immunosuppressive agents added to glucocorticoids are recommended to treat serious SLE. Almost all prospective controlled trials in SLE involving such agents have been conducted in combination with glucocorticoids in patients with lupus nephritis. Therefore, the following recommendations apply to treatment of nephritis. Either cyclophosphamide (an alkylating agent) or mycophenolate mofetil (a relatively lymphocyte-specific inhibitor of inosine monophosphatase and therefore of purine synthesis) is an acceptable choice for induction of improvement in severely ill patients; azathioprine (a purine analogue and cycle-specific antimetabolite) may be effective but is associated with more flares. In patients whose renal biopsies show ISN grade III or IV disease, early treatment with combinations of glucocorticoids and cyclophosphamide reduces progression to ESRD and death. Short-term studies with glucocorticoids plus mycophenolate mofetil (prospective randomized trials of 6 months, follow-up studies of 5 years) show that this regimen is similar to cyclophosphamide in achieving improvement. Comparisons are complicated by effects of race, since higher proportions of African Americans and Latin Americans respond to mycophenolate than to cyclophosphamide, whereas similar proportions of whites and Asians respond to each drug. Regarding toxicity, diarrhea is more common with mycophenolate mofetil; amenorrhea, leukopenia, and nausea are more common with high-dose cyclophosphamide. Importantly, rates of severe infections and death are similar in meta-analyses. Two different regimens of IV cyclophosphamide are available for induction therapy. For white patients with northern European backgrounds, low doses of cyclophosphamide (500 mg every 2 weeks for six total doses, followed by daily azathioprine or mycophenolate maintenance) are as effective as standard high doses, with less toxicity. Ten-year follow-up has shown no differences between the high-dose and low-dose groups (death or ESRD in 9–20% of patients in each group). It is not clear whether the data apply to U.S. populations, especially African Americans and Latinas. In general, it may be better to induce improvement in African-American or Hispanic patients with proliferative glomerulonephritis with mycophenolate mofetil (2–3 g daily) rather than cyclophosphamide, with the option to switch if no evidence of response is detectable after 2–6 months of treatment. For whites and Asians, induction with either mycophenolate mofetil or cyclophosphamide is acceptable. The presence of cellular or fibrotic crescents in glomeruli with proliferative glomerulonephritis, or rapidly progressive glomerulonephritis, indicates more severe disease and a worse prognosis. High-dose cyclophosphamide (500–1000 mg/m² body surface area given monthly IV for 6 months, followed by azathioprine or mycophenolate maintenance) is an acceptable approach for patients with severe nephritis. Cyclophosphamide and mycophenolate

responses begin 3–16 weeks after treatment is initiated, whereas glucocorticoid responses may begin within 24 h. The incidence of ovarian failure, a common effect of high-dose cyclophosphamide therapy (but probably not of low-dose therapy), can be reduced by treatment with a gonadotropin-releasing hormone agonist (e.g., leuprolide 3.75 mg intramuscularly) prior to each monthly cyclophosphamide dose. Recent studies have shown improved short-term responses with a combination of calcineurin inhibitors (tacrolimus, voclosporin) plus mycophenolate (MMF) plus glucocorticoids (GC) compared with MMF or cyclophosphamide with GC. Complete renal responses occurred in 41% on triple therapy at 52 weeks compared with 21% on double therapy. Including partial with complete renal responses, 70% on triple vs 50% on double therapy improved by 24 weeks. Calcineurin inhibitors are nephrotoxic; they should probably be discontinued after 6 months if no signs of improvement occur and used for no more than 12 months in most patients.

For maintenance therapy, mycophenolate and azathioprine probably are similar in efficacy and toxicity; both are safer than cyclophosphamide. In a multicenter international study, mycophenolate was superior to azathioprine in maintaining renal function and survival in patients who responded to induction therapy with either cyclophosphamide or mycophenolate. Patients with high serum creatinine levels (e.g., $\geq 265 \mu\text{mol/L}$ [$\geq 3.0 \text{ mg/dL}$]) many months in duration and high chronicity scores on renal biopsy are not likely to respond to any of these therapies. The number of SLE flares is reduced by maintenance therapy with mycophenolate mofetil (1.5–2 g daily) or azathioprine (1–2.5 mg/kg per day). Mycophenolate, cyclophosphamide, methotrexate, and calcineurin inhibitors can cause fetal harm; patients should be off any of these for at least 3 months before attempting to conceive. Azathioprine can be used if necessary to control active SLE in patients who are pregnant. Patients treated with azathioprine may be prescreened for homozygous deficiency of the TMPT enzyme (which is required to metabolize the 6-mercaptopurine product of azathioprine) because they are at higher risk for bone marrow suppression.

Most SLE patients with membranous (INS class V) nephritis also have proliferative changes and should be treated for proliferative disease. However, some have pure membranous changes. Treatment for this group is less well defined. Some authorities do not recommend immunosuppression unless proteinuria is in the nephrotic range (although treatment with angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers is recommended). Prospective controlled trials suggest that alternate-day glucocorticoids plus cyclophosphamide or mycophenolate mofetil or cyclosporine or tacrolimus are all effective in the majority of patients in reducing proteinuria. It is more controversial whether any of these treatments preserve renal function over the long term.

Good improvement occurs in approximately 60% of lupus nephritis patients receiving either cyclophosphamide or mycophenolate at 1–2 years of follow-up. Addition of a calcineurin inhibitor improves response rates (70–80% in triple therapy vs 40–60% in double therapy) and increases time to flare. However, at least 50% of these individuals have flares of nephritis over the next 5 years, and re-treatment is required; such individuals are more likely to progress to ESRD. Long-term outcome of lupus nephritis to most interventions is better in whites than in African Americans. Small controlled trials (in Asia) of leflunomide, a relatively lymphocyte-specific pyrimidine antagonist licensed for use in rheumatoid arthritis, have suggested it can suppress disease activity in some SLE patients. Methotrexate (a folic acid antagonist) may have a role in the treatment of arthritis and dermatitis but probably not in nephritis or other life-threatening disease. Most patients with SLE of any type should be treated with hydroxychloroquine since it prolongs survival and reduces overall damage. Patients with proteinuria $> 500 \text{ mg daily}$ should receive angiotensin-converting enzyme inhibitors or angiotensin receptor blockers as they reduce the chance for ESRD.

Use of biologics directed against B cells for active SLE is under intense study. Anti-CD20 (rituximab), particularly in patients with SLE who are resistant to the more standard combination therapies discussed above, is widely used. Several open trials have shown efficacy

in a majority of such patients, both for nephritis and for extrarenal lupus. However, prospective placebo-controlled randomized trials, one in renal and one in nonrenal SLE, did not show a difference between anti-CD20 and placebo when added to standard combination therapies. A monoclonal antibody anti-CD20 that depletes tissue B cells better than rituximab (obinutuzumab) has received fast track approval by the U.S. Food and Drug Administration (FDA) for potential approval in SLE, but data from phase 3 clinical trials have not yet been published. Belimumab was recently approved for treatment of lupus nephritis in the USA: when given along with mycophenolate plus glucocorticoids for two years it reduces renal damage significantly. Rituximab in combination with or followed by belimumab is also being studied in lupus nephritis. A fusion protein (telitacicept) that inactivates both BAFF and APRIL growth factors for B cells has been approved for fast-track review by the FDA; phase 3 clinical trials in SLE have not yet been reported.

SPECIAL CONDITIONS IN SLE THAT MAY REQUIRE ADDITIONAL OR DIFFERENT THERAPIES

Pregnancy and Lupus Fertility rates for men and women with SLE are probably normal. However, rate of fetal loss is increased (approximately two- to threefold) in women with SLE. Fetal demise is higher in mothers with high disease activity, antiphospholipid antibodies (especially the lupus anticoagulant), hypertension, and/or active nephritis. Suppression of disease activity can be achieved by administration of systemic glucocorticoids. A placental enzyme, 11- β -dehydrogenase 2, deactivates glucocorticoids; it is more effective in deactivating prednisone and prednisolone than the fluorinated glucocorticoids dexamethasone and betamethasone (fluorinated steroids should be avoided in pregnant patients). Adverse effects of prenatal glucocorticoid exposure (primarily the fluorinated steroid betamethasone) on offspring may include low birth weight, developmental abnormalities in the CNS, and predilection toward adult metabolic syndrome. Glucocorticoids are listed by the FDA as “fetal risk cannot be ruled out.” Also in that category are hydroxychloroquine, belimumab, cyclosporine, in the “may cause fetal harm” category are rituximab, azathioprine, cyclophosphamide, tacrolimus, and voclosporin. In the “fetal risk has been demonstrated” or “avoid in pregnancy” are methotrexate and mycophenolate. Therefore, active SLE in pregnant women should be controlled with hydroxychloroquine and, if necessary, prednisone/prednisolone at the lowest effective doses for the shortest time required. Azathioprine may be added if these treatments do not suppress disease activity. It is likely that each of these glucocorticoids and immunosuppressive medications gets into breast milk, at least in low levels; patients should consider not breastfeeding if they need therapy for SLE. In SLE patients with antiphospholipid antibodies and prior fetal losses, treatment with heparin (usually low-molecular-weight) plus low-dose aspirin has been shown in prospective controlled trials to increase significantly the proportion of live births. Aspirin alone may be used, although most consider it less effective than heparin-plus-aspirin. Warfarin is teratogenic. Direct oral anticoagulants are usually avoided in pregnancy because safety and efficacy have not been established in pregnancy or APS. An additional potential problem for the fetus is the presence of antibodies to Ro, sometimes associated with neonatal lupus consisting of rash and/or congenital heart block with or without cardiomyopathy. The cardiac manifestations can be life-threatening; therefore, the presence of anti-Ro requires vigilant monitoring of fetal heart rates with prompt intervention (delivery if possible) if distress occurs. Hydroxychloroquine treatment of an anti-Ro-positive mother whose prior infant developed congenital heart block significantly reduces the chance that subsequent fetuses will develop heart block. Dexamethasone treatment of a mother in whom fetal first- or second-degree heart block is detected in utero sometimes prevents progression of heart block. Women with SLE usually tolerate pregnancy without disease flares. However, a small proportion develops severe flares requiring aggressive glucocorticoid therapy or early delivery.

Lupus and Antiphospholipid Syndrome Patients with SLE who have venous or arterial clotting and/or repeated fetal losses and at

least two positive tests for antiphospholipid antibodies have APS and should be managed with long-term anticoagulation (**Chap. 357**). With warfarin, a target international normalized ratio (INR) of 2.0–2.5 is recommended for patients with one episode of venous clotting; an INR of 3.0–3.5 is recommended for patients with recurring clots or arterial clotting, particularly in the CNS. Recommendations are based on both retrospective and prospective studies of posttreatment clotting events and adverse effects from anticoagulation. Direct oral anticoagulants are not effective and not recommended in APS.

Microvascular Thrombotic Crisis (Thrombotic Thrombocytopenic Purpura, Hemolytic-Uremic Syndrome) This syndrome of hemolysis, thrombocytopenia, and microvascular thrombosis in kidneys, brain, and other tissues carries a high mortality rate and occurs most commonly in young individuals with lupus nephritis. The most useful laboratory tests are identification of schistocytes on peripheral blood smears, elevated serum levels of lactate dehydrogenase, and low levels of ADAMTS13 activity⁷. Plasma exchange or extensive plasmapheresis is usually life-saving; most authorities recommend concomitant glucocorticoid therapy; there is no evidence that cytotoxic drugs are effective. Rituximab and eculizumab (an inhibitor of C5) have been used in refractory cases.

Lupus Dermatitis Patients with any form of lupus dermatitis should minimize exposure to ultraviolet light, using appropriate clothing and sunscreens with a sun protection factor of at least 30. Topical glucocorticoids and antimalarials (such as hydroxychloroquine) are effective in reducing lesion severity in most patients and are relatively safe. Methotrexate, azathioprine, mycophenolate, belimumab and anifrolumab each may be effective in some patients who need additional treatment. Systemic treatment with retinoic acid is a useful strategy in patients with inadequate improvement after these interventions on adverse effects are potentially severe (particularly fetal abnormalities), and there are stringent reporting requirements for its use in the United States. Extensive, pruritic, bullous, or ulcerating dermatitides usually improve promptly after institution of systemic glucocorticoids; tapering may be accompanied by flare of lesions, thus necessitating use of a second medication such as hydroxychloroquine, retinoids, or belimumab. Cytotoxic medications such as methotrexate, azathioprine, or mycophenolate mofetil may also be effective. In therapy-resistant lupus dermatitis there are reports of success with topical tacrolimus (caution must be exerted because of the possible increased risk for malignancies) or with systemic dapsone or thalidomide or the related lenalidomide (the extreme danger of fetal deformities from thalidomide requires permission from and supervision by the supplier; peripheral neuropathy is also common).

PREVENTIVE THERAPIES

Prevention of complications of SLE and its therapy include providing appropriate vaccinations (the administration of influenza and pneumococcal vaccines has been studied in patients with SLE; flare rates are similar to those receiving placebo) and suppressing recurrent urinary tract infections. In patients receiving glucocorticoids, the higher the daily dose, the lower is the immune response to vaccination; however, the great majority of patients achieve protective levels. Vaccination with attenuated live viruses is generally discouraged in patients who are immunosuppressed; however, a recent study of vaccination of a small number of SLE patient with Zostavax showed safety and efficacy. The availability of Shingrix (which does not contain live virus) should replace Zostavax. Patients receiving ≥20 mg of prednisone daily may be protected from pneumocystis infections with trimethoprim-sulfamethoxazole (Bactrim) or atovaquone (we prefer the latter because SLE patients are predisposed to allergic reactions to sulfa-containing medications) and from recurrent herpes simplex infections with acyclovir, with preventives withdrawn when the prednisone dose is decreased. Strategies to prevent osteoporosis should be initiated in most patients likely to require long-term glucocorticoid therapy and/or with other predisposing factors. Postmenopausal women can be partially protected from steroid-induced osteoporosis with calcium supplementation, vitamin D, and either bisphosphonates or denosumab. Safety of

long-term use of these strategies in premenopausal women is not well established. Control of hypertension and appropriate prevention strategies for atherosclerosis, including monitoring and treatment of dyslipidemias, management of hyperglycemia, and management of obesity, are recommended. Statin therapies reduce all-cause deaths in SLE patients and should be considered in patients with elevated LDL or total cholesterol levels. Finally, the physician must keep in mind that some cancers are increased in SLE patients including non-Hodgkin lymphomas and cancers of thyroid, lung, liver, and vulvar/vaginal tissues.

EXPERIMENTAL THERAPIES

Studies of highly targeted experimental therapies for SLE are in progress. They include (1) depletion of B cells with obinutuzumab; (2) inhibition of B cells by blocking more than one receptor for BAFF (telacicept); (3) elimination of plasma cells; (4) B-cell inhibition through inhibition of BTK, anti-CD20 therapies more depleting than rituximab, or a fusion protein that inhibits both BAFF and APRIL B-cell growth factors; (5) inhibition of B/T-cell second signal coactivation with CTLA-Ig or anti-CD40L; (6) inhibition of innate immune activation via TLR7 or TLR7 and TLR9; (7) induction of regulatory T cells with peptides from immunoglobulins or autoantigens or with low doses of IL-2; (8) inhibition of T effector cells through CD6; (9) targeting lymphocyte migration by modulation of the SIP1 receptor; and (10) inhibition of lymphocyte activation by blockade of Jak/Stat.

A few studies have used vigorous untargeted immunosuppression with high-dose cyclophosphamide plus anti-T-cell strategies, with rescue by transplantation of autologous hematopoietic stem cells for the treatment of severe and refractory SLE. One U.S. report showed an estimated mortality rate over 5 years of 15% and sustained remission in 50%. Mesenchymal stem cell transplant studies are also underway in lupus. It is hoped that in the next edition of this text, we will be able to recommend more effective and less toxic approaches to treatment of SLE based on some of these strategies.

PATIENT OUTCOMES, PROGNOSIS, AND SURVIVAL

Survival in patients with SLE in the United States, Canada, Europe, and China is ~95% at 5 years, 90% at 10 years, and 78% at 20 years. In the United States, African Americans and Hispanic Americans with a mestizo heritage have a worse prognosis than whites, whereas Africans in Africa and Hispanic Americans with a Puerto Rican origin do not. The relative importance of gene mixtures and environmental differences accounting for ethnic differences is not known. Poor prognosis (~50% mortality in 10 years) in most series is associated with (at the time of diagnosis) high serum creatinine levels (>124 µmol/L [>1.4 mg/dL]), hypertension, nephrotic syndrome (24-h urine protein excretion >2.6 g), anemia (hemoglobin <124 g/L [<12.4 g/dL]), hypoalbuminemia, hypocomplementemia, antiphospholipid antibodies, male sex, ethnicity (African American, Hispanic with mestizo heritage), and low socioeconomic status. Data regarding outcomes in SLE patients with renal transplants show mixed results: some series show a twofold increase in graft rejection compared to patients with other causes of ESRD, whereas others show no differences. Overall patient survival is comparable (85% at 2 years). Lupus nephritis occurs in ~5% of transplanted kidneys. Disability in patients with SLE is common due primarily to chronic fatigue, arthritis, and pain, as well as renal disease. As many as 30–50% of patients may achieve low disease activity (defined as mild activity on hydroxychloroquine with or without low-dose glucocorticoids); <10% experience remissions (defined as no disease activity on no medications). The leading causes of death in the first decade of disease are systemic disease activity, renal failure, and infections; subsequently, thromboembolic events become increasingly frequent causes of mortality.

DRUG-INDUCED LUPUS

This is a syndrome of positive ANA associated with symptoms such as fever, malaise, arthritis or intense arthralgias/myalgias, serositis, and/or rash. The syndrome appears during therapy with certain medications and biologic agents, is predominant in whites, has less female predilection than SLE, rarely involves kidneys or brain, is rarely associated

with anti-dsDNA, is commonly associated with antibodies to histones, and usually resolves over several weeks after discontinuation of the offending medication. The list of substances that can induce lupus-like disease is long. Among the most frequent are the antiarrhythmics procainamide, disopyramide, and propafenone; the antihypertensive hydralazine; several angiotensin-converting enzyme inhibitors and beta blockers; the antithyroid propylthiouracil; the antipsychotics chlorpromazine and lithium; the anticonvulsants carbamazepine and phenytoin; the antibiotics isoniazid, minocycline, and nitrofurantoin (Macrodantin); the antirheumatic sulfasalazine; the diuretic hydrochlorothiazide; and the antihyperlipidemics lovastatin and simvastatin. Biologics that can cause drug-induced lupus (DIL) include inhibitors of IFNs and TNF. In DIL, ANA usually appears before symptoms; however, many of the medications mentioned above induce ANA in patients who never develop symptoms of drug-induced lupus. It is appropriate to test for ANA at the first hint of relevant symptoms and to use test results to help decide whether to withdraw the suspect agent.

FURTHER READING

- Chong BF, Werth VP: Management of cutaneous lupus erythematosus, in *Dubois Lupus Erythematosus and Related Syndromes*, 9th ed. DJ Wallace, BH Hahn (eds). Philadelphia, Elsevier, 2019.
- Deng Y, Tsao B: Genetics of human SLE, in *Dubois Lupus Erythematosus and Related Syndromes*, 9th ed. DJ Wallace, BH Hahn (eds). Philadelphia, Elsevier, 2019.
- Fanouriakis A et al: 2019 Update of the EULAR/ACR recommendations for the management of systemic lupus erythematosus. *Ann Rheum Dis* 78:736, 2019.
- Gulati G, Brunner H: Environmental triggers in systemic lupus erythematosus. *Semin Arthritis Rheum* 47:710, 2018.
- Hahn BH et al: American College of Rheumatology guidelines for screening, treatment, and management of lupus nephritis. *Arthritis Care Res (Hoboken)* 64:797, 2012.
- Murphy G, Isenberg DA: New therapies for systemic lupus erythematosus: Past imperfect, future tense. *Nat Rev Rheumatol* 15:403, 2019.
- Ocampo-Piraquive V et al: Mortality in lupus erythematosus: Causes, predictors, and interventions. *Expert Rev Clin Immunol* 14:12, 2018.
- Rees F et al: The worldwide incidence and prevalence of systemic lupus erythematosus: A systematic review of epidemiological studies. *Rheumatology* 56:1945, 2017.
- Tsokos GC: Autoimmunity and organ damage in systemic lupus erythematosus. *Nat Immunol* 21:605, 2020.

TABLE 357-1 Classification and Nomenclature of Antiphospholipid Antibodies

NAME	ASSAY FOR THEIR DETECTION	COMMENTS
Antibodies against cardiolipin (aCL)	Enzyme-linked immunosorbent assay (ELISA) using as antigen cardiolipin (CL), a negatively charged phospholipid	aCL from patients with APS recognize β_2 GPI existing in the human serum as well as in bovine serum, which is used to block the nonspecific binding sites on the ELISA plate. CL simply stabilizes β_2 GPI at high concentration on the polystyrene surface.
Antibodies against β_2 GPI (anti- β_2 GPI)	ELISA using as antigen affinity purified or recombinant β_2 GPI in the absence of PL	Antibodies recognize β_2 GPI bound in the absence of CL to an oxidized polystyrene surface, where oxygen atoms in the moieties C=O or C=O were introduced by γ -irradiation.
Lupus anticoagulant (LA)	Activated partial thromboplastin time (aPTT) Kaolin clotting time (KCT) Dilute Russel viper venom test (DRVVT)	Antibodies recognize β_2 GPI or prothrombin (PT) and elongate aPTT, implying that they interfere with the generation of thrombin by prothrombin. Prolongation of the clotting times is an <i>in vitro</i> phenomenon, and LA induces thromboses <i>in vivo</i> .

Abbreviations: APL, antiphospholipid syndrome; β_2 GPI, β_2 -glycoprotein I; PL, phospholipid.

PLs are components of the cytoplasmic membrane of all living cells. The antibodies are directed against PLs, such as cardiolipin, phosphocholine, and phosphatidylserine. The plasma protein β_2 GPI is a 43-kDa plasma apolipoprotein, which consists of 326 amino acids arranged in five domains (I through V). Domain V forms a positively charged patch, suitable to interact with negatively charged PLs. In plasma, β_2 GPI has a circular conformation with domain V binding to and concealing the B-cell epitopes lying on domain I. The presence of anti-domain I IgG antibodies has been recently associated with increased thrombotic risk. Another group of antibodies termed *lupus anticoagulant* (LA) prolongs clotting times *in vitro*, which are not corrected by adding normal plasma (Table 357-1). Patients with APS often possess antibodies recognizing *Treponema pallidum* PL/cholesterol complexes, detected by Venereal Disease Research Laboratory (VDRL) tests and characterized as biologic false-positive serologic tests for syphilis (BFP-STS). Since patients can present with features highly reminiscent of APS in the absence of classical anti-PL antibodies, the term *seronegative APS* has been coined. In patients with strong suspicion of seronegative APS, testing for antiphosphatidylserine/prothrombin antibodies may have a valuable diagnostic role.

EPIDEMIOLOGY

The incidence of APS is estimated to be ~5 cases per 100,000 persons per year. The prevalence of APS in the general population is estimated to be 40–50 per 100,000. Anti-PL antibodies occur in 1–5% of the general population. Their prevalence increases with age; however, it is questionable whether they are able to induce thrombotic events in elderly individuals. Moreover, although one-third of patients with SLE and other autoimmune diseases (Chap. 356) possess these antibodies, only 5–10% of them develop APS.

PATHOGENESIS

The initiating events for the induction of antibodies to PL-binding proteins seem to be infections, oxidative stress, and major physical stresses such as surgery or trauma in an appropriate genetic background, given the previously demonstrated associations with alleles within the HLA locus. These contributors seem to induce increased apoptosis of the vessel endothelial cells and subsequent exposure of PLs. The latter, bound with serum proteins such as β_2 GPI or prothrombin, lead to neo-antigen formation, which in turn triggers the induction of anti-PLs. The binding of anti-PLs to the disrupted endothelial cells leads to initiation of intravascular coagulation and thrombus formation. Complement

357

Antiphospholipid Syndrome

Haralampos M. Moutsopoulos,
Clio P. Mavragani



DEFINITIONS

Antiphospholipid syndrome (APS) is an autoantibody-mediated acquired thrombophilia characterized by recurrent arterial or venous thrombosis and/or pregnancy morbidity. It affects primarily females. APS may occur alone (primary) or in association with other autoimmune diseases, mainly systemic lupus erythematosus (SLE) (secondary). Catastrophic APS (CAPS) is a life-threatening rapidly progressive thromboembolic disease involving simultaneously three or more organs.

The major autoantibodies detected in patients' sera are directed against negatively charged phospholipids (PLs) and/or PL-binding plasma proteins such as β_2 -glycoprotein I (β_2 GPI) and prothrombin.

CLINICAL MANIFESTATIONS AND LABORATORY FINDINGS

Clinical manifestations represent the consequences of venous or arterial thrombosis and/or pregnancy morbidity (Table 357-2). Venous thrombosis, superficial or deep, occurs primarily in the lower extremities, often leading to pulmonary emboli. Thrombosis of the pulmonary arteries leads to pulmonary hypertension, and thrombosis of the inferior vena cava to Budd-Chiari syndrome. Cerebral venous thrombosis presents with signs and symptoms of intracranial hypertension and retinal vein thrombosis. Arterial thrombosis affects more commonly the arteries of the brain and is manifested as migraines, cognitive dysfunction, transient ischemic attacks, stroke, and retinal artery occlusion. Arterial thrombosis of the extremities presents with ischemic leg ulcers, digital gangrene, and avascular bone necrosis,

whereas thrombosis of other arteries leads to myocardial infarction, renal artery stenosis, glomerular lesions, and infarcts of spleen, pancreas, and adrenals.

Livedo reticularis consists of a mottled reticular vascular pattern that appears as a lace-like, purplish discoloration of the skin. It is probably caused by swelling of the venules due to obstruction of capillaries by thrombi. This clinical manifestation usually occurs together with vascular lesions in the central nervous system and with aseptic bone necrosis. Libman-Sacks endocarditis consists of very small vegetations, histologically characterized by organized platelet-fibrin microthrombi surrounded by growing fibroblasts and macrophages. Glomerular involvement is manifested with hypertension, mildly elevated serum creatinine levels, and proteinuria/hematuria. Histologically, in an acute phase, thrombotic microangiopathy is present in the glomerular capillaries. In a chronic phase, fibrous intima hyperplasia, fibrous and/or fibrocellular arteriolar occlusions, and focal cortical atrophy are present (Table 357-2). Pregnancy morbidity manifests with increased risk of recurrent miscarriages, intrauterine growth retardation, preeclampsia, eclampsia, and preterm birth. The major causes of these complications are due to infarctions of the placenta.

Premature atherosclerosis has been also recognized as a feature of APS. Musculoskeletal manifestations include, in addition to bone necrosis, arthralgia/arthritis, bone marrow necrosis, muscle infarction, nontraumatic fractures, and osteoporosis. Coombs-positive hemolytic anemia and thrombocytopenia are laboratory findings associated with APS.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The diagnosis of APS should be seriously considered in cases of thrombosis, cerebral vascular accidents in individuals <55 years of age, or pregnancy morbidity in the presence of livedo reticularis or thrombocytopenia. In these cases, anti-PL antibodies should be measured. The presence of at least one clinical and one laboratory criterion is compatible with the diagnosis, in the absence of other thrombophilia causes. Clinical criteria include (1) vascular thrombosis, defined as one or more clinical episodes of arterial, venous, or small vessel thrombosis in any tissue or organ; and (2) pregnancy morbidity, defined as (a) one or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation; (b) one or more premature births of a morphologically normal neonate before the 34th week of gestation because of eclampsia, severe preeclampsia, or placental insufficiency; or (c) three or more unexplained consecutive spontaneous abortions before the 10th week of gestation. Laboratory criteria include (1) LA, (2) anticardiolipin (aCL), and/or (3) anti-β₂GPI antibodies, at intermediate or high titers on two occasions 12 weeks apart.

Differential diagnosis is based on the exclusion of other inherited or acquired causes of thrombophilia (Chap. 116), Coombs-positive hemolytic anemia (Chap. 100), and thrombocytopenia (Chap. 115). Livedo reticularis with or without a painful ulceration on the lower extremities may be also a manifestation of disorders affecting (1) the vascular wall, such as atherosclerosis, polyarteritis nodosa, SLE, cryoglobulinemia, and lymphomas; or (2) the vascular lumen, such as myeloproliferative disorders, hypercholesterolemia, or other causes of thrombophilia.

TREATMENT

Antiphospholipid Syndrome

It has been increasingly appreciated that the risk of thrombotic and obstetric events is closely related to the underlying anti-PL profile. The latter depends on the type of autoantibodies (IgG high risk vs IgM low risk), the number of anti-PL antibodies (simultaneous presence of two or three classical autoantibodies denotes a higher risk profile vs a single antibody), their titer (moderate-high titer vs low), and the persistence of anti-PL positivity in repeated measurements.

Following the first thrombotic event, APS patients should be placed on vitamin K antagonists (VKAs) for life, aiming to achieve

TABLE 357-2 Clinical Features of Antiphospholipid Syndrome

MANIFESTATION	%
Venous Thrombosis and Related Consequences	
Deep-vein thrombosis	39
Livedo reticularis	24
Pulmonary embolism	14
Superficial thrombophlebitis	12
Thrombosis in various other sites	11
Arterial Thrombosis and Related Consequences	
Stroke	20
Cardiac valve thickening/dysfunction and/or Libman-Sacks vegetations	14
Transient ischemic attack	11
Myocardial ischemia (infarction or angina) and coronary bypass graft thrombosis	10
Leg ulcers and/or digital gangrene	9
Arterial thrombosis in the extremities	7
Retinal artery thrombosis/amaurosis fugax	7
Ischemia of visceral organs or avascular necrosis of bone	6
Multi-infarct dementia	3
Neurologic Manifestations of Uncertain Etiology	
Migraine	20
Epilepsy	7
Chorea	1
Cerebellar ataxia	1
Transverse myelopathy	0.5
Renal Manifestations Due to Various Reasons (Renal Artery/Renal Vein/Glomerular Thrombosis, Fibrous Intima Hyperplasia)	
	3
Musculoskeletal Manifestations	
Arthralgias	39
Arthritis	27
Obstetric Manifestations (Referred to the Number of Pregnancies)	
Preeclampsia	10
Eclampsia	4
Fetal Manifestations (Referred to the Number of Pregnancies)	
Early fetal loss (<10 weeks)	35
Late fetal loss (10 weeks)	17
Premature birth among the live births	11
Hematologic Manifestations	
Thrombocytopenia	30
Autoimmune hemolytic anemia	10

Source: Adapted from R Cervera et al: Arthritis Rheum 46:1019, 2002.

an international normalized ratio (INR) ranging from 2.0 to 3.0 in case of an unprovoked venous thrombosis. For patients with arterial thrombosis, the corresponding INR target should be 3.0–4.0 or 2.0–3.0 along with low-dose aspirin (LDA, 75–100 mg daily), depending on the thrombotic/hemorrhagic patient profile. Administration of direct oral thrombin inhibitors recently has been shown to increase the risk of arterial events, especially in patients with triple positivity or previous arterial thrombosis. However, they could be considered with extreme caution in cases in which contraindications to VKAs or inability to achieve a target INR despite adherence to the treatment are present. In pregnant women with a history of obstetric APS, combination treatment with LDA and prophylactic dose of low-molecular-weight heparin (LMWH) is recommended, whereas in cases of thrombotic APS, LDA plus therapeutic LMWH dose should be administered. When recurrent obstetric complications occur despite standard treatment, increasing the LMWH dose (from prophylactic to therapeutic) or administering oral hydroxychloroquine 400 mg/d or IV immunoglobulin (IVIg) 400 mg/kg every day for 5 days are alternative options.

For asymptomatic individuals or SLE patients with a high-risk anti-PL profile and no evidence of a previous thrombotic event or pregnancy morbidity, prophylactic treatment with LDA is recommended. In nonpregnant women with a history of APS-related obstetric complications, independently of the presence of underlying SLE diagnosis, treatment with LDA seems to reduce the risk of a subsequent thrombotic event.

Patients with CAPS should be treated with combination therapy with glucocorticoids, heparin, and plasma exchange or IVIG together with appropriate management of triggering events such as infections. For refractory CAPS, B-cell depletion (e.g., with rituximab) or complement inhibition (e.g., with eculizumab) therapies are alternative options.

FURTHER READING

- Sciascia S et al: Diagnosing antiphospholipid syndrome: "Extra-criteria" manifestations and technical advances. *Nat Rev Rheumatol* 13:548, 2017.
 Tebo AE: Laboratory evaluation of antiphospholipid syndrome: An update on autoantibody testing. *Clin Lab Med* 39:553, 2019.
 Tektonidou MG et al: EULAR recommendations for the management of antiphospholipid syndrome in adults. *Ann Rheum Dis* 78:1296, 2019.

Insights gained by a wealth of basic and clinical research over the past two decades have revolutionized the contemporary paradigms for the diagnosis and management of RA. Testing for serum antibodies to anti-citrullinated protein antibodies (ACPA) and rheumatoid factor continues to be valuable in the diagnostic evaluation of patients with suspected RA, and these antibodies serve as biomarkers of prognostic significance. Advances in imaging modalities assist clinical decision-making by improving the detection of joint inflammation and monitoring the progression of damage. The science of RA has taken major leaps forward by illuminating new disease-related genes, environmental interactions, and the molecular components and pathways of disease pathogenesis in even more detail. The relative contribution of these cellular and inflammatory mediators in disease pathogenesis has been further brought to light by the observed benefits of an expanded pipeline of biologic and targeted synthetic disease-modifying therapies. Despite this progress, incomplete understanding of the initiating events of RA and the factors perpetuating the chronic inflammatory response remains a barrier to its cure and prevention.

The past 20 years have witnessed a remarkable improvement in the outcomes of RA. The crippling arthritis of years past is encountered much less frequently today. Much of this progress can be traced to the expanded therapeutic armamentarium and the adoption of early treatment intervention. The shift in treatment strategy dictates a new mindset for primary care practitioners—namely, one that demands early referral of patients with inflammatory arthritis to a rheumatologist for prompt diagnosis and initiation of therapy. Only then will patients achieve their best outcomes.

CLINICAL FEATURES

The incidence of RA increases between 25 and 55 years of age, after which it plateaus until the age of 75 and then decreases. The presenting symptoms of RA typically result from inflammation of the joints, tendons, and bursae. Patients often complain of early morning joint stiffness lasting >1 hour that eases with physical activity. The earliest involved joints are typically the small joints of the hands and feet. The initial pattern of joint involvement may be monoarticular, oligoarticular (< 4 joints), or polyarticular (>5 joints), usually in a symmetric distribution. Some patients with inflammatory arthritis will present with too few affected joints to be classified as having RA—so-called undifferentiated inflammatory arthritis. Those with an undifferentiated arthritis who are most likely to be diagnosed later with RA have a higher number of tender and swollen joints, test positive for serum rheumatoid factor (RF) or ACPA, and have higher scores for physical disability.

Once the disease process of RA is established, the wrists and metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints stand out as the most frequently involved joints (Fig. 358-1). Distal

358

Rheumatoid Arthritis

Ankoor Shah, E. William St. Clair

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disease of unknown etiology characterized by a symmetric polyarthritis and is the most common form of chronic inflammatory arthritis. Since persistently active RA often results in articular cartilage and bone destruction and functional disability, it is vital to diagnose and treat this disease early and aggressively before damage ensues. RA, a systemic disease, may also lead to a variety of extraarticular manifestations, including fatigue, subcutaneous nodules, lung involvement, pericarditis, peripheral neuropathy, vasculitis, and hematologic abnormalities, which must be managed accordingly.



FIGURE 358-1 Metacarpophalangeal joint swelling and subluxation. (RP Usatine, MA Smith, EJ Mayeaux: *The Color Atlas and Synopsis of Family Medicine*, 3rd ed. New York, McGraw Hill, 2019; Fig. 97.5.)

2752 interphalangeal (DIP) joint involvement may occur in RA, but it usually is a manifestation of coexistent osteoarthritis. Flexor tendon tenosynovitis is a frequent hallmark of RA and leads to decreased range of motion, reduced grip strength, and “trigger” fingers. Flexor tendon involvement may also lead to tendon rupture, with the flexor pollicis longest the most common flexor tendon to be affected by RA. Progressive destruction of the joints and soft tissues may lead to chronic, irreversible deformities. Ulnar deviation results from subluxation of the MCP joints, with subluxation, or partial dislocation, of the proximal phalanx to the volar side of the hand. Hyperextension of the PIP joint with flexion of the DIP joint (“swan-neck deformity”), flexion of the PIP joint with hyperextension of the DIP joint (“boutonnière deformity”), and subluxation of the first MCP joint with hyperextension of the first interphalangeal (IP) joint (“Z-line deformity”) also may result from damage to the tendons, joint capsule, and other soft tissues in these small joints. Inflammation about the ulnar styloid and tenosynovitis of the extensor carpi ulnaris may cause subluxation of the distal ulna, resulting in a “piano-key movement” of the ulnar styloid. Although metatarsophalangeal (MTP) joint involvement in the feet is an early feature of disease, chronic inflammation of the ankle and midtarsal regions usually comes later and may lead to pes planovalgus (“flat feet”). Large joints, including the knees and shoulders, are often affected in established disease, although these joints may remain asymptomatic for many years after onset.

Atlantoaxial involvement of the cervical spine is clinically noteworthy because of its potential to cause compressive myelopathy and

neurologic dysfunction. Neurologic manifestations are rarely a presenting sign or symptom of atlantoaxial disease, but they may evolve over time with progressive instability of C1 on C2. The prevalence of atlantoaxial subluxation has been declining in recent years and occurs now in <10% of patients. Unlike the spondyloarthritides (**Chap. 362**), RA rarely affects the thoracic and lumbar spine.

Extraarticular manifestations may develop during the clinical course of RA in up to 40% of patients, even prior to the onset of arthritis (**Fig. 358-2**). Patients most likely to develop extraarticular disease have a history of cigarette smoking, have early onset of significant physical disability, and test positive for serum RF or ACPA. Subcutaneous nodules, secondary Sjögren's syndrome, interstitial lung disease (ILD), pulmonary nodules, and anemia are among the most frequently observed extraarticular manifestations. Recent studies have shown a decrease in the incidence and severity of at least some extraarticular manifestations, particularly Felty's syndrome and vasculitis.

The most common systemic and extraarticular features of RA are described in more detail in the sections below.

CONSTITUTIONAL

These signs and symptoms include weight loss, fever, fatigue, malaise, depression, and in the most severe cases, cachexia; they generally reflect a high degree of inflammation and may even precede the onset of joint symptoms. In general, the presence of a fever of >38.3°C (101°F) at any time during the clinical course should raise suspicion of systemic vasculitis (see below) or infection.

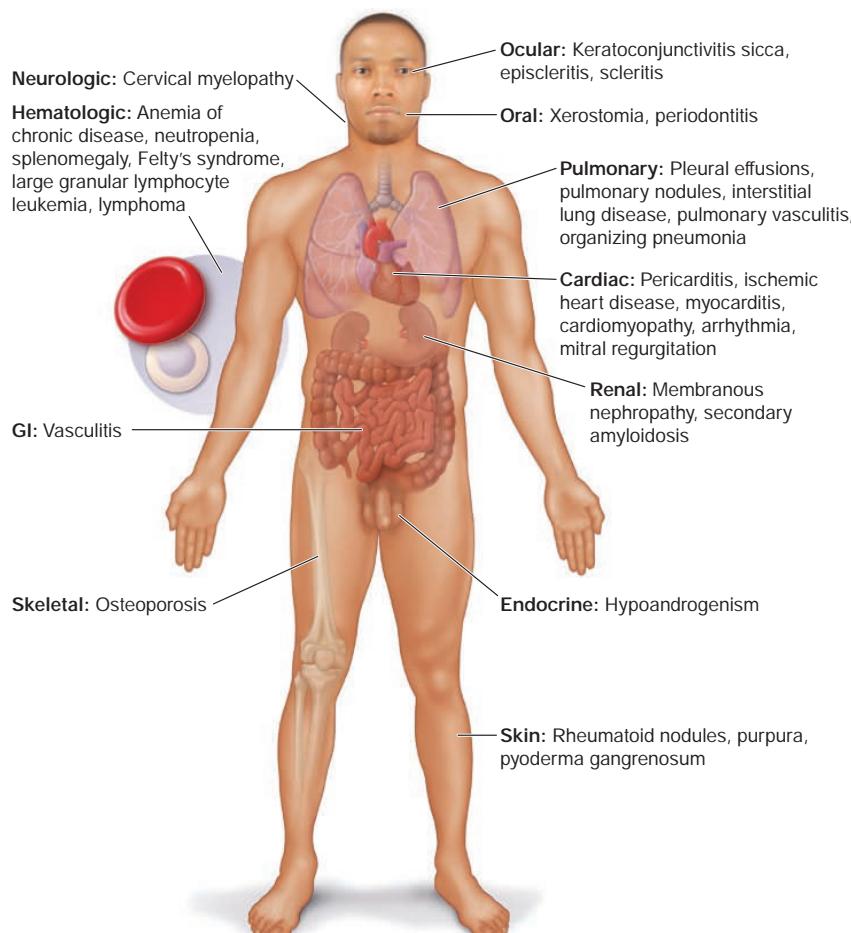


FIGURE 358-2 Extraarticular manifestations of rheumatoid arthritis.

NODULES

Subcutaneous nodules have been reported to occur in 30–40% of patients and more commonly in those with the highest levels of disease activity, the disease-related shared epitope (SE) (see below), a positive test for serum RF, and radiographic evidence of joint erosions. However, more recent cohort studies suggest a declining prevalence of subcutaneous nodules, perhaps related to early and more aggressive disease-modifying therapy. When palpated, the nodules are generally firm, nontender, and adherent to periosteum, tendons, or bursae; they develop in areas of the skeleton subject to repeated trauma or irritation such as the forearm, sacral prominences, and Achilles tendon. They may also occur in the lungs, pleura, pericardium, and peritoneum. Nodules are typically benign, although they can be associated with infection, ulceration, and gangrene. Accelerated growth of smaller nodules may occur in up to 10% of patients taking long-term methotrexate, although the mechanisms behind this phenomenon is unclear.

SJÖGREN'S SYNDROME

Secondary Sjögren's syndrome ([Chap. 361](#)) is defined by the presence of either keratoconjunctivitis sicca (dry eyes) or xerostomia (dry mouth) in association with another connective tissue disease, such as RA. Approximately 10% of patients with RA have secondary Sjögren's syndrome.

PULMONARY

Pleuritis, the most common pulmonary manifestation of RA, may produce pleuritic chest pain and dyspnea, as well as a pleural friction rub and effusion. Pleural effusions tend to be exudative with increased numbers of monocytes and neutrophils. ILD may also occur in patients with RA and is heralded by symptoms of dry cough and progressive shortness of breath. ILD can be associated with cigarette smoking and is generally found in patients with higher disease activity, although it may be diagnosed in up to 3.5% of patients prior to the onset of joint symptoms. Recent studies have shown the overall prevalence of ILD in RA to be as high as 12%. Diagnosis is readily made by high-resolution chest CT scan, which shows infiltrative opacification, or ground-glass opacities, in the periphery of both lungs. Usual interstitial pneumonia (UIP) and nonspecific interstitial pneumonia (NSIP) are the main histologic and radiologic patterns of ILD. UIP causes progressive scarring of the lungs that, on chest CT scan, produces honeycomb changes in the periphery and lower portions of the lungs. In contrast, the most common radiographic changes in NSIP are relatively symmetric and bilateral ground-glass opacities with associated fine reticulations, with volume loss and traction bronchiectasis. In both cases, pulmonary function testing shows a restrictive pattern (e.g., reduced total lung capacity) with a reduced diffusing capacity for carbon monoxide (DL_{CO}). The presence of ILD confers a poor prognosis. The prognosis of ILD in RA, however, is not quite as poor as that of idiopathic pulmonary fibrosis (e.g., usual interstitial pneumonitis) and responds better to immunosuppressive therapy ([Chap. 293](#)). Pulmonary nodules are also common in patients with RA and may be solitary or multiple. Caplan's syndrome is a rare subset of pulmonary nodulosis characterized by the development of nodules and pneumoconiosis following silica exposure. Respiratory bronchiolitis and bronchiectasis are pulmonary disorders less commonly associated with RA.

CARDIAC

The most frequent site of cardiac involvement in RA is the pericardium. However, clinical manifestations of pericarditis occur in <10% of patients with RA despite the fact that pericardial involvement is detectable in nearly one-half of cases by echocardiogram or autopsy studies. Up to 20% of patients with RA may have asymptomatic pericardial effusions on echocardiography. Cardiomyopathy, another clinically important manifestation of RA, may result from necrotizing or granulomatous myocarditis, coronary artery disease, or diastolic dysfunction. This involvement too may be subclinical and only identified by echocardiography or cardiac MRI. Rarely, the heart muscle may contain rheumatoid nodules or be infiltrated with amyloid. Mitral

regurgitation is the most common valvular abnormality in RA, occurring at a higher frequency than in the general population.

VASCULITIS

Rheumatoid vasculitis ([Chap. 363](#)) typically occurs in patients with long-standing disease, a positive test for serum RF or anti-cyclic citrullinated peptide (CCP) antibodies, and hypocomplementemia. The overall incidence has decreased significantly in the past decade to <1% of patients. The cutaneous signs vary and include petechiae, purpura, digital infarcts, gangrene, livedo reticularis, and in severe cases large, painful lower extremity ulcerations. Vasculitic ulcers, which may be difficult to distinguish from those caused by venous insufficiency, may be treated successfully with immunosuppressive agents (requiring cytotoxic treatment in severe cases) as well as skin grafting. Sensorimotor polyneuropathies, such as mononeuritis multiplex, may occur in association with systemic rheumatoid vasculitis and usually clinically present with a new onset of numbness, tingling, or focal muscle weakness depending on its severity.

HEMATOLOGIC

A normochromic, normocytic anemia often develops in patients with RA and is the most common hematologic abnormality. The degree of anemia parallels the degree of inflammation, correlating with the levels of serum C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). Platelet counts may also be elevated in RA as an acute-phase reactant. Immune-mediated thrombocytopenia is rare in this disease.

Felty's syndrome is defined by the clinical triad of neutropenia, splenomegaly, and nodular RA and is seen in <1% of patients, although its incidence appears to be declining in the face of more aggressive treatment of the joint disease. It typically occurs in the late stages of severe RA and is more common in whites than other racial groups. T-cell large granular lymphocyte leukemia (T-LGL) may have a similar clinical presentation and often occurs in association with RA. T-LGL is characterized by a chronic, indolent clonal growth of LGL cells, leading to neutropenia and splenomegaly. As opposed to Felty's syndrome, T-LGL may develop early in the course of RA. Leukopenia apart from these disorders is uncommon and most often a side effect of drug therapy.

LYMPHOMA

Large cohort studies have shown a two- to fourfold increased risk of lymphoma in RA patients compared with the general population. The most common histopathologic type of lymphoma is a diffuse large B-cell lymphoma. The risk of developing lymphoma increases if the patient has high levels of disease activity or Felty's syndrome.

ASSOCIATED CONDITIONS

In addition to extraarticular manifestations, several conditions associated with RA contribute to disease morbidity and mortality rates. They are worthy of mention because they affect chronic disease management.

Cardiovascular Disease The most common cause of death in patients with RA is cardiovascular disease. The incidence of coronary artery disease and carotid atherosclerosis is higher in RA patients than in the general population even when controlling for traditional cardiac risk factors, such as hypertension, obesity, hypercholesterolemia, diabetes, and cigarette smoking. Furthermore, congestive heart failure (including both systolic and diastolic dysfunction) occurs at an approximately twofold higher rate in RA than in the general population. The presence of elevated serum inflammatory markers appears to confer an increased risk of cardiovascular disease in this disease population.

Osteoporosis Osteoporosis is more common in patients with RA than an age- and sex-matched population, with an incidence rate of nearly double that of the healthy population and a prevalence of approximately one-third in postmenopausal women with RA. There is also an increased risk of fragility fracture, with a greater risk among women. The inflammatory milieu of the joint probably spills over into the rest of the body and promotes generalized bone loss by activating osteoclasts. Both trabecular and cortical bone are affected by the

inflammatory response, with cortical sites more susceptible to bone loss. Chronic use of glucocorticoids and disability-related immobility also contribute to osteoporosis. Hip fractures are more likely to occur in patients with RA and are significant predictors of increased disability and mortality rate in this disease.

EPIDEMIOLOGY

RA affects ~0.5–1% of the adult population worldwide. There is evidence that the overall incidence of RA has been decreasing in recent decades, whereas the prevalence has remained the same because individuals with RA are living longer. The incidence and prevalence of RA vary based on geographic location, both globally and among certain ethnic groups within a country (Fig. 358-3). For example, the Native American Yakima, Pima, and Chippewa tribes of North America have reported prevalence rates in some studies of nearly 7%. In contrast, many population studies from Africa and Asia show lower prevalence rates for RA in the range of 0.2–0.4%.

Like many other autoimmune diseases, RA occurs more commonly in females than in males, with a 2–3:1 ratio. Interestingly, studies of RA from some of the Latin American and African countries show an even greater predominance of disease in females compared to males, with ratios of 6–8:1. Given this preponderance of females, various theories have been proposed to explain the possible role of estrogen in disease pathogenesis. Broadly speaking, most of the theories center on the role of estrogens and androgens in enhancing and suppressing the immune response, respectively. However, estrogens have both stimulatory and inhibitory effects on the immune system, and the hormonal mechanisms, if any, influencing the development of RA are unknown.

GENETIC CONSIDERATIONS

 It has been recognized for >30 years that genetic factors contribute to the occurrence of RA as well as to its severity. The likelihood that a first-degree relative of a patient will share the diagnosis of RA is 2–10 times greater than in the general population. There remains, however, some uncertainty in the extent to which genetics plays a role in the causative mechanisms of RA. Heritability estimates range from 40 to 50% and are approximately the same for autoantibody-positive and -negative individuals. The estimate of genetic influence may vary across studies due to gene-environment interactions.

The alleles known to confer the greatest risk of RA are located within the major histocompatibility complex (MHC) and, in particular, MHC class II molecules. MHC class II molecules are typically

expressed on antigen-presenting cells and are comprised of α and β chains. Most, but probably not all, of this risk is associated with allelic variation in the HLA-DRB1 gene, which encodes the MHC II β -chain molecule. The disease-associated HLA-DRB1 alleles share an amino acid sequence at positions 70–74 in the third hypervariable regions of the HLA-DR β -chain, termed the *shared epitope*. These amino acids are located in the antigen-binding groove with the hypervariable regions of the HLA-DRB1 molecule. Hypervariable regions within DR molecules are particularly important for determining antigen recognition and binding of the MHC-peptide complex to the T-cell receptor (TCR). Peptides derived from posttranslationally modified proteins (via citrullination, acetylation, or carbamylolation, for example) may bind with greater avidity to the shared epitope, providing a potential mechanism for increased disease risk at a molecular level.

Carriage of the SE alleles is associated with production of anti-ACPA and worse disease outcomes. Some of these HLA-DRB1 alleles bestow a high risk of disease (*0401), whereas others confer a more moderate risk (*0101, 0404, 1001, and 0901). Over 90% of patients with RA express at least one of these variants. Interestingly, HLA-DRB1*1301 and to a lesser extent HLA-DRB1*1302 confer protection from ACPA-positive RA.

Additionally, there is geographic variation in disease susceptibility and the identity of the HLA-DRB1 risk alleles. In Greece, for example, where RA tends to be milder than in western European countries, RA susceptibility has been associated with the *0101 SE allele. By comparison, the *0401 or *0404 alleles are found in ~50–70% of northern Europeans and are the predominant risk alleles in this group. The most common disease susceptibility SE alleles in Asians, namely the Japanese, Koreans, and Chinese, are *0405 and *0901. Lastly, disease susceptibility of Native American populations such as the Pima and Tlingit Indians, where the prevalence of RA can be as high as 7%, is associated with the SE allele *1042. The risk of RA conferred by these SE alleles is less in African and Hispanic Americans than in individuals of European ancestry.

Genome-wide association studies (GWAS) have made possible the identification of several non-MHC-related genes that contribute to RA susceptibility. GWAS are based on the detection of single nucleotide polymorphisms (SNPs), which allow for examination of the genetic architecture of complex diseases such as RA. There are ~10 million common SNPs within a human genome consisting of 3 billion base pairs. As a rule, GWAS identify only common variants, namely, those with a frequency of >5% in the general population.

European ancestry:

HLA-DRB1:

- *0401
- *0404
- *0301
- *0101

PTPN22: European

STAT4: North American

TNFAIP3: North American

TRAFL/CF: North American

CTLA4: European

Asian ancestry:

HLA-DRB1:

- *0401 (East Asian)
- *0405
- *0901 (Japanese, Malaysian, Korean)

PADI4

CD244

Other:

CD40

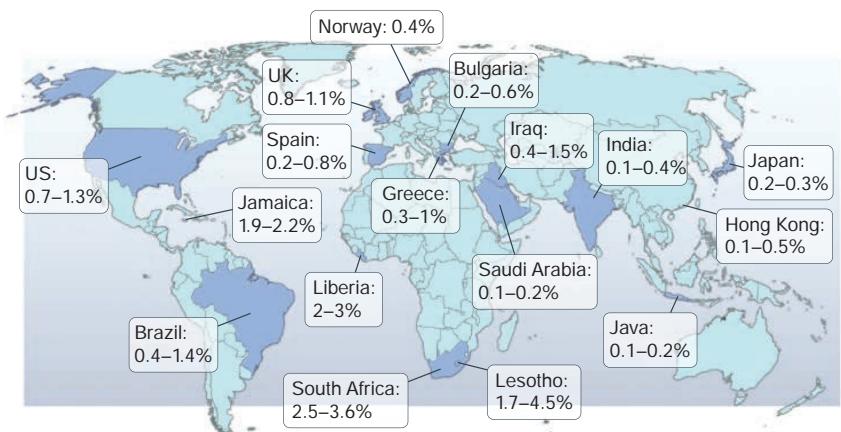


FIGURE 358-3 Global prevalence rates of rheumatoid arthritis (RA) with genetic associations. Listed are the major genetic alleles associated with RA. Although human leukocyte antigen (HLA)-DRB1 mutations are found globally, some alleles have been associated with RA in only certain ethnic groups.

Overall, several themes have emerged from GWAS in RA. First, among the >100 non-MHC loci identified as risk alleles for RA, they individually have only a modest effect on risk; they also contribute to the risk for developing other autoimmune diseases, such as type 1 diabetes mellitus, systemic lupus erythematosus, and multiple sclerosis. Second, although most of the non-HLA associations are described in patients with ACPA-positive disease, there are several risk loci that are unique to ACPA-negative disease. Third, risk alleles vary among ethnic groups. And fourth, the risk loci mostly reside in genes encoding proteins involved in the regulation of the immune response. However, the risk alleles identified by GWAS only account at present for ~5% of the genetic risk, suggesting that rare variants or other classes of DNA variants, such as variants in copy number, may be yet found that significantly contribute to the overall risk model.

Among the best examples of the non-MHC genes contributing to the risk of RA is the gene encoding protein tyrosine phosphatase non-receptor 22 (*PTPN22*). This gene varies in frequency among patients from different parts of Europe (e.g., 3–10%) but is absent in patients of East Asian ancestry. *PTPN22* encodes lymphoid tyrosine phosphatase, a protein that regulates T- and B-cell function. Inheritance of the risk allele for *PTPN22* produces a gain-of-function in the protein that is hypothesized to result in the abnormal thymic selection of autoreactive T and B cells and appears to be associated exclusively with ACPA-positive disease. The peptidyl arginine deiminase type IV (*PADI4*) gene is another risk allele that encodes an enzyme involved in the conversion of arginine to citrulline and is postulated to play a role in the development of antibodies to citrullinated antigens. A polymorphism in *PADI4* has been associated with a twofold increase in the risk of RA, primarily in those of East Asian descent. Recently, polymorphisms in apolipoprotein M (*APOM*) have been demonstrated in an East Asian population to confer an increased risk for RA as well as risk for dyslipidemia, independent of RA disease activity.

In addition to *PTPN22*, other genes associated with B-cell function and/or antigen presentation such as *BTLA* (B- and T-lymphocyte attenuator), Fc receptors, and *CD40* have been identified. Signal transduction genes and pathways that regulate immune function (e.g., *TRAF1-C5* and *STAT4*), cell migration (*ELMO1*) and fetal development (*LBH*) have also been discovered to be linked to RA. Other risk alleles affect cytokine signaling, such as tumor necrosis factor (TNF) promoter polymorphisms that can potentially modulate TNF gene expression and an interleukin (IL) 6 receptor polymorphism that is functionally implicated in the strength of IL-6 signaling. Thus, the genetic clues implicate both adaptive and innate immune mechanisms in disease pathogenesis.

Epigenetics is the study of heritable traits that affect gene expression but do not modify DNA sequence. It may provide a link between environmental exposure and predisposition to disease. Epigenetic mechanisms are theoretically involved in three important aspects of RA: contribution to disease etiology, perpetuation of chronic inflammatory responses, and disease severity. The best-studied epigenetic mechanisms are those regulating posttranslational histone modifications and DNA methylation. DNA methylation patterns have been shown to differ between RA patients and healthy controls, as well as from patients with osteoarthritis. MicroRNAs, which are noncoding RNAs that function as posttranscriptional regulators of gene expression, represent an additional epigenetic mechanism that may potentially influence cellular responses. Many microRNAs have been identified as contributing to the activated phenotype of synovial fibroblasts, such as miR146a or miR155.

ENVIRONMENTAL FACTORS

In addition to genetic predisposition, a host of environmental factors have been implicated in the pathogenesis of RA. The most reproducible of these environmental links is cigarette smoking. Numerous cohort and case-control studies have demonstrated that smoking confers a relative risk for developing RA of 1.5–3.5 times. Smoking-related risk interacts in a synergistic manner with MHC risk alleles. The classic shared epitope alleles alone modestly increase the likelihood of developing RA by four- to sixfold; however, this risk increases to 20- to

40-fold when combined with smoking. In particular, women who smoke cigarettes have a nearly 2.5 times greater risk of RA, a risk that persists even 15 years after smoking cessation. A twin who smokes will have a significantly higher risk for RA than his or her monozygotic co-twin, theoretically with the same genetic risk, who does not smoke. Interestingly, the risk from smoking is almost exclusively related to RF and ACPA-positive disease. However, it has not been shown that smoking cessation, while having many health benefits, improves disease activity. Inhalant-related occupations and silica inhalants also may increase RA risk. These observations have led to the theory that lung disease may play a critical early role in the initial development of autoreactive immune cells, as well as to the known occurrence of autoantibodies more than a decade prior to the clinical development of joint disease.

Researchers began to aggressively seek an infectious etiology for RA after the discovery in 1931 that sera from patients with this disease could agglutinate strains of streptococci. Certain viruses such as Epstein-Barr virus (EBV) have garnered the most interest over the past 30 years given their ubiquity, ability to persist for many years in the host, and frequent association with arthritic complaints. For example, titers of IgG antibodies against EBV antigens in the peripheral blood and saliva are significantly higher in patients with RA than the general population. EBV DNA has also been found in synovial fluid and synovial cells of RA patients. Because the evidence for these links is largely circumstantial, it has not been possible to directly implicate infection as a causative factor in RA.

An attractive hypothesis is that microbial dysbiosis of the oral or gut microbiome may predispose to the development of RA. Recent studies suggest that periodontitis in the oral cavity may play a role in disease mechanisms. Multiple studies provide evidence for a link between ACPA-positive RA and cigarette smoking, periodontal disease, and the oral microbiome, specifically *Porphyromonas gingivalis*. It has been hypothesized that the immune response to *P. gingivalis* may trigger the development of RA and that induction of ACPA results from citrullination of arginine residues in human tissues by the bacterial enzyme peptidyl arginine deiminase (PAD). Interestingly, *P. gingivalis* is the only oral bacterial species known to harbor this enzyme. Some studies have shown a relationship between circulating antibodies to *P. gingivalis* and RA, as well as these antibodies and first-degree relatives at risk for this disease. However, it remains unproven whether the observed dysbiosis in the oral cavity precedes the development of disease, and results from other studies argue against a causal link between periodontitis and the development of RA.

There are also limited data suggesting a role for the gut microbiome in the etiology of RA. Some studies have found that the gut microbiome is different in patients with early RA compared with controls. In particular, *Prevotella copri* was reported to be enriched in early untreated RA as well as an “at-risk” population. On the other hand, a common dysbiotic signature does not seem to predominate in patients with RA, and evidence is lacking for direct immune-modulating mechanisms.

PATHOLOGY

RA affects the synovial tissue primarily of the diarthrodial joints and underlying cartilage and bone. The synovial membrane, which covers most articular surfaces, tendon sheaths, and bursae, normally is a thin layer of connective tissue. In joints, it faces the bone and cartilage, bridging the opposing bony surfaces and inserting at periosteal regions close to the articular cartilage. It consists primarily of two cell types—type A synoviocytes (macrophage-derived) and type B synoviocytes (fibroblast-derived). The synovial fibroblasts are the most abundant and produce the structural components of joints, including collagen, fibronectin, and laminin, as well as other extracellular constituents of the synovial matrix. The sublining layer consists of blood vessels and a sparse population of mononuclear cells within a loose network of connective tissue. Synovial fluid, an ultrafiltrate of blood, diffuses through the subsynovial lining tissue across the synovial membrane and into the joint cavity. Its main constituents are hyaluronan and lubricin. Hyaluronan is a glycosaminoglycan that contributes to the

The pathologic hallmarks of RA are synovial inflammation and proliferation, focal bone erosions, and thinning of articular cartilage. Chronic inflammation leads to synovial lining hyperplasia and the formation of pannus, a thickened cellular membrane containing multiple layers of fibroblast-like synoviocytes and granulation-reactive fibrovascular tissue that invades the underlying cartilage and bone. The inflammatory infiltrate is made up of no less than six cell types: T cells, B cells, plasma cells, dendritic cells, mast cells, and, to a lesser extent, granulocytes. The T cells compose 30–50% of the infiltrate, with the other cells accounting for the remainder. The topographical organization of these cells is complex and may vary among individuals with RA. Most often, the lymphocytes are diffusely organized among the tissue resident cells; however, in some cases, the B cells, T cells, and dendritic cells may form higher levels of organization, such as lymphoid follicles and germinal center-like structures. Growth factors secreted by synovial fibroblasts and macrophages promote the formation of new blood vessels in the synovial sublining that supply the increasing demands for oxygenation and nutrition required by the infiltrating leukocytes and expanding synovial tissue.

The structural damage to the mineralized cartilage and subchondral bone is mediated by the osteoclast. Osteoclasts are multinucleated giant cells that can be identified by their expression of CD68, tartrate-resistant acid phosphatase, cathepsin K, and the calcitonin receptor. They appear at the pannus–bone interface where they eventually form resorption lacunae. These lesions typically localize where the synovial membrane inserts into the periosteal surface at the edges of bones close to the rim of articular cartilage and at the attachment sites of ligaments and tendon sheaths. This process most likely explains why bone erosions usually develop at the radial sites of the MCP joints juxtaposed to the insertion sites of the tendons, collateral ligaments, and synovial membrane. Another form of bone loss is periarthritis osteopenia that occurs in joints with active inflammation. It is associated with substantial thinning of the bony trabeculae along the metaphyses of bones, and likely results from inflammation of the bone marrow cavity. These lesions can be visualized on MRI scans, where they appear as signal alterations in the bone marrow adjacent to inflamed joints. Their signal characteristics show they are water-rich with a low-fat content and are consistent with highly vascularized inflammatory tissue. These bone marrow lesions are often the forerunner of bone erosions.

The cortical bone layer that separates the bone marrow from the invading pannus is relatively thin and susceptible to penetration by the inflamed synovium. The bone marrow lesions seen on MRI scans are associated with an endosteal bone response characterized by the accumulation of osteoblasts and deposition of osteoid. Finally, generalized osteoporosis, which results in the thinning of trabecular bone throughout the body, is a third form of bone loss found in patients with RA.

Articular cartilage is an avascular tissue comprised of a specialized matrix of collagens, proteoglycans, and other proteins. It is organized in four distinct regions (superficial, middle, deep, and calcified cartilage zones)—chondrocytes constitute the unique cellular component in these layers. Originally, cartilage was considered to be an inert tissue, but it is now known to be a highly responsive tissue that reacts to inflammatory mediators and mechanical factors, which in turn, alter the balance between cartilage anabolism and catabolism. In RA, the initial areas of cartilage degradation are juxtaposed to the synovial pannus. The cartilage matrix is characterized by a generalized loss of proteoglycan, most evident in the superficial zones adjacent to the synovial fluid. Degradation of cartilage may also take place in the perichondrocytic zone and in regions adjacent to the subchondral bone.

PATHOGENESIS

The pathogenic mechanisms of synovial inflammation are likely to result from a complex interplay of genetic, environmental, and immunologic factors that produces dysregulation of the immune system and a breakdown in self-tolerance (**Fig. 358-4**). Precisely what triggers these initiating events and what genetic and environmental factors disrupt the immune system remain a mystery. However, a detailed

molecular picture is emerging of the mechanisms underlying the chronic inflammatory response and the destruction of the articular cartilage and bone.

In RA, the preclinical stage appears to be characterized by a breakdown in self-tolerance. This idea is supported by the finding that autoantibodies, such as RF and ACPA, may be found in sera from patients many years before onset of clinical disease. However, the antigenic targets of ACPA and RF are not restricted to the joint, and their role in disease pathogenesis remains speculative. ACPA are directed against deaminated peptides, which result from posttranslational modification by the enzyme PADI4. They recognize citrulline-containing regions of several different matrix proteins, including filaggrin, keratin, fibrinogen, and vimentin, and are present at higher levels in the joint fluid compared to the serum. Other autoantibodies have been found in a minority of patients with RA, but they also occur in the setting of other types of arthritis. They bind to a diverse array of autoantigens, including type II collagen, human cartilage gp-39, aggrecan, calpastatin, immunoglobulin binding protein (BiP), and glucose-6-phosphate isomerase.

In theory, environmental stimulants may synergize with other factors to bring about inflammation in RA. People who smoke display higher citrullination of proteins in bronchoalveolar fluid than those who do not smoke. Thus, it has been speculated that long-term exposure to tobacco smoke might induce citrullination of cellular proteins via increased PADI expression in the lung and generate a neoepitope capable of inducing self-reactivity, which in turns, leads to formation of immune complexes that trigger joint inflammation.

How might microbes or their products be involved in the initiating events of RA? The immune system is alerted to the presence of microbial infections through the binding of pathogen-associated molecular patterns (PAMPs) to Toll-like receptors (TLRs). There are 10 TLRs in humans that recognize a variety of microbial products, including bacterial cell-surface lipopolysaccharides and heat-shock proteins (TLR4), lipoproteins (TLR2), double-strand RNA viruses (TLR3), and unmethylated CpG DNA from bacteria (TLR9). TLR2, 3, and 4 are abundantly expressed by synovial fibroblasts in early RA and, when bound by their ligands, upregulate production of proinflammatory cytokines. Although TLR ligands may theoretically amplify inflammatory pathways in RA, their specific role in disease pathogenesis remains uncertain.

The pathogenesis of RA is built upon the concept that self-reactive T cells drive the chronic inflammatory response. In theory, self-reactive T cells might arise in RA from abnormal central (thymic) selection or intrinsic defects lowering the threshold in the periphery for T-cell activation. Either mechanism might result in abnormal expansion of the self-reactive T-cell repertoire and a breakdown in T-cell tolerance. The support for these theories comes mainly from studies of arthritis in mouse models. It has not been shown that patients with RA have abnormal thymic selection of T cells or defective apoptotic pathways regulating cell death. At least some antigen stimulation inside the joint seems likely, owing to the fact that T cells in the synovium express a cell-surface phenotype indicating prior antigen exposure and show evidence of clonal expansion. Of interest, peripheral blood T cells from patients with RA have been shown to display a fingerprint of premature aging that mostly affects inexperienced naïve T cells. In these studies, the most glaring findings have been the loss of telomeric sequences and a decrease in the thymic output of new T cells. Although intriguing, it is not clear how generalized T-cell abnormalities might provoke a systemic disease with a predominance of synovitis.

There is substantial evidence of a role for CD4+ T cells in the pathogenesis of RA. First, the co-receptor CD4 on the surface of T cells binds to invariant sites on MHC class II molecules, stabilizing the MHC-peptide–T-cell receptor complex during T-cell activation. Because the SE on MHC class II molecules is a risk factor for RA, it follows that CD4+ T-cell activation may play a role in the pathogenesis of this disease. Second, CD4+ memory T cells are enriched in the synovial tissue from patients with RA and can be implicated through “guilt by association.” Third, CD4+ T cells have been shown to be important in the initiation of arthritis in animal models. Fourth, some, but not all,

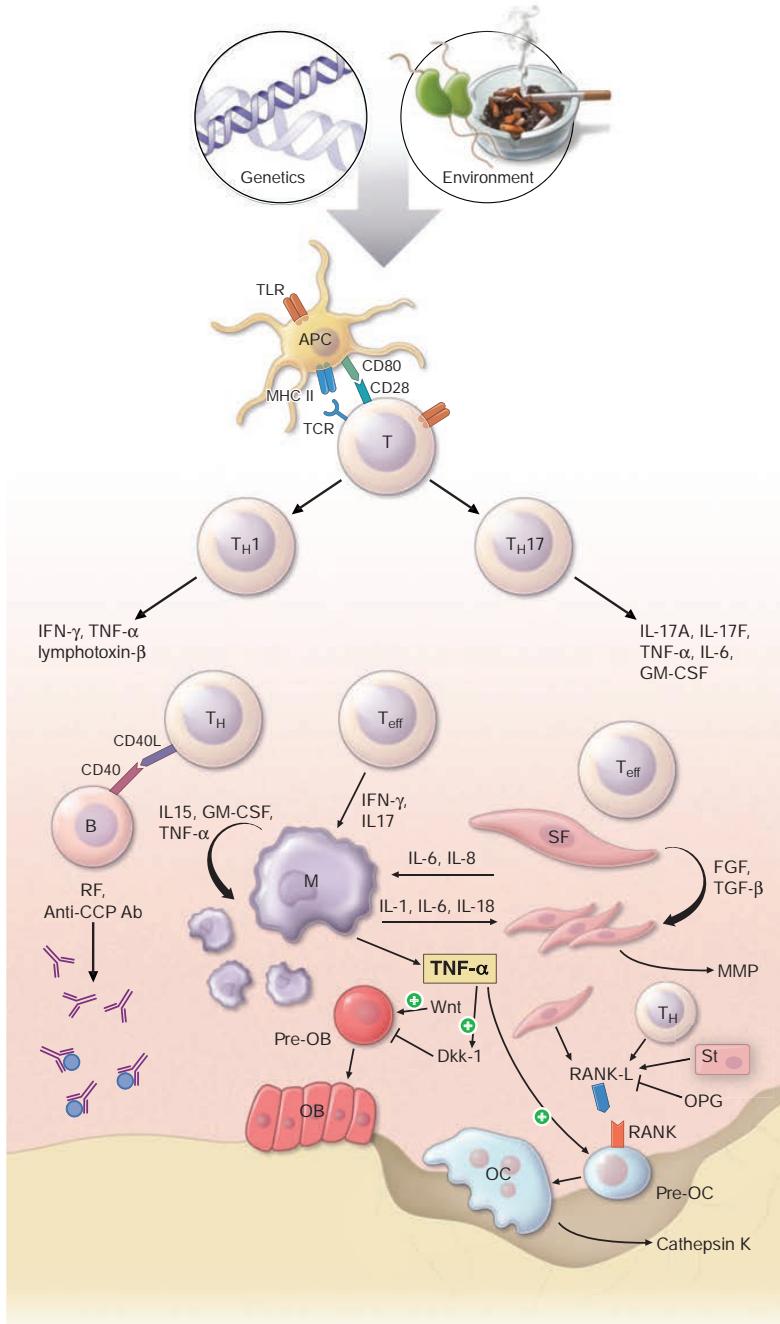


FIGURE 358-4 Pathophysiologic mechanisms of inflammation and joint destruction. Genetic predisposition along with environmental factors may trigger the development of rheumatoid arthritis (RA), with subsequent synovial T-cell activation. CD4+ T cells become activated by antigen-presenting cells (APCs) through interactions between the T-cell receptor and class II MHC-peptide antigen (signal 1) with co-stimulation through the CD28-CD80/86 pathway, as well as other pathways (signal 2). In theory, ligands binding Toll-like receptors (TLRs) may further stimulate activation of APCs inside the joint. Synovial CD4+ T cells differentiate into $T_{H}1$ and $T_{H}17$ cells, each with their distinctive cytokine profile. CD4+ T_{H} cells in turn activate B cells, some of which are destined to differentiate into autoantibody-producing plasma cells. Immune complexes, possibly comprised of rheumatoid factors (RFs) and anti-cyclic citrullinated peptides (CCP) antibodies, may form inside the joint, activating the complement pathway and amplifying inflammation. T effector cells stimulate synovial macrophages (M) and fibroblasts (SF) to secrete proinflammatory mediators, among which is tumor necrosis factor α (TNF- α). TNF- α upregulates adhesion molecules on endothelial cells, promoting leukocyte influx into the joint. It also stimulates the production of other inflammatory mediators, such as interleukin 1 (IL-1), IL-6, and granulocyte-macrophage colony-stimulating factor (GM-CSF). TNF- α has a critically important function in regulating the balance between bone destruction and formation. It upregulates the expression of dickkopf-1 (DKK-1), which can then internalize Wnt receptors on osteoblast precursors. Wnt is a soluble mediator that promotes osteoblastogenesis and bone formation. In RA, bone formation is inhibited through the Wnt pathway, presumably due to the action of elevated levels of DKK-1. In addition to inhibiting bone formation, TNF- α stimulates osteoclastogenesis. However, it is not sufficient by itself to induce the differentiation of osteoclast precursors (Pre-OC) into activated osteoclasts capable of eroding bone. Osteoclast differentiation requires the presence of macrophage colony-stimulating factor (M-CSF) and receptor activator of nuclear factor- κ B (RANKL) ligand (RANKL), which binds to RANK on the surface of Pre-OC. Inside the joint, RANKL is mainly derived from stromal cells, synovial fibroblasts, and T cells. Osteoprotegerin (OPG) acts as a decoy receptor for RANKL, thereby inhibiting osteoclastogenesis and bone loss. FGF, fibroblast growth factor; IFN, interferon; MMP, matrix metalloproteinase; TGF, transforming growth factor.

T cell-directed therapies have shown clinical efficacy in this disease. Taken together, these lines of evidence suggest that CD4+ T cells play an important role in orchestrating the chronic inflammatory response in RA. However, other cell types, such as CD8+ T cells, natural killer (NK) cells, and B cells are present in synovial tissue and may also influence pathogenic responses.

In the rheumatoid joint, by mechanisms of cell-cell contact and release of soluble mediators, activated T cells stimulate macrophages and fibroblast-like synoviocytes to generate proinflammatory mediators and proteases that drive the synovial inflammatory response and destroy the cartilage and bone. CD4+ T-cell activation is dependent on two signals: (1) T-cell receptor binding to peptide-MHC on antigen-presenting cells; and (2) CD28 binding to CD80/86 on antigen-presenting cells. This interaction then leads to downstream signals that differentiate CD4+ T cells into effector and memory cell populations, as well as activate CD8+ T cells. Certain subsets of CD4+ T cells, called T helper cells, enable B cells to differentiate into antibody-secreting cells. An earlier T cell-centric model for the pathogenesis of RA was based on a $T_{H}1$ -driven paradigm, which came from studies indicating that CD4+ T helper (T_{H}) cells differentiated into $T_{H}1$ and $T_{H}2$ subsets, each with their distinctive cytokine profiles. $T_{H}1$ cells were found to mainly produce interferon γ (IFN- γ), lymphotoxin β , and TNF- α , whereas $T_{H}2$ cells predominately secreted IL-4, IL-5, IL-6, IL-10, and IL-13. In humans, naïve T cells may be induced to differentiate into $T_{H}17$ cells by exposure to transforming growth factor β (TGF- β), IL-1, IL-6, and IL-23. Upon activation, $T_{H}17$ cells secrete a variety of proinflammatory mediators such as IL-17, IL-21, IL-22, TNF- α , IL-26, IL-6, and granulocyte-macrophage colony-stimulating factor (GM-CSF). Substantial evidence now exists from studies in both animal models and humans that IL-17 plays an important role not only in promoting joint inflammation but also in destroying cartilage and subchondral bone. However, in a phase 2 clinical trial, treatment with secukinumab, an anti-IL-17 receptor antibody, failed to produce significant clinical benefit in patients with RA.

The immune system has evolved mechanisms to counterbalance the potential harmful immune-mediated inflammatory responses provoked by infectious agents and other triggers. Among these negative regulators are regulatory T (Treg) cells, which are produced in the thymus and induced in the periphery to suppress immune-mediated inflammation. They are characterized by the surface expression of CD25 and the expression of the transcription factor forkhead box P3 (FOXP3) and the absence of CD127, the IL-7 receptor. Tregs orchestrate dominant tolerance through contact with other immune cells and secretion of inhibitory cytokines, such as TGF- β , IL-10, and IL-35. They are heterogeneous and capable of suppressing distinct classes ($T_{H}1$, $T_{H}2$, $T_{H}17$) of the immune response. In RA, the data that Treg numbers and suppressive capacity are deficient compared with normal healthy controls are contradictory and inconclusive. Some experimental evidence suggests that Treg suppressive activity is lost due to dysfunctional expression of cytotoxic T lymphocyte antigen 4 (CTLA-4). The nature of Treg defects in RA and their role in disease mechanisms remain unclear.

Cytokines, chemokines, antibodies, and endogenous danger signals bind to receptors on the surface of immune cells and stimulate a cascade of intracellular signaling events that can amplify the inflammatory response. Signaling molecules and their binding partners in these pathways are the target of small-molecule drugs designed to interfere with signal transduction and, in turn, block these reinforcing inflammatory loops. Examples of signaling molecules in these critical inflammatory pathways include Janus kinase (JAK)/signal transducers and activators of transcription (STAT), spleen tyrosine kinase (Syk), mitogen-activated protein kinases (MAPKs), and nuclear factor- κ B (NF- κ B). These pathways exhibit significant crosstalk and are found in many cell types. Some signal transducers, such as the JAKs, are expressed in hematopoietic cells and play an important role in the inflammatory response in RA.

Activated, autoreactive B cells are also important players in the chronic inflammatory response. B cells give rise to plasma cells, which in turn, produce antibodies, including RF and ACPA. RFs may

form large immune complexes inside the joint that contribute to the pathogenic process by fixing complement and promoting the release of proinflammatory cytokines and chemokines. In mouse models of arthritis, RF-containing immune complexes and ACPA-containing immune complexes synergize with other mechanisms to exacerbate the synovial inflammatory response.

RA is often considered to be a macrophage-driven disease because this cell type is the predominant source of proinflammatory cytokines inside the joint. Key proinflammatory cytokines released by synovial macrophages include TNF- α , IL-1, IL-6, IL-12, IL-15, IL-18, and IL-23. Synovial fibroblasts, the other major cell type in this microenvironment, produce the cytokines IL-1 and IL-6 as well as TNF- α . TNF- α is a pivotal cytokine in the pathobiology of synovial inflammation. It upregulates adhesion molecules on endothelial cells, promoting the influx of leukocytes into the synovial microenvironment; activates synovial fibroblasts; stimulates angiogenesis; promotes pain receptor sensitizing pathways; and drives osteoclastogenesis. Fibroblasts secrete matrix metalloproteinases (MMPs) as well as other proteases that are chiefly responsible for the breakdown of articular cartilage; they also promote inflammation and synovial proliferation by secreting cytokines such as IL-6, IL-1, IL-18, and GM-CSF, chemokines, and vascular endothelial growth factor.

Osteoclast activation at the site of the pannus is closely tied to the presence of focal bone erosion. Receptor activator of nuclear factor- κ B ligand (RANKL) is expressed by stromal cells, synovial fibroblasts, and T cells. Upon binding to its receptor RANK on osteoclast progenitors, RANKL stimulates osteoclast differentiation and bone resorption. RANKL activity is regulated by osteoprotegerin (OPG), a decoy receptor of RANKL that blocks osteoclast formation. Monocytic cells in the synovium serve as the precursors of osteoclasts and, when exposed to macrophage colony-stimulating factor (M-CSF) and RANKL, fuse to form polykaryons termed *preosteoclasts*. These precursor cells undergo further differentiation into osteoclasts with the characteristic ruffled membrane. Cytokines such as TNF- α , IL-1, IL-6, and IL-17 increase the expression of RANKL in the joint and thus promote osteoclastogenesis. Osteoclasts also secrete cathepsin K, a cysteine protease that degrades the bone matrix by cleaving collagen and contributes to generalized bone loss and osteoporosis.

Increased bone loss is only part of the story in RA, as decreased bone formation plays a crucial role in bone remodeling at sites of inflammation. Recent evidence shows that inflammation suppresses bone formation. TNF- α plays a key role in actively suppressing bone formation by enhancing the expression of dickkopf-1 (DKK-1). DKK-1 is an important inhibitor of the Wnt pathway, which acts to promote osteoblast differentiation and bone formation. The Wnt system is a family of soluble glycoproteins that binds to cell-surface receptors known as frizzled (fz) and low-density lipoprotein (LDL) receptor-related proteins (LRPs) and promotes cell growth. In animal models, increased levels of DKK-1 are associated with decreased bone formation, whereas inhibition of DKK-1 protects against structural damage in the joint. Wnt proteins also induce the formation of OPG and thereby shut down bone resorption, emphasizing their key role in tightly regulating the balance between bone resorption and formation.

DIAGNOSIS

The clinical diagnosis of RA is largely based on signs and symptoms of a chronic inflammatory arthritis, with laboratory and radiographic results providing important corroborating information. In 2010, a collaborative effort between the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) revised the 1987 ACR classification criteria for RA in an effort to improve early diagnosis with the goal of identifying patients who would benefit from early introduction of disease-modifying therapy (Table 358-1). Application of the newly revised criteria yields a score of 0–10, with a score of ≥ 6 fulfilling the requirements for definite RA. The new classification criteria differ in several ways from the older criteria set. Early clinical classifications for RA required symptoms to be present for >6 weeks. There are several conditions, including virus-related syndromes, that can cause a polyarthritis mimicking

TABLE 358-1 Classification Criteria for Rheumatoid Arthritis

		SCORE
Joint involvement	1 large joint (shoulder, elbow, hip, knee, ankle)	0
	2–10 large joints	1
	1–3 small joints (MCP, PIP, thumb IP, MTP, wrists)	2
	4–10 small joints	3
	>10 joints (at least 1 small joint)	5
Serology	Negative RF and negative ACPA	0
	Low-positive RF or low-positive anti-CCP antibodies (< 3 times ULN)	2
	High-positive RF or high-positive anti-CCP antibodies (>3 times ULN)	3
Acute-phase reactants	Normal CRP and normal ESR	0
	Abnormal CRP or abnormal ESR	1
Duration of symptoms	<6 weeks	0
	6 weeks	1

Note: These criteria are aimed at classification of newly presenting patients who have at least one joint with definite clinical synovitis that is not better explained by another disease. A score of 6 fulfills requirements for definite RA.

Abbreviations: ACPA, anti-citrullinated peptide antibodies; CCP, cyclic citrullinated peptides; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IP, interphalangeal joint; MCP, metacarpophalangeal joint; MTP, metatarsophalangeal joint; PIP, proximal interphalangeal joint; RF, rheumatoid factor; ULN, upper limit of normal.

Source: Reproduced with permission from D Aletaha et al: 2010 Rheumatoid arthritis classification criteria: An American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Arthritis Rheum* 62:2569, 2010.

RA and stimulate the transient production of RF. Such conditions usually last only 2–3 weeks. The newer criteria, however, do not mandate symptoms be present for >6 weeks. The new criteria also include as an item a positive test for serum ACPA, which carries greater specificity for the diagnosis of RA than a positive test for RF. The newer classification criteria also do not take into account whether the patient has rheumatoid nodules or radiographic joint damage because these findings occur rarely in early RA. It is important to emphasize that the 2010 ACR-EULAR criteria are “classification criteria” as opposed to “diagnostic criteria” and serve to distinguish patients at the onset of disease who have a high likelihood of evolution to chronic disease with persistent synovitis and joint damage. The presence of radiographic joint erosions or subcutaneous nodules may inform the diagnosis in the later stages of the disease. About three-fourths of patients with the clinical and radiographic features of RA test positive for RF and/or ACPA (seropositive), while the remaining one-fourth of patients with RA test negative for RF and/or ACPA (seronegative).

The differential diagnosis for RA includes all types of acute and chronic inflammatory arthritides, many of which may be differentiated from RA based on the clinical course, pattern of joint involvement, and the presence of disease in other organ systems. Patients with primary Sjögren’s syndrome whose predominate clinical manifestations are dry eyes and dry mouth often also have symptoms of polyarthralgia and may show a mild inflammatory synovitis similar to RA. Moreover, 50% of patients with primary Sjögren’s syndrome test positive for RF and therefore, may be confused with early RA. Spondyloarthropathies such as psoriatic arthritis or enteropathy-associated arthritis may present similarly to RA. However, they may be distinguished by the presence of sacroiliitis and other enthesopathic features and are generally accompanied by signs of psoriasis or inflammatory bowel disease, respectively. In elderly patients, seronegative RA may be difficult at times to distinguish from polymyalgia rheumatica (PMR). While PMR has been associated in a minority with distal limb involvement, RA may be distinguished by predominant involvement of the wrists/hands and ankles/feet in most cases. Similarly, the relatively rare condition called remitting seronegative symmetrical synovitis with pitting edema (the so-called RS3PE syndrome) and paraneoplastic syndromes may also be confused with early RA. RS3PE is typically characterized by prominent distal limb pitting edema, which is unusual in RA, and particular responsive to treatment with low doses of prednisone. Chronic tophaceous gout may mimic severe RA in some cases, and tophi may

be confused with rheumatoid nodules. Hepatitis C-related arthropathy often involves the small joints of the hands and is associated with a positive RF in about half the cases, but generally not ACPA.

LABORATORY FEATURES

Patients with systemic inflammatory diseases such as RA will often present with elevated nonspecific inflammatory markers such as an ESR or CRP. Detection of serum RF and anti-CCP antibodies is important in differentiating RA from other polyarticular diseases, although RF lacks diagnostic specificity and may be found in association with other chronic inflammatory diseases in which arthritis figures in the clinical manifestations.

IgM, IgG, and IgA isotypes of RF occur in sera from patients with RA, although the IgM isotype is the one most frequently measured by commercial laboratories. Serum IgM RF has been found in 75% of patients with RA; therefore, a negative result does not exclude the presence of this disease. It is also found in other connective tissue diseases, such as primary Sjögren’s syndrome, systemic lupus erythematosus, and type II mixed essential cryoglobulinemia, as well as chronic infections such as subacute bacterial endocarditis and hepatitis B and C. Serum RF may also be detected in 1–5% of the healthy population.

The presence of serum anti-CCP antibodies has about the same sensitivity as serum RF for the diagnosis of RA. However, its diagnostic specificity approaches 95%, so a positive test for anti-CCP antibodies in the setting of an early inflammatory arthritis is useful for distinguishing RA from other forms of arthritis. There is some incremental value in testing for the presence of both RF and anti-CCP, as some patients with RA are positive for RF but negative for anti-CCP and vice versa. The presence of RF or anti-CCP antibodies also has prognostic significance, with anti-CCP antibodies showing the most value for predicting worse outcomes.

Patients with RA may also have other antibodies associated with autoimmune disease. Approximately 30% of patients with RA test positive for antinuclear antibodies (ANAs), and some sera from some patients contain antineutrophil cytoplasmic antibodies (ANCA; particularly p-ANCA). However, patients with RA would not be expected to test positive for anti-MPO or anti-PR3 antibodies.

SYNOVIAL FLUID ANALYSIS

Typically, the cellular composition of synovial fluid from patients with RA reflects an acute inflammatory state. Synovial fluid white blood cell (WBC) counts can vary widely but generally range between 5000 and 50,000 WBC/ μL , compared with <2000 WBC/ μL for a noninflammatory condition such as osteoarthritis. In contrast to the synovial tissue, the overwhelming cell type in the synovial fluid is the neutrophil. Clinically, the analysis of synovial fluid is most useful for confirming an inflammatory arthritis (as opposed to osteoarthritis), while at the same time excluding infection or a crystal-induced arthritis such as gout or pseudogout (*Chap. 372*).

JOINT IMAGING

Joint imaging is a valuable tool not only for diagnosing RA but also for tracking progression of any joint damage. Plain x-ray is the most common imaging modality, but it is limited to visualization of the bony structures and inferences about the state of the articular cartilage based on the amount of joint space narrowing. MRI and ultrasound techniques offer the added value of detecting changes in the soft tissues such as synovitis, tenosynovitis, and effusions, as well as providing greater sensitivity for identifying bony abnormalities. Plain radiographs are usually relied upon in clinical practice for the purpose of diagnosis and monitoring of affected joints. However, in selected cases, MRI and ultrasound can provide additional diagnostic information that may guide clinical decision making. Musculoskeletal ultrasound with power Doppler is increasingly used in rheumatology clinical practice for detecting synovitis and bone erosion.

Plain Radiography Classically in RA, the initial radiographic finding is peripherally osteopenia. Practically speaking, however, this finding is difficult to appreciate on plain films and on the newer digitalized x-rays. Other findings on plain radiographs include soft tissue swelling, symmetric joint space loss, and subchondral erosions,



FIGURE 358-5 X-ray demonstrating joint space loss and erosions of carpi, metacarpophalangeal and proximal interphalangeal joints. (K Kgoebane et al: The role of imaging in rheumatoid arthritis. *SA Journal of Radiology*. S Afr J Radiol (Online) 22 (1), 2018.)

most frequently in the wrists and hands (MCPs and PIPs) and the feet (MTPs). In the feet, the lateral aspect of the fifth MTP is often targeted first, but other MTP joints may be involved at the same time. X-ray imaging of advanced RA may reveal signs of severe destruction, including joint subluxation and collapse (**Fig. 358-5**).

MRI MRI offers the greatest sensitivity for detecting synovitis and joint effusions, as well as early bone and bone marrow changes. These soft tissue abnormalities often occur before osseous changes are noted on x-ray. Presence of bone marrow edema has been recognized to be an early sign of inflammatory joint disease and can predict the subsequent development of erosions on plain radiographs as well as MRI scans. Cost and availability of MRI are the main factors limiting its routine clinical use.

Ultrasound Ultrasound, including power color Doppler, can detect more erosions than plain radiography, especially in easily accessible joints. It can also reliably detect synovitis, including increased joint vascularity indicative of inflammation. The usefulness of ultrasound is dependent on the experience of the sonographer; however, it does offer the advantages of portability, lack of radiation, and low expense relative to MRI, factors that make it attractive as a clinical tool (**Fig. 358-6**).

CLINICAL COURSE

The natural history of RA is complex and affected by a number of factors including age of onset, gender, genotype, phenotype (i.e., extraarticular manifestations or variants of RA), and comorbid conditions,

which make for a truly heterogeneous disease. There is no simple way to predict the clinical course. It is important to realize that as many as 10% of patients with inflammatory arthritis fulfilling ACR classification criteria for RA will undergo a spontaneous remission within 6 months (particularly seronegative patients). However, the vast majority of patients will exhibit a pattern of persistent and progressive disease activity that waxes and wanes in intensity over time. A minority of patients will show intermittent and recurrent explosive attacks of inflammatory arthritis interspersed with periods of disease quiescence. Finally, an aggressive form of RA may occur in an unfortunate few with inexorable progression of severe erosive joint disease, although this highly destructive course is less common in the modern treatment era.

Disability, as measured by the Health Assessment Questionnaire (HAQ), shows gradual worsening of disability over time in the face of poorly controlled disease activity and disease progression. Disability may result from both a disease activity-related component that is potentially reversible with therapy and a joint damage-related component owing to the cumulative and largely irreversible effects of soft tissue, cartilage, and bone breakdown. Early in the course of disease, the extent of joint inflammation is the primary determinant of disability, while in the later stages of disease, the amount of joint damage is the dominant contributing factor. Previous studies have shown that more than one-half of patients with RA are unable to work 10 years after the onset of their disease; however, increased employability and less work absenteeism have been reported recently with the use of newer therapies and earlier treatment intervention.

The overall mortality rate in RA is two times greater than the general population, with ischemic heart disease being the most common cause of death followed by infection. Median life expectancy is shortened by an average of 7 years for men and 3 years for women compared with control populations. Patients at higher risk for shortened survival are those with systemic extraarticular involvement, low functional capacity, low socioeconomic status, low education, and chronic prednisone use.

TREATMENT

Rheumatoid Arthritis

The amount of clinical disease activity in patients with RA reflects the overall burden of inflammation and is the variable that most influences treatment decisions. Joint inflammation is the main driver of joint damage and is the most important cause of functional disability in the early stages of disease. Several composite indices have been developed to assess clinical disease activity. The ACR 20, 50, and 70 improvement criteria (which correspond to a 20, 50, and 70% improvement, respectively, in joint counts, physician/

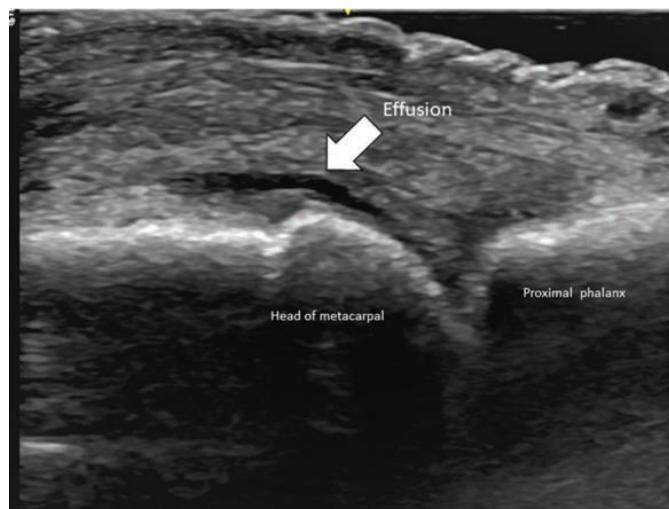


FIGURE 358-6 Ultrasound demonstrating an effusion (arrow) within the metacarpophalangeal joint. (Courtesy of Dr. Ryan Jessee.)

patient assessment of disease severity, pain scale, serum levels of acute-phase reactants [ESR or CRP], and a functional assessment of disability using a self-administered patient questionnaire) are a composite index with a dichotomous response variable. The ACR improvement criteria are commonly used in clinical trials as an endpoint for comparing the proportion of responders between treatment groups. In contrast, the Disease Activity Score (DAS), Simplified Disease Activity Index (SDAI), the Clinical Disease Activity Index (CDAI), and the Routine Assessment of Patient Index Data 3 (RAPID3) are continuous measures of disease activity that are used in clinical practice for tracking disease status and documenting treatment response.

Several developments during the past two decades have changed the therapeutic landscape in RA. They include (1) the emergence of methotrexate as the disease-modifying antirheumatic drug (DMARD) of first choice for the treatment of early RA; (2) the development of novel highly efficacious biologicals that can be used alone or in combination with methotrexate; and (3) the proven superiority of combination DMARD regimens over methotrexate alone. The medications used for the treatment of RA may be divided into broad categories: nonsteroidal anti-inflammatory drugs (NSAIDs); glucocorticoids, such as prednisone and methylprednisolone; conventional DMARDs; and biologic DMARDs (**Table 358-2**). Although disease for some patients with RA is managed adequately with a single DMARD, such as methotrexate, it demands in most cases the use of a combination DMARD regimen that may vary in its components over the treatment course depending on fluctuations in disease activity and emergence of drug-related toxicities and comorbidities.

NSAIDS

NSAIDs were formerly viewed as the core of RA therapy, but they are now considered to be adjunctive agents for management of symptoms uncontrolled by other measures. NSAIDs exhibit both analgesic and anti-inflammatory properties. The anti-inflammatory effects of NSAIDs derive from their ability to nonselectively inhibit cyclooxygenase (COX)-1 and COX-2. Although the results of clinical trials suggest that NSAIDs are roughly equivalent in their efficacy, experience suggests that some individuals may preferentially respond to a particular NSAID. Chronic use should be minimized due to the possibility of side effects, including gastritis and peptic ulcer disease as well as impairment of renal function.

GLUCOCORTICOIDS

Glucocorticoids may serve in several ways to control disease activity in RA. First, they may be administered in low to moderate doses to achieve rapid disease control before the onset of fully effective DMARD therapy, which often takes several weeks or even months. Second, a 1- to 2-week burst of glucocorticoids may be prescribed for the management of acute disease flares, with dose and duration guided by the severity of the exacerbation. Chronic administration of low doses (5–10 mg/d) of prednisone (or its equivalent) may also be warranted to control disease activity in patients with an inadequate response to DMARD therapy. As much as possible, chronic glucocorticoid therapy should be avoided in favor of finding an effective DMARD that adequately controls the disease. Best practices minimize chronic use of low-dose prednisone therapy owing to the risk of osteoporosis and other long-term complications; however, the use of chronic prednisone therapy is unavoidable in some cases. High-dose glucocorticoids may be necessary for the treatment of severe extraarticular manifestations of RA, such as ILD. Finally, if a patient exhibits one or a few actively inflamed joints, the clinician may consider intraarticular injection of an intermediate-acting glucocorticoid such as triamcinolone acetonide. This approach may allow for rapid control of inflammation in a limited number of affected joints. Caution must be exercised to appropriately exclude joint infection as it often mimics an RA flare.

Osteoporosis ranks as an important long-term complication of chronic prednisone use. Based on a patient's risk factors, including

total prednisone dosage, length of treatment, gender, race, and bone density, treatment with a bisphosphonate may be appropriate for primary prevention of glucocorticoid-induced osteoporosis. Other agents, including teriparatide and denosumab, have been approved for the treatment of osteoporosis and may be indicated in certain cases. Although prednisone use is known to increase the risk of peptic ulcer disease, especially with concomitant NSAID use, no evidence-based guidelines have been published regarding the use of gastrointestinal ulcer prophylaxis in this situation.

DMARDs

DMARDs are so named because of their ability to slow or prevent structural progression of RA. The conventional DMARDs include hydroxychloroquine, sulfasalazine, methotrexate, and leflunomide; they exhibit a delayed onset of action of ~6–12 weeks. Methotrexate is the DMARD of choice for the treatment of RA and is the anchor drug for most combination therapies. It was approved for the treatment of RA in 1988 and remains the benchmark for the efficacy and safety of new disease-modifying therapies. At the dosages used for the treatment of RA, methotrexate has been shown to stimulate adenosine release from cells, producing an anti-inflammatory effect. Methotrexate is administered weekly by the oral or subcutaneous route. Folic acid is taken as co-therapy to mitigate some of methotrexate's side effects. The clinical efficacy of leflunomide, an inhibitor of pyrimidine synthesis, appears similar to that of methotrexate; it has been shown in well-designed trials to be effective for the treatment of RA as monotherapy or in combination with methotrexate and other DMARDs.

Although similar to the other DMARDs in its slow onset of action, hydroxychloroquine has not been shown to delay radiographic progression of disease and thus is not considered to be a true DMARD. In clinical practice, hydroxychloroquine is generally used for treatment of early, mild disease or as adjunctive therapy in combination with other DMARDs. It is a prescribed at a dosage of 5 mg/kg of body weight or less to decrease the risk of retinal toxicity. Sulfasalazine is used in a similar manner and has been shown in randomized, controlled trials to reduce radiographic progression of disease. Minocycline, gold salts, penicillamine, azathioprine, and cyclosporine have all been used for the treatment of RA with varying degrees of success; however, they are used sparingly now due to their inconsistent clinical efficacy or unfavorable toxicity profile.

BIOLOGICALS

Biologic DMARDs have revolutionized the treatment of RA over the past decade (Table 358-2). They are protein therapeutics designed mostly to target cytokines and cell-surface molecules. The TNF inhibitors were the first biologics approved for the treatment of RA. Anakinra, an IL-1 receptor antagonist, was approved shortly thereafter; however, its benefits have proved to be relatively modest compared with the other biologics, and therefore, this biological is rarely used for the treatment of RA with the availability of other more effective agents. Abatacept, rituximab, and tocilizumab are the newest members of this class.

Anti-TNF Agents The development of TNF inhibitors was originally spurred by the experimental finding that TNF- α is a critical upstream mediator of joint inflammation. Currently, five agents that inhibit TNF- α are approved for the treatment of RA. There are three different anti-TNF monoclonal antibodies. Infliximab is a chimeric (part mouse and human) monoclonal antibody, whereas adalimumab and golimumab are humanized monoclonal antibodies. Certolizumab pegol is a pegylated Fab' fragment of a humanized monoclonal antibody to TNF- α . Lastly, etanercept is a soluble fusion protein comprising the TNF receptor 2 in covalent linkage with the Fc portion of IgG1. All of the TNF inhibitors have been shown in randomized controlled clinical trials to reduce the signs and symptoms of RA, slow radiographic progression of joint damage, and improve physical function and quality of life. Anti-TNF drugs are typically used in combination with background methotrexate therapy. This combination regimen, which affords

TABLE 358-2 DMARDs Used for the Treatment of Rheumatoid Arthritis

DRUG	DOSAGE	SERIOUS TOXICITIES	OTHER COMMON SIDE EFFECTS	INITIAL EVALUATION	MONITORING
Hydroxychloroquine	200–400 mg/d orally (5 mg/kg)	Irreversible retinal damage Cardiotoxicity Blood dyscrasia	Nausea Diarrhea Headache Rash	Eye examination if >40 years old or prior ocular disease	Optical coherence tomography and visual field testing every 12 months
Sulfasalazine	Initial: 500 mg orally twice daily Maintenance: 1000–1500 mg twice daily	Granulocytopenia Hemolytic anemia (with G6PD deficiency)	Nausea Diarrhea Headache	CBC, LFTs G6PD level	CBC every 2–4 weeks for first 3 months, then every 3 months
Methotrexate	10–25 mg/week orally or SQ Folic acid 1 mg/d to reduce toxicities	Hepatotoxicity Myelosuppression Infection Interstitial pneumonitis Pregnancy category X	Nausea Diarrhea Stomatitis/mouth ulcers Alopecia Fatigue	CBC, LFTs Viral hepatitis panel ^a Chest x-ray	CBC, creatinine, LFTs every 2–3 months
Leflunomide	10–20 mg/d	Hepatotoxicity Myelosuppression Infection Pregnancy category X	Alopecia Diarrhea	CBC, LFTs Viral hepatitis panel ^a	CBC, creatinine, LFTs every 2–3 months
TNF- α inhibitors	Infliximab: 3 mg/kg IV at weeks 0, 2, 6, then every 8 weeks. May increase dose up to 10 mg/kg every 4 weeks Etanercept: 50 mg SQ weekly, or 25 mg SQ biweekly Adalimumab: 40 mg SQ every other week Golimumab: 50 mg SQ monthly Certolizumab: 400 mg SQ weeks 0, 2, 4, then 200 mg every other week	↑ Risk bacterial, fungal infections Reactivation of latent TB ↑ Lymphoma risk (controversial) Drug-induced lupus Neurologic deficits As above As above As above As above	Infusion reaction ↑ LFTs Injection site reaction Injection site reaction Injection site reaction Injection site reaction	Tuberculosis screening ^b	LFTs periodically Monitor for injection site reactions Monitor for injection site reactions Monitor for injection site reactions Monitor for injection site reactions Monitor for injection site reactions
Abatacept	Weight based: <60 kg: 500 mg 60–100 kg: 750 mg >100 kg: 1000 mg IV dose at weeks 0, 2, and 4, and then every 4 weeks OR 125 mg SQ weekly	↑ Risk bacterial, viral infections	Headache Nausea	Tuberculosis screening	Monitor for infusion reactions
Anakinra	100 mg SQ daily	↑ Risk bacterial, viral infections Reactivation of latent TB Neutropenia	Injection site reaction Headache	Tuberculosis screening CBC with differential	CBC every month for 3 months, then every 4 months for 1 year Monitor for injection site reactions
Rituximab	1000 mg IV \times 2, days 0 and 14 May repeat course every 24 weeks or more Premedicate with methylprednisolone 100 mg to decrease infusion reaction	↑ Risk bacterial, viral infections Infusion reaction Cytopenia Hepatitis B reactivation	Rash Fever	CBC Viral hepatitis panel ^a	CBC at regular intervals
Interleukin-6 inhibitors	Tocilizumab: 4–8 mg/kg IV monthly OR 162 mg SQ every other week (<100 kg weight) 162 mg SQ every week (100 kg weight) Sarilumab: 200 mg SQ every other week	Risk of infection Infusion reaction LFT elevation Dyslipidemia Cytopenias		Tuberculosis screening	CBC and LFTs at regular intervals

(Continued)

TABLE 358-2 DMARDs Used for the Treatment of Rheumatoid Arthritis (Continued)

DRUG	DOSAGE	SERIOUS TOXICITIES	OTHER COMMON SIDE EFFECTS	INITIAL EVALUATION	MONITORING
JAK inhibitors	Tofacitinib: 5 mg orally twice daily OR 11 mg orally daily Upadacitinib: 15 mg orally daily Baricitinib: 2 mg orally daily	Risk of infection LFT elevation Dyslipidemia Neutropenia Thrombosis	Upper respiratory tract infections Diarrhea Headache Nasopharyngitis	Tuberculosis screening	CBC, LFTs, and lipids at regular intervals

^aViral hepatitis panel: hepatitis B surface antigen, hepatitis C viral antibody. ^bTuberculosis screening can be performed using a Mantoux tuberculin skin test or blood interferon-gamma release assay.

Abbreviations: CBC, complete blood count; DMARDs, disease-modifying antirheumatic drugs; G6PD, glucose-6-phosphate dehydrogenase; IV, intravenous; LFTs, liver function tests; JAK, Janus kinase; SQ, subcutaneous; TB, tuberculosis.

maximal benefit in many cases, is often the next step for treatment of patients with an inadequate response to methotrexate therapy. Etanercept, adalimumab, certolizumab pegol, and golimumab have also been approved for use as monotherapy.

Anti-TNF agents should be avoided in patients with active infection or a history of hypersensitivity to these agents and are contraindicated in patients with chronic hepatitis B infection or class III/IV congestive heart failure. The major concern is the increased risk for infection, including serious bacterial infections, opportunistic fungal infection, and reactivation of latent tuberculosis. For this reason, all patients are screened for latent tuberculosis according to national guidelines prior to starting anti-TNF therapy (Chap. 178). In the United States, patients have historically been skin tested for tuberculosis using an intradermal injection of purified protein derivative (PPD); individuals with skin reactions of >5 mm are presumed to have had previous exposure to tuberculosis and are evaluated for active disease and treated accordingly. Use of an IFN- γ release assay may also be appropriate for screening as some data suggest a lower rate of false-negative and false-positive tests with an IFN- γ release assay compared with skin testing with PPD in patients treated with corticosteroids. While a combination of PPD skin test and IFN- γ release assay may offer the highest sensitivity for screening purposes, no consensus guidelines exist.

Anakinra Anakinra is the recombinant form of the naturally occurring IL-1 receptor antagonist. Although anakinra has seen limited use for the treatment of RA, it has enjoyed a resurgence of late as an effective therapy of systemic juvenile-onset inflammatory arthritis and adult Still's disease and some rare inherited syndromes dependent on IL-1 production, including neonatal-onset inflammatory disease, Muckle-Wells syndrome, familial cold urticaria, and macrophage activation syndrome.

Abatacept Abatacept is a soluble fusion protein consisting of the extracellular domain of human CTLA-4 linked to the modified portion of human IgG. It inhibits the co-stimulation of T cells by blocking CD28-CD80/86 interactions and may also inhibit the function of antigen-presenting cells by reverse signaling through CD80 and CD86. Abatacept has been shown in clinical trials to reduce disease activity, slow radiographic progression of damage, and improve functional disability. Many patients receive abatacept in combination with a conventional DMARD. Abatacept therapy has been associated with an increased risk of infection.

Rituximab Rituximab is a chimeric monoclonal antibody directed against CD20, a cell-surface molecule expressed by most mature B lymphocytes. It works by depleting B cells, which in turn, leads to a reduction in the inflammatory response by unknown mechanisms. These mechanisms may include a reduction in autoantibodies, inhibition of T-cell activation, and alteration of cytokine production. Rituximab has been approved for the treatment of refractory RA (failure of treatment with a TNF- α inhibitor) in combination with

methotrexate and has been shown to be more effective for patients with seropositive than seronegative disease. Rituximab therapy has been associated with mild to moderate infusion reactions as well as an increased risk of infection. Notably, there have been rare isolated reports of a potentially lethal brain disorder, progressive multifocal leukoencephalopathy (PML), in association with rituximab therapy, although the absolute risk of this complication appears to be very low in patients with RA. Most of these cases have occurred on a background of previous or current exposure to other potent immunosuppressive drugs.

Anti-IL-6 Agents IL-6 is a proinflammatory cytokine implicated in the pathogenesis of RA, with effects on both joint inflammation and damage. IL-6 binding to its receptor activates intracellular signaling pathways that affect the acute-phase response, cytokine production, and osteoclast activation. Tocilizumab and sarilumab are both monoclonal antibodies directed against the membrane and soluble forms of the IL-6 receptor. Clinical trials attest to the clinical efficacy of these therapies for RA, both as monotherapy and in combination with methotrexate and other DMARDs. Anti-IL-6 receptor agents have been associated with an increased risk of infection, neutropenia, and thrombocytopenia; the hematologic abnormalities appear to be reversible upon stopping the drug. In addition, this agent has been shown to increase LDL cholesterol. However, it is not known if this effect on lipid levels increases the risk for development of atherosclerotic disease.

TARGETED SYNTHETIC DMARDS

Because some patients do not adequately respond to conventional DMARDs or biologic therapy, other therapeutic targets have been investigated to fill this gap. Recently, drug development in RA has focused attention on the intracellular signaling pathways that transduce the positive signals of cytokines and other inflammatory mediators binding to their cell-surface receptors that create the positive feedback loops in the immune response. These targeted synthetic DMARDs aim to provide the same efficacy as biological therapies in an oral formulation.

JAK Inhibitors Although several different kinases have been evaluated as potential treatment targets in RA, only JAK inhibitors have demonstrated safety and efficacy for the treatment of RA; they are classified as targeted synthetic (ts) DMARDs. The JAK family comprises four members (JAK1, JAK2, JAK3, and tyrosine kinase 2 [Tyk2]) that link extracellular cytokine receptors with intracellular signaling domains. They mediate signaling of the receptors for the common γ -chain-related cytokines IL-2, -4, -7, -9, -15, and -21, as well as IFN- γ and IL-6. These cytokines all play roles in promoting T- and B-cell activation as well as inflammation.

Tofacitinib is a selective JAK1 and JAK3 inhibitor with minor inhibitory effects on JAK2 and Tyk2, whereas baricitinib is a selective JAK1 and JAK2 inhibitor with moderate inhibition of Tyk2 and minimal inhibition of JAK3. Upadacitinib is a predominately

selective inhibitor of JAK1. It has been hypothesized that preferential inhibition of JAK1 might reduce dose-related toxicity, without a significant detriment of its efficacy. JAK inhibitors can be used as monotherapy or in combination with methotrexate. Possible side effects of these agents include elevated serum transaminases indicative of liver injury, neutropenia, increased cholesterol levels, and elevation in serum creatinine. Recent studies have found an increased risk of thrombosis, major adverse cardiovascular events and malignancies in patients taking tofacitinib compared with TNF inhibitors. Its use is also associated with an increased risk of infections, including bacterial infections and herpes zoster.

TREATMENT OF EXTRAARTICULAR MANIFESTATIONS

In general, treatment of the underlying RA favorably modifies extraarticular manifestations, and it appears that aggressive management of early disease can potentially prevent their occurrence in the first place. RA-ILD, however, can be particularly challenging to treat because some of the DMARDs used for the treatment of RA are associated with pulmonary toxicity, such as methotrexate and leflunomide. High doses of corticosteroids and adjunctive immunosuppressive agents, such as azathioprine, mycophenolate mofetil, and rituximab have been used for treatment of RA-ILD.

APPROACH TO THE PATIENT

Rheumatoid Arthritis

The treatment of RA adheres to the following principles and goals: (1) early, aggressive therapy to prevent joint damage and disability; (2) frequent modification of DMARD therapy to achieve treatment goals with utilization of combination therapy where appropriate; (3) individualization of DMARD therapy in an attempt to maximize response and minimize side effects; (4) minimal use of long-term glucocorticoid therapy; and (5) achieving, whenever possible, low disease activity or clinical remission. A considerable amount of evidence supports this intensive treatment approach.

As mentioned earlier, methotrexate is the DMARD of first choice for initial treatment of moderate to severe RA. Failure to achieve adequate improvement with methotrexate therapy calls for a change in DMARD therapy, usually a transition to an effective combination regimen. Effective combinations include methotrexate, sulfasalazine, and hydroxychloroquine (oral triple therapy); methotrexate and leflunomide; and methotrexate plus a biological. The combination of methotrexate and an anti-TNF agent, for example, has been shown in randomized controlled trials to be superior to methotrexate alone, not only for reducing signs and symptoms of disease but also for retarding the progression of structural joint damage. Predicting which patients are at higher risk for developing radiologic joint damage is imprecise at best, although some factors such as an elevated serum level of acute-phase reactants, high burden of joint inflammation, and the presence of erosive disease are associated with increased likelihood of developing structural injury.

In 2015, the ACR updated and published their guidelines for the treatment of RA. They do make a distinction in the treatment of patients with early (<6 months of disease duration) and established disease and highlight the use of a treat-to-target approach and the need to switch or add therapies for worsening or persistent moderate/high disease activity. For example, in patients with early RA who have persistent moderate/high disease activity on DMARD monotherapy, providers should consider escalation to combination DMARD therapy or switching to an anti-TNF +/- methotrexate or a non-TNF biologic +/- methotrexate. Since a more intensive initial approach (e.g., combination DMARD therapy) has been shown to produce superior long-term outcomes compared with starting methotrexate alone, the usual approach is to begin with methotrexate and rapidly step up (e.g., after 3–6 months) to a combination of DMARDs or an anti-TNF or non-TNF biological agent in the absence of an adequate therapeutic response.

TABLE 358-3 ACR/EULAR Provisional Definition of Remission in Rheumatoid Arthritis

At any time point, patient must satisfy all of the following:

- Tender joint count 1
- Swollen joint count 1
- C-reactive protein 1 mg/dL
- Patient global assessment 1 (on a 0–10 scale)

OR

At any time point, patient must have a Simplified Disease Activity Index score of 3.3

Abbreviations: ACR, American College of Rheumatology; EULAR, European League Against Rheumatism.

Source: Reproduced with permission from DT Felson et al; American College of Rheumatology/European League Against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. *Arthritis Rheum* 63:573, 2011.

Some patients may not respond to an anti-TNF drug or may be intolerant of its side effects. Initial responders to an anti-TNF agent who later experience worsening of their condition may benefit from switching to another anti-TNF agent or an alternative biological with a different mechanism of action. Indeed, some studies suggest that switching to an alternative biological such as abatacept is more effective than switching to another anti-TNF drug. Unacceptable toxicity from an anti-TNF agent may also call for switching to another biological or tsDMARD with a different mechanism of action or a conventional DMARD regimen.

Studies have also shown that oral triple therapy (hydroxychloroquine, methotrexate, and sulfasalazine) may be used effectively for the treatment of early RA. Treatment may be initiated with methotrexate alone and, lacking an adequate treatment response, followed within 6 months by a step-up to oral triple therapy.

A clinical state defined as low disease activity or remission is the optimal goal of therapy, although most patients never achieve complete remission despite every effort to achieve it. Composite indices, such as the Disease Activity Score-28 (DAS-28), are useful for classifying states of low disease activity and remission; however, they are imperfect tools due to the limitations of the clinical joint examination in which low-grade synovitis may escape detection. Complete remission has been stringently defined as the total absence of all articular and extraarticular inflammation and immunologic activity related to RA. However, evidence for this state can be difficult to demonstrate in clinical practice. In an effort to standardize and simplify the definition of remission for clinical trials, the ACR and EULAR developed two provisional operational definitions of remission in RA (**Table 358-3**). A patient may be considered in remission if the patient (1) meets all the clinical and laboratory criteria listed in Table 358-3 or (2) has a composite SDAI score of <3.3. The SDAI is calculated by taking the sum of a tender joint and swollen joint count (using 28 joints), patient global assessment (0–10 scale), physician global assessment (0–10 scale), and CRP (in mg/dL). This definition of remission does not take into account the possibility of subclinical synovitis or that damage alone may produce a tender or swollen joint. Ignoring the semantics of these definitions, the aforementioned remission criteria are nonetheless useful for setting a level of disease control that will likely result in minimal or no progression of structural damage and disability.

PHYSICAL ACTIVITY AND ASSISTIVE DEVICES

In principle, all patients with RA should receive a prescription for exercise and physical activity. Dynamic strength training, community-based comprehensive physical therapy, and physical-activity coaching (emphasizing achieving 150 min of moderate-to-vigorous physical activity per week) have all been shown to improve muscle strength and perceived health status, as well as improve DAS-28 scores and inflammatory markers. Foot orthotics for painful valgus deformity decrease foot pain and may reduce disability and functional limitations. Judicious use of wrist splints can also decrease

pain; however, their benefits may be offset by decreased dexterity and variably curb grip strength.

SURGERY

Surgical procedures may improve pain and disability in RA with varying degrees of reported long-term success—most notably the hands, wrists, and feet. For large joints, such as the knee, hip, shoulder, or elbow, the preferred option for advanced joint disease may be total joint arthroplasty. A few surgical options exist for dealing with the smaller hand joints. Silicone implants are the most common prosthetic for MCP arthroplasty and are generally implanted in patients with severe decreased arc of motion, marked flexion contractures, MCP joint pain with radiographic abnormalities, and severe ulnar drift. Arthrodesis and total wrist arthroplasty are reserved for patients with severe disease who have substantial pain and functional impairment. These two procedures appear to have equal efficacy in terms of pain control and patient satisfaction. Numerous surgical options exist for correction of hallux valgus in the forefoot, including arthrodesis and arthroplasty, as well as primarily arthrodesis for refractory hindfoot pain.

OTHER MANAGEMENT CONSIDERATIONS

Pregnancy Up to 75% of female RA patients will note overall improvement in symptoms during pregnancy but often will flare after delivery. Flares during pregnancy are generally treated with low doses of prednisone; hydroxychloroquine and sulfasalazine are probably the safest DMARDs to use during pregnancy. Methotrexate and leflunomide therapy are contraindicated during pregnancy due to their teratogenicity in animals and humans. The experience with biologic agents has been insufficient to make specific recommendations for their use during pregnancy. Many patients will discontinue biologic agents during pregnancy; however, active inflammatory disease is associated with worse pregnancy outcomes, and thus controlling disease activity may take precedence. In general, biologics are thought to be safe through the second trimester.

Elderly Patients RA presents in up to one-third of patients after the age of 60; however, older individuals may receive less aggressive treatment due to concerns about increased risks of drug toxicity. Studies suggest that conventional DMARDs and biological agents are equally effective and safe in younger and older patients. Due to comorbidities, many elderly patients have an increased risk of infection. Aging also leads to a gradual decline in renal function that may raise the risk for side effects from NSAIDs and some DMARDs, such as methotrexate. Renal function must be taken into consideration before prescribing methotrexate, which is mostly cleared by the kidneys. To reduce the risks of side effects, methotrexate doses may need to be adjusted downward for the drop in renal function that usually comes with the seventh and eighth decades of life. Methotrexate is usually not prescribed for patients with a serum creatinine >2 mg/dL.

GLOBAL CHALLENGES

Developing countries are finding an increase in the incidence of non-communicable, chronic diseases such as diabetes, cardiovascular disease, and RA in the face of ongoing poverty, rampant infectious disease, and poor access to modern health care facilities. In these areas, patients tend to have a greater delay in diagnosis and limited access to specialists and, thus, greater disease activity and disability at presentation. In addition, infection risk remains a significant issue for the treatment of RA in developing countries because of the immunosuppression associated with the use of glucocorticoids and most DMARDs. For example, in some developing countries, patients undergoing treatment for RA have a substantial increase in the incidence of tuberculosis, which demands the implementation of far more comprehensive screening practices and liberal use of isoniazid prophylaxis than in developed countries. The increased prevalence of hepatitis B and C, as well as human immunodeficiency virus (HIV), in these developing countries

also poses challenges. Reactivation of viral hepatitis has been observed in association with some of the DMARDs, such as rituximab. Also, reduced access to antiretroviral therapy may limit the control of HIV infection and therefore the choice of DMARD therapies.

Despite these challenges, one should attempt to initiate early treatment of RA in the developing countries with the resources at hand. Hydroxychloroquine, sulfasalazine, and methotrexate are all reasonably accessible throughout the world where they can be used as both monotherapy and in combination with other drugs. The use of biological agents is increasing in the developed countries as well as in other areas around the world, although their use is limited by high cost; national protocols restrict their use, and concerns remain about the risk for opportunistic infections.

SUMMARY

Improved understanding of the pathogenesis of RA and its treatment has dramatically revolutionized the management of this disease. The outcomes of patients with RA are vastly superior to those of the prebiologic modifier era; more patients than in years past are able to avoid significant disability and continue working, albeit with some job modifications in many cases. The need for early and aggressive treatment of RA as well as frequent follow-up visits for monitoring of drug therapy has implications for our health care system. Primary care physicians and rheumatologists must be prepared to work together as a team to reach the ambitious goals of best practice. In many settings, rheumatologists have reengineered their practice in a way that places high priority on consultations for any new patient with early inflammatory arthritis.

The therapeutic regimens for RA are becoming increasingly complex with the rapidly expanding armamentarium. Patients receiving these therapies must be carefully monitored by both the primary care physician and the rheumatologist to minimize the risk of side effects and identify quickly any complications of chronic immunosuppression. Also, prevention and treatment of RA-associated conditions such as ischemic heart disease and osteoporosis will likely benefit from a team approach owing to the value of multidisciplinary care.

Research will continue to search for new therapies with superior efficacy and safety profiles and investigate treatment strategies that can bring the disease under control more rapidly and nearer to remission. However, prevention and cure of RA will likely require new breakthroughs in our understanding of disease pathogenesis. Several prevention trials in RA are currently underway and focus on a variety of prevention strategies in individuals who have serologic and/or clinical features at higher risk than the general population for developing RA. Equally important is the identification of predictive biomarkers that enable a personalized approach to DMARD therapy for RA.

FURTHER READING

- Aletaha D, Smolen JS: Diagnosis and management of rheumatoid arthritis: A review. *JAMA* 320:1360, 2018.
- Catrina AI et al: Lungs, joints and immunity against citrullinated proteins in rheumatoid arthritis. *Nat Rev Rheumatol* 10:645, 2014.
- Erickson AR et al: Clinical features of rheumatoid arthritis, in *Kelley and Firestein's Textbook of Rheumatology*, 10th ed, Firestein GS et al (eds). Philadelphia, Elsevier, 2017, pp 1167–1186.
- Karimi J et al: Genetic implications in the pathogenesis of rheumatoid arthritis; an updated review. *Gene* 702:8, 2019.
- McInnes IB, Schett G: The pathogenesis of rheumatoid arthritis. *N Engl J Med* 365:2205, 2011.
- Morel and LW et al: A randomized comparative effectiveness study of oral triple therapy versus methotrexate plus etanercept in early aggressive rheumatoid arthritis: The Treatment of Early Aggressive Rheumatoid Arthritis Trial. *Arthritis Rheum* 64:2824, 2012.
- Singh JA et al: 2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. *Arthritis Rheumatol* 68:1, 2016.

Acute rheumatic fever (ARF) is a multisystem disease resulting from an autoimmune reaction to infection with group A *Streptococcus*. Although many parts of the body may be affected, almost all of the manifestations resolve completely. The major exception is cardiac valvular damage (rheumatic heart disease [RHD]), which may persist after the other features have disappeared.

GLOBAL CONSIDERATIONS

ARF and RHD are diseases of poverty. They were common in all countries until the early twentieth century, when their incidence began to decline in industrialized nations. This decline was largely attributable to improved living conditions—particularly less crowded housing and better hygiene—which resulted in reduced transmission of group A streptococci. The introduction of antibiotics and improved systems of medical care had a supplemental effect.

The virtual disappearance of ARF and reduction in the incidence of RHD in industrialized countries during the first half of the twentieth century unfortunately was not replicated in developing countries, where these diseases continue unabated. RHD is the most common cause of acquired heart disease in children in developing countries and is a major cause of mortality and morbidity in adults as well. It has

been estimated that between 29.7 and 43.1 million people worldwide are affected by RHD, with >300,000 deaths occurring each year. Some 95% of ARF cases and RHD deaths now occur in developing countries, with particularly high rates in sub-Saharan Africa, Pacific nations, Australasia, and South and Central Asia. The pathogenetic pathway from exposure to group A *Streptococcus* followed by pharyngeal or superficial skin infection and subsequent development of ARF, ARF recurrences, and development of RHD and its complications is associated with a range of risk factors and, therefore, potential interventions at each point (Fig. 359-1). In affluent countries, many of these risk factors are well controlled, and where needed, interventions are in place. Unfortunately, the greatest burden of disease is found in developing countries, most of which do not have the resources, capacity, and/or interest to tackle this multifaceted disease. In particular, few developing countries have a coordinated, register-based RHD control program, which is proven to be cost-effective in reducing the burden of RHD. Enhancing awareness of RHD and mobilizing resources for its control in developing countries are issues requiring international attention.

EPIDEMIOLOGY

ARF is mainly a disease of children age 5–14 years. Initial episodes become less common in older adolescents and young adults and are rare in persons aged >30 years. By contrast, recurrent episodes of ARF remain relatively common in adolescents and young adults. This pattern contrasts with the prevalence of RHD, which peaks between 25 and 40 years. There is no clear gender association for ARF, but RHD more commonly affects females, sometimes up to twice as frequently as males.

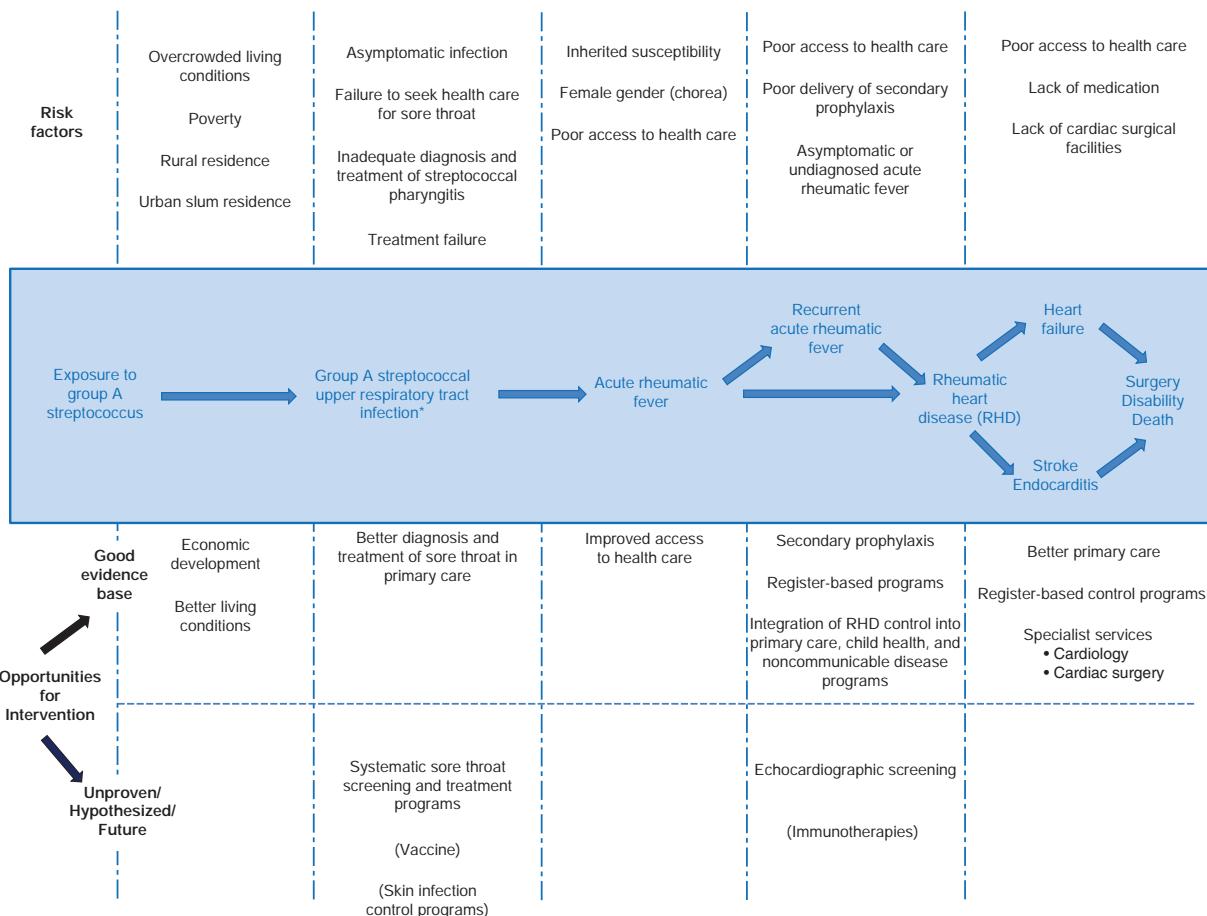


FIGURE 359-1 Pathogenetic pathway for acute rheumatic fever and rheumatic heart disease (RHD), with associated risk factors and opportunities for intervention at each step. Interventions in parentheses are either unproven or currently unavailable.

PATHOGENESIS

ORGANISM FACTORS

Conventional teaching has it that ARF is exclusively caused by infection of the upper respiratory tract with group A streptococci ([Chap. 148](#)). Although classically, certain M-serotypes (particularly types 1, 3, 5, 6, 14, 18, 19, 24, 27, and 29) were associated with ARF, recent evidence demonstrates that many more M-serotypes are rheumatogenic and that so-called “rheumatogenic motifs” are found in only a minority of serotypes associated with rheumatic fever. This epidemiologic evidence also points to a clear role of skin infection in the pathogenesis of ARF. The potential role of groups C and G streptococci is unclear at this time.

HOST FACTORS

Based on epidemiologic evidence, ~3–6% of any population may be susceptible to ARF, and this proportion does not vary dramatically between populations. Findings of familial clustering of cases and concordance in monozygotic twins—particularly for chorea—confirm that susceptibility to ARF is an inherited characteristic, with 44% concordance in monozygotic twins compared to 12% in dizygotic twins and heritability more recently estimated at 60%. Most evidence for host factors focuses on immunologic determinants. Some human leukocyte antigen (HLA) class II alleles, particularly HLA-DR7 and HLA-DR4, appear to be associated with susceptibility, whereas other class II alleles have been associated with protection (HLA-DR5, HLA-DR6, HLA-DR51, HLA-DR52, and HLA-DQ). Associations have also been described with polymorphisms at the tumor necrosis factor α locus (TNF- α -308 and TNF- α -238), high levels of circulating mannose-binding lectin, and Toll-like receptors. Recent genome-wide association studies in different populations have identified connections at the HLA region, particularly HLA-DQA1 to HLA-DQB1, and the immunoglobulin heavy chain locus.

THE IMMUNE RESPONSE

The most widely accepted theory of rheumatic fever pathogenesis is based on the concept of molecular mimicry, whereby an immune response targeted at streptococcal antigens (mainly thought to be on the M protein and the N-acetylglucosamine of group A streptococcal carbohydrate) also recognizes human tissues. In this model, cross-reactive antibodies bind to endothelial cells on the heart valve, leading to activation of the adhesion molecule VCAM-1, with resulting recruitment of activated lymphocytes and lysis of endothelial cells in the presence of complement. The latter leads to release of peptides including laminin, keratin, and tropomyosin, which, in turn, activates cross-reactive T cells that invade the heart, amplifying the damage and causing epitope spreading. An alternative hypothesis proposes that the initial damage is due to streptococcal invasion of epithelial surfaces, with binding of M protein to type IV collagen allowing it to become immunogenic, but not through the mechanism of molecular mimicry.

CLINICAL FEATURES

There is a latent period of ~3 weeks (1–5 weeks) between the precipitating group A streptococcal infection and the appearance of the clinical features of ARF. The exceptions are chorea and indolent carditis, which may follow prolonged latent periods lasting up to 6 months. Although many patients report a prior sore throat, the preceding group A streptococcal infection is commonly subclinical; in these cases, it can only be confirmed using streptococcal antibody testing. The most common clinical features are polyarthritis (present in 60–75% of cases) and carditis (50–75%). The prevalence of chorea in ARF varies substantially between populations, ranging from <2 to 30%. Erythema marginatum and subcutaneous nodules are now rare, being found in <5% of cases.

HEART INVOLVEMENT

Up to 75% of patients with ARF progress to RHD. The endocardium, pericardium, or myocardium may be affected. Valvular damage is the hallmark of rheumatic carditis. The mitral valve is almost always affected, sometimes together with the aortic valve; isolated aortic valve

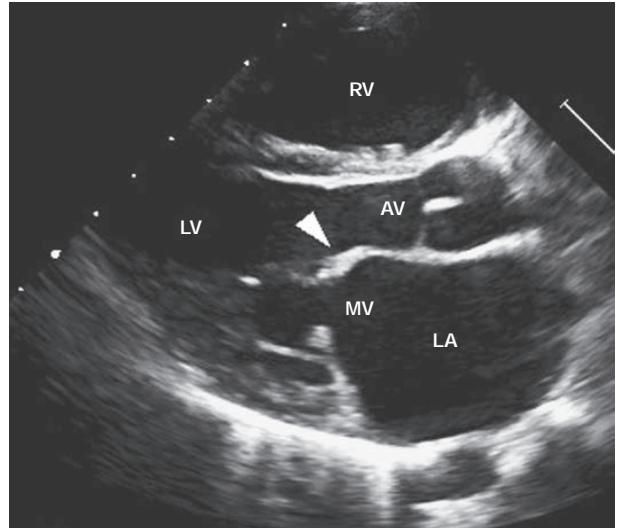


FIGURE 359-2 Transthoracic echocardiographic image from a 5-year-old boy with chronic rheumatic heart disease. This diastolic image demonstrates leaflet thickening, restriction of the anterior mitral valve leaflet tip and doming of the body of the leaflet toward the interventricular septum. This appearance (marked by the arrowhead) is commonly described as a “hockey stick” or an “elbow” deformity. AV, aortic valve; LA, left atrium; LV, left ventricle; MV, mitral valve; RV, right ventricle. (Courtesy of Dr. Bo Remenyi, Department of Paediatric and Congenital Cardiac Services, Starship Children’s Hospital, Auckland, New Zealand.)

involvement is rare. Damage to the pulmonary or tricuspid valves is usually secondary to increased pulmonary pressures resulting from left-sided valvular disease. Early valvular damage leads to regurgitation. Over ensuing years, usually as a result of recurrent episodes, leaflet thickening, scarring, calcification, and valvular stenosis may develop ([Fig. 359-2](#)). See [Videos 359-1](#) and [359-2](#). Therefore, the characteristic manifestation of carditis in previously unaffected individuals is mitral regurgitation, sometimes accompanied by aortic regurgitation. Myocardial inflammation may affect electrical conduction pathways, leading to P-R interval prolongation (first-degree atrioventricular block or rarely higher-level block) and softening of the first heart sound.

People with RHD are often asymptomatic for many years before their valvular disease progresses to cause cardiac failure. Moreover, particularly in resource-poor settings, the diagnosis of ARF is often not made, so children, adolescents, and young adults may have RHD but not know it. These cases can be diagnosed using echocardiography; auscultation is poorly sensitive and specific for RHD diagnosis in asymptomatic patients. Echocardiographic screening of school-aged children in populations with high rates of RHD is becoming more widespread and has been facilitated by improving technologies in portable echocardiography and the availability of consensus guidelines for the diagnosis of RHD on echocardiography ([Table 359-1](#)). Although a diagnosis of definite RHD on screening echocardiography should lead to commencement of secondary prophylaxis, the clinical significance of borderline RHD has yet to be determined.

JOINT INVOLVEMENT

The most common form of joint involvement in ARF is arthritis, i.e., objective evidence of inflammation, with hot, swollen, red, and/or tender joints, and involvement of more than one joint (i.e., polyarthritis). Polyarthritis is typically migratory, moving from one joint to another over a period of hours. ARF almost always affects the large joints—most commonly the knees, ankles, hips, and elbows—and is asymmetric. The pain is severe and usually disabling until anti-inflammatory medication is commenced.

Less severe joint involvement is also relatively common and has been recognized as a potential major manifestation in high-risk

TABLE 359-1 World Heart Federation Criteria for Echocardiographic Diagnosis of Rheumatic Heart Disease (RHD) in Individuals <20 Years of Age^a**Definite RHD (either A, B, C, or D)**

- (A) Pathologic MR and at least two morphologic features of RHD of the mitral valve
- (B) MS mean gradient ≥ 4 mmHg (note: congenital MV anomalies must be excluded)
- (C) Pathologic AR and at least two morphologic features of RHD of the AV (note: bicuspid AV and dilated aortic root must be excluded)
- (D) Borderline disease of both the MV and AV

Borderline RHD (either A, B, or C)

- (A) At least two morphologic features of RHD of the MV without pathologic MR or MS
- (B) Pathologic MR
- (C) Pathologic AR

Normal Echocardiographic Findings (all of A, B, C, and D)

- (A) MR that does not meet all four Doppler criteria (physiologic MR)
- (B) AR that does not meet all four Doppler criteria (physiologic AR)
- (C) An isolated morphologic feature of RHD of the MV (e.g., valvular thickening), without any associated pathologic stenosis or regurgitation
- (D) Morphologic feature of RHD of the AV (e.g., valvular thickening), without any associated pathologic stenosis or regurgitation

Definitions of Pathologic Regurgitation and Morphologic Features of RHD

Pathologic MR: All of the following: seen in two views; in at least one view, jet length ≥ 2 cm; peak velocity ≥ 3 m/s; pansystolic jet in at least one envelope

Pathologic AR: All of the following: seen in two views; in at least one view, jet length ≥ 1 cm; peak velocity ≥ 3 m/s; pandiastolic jet in at least one envelope

Morphologic features of RHD in MV: anterior MV leaflet thickening ≥ 3 mm (age specific); chordal thickening; restricted leaflet motion; excessive leaflet tip motion during systole

Morphologic features of RHD in AV: irregular or focal thickening; coaptation defect; restricted leaflet motion; prolapse

^aFor criteria in individuals >20 years of age, see source document.

Abbreviations: AR, aortic regurgitation; AV, aortic valve; MR, mitral regurgitation; MS, mitral stenosis; MV, mitral valve.

Source: Reproduced with permission from B Remenyi et al: World Heart Federation criteria for echocardiographic diagnosis of rheumatic heart disease—an evidence-based guideline. Nat Rev Cardiol 9:297, 2012.

populations in the most recent revision of the Jones criteria. Arthralgia without objective joint inflammation usually affects large joints in the same migratory pattern as polyarthritis. In some populations, aseptic monoarthritis may be a presenting feature of ARF, which may, in turn, result from early commencement of anti-inflammatory medication before the typical migratory pattern is established.

The joint manifestations of ARF are highly responsive to salicylates and other nonsteroidal anti-inflammatory drugs (NSAIDs). Indeed, joint involvement that persists for more than 1 or 2 days after starting salicylates is unlikely to be due to ARF.

CHOREA

Sydenham's chorea commonly occurs in the absence of other manifestations, follows a prolonged latent period after group A streptococcal infection, and is found mainly in females. The choreiform movements affect particularly the head (causing characteristic darting movements of the tongue) and the upper limbs (**Chap. 436**). They may be generalized or restricted to one side of the body (hemi-chorea). In mild cases, chorea may be evident only on careful examination, whereas in the most severe cases, the affected individuals are unable to perform activities of daily living. There is often associated emotional lability or obsessive-compulsive traits, which may last longer than the choreiform movements (which usually resolve within 6 weeks but sometimes may take up to 6 months). More than 50% of patients presenting with chorea will have carditis, for which reason echocardiography should be part of the workup.

SKIN MANIFESTATIONS

The classic rash of ARF is *erythema marginatum* (**Chap. 19**), which begins as pink macules that clear centrally, leaving a serpiginous, spreading edge. The rash is evanescent, appearing and disappearing before the examiner's eyes. It occurs usually on the trunk, sometimes on the limbs, but almost never on the face.

Subcutaneous nodules occur as painless, small (0.5–2 cm), mobile lumps beneath the skin overlying bony prominences, particularly of the hands, feet, elbows, occiput, and occasionally the vertebrae. They are a delayed manifestation, appearing 2–3 weeks after the onset of disease, last for just a few days up to 3 weeks, and are commonly associated with carditis.

OTHER FEATURES

Fever occurs in most cases of ARF, although rarely in cases of pure chorea. Although high-grade fever ($\geq 39^{\circ}\text{C}$) is the rule, lower grade temperature elevations are not uncommon. Elevated acute-phase reactants are also present in most cases.

EVIDENCE OF A PRECEDING GROUP A STREPTOCOCCAL INFECTION

With the exception of chorea and low-grade carditis, both of which may become manifest many months later, evidence of a preceding group A streptococcal infection is essential in making the diagnosis of ARF. Because most cases do not have a positive throat swab culture or rapid antigen test, serologic evidence is usually needed. The most common serologic tests are the anti-streptolysin O (ASO) and anti-DNase B (ADB) titers. Where possible, age-specific reference ranges should be determined in a local population of healthy people without a recent group A streptococcal infection.

CONFIRMING THE DIAGNOSIS

Because there is no definitive test, the diagnosis of ARF relies on the presence of a combination of typical clinical features together with evidence of the precipitating group A streptococcal infection, and the exclusion of other diagnoses. This uncertainty led Dr. T. Duckett Jones in 1944 to develop a set of criteria (subsequently known as the *Jones criteria*) to aid in the diagnosis. The most recent revision of the Jones criteria (**Table 359-2**) requires the clinician to determine if the patient is from a setting or population known to experience low rates of ARF. For this group, there is a set of "low-risk" criteria; for all others, there is a set of more sensitive criteria.

TREATMENT**Acute Rheumatic Fever**

Patients with possible ARF should be followed closely to ensure that the diagnosis is confirmed, treatment of heart failure and other symptoms is undertaken, and preventive measures including commencement of secondary prophylaxis, inclusion on an ARF registry, and health education are commenced. Echocardiography should be performed on all possible cases to aid in making the diagnosis and to determine the severity at baseline of any carditis. Other tests that should be performed are listed in **Table 359-3**.

There is no treatment for ARF that has been proven to alter the likelihood of developing, or the severity of, RHD. With the exception of treatment of heart failure, which may be life-saving in cases of severe carditis, the treatment of ARF is symptomatic.

ANTIBIOTICS

All patients with ARF should receive antibiotics sufficient to treat the precipitating group A streptococcal infection (**Chap. 148**). Penicillin is the drug of choice and can be given orally (as phenoxymethyl penicillin, 500 mg [250 mg for children ≤ 27 kg] PO twice daily, or amoxicillin, 50 mg/kg [maximum, 1 g] daily, for 10 days) or as a single dose of 1.2 million units (600,000 units for children ≤ 27 kg) IM benzathine penicillin G.

SALICYLATES AND NSAIDS

These may be used for the treatment of arthritis, arthralgia, and fever, once the diagnosis is confirmed. They are of no proven

TABLE 359-2 Jones Criteria

A. For All Patient Populations with Evidence of Preceding Group A Streptococcal Infection	
Diagnosis: initial ARF	2 major manifestations or 1 major plus 2 minor manifestations
Diagnosis: recurrent ARF	2 major or 1 major and 2 minor or 3 minor
B. Major Criteria	
Low-risk populations ^a	Moderate- and high-risk populations
Carditis ^b	Carditis
• Clinical and/or subclinical	• Clinical and/or subclinical
Arthritis	Arthritis
• Polyarthritis only	• Monoarthritis or polyarthritis
	• Polyarthralgia ^c
Chorea	Chorea
Erythema marginatum	Erythema marginatum
SC nodules	SC nodules
C. Minor Criteria	
Low-risk populations ^a	Moderate- and high-risk populations
Polyarthralgia	Monoarthralgia
Fever ($>38.5^{\circ}\text{C}$)	Fever ($>38^{\circ}\text{C}$)
ESR $>60\text{ mm in the first hour and/or CRP }>3.0\text{ mg/dL}^d$	ESR $>30\text{ mm/h and/or CRP }>3.0\text{ mg/dL}^d$
Prolonged PR interval ^e , after accounting for age variability (unless carditis is a major criterion)	Prolonged PR interval ^e , after accounting for age variability (unless carditis is a major criterion)

^aLow-risk populations are those with ARF incidence $<2\text{ per 100,000 school-age children or all-age rheumatic heart disease prevalence of }<1\text{ per 1000 population per year.}$ ^bSubclinical carditis indicates echocardiographic valvulitis. (See source document.) ^cPolyarthralgia should only be considered as a major manifestation in moderate- to high-risk populations after exclusion of other causes. As in past versions of the criteria, erythema marginatum and SC nodules are rarely "stand-alone" major criteria. Additionally, joint manifestations can only be considered in either the major or minor categories but not both in the same patient. (See source document for more information.) ^dCRP value must be greater than upper limit of normal for laboratory. Also, because ESR may evolve during the course of ARF, peak ESR values should be used. ^eProlonged PR interval can only be considered in the absence of carditis as a major criterion.

Abbreviations: ARF, acute rheumatic fever; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

Source: Reproduced with permission from MH Gewitz et al: Revision of the Jones criteria for the diagnosis of acute rheumatic fever in the era of Doppler echocardiography: A scientific statement from the American Heart Association. Circulation 131(20):1806, 2015. <https://www.ahajournals.org/doi/full/10.1161/CIR.0000000000000205>.

value in the treatment of carditis or chorea. Aspirin is a common first-line choice, delivered at a dose of 50–60 mg/kg per day, up to a maximum of 80–100 mg/kg per day (4–8 g/d in adults) in 4–5 divided doses. At higher doses, the patient should be monitored for symptoms of salicylate toxicity such as nausea, vomiting, or tinnitus; if symptoms appear, lower doses should be used. When the acute symptoms are substantially resolved, usually within the first 2 weeks, patients on higher doses can have the dose reduced to 50–60 mg/kg per day for a further 2–4 weeks. Fever, joint manifestations, and elevated acute-phase reactants sometimes recur up to 3 weeks after the medication is discontinued. This does not indicate a recurrence and can be managed by recommencing salicylates for a brief period. Many clinicians prefer to use naproxen at a dose of 10–20 mg/kg per day, because it may be safer than aspirin and has the advantage of twice-daily dosing.

CONGESTIVE HEART FAILURE

Glucocorticoids The use of glucocorticoids in ARF remains controversial. Two meta-analyses have failed to demonstrate a benefit of glucocorticoids compared to placebo or salicylates in improving the short- or longer-term outcome of carditis. However, the studies included in these meta-analyses all took place >40 years ago and did not use medications in common usage today. Many clinicians treat cases of severe carditis (causing heart failure) with glucocorticoids

TABLE 359-3 Testing and Monitoring of ARF in the Acute Setting

Investigations
Always request:
• Electrocardiogram (ECG)
• Echocardiogram
• Complete blood count (CBC)
• C-reactive protein (CRP)
• Streptococcal serology (antistreptolysin and anti-DNase B)
In relevant situations:
• Throat swab
• Skin sore swab
• Blood cultures
• Synovial fluid aspirate
• Ensure sample does not clot by using correct tubes that have been well mixed and transported promptly to the laboratory
• Include request for cell count, microscopy, culture, and gonococcal polymerase chain reaction (PCR)
• Pregnancy test
• Creatinine test (UEC [urea, electrolytes, creatinine]) since nonsteroidal anti-inflammatory drugs can affect renal function
Tests to exclude alternative diagnoses, depending on clinical presentation and locally endemic infections:
• Autoantibodies, double-stranded DNA, anti-cyclic citrullinated peptide (anti-CCP) antibodies
• Urine for <i>Neisseria gonorrhoeae</i> molecular test
• Urine for <i>Chlamydia trachomatis</i> molecular test
• Serologic or other testing for viral hepatitis, <i>Yersinia</i> spp., cytomegalovirus (CMV), parvovirus B19, respiratory viruses, Ross River virus, Barmah Forest virus

Source: Reproduced with permission from RDHAustralia, Menzies School of Health Research. RHDAustralia (ARF/RHD writing group). The 2020 Australian guideline for prevention, diagnosis and management of acute rheumatic fever and rheumatic heart disease (3rd edition): 2020. Available at <https://www.rhdaustralia.org.au/arf-rhd-guideline>.

in the belief that they may reduce the acute inflammation and result in more rapid resolution of failure. However, the potential benefits of this treatment should be balanced against the possible adverse effects. If used, prednisone or prednisolone is recommended at a dose of 1–2 mg/kg per day (maximum, 80 mg), usually for a few days or up to a maximum of 3 weeks.

MANAGEMENT OF HEART FAILURE

See Chap. 258.

BED REST

Traditional recommendations for long-term bed rest, once the cornerstone of management, are no longer widely practiced. Instead, bed rest should be prescribed as needed while arthritis and arthralgia are present and for patients with heart failure. Once symptoms are well controlled, gradual mobilization can commence as tolerated.

CHOREA

Medications to control the abnormal movements do not alter the duration or outcome of chorea. Milder cases can usually be managed by providing a calm environment. In patients with severe chorea, carbamazepine or sodium valproate is preferred to haloperidol. A response may not be seen for 1–2 weeks, and medication should be continued for 1–2 weeks after symptoms subside. There is recent evidence that corticosteroids are effective and lead to more rapid symptom reduction in chorea. They should be considered in severe or refractory cases. Prednisone or prednisolone may be commenced at 0.5 mg/kg daily, with weaning as early as possible, preferably after 1 week if symptoms are reduced, although slower weaning or temporary dose escalation may be required if symptoms worsen.

INTRAVENOUS IMMUNOGLOBULIN (IVIG)

Small studies have suggested that IVIG may lead to more rapid resolution of chorea but have shown no benefit on the short- or

long-term outcome of carditis in ARF without chorea. In the absence of better data, IVIg is *not* recommended except in cases of severe chorea refractory to other treatments.

PROGNOSIS

Untreated, ARF lasts on average 12 weeks. With treatment, patients are usually discharged from hospital within 1–2 weeks. Inflammatory markers should be monitored every 1–2 weeks until they have normalized (usually within 4–6 weeks), and an echocardiogram should be performed after 1 month to determine if there has been progression of carditis. Cases with more severe carditis need close clinical and echocardiographic monitoring in the longer term.

Once the acute episode has resolved, the priority in management is to ensure long-term clinical follow-up and adherence to a regimen of secondary prophylaxis. Patients should be entered onto the local ARF registry (if present) and contact made with primary care practitioners to ensure a plan for follow-up and administration of secondary prophylaxis before the patient is discharged. Patients and their families should also be educated about their disease, emphasizing the importance of adherence to secondary prophylaxis.

PREVENTION

PRIMARY PREVENTION

Ideally, primary prevention would entail elimination of the major risk factors for streptococcal infection, particularly overcrowded housing. This is difficult to achieve in most places where ARF is common.

Concerted international efforts are underway to develop a vaccine against group A *Streptococcus* that would prevent infection of the throat or skin and consequently prevent ARF in the absence of a suitable vaccine; however, the mainstay of primary prevention for ARF remains primary prophylaxis (i.e., the timely and complete treatment of group A streptococcal sore throat with antibiotics). If commenced within 9 days of sore throat onset, a course of penicillin (as outlined above for treatment of ARF) will prevent almost all cases of ARF that would otherwise have developed. In settings where ARF and RHD are common but microbiologic diagnosis of group A streptococcal pharyngitis is not available, such as in resource-poor countries, primary care guidelines often recommend that all patients with sore throat be treated with penicillin or, alternatively, that a clinical algorithm be used to identify patients with a higher likelihood of group A streptococcal pharyngitis. Although imperfect, such approaches recognize the importance of ARF prevention at the expense of overtreating many cases of sore throat that are not caused by group A *Streptococcus*. Although there is no proof that antibiotic treatment of group A streptococcal skin infections can prevent ARF, the increasing evidence that impetigo is strongly associated with ARF in some populations argues for a focus on treatment and prevention of group A streptococcal skin infections as part of a comprehensive ARF control strategy in regions with endemic impetigo.

SECONDARY PREVENTION

The mainstay of controlling ARF and RHD is secondary prevention. Because patients with ARF are at dramatically higher risk than the general population of developing a further episode of ARF after a group A streptococcal infection, they should receive long-term penicillin prophylaxis to prevent recurrences. The best antibiotic for secondary prophylaxis is benzathine penicillin G (1.2 million units, or 600,000 units if ≤ 27 kg) delivered every 4 weeks. It can be given every 3 weeks, or even every 2 weeks, to persons considered to be at particularly high risk, although in settings where good compliance with an every-4-week dosing schedule can be achieved, more frequent dosing is rarely needed. Oral penicillin V (250 mg) can be given twice daily instead but is less effective than benzathine penicillin G. Penicillin-allergic patients can receive erythromycin (250 mg) twice daily.

The duration of secondary prophylaxis is determined by many factors, in particular the duration since the last episode of ARF (recurrences become less likely with increasing time), age (recurrences are less likely with increasing age), and the severity of RHD (if severe, it may be prudent to avoid even a very small risk of recurrence

TABLE 359-4 American Heart Association Recommendations for Duration of Secondary Prophylaxis^a

CATEGORY OF PATIENT	DURATION OF PROPHYLAXIS
Rheumatic fever without carditis	For 5 years after the last attack or 21 years of age (whichever is longer)
Rheumatic fever with carditis but no residual valvular disease	For 10 years after the last attack, or 21 years of age (whichever is longer)
Rheumatic fever with persistent valvular disease, evident clinically or on echocardiography	For 10 years after the last attack, or 40 years of age (whichever is longer); sometimes lifelong prophylaxis

^aThese are only recommendations and must be modified by individual circumstances as warranted. Note that some organizations recommend a minimum of 10 years of prophylaxis after the most recent episode, or until 21 years of age (whichever is longer), regardless of the presence of carditis with the initial episode.

Source: Reproduced with permission from MA Gerber et al: Prevention of rheumatic fever and diagnosis and treatment of acute streptococcal pharyngitis. Circulation 119:1541, 2009. https://www.ahajournals.org/doi/10.1161/CIRCULATIONAHA.109.191959?url_ver=Z39.88-2003&fr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%20pubmed.

because of the potentially serious consequences) (Table 359-4). Secondary prophylaxis is best delivered as part of a coordinated RHD control program, based around a registry of patients. Registries improve the ability to follow patients and identify those who default from prophylaxis and to institute strategies to improve adherence.

FURTHER READING

- Carapetis JR et al: Acute rheumatic fever and rheumatic heart disease. Nat Rev Dis Primers 14:15084, 2016.
- Gewitz MH et al: Revision of the Jones Criteria for the diagnosis of acute rheumatic fever in the era of Doppler echocardiography: A scientific statement from the American Heart Association. Circulation 131:1806, 2015.
- RHD Australia (ARF/RHD Writing Group): The 2020 Australian guideline for prevention, diagnosis and management of acute rheumatic fever and rheumatic heart disease (3rd edition); 2020. Available at <https://www.rhdaustralia.org.au/arf-rhd-guideline>.
- Vekemans J et al: The path to group A *Streptococcus* vaccines: World Health Organization research and development technology roadmap and preferred product characteristics. Clin Infect Dis 69:5, 2019.
- Zühlke L et al: Clinical outcomes in 3343 children and adults with rheumatic heart disease from 14 low- and middle-income countries: Two-year follow-up of the Global Rheumatic Heart Disease Registry (the REMEDY Study). Circulation 134:1456, 2016.

VIDEO 359-1A Transthoracic echocardiographic images of a 9-year-old girl with first episode of acute rheumatic fever. Images demonstrate the typical echocardiographic findings of acute rheumatic carditis. The valve leaflets are relatively thin and highly mobile. The failure of coaptation of the mitral valve leaflets is the result of chordal elongation and annular dilatation. The mitral valve regurgitation is moderate with a typical posterolaterally directed regurgitant jet of rheumatic carditis. **A.** Acute rheumatic carditis (apical four-chamber view echocardiogram).

VIDEO 359-1B Transthoracic echocardiographic images of a 9-year-old girl with first episode of acute rheumatic fever. Images demonstrate the typical echocardiographic findings of acute rheumatic carditis. The valve leaflets are relatively thin and highly mobile. The failure of coaptation of the mitral valve leaflets is the result of chordal elongation and annular dilatation. The mitral valve regurgitation is moderate with a typical posterolaterally directed regurgitant jet of rheumatic carditis. **B.** Acute rheumatic carditis (apical four-chamber view color Doppler echocardiogram).

VIDEO 359-1C Transthoracic echocardiographic images of a 9-year-old girl with first episode of acute rheumatic fever. Images demonstrate the typical echocardiographic findings of acute rheumatic carditis. The valve leaflets are relatively thin and highly mobile. The failure of coaptation of the mitral valve leaflets is the result of chordal elongation and annular dilatation. The mitral valve regurgitation is moderate with a typical posterolaterally directed regurgitant jet of rheumatic carditis. **C.** Acute rheumatic carditis (parasternal long-axis view echocardiogram).

VIDEO 359-1D Transthoracic echocardiographic images of a 9-year-old girl with first episode of acute rheumatic fever. Images demonstrate the typical echocardiographic findings of acute rheumatic carditis. The valve leaflets are relatively thin and highly mobile. The failure of coaptation of the mitral valve leaflets is the result of chordal elongation and annular dilatation. The mitral valve regurgitation is moderate with a typical posterolaterally directed regurgitant jet of rheumatic carditis. **D.** Acute rheumatic carditis (parasternal long-axis view color Doppler echocardiogram).

VIDEO 359-2A Transthoracic echocardiographic images are from a 5-year-old boy with chronic rheumatic heart disease with severe mitral valve regurgitation and moderate mitral valve stenosis. Images demonstrate the typical echocardiographic findings in advanced chronic rheumatic heart disease. Both the anterior and posterior mitral valve leaflets are markedly thickened. During diastole, the motion of the anterior mitral valve leaflet tip is restricted with doming of the body of the leaflet toward the interventricular septum. This appearance is commonly described as a "hockey stick" or an "elbow" deformity. **A.** Chronic rheumatic heart disease (parasternal long-axis view).

VIDEO 359-2B Transthoracic echocardiographic images are from a 5-year-old boy with chronic rheumatic heart disease with severe mitral valve regurgitation and moderate mitral valve stenosis. Images demonstrate the typical echocardiographic findings in advanced chronic rheumatic heart disease. Both the anterior and posterior mitral valve leaflets are markedly thickened. During diastole, the motion of the anterior mitral valve leaflet tip is restricted with doming of the body of the leaflet toward the interventricular septum. This appearance is commonly described as a "hockey stick" or an "elbow" deformity. **B.** Chronic rheumatic heart disease (apical two-chamber view echocardiogram).

display the characteristic constellation of clinical findings (calcinosis cutis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia), historically termed the *CREST syndrome*. In lcSSc, visceral organ involvement tends to follow an insidious and often benign course, while digital ischemic ulcers, pulmonary arterial hypertension (PAH), hypothyroidism, Sjogren's symptoms, and primary biliary cirrhosis may occur as late complications. In some patients, Raynaud's phenomenon and characteristic clinical and laboratory features of SSc occurs in the absence of detectable skin thickening. This relatively benign disease subset has been termed *SSc sine scleroderma*.

INCIDENCE AND PREVALENCE

SSc is an acquired sporadic disease with a worldwide distribution and affecting all races. In the United States, the incidence is 9–46 cases per million per year. There are an estimated 100,000 U.S. cases, although this number may be significantly higher if patients who do not fulfill classification criteria are also included. There are large regional variations in incidence rates of SSc, potentially reflecting differences in case definition, environmental exposures, or genetic susceptibility genes in populations with different ancestries. Prevalence rates in England, northern Europe, and Japan appear to be lower than in North America and Australia. Age, sex, and ethnicity influence disease susceptibility, and blacks have higher age-specific incidence rates and mortality. In common with other connective tissue diseases, SSc shows a strong female predominance (4.6:1), which is most pronounced in the childbearing years and declines after menopause. An additional risk factor for SSc is having an affected first-degree family member, which increases disease risk 13-fold. Although SSc can present at any age, the peak age of onset in women with both limited and diffuse cutaneous forms is 65–74 years, although in blacks, disease onset occurs at an earlier age. Furthermore, blacks with SSc are more likely to have diffuse cutaneous disease, ILD, and a worse prognosis.

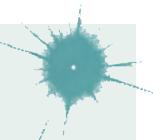
GENETIC CONTRIBUTION TO DISEASE PATHOGENESIS

In general, the genetic associations of SSc identified to date make only a relatively modest contribution to disease susceptibility. Twin studies showed low disease concordance rates (4.7%) in monozygotic twins, a rate much lower than in other autoimmune diseases such as rheumatoid arthritis (12.3%). On the other hand, supporting the genetic contribution to disease susceptibility is the observation that 1.6% of SSc patients have a first-degree relative with SSc, a prevalence rate that is markedly increased compared to the general population. Moreover, the risk of Raynaud's phenomenon, ILD, and other autoimmune diseases, including systemic lupus erythematosus (SLE) (Chap. 356), rheumatoid arthritis (Chap. 358), and autoimmune thyroiditis (Chap. 383), is also increased in first-degree relatives of patients with SSc. Current approaches to uncover the genetic factors that contribute to SSc include DNA sequencing and single nucleotide polymorphism (SNP) analysis of candidate genes and SNP analysis of the entire genome in a hypothesis-free manner. Genome-wide association studies (GWAS) involve large multicenter and multinational cohorts. A majority of the robustly validated genetic susceptibility loci for SSc are genes at the highly polymorphic human leukocyte antigen (HLA) region and other genes involved in innate and adaptive immunity and interferon responses, highlighting the importance of autoimmunity as the initial trigger for the disease. Genetic studies have shown associations with common (small effect size) variants related to B and T lymphocyte activation (*BANK1*, *BLK*, *CD247*, *STAT4*, *IL2RA*, *CCR6*, *IDO1*, *TNFSF4/OX40L*, *PTPN22*, and *TNIP1*). In addition, candidate gene studies and GWAS identified a strong and consistent association with HLA class II haplotypes on chromosome 6, including *HLA-DRB1*11:04*, *DQA1*05:01*, and *DQB1*03:01*, and the non-HLA histocompatibility complex (MHC) genes *NOTCH4* and *PSORS1*. Other genetic variants associated with SSc are involved in innate immunity and type 1 interferon signalling (*IRF5*, *IRF7*, *STAT4*, *TNFAIP3*, and *TLR2*). Additional associations with *IL12RB2*, *IL-21*, the autophagy and apoptosis-related genes *DNASE1L3* and *SOX5*, and the

360

Systemic Sclerosis (Scleroderma) and Related Disorders

John Varga



DEFINITION AND CLASSIFICATION

Systemic sclerosis (SSc) is an orphan disease of unknown etiology, complex pathogenesis, and variable clinical presentations. SSc frequently follows a progressive course and is associated with significant disability and mortality. Virtually every organ can be affected (Fig. 360-1).

There is marked variability among SSc patients in patterns of skin involvement and organ complications, rates of disease progression, response to treatment, disease severity, and survival. The early stages of SSc are associated with prominent inflammatory features, but over time, structural alterations in multiple vascular beds and visceral organ dysfunction due to fibrosis and atrophy progressively dominate the clinical picture. Recently developed classification criteria for the diagnosis of SSc (shown in Table 360-1) are >90% specific and selective.

Although thickened and indurated skin (*scleroderma*) is the distinguishing hallmark of SSc, similar skin changes can also be seen in localized forms of scleroderma, along with a variety of metabolic, inherited, autoimmune, and iatrogenic conditions (Table 360-2). Patients with SSc can be broadly segregated into two major subsets defined by the pattern of skin involvement and associated with characteristic clinical and serologic features and natural history (Table 360-3). Patients with diffuse cutaneous SSc (dcSSc) have extensive skin induration, starting in the fingers (sclerodactyly) and ascending from distal to proximal limbs and the trunk. In these patients, progressive skin disease, interstitial lung disease (ILD), and less commonly acute renal involvement may develop relatively early. In contrast, in patients with limited cutaneous SSc (lcSSc), Raynaud's phenomenon generally precedes sclerodactyly and other disease manifestations, sometimes by years. In these patients, skin involvement remains confined to the fingers, distal limbs, and face, while the trunk is spared. A subset of patients with lcSSc

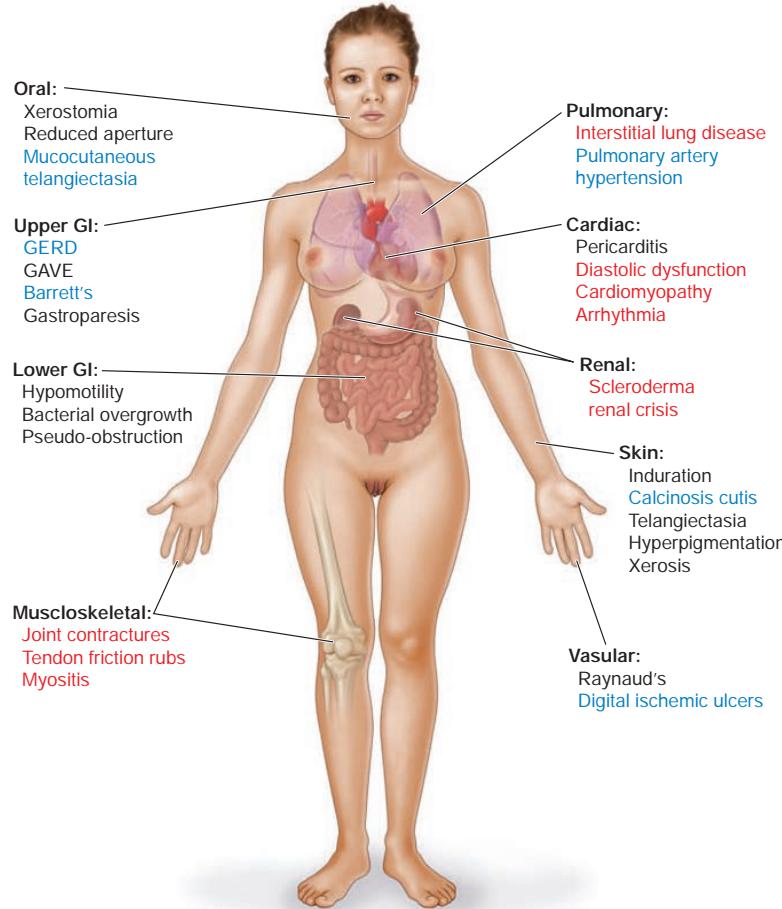


FIGURE 360-1 Multiorgan involvement in systemic sclerosis (SSc). Prominent complications of SSc: red, those more common in diffuse cutaneous SSc; black, those more common in limited cutaneous SSc; blue, complications common in both SSc subsets. GAVE, gastric antral vascular ectasia; GERD, gastroesophageal reflux disease; GI, gastrointestinal.

TABLE 360-1 Classification Criteria for Diagnosis of Systemic Sclerosis

ITEM	SUBITEM	WEIGHT/SCORE
Skin thickening (bilateral); fingers extending proximal to MCP joints		9
Skin thickening of fingers only	Puffy fingers Sclerodactyly (skin thickened distal to MCP joints)	2 4
Fingertip lesions	Digital tip ulcer Fingertip pitting scars	2 3
Mucocutaneous telangiectasia		2
Abnormal nailfold capillary pattern		2
Lung involvement	PAH Interstitial lung disease	2 2
Raynaud's phenomenon		3
SSc-specific autoantibodies	ACA Scl-70 RNA polymerase III	3

Abbreviations: ACA, anticentromere antibodies; MCP, metacarpophalangeal joint; PAH, pulmonary arterial hypertension.

TABLE 360-2 Conditions Associated with Skin Induration

Systemic sclerosis (SSc)
Limited cutaneous SSc
Diffuse cutaneous SSc
Localized scleroderma
Guttate (plaque) morphea, diffuse (pansclerotic) morphea, bullous morphea
Linear scleroderma, coup de sabre, hemifacial atrophy
Pansclerotic morphea
Overlap syndromes
Mixed connective tissue disease
SSc/polymyositis
Diabetic scleredema and scleredema of Buschke
Scleromyxedema (papular mucinosis)
Chronic graft-versus-host disease
Diffuse fasciitis with eosinophilia (Shulman's disease, eosinophilic fasciitis)
Stiff skin syndrome
Pachydermoperiostosis (primary hypertrophic osteoarthropathy)
Chemically induced and drug-associated scleroderma-like conditions
Vinyl chloride-induced disease
Eosinophilia-myalgia syndrome (associated with L-tryptophan contaminant exposure)
Nephrogenic systemic fibrosis (associated with gadolinium exposure)
Paraneoplastic syndrome

CHARACTERISTIC FEATURE	LIMITED CUTANEOUS SSc	DIFFUSE CUTANEOUS SSc
Skin involvement	Indolent onset. Limited to fingers, distal to elbows, face; slow progression	Rapid onset. Diffuse: fingers, extremities, face, trunk; rapid progression
Raynaud's phenomenon	Antecedes skin involvement, sometimes by years; may be associated with critical ischemia in the digits	Onset coincident with skin involvement; critical ischemia less common
Musculoskeletal	Mild arthralgia	Severe arthralgia, carpal tunnel syndrome, tendon friction rubs
Interstitial lung disease	Slowly progressive, generally mild	Frequent, early onset and progression, can be severe
Pulmonary arterial hypertension	Frequent, late, may occur as an isolated complication	Often occurs in association with interstitial lung disease
Scleroderma renal crisis	Very rare	Occurs in 15%; generally early (<4 years from disease onset)
Calcinosis cutis	Frequent, prominent	Less common, mild
Characteristic autoantibodies	Anti-centromere	Anti-topoisomerase I (Scl-70), anti-RNA polymerase III

extracellular matrix-related genes *CSK*, *CAV1*, *PPARG*, and *GRB10* have been reported. In addition to SSc susceptibility, some of these genetic loci are associated with particular disease manifestations or serologic subsets, including ILD (*CTGF*, *CD226*), PAH (*TNIP1*), scleroderma renal crisis (*HLA-DRB1*), and anticentromere antibodies (*HLA-DPB1*:*05:01*). While the functional consequences of these gene variants and their potential roles in pathogenesis are not well understood, it seems likely that in combination they cause a state of altered immune regulation, leading to increased susceptibility to autoimmunity and persistent inflammation. Of note, several of the SSc genetic variants are also implicated in other autoimmune disorders, including SLE, Sjögren's syndrome, rheumatoid arthritis, multiple sclerosis, and psoriasis, suggesting common pathogenic pathways shared among these phenotypically dissimilar conditions. Notably, the genetic associations identified to date only explain a fraction of the heritability of SSc and focus on common variants. By contrast, next-generation sequencing, such as whole exome sequencing, may help identify additional genetic susceptibility factors in SSc, particularly rare (and potentially causal) coding variants and their association with specific phenotypes.

ENVIRONMENTAL AND OCCUPATIONAL EXPOSURES

The etiology of SSc is unknown. Given the relatively modest genetic contribution to susceptibility in SSc, environmental factors, such as infectious agents, microbiome, and occupational, dietary, lifestyle, and drug exposures, are likely to play a major role. Evidence suggests potential pathogenic roles for viruses, including parvovirus B19, Epstein-Barr virus (EBV), and cytomegalovirus (CMV), and *Rhodotorula glutinosa*. Toxic oil syndrome, a novel disease with features suggestive of SSc, occurred as an epidemic outbreak in Spain in the 1980s and was linked to contaminated rapeseed oil used for cooking. Another epidemic outbreak, termed *eosinophilia-myalgia syndrome* (EMS), occurred in the United States in the 1990s and was linked to consumption of L-tryptophan-containing dietary supplements. Exposure to gadolinium contrast material in individuals with compromised renal function undergoing magnetic resonance scanning has been associated with nephrogenic systemic fibrosis. While each of these novel toxic-epidemic syndromes was characterized by chronic indurative skin changes

and variable visceral organ involvement, the constellation of associated clinical, pathologic, and laboratory features distinguishes them from SSc. Occupational exposures tentatively linked with SSc include particulate silica (quartz), polyvinyl chloride, epoxy resins, welding fumes, and organic solvents and aromatic hydrocarbons including paint thinners, toluene, xylene, and trichloroethylene. These exposures can elicit cell type-specific stable and heritable epigenetic modifications such as DNA methylation and histone modification that could drive pathogenic alterations in cellular gene expression. Several of these epigenetic modifications are reversible and represent potential targets for therapy. Drugs implicated in SSc-like illnesses include bleomycin, pentazocine, cocaine, and appetite suppressants linked with PAH. Most recently, immune checkpoint inhibitors such as PD-1 blockers used in cancer therapy have been implicated as triggers for SSc-like illnesses. Radiation therapy for cancer has been linked with de novo onset of SSc as well as with exacerbation of preexisting SSc. In contrast to rheumatoid arthritis, cigarette smoking does not increase the risk of SSc. Although case reports and series describing the occurrence of SSc in women with silicone breast implants had raised concern regarding a putative pathogenic role of silicone in SSc, large-scale epidemiologic investigations found no evidence of increased prevalence of SSc.

PATHOGENESIS

The pathogenesis of SSc involves putative environmental insults that trigger epigenetic modifications in a genetically predisposed host, causing alterations in gene expression underlying durable changes in the behavior of multiple cell types (Fig. 360-2).

Three cardinal pathomechanistic processes underlie the protean clinical manifestations and pathologic changes of SSc: (1) diffuse microangiopathy, (2) inflammation and autoimmunity, and (3) visceral and vascular fibrosis affecting multiple organs (Fig. 360-3). While each of these distinct processes may be synchronously active in a given SSc patient, their relative severity, progression, and contribution to the overall clinical picture vary among individual patients and over time. In general, autoimmunity and reversible vascular reactivity are early features of SSc, whereas fibrosis and atrophy occur later in the disease.

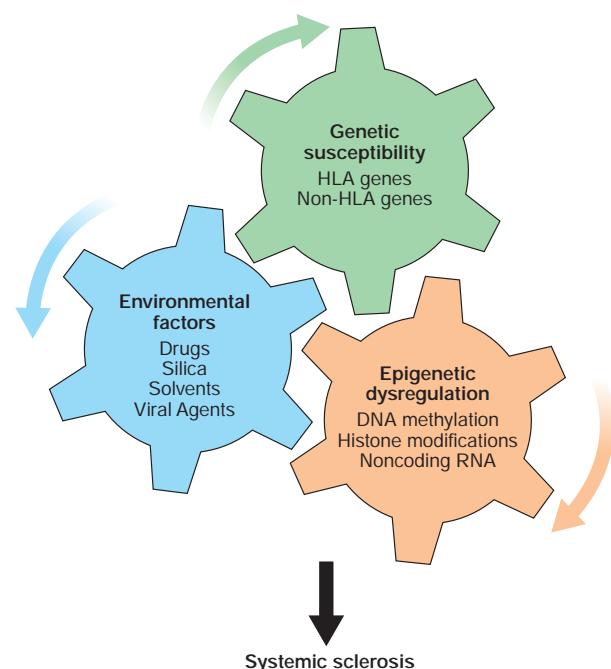


FIGURE 360-2 The interplay of genetic risk factors and environmental exposure-induced epigenetic modifications underlying the complex pathogenesis of systemic sclerosis. HLA, human leukocyte antigen. (Reproduced with permission from Amr Sawalha and Pei-Suen Tsou, University of Pittsburgh and University of Michigan.)

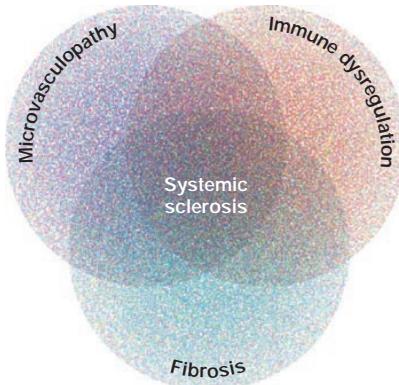


FIGURE 360-3 The pathogenic systemic sclerosis (SSc) triad. The characteristic constellation of synchronously occurring vasculopathy, autoimmunity/inflammation, and fibrosis distinguishes SSc and underlies its protean clinical manifestations.

ANIMAL MODELS OF DISEASE

There is no single animal model of SSc that fully reproduces the three cardinal processes that underlie pathogenesis. Tight-skin mice (*Tsk1/+*) spontaneously develop skin (hypodermal) fibrosis due to a duplication mutation in the fibrillin-1 gene. Mutant fibrillin-1 protein disrupts extracellular matrix assembly, leading to aberrant activation of the profibrotic transforming growth factor β (TGF- β). In humans, fibrillin-1 mutations are associated with Marfan's disease and stiff skin syndrome but have not been reported in SSc. In mice, skin and lung fibrosis accompanied by variable vasculopathy and autoimmunity can be elicited by repeated injection of bleomycin or angiotensin II or by transplantation of HLA-mismatched bone marrow or spleen cells. Targeted genetic modifications in mice give rise to new disease models for investigating the pathogenetic roles of individual molecules, pathways, and cell types. For example, mice lacking IRF5, the ciliary proteins SPAG17, tenascin-C, or peroxisome proliferator-activated receptor (PPAR)- γ , or constitutively overexpressing β -catenin, Wnt10b, sirtuin 3, Fra2, PDGFR α , or adiponectin are either resistant or hypersensitive to experimental scleroderma or spontaneously develop multiple-organ fibrosis. These disease models can be useful as experimental tools to understand SSc pathogenesis and discover and validate novel targets for therapy.

MICROANGIOPATHY

In a progressive model of disease pathogenesis (Fig. 360-4), vascular injury is an early and possibly primary pathogenic event that underlies protean manifestations of small vessel vasculopathy.

Prominent microangiopathy in multiple vascular beds is a hallmark of SSc with important clinical sequelae including mucocutaneous telangiectasia, Raynaud's phenomenon, ischemic digital ulcers, scleroderma renal crisis, myocardial involvement, and PAH. Raynaud's phenomenon, commonly the initial manifestation of SSc, is characterized by altered blood-flow response to cold challenge in small digital arteries. This reversible functional abnormality is associated with autonomic and peripheral nervous system alterations, including impaired production of the neuropeptide calcitonin gene-related peptide from sensory afferent nerves and heightened sensitivity of α_2 -adrenergic receptors on vascular smooth-muscle cells. Isolated (primary) Raynaud's disease is common, generally benign, and nonprogressive. In contrast, SSc-associated secondary Raynaud's phenomenon often progresses to irreversible structural changes in the small blood vessels, culminating in ischemic digital tip ulcers, necrosis, and amputation.

Viruses, cytotoxic factors, chemokines, thrombogenic microparticles, alternate complement pathway activation, and autoantibodies targeting endothelial cells, phospholipids, and β_2 -glycoprotein I (β_2 GPI) have all been implicated as putative triggers of endothelial cell injury in SSc. Endothelial damage disrupts the production of vasodilatory (nitric oxide and prostacyclin) and vasoconstricting (endothelin-1) substances, while causing upregulation of intercellular adhesion molecule

1 (ICAM-1) and other surface adhesion molecules. Microvessels show enhanced permeability and transendothelial leukocyte diapedesis, activation of coagulation cascades, elevated thrombin production, and impaired fibrinolysis. Spontaneous platelet aggregation causes release of serotonin, platelet-derived growth factor (PDGF), and platelet alpha granules including thromboxane, a potent vasoconstrictor. Smooth-muscle cell-like myointimal cells accumulate in the media, potentially arising through a process called endothelial-mesenchymal transition (EndoMT). The basement membrane is thickened and reduplicated, and perivascular adventitial fibrosis develops. The vasculopathic process primarily affects capillaries, arterioles, and less commonly even large vessels in many organs, resulting in impaired blood flow and tissue ischemia. Progressive luminal occlusion due to intimal and medial hypertrophy, combined with persistent endothelial cell damage and adventitial fibrosis, establish a vicious cycle that underlies fibroproliferative vasculopathy and culminates in the striking absence of small blood vessels (rarefaction) in late-stage disease. Recurrent ischemia-reperfusion generates reactive oxygen species (ROS) that further damage the endothelium through peroxidation of membrane lipids. Paradoxically, the process of revascularization that normally reestablishes blood flow to ischemic tissue is defective in SSc despite elevated levels of other angiogenic factors. Moreover, bone marrow-derived circulating endothelial progenitor cells are reduced in number and impaired in function.

There is increasing evidence implicating EndoMT in the pathogenesis of SSc vasculopathy. The process of EndoMT is characterized by transition of endothelial cells into myofibroblasts accompanied by loss of endothelial cell markers and acquisition of myofibroblast markers associated with nuclear localization of the transcription factor Snail1. In arterioles and small arteries, EndoMT leads to accumulation of endothelial cell-derived myofibroblasts in the intima and media, resulting in fibroproliferative vasculopathy and luminal occlusion. In contrast, EndoMT affecting the capillary vessels leads to a destructive vasculopathy characterized by loss of endothelial cells and accumulation of interstitial myofibroblasts derived from endothelial cells, resulting in interstitial fibrosis and microvessel rarefaction, as can be observed by nailfold capillaroscopy. Widespread capillary loss combined with fibroproliferative vasculopathy affecting arterioles and arteries and impaired ability to repair and replace damaged vessels are hallmarks of SSc.

INFLAMMATION AND AUTOIMMUNITY

Cellular Immunity While the initial events triggering the activation of innate and adaptive autoimmunity in SSc are unknown, a number of observations support the inflammatory/autoimmune nature of SSc: near-universal presence of circulating autoantibodies with defined specificities; clustering of SSc with other autoimmune diseases; activated immune cells, including autoreactive T cells with oligoclonal antigen receptors, within target organs; prominent type I interferon (IFN) signatures, characterized by elevated expression of IFN-regulated genes, in a variety of immune cell types in circulation and in skin biopsies; elevated circulating levels and spontaneous mononuclear cell secretion of cytokines and chemokines such as interleukin (IL) 6, tumor necrosis factor, IL-4, IL-10, IL-17, IL-33, CCL2, and CXCL4; genetic association of SSc (shared with other autoimmune diseases) with variants of MHC and other immune response genes; and the rapid clinical response, fibrosis resolution, and vascular regeneration observed in some SSc patients treated with immunomodulatory or immunoablative therapies.

Circulating monocytes from SSc patients overexpress IFN-regulated genes such as Siglec-1, have reduced levels of caveolin-1, and exhibit a profibrotic phenotype. In early (edematous) stage SSc, mononuclear cell infiltrates composed of activated T cells, monocytes/macrophages, and dendritic cells can be detected in skin, lungs, and other affected organs even prior to fibrosis or vascular damage. Dendritic cells in close proximity to activated fibroblasts and myofibroblasts express toll-like receptors (TLRs) that are activated by self-nucleic acids and other endogenous ligands. TLR stimulation induces the secretion

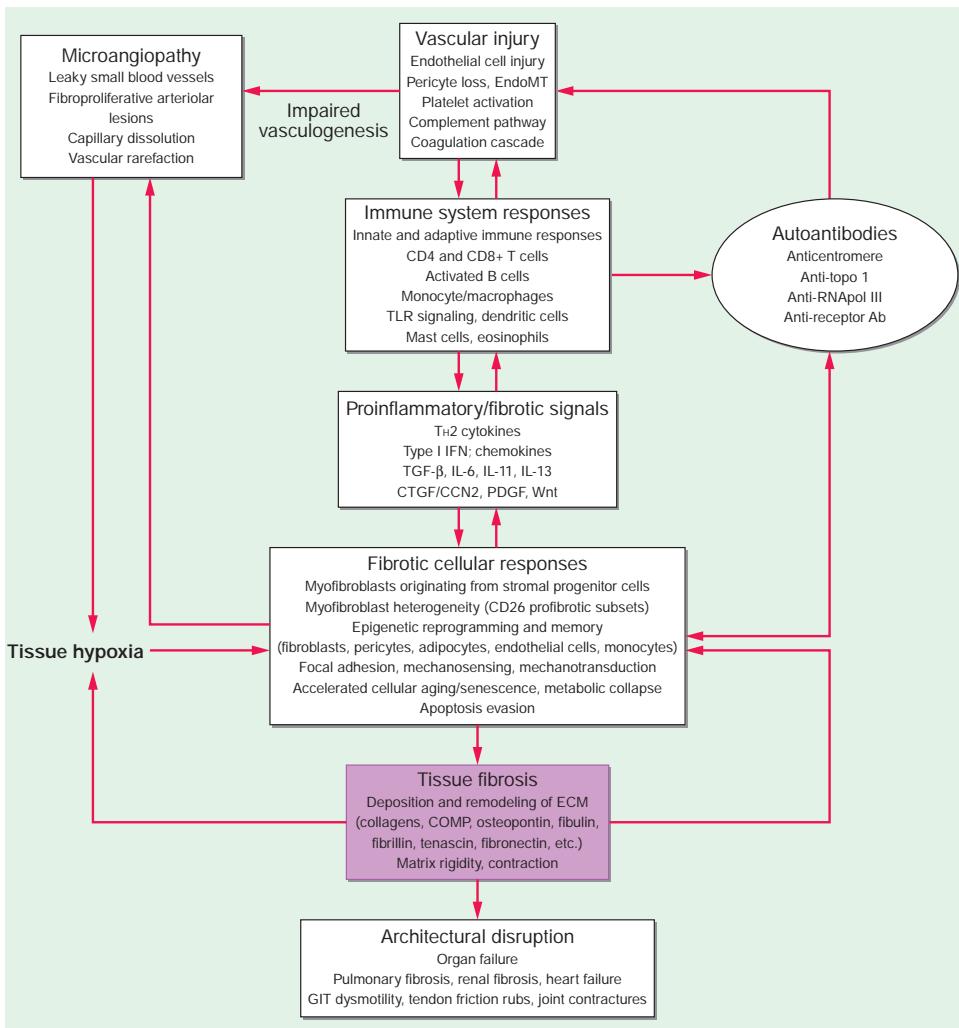


FIGURE 360-4 Integrated progressive model of systemic sclerosis (SSc) pathogenesis. Initial vascular insult in a genetically predisposed individual triggers a cascade of functional and structural vascular alterations associated with inflammation and autoimmunity. Early immune responses elicit fibroblast activation and differentiation, resulting in sustained pathologic fibrogenesis, irreversible tissue damage, and failure of affected organs. Vascular damage also leads to tissue ischemia that further contributes to progressive fibrosis and atrophy. Ab, antibody; CTGF, connective tissue growth factor; ECM, extracellular matrix; EndoMT, endothelial-mesenchymal transition; GIT, gastrointestinal tract; IFN, interferon; IL, interleukin; PDGF, platelet-derived growth factor; TGF-β, transforming growth factor β; TLR, toll-like receptor.

of mediators including IFN, IL-10, thymic stromal lymphopoietin (TSLP), and CXCL4, shaping the adaptive immune response and contributing to loss of immune tolerance. Tissue-infiltrating T cells express CD45 and HLA-DR activation markers and display restricted T-cell receptor signatures indicative of oligoclonal expansion in response to recognition of as-yet-unknown antigen. Of note, in patients diagnosed with SSc in close temporal association with cancer who are positive for RNA polymerase III antibody, the tumor commonly harbors genetic alterations in RNAPol3, which results in the generation of autoantigen-specific T-cell immunity and cross-reactive antibodies.

Circulating T cells in SSc express chemokine receptors and α_v integrin, accounting for their enhanced binding to endothelium and to fibroblasts, while endothelial cells express ICAM-1 and other adhesion molecules that facilitate leukocyte diapedesis. Activated T cells show a T_H2-polarized immune response driven by dendritic cells. The T_H2 cytokines IL-4, IL-13, IL-33, and TSLP induce fibroblast activation, whereas the T_H1 cytokine interferon γ (IFN-γ) blocks cytokine-mediated fibroblast activation and exhibits antifibrotic properties. Evidence for altered T_H17 and regulatory T-cell function in SSc has been reported. Type 2 innate lymphoid cells (iLCs), a recently discovered distinct lymphoid cell population implicated in type 2 immunity and

tissue remodeling, are also elevated in SSc skin biopsies. Alternately activated macrophages expressing CD163, which produce TGF-β and promote angiogenesis and tissue remodeling, are increased in the skin and lung in SSc. Regulatory T cells (Tregs) enforce immune tolerance, and although their frequency is elevated in the circulation and tissues in SSc patients, their immunosuppressive function appears to be defective. A recent report demonstrated that Tregs play a critical role in preventing spontaneous fibrosis in the skin, possibly by sequestering activated TGF-β. Some evidence implicates altered B-cell homeostasis and function in SSc. Circulating B cells show elevated CD19 and co-stimulatory molecules CD80 and CD86, suggesting B-cell chronic activation. Serum levels of a proliferation-inducing ligand (APRIL) and B-cell activating factor (BAFF), members of the TNF superfamily with potent effects on B-cell activation, are elevated in SSc and associated with extent of skin and lung involvement. B cells secrete IL-6, TGF-β, and other profibrotic cytokines implicated in pathogenesis. Thus, B-cell hyperactivity might directly contribute to the inflammatory and fibrotic processes in SSc, as well as generation of autoantibodies.

Humoral Autoimmunity Circulating antinuclear antibodies (ANAs) can be detected in virtually all patients with SSc, even in

TABLE 360-4 Major Systemic Sclerosis (SSc)–Specific Autoantibodies and Principal Associated Features

TARGET ANTIGEN	SSc SUBSET	PROMINENT CHARACTERISTIC CLINICAL ASSOCIATION
Topoisomerase I (Scl-70) Speckled pattern	dcSSc	Tendon friction rubs, digital ischemic ulcers, scleroderma, extensive skin involvement, early ILD, cardiac involvement, scleroderma renal crisis
Centromere proteins Discrete speckled (centromere) pattern	IcSSc	Digital ischemic ulcers, calcinosis cutis, isolated PAH; renal crisis rare
RNA polymerase III Speckled pattern	dcSSc	Rapidly progressive skin involvement, tendon friction rubs, joint contractures, GAVE, renal crisis, contemporaneous cancers; digital ulcers rare
U3-RNP (fibrillarin) Nucleolar pattern	dc/IcSSc	PAH, ILD, scleroderma renal crisis, GI tract involvement, myositis
Th/T ₀ Nucleolar pattern	IcSSc	ILD, PAH
PM/Scl Nucleolar pattern	IcSSc	Calcinosis cutis, ILD, myositis overlap
Ku Speckled pattern	Overlap	SLE, myositis overlap
U1-RNP Speckled pattern	MCTD	PAH, inflammatory arthritis, myositis overlap
U11/U12 RNP Speckled pattern	dc/IcSSc	ILD

Abbreviations: dcSSc, diffuse cutaneous SSc; GAVE, gastric antral vascular ectasia; GI, gastrointestinal; ILD, interstitial lung disease; IcSSc, limited cutaneous SSc; MCTD, mixed connective tissue disease; PAH, pulmonary arterial hypertension; SLE, systemic lupus erythematosus.

early and possibly preclinical stages of disease. In addition, several SSc-specific autoantibodies with distinct patterns of immunofluorescence show strong associations with unique disease phenotypes as well as HLA haplotype (Table 360-4). Owing to their specificity, mutual exclusivity, and association with unique disease manifestations, SSc-associated autoantibodies have substantial utility in clinical practice for diagnosis and risk stratification, while their role in monitoring disease activity or response to therapy remains uncertain. Recently, antibodies directed against fibrillin-1, matrix metalloproteinases, cell surface markers, angiotensin II receptor, endothelin-1 receptor, or the PDGF receptor have been identified in patients with SSc, although their clinical relevance is not yet established. These antibodies have functional receptor agonist activity and might have direct pathogenic roles.

A variety of mechanisms have been proposed to account for the generation of SSc-associated autoantibodies. Proteolytic cleavage, increased expression or altered subcellular localization of normal proteins, or their alterations due to mutation in the case of certain tumors could lead to their immune recognition as neoepitopes, resulting in a break of immune tolerance.

FIBROSIS

Fibrosis synchronously affecting multiple organs is a distinguishing feature of SSc. The process is characterized by replacement of normal tissue architecture with rigid, avascular, and relatively acellular connective tissue. Fibrosis in SSc follows, and is a consequence of, inflammation and microvascular damage (Fig. 360-4). Fibroblasts are mesenchymal cells primarily responsible for the functional and structural integrity of connective tissue. Upon their activation by extracellular cues, fibroblasts proliferate; migrate; secrete collagens and other matrix molecules, growth factors, chemokines, and cytokines; and transdifferentiate into contractile myofibroblasts. Under normal conditions, these are responses self-limited to accomplish tissue regulated repair and regeneration. In contrast, when these responses become

sustained and amplified, pathologic fibrosis results. A panoply of stimulatory signals are potentially implicated in SSc pathogenesis. In addition to TGF- β , these include paracrine mediators IL-6, IL-11, IL-13, and IL-23, morphogens and Wnt ligands, connective tissue growth factor (CTGF), PDGF, lysophosphatidic acid, endothelin-1, hypoxia, ROS, thrombin, and mechanical forces; these signals might contribute to sustained fibroblast activation underlying maladaptive repair in SSc. Buildup of damage-associated endogenous ligands for TLR4 (EDA-fibronectin and tenascin-C) and TLR9 (mitochondrial DNA) within the microenvironment further contributes to nonresolving fibrosis via unchecked TLR activation and innate immune signaling.

In addition to tissue-resident fibroblasts and transformed myofibroblasts, bone marrow–derived circulating mesenchymal progenitor cells also contribute to fibrosis. The factors that regulate the differentiation of mesenchymal progenitor cells and their trafficking from the circulation into lesional tissue are unknown. Endothelial cells in injured arterioles and small arteries undergo EndoMT, giving rise to myofibroblasts that drive perivascular fibrosis. Epithelial cells, preadipocytes, and tissue fibroblasts are all putative sources of pathogenic myofibroblasts. Although myofibroblasts are transiently found in normal wound healing, their persistence in fibrotic tissue, possibly due to their ability to evade apoptosis, contributes to scar formation.

Planted SSc fibroblasts display an abnormally activated phenotype ex vivo, characterized by increased collagen production, spontaneous ROS generation, prominent stress fibers, and constitutive expression of alpha smooth-muscle actin. Persistence of the “scleroderma phenotype” during serial ex vivo passage of SSc fibroblasts may reflect autocrine TGF- β stimulatory loops, deregulated microRNA expressions, cell-autonomous metabolic changes, or stable acquired epigenetic modifications. More recently, tools such as single-cell RNA sequencing have revealed functional heterogeneity among fibrotic fibroblasts.

PATHOLOGY

While pathologic findings vary across anatomic sites, the distinguishing hallmarks of SSc irrespective of the organ system are widespread microangiopathy (fibroproliferative vasculopathy), capillary loss and obliteration, and fibrosis. In early-stage disease, perivascular inflammatory cell infiltrates composed of T and B lymphocytes, activated monocytes and macrophages, and mast cells may be detected in multiple organs. A noninflammatory obliterative microangiopathy in the heart, lungs, kidneys, and gastrointestinal tract is a prominent late finding. Fibrosis most prominently affects the skin, lungs, cardiovascular system, gastrointestinal tract, tendon sheaths, perifascicular tissue surrounding skeletal muscle, and some endocrine organs such as the thyroid gland. Excessive accumulation of collagens and other structural matrix macromolecules progressively disrupts normal architecture, resulting in impaired function and failure of affected organs.

SKIN

In the skin, the dermis is thickened due to accumulation of broad bundles of homogenized collagen oriented parallel to the epithelium (Fig. 360-5A). Adnexal glands are atrophic, and loss of periadnexal and intradermal white adipose tissue and its replacement with collagen can be striking. While perivascular mononuclear cell infiltrates may be seen early, established skin fibrosis shows absence of inflammation.

LUNGS

Autopsy studies universally show evidence of lung involvement in both limited and diffuse cutaneous subsets of SSc. Most common is the nonspecific interstitial pneumonia (NSIP) pattern characterized variable interstitial fibrosis and mild chronic inflammation with T lymphocytes, macrophages, and eosinophils. With progression, interstitial fibrosis and vascular damage dominate, often coexisting within the same biopsy. The usual interstitial pneumonia (UIP) pattern of spatial and temporal heterogeneity of inflammation and fibrosis and fibrotic foci, a hallmark of idiopathic pulmonary fibrosis, is less common in SSc (Fig. 360-5B). Fibrosis of the alveolar septae results in obliteration of the airspaces and loss of pulmonary blood vessels. This process impairs gas exchange and contributes to pulmonary hypertension. Intimal

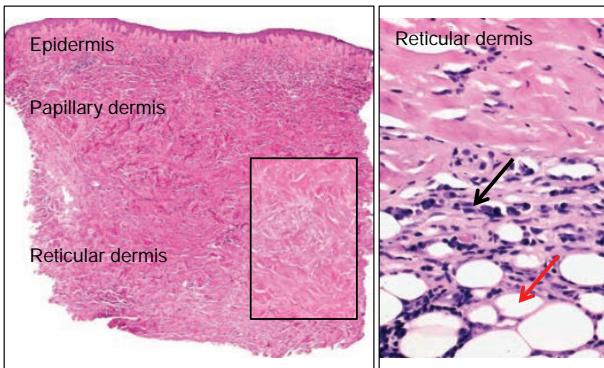
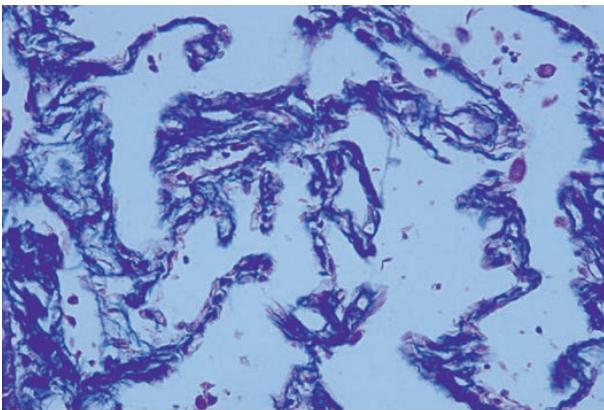
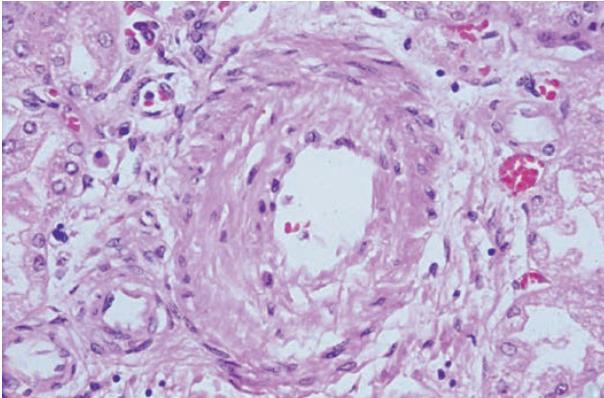
**A****B****C**

FIGURE 360-5 Pathologic findings in multiple organs in systemic sclerosis (SSc). **A.** Left panel: The skin is thickened due to fibrotic expansion of the dermis. Inset, higher magnification showing thick hyalinized collagen bundles replacing skin appendages. Right panel: Mononuclear inflammatory cells in the dermis and intradermal adipose tissue. **B.** Early SSc interstitial lung disease. Diffuse fibrosis of the alveolar septae and a chronic inflammatory cell infiltrate. Trichrome stain. **C.** Pulmonary arterial obliterative vasculopathy. Striking intimal hyperplasia and luminal narrowing of small artery, with little inflammation and minimal interstitial lung fibrosis, in a patient with SSc pulmonary arterial hypertension.

thickening of the pulmonary arteries, best seen with elastin stain, underlies SSc-associated PAH (**Fig. 360-5C**) and, at autopsy, is often associated with pulmonary emboli and myocardial fibrosis. Patients with SSc-associated PAH also show fibrosis and intimal proliferation in preseptal venules and veins in the lung, accounting for veno-occlusive disease. Lymphocytic bronchiolitis involving the submucosa of the terminal bronchioles is occasionally seen.

GASTROINTESTINAL TRACT

Pathologic changes can be found at any level from the mouth to the rectum. Atrophy and fibrosis of the muscularis propria and characteristic vascular lesions are prominent in the lower esophagus, while striated muscle in the upper third of the esophagus is generally spared. Collagenous replacement of the intestinal tract architecture results in impaired smooth-muscle contractility and diminished peristaltic activity, underlying gut dysmotility, bacterial overgrowth, small-bowel pseudo-obstruction, and perforation. Chronic gastroesophageal reflux is associated with esophageal inflammation, mucosal ulceration, and stricture formation and may lead to Barrett's metaplasia with attendant risk of adenocarcinoma. Esophageal dilatation and reflux may aggravate ILD due to chronic microaspiration.

KIDNEYS

In the kidneys, vascular lesions affecting the interlobular and arcuate arteries predominate. Chronic renal ischemia is associated with shrunken glomeruli. Patients with scleroderma renal crisis, a life-threatening acute complication of SSc, show acute fibrinoid necrosis of afferent arterioles, followed by intimal proliferation (onion-skin pattern) and ischemic collapse of glomeruli. These changes are reminiscent of thrombotic microangiopathies such as atypical hemolytic-uremic syndrome (**Chap. 115**) and are accompanied by thrombosis, thrombocytopenia due to platelet consumption, and intravascular hemolysis. Evidence of complement activation may be seen in kidney biopsies. Extensive vascular thrombosis, glomerular collapse, and peritubular capillary deposits predict irreversible renal failure.

HEART

Subclinical cardiac pathology is common in SSc and may affect the myocardium and pericardium. The characteristic arteriolar lesions in the heart are concentric intimal hypertrophy and luminal narrowing, patchy contraction band necrosis, loss of cardiac myocytes, and myocardial fibrosis due to microvascular involvement and ischemia-reperfusion injury. Fibrosis of the conduction system is also common, especially at the sinoatrial node. The frequency of epicardial atherosclerotic coronary artery disease may be increased in SSc compared to the general population, similar to other systemic inflammatory diseases. Pericardial involvement with chronic inflammatory infiltrates and fibrinous exudates is common and is sometimes associated with pericardial effusions.

PATHOLOGY IN OTHER ORGANS

Synovitis of the hands may occur in SSc; with disease progression, the synovium becomes fibrotic, and in contrast to rheumatoid disease, pannus formation and bone resorption are uncommon. Fibrosis of tendon sheaths and fascia, sometimes accompanied by calcifications, produces palpable and sometimes audible tendon friction rubs. Inflammation and, in later stages, atrophy and fibrosis of skeletal muscles are common findings and are similar to those in polymyositis. Fibrosis of the thyroid and of the minor salivary glands may be seen and underlie hypothyroidism and the sicca syndrome. Placentas from SSc pregnancies show decidual vasculopathy, which is associated with poor perinatal outcomes and fetal death.

CLINICAL FEATURES

OVERVIEW

SSc is truly a systemic disease that can affect virtually any organ (**Fig. 360-1** and **Table 360-5**). Although a dichotomous stratification into diffuse and limited cutaneous subsets (**Table 360-2**) is useful, SSc is far more complex, and multiple distinct clusters or endophenotypes of SSc with characteristic manifestations and trajectories and outcomes can be recognized within each subset. Unique endophenotypes associate with autoantibodies with distinct and mutually exclusive specificities (**Table 360-4**). Moreover, patients with “overlap” have typical features of SSc coexisting with clinical and laboratory evidence of another autoimmune disease, most commonly polymyositis, Sjögren's syndrome, polyarthritis, autoimmune liver disease, or SLE.

TABLE 360-5 Frequency of Clinical Organ Involvement in Limited Cutaneous and Diffuse Cutaneous Systemic Sclerosis (SSc)

FEATURES	LIMITED CUTANEOUS SSc (%)	DIFFUSE CUTANEOUS SSc (%)
Skin involvement	90 ^a	100
Raynaud's phenomenon	99	98
Ischemic digital ulcers	50	25
Esophageal involvement	90	80
Interstitial lung disease	35	65
Pulmonary arterial hypertension	15	15
Myopathy	11	23
Clinical cardiac involvement	9	12
Scleroderma renal crisis	2	15
Calcinosis cutis	40	35

^aApproximately 10% of patients have SSc *sine* scleroderma.

INITIAL CLINICAL PRESENTATION

Characteristic initial presentation is quite different in patients with the diffuse (dcSSc) versus limited (lcSSc) cutaneous forms of the disease. In dcSSc, the interval between Raynaud's phenomenon and onset of other disease manifestations is typically brief (weeks to months). Soft tissue swelling, puffy fingers, and pruritus are signs of the early inflammatory "edematous" phase. The fingers, distal limbs, and face are usually affected first. Diffuse hyperpigmentation of the skin, carpal tunnel syndrome, arthralgias, muscle weakness, fatigue, and decreased joint mobility are common. During the ensuing weeks to months, the inflammatory edematous phase evolves into the "fibrotic" phase, with skin induration associated with hair loss, reduced production of skin oils, and decline in sweating capacity. Progressive flexion contractures of the fingers ensue. The wrists, elbows, knees, and ankles become stiff due to fibrosis of the supporting joint structures. While advancing skin involvement is the most visible manifestation of early dcSSc, important and clinically silent internal organ involvement can occur during this stage. The initial 4 years from disease onset is the period of most rapidly evolving and potentially irreversible lung and renal damage. If organ failure does not occur during this phase of dcSSc, the systemic process may plateau and stabilize.

Compared to dcSSc, the course of lcSSc tends to be more indolent. The interval between onset of Raynaud's phenomenon and disease manifestations such as gastroesophageal reflux disease (GERD), cutaneous telangiectasia, ischemic digital ulcers, or soft tissue calcifications can be as long as years. Scleroderma renal crisis, significant ILD, and tendon friction rubs occur rarely in lcSSc, whereas PAH and overlap with keratoconjunctivitis sicca, polyarthritis, cutaneous vasculitis, and biliary cirrhosis can develop even many years after disease onset.

ORGAN INVOLVEMENT

RAYNAUD'S PHENOMENON

Raynaud's phenomenon, the most frequent extracutaneous complication of SSc, is characterized by episodic vasoconstriction in the fingers and toes, sometimes also affecting the tip of the nose and earlobes. Attacks are reversible, and can be triggered by a decrease in temperature, as well as emotional stress and vibration. Attacks typically start with pallor of the fingers, followed by cyanosis of variable duration. Hyperemia ensues spontaneously or with rewarming of the digit. The progression of the three color phases reflects the underlying vasoconstriction, ischemia, and reperfusion. It is important to note that up to 5% of the general population has Raynaud's phenomenon. In the absence of signs or symptoms of an underlying condition, Raynaud's phenomenon is classified as primary (Raynaud's disease), which represents an exaggerated physiologic vasomotor response to cold. Secondary Raynaud's phenomenon occurs in SSc and other connective tissue diseases, hematologic and endocrine conditions, and



FIGURE 360-6 Digital necrosis. Sharply demarcated necrosis of the fingertip secondary to ischemia in a patient with limited cutaneous systemic sclerosis (SSc) associated with severe Raynaud's phenomenon.

occupational disorders, and can complicate treatment with beta blockers and anticancer drugs such as cisplatin and bleomycin. Distinguishing primary Raynaud's disease from secondary Raynaud's phenomenon can present a diagnostic challenge. Raynaud's disease is supported by the following: absence of an underlying cause; a family history of Raynaud's phenomenon; absence of digital tissue necrosis or ulceration; and a negative ANA test. Secondary Raynaud's phenomenon tends to occur at an older age, is more severe (episodes are more frequent, prolonged, and painful), and is frequently complicated by ischemic digital ulcers and loss of digits (**Fig. 360-6**).

Nailfold capillaroscopy using a low-power stereoscopic microscope or ophthalmoscope permits visualization of nailbed cutaneous capillaries under immersion oil (**Fig. 360-7**). Raynaud's disease is associated with evenly spaced parallel vascular loops, whereas in secondary Raynaud's phenomenon, nailfold capillaries are distorted with widened and irregular loops, dilated lumen, microhemorrhages, and areas of vascular "dropout." Thus, nailfold capillaroscopy can be helpful for both differentiating primary from secondary Raynaud's phenomenon and for establishing the early diagnosis of SSc.

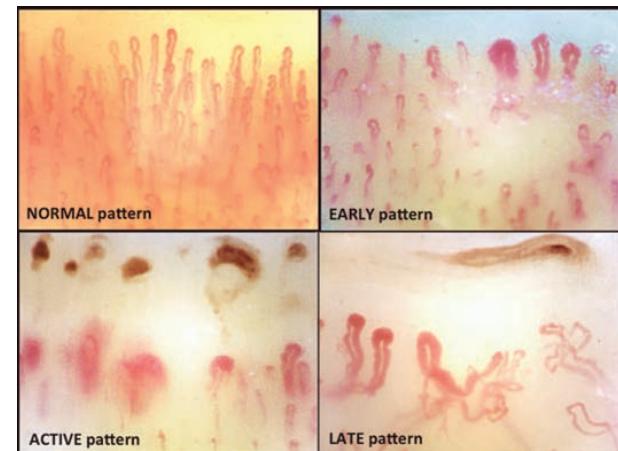


FIGURE 360-7 Systemic sclerosis-associated nailfold capillary alterations. In healthy subjects, note regularly arrayed and uniform-size "hairpin" microvessels. In early pattern, note dilations of microvessels and symmetrically increased microvessels (giant capillaries). In active pattern, note giant capillaries, collapse with microhemorrhages, and loss of capillaries. In late pattern, note massive loss of capillaries, fibrosis, and neoangiogenesis with secondary dilations (nailfold videocapillaroscopy; magnification 220×). (Courtesy Professor Maurizio Cutolo, University of Genoa, Italy.)

SKIN FEATURES

Bilateral symmetrical skin thickening is the hallmark that distinguishes SSc from other connective tissue diseases. Skin involvement starts in the fingers and characteristically advances from distal to proximal extremities in an ascending fashion. Some patients note diffuse tanning in the absence of sun exposure as a very early manifestation. In dark-skinned individuals, vitiligo-like hypopigmentation may occur. Pigment loss sparing the perifollicular areas gives rise to a “salt-and-pepper” appearance of the skin, most prominently on the scalp, upper back, and chest. Dermal sclerosis obliterating hair follicles, sweat glands, and eccrine and sebaceous glands causes hair loss, decreased sweating, and xerosis and itching in affected areas of the skin. Transverse creases on the dorsum of the fingers disappear (Fig. 360-8). Fixed flexion contractures of the fingers cause reduced hand mobility and lead to muscle atrophy. Skin and subjacent tendon fibrosis accounts for fixed contractures of the wrists, elbows, and knees. Thick ridges at the neck due to firm adherence of skin to the underlying platysma muscle interfere with neck extension.

Patients with established SSc may show a characteristic “mauskopf” facial appearance with taut and shiny skin, loss of wrinkles, and occasionally an expressionless facies due to reduced mobility of the eyelids, cheeks, and mouth. Thinning of the lips with accentuation of the central incisor teeth and prominent perioral radial furrowing (rhytides) complete the picture. Reduced oral aperture (microstomia) interferes with eating and oral hygiene. The nose assumes a pinched, beak-like appearance. In late-stage disease, the skin becomes thin and atrophic and is firmly bound to the subcutaneous fat (tethering). Dilated skin capillaries 2–20 mm in diameter (telangiectasia), reminiscent of hereditary hemorrhagic telangiectasia, are frequently on the face, hands, lips, and oral mucosa (Fig. 360-9). The number of telangiectasias correlates with the severity of microvascular disease, including PAH. Breakdown of atrophic skin leads to chronic ulcerations at the extensor surfaces of the proximal interphalangeal joints, the volar pads of the fingertips, and bony prominences such as elbows and malleoli. Ulcers are often painful, heal slowly, and become secondarily infected, resulting in osteomyelitis. Healing of ischemic fingertip ulcerations leaves characteristic fixed digital “pits.” Loss of soft tissue at the fingertips due to ischemia may be associated with striking resorption of the terminal phalanges (acro-osteolysis) (Fig. 360-10).

Dystrophic calcifications in the skin, subcutaneous, and soft tissues (calcinosus cutis) in the presence of normal serum calcium and phosphate levels occur in up to 40% of patients, most commonly in those with long-standing anti-centromere antibody-positive lcSSc. Calcific deposits, composed of calcium hydroxyapatite crystals, vary in size from tiny punctate lesions to large conglomerate masses, and can be readily visualized on plain radiographs or dual-energy CT. These deposits occur when calcium precipitates in tissue damaged by



FIGURE 360-8 Sclerodactyly. Note skin induration on the fingers and fixed flexion contractures of proximal interphalangeal joints in a patient with limited cutaneous systemic sclerosis (lcSSc).



A



B

FIGURE 360-9 Cutaneous vascular changes in systemic sclerosis. A. Vascular changes at the nailfold in a patient with lcSSc. B. Telangiectasia on the face.

inflammation, hypoxia, or local trauma. Common locations include the finger pads, palms, extensor surfaces of the forearms, and the olecranon and prepatellar bursae (Fig. 360-11). Large calcific deposits can cause pain and nerve compression and may ulcerate through the



FIGURE 360-10 Acro-osteolysis. Note dissolution of distal terminal phalanges (arrows). Acro-osteolysis is associated with digital ischemia and is seen in patients with long-standing limited cutaneous systemic sclerosis (lcSSc) and Raynaud's phenomenon.



A



B

FIGURE 360-11 Calcinosis cutis in systemic sclerosis. A. Note calcific deposit breaking through the skin in a patient with limited cutaneous systemic sclerosis (lcSSc). B. Dual-energy computed tomography showing calcific deposits at the proximal interphalangeal joints.

overlying skin with drainage of chalky white material and secondary infections. Paraspinal sheet calcifications may cause neurologic complications.

PULMONARY FEATURES

The two principal forms of lung involvement in SSc, ILD and pulmonary vascular disease, are frequent and together account for a majority of SSc-related deaths. Survival is particularly poor in SSc patients with concurrent presence of these two processes. Less common pulmonary complications of SSc include aspiration pneumonitis complicating chronic gastroesophageal reflux, pulmonary hemorrhage due to endobronchial telangiectasia, obliterative bronchiolitis, pleural reactions, restrictive physiology due to chest wall fibrosis, spontaneous pneumothorax, and drug-induced lung toxicity. The incidence of lung cancer is increased in SSc.

Interstitial Lung Disease While evidence of ILD can be found in up to 65% of SSc patients by high-resolution computed tomography (HRCT), clinically significant ILD develops in 16–43%; the frequency varies depending on the detection method used. Risk factors for significant ILD include male sex, African-American race, diffuse

skin involvement, severe gastroesophageal reflux, and presence of topoisomerase-I (Scl-70) autoantibodies, whereas anti-centromere antibody-positive patients have a reduced risk of ILD. Additional risk factors for significant ILD include low forced vital capacity (FVC) or single-breath diffusing capacity of the lung for carbon monoxide (DL_{CO}) at initial presentation. Esophageal dilatation with chronic acid reflux in SSc causes recurrent micro-aspiration, a risk factor for the development and progression of ILD. The most rapid progression in ILD generally occurs early in the disease course (within the first 3–5 years), when the FVC can decline by 30% per year. In contrast, new onset of ILD is rare in SSc patients with long-standing disease.

Pulmonary involvement can remain asymptomatic until it is advanced. The most common presenting respiratory symptoms—exertional dyspnea, fatigue, and reduced exercise tolerance—are subtle and slowly progressive. A chronic dry cough may be present. Physical examination may reveal fine inspiratory “Velcro” crackles at the lung bases. Pulmonary function testing (PFT) is relatively insensitive for detecting early pulmonary involvement. In patients with established SSc-ILD, PFT typically shows a restrictive ventilatory defect (FVC <70% predicted and/or forced expiratory volume in 1 s [FEV_1]/FVC ratio >0.8) and reduced total lung capacity (TLC) and diffusing capacity (DL_{CO}). A reduction in DL_{CO} that is significantly out of proportion to the reduction in lung volumes should raise suspicion for pulmonary vascular disease but may also be due to anemia. Oxygen desaturation with exercise is common.

Chest radiography can be used as an initial screening tool to rule out infection and other causes of respiratory symptoms in SSc, but compared to HRCT, it is relatively insensitive for detection of early ILD. Characteristic imaging findings include lower lobe subpleural reticular linear opacities and ground-glass opacifications with an apicobasal gradient, even in asymptomatic patients with normal PFTs (Fig. 360-12). Additional HRCT findings include mediastinal lymphadenopathy, pulmonary nodules, traction bronchiectasis, and uncommonly, honeycomb changes. The extent of interstitial changes on chest HRCT at baseline is a predictor of ILD progression and mortality. While bronchoalveolar lavage (BAL) can demonstrate inflammatory cells in the lower respiratory tract and may be useful for ruling out tuberculosis and other infections, it does not appear to be useful for SSc diagnosis or for identifying reversible alveolitis. Surgical lung biopsy in SSc is

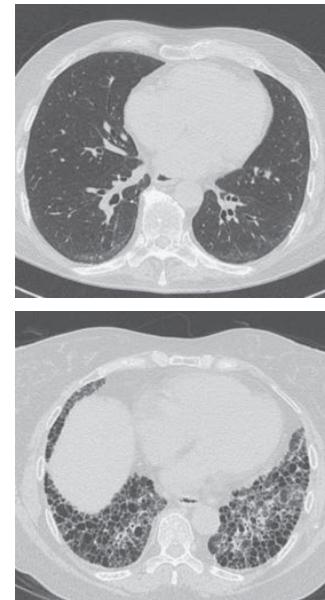


FIGURE 360-12 High-resolution chest CT findings in systemic sclerosis. Top panel: Early interstitial lung disease with subpleural reticular and ground-glass opacities in the lower lobes. Patient in supine position. Bottom panel: Extensive lung fibrosis with coarse reticular honeycombing and traction bronchiectasis. (Courtesy of Rishi Agrawal, Northwestern University.)

indicated only in patients with atypical findings on chest imaging. The histologic pattern on lung biopsy may predict the risk of progression of ILD, with the NSIP pattern having a better prognosis than UIP.

Pulmonary Arterial Hypertension PAH results from vascular remodeling of small ($<500 \mu\text{m}$) pulmonary arteries. PAH develops in 8–12% of patients with SSc as a late complication and can be an isolated abnormality or associated with ILD. PAH is defined as a mean pulmonary artery pressure $\geq 20 \text{ mmHg}$ with a pulmonary capillary wedge pressure $\leq 15 \text{ mmHg}$ and pulmonary vascular resistance $> 3 \text{ Wood units}$. The natural history of SSc-associated PAH is variable but often follows a progressive course leading to right heart failure. The 3-year survival of SSc patients with untreated PAH is $< 50\%$. Risk factors include limited cutaneous disease, older age at disease onset, high numbers of cutaneous telangiectasia, and antibodies to centromere, U3-RNP (fibrillarin), and B23. Mutations in the *BMPR2* gene implicated in idiopathic PAH are not associated with SSc-PAH.

In SSc, PAH is often asymptomatic in early stages. Patients present with exertional dyspnea and reduced exercise capacity. With progression, angina, near-syncope, and symptoms and signs of right-sided heart failure appear. Physical examination may show tachypnea, a loud pulmonic component of the S_2 heart sound, pulmonic/tricuspid regurgitation murmur, palpable right ventricular heave, elevated jugular venous pressure, and dependent edema. Doppler echocardiography is a noninvasive screening method for estimating the pulmonary arterial pressure. In light of the poor prognosis of untreated PAH and better therapeutic response in patients with early diagnosis, SSc patients should be screened for PAH at initial evaluation and annually thereafter. Estimated pulmonary artery systolic pressure $> 40 \text{ mmHg}$ at rest or tricuspid regurgitation jet velocities $> 3 \text{ m/s}$ suggest PAH. Pulmonary function testing may show a reduced DL_{CO} in isolation or out of proportion with the severity of restriction. Because echocardiography can over- or underestimate pulmonary artery pressures, cardiac catheterization is required to confirm the diagnosis of suspected PAH; assess its severity, including the degree of right heart dysfunction; rule out veno-occlusive disease and other cardiac (postcapillary) causes of pulmonary hypertension; and provide prognostic parameters. Distinguishing PAH in SSc patients from pulmonary hypertension secondary to pulmonary fibrosis and hypoxia can be difficult. Serum levels of N-terminal pro-brain natriuretic peptide (NT-proBNP) correlate with the presence and severity of PAH, as well as survival. While NT-proBNP can be useful in PAH screening and in monitoring the response to treatment, elevated levels are not specific for PAH and also occur in other forms of right and left heart disease. Despite more favorable hemodynamics of SSc-associated PAH, its prognosis is worse and treatment response poorer than for idiopathic PAH. This is most likely due to frequent concurrence of ILD and cardiac disease in patients.

GASTROINTESTINAL INVOLVEMENT

Variable involvement of the gastrointestinal (GI) tract, which can affect any level, is the most common internal organ manifestation of SSc, seen in up to 90% of SSc patients with both limited and diffuse cutaneous disease (Table 360-6). Severe GI tract involvement is associated with male sex and specific autoantibodies. The pathologic findings of GI involvement in SSc include fibrosis, smooth-muscle atrophy, and obliterative small vessel vasculopathy throughout the length of the GI tract. Together they have major impact on quality of life, malnutrition, and mortality.

Upper Gastrointestinal Tract Involvement Decreased oral aperture interferes with regular dental hygiene. Loss of periodontal ligament attaching teeth to the alveolar bone leads to teeth loosening. Additional oropharyngeal manifestations due to a combination of xerostomia, shortened frenulum, and resorption of the mandibular condyles cause much distress. Most SSc patients show symptoms of GERD (heartburn, regurgitation, and dysphagia) due to a combination of reduced lower esophageal sphincter pressure resulting in reflux, impaired esophageal clearance of refluxed gastric contents due to diminished motility, and delayed gastric emptying. Calcium channel

TABLE 360-6 Prominent Gastrointestinal Manifestations of Systemic Sclerosis and Their Management

SITE	PRINCIPAL MANIFESTATION	MANAGEMENT
Oropharynx	Diminished oral aperture Dry mouth Periodontitis, gingivitis Swallowing difficulty	Periodontal care Artificial saliva Swallowing therapy
Esophagus	Reflux Dysphagia Strictures Barrett's metaplasia	Lifestyle modifications Prokinetic drugs Proton pump inhibitors Endoscopic procedures
Stomach	Gastroparesis Gastric antral vascular ectasia (GAVE, watermelon stomach)	Prokinetic agents Endoscopic laser cryotherapy
Small and large intestines	Bacterial overgrowth (SIBO) Diarrhea/constipation Pseudo-obstruction Pneumatosis intestinalis Malabsorption Colonic pseudodiverticula	Laxatives Prokinetic agents Rotating antibiotics Octreotide Parenteral nutritional support
Anorectum	Sphincter incompetence	Biofeedback, sacral nerve stimulation, surgery

Abbreviation: SIBO, small intestinal bacterial overgrowth.

antagonists and phosphodiesterase inhibitors commonly used to treat Raynaud's phenomenon in SSc can further aggravate reflux. Esophageal manometry shows abnormal motility in most patients, even in the absence of symptoms. Common extraesophageal GERD manifestations in SSc include hoarseness, cough, and chronic microaspiration, which can aggravate underlying ILD. Characteristic chest CT findings include dilated patulous esophagus with intraluminal air. Esophageal dilation is associated with the severity of ILD. Endoscopy may be indicated in patients with dysphagia in order to rule out opportunistic infections with *Candida*, herpes virus, and cytomegalovirus. Severe erosive esophagitis may be found in patients with minimal symptoms. Esophageal strictures and Barrett's esophagus may complicate chronic GERD in SSc patients. Because Barrett's metaplasia is associated with increased risk of adenocarcinoma, these patients require regular surveillance endoscopy with biopsy.

Gastroparesis with early satiety, abdominal distention, and aggravated reflux symptoms is common. Barium contrast studies are neither sensitive nor specific for evaluation of gastric involvement in SSc. Gastric antral vascular ectasia (GAVE) in the antrum may occur. These subepithelial lesions, reflecting the widespread small vessel vasculopathy of SSc, are called "watermelon stomach" due to their endoscopic appearance. GAVE may present with recurrent episodes of GI bleeding, resulting in chronic unexplained anemia. Patients with SSc show increased prevalence of *Helicobacter pylori* infection in the stomach.

Lower Gastrointestinal Tract and Anorectal Involvement

Weight loss and malnutrition due to a combination of impaired intestinal motility, malabsorption, and chronic diarrhea secondary to bacterial overgrowth are common. Fat and protein malabsorption and vitamin B₁₂ and vitamin D deficiency ensue and may be further exacerbated by pancreatic insufficiency. Disturbed intestinal motor function can also lead to episodic intestinal pseudo-obstruction, with symptoms that are indistinguishable from those of delayed gastric emptying. Patients present with acute abdominal pain, nausea, and vomiting, and radiographic studies show acute intestinal obstruction. A major diagnostic challenge is differentiating pseudo-obstruction, which responds to supportive care and intravenous nutritional supplementation, from mechanical obstruction. Colonic involvement in SSc may result in constipation, occasionally complicated by sigmoid volvulus, fecal incontinence, GI bleeding from telangiectasia, and rectal prolapse. In late-stage SSc, wide-mouth sacculations or diverticula occur in the

colon and occasionally cause perforation and bleeding. An unusual radiologic finding is pneumatosis cystoides intestinalis, which is due to air trapping in the bowel wall that may rarely rupture and cause benign pneumoperitoneum. Studies of the fecal microbiota in SSc show a reduction in protective butyrate-producing bacteria, potentially promoting a proinflammatory intestinal microenvironment. Although the liver is rarely affected in patients with SSc, primary biliary cirrhosis may occur, particularly in patients with limited cutaneous disease.

RENAL INVOLVEMENT: SCLERODERMA RENAL CRISIS

Scleroderma renal crisis presents with accelerated hypertension accompanied by acute kidney injury and progressive failure. This acute life-threatening complication occurs in <15% of SSc patients, almost always within 4 years of disease onset. Scleroderma renal crisis can occasionally even be the presenting manifestation of SSc. While short-term survival in scleroderma renal crisis was <10% prior to the advent of angiotensin-converting enzyme (ACE) inhibitors, outcomes for this serious complication have shown great improvement. The pathogenesis involves obliterative vasculopathy of the renal arcuate and interlobular arteries, with consequent intravascular hemolysis (Fig. 360-13). Progressive reduction in renal blood flow, aggravated by vasospasm, leads to increased juxtaglomerular renin secretion and angiotensin II generation, with further renal vasoconstriction resulting in a vicious cycle that culminates in accelerated hypertension. Risk factors for scleroderma renal crisis include African-American race, male sex, and diffuse or progressive skin involvement. Up to 50% of patients with scleroderma renal crisis have antibodies to anti-RNA polymerase III, whereas patients with anti-centromere antibodies appear protected. Palpable tendon friction rubs, pericardial effusion, new unexplained anemia, and thrombocytopenia may be harbingers of impending scleroderma renal crisis. High-risk patients with early-stage SSc should monitor their blood pressure daily. Because glucocorticoid use is associated with scleroderma renal crisis, prednisone in high-risk SSc patients should be taken only when absolutely required and at low doses (<10 mg/d).

Patients with scleroderma renal crisis characteristically present with accelerated hypertension (generally >150/90 mmHg) and progressive oliguric renal insufficiency. However, ~10% of patients present with blood pressure in the normal range. Normotensive renal crisis is generally associated with a poor outcome. Headache, blurred vision, congestive heart failure, and pulmonary edema may accompany elevation of blood pressure. Moderate thrombocytopenia and microangiopathic hemolysis with fragmented red blood cells can be seen, and urinalysis typically shows mild proteinuria, granular casts, and microscopic hematuria. Progressive oliguric renal failure over several days generally follows. Scleroderma renal crisis is sometimes misdiagnosed as thrombotic thrombocytopenic purpura (TTP) or other forms of thrombotic microangiopathy. In such cases, renal biopsy and determination of serum von Willebrand factor-cleaving protease activity may be of benefit. The presence of oliguria or a creatinine >3 mg/dL at initial presentation predicts poor outcome (permanent hemodialysis and mortality), as do vascular thrombosis and glomerular ischemic collapse on renal biopsy. Crescentic glomerulonephritis in the setting of SSc has been described and may be associated with myeloperoxidase-specific antineutrophil cytoplasmic antibodies (ANCA). Membranous glomerulonephritis may occur in patients treated with D-penicillamine. Asymptomatic renal impairment can

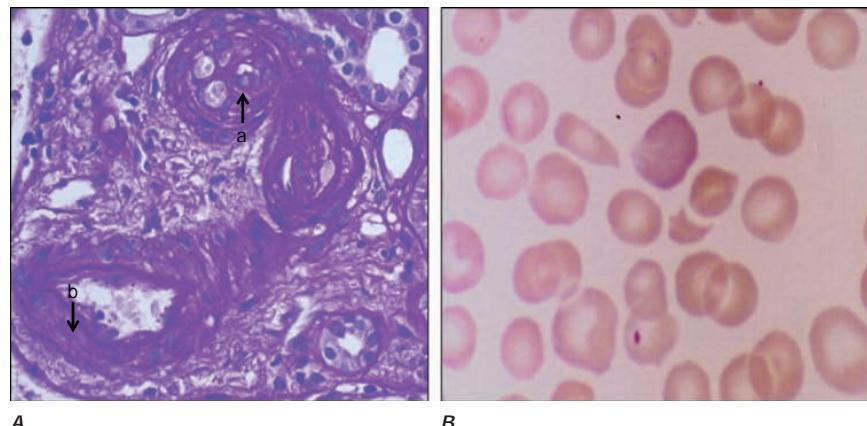


FIGURE 360-13 Biopsy and hematologic findings in scleroderma renal crisis. **A.** Renal biopsy demonstrating intimal proliferation and myxoid changes in medium-sized renal arteries. **B.** Fragmentation of red blood cells due to intravascular hemolysis. (Courtesy of Drs. Edward Stern and Christopher Denton, Royal Free Hospital, London, UK.)

occur in up to half of SSc patients, is commonly associated with other vascular manifestations, and rarely progresses to end-stage renal failure.

CARDIAC INVOLVEMENT

Although it is often silent, cardiac involvement is detected in 10–50% of SSc patients screened with sensitive diagnostic tools. Clinical cardiac involvement is more frequent in dcSSc than in lcSSc and may be primary or secondary to PAH, ILD, or renal involvement. Cardiac involvement in SSc is associated with poor outcomes. The endocardium, myocardium, and pericardium may each be affected separately or together. Pericardial involvement is manifested as pericarditis, pericardial effusions, constrictive pericarditis, and rarely, cardiac tamponade. Conduction system fibrosis is common and may be silent or manifested by heart block. Other arrhythmias include premature ventricular contractions, atrial fibrillation, and supraventricular tachycardia. Microvascular involvement, recurrent vasospasm, and ischemia-reperfusion injury contribute to patchy myocardial fibrosis, and the resulting systolic or diastolic left ventricular dysfunction may progress to overt heart failure. Acute or subacute myocarditis leading to left ventricular dysfunction may occur, best diagnosed by cardiac magnetic resonance imaging or endomyocardial biopsy. While conventional echocardiography has low sensitivity for detecting preclinical heart involvement in SSc, newer modalities such as tissue Doppler echocardiography (TDE), cardiac MRI, and nuclear imaging (single-photon emission CT [SPECT]) reveal a high prevalence of abnormal myocardial function or perfusion. The serum levels of NT-proBNP, a ventricular hormone elevated in SSc-PAH, may also have utility as a marker of primary cardiac involvement.

MUSCULOSKELETAL COMPLICATIONS

Musculoskeletal complications are commonly seen in SSc. Carpal tunnel syndrome may be a presenting disease manifestation, and generalized arthralgia and stiffness are prominent in early disease. Mobility of both small and large joints is progressively impaired, and fixed contractures at the proximal interphalangeal joints and wrists ensue. Large joint contractures occur in patients with dcSSc and are frequently accompanied by tendon friction rubs. These are characterized by coarse leathery crepitus heard or palpated upon passive joint movement and are caused by fibrosis and adhesion of the tendon sheaths and fascial planes at the affected joint. The presence of tendon friction rubs is associated with increased risk for renal and cardiac complications and reduced survival. Synovitis seen on ultrasound or MRI is common; occasional SSc patients develop erosive polyarthritis in the hands, and some may have a seropositive rheumatoid arthritis overlap. Muscle weakness is common and multifactorial; deconditioning, disuse

atrophy, malnutrition, inflammation, and fibrosis may all contribute. A chronic noninflammatory form of myopathy characterized by atrophy and fibrosis with mildly elevated muscle enzymes occurs in late-stage SSc. Bone resorption in the terminal phalanges causes the characteristic loss of the distal tufts (acro-osteolysis) (Fig. 360-5). Resorption of the mandibular condyles can lead to bite difficulties. Osteolysis can also affect the ribs and distal clavicles.

LESS RECOGNIZED DISEASE MANIFESTATIONS

Dry eyes and dry mouth (sicca complex) are common in SSc. Biopsy of the minor salivary glands in these cases shows fibrosis rather than focal lymphocytic infiltration characteristic of primary Sjögren's syndrome (Chap. 361). Hypothyroidism resulting from Graves' or Hashimoto's disease is common, particularly in lcSSc, and may be underrecognized. Whereas the central nervous system is generally spared in SSc, unilateral or bilateral sensory trigeminal neuropathy can occur. Erectile dysfunction is a frequent and occasionally initial disease manifestation. Inability to attain or maintain penile erection is due to vascular insufficiency and fibrosis of corporeal smooth muscle and responds poorly to medical therapy. Sexual performance is also adversely affected in women. While fertility is not impaired in SSc, pregnancy is associated with a higher risk of adverse fetal outcomes. Furthermore, cardiopulmonary involvement may worsen during pregnancy, and new onset of scleroderma renal crisis has been described.

Cancer Epidemiologic studies indicate an increased cancer risk in SSc. Lung cancer and esophageal adenocarcinoma typically occur in the setting of long-standing ILD or GERD and may be linked to chronic inflammation and tissue repair. In contrast, breast, lung, and ovarian carcinomas and lymphomas tend to occur in close temporal association with the onset of SSc, particularly in patients who have autoantibodies to RNA polymerase III. In this scenario, SSc may represent a paraneoplastic syndrome that is triggered by the antitumor immune response.

LABORATORY EVALUATION AND BIOMARKERS

Mild microcytic anemia is frequent and may indicate recurrent GI bleeding caused by GAVE or chronic esophagitis. Macrocytic anemia may be caused by folate and vitamin B₁₂ deficiency due to small-bowel bacterial overgrowth and malabsorption or by drugs such as methotrexate. Microangiopathic hemolytic anemia caused by mechanical fragmentation of red blood cells during their passage through microvessels coated with fibrin or platelet thrombi is a hallmark of scleroderma renal crisis. The erythrocyte sedimentation rate (ESR) is generally normal in SSc; an elevation may signal coexisting myositis or malignancy.

Antinuclear autoantibodies are detected in almost all patients with SSc. Anti-topoisomerase I (Scl-70) and anti-centromere antibodies are mutually exclusive and highly specific for SSc. Topoisomerase I (Scl-70) antibodies are associated with increased risk of ILD and poor outcomes. Anti-centromere antibodies are associated with PAH, but only infrequently with significant cardiac, pulmonary, or renal involvement. Nucleolar immunofluorescence pattern may indicate antibodies to U3-RNP (fibrillarin), Th/To, or PM/Scl, whereas speckled immunofluorescence indicates antibodies to RNA polymerase III, associated with increased risk of scleroderma renal crisis and malignancy (Fig. 360-14).

DIAGNOSIS, STAGING, AND MONITORING

The diagnosis of SSc is made primarily on clinical grounds and is generally straightforward in patients with established disease. Diagnostic criteria developed for classification are >90% specific and sensitive for SSc. The presence of skin induration with a characteristic symmetric distribution pattern associated with typical visceral organ manifestations establishes the diagnosis with a high degree of certainty. In lcSSc, a history of Raynaud's phenomenon and GERD symptoms, coupled with sclerodactyly and nailfold capillary changes, often in combinations with cutaneous telangiectasia and calcinosis cutis, helps

to establish the diagnosis. Primary Raynaud's disease is a benign condition that must be differentiated from early or limited SSc. Nailfold microscopy is particularly helpful in this situation, because in contrast to SSc, nailfold capillaries are normal. Diagnosing SSc at an early stage may be a challenge. In dcSSc, initial symptoms are often nonspecific, Raynaud's phenomenon may be absent, and physical examination may only show upper extremity edema and puffy fingers. Early-stage SSc might be initially misdiagnosed as arthritis, SLE, myositis, or, most commonly, undifferentiated connective tissue disease leading to delays in diagnosis. Within weeks to months, Raynaud's phenomenon and advancing skin induration appear. SSc-specific autoantibodies provide a high degree of diagnostic certainty. Raynaud's phenomenon with fingertip ulcerations or other evidence of digital ischemia, coupled with telangiectasia, distal esophageal dysmotility, unexplained ILD or PAH, or accelerated hypertension with renal failure in the absence of clinically evident skin induration, suggests the diagnosis of SSc *sine scleroderma*. Patients with a new diagnosis of SSc should be screened for ILD, followed by regular pulmonary monitoring for several years (Fig. 360-15).

MANAGEMENT OF SYSTEMIC SCLEROSIS

OVERVIEW: GENERAL PRINCIPLES

To date, no therapy has been shown to significantly alter the natural history of SSc. In contrast, numerous interventions are effective in alleviating the symptoms, slowing the progression of the cumulative organ damage, and reducing disability. Moreover, a significant decrease in disease-related mortality has been noted during the past 25 years. In light of the marked heterogeneity in disease manifestations, course, and outcomes, optimized care for patients with SSc requires a thoughtful "precision medicine" approach that is tailored specifically to each individual patient's unique needs.

The following general principles should guide management (Table 360-7): prompt and accurate diagnosis; patient subclassification and risk stratification based on clinical, radiologic, and laboratory evaluation, including autoantibody profiles and prognostic and predictive biomarkers; early recognition of organ-based complications and assessment of their extent, severity, and likelihood of deterioration; regular monitoring for disease progression, new complications, and response to and side effects of therapy; adjusting therapy; and patient education. In order to minimize the risk of irreversible organ damage, management should be individualized and proactive, with regular screening and initiation of appropriate intervention at the earliest possible opportunity. In light of the complex and multisystemic nature of the SSc, a team-oriented management approach integrating appropriate specialists should be pursued. Most patients are treated with a combination of drugs that impact different aspects of the disease. Patients should be encouraged to become familiar with potential complications and therapeutic options, including interventional trials, and natural history and should be empowered to partner with their treating physicians. This requires a long-term relationship between patient and physician, with ongoing counseling, encouragement, and two-way dialogue.

DISEASE-MODIFYING THERAPY: IMMUNOSUPPRESSIVE AGENTS

Immunosuppressive agents used in other autoimmune diseases have generally shown modest or no benefit in SSc. Glucocorticoids alleviate stiffness and aching in early inflammatory-stage dcSSc but do not influence the progression of skin or internal organ involvement. Since their use is associated with an increased risk of scleroderma renal crisis, glucocorticoids should be given only when absolutely necessary, at the lowest dose possible, and for brief periods only.

Cyclophosphamide has been extensively studied in light of its efficacy in the treatment of vasculitis (Chap. 363), SLE (Chap. 356), and other autoimmune diseases (Chap. 355). Both oral and intravenous cyclophosphamide have been shown to reduce the progression of SSc-associated ILD, with stabilization and, rarely, modest improvement

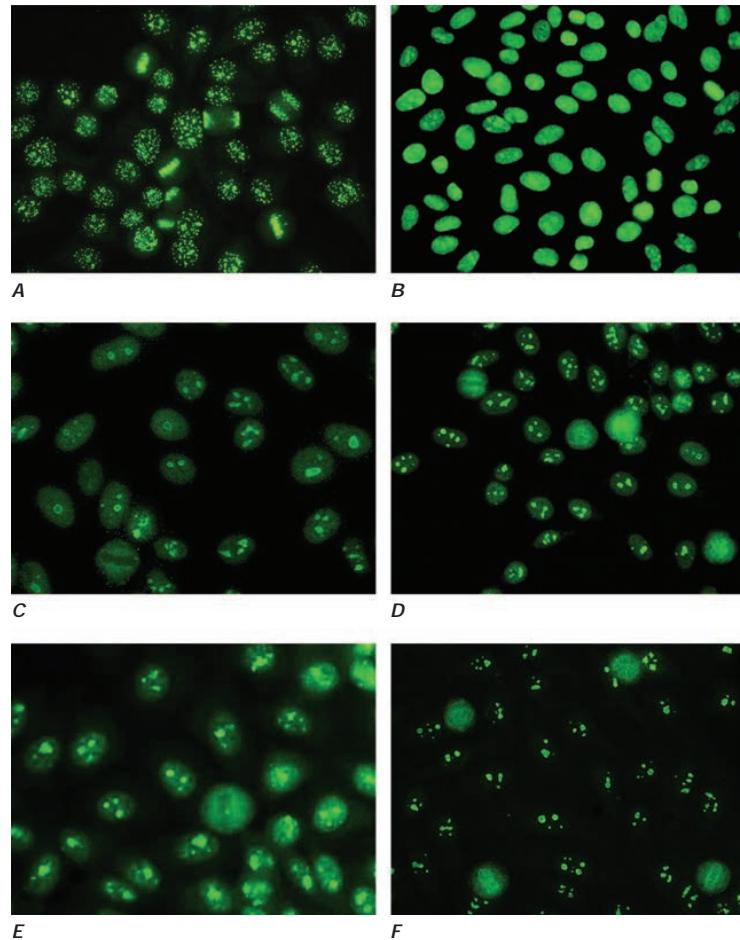


FIGURE 360-14 SSc-associated autoantibodies: immunofluorescence. Indirect immunofluorescence of SSc serum samples using HEp-2 substrate. Representative images show (A) anti-centromere; (B) anti-Scl-70/topoisomerase I; (C) anti-PM/Scl; (D) anti-Th/Tn; (E) anti-RNA polymerase III; and (F) anti-fibrillarin/U3RNP antibodies. Variations in immunostaining are clues to autoantibody specificity, but immunoassays with purified autoantigens are needed to confirm antigen specificity. (Courtesy of Marvin Fritzler and Susan Copple, Inova Diagnostics Inc., San Diego, CA.)

of pulmonary function, HRCT findings, respiratory symptoms, and skin induration. These benefits of cyclophosphamide need to be balanced against its potential toxicity, including bone marrow suppression, opportunistic infections, hemorrhagic cystitis and bladder cancer, premature ovarian failure, and late secondary malignancies.

Methotrexate had modest effect on SSc skin involvement in small studies. Mycophenolate mofetil was evaluated in both open-label and randomized controlled trials. Both skin induration and ILD improved in patients treated with mycophenolate mofetil, and the drug was well tolerated. Tocilizumab, a monoclonal antibody that blocks IL-6 receptor signaling, also showed benefit on both skin and lung involvement in randomized SSc trials. Open-label studies and small clinical trials provide some support for rituximab, a monoclonal antibody directed against the mature B-cell marker CD20, along with extracorporeal photopheresis, IV immunoglobulin, and abatacept, a fusion protein that inhibits T-cell co-stimulation and function. The use of cyclosporine, azathioprine, hydroxychloroquine (Plaquenil), thalidomide, and rapamycin for SSc therapy is currently not well supported by the literature. Intensive immune ablation using high-dose chemotherapy, followed by autologous hematopoietic stem cell reconstitution therapy (HSCT), was associated with durable remission and improved long-term survival in multiple randomized clinical trials. Currently, HSCT is indicated for selected patients with severe SSc but carries potential morbidity and mortality, as well as significant cost. Additional

forms of potentially disease-modifying cellular therapies are under investigation.

Antifibrotic Therapy Because tissue fibrosis underlies organ damage in SSc, drugs that interfere with the fibrotic process represent a rational therapeutic approach. In older retrospective studies, D-penicillamine was shown to stabilize skin induration, prevent new internal organ involvement, and improve survival. However, a randomized controlled clinical trial in early active SSc found no difference in the extent of skin involvement between patients treated with standard-dose (750 mg/d) or very low-dose (125 mg every other day) D-penicillamine. Recent clinical trials show benefit of the tyrosine kinase inhibitor nintedanib, alone or in combination with mycophenolate, in patients with SSc-ILD, with significant slowing of the loss of lung function.

Vascular Therapy The goal of Raynaud's therapy is to control episodes, prevent and enhance the healing of ischemic complications, and slow the progression of obliterative vasculopathy. Patients should dress warmly, minimize cold exposure, and avoid drugs that precipitate or exacerbate vasospastic episodes. Extended-release dihydropyridine calcium channel blockers such as amlodipine and nifedipine, as well as diltiazem, ameliorate Raynaud's phenomenon, but their use is often limited by side effects (palpitations, dependent edema, worsening gastroesophageal reflux). While ACE inhibitors do not reduce the

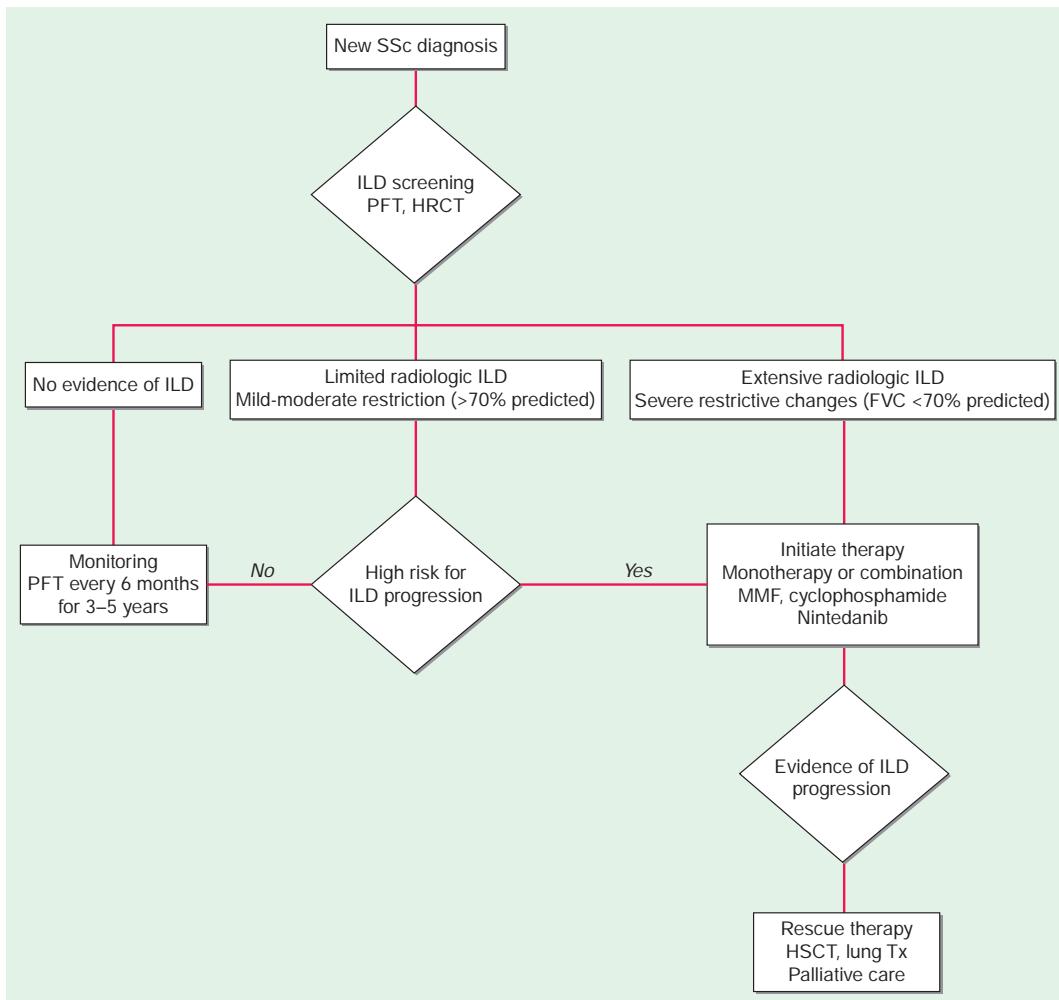


FIGURE 360-15 Proposed algorithm for screening, monitoring, and treatment of systemic sclerosis (SSc)-associated interstitial lung disease (ILD). FVC, forced vital capacity; HRCT, high-resolution computed tomography; HSCT, hematopoietic stem cell transplantation; MMF, mycophenolate mofetil; PFT, pulmonary function testing; Tx, transplantation. (Adapted from A Perelas et al: *Lancet Respir Med* 8:304, 2020.)

frequency or severity of episodes, angiotensin II receptor blockers such as losartan are effective and well tolerated. Patients with Raynaud's phenomenon unresponsive to these therapies may require the addition of α_1 -adrenergic receptor blockers (e.g., prazosin), phosphodiesterase-5 inhibitors (e.g., sildenafil), topical nitroglycerine, and intermittent IV infusions of prostaglandins. Low-dose aspirin and dipyridamole prevent platelet aggregation and may have a role as adjunctive agents. In patients with ischemic digital tip ulcerations, the endothelin-1 receptor antagonist bosentan reduces the risk of new ulcers. Digital sympathectomy and intradigital injections of botulinum type A (Botox) may be considered in patients with severe ongoing ischemia. Empirical long-term therapy with statins and antioxidants may retard the progression of vascular damage and obliteration. There is limited evidence-based

information for the treatment of cardiac complications of SSc, which should be guided by specialists experienced in their diagnosis and management. While selective beta blockers such as metoprolol can precipitate vasospasm, nondihydropyridine calcium channel blockers can be used for rate control in atrial arrhythmias, and nonselective alpha/beta blockers such as carvedilol can be used for improving myocardial perfusion and left ventricular systolic function.

TREATMENT

SSC-ASSOCIATED INTERSTITIAL LUNG DISEASE

ILD is a leading cause of death in patients with SSc. However, because the course of SSc-associated ILD is highly variable, it is important to identify patients who are at high risk for disease progression. The extent of ILD on HRCT and the FVC at initial evaluation and the decline in FVC during the preceding 12-month period are helpful in identifying these patients. Additionally, male sex, older age at initial presentation, progressive skin involvement, and myocardial disease may be risk factors for ILD progression. Patients at high risk for ILD should be monitored by performing PFTs every 6 months (Fig. 360-15); serial HRCT imaging is not recommended. Cyclophosphamide, given IV or orally for 6–12 months,

TABLE 360-7 Key Principles in Management

- Establish early and accurate diagnosis.
- Detect and evaluate internal organ involvement.
- Define clinical disease stage and activity.
- Tailor individualized therapy to each patient's unique needs.
- Assess treatment response, and adjust therapy as needed; monitor for disease activity, progression, and new complications.

and mycophenolate mofetil slow the decline in lung function and improve respiratory symptoms, but cyclophosphamide is associated with more frequent side effects. The efficacy and optimal duration of antifibrotic therapy with nintedanib, which was recently approved for SSc-associated ILD, are currently under investigation. In patients who show continued progression of ILD despite medical therapy, lung transplantation might be considered as a life-prolonging procedure, although significant GERD contributing to organ rejection is a concern in SSc. Recurrence of SSc-ILD in transplanted lung allografts has not been reported.

TREATMENT OF GASTROINTESTINAL COMPLICATIONS

Because oral problems, including decreased oral aperture, decreased saliva production, gum recession, periodontal disease, and teeth loss, are common, regular dental care is recommended. Gastroesophageal reflux is very common in SSc and may occur in the absence of symptoms. Patients should be instructed to elevate the head of the bed, eat frequent small meals, and avoid alcohol, caffeine, known reflux exacerbants, and meals before bedtime. Proton pump inhibitors to reduce acid reflux may need to be given in relatively high doses. Prokinetic agents such as metoclopramide, erythromycin (a motilin agonist), and domperidone may occasionally be helpful in SSc but are frequently associated with side effects. Botulinum toxin injection sometimes ameliorates impaired gastric emptying. Antireflux procedures such as Nissen fundoplication can result in secondary achalasia and generally should be avoided. Episodic bleeding from GAVE (watermelon stomach) may be treated with endoscopic ablation using laser or argon plasma photoablation, although it commonly recurs. In some patients, enteral feeding and/or decompression via percutaneous gastrostomy or jejunostomy may become necessary. Small intestinal bacterial overgrowth secondary to gut dysmotility causes abdominal bloating and diarrhea and may lead to malabsorption and severe malnutrition. Short courses of rotating broad-spectrum antibiotics such as metronidazole, erythromycin, and rifaximin can eradicate bacterial overgrowth. Small bowel hypomotility may respond to octreotide, but pseudo-obstruction is difficult to treat. Fecal incontinence, a frequent but underreported complication, may respond to antidiarrheal medication, biofeedback, sphincter augmentation, and sacral neuromodulation. Potential malnutrition should be routinely assessed.

TREATMENT OF PULMONARY ARTERIAL HYPERTENSION

In SSc, PAH carries an extremely poor prognosis and accounts for 30% of deaths. Because PAH is asymptomatic until advanced, patients with SSc should be screened at initial evaluation and regularly thereafter. Treatment is generally started with an oral endothelin-1 receptor antagonist such as bosentan or a phosphodiesterase-5 inhibitor such as sildenafil. Recently, the soluble guanylate cyclase stimulator riociguat, which acts by increasing the production of nitric oxide, and the selective IP prostanoid receptor agonist selexipag were shown to improve PAH symptoms and survival. Patients may also require diuretics and digoxin. If hypoxemia is documented, supplemental oxygen should be prescribed in order to avoid secondary pulmonary vasoconstriction. Prostacyclin analogues such as epoprostenol or treprostinil can be given by continuous IV or SC infusion or via intermittent nebulized inhalations. Combination therapy with different classes of agents acting additively or synergistically is often necessary. Lung transplantation remains an option for selected SSc patients with PAH who fail medical therapy, and 2-year survival rates (64%) are comparable to those of idiopathic ILD or PAH.

MANAGEMENT OF RENAL CRISIS

Scleroderma renal crisis represents a medical emergency. Since its outcome is largely determined by the extent of renal damage at the time that aggressive therapy is initiated, prompt recognition of impending or early scleroderma renal crisis is essential, and efforts should be made to avoid its occurrence. High-risk SSc patients

(early disease, extensive and progressive skin involvement, tendon friction rubs, and anti-RNA polymerase III antibodies) should be instructed to monitor their blood pressure daily and report significant alterations immediately. Potentially nephrotoxic drugs should be avoided, and glucocorticoids should be used only when absolutely necessary and at low doses. Patients presenting with scleroderma renal crisis should be immediately hospitalized. Once other causes of acute renal disease are excluded, treatment should be started promptly with titration of short-acting ACE inhibitors, with the goal of rapid normalization of the blood pressure. In patients with persistent hypertension, addition of angiotensin II receptor blockers, calcium channel blockers, endothelin-1 receptor blockers, prostacyclins, and direct renin inhibitors should be considered. In light of evidence for intrarenal complement pathway activation in some patients with scleroderma renal crisis, addition of eculizumab to ACE inhibitors may be considered. Up to two-thirds of patients with scleroderma renal crisis necessitate dialysis. Substantial renal recovery can occur following an episode of scleroderma renal crisis, and renal replacement therapy can be ultimately discontinued in 30–50% of patients. Kidney transplantation is appropriate for patients unable to discontinue dialysis after 2 years. Survival of transplanted SSc patients is comparable to that of other diseases, and recurrence of renal crisis is rare.

SKIN CARE

Because skin involvement in SSc is never life-threatening and stabilizes, and may even regress spontaneously, disease management should not be dictated by its cutaneous manifestations. The inflammatory symptoms of early skin involvement can be controlled with antihistamines and short-term use of low-dose glucocorticoids (<5 mg/d of prednisone). Cyclophosphamide and methotrexate have modest effects on skin induration. Because the skin is dry, the use of hydrophilic ointments and bath oils is encouraged, and regular skin massage is helpful. Telangiectasia, which presents a cosmetic problem, especially on the face, can be treated with pulsed dye laser. Ischemic digital ulcerations should be protected by occlusive dressings to promote healing and prevent infection. Infected skin ulcers are treated with topical antibiotics and surgical debridement. While no therapy has been shown to be effective in preventing soft-tissue calcific deposition or promoting its dissolution, reports support the use of minocycline, bisphosphonates, and topical or IV sodium thiosulfate (STS). Additional approaches include carbon dioxide laser treatment, extracorporeal shock-wave lithotripsy, and surgical high-speed microdrilling.

TREATMENT OF MUSCULOSKELETAL COMPLICATIONS

Arthralgia and joint stiffness are very common and distressing manifestations in early-stage disease. Short courses of nonsteroidal anti-inflammatory agents, methotrexate, and cautious use of low-dose glucocorticoids alleviate symptoms. Physical and occupational therapy can be effective for preventing loss of musculoskeletal function and joint contractures and should be initiated early.

COURSE

The natural history of SSc is highly variable and difficult to predict, especially in early stages of the disease. Patient with dcSSc tend to have a more rapidly progressive course and worse prognosis than those with lcSSc. Inflammatory symptoms of early dcSSc, such as fatigue, edema, joint pain, and pruritus, subside, and skin thickening reaches a plateau at 2–4 years after disease onset. It is during the early edematous/inflammatory stage that life-threatening visceral organ involvement may develop. While existing visceral organ involvement, such as ILD, may progress even after skin involvement peaks, new organ involvement is rare. Scleroderma renal crisis generally occurs within the first 4 years of disease. In late-stage disease (>6 years), the skin is usually soft and atrophic. Skin regression characteristically occurs in an order that is the reverse of initial involvement, with softening on the trunks followed by proximal and finally distal extremities; however, sclerodactyly and

fixed finger contractures generally persist. Relapse or recurrence of skin thickening after peak skin involvement has been reached is uncommon. Patients with lcSSc follow a clinical course that is markedly different than that of dcSSc. Raynaud's phenomenon typically precedes other disease manifestations by years or even decades. Visceral organ complications such as PAH generally develop late and progress slowly.

PROGNOSIS

SSc confers a substantial increase in the risk of premature death. Age- and gender-adjusted mortality rates are five- to eightfold higher compared to the general population, and more than half of all patients with SSc die from their disease. In one population-based study of SSc, the median survival was 11 years. In patients with dcSSc, 5- and 10-year survival rates are 70% and 55%, respectively, whereas in patients with lcSSc, 5- and 10-year survival rates are 90% and 75%, respectively. The prognosis correlates with the extent of skin involvement, which itself is a surrogate for visceral organ involvement. Major causes of death are PAH, pulmonary fibrosis, GI involvement, and cardiac disease. Scleroderma renal crisis is associated with a 30% 3-year mortality. Lung cancer and excess cardiovascular deaths also contribute to increased mortality. Markers of poor prognosis include male gender, African-American race, older age at disease onset, extensive skin thickening with truncal involvement, palpable tendon friction rubs, and evidence of significant or progressive visceral organ involvement. Laboratory predictors of increased mortality at initial evaluation include an elevated ESR, anemia, proteinuria, and anti-topoisomerase I (Scl-70) antibodies. In one study, SSc patients with extensive skin involvement, lung vital capacity <55% predicted, significant GI involvement (pseudo-obstruction or malabsorption), clinical cardiac involvement, or scleroderma renal crisis had a 9-year survival <40%. The severity of PAH predicts mortality, and patients with mean pulmonary arterial pressure ≥45 mmHg had a 33% 3-year survival. The advent of ACE inhibitors in scleroderma renal crisis had a dramatic impact on survival, increasing survival from <10% at 1 year in the pre-ACE inhibitor era to >70% 3-year survival at the present time. Moreover, 10-year survival in SSc improved from <60% in the 1970s to >66–78% in the 1990s, a trend that reflects both earlier detection and better management of complications.

LOCALIZED SCLERODERMA

The term *scleroderma* describes a group of localized skin disorders (Table 360-1). These occur more commonly in children than in adults and, in marked contrast to SSc, are generally not complicated by Raynaud's phenomenon or significant internal organ involvement. Morphea presents as solitary or multiple circular patches of thick skin or, rarely, as widespread induration (generalized or pansclerotic morphea); the fingers are generally spared. Linear scleroderma may affect subcutaneous tissues, leading to fibrosis and atrophy of supporting structures, tendons, muscle, and even bone. In children, the growth of affected long bones can be retarded. When linear scleroderma crosses large joints, significant contractures can develop.

MIXED CONNECTIVE TISSUE DISEASE

Patients who have lcSSc coexisting with features of SLE, polymyositis, and rheumatoid arthritis may have mixed connective tissue disease (MCTD). This overlap syndrome is generally associated with the presence of high titers of autoantibodies to U1-RNP. The characteristic initial presentation is Raynaud's phenomenon associated with puffy fingers and myalgia. Over time, sclerodactyly, soft-tissue calcinosis, and cutaneous telangiectasia may appear. Skin rash suggestive of SLE (malar erythema, photosensitivity) or dermatomyositis (heliotrope rash on the eyelids, erythematous rash on knuckles) occurs. Arthralgia is common, and some patients develop erosive polyarthritis. Pulmonary fibrosis and isolated or secondary PAH may develop. Other manifestations include esophageal dysmotility, pericarditis, Sjögren's syndrome, and renal disease, especially membranous glomerulonephritis. Laboratory evaluation shows elevated ESR and hypergammaglobulinemia. While anti-U1RNP antibodies are detected in high titers, SSc-specific autoantibodies are absent. In contrast to SSc, MCTD often

responds to glucocorticoids, and the long-term prognosis is better than that of SSc. Whether MCTD is truly a distinct entity or is a subset of SLE or SSc remains controversial.

EOSINOPHILIC FASCIITIS (DIFFUSE FASCIITIS WITH EOSINOPHILIA)

Eosinophilic fasciitis is a rare idiopathic disorder of adults associated with abrupt skin induration. The skin characteristically shows a coarse cobblestone "peau d'orange" appearance. In contrast to SSc, Raynaud's phenomenon and SSc-associated internal organ involvement and autoantibodies are absent. Furthermore, skin involvement spares the fingers. Full-thickness biopsy of the lesional skin reveals fibrosis of the subcutaneous fascia, with variable inflammation and eosinophil infiltration. In the acute phase of the illness, peripheral blood eosinophilia may be prominent. MRI appears to be a sensitive tool for the diagnosis of eosinophilic fasciitis. Eosinophilic fasciitis can occur in association with, or preceding, various myelodysplastic syndromes or multiple myeloma. Although glucocorticoids cause prompt resolution of eosinophilia, the skin shows slow and variable improvement. The prognosis of patients with eosinophilic fasciitis is generally good.

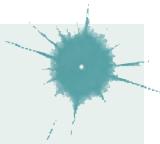
FURTHER READING

- Allanore Y et al: Systemic sclerosis. *Nat Rev Dis Primers* 1:15002, 2015.
- Herzog EL et al: Interstitial lung disease associated with systemic sclerosis and idiopathic pulmonary fibrosis: How similar or distinct? *Arthritis Rheum* 66:1967, 2014.
- Joseph CG et al: Association of the autoimmune disease scleroderma with an immunologic response to cancer. *Science* 343:152, 2014.
- Martyanov V, Whitfield ML: Molecular stratification and precision medicine in systemic sclerosis from genomic and proteomic data. *Curr Opin Rheumatol* 28:83, 2016.
- Tashkin DP et al: Mycophenolate mofetil versus oral cyclophosphamide in scleroderma-related interstitial lung disease (SLS II): A randomised controlled, double-blind, parallel group trial. *Lancet Respir Med* 4:708, 2016.

361

Sjögren's Syndrome

Haralampos M. Moutsopoulos,
Clio P. Mavragani



DEFINITION, INCIDENCE, AND PREVALENCE

Sjögren's syndrome is a prototype autoimmune disease characterized by lymphocytic infiltration of the exocrine glands resulting in xerostomia, dry eyes (keratoconjunctivitis sicca), and profound B-cell hyperactivity. The syndrome has unique features since it presents with a wide clinical spectrum from organ-specific to systemic disease; can occur alone or in association with other systemic rheumatic diseases, more commonly rheumatoid arthritis, limited scleroderma, and systemic lupus erythematosus; and displays high probability of the development of lymphoma. Because of all these characteristics, it is an ideal model to study not only autoimmunity but also lymphoid malignancy.

Middle-aged women (female-to-male ratio 10–20:1) are primarily affected, although Sjögren's syndrome may occur at any age, including childhood. Patients with earlier disease onset express a more aggressive disease phenotype manifested by a high occurrence of systemic manifestations and serum autoantibodies. The prevalence of Sjögren's syndrome is ~0.5–1%, while 5–20% of patients with other autoimmune diseases can express sicca manifestations.

The autoimmune phenomena observed in Sjögren's syndrome include lymphocytic infiltration of the exocrine glands (primarily salivary and lachrymal glands) and B lymphocyte hyperreactivity. The latter is mainly manifested by hypergammaglobulinemia and the presence of serum autoantibodies toward non-organ-specific antigens such as immunoglobulins (rheumatoid factors) and extractable cellular antigens (Ro52, Ro60, and La). The major infiltrating cells in the affected exocrine glands are activated T lymphocytes. In labial minor salivary gland tissues with extensive lymphocytic infiltrations, B-cell populations prevail. Other cellular subsets detected in the labial minor salivary gland histopathologic lesion of Sjögren's syndrome include follicular, myeloid, and plasmacytoid dendritic cells, as well as macrophages. Inflamasome activation and macrophages positive for interleukin (IL) 18 in the salivary gland lesion have been shown to be associated with adverse predictors for lymphoma development.

The interplay of endogenous (e.g., intracellular stress, inappropriate overexpression of endogenous nucleic acids) and exogenous triggers (e.g., viruses, hormonal triggers, stressful life events) in a background of a genetically determined hyperactive immune response seems to be crucial for the initiation and perpetuation of the disease. Ductal and acinar epithelial cells appear to play a significant role in the initiation and perpetuation of autoimmune injury. These cells (1) express inappropriately costimulatory molecules and the intracellular autoantigens Ro and La on their cell surfaces, acquiring the capacity to provide signals essential for lymphocytic activation; (2) produce proinflammatory cytokines and lymphocyte-attracting chemokines necessary for sustaining the autoimmune lesion and allowing the formation of ectopic germinal centers; (3) express functional receptors of innate immunity, particularly Toll-like receptors (TLRs) 3, 7, and 9 molecules, which may account for the initiation of the autoimmune reactivity; and (4) display immunoregulatory molecules such as ICAM and CD40. Glandular epithelial cells also seem to have an active role in the production of B cell-activating factor (BAFF), which is induced after stimulation with type I and II interferons. Circulating BAFF has been found to be elevated also in the serum of Sjögren's syndrome patients, especially those with hypergammaglobulinemia and serum autoantibodies, and probably accounts for the antiapoptotic effect on B lymphocytes.

In contrast to B and T lymphocytes, glandular epithelial cells display increased rates of apoptotic death. Established risk genetic loci implicated in Sjögren's syndrome include the human leukocyte antigen DQA1*0501 allele, as well as variants involved in the interferon/BAFF axis (*IRF 5, STAT 4, BAFF*), B-cell function (*EBF1, BLK*), and chronic inflammation (*TNFAIP3*).

CLINICAL MANIFESTATIONS

The majority of patients with Sjögren's syndrome have symptoms related to impaired exocrine gland, particularly lacrimal and salivary gland, function. The disease evolution is slow and, in the majority of patients, runs a benign course. Studies have shown that prior to disease onset, patients with Sjögren's syndrome experience major stressful life events with which they cannot cope adequately.

The principal oral symptom of Sjögren's syndrome is dryness (xerostomia). Patients report difficulty in swallowing dry food, a burning mouth sensation, an increase in dental caries, and problems in wearing complete dentures. Physical examination shows a dry, erythematous, sticky oral mucosa. There is atrophy of the filiform papillae on the dorsum of the tongue, and saliva from the major glands is either not expressible or cloudy. Intermittent or persistent enlargement of the parotid or other major salivary glands occurs in two-thirds of patients with Sjögren's syndrome. Diagnostic tests include sialometry and several imaging techniques, including ultrasound, MRI, and magnetic resonance sialography of the major salivary glands. In particular, salivary gland ultrasound is an emerging tool of both diagnostic and prognostic utility. Biopsy of the labial minor salivary gland allows histopathologic confirmation of focal lymphocytic infiltrates.

Ocular involvement is the other major manifestation of Sjögren's syndrome. Patients usually report a sandy or gritty feeling under

TABLE 361-1 Prevalence of Extraglandular Manifestations in Primary Sjögren's Syndrome

Clinical Manifestation	Percent	Remarks
Nonspecific		
Fatigability/myalgias	25	Fibromyalgia
Arthralgias/arthritis	60	Usually nonerosive, leading to Jaccoud's arthropathy
Raynaud's phenomenon	37	In one-third of patients, precedes sicca manifestations
Periepithelial		
Lung involvement	14	Small airway disease/lymphocyte interstitial pneumonitis
Kidney involvement	9	Interstitial kidney disease is usually asymptomatic
Liver involvement	6	Primary biliary cirrhosis stage I
Immune complex-mediated		
Small vessel vasculitis	9	Purpura, urticarial lesions
Peripheral neuropathy	2	Polyneuropathy, either sensory or sensorimotor
Glomerulonephritis	2	Membranoproliferative
Lymphoma		
Lymphoma	6	Glandular MALT ^a lymphoma is most common

^aMucosa-associated lymphoid tissue.

the eyelids. Other ocular symptoms include burning, accumulation of secretions in thick strands at the inner canthi, decreased tearing, redness, itching, eye fatigue, and increased photosensitivity. These symptoms are attributed to the destruction of corneal and bulbar conjunctival epithelium, a pathology termed *keratoconjunctivitis sicca*. Diagnostic evaluation of keratoconjunctivitis sicca includes measurement of tear flow by Schirmer's I test, determination of tear composition by tear breakup time or tear lysozyme content, and slit-lamp examination of the cornea and conjunctiva after lissamine green or Rose Bengal staining that reveals punctate corneal and bulbar conjunctival ulcerations and attached filaments.

Involvement of other exocrine glands, which occurs less frequently, includes a decrease in mucous gland secretions of the upper and lower respiratory tree, resulting in dry nose, throat, and trachea (xerotrachea). In addition, diminished secretion of the exocrine glands of the gastrointestinal tract leads to esophageal mucosal dysmotility and atrophic gastritis. Dyspareunia, in premenopausal women, due to dryness of the external genitalia and dry skin also may occur.

Extraglandular (systemic) manifestations are seen in one-third of patients with Sjögren's syndrome (Table 361-1) and can be classified as follows: **nonspecific**, **periepithelial** (surrounding of epithelial tissues by lymphocytes), **immune complex-mediated**, and **lymphoma**. **Nonspecific** manifestations include fatigability, low-grade fever, Raynaud's phenomenon, myalgias, arthralgias, and arthritis. Arthritis in patients with primary Sjögren's syndrome is nonerosive. **Periepithelial** pathology due to periepithelial accumulation of lymphocytes results from the involvement of parenchymal organs such as the lungs, kidneys, and liver. On the basis of this observation, one of the authors (H.M.M.) has coined the term **autoimmune epithelitis**. Lung involvement is usually manifested with dry cough and rarely with dyspnea. The underlying lung pathology includes peribronchial infiltrates (bronchitis sicca) and interstitial pneumonitis. Renal involvement includes interstitial nephritis, clinically manifested by hyposthenuria and renal tubular dysfunction with or without acidosis. Untreated acidosis may lead to nephrocalcinosis. **Immune complex-mediated** disease is expressed with vasculitis affecting primarily small-sized vessels, mainly manifested with purpura and rarely with urticarial rash, skin ulcerations, mononeuritis multiplex, and membranoproliferative glomerulonephritis

associated with mixed type II or III cryoglobulinemia. Central nervous system involvement is rarely recognized. A few cases of myelitis associated with antibodies to aquaporin 4 have been described.

Sjögren's syndrome is characterized by the highest risk for lymphoma development among all autoimmune diseases. Tongue atrophy, persistent parotid gland enlargement, purpura, mixed type II cryoglobulinemia, low serum C4 complement levels, autoantibodies (rheumatoid factor, anti-Ro52, anti-Ro60, anti-La), and extensive lymphocytic infiltration in minor salivary glands are among the main features predicting the development of lymphoma. Most lymphomas are extranodal, low-grade, marginal zone B cell and are usually detected incidentally during evaluation of the labial minor salivary gland biopsy. The affected lymph nodes are usually peripheral. Survival rates are decreased in patients with B symptoms, lymph node mass >7 cm in diameter, and high or intermediate histologic grade. Despite that, pathogenesis of lymphoma in the setting of Sjögren's syndrome remains to be elucidated, and genetic alterations involved in chronic inflammatory, B-cell activation and the type I interferon pathways, as well as epigenetic abnormalities, have been shown to be significant contributors.

Recent data reveal an increased risk for multiple myeloma as well for Sjögren's syndrome patients with anti-Ro52, anti-Ro60, or anti-La autoantibodies. In line with observations in rheumatoid arthritis and systemic lupus erythematosus, patients with Sjögren's syndrome also display an increased risk of cardiovascular disease.

Routine laboratory tests in Sjögren's syndrome can reveal leukopenia and infrequently lymphopenia. In two-thirds of patients, elevated erythrocyte sedimentation rate, hypergammaglobulinemia, antinuclear antibodies, rheumatoid factors, and antibodies against Ro52/Ro60 and La autoantigens are detected. Anticentromere autoantibodies are present in Sjögren's patients with a clinical picture similar to that of limited scleroderma ([Chap. 360](#)), while the presence of antimitochondrial antibodies may connote liver involvement in the form of autoimmune cholangitis ([Chap. 346](#)). Autoantibodies to 21-hydroxylase are found in patients with a blunted adrenal response, while autoantibodies to citrullinated peptides are seen in Sjögren's patients with

TABLE 361-3 Differential Diagnosis of Sjögren's Syndrome

HIV INFECTION AND SICCA SYNDROME	SJÖGREN'S SYNDROME	SARCOIDOSIS
Predominant in young males	Predominant in middle-aged women	No age or sex preference
Lack of autoantibodies to Ro and/or La	Presence of autoantibodies	Lack of autoantibodies to Ro and/or La
Lymphoid infiltrates of salivary glands by CD8+ T lymphocytes	Lymphoid infiltrates of salivary glands by CD4+ T lymphocytes	Granulomas in salivary glands
Association with HLA-DR5	Association with HLA-DR3 and DRw52	Unknown
Positive serologic tests for HIV	Negative serologic tests for HIV	Negative serologic tests for HIV

arthritis. Anticalponin-3 antibodies have been recently associated with the occurrence of peripheral neuropathies.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Sjögren's syndrome should be suspected if a patient presents with eye and/or mouth dryness, major salivary gland enlargement, or systemic manifestations such as Raynaud's phenomenon, palpable purpura, or symptomatology of renal tubular acidosis. A careful history of medications causing dryness should be obtained. Recently, cases of Sjögren's syndrome were triggered by PD-1/PD-L1 checkpoint inhibitors.

The workup should include eye tests that might reveal keratoconjunctivitis sicca, salivary flow tests or ultrasonography, and serum evaluation for specific autoantibodies. Testing for chronic viral infections (hepatitis C virus, HIV), chest x-ray to rule out sarcoidosis, protein electrophoresis, IgG4 serum levels, and autoantibodies to thyroid antigens can be also offered. Labial biopsy is valuable to rule out conditions that may cause dry mouth, dry eyes, or parotid gland enlargement ([Tables 361-2 and 361-3](#)). Classification criteria are not valuable for everyday practice but are of paramount importance for research. A diagnostic algorithm based on recent classification criteria is presented ([Fig. 361-1](#)).

TABLE 361-2 Differential Diagnosis of Sicca Symptoms

XEROSTOMIA	DRY EYE	BILATERAL PAROTID GLAND ENLARGEMENT
Viral infections (HCV, HIV)	Inflammation	Viral infections
Drugs	Stevens-Johnson syndrome	Mumps
Psychotherapeutic	Pemphigoid	Influenza
Parasympatholytic	Chronic conjunctivitis	Epstein-Barr virus
Antihypertensive	Chronic blepharitis	Coxsackievirus A
Psychogenic origin	Sjögren's syndrome	Cytomegalovirus
Irradiation	Toxicity	HIV, HCV
Diabetes mellitus	Burns	Sarcoidosis, tuberculosis
Trauma	Drugs	IgG4 syndrome
Sjögren's syndrome	Neurologic conditions	Sjögren's syndrome
Amyloidosis	Impaired lacrimal gland function	Metabolic disorders
Autoimmune thyroid disease	Impaired eyelid function	Diabetes mellitus
	Miscellaneous	Hyperlipoproteinemias (types IV and V)
	Trauma	Chronic pancreatitis
	Hypovitaminosis A	Hepatic cirrhosis
	Blink abnormality	Endocrine
	Anesthetic cornea	Acromegaly
	Lid scarring	Gonadal hypofunction
	Epithelial irregularity	Lymphoma
	Autoimmune thyroid disease	

Abbreviation: HCV, hepatitis C virus.

TREATMENT

Sjögren's Syndrome

Treatment of Sjögren's syndrome aims to relieve symptoms and limit the damage from chronic xerostomia and keratoconjunctivitis sicca through substitution or stimulation of impaired secretions.

To replace deficient tears, several ophthalmic preparations are readily available (hydroxypropyl methylcellulose; polyvinyl alcohol; 0.5% methylcellulose; Hypo Tears). If corneal ulcerations are present, eye patching and boric acid ointments are recommended, as well as cyclosporine eye drops. Certain drugs that may decrease lacrimal and salivary secretions, such as diuretics, antihypertensive drugs, anticholinergics, and antidepressants, should be avoided.

For xerostomia, the best replacement is water. Propionic acid gels may be used to treat vaginal dryness. To stimulate secretions, orally administered pilocarpine (5 mg thrice daily) or cevimeline (30 mg thrice daily) appears to improve sicca manifestations, and both are well tolerated. Hydroxychloroquine (200 mg daily) is helpful for arthralgias and mild arthritis.

Patients with renal tubular acidosis should receive sodium bicarbonate by mouth (0.5–2 mmol/kg in four divided doses). Glucocorticoids and monoclonal antibody to CD20 (rituximab) appear to be effective in patients with systemic disease, particularly in those with purpura and arthritis. Novel monoclonal antibodies targeting the CD40L/CD40 costimulatory pathway or the BAFF receptor seem to be promising therapeutic strategies for the management of Sjögren's syndrome patients with systemic manifestations. Treatment of lymphoma in the setting of Sjögren's syndrome follows the general guidelines for lymphoma management in the general population.

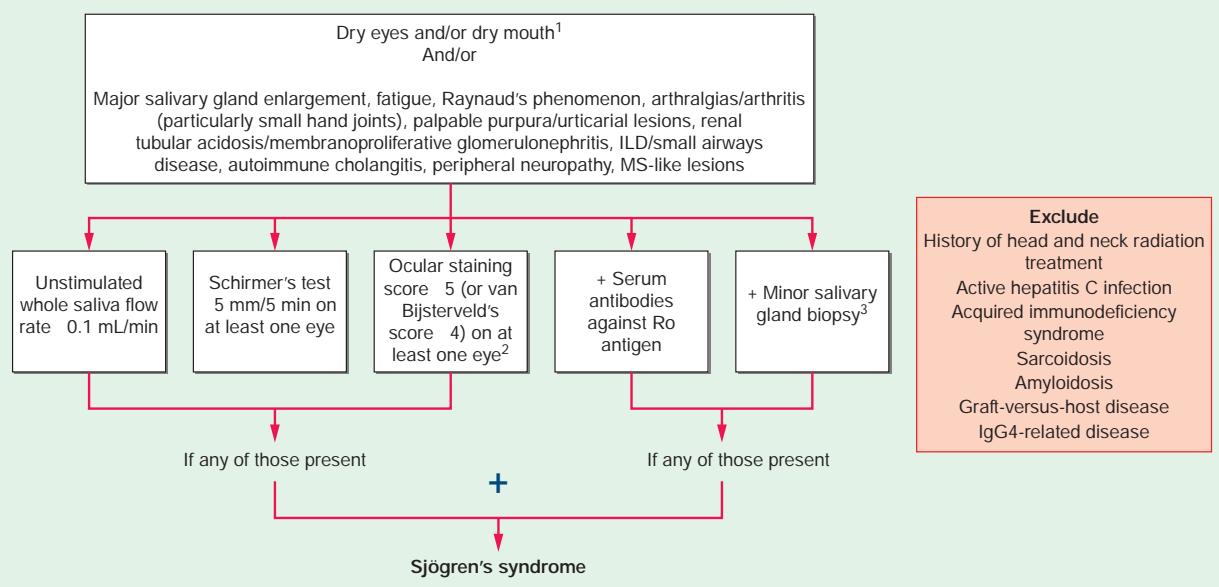


FIGURE 361-1 Diagnostic algorithm for Sjögren's syndrome. ¹Defined as a positive response to at least one of the following questions: (a) Have you had daily, persistent, troublesome dry eyes for more than 3 months? (b) Do you have a recurrent sensation of sand or gravel in the eyes? (c) Do you use tear substitutes more than three times a day? (d) Have you had a daily feeling of dry mouth for more than 3 months? (e) Do you frequently drink liquids to aid in swallowing dry food? ²Ocular staining score described in Whitcher et al. ³Focus score count · 1 (based on the number of foci per 4 mm of salivary gland tissue) following a protocol described in Daniels et al. ILD, interstitial lung disease; MS, multiple sclerosis.

FURTHER READING

- Daniels TE et al: Associations between salivary gland histopathologic diagnoses and phenotypic features of Sjögren's syndrome among 1,726 registry participants. *Arthritis Rheum* 63:2021, 2011.
 Mavragani CP, Moutsopoulos HM: Sjögren's syndrome. *CMAJ* 186:579, 2014.
 Mavragani CP, Moutsopoulos HM: Sjogren's syndrome: Old and new therapeutic targets. *J Autoimmun* 110:102364, 2020.
 Moutsopoulos HM: Sjögren's syndrome: A forty-year scientific journey. *J Autoimmun* 51:1, 2014.
 Shiboski CH et al: 2016 American College of Rheumatology/European League Against Rheumatism Classification Criteria for Primary Sjögren's Syndrome: A consensus and data-driven methodology involving three international patient cohorts. *Arthritis Rheumatol* 69:35, 2017.
 van Bijsterveld OP: Diagnostic tests in the Sicca syndrome. *Arch Ophthalmol* 82:10, 1969.
 Vivino FB et al: Sjögren's syndrome: An update on disease pathogenesis, clinical manifestations and treatment. *Clin Immunol* 203:81, 2019.
 Whitcher JP et al: A simplified quantitative method for assessing keratoconjunctivitis sicca from the Sjögren's Syndrome International Registry. *Am J Ophthalmol* 149:405, 2010.

as predominantly axial SpA, affecting the spine, pelvis, and thoracic cage, or predominantly peripheral SpA, affecting the extremities.

ANKYLOSING SPONDYLITIS AND AXIAL SPONDYLOARTHRITIS

Axial spondyloarthritis (axSpA) is the current term used to describe the most common inflammatory disorder affecting the axial skeleton, with variable involvement of peripheral joints and extraarticular structures. AxSpA includes patients with significant radiographic damage of the sacroiliac joints, classically termed AS and now considered radiographic axial spondyloarthritis (r-axSpA), and those patients with a similar clinical presentation but lacking significant radiographic sacroiliitis. In this latter group, some eventually develop significant radiographic sacroiliitis; however, many do not. The general concept of axSpA is supported by classification criteria formulated in 2009 (**Table 362-1**). AxSpA patients with sacroiliitis on MRI without significant damage on x-ray are categorized as having nonradiographic axial spondyloarthritis (nr-axSpA).

EPIDEMIOLOGY

The estimated adult prevalence of AS in 20 countries during the past 2 decades is ~0.17% (range 0.02–0.5%). In the few studies that have addressed ax-SpA, prevalence is ~1.3- to 2-fold higher than that of AS. AS shows a striking correlation with the histocompatibility antigen HLA-B27 and occurs worldwide roughly in proportion to the prevalence of B27. In North American whites, the prevalence of B27 is 6%, whereas it is 80–90% in patients with AS.

In population surveys, AS is found in 1–6% of adults inheriting B27, whereas the prevalence is 10–30% among B27+ adult first-degree relatives of AS probands. The concordance rate in identical twins is about 65%. Susceptibility to AS is determined largely by genetic factors, with B27 comprising ~20% of the genetic component. Single-nucleotide polymorphism (SNP) analysis has identified 115 additional non-HLA alleles that altogether contribute another ~7–8% of genetic susceptibility. The prevalence of HLA-B27 in nr-axSpA is somewhat lower than in AS and the proportion of females is higher. Little information is available about non-HLA susceptibility loci in nr-axSpA, which is genetically more heterogeneous than AS.

362 Spondyloarthritis

Joel D. Taurog, Lianne S. Gensler,
 Nigil Haroon

Spondyloarthritis (SpA) refers to a group of overlapping disorders that share clinical features, genetic associations, and pathogenic mechanisms. The classic designations include ankylosing spondylitis (AS), reactive arthritis (ReA), psoriatic arthritis (PsA), arthritis associated with inflammatory bowel disease (IBD), juvenile spondyloarthritis (JSpA), and undifferentiated SpA. These disorders are broadly classified

TABLE 362-1 ASAS Criteria for Classification of Axial Spondyloarthritis (to be applied for patients with back pain 3 months and age of onset <45 years)^a

SACROILIITIS ON IMAGING PLUS 1 SpA FEATURE	OR	HLA-B27 PLUS 2 OTHER SpA FEATURES
Sacroiliitis on imaging • Active (acute) inflammation on MRI highly suggestive of SpA-associated sacroiliitis ^b and/or • Definite radiographic sacroiliitis according to modified New York criteria ^c		SpA features • Inflammatory back pain ^d • Arthritis ^e • Enthesitis (heel) ^f • Anterior uveitis ^g • Dactylitis ^h • Psoriasis ⁱ • Crohn's disease or ulcerative colitis ^j • Good response to NSAIDs ^k • Family history of SpA ^l • HLA-B27 • Elevated CRP ^m

^aSensitivity 83%, specificity 84%. The imaging arm (sacroiliitis) alone has a sensitivity of 66% and a specificity of 97%. ^bBone marrow edema and/or osteitis on short tau inversion recovery (STIR) or gadolinium-enhanced T1 image. ^cBilateral grade 2 or unilateral grade 3 or 4. ^dSee text for criteria. ^ePast or present, diagnosed by a physician. ^fPast or present pain or tenderness on examination at calcaneus insertion of Achilles tendon or plantar fascia. ^gPast or present, confirmed by an ophthalmologist. ^hSubstantial relief of back pain at 24–48 h after a full dose of NSAID. ⁱFirst- or second-degree relatives with ankylosing spondylitis (AS), psoriasis, uveitis, reactive arthritis (ReA), or inflammatory bowel disease (IBD). ^jAfter exclusion of other causes of elevated CRP.

Abbreviations: ASAS, Assessment of Spondyloarthritis international Society; CRP, C-reactive protein; MRI, magnetic resonance imaging; NSAIDs, nonsteroidal anti-inflammatory drugs; SpA, spondyloarthritis.

Source: Adapted from M Rudwaleit et al: The development of assessment of spondyloarthritis international society classification criteria for axial spondyloarthritis (part II): Validation and final selection. Ann Rheum Dis 68:777, 2009.

PATHOLOGY

Sacroiliitis is typically an early manifestation of axSpA, whether or not it is evident radiographically. In biopsy and autopsy studies of sacroiliac joints, covering a range of disease durations, synovitis and myxoid marrow represent the earliest changes, followed by pannus and subchondral granulation tissue. Marrow edema, enthesitis, and chondroid differentiation are also found. Macrophages, T cells, plasma cells, and osteoclasts are prevalent. If the process progresses, eventually the eroded joint margins are replaced by fibrocartilage regeneration and then by ossification.

In the spine, inflammatory granulation tissue is seen in the paravertebral connective tissue at the junction of annulus fibrosus and vertebral bone, or even along the entire outer annulus. The outer annular fibers are eroded and eventually replaced by bone, forming an early syndesmophyte, which then grows by endochondral ossification, ultimately bridging the adjacent vertebral bodies (Fig. 362-1F, G). Progression of this process can lead to “bamboo spine.” Other spinal lesions include osteoporosis (loss of trabecular bone despite accretion of periosteal bone), erosion of vertebral bodies at the disk margin, and inflammation and destruction of the disk-bone border. Inflammatory arthritis of the facet joints is common, with erosion of joint cartilage by pannus often followed by bony ankylosis. This may precede formation of syndesmophytes bridging the adjacent disks. Bone mineral density is diminished in the spine and proximal femur early in the disease course.

Peripheral synovitis in AS shows marked vascularity, evident as tortuous macrovasculature seen during arthroscopy. Lining layer hyperplasia, lymphoid infiltration, and pannus formation are also found. Central cartilaginous erosions from proliferation of subchondral granulation tissue are common. The characteristics of peripheral arthritis in AS are shared by other forms of SpA and are distinct from those of RA.

Extensive investigation has implicated the *enthesis*, the fibrocartilaginous region where a tendon, ligament, or joint capsule attaches to bone, as a primary site of pathology in AS and other SpAs, at both axial and peripheral sites. Entheses transduce mechanical forces from muscles to bones and hence are widely distributed anatomically. Enthesitis

is associated with prominent edema of the adjacent bone marrow and is often characterized by erosive lesions that eventually undergo ossification.

Subclinical intestinal inflammation has been found in the colon or distal ileum in most patients with SpA. The histology is described below under “IBD-Associated Arthritis.”

PATHOGENESIS

AS is immune-mediated, and increasing evidence suggests more of an autoinflammatory rather than antigen-specific autoimmune pathogenesis. Uncertainty remains regarding the primary site of disease initiation. The dramatic response of the disease to therapeutic blockade of tumor necrosis factor (TNF) or IL-17A indicates that these cytokines play a central immunopathogenic role. Genes related to TNF pathways show association with AS, including *TNFRSF1A*, *TNFAIP3*, *LTBR*, and *TBKB1*. Genes in the IL-23/IL-17 pathway show association with AS, including *IL23R*, *PTER4*, *IL12B*, *CARD9*, *IL6R*, *TYK2*, *JAK2*, and *STAT3*. Of these 12 genes, 11 are also associated with IBD, and 6 with psoriasis. Serum levels of IL-23 and IL-17 are elevated in AS patients. In mice, tissue-resident thymus-dependent T cells expressing $\gamma\delta$ T-cell receptors and IL-23 receptors are found at entheses, in the aortic root, and near the ciliary body in the eye. These cells express abundant IL-17 and IL-22 upon exposure to systemic IL-23. This finding suggests that site-specific innate immune cells play a critical role in the anatomic specificity of these lesions. IL-23 signals through the Janus kinase (Jak) TYK2. TYK2 loss of function SNPs are protective against AS, and Tyk2 inhibition blocks IL-23-dependent immunity and SpA progression in a mouse model.

High levels of circulating $\gamma\delta$ T cells expressing IL-23 receptors and producing IL-17 have been found in AS patients. Recent studies of human spinal entheses identified IL-23-producing CD14+ myeloid cells and IL-17A-producing $\gamma\delta$ -T cells. One subset of these $\gamma\delta$ -T cells lacked IL-23 receptors. This population evidently produces IL-17A independently of IL-23 and may explain the therapeutic failure in ax-SpA of agents targeting IL-23, despite the positive response of peripheral SpA to these agents and the dramatic response of both axial and peripheral SpA to agents targeting IL-17A (see Fig. 362-3).

Other associated genes encode other cytokines or cytokine receptors (*IL1R1*, *IL1R2*, *IL7R*, *IL27*), transcription factors involved in the differentiation of immune cells (*RUNX3*, *EOMES*, *BACH2*, *NKK2-3*, *TBX21*), or other molecules involved in activation or regulation of immune or inflammatory responses (*FCGR2A*, *ZMIZ1*, *NOS2*, *ICOSLG*).

The inflamed sacroiliac joint is infiltrated with CD4+ and CD8+ T cells and macrophages and shows high levels of TNF, particularly early in the disease. Abundant transforming growth factor β (TGF- β) is found in more advanced lesions. Peripheral synovitis in SpA is characterized by neutrophils, macrophages expressing CD68 and CD163, CD4+ and CD8+ T cells, and B cells. There is prominent staining for intercellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1), matrix metalloproteinase 3 (MMP-3), and myeloid-related proteins 8 and 14 (MRP-8 and MRP-14).

Gut microbiota dysbiosis is consistently found in SpA patients and animal models, and in both may be influenced by HLA genotype, including HLA-B27. Bacteria species with mucolytic properties are expanded in patients, suggesting a pathogenic role for degradation of intestinal mucus. Overlapping features with ReA and IBD and involvement of the IL-23/IL-17 pathway, which is fundamentally associated with host defense at mucosal sites, provide additional support for the importance of the microbiome in SpA pathogenesis. It has been hypothesized that systemic inflammation, dysbiosis, and increased intestinal permeability form an amplification loop driving sustained inflammation in SpA.

HLA-B27 plays a direct role in AS pathogenesis, but its precise molecular role remains unresolved. Rats transgenic for HLA-B27 develop arthritis and spondylitis, and this is unaffected by the absence of CD8. It thus appears that classical peptide antigen presentation to CD8+ T cells may not be the primary disease mechanism. However, the association of AS with ERAP1 and ERAP2, which strongly influence the MHC class I peptide repertoire, suggests that peptide binding to

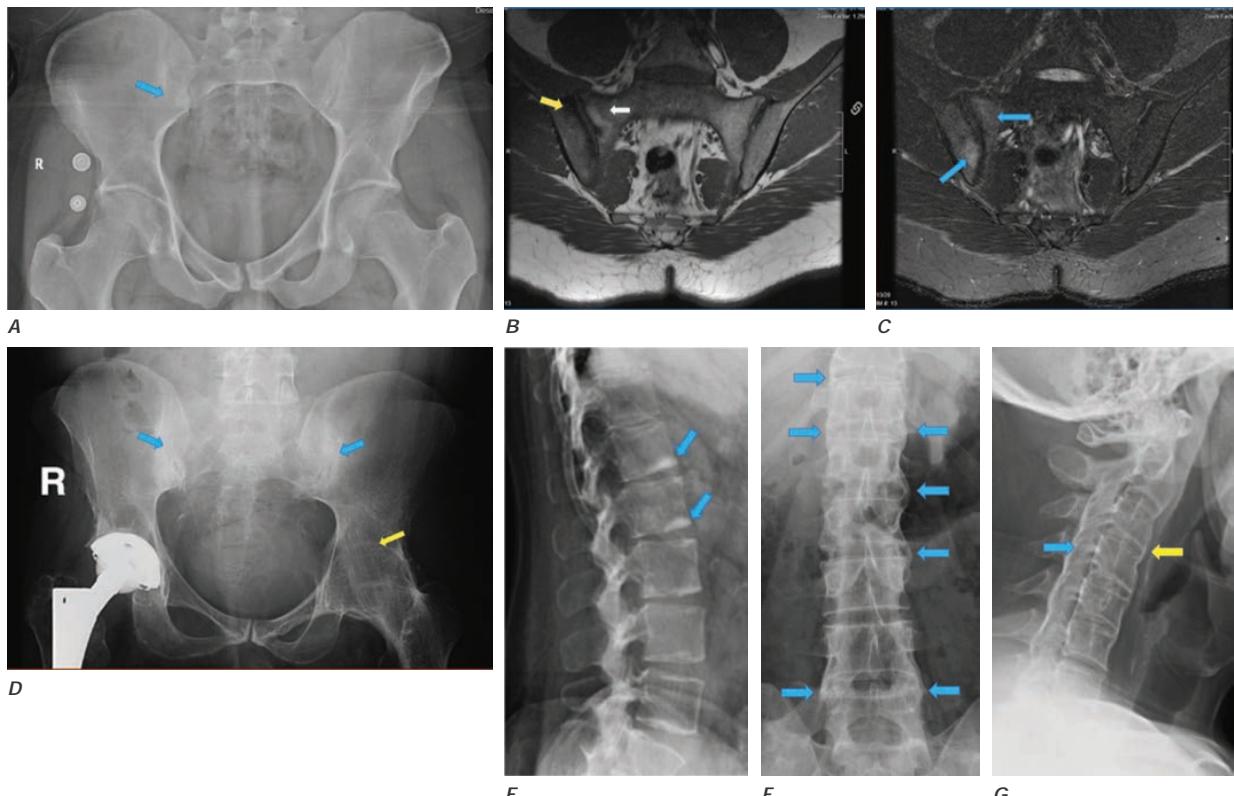


FIGURE 362-1 Imaging in nonradiographic axial spondyloarthritis (nr-axSpA) and in ankylosing spondylitis (radiographic axial spondyloarthritis).

- Anterior posterior (AP) pelvis radiograph in a patient with nr-axSpA, showing insignificant sacroiliac (SI) joint changes. There is minimal right-sided SI joint sclerosis (blue arrow).
- T1-weighted MRI of the sacrum from the patient shown in A. The yellow arrow indicates cortical erosion of the right SI joint and the white arrow indicates subchondral fat.
- Short tau inversion recovery (STIR) sequence MRI from the same patient shows bone marrow edema on both sides of the SI joint (blue arrows).
- AP pelvis radiograph in a patient with AS. Blue arrows indicate advanced bilateral radiographic sacroiliitis (sclerosis, partial fusion, erosions). There is severe bilateral hip disease with autofusion on the left (yellow arrow), and diffuse osteoporosis.
- Lateral lumbar spine radiograph in a patient with AS. Blue arrows indicate Romanus lesions (shiny corners).
- AP lumbar spine radiograph in a patient with AS. Blue arrows indicate bridging syndesmophytes.
- Lateral cervical spine radiograph in a patient with AS. There is complete ankylosis of the facet joints (blue arrow) and bridging syndesmophytes throughout (yellow arrow).

B27 is nonetheless important. CD8+ T cells are decreased in peripheral blood and increased in synovial fluid in AS patients, but their role in AS pathogenesis remains unclear. The B27 heavy chain has an unusual tendency to misfold, a process that can be proinflammatory. Genetic and functional studies in humans have suggested a role for natural killer (NK) cells in AS, possibly through interaction with B27 heavy chain homodimers. SpA-prone B27 rats show defective dendritic cell function and share with AS patients a characteristic “reverse interferon” gene expression signature in antigen-presenting cells. A recent study provided evidence for an interaction between HLA-B27 and activin receptor-like kinase-2, a bone morphogenic protein family member, mutations of which are associated with fibrodysplasia ossificans progressiva, a disease of uncontrolled bone formation.

Enthesitis can arise in healthy individuals from repetitive mechanical strain at a particular anatomic site. In SpA, it is thought that the threshold for strain-induced enthesal inflammation is lowered by genetic factors and/or microbial products, resulting in widespread, chronic lesions arising at enthesal sites subjected only to normal use. Supporting this concept, mice transgenic for constitutive TNF production develop peripheral enthesitis and arthritis mediated by innate immunity, and nonweightbearing reduces inflammation and new bone formation at these sites.

New bone formation in AS appears to be largely based on endochondral bone formation and occurs only in the periosteal compartment. It correlates with lack of regulation of the Wnt signaling pathway, which

controls the differentiation of mesenchymal cells into osteophytes, by the inhibitors DKK-1 and sclerostin. Indirect evidence and data from animal models also implicate bone morphogenic proteins, hedgehog proteins, and prostaglandin E₂. Patients with high inflammatory markers and inflammation at vertebral corners on MRI are the ones most likely to develop syndesmophytes. Mounting evidence suggests that early and prolonged anti-TNF therapy may decrease spinal fusion. Vertebral inflammatory lesions that undergo metaplasia to fat (increased T1-weighted signal) are a preferential site of subsequent syndesmophyte formation despite anti-TNF therapy, whereas early acute inflammatory lesions resolve, reinforcing the importance of early treatment to resolve inflammation.

CLINICAL MANIFESTATIONS

The initial AS symptoms are usually first noticed in late adolescence or early adulthood, at a median age in the mid-twenties. In 5% of patients, symptoms begin after age 40. The initial symptom is pain that can be either sharp or dull, insidious in onset, felt deep in the lower lumbar or gluteal region, and accompanied by low-back morning stiffness of up to a few hours' duration that improves with activity and returns following inactivity. Within a few months, the pain usually becomes persistent and bilateral. Nocturnal exacerbation of pain often forces the patient to rise and move around.

In some patients, bony tenderness (presumably reflecting enthesitis or osteitis) accompanies back pain or stiffness, whereas in others it may

be the predominant complaint. Common sites include the costosternal junctions, spinous processes, iliac crests, greater trochanters, ischial tuberosities, tibial tubercles, and heels. Hip and shoulder ("root" joint) arthritis is considered part of axial disease. Hip arthritis occurs in 25–35% of patients. Severe isolated hip arthritis or bony chest pain may be the presenting complaint, and symptomatic hip disease can dominate the clinical picture, especially in those with juvenile-onset disease. Arthritis of peripheral joints is usually asymmetric and may occur at any point in the disease course. Neck pain and stiffness from cervical spine involvement may be later manifestations but are occasionally dominant symptoms. Chest pain is common at any stage of ax-SpA and if not accurately diagnosed can be confused with cardiovascular disease.

In juvenile spondyloarthritis, peripheral arthritis and enthesitis predominate, with axial symptoms supervening in late adolescence.

Initially, axial physical findings mirror the inflammatory process. The most specific findings involve loss of spinal mobility, with limitation of anterior and lateral flexion and extension of the lumbar spine and of chest expansion. Limitation of motion is usually out of proportion to the degree of bony ankylosis and may reflect muscle spasm secondary to pain and inflammation. Pain in the sacroiliac joints may be elicited either with direct pressure or with stress on the joints. In addition, there is commonly tenderness upon palpation of the posterior spinous processes and other sites of symptomatic bony tenderness.

The modified Schober test is a useful measure of lumbar spine flexion. The patient stands erect, with heels together, and marks are made on the spine at the lumbosacral junction (identified by a horizontal line between the posterosuperior iliac spines) and 10 cm above. The patient then bends forward maximally with knees fully extended, and the distance between the two marks is measured. This distance increases by ≥ 2 cm with normal mobility. Chest expansion is measured as the difference between maximal inspiration and maximal forced expiration at the levels of either the fourth intercostal space or the xiphisternum, with the patient's hands resting on or just behind the head. Normal chest expansion is ≥ 2.5 cm. Lateral bending measures the distance the patient's middle finger travels down the leg with maximal lateral bending. Normal is >10 cm.

Limitation or pain with motion of the hips or shoulders is usually present if these joints are involved. It should be emphasized that in early, mild, or atypical cases, the symptoms and/or physical findings may be subtle and/or nonspecific.

The course of ax-SpA is extremely variable, ranging from the individual with mild stiffness and normal radiographs to the patient with a totally fused spine and severe bilateral hip arthritis, severe peripheral arthritis, and extraarticular manifestations. Available data on natural history pertain predominantly to AS, although the prevalence of peripheral arthritis, enthesitis, psoriasis, and IBD appears to be similar in nr-axSpA and AS. Pain tends to be persistent early in the disease and intermittent later, with alternating exacerbations and quiescent periods. In a typical severe untreated case with progression to syndesmophyte formation, the posture undergoes characteristic changes, with obliterated lumbar lordosis, buttock atrophy, and accentuated thoracic kyphosis. There may be a forward stoop of the neck or flexion contractures at the hips, compensated by flexion at the knees. Disease progression can be estimated clinically from loss of height, limitation of chest expansion and spinal flexion, and increasing occiput-to-wall distance. Occasional individuals are encountered with advanced deformities who deny ever having significant symptoms.

The factors most predictive of radiographic progression (see below) are the presence of existing syndesmophytes, high inflammatory markers, and smoking. In some but not all studies, onset of AS in adolescence and early hip involvement correlate with a worse prognosis. In women, AS tends to progress less frequently to total spinal ankylosis, although there may be an increased prevalence of peripheral arthritis. Peripheral arthritis occurs in up to 30% of patients. Pregnancy has no consistent effect on AS, with symptoms improving, remaining the same, or deteriorating in one-third of pregnant patients, respectively. However, those requiring biologic therapy before pregnancy are quite likely to flare during the second and third trimester if the medication is discontinued during pregnancy.

The most serious complication of advanced spinal disease is spinal fracture, which can occur with even minor trauma to the rigid, osteoporotic spine. The lower cervical spine is most commonly involved. These fractures are often displaced, causing spinal cord injury. A recent survey suggested a $>10\%$ lifetime risk of fracture. Occasionally, fracture through a diskovertebral junction and adjacent neural arch, termed *pseudarthrosis*, most common in the thoracolumbar spine, can be an unrecognized source of persistent localized pain and/or neurologic dysfunction. Wedging of thoracic vertebrae can lead to accentuated kyphosis.

The most common extraarticular manifestation is acute anterior uveitis, which occurs in up to 50% of patients and can antedate the spondylitis. Attacks are typically unilateral, causing pain, photophobia, and pain with accommodation. These may recur, often in the opposite eye. Cataracts and secondary glaucoma may ensue. Up to 60% of patients with AS have inflammation in the colon or ileum. This is usually asymptomatic, but overt IBD occurs in 5–10% of patients with AS (see "IBD-Associated Arthritis," below). About 10% of patients meeting criteria for AS have psoriasis (see "Psoriatic Arthritis," below). Occasional patients are seen with AS in association with skin manifestations seen in SAPHO syndrome (see below), such as acne fulminans or hidradenitis suppurativa. There is an apparently increased risk of ischemic heart disease. Aortic insufficiency occurs in a small percentage of patients, usually after longstanding disease. Third-degree heart block may occur alone or together with aortic insufficiency, and association with lesser degrees of heart block has been described. Cauda equina syndrome and upper pulmonary lobe fibrosis are rare late complications. Prostatitis has been reported to have an increased prevalence. Amyloidosis is rare (Chap. 112).

Several validated measures of disease activity and functional outcome are in widespread use in the study and management of ax-SpA, particularly the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and the Ankylosing Spondylitis Disease Activity Score (ASDAS), both measures of disease activity; the Bath Ankylosing Spondylitis Functional Index (BASFI), a measure of limitation in activities of daily living; and several measures of radiographic changes. The new Assessment of Spondyloarthritis international Society (ASAS) Health Index is a spondyloarthritis-specific tool for assessing impairment of function and health. Despite persistence of the disease, most patients remain gainfully employed. Some but not all studies of survival in AS have suggested that AS shortens life span, compared with the general population. Mortality attributable to AS is largely the result of spinal trauma, aortic insufficiency, respiratory failure, amyloid nephropathy, or complications of therapy such as upper gastrointestinal hemorrhage. The impact of biologic therapy on outcome and mortality is not yet known, except for significantly improved work productivity.

LABORATORY FINDINGS

No laboratory test is diagnostic of AS. In most ethnic groups, HLA-B27 is present in 75–90% of patients. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are often, but not always, elevated. Mild anemia may be present. Patients with severe disease may show elevated alkaline phosphatase. Elevated serum IgA is common. Rheumatoid factor, anti-cyclic citrullinated peptide (CCP), and antinuclear antibodies (ANAs) are largely absent unless caused by a coexistent disease, although ANAs may appear with anti-TNF therapy. Circulating levels of CD8+ T cells tend to be low, and serum matrix metalloproteinase 3 levels correlate with disease activity. Synovial fluid from peripheral joints is non-specifically inflammatory. Restricted chest wall motion causes decreased vital capacity, but ventilatory function is usually well maintained.

RADIOGRAPHIC FINDINGS (FIG. 362-1)

By definition, the diagnosis of AS is associated with advanced radiographically demonstrable sacroiliitis, usually symmetric. The earliest changes by standard radiography are blurring of the cortical margins of the subchondral bone, followed by erosions and sclerosis. Progression of the erosions leads to "pseudowidening" of the joint space; as fibrous and then bony ankylosis supervene, the joints may become obliterated.

In the lumbar spine, progression of the disease can lead to loss of lordosis, and osteitis of the anterior corners of the vertebral bodies

with subsequent erosion, and new bone formation causing “squaring” or even “barreling” of one or more vertebral bodies. Progressive ossification leads to eventual formation of marginal syndesmophytes, visible on plain films as bony bridges connecting successive vertebral bodies anteriorly and laterally.

Only a minority of patients meeting criteria for nr-axSpA develop radiographic sacroiliitis within a decade or more, and even fewer develop spinal changes. MRI is thus much more useful for the timely diagnosis of ax-SpA, provided that it is done correctly. *It must be emphasized that MRI protocols routinely used to evaluate low back pain have low sensitivity for detecting inflammation and often give false-negative results in ax-SpA.* Active sacroiliitis is best visualized by dynamic MRI on semicoronal slices with fat saturation, either T2-weighted turbo spin-echo sequence or short tau inversion recovery (STIR) with high resolution, or T1-weighted images with contrast enhancement. These techniques identify early intraarticular inflammation, cartilage changes, and underlying bone marrow edema in sacroiliitis (Fig. 362-1). These protocols are also sensitive for evaluation of acute and chronic spinal changes. Bone marrow edema alone is not specific for spondyloarthritis. The presence of erosions enhances specificity and is best detected on conventional T1-weighted images. Optimal MRI results require a high index of suspicion, an appropriate protocol, an experienced radiologist, and close communication between radiologist and clinician.

Reduced bone mineral density can be detected by dual-energy x-ray absorptiometry of the femoral neck and the lumbar spine. Employing a lateral projection of the L3 vertebral body can prevent falsely elevated readings related to spinal ossification.

DIAGNOSIS

It is important to recognize ax-SpA before the development of irreversible deformity. This goal is challenging for several reasons: (1) only a minority of back pain patients have ax-SpA; (2) an early diagnosis often relies on clinical grounds and/or an appropriate MRI protocol requiring considerable expertise; (3) young individuals with symptoms of ax-SpA often do not seek medical care; and (4) reliance on definite radiographic sacroiliitis causes early or mild cases to be missed. The classification criteria for ax-SpA proposed by ASAS are shown in Table 362-1. They were developed for research purposes only and should not be strictly applied as diagnostic criteria but can be considered an aid to diagnosis. They are applicable to individuals with ≥3 months of back pain and age of onset <45 years. Active inflammation of the sacroiliac joints as determined by MRI is considered equivalent to definite radiographic sacroiliitis (see below).

AxSpA must be differentiated from numerous other causes of low-back pain, some substantially more common than axSpA. Increased specificity is obtained when the nature and pattern of the pain and the age of the patient are considered. The most typical symptom is inflammatory back pain (IBP), present in 70–80% of patients with axSpA. In chronic (≥3 months) back pain, IBP has the following characteristic features: (1) age of onset <40 years; (2) insidious onset; (3) improvement with exercise; (4) no improvement with rest; (5) pain at night with improvement upon getting up; (6) morning stiffness >30 min; (7) awakening from back pain during only the second half of the night; and (8) alternating buttock pain. The presence of two or more of these features should arouse suspicion for IBP, and four or more can be considered presumptively diagnostic. The most common causes of back pain other than SpA are primarily mechanical or degenerative rather than primarily inflammatory. These are less likely to show clustering of SpA features, but IBP can be present in up to 30% of patients with mechanical back pain.

Less-common causes of back pain must also be differentiated from axSpA, including infectious spondylitis, spondyloskisis, or sacroiliitis; and primary or metastatic tumor. Ochronosis can produce a phenotype similar to AS. Calcification and ossification of paraspinous ligaments occur in *diffuse idiopathic skeletal hyperostosis* (DISH), which occurs in middle age and above and is usually asymptomatic. Ligamentous calcification gives the appearance of “flowing wax” on the anterior bodies of the vertebrae. Intervertebral disk spaces are preserved, and sacroiliac and facet joints appear normal, helping to differentiate DISH from

spondylosis and from AS, respectively. Both primary and secondary hyperparathyroidism can cause subchondral bone resorption around the SI joints, with bilateral widened and ill-defined joints on radiographs, but without joint space narrowing.

An algorithm for making or excluding the diagnosis of ax-SpA in patients with chronic back pain is shown in Fig. 362-2.

TREATMENT

Axial Spondyloarthritis

All management of ax-SpA should include an exercise program to maintain posture and range of motion. Exercise videos are available from the Spondylitis Association of America (<https://spondylitis.org/resources-support/educational-materials-resources/back-in-action-again/>).

Nonsteroidal anti-inflammatory drugs (NSAIDs) are the first line of pharmacologic therapy. They reduce pain and tenderness and increase mobility in many patients. Continuous high-dose NSAID therapy may slow radiographic progression, particularly in patients who are at higher risk for progression. However, many patients have persistent symptoms despite NSAID therapy and may benefit from biologic therapy. Patients with AS treated with the anti-TNF agents infliximab (chimeric human/mouse anti-TNF monoclonal antibody), etanercept (soluble p75 TNF receptor-IgG fusion protein), adalimumab or golimumab (human anti-TNF monoclonal antibodies), or certolizumab pegol (humanized mouse anti-TNF monoclonal antibody) have shown rapid, profound, and sustained reductions in all clinical and laboratory measures of disease activity. In a good response, there is significant improvement in both objective and subjective indicators of disease activity and function, including morning stiffness, pain, spinal mobility, peripheral joint swelling, CRP, ESR, and bone mineral density. MRI studies indicate substantial resolution of bone marrow edema, enthesitis, and joint effusions in the sacroiliac, facet, and peripheral joints. These results have been obtained in large randomized controlled trials of all five agents and many open-label studies. About one-half of the patients achieve a ≥50% reduction in the BASDAI. The response tends to persist over time and remission of symptoms is feasible in a proportion of patients. Predictors of the best responses include younger age, shorter disease duration, higher baseline inflammatory markers, and lower baseline functional disability. Nonetheless, some patients with long-standing disease and even spinal ankylosis obtain significant benefit. There is greater chance of slowing syndesmophyte formation with sustained therapy, especially if started early. The response of patients with nr-axSpA to anti-TNF therapy is generally similar to that of patients with AS.

Typically, infliximab is given intravenously, 5 mg/kg body weight, and then repeated 2 weeks later, again 6 weeks later, and then at 6- to 8-week intervals. Etanercept is given by subcutaneous injection, 50 mg once weekly. Adalimumab is given by subcutaneous injection, 40 mg biweekly. Golimumab is given by subcutaneous injection, 50 mg every 4 weeks. Certolizumab pegol is given by subcutaneous injection, 200 mg biweekly or 400 mg every 4 weeks. Dosage adjustments can be considered in selected cases.

These potent immunosuppressive agents are relatively safe, but patients are at increased risk for serious infections, including disseminated tuberculosis. Hypersensitivity infusion or injection site reactions are not uncommon. Cases of anti-TNF-induced psoriasis have been increasingly recognized. Rare cases of systemic lupus erythematosus (SLE)-related disease have been reported, as have hematologic disorders such as pancytopenia, demyelinating disorders, exacerbation of congestive heart failure, and severe liver disease. The overall incidence of malignancy is not increased in AS patients treated with anti-TNF therapy, but isolated cases of hematologic malignancy have occurred shortly after initiation of treatment.

Because of the expense, potentially serious side effects, and unknown long-term effects of these agents, their use should be

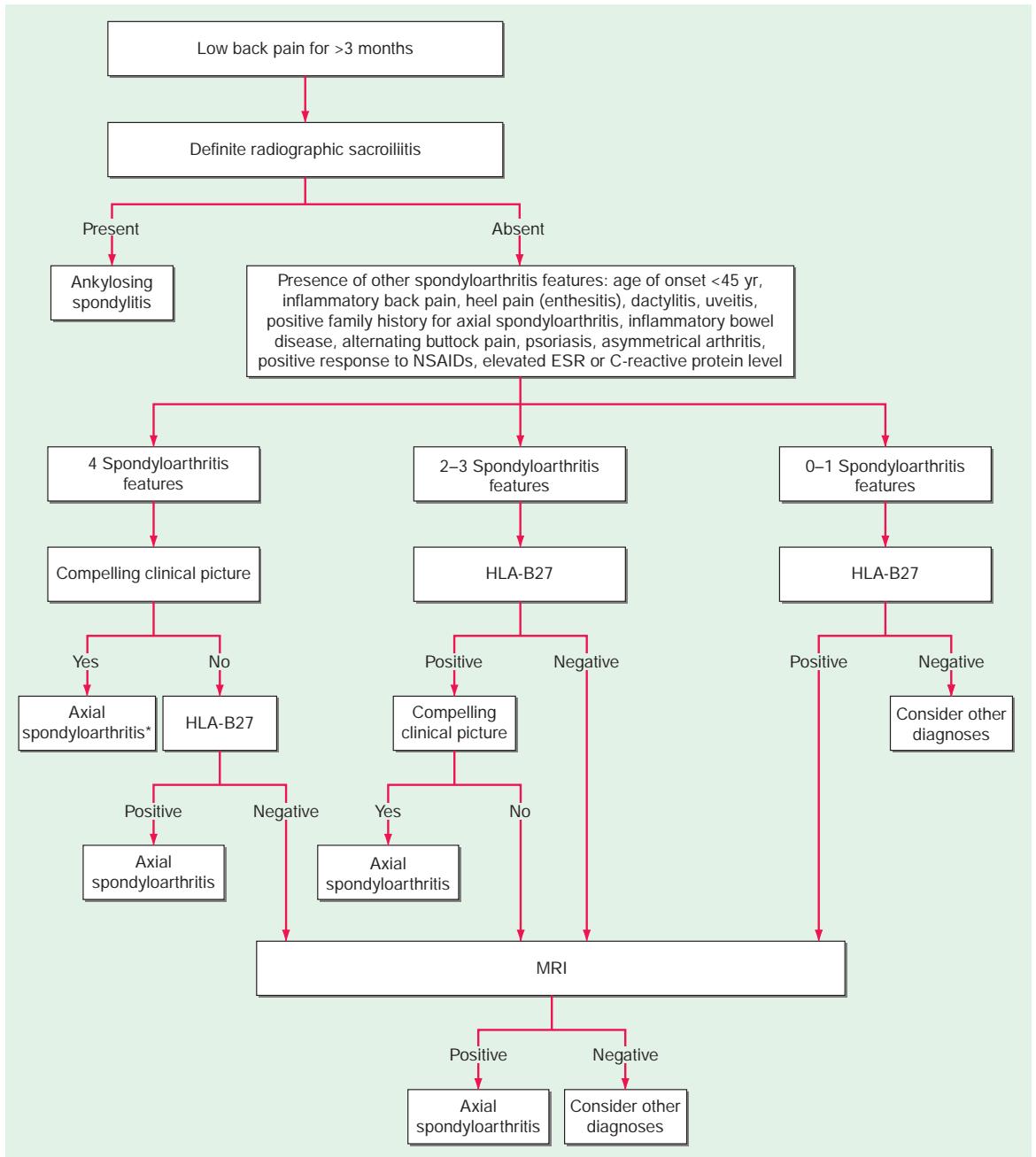


FIGURE 362-2 Algorithm for the diagnosis or exclusion of axial spondyloarthritis. The algorithm is designed for use in patients with at least a 3-month history of unexplained chronic low-back pain. Definite radiographic sacroiliitis is based on the modified New York criteria for ankylosing spondylitis (*van der Linden S et al: Arthritis Rheum* 27:361, 1984). The algorithm is adapted from *van den Berg R et al: Ann Rheum Dis* 72:1646, 2013. The determination of whether or not a clinical picture is compelling is based on the relative weights of the spondyloarthritis features (Feldtkeller E et al: *Rheumatology [Oxford]* 52:1648, 2013) and on clinical judgment. The list of clinical features includes features of both axial and peripheral spondyloarthritis. *Confirming MRI is recommended. (From Taurog JD et al: *N Engl J Med* 374:2563, 2016.)

restricted to patients with a definite diagnosis and active disease that is inadequately responsive to therapy with at least two different NSAIDs. Before initiation of anti-TNF therapy, all patients should be tested for latent tuberculosis (TB) and for hepatitis B, and treated appropriately if either is found. Contraindications to TNF inhibitors include active infection or high risk of infection; multiple sclerosis; and history of hematologic malignancy, SLE, or related autoimmunity. Pregnancy and breast-feeding are no longer considered contraindications if appropriate precautions are taken. Certolizumab pegol's label includes minimal transplacental or breast milk transfer.

However, infants exposed to anti-TNF in utero should not be given live vaccines before age 6 months. Switching to a second anti-TNF agent may be effective, especially if there was a response to the first that was lost, rather than primary failure.

Secukinumab, a human monoclonal antibody to IL-17A, and ixekizumab, a humanized monoclonal antibody to IL-17A, are FDA-approved for use in AS and show efficacy similar to that of anti-TNF. Both are effective in some patients who have failed or not tolerated anti-TNF therapy, as well as in patients naïve to biologic therapy. Both are also effective in nr-axSpA. The recommended

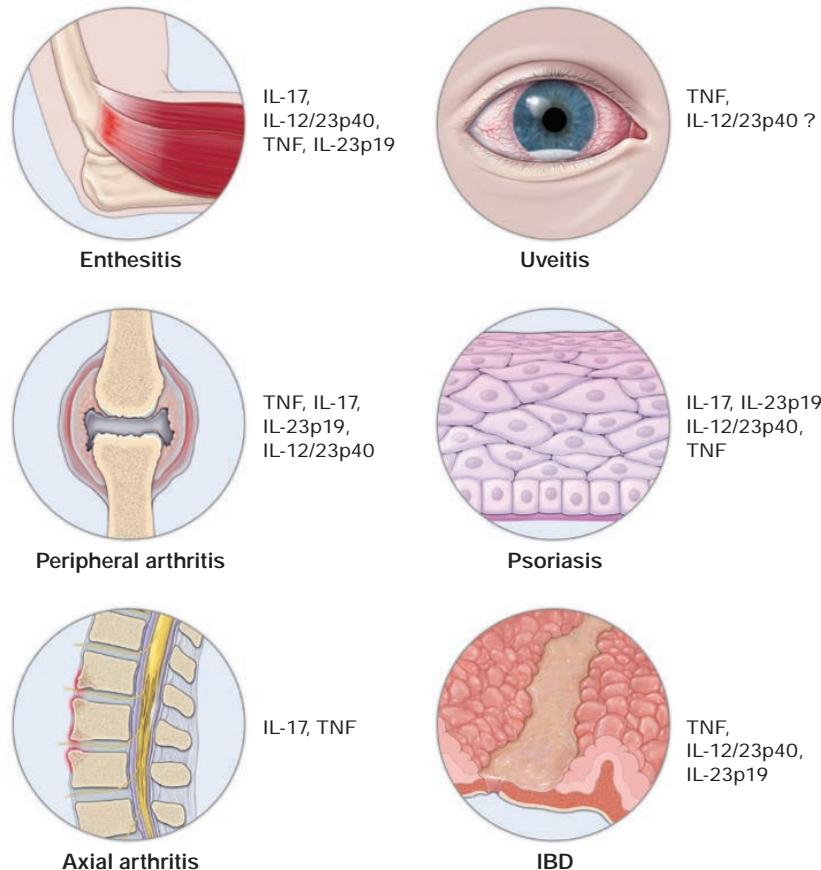


FIGURE 362-3 Proposed hierarchy of cytokine participation in disease pathogenesis in affected tissues in spondyloarthritis, based on the therapeutic response in clinical trials to biologic agents targeting the indicated cytokines. Peripheral arthritis, enthesitis, and psoriasis respond to agents targeting IL-17A, IL-23 (p19 subunit), IL-12/23 (p40 subunit), and TNF. Axial arthritis responds to anti-TNF and anti-IL17A, but failed to respond to anti-IL-23 and anti-IL12/23. Uveitis responds to anti-TNF, and anecdotally to anti-IL-12/23. The effect of anti-IL-17A in uveitis is not yet resolved. IBD responds to anti-TNF, anti-IL-23, and anti-IL-12/23, but failed to respond to anti-IL-17A and anti-IL-17 receptor. (Adapted from S Siebert et al: Ann Rheum Dis 78:1015, 2019.)

dose of secukinumab is 150 mg subcutaneously weekly for 4 weeks, and then at 4-week intervals. The recommended initiation of ixekizumab is with two 80 mg injections, followed by 80 mg every 4 weeks. Precautions regarding infection are similar to those for anti-TNF agents. An additional concern is potential exacerbation of underlying IBD, whether previously recognized or not, and careful monitoring is advised.

Two antibodies targeting IL-23, ustakinumab and risankizumab, failed to show efficacy in AS, whereas both show efficacy in psoriatic arthritis (see Fig. 362-3).

Sulfasalazine, in doses of 2–3 g/d, is used for peripheral arthritis. Methotrexate, although widely used, has not been shown to be of benefit in AS, nor has any therapeutic role for oral glucocorticoids been documented.

The oral Janus kinase (JAK) inhibitors, tofacitinib, upadacitinib, and filgotinib, have all shown efficacy in AS in clinical trials, with reduction of inflammation evident on MRI, and further clinical trials are in progress. Precautions regarding infection are similar to those for anti-TNF agents, with additional concern for herpes zoster.

The most common indication for surgery in patients with AS is severe hip joint arthritis, the pain and stiffness of which are usually dramatically relieved by total hip arthroplasty. Rare patients may benefit from surgical correction of extreme flexion deformities of the spine or of atlantoaxial subluxation.

Attacks of uveitis are usually managed effectively with local glucocorticoids and mydriatic agents, although systemic glucocorticoids, immunosuppressive drugs, or anti-TNF therapy may be

required. TNF inhibitors may reduce the frequency of attacks of uveitis in patients with ax-SpA. Cases of new or recurrent uveitis with use of a TNF inhibitor have been observed, especially with etanercept. Adalimumab is FDA approved to treat intermediate, posterior, or panuveitis. These presentations are rare in AS but not unusual in psoriatic or IBD-associated arthritis (see below). Anti-IL-17A agents have not been directly studied as treatment for SpA-associated uveitis, but secukinumab-treated AS patients showed no increased incidence of uveitis in clinical trials.

Spinal manipulation is strongly discouraged and can be particularly dangerous in patients with osteoporosis or structural lesions on x-ray.

Management of axial osteoporosis is similar to that used for primary osteoporosis because data specific for AS are not available.

REACTIVE ARTHRITIS

ReA refers to acute nonpurulent arthritis complicating an infection elsewhere in the body. In recent years, the term has been used primarily to refer to SpA following enteric or urogenital infections.

Other forms of reactive and infection-related arthritis not associated with B27 and showing a spectrum of clinical features different from SpA, such as Lyme disease, rheumatic fever, and poststreptococcal ReA, are discussed in Chaps. 186 and 359.

HISTORIC BACKGROUND

The association of acute arthritis with episodes of diarrhea or urethritis has been recognized for centuries. A high incidence during World

Wars I and II focused attention on the triad of arthritis, urethritis, and conjunctivitis, often with additional mucocutaneous lesions, which became known by eponyms that are now of historic interest only.

The identification of bacterial species triggering the clinical syndrome and the finding of an association with HLA-B27 led to the unifying concept of ReA as a clinical syndrome triggered by specific etiologic agents in a genetically susceptible host. A characteristic spectrum of clinical manifestations can be triggered by enteric infection with certain *Shigella*, *Salmonella*, *Yersinia*, and *Campylobacter* species; by genital infection with *Chlamydia trachomatis*; and by many other agents as well, apparently in some cases via nasopharyngeal infection with *Chlamydia pneumoniae* or other agents. The “classic triad” represents a small part of the clinical spectrum and is present only in a small minority of patients. For the purposes of this chapter, the use of the term *ReA* will be restricted to those cases of SpA with at least presumptive evidence for a related antecedent infection.

EPIDEMIOLOGY

In early reports, 60–85% of patients who developed ReA triggered by *Shigella*, *Yersinia*, or *Chlamydia* were HLA-B27-positive. However, a lower prevalence of B27 is found in ReA triggered by *Salmonella*, and little or no B27 association is seen in *Campylobacter*-induced ReA. Recent community-based or common-source epidemic studies showed an overall prevalence of B27 in ReA <50%. The most common age range is 18–40 years, but ReA can occur in children and older adults.

The reported attack rate of postenteric ReA ranges from 1% to about 30%, depending on the study and causative organism, whereas the attack rate of postchlamydial ReA is ~4–8%. The gender ratio following enteric infection is nearly 1:1, whereas venereally acquired ReA occurs mainly in men. The overall prevalence and incidence of ReA are difficult to assess because of lack of validated diagnostic criteria, variable prevalence and arthritogenic potential of the triggering microbes, and varying genetic susceptibility in different populations. In Scandinavia, an annual incidence of 10–28:100,000 has been reported. SpA was formerly almost unknown in sub-Saharan Africa. However, ReA and other peripheral SpAs became common in black Africans in the wake of the AIDS epidemic, without association to B27, which is rare in these populations. In Africans, ReA is often the first manifestation of HIV infection and often remits with disease progression. In contrast, Western white patients with HIV and SpA are usually B27-positive, and the arthritis flares as AIDS advances.

PATHOLOGY

Synovial histology is similar to that of other SpAs. Enthesitis shows increased vascularity and macrophage infiltration of fibrocartilage. Microscopic histopathologic evidence of inflammation mimicking IBD has routinely been demonstrated in the colon and ileum of patients with postenteric ReA and less commonly in postvenereal ReA. The skin lesions of keratoderma blennorrhagica, associated mainly with venereally acquired ReA, are histologically indistinguishable from pustular psoriasis.

ETIOLOGY AND PATHOGENESIS

Definite bacterial triggers of ReA include several *Salmonella* spp., *Shigella* spp., *Yersinia enterocolitica*, *Yersinia pseudotuberculosis*, *Campylobacter jejuni*, and *Chlamydia trachomatis*. These are all gram-negative bacteria containing lipopolysaccharide (LPS). All *Shigella* species have been implicated in cases of ReA, with *S. flexneri* and *S. sonnei* being the most common. *Yersinia* species in Europe and Scandinavia may have greater arthritogenic potential than elsewhere, and *C. trachomatis* appears to be a common trigger worldwide. The ocular serovars of *C. trachomatis* appear to be particularly, perhaps uniquely, arthritogenic.

There is also evidence implicating *Clostridium difficile*, *Campylobacter coli*, certain toxigenic *Escherichia coli*, *Ureaplasma urealyticum*, and *Mycoplasma genitalium* as potential triggers of ReA. *Chlamydia pneumoniae* can trigger ReA, but far less commonly so than *C. trachomatis*. There have been numerous isolated reports of acute arthritis following many other bacterial, viral, or parasitic infections, and arthritis following intravesicular bacillus Calmette-Guérin (BCG) treatment for bladder cancer is well documented.

It is not known whether there is a common pathogenic mechanism for triggering ReA that is shared by all of these microorganisms, nor has the mechanism been elucidated for any particular trigger. Many of the established triggers share a capacity to attack mucosal surfaces, to invade host cells, and to survive intracellularly. Antigens from *Chlamydia*, *Yersinia*, *Salmonella*, and *Shigella* have been found in synovium and/or synovial fluid leukocytes of patients with ReA for long periods following the acute attack. In ReA triggered by *Y. enterocolitica*, bacterial LPS and heat-shock protein antigens have been found in peripheral blood cells years after the triggering infection. *Yersinia* DNA and *C. trachomatis* DNA and RNA have been detected in synovial tissue from ReA patients, suggesting the presence of viable organisms despite uniform failure to culture organisms from these specimens. The specificity of these findings is unclear, however, since chromosomal bacterial DNA and 16S rRNA from a wide variety of bacteria have also been found in synovium in other rheumatic diseases, albeit less frequently.

Recent work has documented high levels of IL-17 in ReA synovial fluid, but the source has not been identified. HLA-B27 seems to be associated with more severe and chronic ReA, but its pathogenic role remains to be determined. HLA-B27 significantly prolongs the intracellular survival of *Y. enterocolitica* and *Salmonella enteritidis* in human and mouse cell lines. This may permit trafficking of infected leukocytes from the site of primary infection to joints, where an innate and/or adaptive immune response to persistent bacterial antigens may then promote arthritis.

A recent study using 16S ribosomal RNA gene sequencing of intestinal microbiota showed a higher abundance of *Erwinia* and *Pseudomonas* species and an increased prevalence of typical enteropathogens in ReA patients, compared with controls. Correlations were found between specific bacteria and disease manifestations, and there was an HLA correlation with microbiome diversity.

CLINICAL FEATURES

The clinical manifestations of ReA range from an isolated, transient monoarthritis or enthesitis to severe multisystem disease. A careful history will often elicit evidence of an antecedent infection 1–4 weeks before onset of symptoms of the reactive disease, particularly in postenteric ReA. However, in a sizable minority, no clinical or laboratory evidence of an antecedent infection can be found, particularly in the case of postchlamydial ReA. In cases of presumed venereally acquired reactive disease, there is often a history of a recent new sexual partner.

Constitutional symptoms are common, including fatigue, malaise, fever, and weight loss. The musculoskeletal symptoms are usually acute in onset. Arthritis is usually asymmetric and additive, with involvement of new joints occurring over a few days to 1–2 weeks. The joints of the lower extremities, especially the knee, ankle, subtalar, metatarsophalangeal, and toe interphalangeal joints, are most commonly involved, but the wrist and fingers may be involved. The arthritis is usually quite painful, and tense joint effusions are not uncommon, especially in the knee. Dactylitis, or “sausage digit,” a diffuse swelling of a solitary finger or toe, is a distinctive feature of ReA and PsA, but can be seen in polyarticular gout and sarcoidosis. Tendinitis and fasciitis are particularly characteristic lesions, producing pain at multiple entheses, especially the Achilles insertion, the plantar fascia, and sites along the axial skeleton. Back and buttock pain are quite common and may be caused by insertional inflammation, muscle spasm, acute sacroiliitis, or, presumably, arthritis in intervertebral joints.

Urogenital lesions may occur throughout the course of the disease. In men, urethritis may be marked or relatively asymptomatic and may be either an accompaniment of the triggering infection or a result of the reactive phase of the disease; interestingly, it occurs in both postvenereal and postenteric ReA. Prostatitis is common. In women, cervicitis or salpingitis may be caused either by the infectious trigger or by the sterile reactive process.

Ocular disease is common, ranging from transient, asymptomatic conjunctivitis to an aggressive anterior uveitis that occasionally proves refractory to treatment and may result in blindness.

Mucocutaneous lesions are frequent. Oral ulcers tend to be superficial, transient, and often asymptomatic. The characteristic skin lesion,

keratoderma blennorrhagica, consists of vesicles and/or pustules that become hyperkeratotic, ultimately forming a crust before disappearing. They are most common on the palms and soles but may occur elsewhere as well. In patients with HIV infection, these lesions are often severe and extensive, sometimes dominating the clinical picture (**Chap. 202**). Lesions on the glans penis, termed *circinate balanitis*, consist of vesicles that quickly rupture to form painless superficial erosions, which in circumcised individuals can form crusts similar to those of *keratoderma blennorrhagica*. Nail changes are common and consist of onycholysis, distal yellowish discoloration, and/or heaped-up hyperkeratosis.

Less frequent or rare manifestations of ReA include cardiac conduction defects, aortic insufficiency, central or peripheral nervous system lesions, and pleuropulmonary infiltrates.

In resolving cases, arthritis typically lasts for 3–5 months. Chronic joint symptoms persist in about 15% of patients, and in up to 60% of patients in hospital-based series. The chronic symptoms tend to be less severe than in the acute stage, but work disability or forced change in occupation is common. Chronic heel pain is often particularly distressing. Low-back pain, sacroiliitis, or even overt AS are common sequelae. Recurrences of the acute syndrome may occur. In most studies, HLAB27-positive patients showed a worse outcome than B27-negative patients. Patients with *Yersinia*- or *Salmonella*-induced arthritis have less chronic disease than those whose initial episode follows epidemic shigellosis.

LABORATORY AND RADIOGRAPHIC FINDINGS

The ESR and acute-phase reactants are usually elevated during the acute phase of the disease, often markedly. Mild anemia may be present. Synovial fluid is nonspecifically inflammatory. In most ethnic groups, 30–50% of the patients are B27-positive. The triggering infection usually does not persist at the site of primary mucosal infection through the time of onset of the reactive disease, but it may be possible to culture the organism, for example, in the case of *Yersinia*- or *Chlamydia*-induced disease. Serologic evidence of exposure to a causative organism is nonspecific and of questionable utility. Polymerase chain reaction (PCR) for chlamydial DNA in first-voided urine specimens may have high sensitivity in the acute stage but is less useful with chronic disease.

In early or mild disease, radiographic changes may be absent or confined to juxtaarticular osteoporosis. With long-standing disease, radiographic features share those of PsA; marginal erosions and loss of joint space can be seen in affected joints. Periostitis with reactive new bone formation is characteristic, as in all the SpAs. Spurs at the insertion of the plantar fascia are common. Sacroiliitis and spondylitis may be seen as late sequelae. Sacroiliitis is more commonly asymmetric than in AS, and spondylitis can begin anywhere along the lumbar spine. The syndesmophytes are described as nonmarginal; they are coarse, asymmetric, and “comma”-shaped, arising from the middle of a vertebral body, a pattern less commonly seen in primary AS. Progression to spinal fusion is uncommon.

DIAGNOSIS

ReA is a clinical diagnosis with no definitively diagnostic laboratory test or radiologic finding. The diagnosis should be entertained in any patient with an acute inflammatory, asymmetric, additive arthritis or tendinitis. The evaluation should include thorough but tactful questioning regarding possible triggering events. On physical examination, attention must be paid to the distribution of the joint and tendon involvement and to possible sites of extraarticular involvement, including the eyes, mucous membranes, skin, nails, and genitalia. Synovial fluid analysis is usually necessary to exclude septic or crystal-induced arthritis. Culture, serology, or molecular methods may help identify a triggering infection, but they cannot be relied upon.

Although typing for B27 has low negative predictive value in ReA, it may have prognostic significance in terms of severity, chronicity, and the propensity for spondylitis and uveitis. Furthermore, if positive, it can be helpful diagnostically in atypical cases. HIV testing is often indicated and may be necessary in selecting therapy.

Both ReA and disseminated gonococcal disease (**Chap. 156**) can be venereally acquired and associated with urethritis. Unlike ReA, gonococcal arthritis and tenosynovitis tend to involve both upper and lower extremities equally, spare the axial skeleton, and be associated with characteristic vesicular skin lesions. A positive gonococcal culture from the urethra or cervix does not exclude ReA; however, culturing gonococci from blood, skin lesion, or synovium establishes the diagnosis of disseminated gonococcal disease. PCR assay for *Neisseria gonorrhoeae* and *C. trachomatis* may be helpful. Occasionally, only a therapeutic trial of antibiotics can distinguish ReA from disseminated gonococcal disease.

ReA shares many features with PsA. However, PsA is usually gradual in onset; the arthritis tends to affect primarily the upper extremities; and there are usually no associated mouth ulcers, urethritis, or bowel symptoms.

TREATMENT

Reactive Arthritis

Most patients with ReA benefit to some degree from high-dose NSAIDs, although acute symptoms are rarely completely ameliorated, and some patients fail to respond at all.

Prompt, appropriate antibiotic treatment of acute chlamydial urethritis or enteric infection may prevent the emergence of ReA but is not universally successful. Data regarding the potential benefit of antibiotic therapy initiated after onset of arthritis are conflicting; however, a systematic review and meta-analysis of 10 controlled trials suggested no benefit. One of these trials reported that a majority of patients with chronic ReA associated with *C. trachomatis* or *C. pneumoniae* benefited significantly from a 6-month course of rifampin plus either azithromycin or doxycycline. This 2010 study still awaits confirmation.

Multicenter trials have suggested that sulfasalazine, up to 3 g/d in divided doses, may be beneficial to patients with persistent ReA.¹ Patients with persistent disease may respond to azathioprine, 1–2 mg/kg per day, or to methotrexate, up to 20 mg per week; however, these regimens have never formally been studied. Anecdotal evidence from 30 patients supports the use of anti-TNF in severe chronic cases, and there are isolated reports of responses to anti-IL-17A or anti-IL-6 receptor therapy.¹

Tendinitis and other enthesitic lesions may benefit from intralesional glucocorticoids. Uveitis may require aggressive treatment to prevent serious sequelae. Skin lesions ordinarily require only symptomatic topical treatment. In patients with HIV infection and ReA, many of whom have severe skin lesions, the skin lesions in particular respond to antiretroviral therapy. Cardiac complications are managed conventionally; management of neurologic complications is symptomatic.

Comprehensive management includes counseling patients to avoid sexually transmitted disease and exposure to enteropathogens, as well as appropriate use of physical therapy, vocational counseling, and continued surveillance for long-term complications such as AS. Patients with a history of ReA are at increased risk for recurrent attacks following repeat exposure.

¹Azathioprine, methotrexate, sulfasalazine, pamidronate, anti-TNF_α agents, anti-IL-17A agents, and anti-IL-6 receptor agents have not been approved for this purpose by the FDA at the time of publication.

PSORIATIC ARTHRITIS

Psoriatic arthritis refers to an inflammatory musculoskeletal disease that has both autoimmune and autoinflammatory features characteristically occurring in individuals with psoriasis.

HISTORIC BACKGROUND

The association between arthritis and psoriasis was noted in the nineteenth century. In the 1960s, it became clear that unlike RA, arthritis associated with psoriasis was usually seronegative, often involved the

distal interphalangeal (DIP) joints of the fingers and the spine and sacroiliac joints, had distinctive radiographic features, and showed considerable familial aggregation. In the 1970s, PsA was included in the broader category of spondyloarthritis because of features similar to those of AS and ReA.

EPIDEMIOLOGY

The prevalence of PsA appears to be increasing in parallel with disease awareness. Recent data suggest that up to 30% of patients with psoriasis develop PsA. Longer duration and greater severity of psoriasis increase the likelihood of developing PsA. In white populations, psoriasis is estimated to have a prevalence of 1–3%. In other races, psoriasis and PsA are less common in the absence of HIV infection, and the prevalence of PsA in individuals with psoriasis may be less common. First-degree relatives of PsA patients have an elevated risk for psoriasis, for PsA, and for other forms of SpA. Of patients with psoriasis, up to 30% have an affected first-degree relative. In monozygotic twins, the reported concordance for psoriasis varies from 35–72%, and for PsA from 10–30%. A variety of HLA associations have been found. HLA-C6 is directly associated with psoriasis, particularly familial juvenile-onset (type I) psoriasis. HLA-B27 is associated with psoriatic spondylitis (see below). HLA-DR7, -DQ3, and -B57 are associated with PsA because of linkage disequilibrium with C6. A recent study found additive associations of PsA with haplotypes containing HLA-B8, -C6, -B27, -B38, and -B39. A correlation was also found between different haplotype combinations and enthesal, synovial, or axial predominant phenotypes. Genome-wide analyses have identified associations of PsA with polymorphisms in the IL-23 receptor (*IL23R*), molecules involved in nuclear factor κB gene expression (*TNIP1*, *TRAF3IP2*) and signaling (*TNFAIP3*, *TYK2*), and cytokines *TNF*, *IL12A*, and *IL12B*. A specific *IL23R* SNP is associated with PsA distinct from psoriasis without arthritis. Overall genetic sharing of AS with psoriasis is 0.28, lower than with IBD (see below). Polymorphisms in *IL-23A* are associated with psoriasis and with PsA, but not with AS.

PATHOLOGY

The inflamed synovium in PsA resembles that of RA, although with somewhat less hyperplasia and cellularity than in RA. As noted with AS above, the synovial vascular pattern in PsA is generally greater and more tortuous than in RA, independent of disease duration. Some studies have indicated a higher tendency to synovial fibrosis in PsA. Unlike RA, PsA shows prominent enthesitis, with histology similar to other forms of SpA.

PATHOGENESIS

PsA presumably shares immunopathogenic mechanisms with psoriasis. PsA synovium is characterized by lining layer hyperplasia; diffuse infiltration with T cells, B cells, macrophages, and NK receptor-expressing cells, with upregulation of leukocyte homing receptors; and neutrophil proliferation with angiogenesis. Clonally expanded T-cell subpopulations are frequent and have been demonstrated both in the synovium and the skin. Plasmacytoid dendritic cells are thought to play a key role in psoriasis, and there is some evidence for their participation in PsA. Interferon γ, TNF, and IL-1β, 2, 6, 8, 10, 12, 13, 15, and 17A, and myeloid-related protein (S100A8/A9) are found in PsA synovium or synovial fluid. IL-23/17 pathway cytokines are critical drivers of PsA pathogenesis. Both T_H17 cells and type 3 innate lymphocytes (ILC3) have been identified in dermal extracts of psoriatic lesions and in synovial fluid of PsA patients. Consistent with the extensive bone remodeling in PsA, patients with PsA have been found to have a marked increase in osteoclastic precursors in peripheral blood and upregulation of receptor activator of nuclear factor κB ligand (RANKL) in the synovial lining layer. Increased serum levels of TNF, RANKL, leptin, and omentin positively correlate with these osteoclastic precursors.

CLINICAL FEATURES

In 70% of cases, psoriasis precedes joint disease. In 15% of cases, the two manifestations appear within 1 year of each other. In about 15% of cases, the arthritis precedes the onset of psoriasis and can present a diagnostic challenge. The frequency in men and women is almost

equal, although the frequency of disease patterns differs somewhat in the two sexes. The disease can begin in childhood or late in life but typically begins in the fourth or fifth decade, at an average age of 37 years.

Many classification schemes have been proposed for the broad spectrum of arthropathy in PsA. Wright and Moll described five patterns: (1) arthritis of the DIP joints; (2) asymmetric oligoarthritis; (3) symmetric polyarthritis similar to RA; (4) axial involvement (spine and sacroiliac joints); and (5) arthritis mutilans, a highly destructive form of the disease. These patterns frequently coexist, and the pattern that persists chronically often differs from that of the initial presentation. A simpler scheme in recent use contains three patterns: oligoarthritis, polyarthritis, and axial arthritis.

Nail changes in the fingers or toes occur in most patients with PsA, compared with only a minority of psoriatic patients without arthritis, and pustular psoriasis is said to be associated with more severe arthritis. Dactylitis and enthesitis are common in PsA and help to distinguish it from other joint disorders. Dactylitis occurs in >30%; enthesitis and tenosynovitis are probably present in most patients, although often not appreciated on physical examination. Shortening of digits because of underlying osteolysis is particularly characteristic of PsA, and there is a much greater tendency than in RA for both fibrous and bony ankylosis of small joints. Rapid ankylosis of one or more proximal interphalangeal (PIP) joints early in the course of disease is not uncommon. Joint involvement tends to follow a “ray” distribution, with all of the joints of one finger involved, while sparing adjacent fingers entirely. Back and neck pain and stiffness are also common in PsA.

Arthropathy confined to the DIP joints occurs in ~5% of cases. Accompanying nail changes in the affected digits are almost always present. These joints are also often affected in the other patterns of PsA. Approximately 30% of patients have asymmetric oligoarthritis. This pattern commonly involves a knee or another large joint with a few small joints in the fingers or toes, often with dactylitis. Symmetric polyarthritis occurs in about 40% of PsA patients at presentation. It may be indistinguishable from RA in terms of the joints involved, but other features characteristic of PsA are usually also present. Almost any peripheral joint can be involved. Axial arthritis without peripheral involvement is found in ~5% of PsA patients. It may be clinically indistinguishable from idiopathic AS, although more neck involvement and less thoracolumbar spinal involvement are characteristic, and nail changes are not found in idiopathic AS. A small percentage of PsA patients have arthritis mutilans, in which there can be widespread shortening of digits (“telescoping”), sometimes coexisting with ankylosis and contractures in other digits.

Six patterns of nail involvement are identified: pitting, horizontal ridging, onycholysis, yellowish discoloration of the nail margins, dystrophic hyperkeratosis, and combinations of these findings. Extraarticular and extradermal manifestations are common. Eye involvement, either conjunctivitis or uveitis, is reported in 7–33% of PsA patients. Unlike uveitis associated with AS, the uveitis in PsA is more often insidious in onset, bilateral, chronic, and/or nonanterior. The prevalences of aortic valve insufficiency and heart block are apparently similar to those in AS.

Widely varying estimates of clinical outcome have been reported in PsA. At its worst, severe PsA with arthritis mutilans is potentially at least as crippling and ultimately fatal as severe untreated RA. Unlike RA, however, many patients with PsA experience temporary remissions. Overall, erosive disease develops in the majority of patients, progressive disease with deformity and disability is common, and in some large series, mortality was found to be significantly increased compared with the general population.

The psoriasis and associated arthropathy seen with HIV infection both tend to be severe and can occur in populations with low prevalence of psoriasis. Severe enthesitis, dactylitis, and rapidly progressive joint destruction are seen, but axial involvement is very rare. This condition is prevented by or responds well to antiretroviral therapy.

LABORATORY AND RADIOGRAPHIC FINDINGS

There are no laboratory tests diagnostic of PsA. ESR and CRP are elevated in only 30% of patients. A small percentage of patients may

have low titers of rheumatoid factor or ANAs. About 10% of patients have anti-CCP antibodies. Uric acid may be elevated in the presence of extensive psoriasis. HLA-B27 is found in 50–70% of patients with axial disease but in ≤20% of patients with only peripheral joint involvement.

Peripheral and axial arthritis in PsA show several radiographic features that distinguish them from RA and AS, respectively. Characteristics of peripheral PsA include DIP involvement, including the classic “pencil-in-cup” deformity; marginal erosions with adjacent bony proliferation (“whiskering”); small-joint ankylosis; osteolysis of phalangeal and metacarpal bone, with telescoping of digits; periostitis and proliferative new bone at sites of enthesitis; and a “ray” distribution of lesions. Characteristics of axial PsA that differ from idiopathic AS include asymmetric sacroiliitis; less facet joint arthritis; nonmarginal, bulky, “comma”-shaped syndesmophytes that tend to be fewer, less symmetric, and less delicate than the marginal syndesmophytes of AS; fluffy hyperperiostosis on anterior vertebral bodies; severe cervical spine involvement, with a tendency to atlantoaxial subluxation but relative sparing of the thoracolumbar spine; and paravertebral ossification. Ultrasound and MRI both readily demonstrate enthesitis and tendon sheath effusions that can be difficult to assess on physical examination. A recent MRI study of 68 PsA patients found sacroiliitis in 35%, unrelated to B27 but correlated with restricted spinal movement.

DIAGNOSIS

Classification criteria for PsA were published in 2006 (Classification of Psoriatic Arthritis [CASPAR] criteria) (**Table 362-2**). The sensitivity and specificity of these criteria exceed 90%, and they are useful in clinical practice as a guide for early diagnosis. Diagnosis can be challenging when the arthritis precedes psoriasis, the psoriasis is undiagnosed or obscure, or the joint involvement closely resembles another form of arthritis. A high index of suspicion is needed in any patient with an undiagnosed inflammatory arthritis. The history should include inquiry about psoriasis in the patient and family members. Patients should be examined disrobed, and psoriasisiform lesions should be sought in the scalp, ears, umbilicus, and gluteal folds in addition to more accessible sites; the fingernails and toenails should also be carefully examined. Axial symptoms or signs, dactylitis, enthesitis, ankylosis, the pattern of joint involvement, and characteristic radiographic changes can be helpful clues. The differential diagnosis includes all other forms of arthritis, which can occur coincidentally in individuals with psoriasis. The differential diagnosis of isolated DIP involvement is short. Osteoarthritis (Heberden’s nodes) is usually not inflammatory; gout involving more than one DIP joint often involves other sites and may be accompanied by tophi; the very rare entity multicentric reticulohistiocytosis involves other joints and has characteristic small pearly periungual skin nodules; and the uncommon entity, inflammatory osteoarthritis, like the others, lacks the nail changes of PsA. Radiography can be helpful in all these cases,

TABLE 362-2 The CASPAR (Classification Criteria for Psoriatic Arthritis) Criteria^a

To meet the CASPAR criteria, a patient must have inflammatory articular disease (joint, spine, or entheseal) with 3 points from any of the following five categories:

1. Evidence of current psoriasis,^{b,c} a personal history of psoriasis, or a family history of psoriasis^d
2. Typical psoriatic nail dystrophy^e observed on current physical examination
3. A negative test result for rheumatoid factor
4. Either current dactylitis^f or a history of dactylitis recorded by a rheumatologist
5. Radiographic evidence of juxtaarticular new bone formation^g in the hand or foot

^aSpecificity of 99% and sensitivity of 91%. ^bCurrent psoriasis is assigned 2 points; all other features are assigned 1 point. ^cPsoriatic skin or scalp disease present at the time of examination, as judged by a rheumatologist or dermatologist.

^dHistory of psoriasis in a first- or second-degree relative. ^eOnycholysis, pitting, or hyperkeratosis. ^fSwelling of an entire digit. ^gIll-defined ossification near joint margins, excluding osteophyte formation.

Source: Reproduced with permission from W Taylor et al: Classification criteria for psoriatic arthritis: development of new criteria from a large international study. *Arthritis Rheum* 54:2665, 2006.

and in distinguishing between psoriatic spondylitis and idiopathic AS. A history of trauma to an affected joint preceding the onset of arthritis may occur more frequently in PsA than in other types of arthritis, perhaps reflecting the Koebner phenomenon in which psoriatic skin lesions arise at sites of skin trauma.

TREATMENT

Psoriatic Arthritis

Ideally, coordinated therapy is directed at both the skin and joints in PsA, and biologic agents have dramatically facilitated this goal. This was first observed with anti-TNF agents, with prompt and dramatic resolution of both arthritis and skin lesions observed in large, randomized controlled trials of all five agents. Many of the responding patients had long-standing disease that was resistant to all previous therapy, as well as extensive skin disease. The clinical response is often more dramatic than in RA, and delay of disease progression has been demonstrated radiographically. The potential additive effect of methotrexate to anti-TNF agents in PsA remains uncertain. As noted above, anti-TNF therapy, paradoxically, has been reported to trigger exacerbation or de novo appearance of psoriasis, typically the palmoplantar pustular variety. In some cases, the therapy can nevertheless be continued.

Antagonists of the IL-23/IL-17 pathway show efficacy at least comparable to that of anti-TNF for PsA and in some cases superior for psoriasis. Approved agents include secukinumab and ixekizumab, monoclonal antibodies to IL-17A; and ustekinumab, a monoclonal antibody to the shared IL-23/IL-12p40 subunit. Three monoclonal antibodies to IL-23 (p19 subunit) that are approved for plaque psoriasis—guselkumab, risankizumab, and tildrakizumab—showed efficacy in PsA in clinical trials (Fig. 362-3).

Apremilast, an oral phosphodiesterase-4 inhibitor, is approved for both psoriasis and PsA. Although not quite as effective for PsA as the biologics, apremilast has a more favorable safety profile. It is not indicated in patients with radiographically evident joint damage or axial involvement.

The oral JAK inhibitor, tofacitinib, is approved for treatment of PsA. When directly compared, its efficacy was comparable to the anti-TNF agent adalimumab. At least five other JAK inhibitors are currently being studied in PsA clinical trials.

Older treatments for PsA have been based on drugs that have efficacy in RA and/or in psoriasis. Methotrexate in doses of 15–25 mg/week has moderate efficacy for psoriasis, and expert opinion favors its use in PsA not requiring biologics. Agents with efficacy in psoriasis reported to benefit PsA are cyclosporine, retinoic acid derivatives, and psoralens plus ultraviolet A light (PUVA). The pyrimidine synthetase inhibitor leflunomide has been shown to be beneficial in PsA, with modest benefit for psoriasis.

All these treatments require careful monitoring. Immunosuppressive therapy may be used cautiously in HIV-associated PsA if the HIV infection is well controlled.

UNDIFFERENTIATED AND JUVENILE SPONDYLOARTHRITIS

Many patients present with one or more SpA features but lack sufficient findings for one of the preceding diagnoses. These patients were formerly said to have *undifferentiated spondyloarthritis*, or simply *spondyloarthritis*, as defined by the 1991 European Spondyloarthropathy Study Group criteria. Some of these patients may have ReA in which the triggering infection remains clinically silent. In other cases, the patient may subsequently develop IBD or psoriasis. The diagnosis of undifferentiated SpA was commonly applied to patients with peripheral arthritis and/or enthesitis, and to patients with IBD and other SpA features who did not meet radiographic criteria for AS. Many of these latter patients would now be classified as nr-axSpA (Table 362-1).

Comparable to the classification criteria for axial SpA, the ASAS has formulated criteria for peripheral SpA. This is intended to exclude patients with axial symptoms and thus to divide the universe of patients

TABLE 362-3 ASAS Criteria for Peripheral Spondyloarthritis***ARTHRITIS^b OR ENTHESITIS OR DACTYLITIS****PLUS EITHER**

One or more of the following SpA features:

- Psoriasis
- Crohn's disease or ulcerative colitis
- Preceding infection
- Uveitis
- HLA-B27
- Sacroiliitis on imaging (radiographs or MRI)

OR two or more of the following SpA features:

- Arthritis
- Enthesitis
- Dactylitis
- Inflammatory back pain ever
- Family history for SpA

*Sensitivity 78%, specificity 82%. ^bPeripheral arthritis, usually predominantly lower limb and/or asymmetric. The various SpA features are as defined in Table 362-1.

Preceding infection refers to preceding gastrointestinal or urogenital infection.

Source: M Rudwaleit et al: Ann Rheum Dis 70:25, 2011.

with SpA into predominantly axial and predominantly peripheral subsets. These criteria are shown in **Table 362-3**.

In juvenile SpA, which usually begins between ages 7 and 16 years, an asymmetric, predominantly lower-extremity oligoarthritis and enthesitis without extraarticular features is the typical mode of presentation. This condition is termed the *seronegative enthesitis and arthritis (SEA) syndrome*. There is male predominance (60–80%), and the prevalence of B27 is ~80%. Despite the absence of axial symptoms, active sacroiliitis by MRI has commonly been found at diagnosis. Many, but not all, of these patients go on to develop AS in late adolescence or adulthood.

Management of peripheral SpA is similar to that of the other spondyloarthritides. Biologic therapy is indicated in severe, persistent cases not responsive to other treatment.

Current pediatric literature should be consulted for information on management of juvenile SpA.

IBD-ASSOCIATED ARTHRITIS

HISTORIC BACKGROUND

The relationship between arthritis and IBD, first observed in the 1930s, was further defined by epidemiologic studies in the 1950s and 1960s, and included in the concept of the spondyloarthritides in the 1970s.

EPIDEMIOLOGY

Both common forms of IBD, ulcerative colitis (UC) and Crohn's disease (CD) (**Chap. 326**), are associated with SpA. UC and CD both have an estimated prevalence of 0.1–0.2%, and the incidence of each is thought to have increased in recent decades. Both axial and peripheral SpA are associated with UC and CD. Wide variations have been reported in the estimated frequencies of these associations. In recent series, AS was diagnosed in 1–10%, and peripheral arthritis in 10–50% of patients with IBD. IBP and enthesitis are common, and many patients have sacroiliitis on imaging studies.

The prevalence of UC or CD in patients with AS is thought to be 5–10%, and a recent meta-analysis found the prevalence in patients with nr-axSpA to be 6.4%. However, investigation of unselected SpA patients by ileocolonoscopy has revealed that up to two-thirds of patients with AS have subclinical intestinal inflammation that is evident either macroscopically or histologically. These lesions have also been found in patients with undifferentiated SpA or ReA (both enterically and urogenitally acquired).

Both UC and CD show familial aggregation, more so for CD. HLA associations have been weak and inconsistent. HLA-B27 is found in up to 70% of patients with IBD and AS, but in ≤15% of patients with IBD and peripheral arthritis or IBD alone. Three alleles of the *NOD2/CARD15* gene have been found in approximately one-half of patients with CD. These alleles are not associated with SpA per se. In addition, more than 200 other genes have been found to be associated with CD, UC, or both. Many of the SNPs associated with AS are also associated with IBD, almost all with the same direction of association. Overall, the genetic correlation of AS is 0.49 with CD and 0.47 with UC.

CARD15 gene have been found in approximately one-half of patients with CD. These alleles are not associated with SpA per se. In addition, more than 200 other genes have been found to be associated with CD, UC, or both. Many of the SNPs associated with AS are also associated with IBD, almost all with the same direction of association. Overall, the genetic correlation of AS is 0.49 with CD and 0.47 with UC.

PATHOLOGY

Available data for IBD-associated peripheral arthritis suggest a synovial histology similar to other forms of SpA. Association with arthritis does not affect the gut histology of UC or CD (**Chap. 326**). The subclinical inflammatory lesions in the colon and distal ileum associated with SpA are classified as either acute or chronic. The former resembles acute bacterial enteritis, with largely intact architecture and neutrophilic infiltration in the lamina propria. The latter resemble the lesions of CD, with distortion of villi and crypts, aphthoid ulceration, and mononuclear cell infiltration in the lamina propria.

PATHOGENESIS

Both IBD and SpA are immune-mediated, and the shared genetics presumably reflect shared pathogenic mechanisms, but the specific connection between them remains obscure. Rodent models showing various immune perturbations manifest both IBD and arthritis. Resident innate immune cells and intestinal dysbiosis have been implicated in both conditions. Several lines of evidence indicate trafficking of leukocytes between the gut and the joint. Mucosal leukocytes from IBD patients have been shown to bind avidly to synovial vasculature through several different adhesion molecules. Macrophages expressing CD163 are prominent in the inflammatory lesions of both gut and synovium in the spondyloarthritides.

CLINICAL FEATURES

AS associated with IBD is clinically indistinguishable from idiopathic AS. It runs a course independent of the bowel disease, and in some patients, it precedes the onset of IBD. Peripheral arthritis may also begin before onset of overt bowel disease. The spectrum of peripheral arthritis includes acute self-limited attacks of oligoarthritis that often coincide with relapses of IBD, and more chronic and symmetric polyarticular arthritis that runs an independent course. The patterns of joint involvement are similar in UC and CD. In general, erosions and deformities are infrequent in IBD-associated peripheral arthritis. Isolated destructive hip arthritis is a rare complication of CD, apparently distinct from osteonecrosis and septic arthritis. Dactylitis and enthesopathy are occasionally found. In addition to the ~20% of IBD patients with SpA, a comparable percentage have arthralgias or fibromyalgia symptoms.

Other extraintestinal manifestations of IBD are seen in addition to arthritis, including uveitis, psoriasis, pyoderma gangrenosum, erythema nodosum, pulmonary nodules, and clubbing, all somewhat more commonly in CD than UC. The uveitis shares the features described above for PsA-associated uveitis.

LABORATORY AND RADIOGRAPHIC FINDINGS

Laboratory findings reflect the inflammatory and metabolic manifestations of IBD. Joint fluid is usually at least mildly inflammatory. Of patients with AS and IBD, 30–70% carry HLA-B27, compared with 80–90% of patients with AS alone and 50–70% of those with AS and psoriasis. Hence, definite or probable AS in a B27-negative individual in the absence of psoriasis should raise concern for occult IBD. Radiographic changes in the axial skeleton are the same as in uncomplicated AS. Erosions are uncommon in peripheral arthritis but may occur, particularly in the metatarsophalangeal joints.

DIAGNOSIS

Diarrhea and arthritis are both common conditions that can coexist for a variety of reasons. When etiopathogenically related, ReA and IBD-associated arthritis are the most common causes. Rare causes include celiac disease and Whipple's disease. Behcet's disease can mimic CD and cause arthritis. In most cases, diagnosis depends on investigation of the bowel disease.

TREATMENT**IBD-Associated Arthritis**

Treatment of CD has been improved by anti-TNF agents. Infliximab, adalimumab, and certolizumab pegol are effective for induction and maintenance of clinical remission in CD, and infliximab is effective in fistulizing CD. IBD-associated arthritis also responds to these agents. Other biologics with efficacy in IBD that may have efficacy for peripheral arthritis include ustekinumab (anti-IL12/23) and risankizumab (anti-IL-23), but anti-IL-17 therapy is not indicated (Fig. 362-3). Tofacitinib is approved for treatment of UC. Other promising JAK inhibitors include upadacitinib and filgotinib. Other treatments for IBD include sulfasalazine and related drugs as well as systemic and local glucocorticoids. NSAIDs, especially COX-selective formulations, are helpful for arthritis and generally well tolerated, but they can precipitate IBD flares. As noted above for psoriasis, rare cases of IBD, either CD or UC, have apparently been precipitated by anti-TNF therapy. Vedolizumab is a gut-selective integrin inhibitor approved for both CD and UC. It is not given specifically for joint disease, but coexistent arthritis can improve during treatment of the IBD. However, there are many reports of de novo or flaring arthritis, either axial or peripheral, in IBD patients treated with vedolizumab.

SAPHO SYNDROME

The syndrome of synovitis, acne, pustulosis, hyperostosis, and osteitis (SAPHO) is characterized by a variety of skin and musculoskeletal manifestations. Dermatologic manifestations include palmoplantar pustulosis, acne conglobata, acne fulminans, and hidradenitis suppurativa. The main musculoskeletal findings are sternoclavicular and spinal hyperostosis, chronic recurrent foci of sterile osteomyelitis, and axial or peripheral arthritis. Cases with one or a few manifestations are probably the rule. The ESR and/or CRP are usually mildly to moderately elevated, occasionally dramatically. Bacteria, most often *Propionibacterium acnes*, have been cultured from bone biopsy specimens and occasionally other sites. IBD was coexistent in 8% of patients in one large series. No gene associations have been found, despite the resemblance to autoinflammatory syndromes. Radionuclide bone scan is very helpful diagnostically, often showing the classic “bull’s head” sign involving the sternoclavicular joints and clavicles. High-dose NSAIDs may provide relief from bone pain. Uncontrolled series and case reports describe successful therapy with pamidronate or other bisphosphonates. Anecdotal benefit from biologic agents has been reported, including anti-TNF, anti-IL-17A, anti-IL-12/23, anti-IL-6, and anti-IL-1 agents. Successful prolonged antibiotic therapy has also been reported.

FURTHER READING

- Bravo A, Kavanagh A: Bedside to bench: defining the immunopathogenesis of psoriatic arthritis. *Nat Rev Rheumatol* 15:645, 2019.
- Breban M et al: The microbiome in spondyloarthritis. *Best Pract Res Clin Rheumatol* 33:101495, 2019.
- Bridgewood C et al: Interleukin-23 pathway at the enthesis: The emerging story of enthesitis in spondyloarthropathy. *Immunol Rev* 294:27, 2020.
- Ellinghaus D et al: Analysis of five chronic inflammatory diseases identifies 27 new associations and highlights disease-specific patterns at shared loci. *Nat Genet* 48:510, 2016.
- Gladman DD: Editorial: What is peripheral spondyloarthritis? *Arthritis Rheumatol* 67:865, 2015.
- Gmuca S, Weiss PF: Juvenile spondyloarthritis. *Curr Opin Rheumatol* 27:364, 2015.
- Gracey E et al: TYK2 inhibition reduces type 3 immunity and modifies disease progression in murine spondyloarthritis. *J Clin Invest* 130:1863, 2020.
- Kiltz U et al: Development of a health index in patients with ankylosing spondylitis (ASAS HI): Final result of a global initiative based on the ICF guided by ASAS. *Ann Rheum Dis* 74:830, 2015.

Maksymowych WP et al: MRI lesions in the sacroiliac joints of patients with spondyloarthritis: An update of definitions and validation by the ASAS MRI working group. *Ann Rheum Dis* 78:1550, 2019.

Manasson J et al: Gut microbiota perturbations in reactive arthritis and postinfectious spondyloarthritis. *Arthritis Rheumatol* 70:242, 2018.

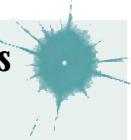
Mease P, Khan MA (eds): *Axial Spondyloarthritis*. Elsevier, 2019.

Ranganathan V et al: Pathogenesis of ankylosing spondylitis—recent advances and future directions. *Nat Rev Rheumatol* 13:359, 2017.

Ward MM et al: 2019 update of the American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network recommendations for the treatment of ankylosing spondylitis and nonradiographic axial spondyloarthritis. *Arthritis Rheumatol* 71:1519, 2019.

363**The Vasculitis Syndromes**

Carol A. Langford, Anthony S. Fauci

**DEFINITION**

Vasculitis is a clinicopathologic process characterized by inflammation of and damage to blood vessels. The vessel lumen is usually compromised, and this is associated with ischemia of the tissues supplied by the involved vessel. A broad and heterogeneous group of syndromes may result from this process, since any type, size, and location of blood vessel may be involved. Vasculitis and its consequences may be the primary or sole manifestation of a disease; alternatively, vasculitis may be a secondary component of another disease. Vasculitis may be confined to a single organ, such as the skin, or it may simultaneously involve several organ systems.

CLASSIFICATION

A major feature of the vasculitic syndromes as a group is the fact that there is a great deal of heterogeneity at the same time as there is considerable overlap among them. **Table 363-1** lists the major vasculitis

TABLE 363-1 Vasculitis Syndromes

PRIMARY VASCULITIS SYNDROMES	SECONDARY VASCULITIS SYNDROMES
Granulomatosis with polyangiitis	Vasculitis associated with probable etiology
Microscopic polyangiitis	Drug-induced vasculitis
Eosinophilic granulomatosis with polyangiitis (Churg-Strauss)	Hepatitis C virus-associated cryoglobulinemic vasculitis
IgA vasculitis (Henoch-Schönlein)	Hepatitis B virus-associated vasculitis
Cryoglobulinemic vasculitis	Cancer-associated vasculitis
Polyarteritis nodosa	Vasculitis associated with systemic disease
Kawasaki disease	Lupus vasculitis
Giant cell arteritis	Rheumatoid vasculitis
Takayasu arteritis	Sarcoid vasculitis
Behcet’s disease	
Cogan’s syndrome	
Single-organ vasculitis	
Cutaneous leukocytoclastic angiitis	
Cutaneous arteritis	
Primary central nervous system vasculitis	
Isolated aortitis	

Source: Adapted from JC Jennette et al: *Arthritis Rheum* 65:1, 2013.

syndromes. The distinguishing and overlapping features of these syndromes are discussed below.

PATHOPHYSIOLOGY AND PATHOGENESIS

Generally, most of the vasculitic syndromes are assumed to be mediated at least in part by immunopathogenic mechanisms that occur in response to certain antigenic stimuli. However, evidence supporting this hypothesis is for the most part indirect and may reflect epipheno-mena as opposed to true causality. Furthermore, it is unknown why some individuals might develop vasculitis in response to certain antigenic stimuli, whereas others do not. It is likely that a number of factors are involved in the ultimate expression of a vasculitic syndrome. These include the genetic predisposition, environmental exposures, and the regulatory mechanisms associated with immune response to certain antigens. Although immune complex formation, antineutrophil cytoplasmic antibodies (ANCA), and pathogenic T lymphocyte responses (Table 363-2) have been among the prominent hypothesized mechanisms, it is likely that the pathogenesis of individual forms of vasculitis is complex and varied.

PATHOGENIC IMMUNE-COMPLEX FORMATION

Deposition of immune complexes was the first and most widely accepted pathogenic mechanism of vasculitis. However, the causal role of immune complexes has not been clearly established in most of the vasculitic syndromes. Circulating immune complexes need not result in deposition of the complexes in blood vessels with ensuing vasculitis, and many patients with active vasculitis do not have demonstrable circulating or deposited immune complexes. The actual antigen contained in the immune complex has only rarely been identified in vasculitic syndromes. In this regard, hepatitis B antigen has been identified in both the circulating and deposited immune complexes in a subset of patients who have features of a systemic vasculitis clinically similar to polyarteritis nodosa (see "Polyarteritis Nodosa"). Cryoglobulinemic vasculitis is strongly associated with hepatitis C virus infection; hepatitis C virions and hepatitis C virus antigen-antibody complexes have been identified in the cryoprecipitates of these patients (see "Cryoglobulinemic Vasculitis").

The mechanisms of tissue damage in immune complex-mediated vasculitis resemble those described for serum sickness. In this model, antigen-antibody complexes are formed in antigen excess and are deposited in vessel walls whose permeability has been increased by vasoactive amines such as histamine, bradykinin, and leukotrienes released from platelets or from mast cells as a result of IgE-triggered mechanisms. The deposition of complexes results in activation of complement components, particularly C5a, which is strongly chemotactic for neutrophils. These cells then infiltrate the vessel wall, phagocytose the immune complexes, and release their intracytoplasmic enzymes,

which damage the vessel wall. As the process becomes subacute or chronic, mononuclear cells infiltrate the vessel wall. The common denominator of the resulting syndrome is compromise of the vessel lumen with ischemic changes in the tissues supplied by the involved vessel. Several variables may explain why only certain types of immune complexes cause vasculitis and why only certain vessels are affected in individual patients. These include the ability of the reticuloendothelial system to clear circulating complexes from the blood, the size and physicochemical properties of immune complexes, the relative degree of turbulence of blood flow, the intravascular hydrostatic pressure in different vessels, and the preexisting integrity of the vessel endothelium.

ANTINEUTROPHIL CYTOPLASMIC ANTIBODIES

ANCA are antibodies directed against certain proteins in the cytoplasmic granules of neutrophils and monocytes. These autoantibodies are present in a high percentage of patients with active granulomatosis with polyangiitis and microscopic polyangiitis and in a lower percentage of patients with eosinophilic granulomatosis with polyangiitis (Churg-Strauss). Because these diseases share the presence of ANCA and small-vessel vasculitis, they have been grouped collectively as "ANCA-associated vasculitis." However, these diseases possess unique clinical phenotypes, such that they should continue to be viewed as separate entities.

There are two major categories of ANCA based on different targets for the antibodies. The terminology of *cytoplasmic ANCA* (cANCA) refers to the diffuse, granular cytoplasmic staining pattern observed by immunofluorescence microscopy when serum antibodies bind to indicator neutrophils. Proteinase-3, a 29-kDa neutral serine proteinase present in neutrophil azurophilic granules, is the major cANCA antigen. More than 90% of patients with active granulomatosis with polyangiitis have detectable antibodies to proteinase-3 (see below). The terminology of *perinuclear ANCA* (pANCA) refers to the more localized perinuclear or nuclear staining pattern of the indicator neutrophils. The major target for pANCA is the enzyme myeloperoxidase; other targets that can produce a pANCA pattern of staining include elastase, cathepsin G, lactoferrin, lysozyme, and bactericidal/permeability-increasing protein. However, only antibodies to myeloperoxidase have been convincingly associated with vasculitis. Antimyeloperoxidase antibodies have been reported to occur in variable percentages of patients with microscopic polyangiitis, eosinophilic granulomatosis with polyangiitis (Churg-Strauss), isolated necrotizing crescentic glomerulonephritis, and granulomatosis with polyangiitis (see below). A pANCA pattern of staining that is not due to antimyeloperoxidase antibodies has been associated with nonvasculitic entities such as rheumatic and nonrheumatic autoimmune diseases, inflammatory bowel disease, certain drugs, and infections such as endocarditis and bacterial airway infections in patients with cystic fibrosis.

It is unclear why patients with these vasculitis syndromes develop antibodies to myeloperoxidase or proteinase-3 or what role these antibodies play in disease pathogenesis. There are a number of in vitro observations that suggest possible mechanisms whereby these antibodies can contribute to the pathogenesis of the vasculitis syndromes. Proteinase-3 and myeloperoxidase reside in the azurophilic granules and lysosomes of resting neutrophils and monocytes, where they are apparently inaccessible to serum antibodies. However, when neutrophils or monocytes are primed by tumor necrosis factor α (TNF- α) or interleukin 1 (IL-1), proteinase-3 and myeloperoxidase translocate to the cell membrane, where they can interact with extracellular ANCA. The neutrophils then degranulate and produce reactive oxygen species that can cause tissue damage. Furthermore, ANCA-activated neutrophils can adhere to and kill endothelial cells in vitro. Activation of neutrophils and monocytes by ANCA also induces the release of proinflammatory cytokines such as IL-1 and IL-8. Adoptive transfer experiments in genetically engineered mice provide further evidence for a direct pathogenic role of ANCA in vivo. In contradiction, however, a number of clinical and laboratory observations argue against a primary pathogenic role for ANCA. Patients may have active granulomatosis with polyangiitis in the absence of ANCA; the absolute height

TABLE 363-2 Potential Mechanisms of Vessel Damage in Vasculitis Syndromes

Pathogenic immune-complex formation and/or deposition
IgA vasculitis (Henoch-Schönlein)
Lupus vasculitis
Serum sickness and cutaneous vasculitis syndromes
Hepatitis C virus-associated cryoglobulinemic vasculitis
Hepatitis B virus-associated vasculitis
Production of antineutrophilic cytoplasmic antibodies
Granulomatosis with polyangiitis
Microscopic polyangiitis
Eosinophilic granulomatosis with polyangiitis (Churg-Strauss)
Pathogenic T lymphocyte responses and granuloma formation
Giant cell arteritis
Takayasu arteritis
Granulomatosis with polyangiitis
Eosinophilic granulomatosis with polyangiitis (Churg-Strauss)

Source: Reproduced with permission from MC Sneller, AS Fauci: Pathogenesis of vasculitis syndromes. *Med Clin North Am* 81:221, 1997.

of the antibody titers does not correlate well with disease activity; and patients with granulomatosis with polyangiitis in remission may continue to have high ANCA levels for years (see below).

PART 11 PATHOGENIC T LYMPHOCYTE RESPONSES AND GRANULOMA FORMATION

The histopathologic feature of granulomatous vasculitis has provided evidence to support a role of pathogenic T lymphocyte responses and cell-mediated immune injury. Vascular endothelial cells can express human leukocyte antigen (HLA) class II molecules following activation by cytokines such as interferon (IFN) γ . This allows these cells to participate in immunologic reactions such as interaction with CD4+ T lymphocytes in a manner similar to antigen-presenting macrophages. Endothelial cells can secrete IL-1, which may activate T lymphocytes and initiate or propagate *in situ* immunologic processes within the blood vessel. In addition, IL-1 and TNF- α are potent inducers of endothelial-leukocyte adhesion molecule 1 (ELAM-1) and vascular cell adhesion molecule 1 (VCAM-1), which may enhance the adhesion of leukocytes to endothelial cells in the blood vessel wall.

APPROACH TO THE PATIENT

General Principles of Diagnosis

The diagnosis of vasculitis should be considered in any patient with an unexplained systemic illness. However, there are certain clinical abnormalities that when present alone or in combination should suggest a diagnosis of vasculitis. These include palpable purpura, pulmonary infiltrates and microscopic hematuria, chronic inflammatory sinusitis, mononeuritis multiplex, unexplained ischemic events, and glomerulonephritis with evidence of multisystem disease. A number of nonvasculitic diseases may also produce some or all of these abnormalities. Thus, the first step in the workup of a patient with suspected vasculitis is to exclude other diseases that produce clinical manifestations that can mimic vasculitis (**Table 363-3**). It is particularly important to exclude infectious diseases with features that overlap those of vasculitis, especially if the patient's clinical condition is deteriorating rapidly and empirical immunosuppressive treatment is being contemplated.

Once diseases that mimic vasculitis have been excluded, the workup should follow a series of progressive steps that establish the diagnosis of vasculitis and determine, where possible, the category of the vasculitis syndrome (**Fig. 363-1**). This approach is of considerable importance since several of the vasculitis syndromes require aggressive therapy with glucocorticoids and other immunosuppressive agents, whereas other syndromes usually resolve spontaneously and require symptomatic treatment only. The definitive diagnosis of vasculitis is usually made based on biopsy of involved tissue. The yield of "blind" biopsies of organs with no subjective or objective evidence of involvement is very low and should be avoided. When syndromes such as polyarteritis nodosa, Takayasu arteritis, or primary central nervous system (CNS) vasculitis are suspected, arteriogram of organs with suspected involvement should be performed.

GENERAL PRINCIPLES OF TREATMENT

Once a diagnosis of vasculitis has been established, a decision regarding therapeutic strategy must be made (**Fig. 363-1**). If an offending antigen that precipitates the vasculitis is recognized, the antigen should be removed where possible. If the vasculitis is associated with an underlying disease such as an infection, neoplasm, or connective tissue disease, the underlying disease should be treated. If the syndrome represents a primary vasculitic disease, treatment should be initiated according to the category of the vasculitis syndrome. Specific therapeutic regimens are discussed below for the individual vasculitis syndromes; however, certain general principles regarding therapy should be considered. Decisions regarding treatment should be based on the use of regimens for which there

TABLE 363-3 Conditions That Can Mimic Vasculitis

Infectious Diseases

- Bacterial endocarditis
- Disseminated gonococcal infection
- Pulmonary histoplasmosis
- Coccidioidomycosis
- Syphilis
- Lyme disease
- Rocky Mountain spotted fever
- Whipple's disease

Coagulopathies/Thrombotic Microangiopathies

- Antiphospholipid syndrome
- Thrombotic thrombocytopenic purpura

Neoplasms

- Atrial myxoma
- Lymphoma
- Carcinomatosis

Drug Toxicity

- Cocaine
- Levamisole
- Amphetamines
- Ergot alkaloids
- Methysergide
- Arsenic

Other

- Sarcoidosis
- Atheroembolic disease
- Antiglomerular basement membrane disease (Goodpasture's syndrome)
- Amyloidosis
- Migraine
- Fibromuscular dysplasia
- Heritable disorders of connective tissue
- Segmental arterial mediolysis (SAM)
- Reversible cerebral vasoconstrictive syndrome

has been published literature supporting efficacy for that particular vasculitic disease. Since the potential toxic side effects of certain therapeutic regimens may be substantial, the risk-versus-benefit ratio of any therapeutic approach should be weighed carefully. Glucocorticoids and/or other immunosuppressive agents should be instituted immediately in diseases where irreversible organ system dysfunction and high morbidity and mortality rates have been clearly established. Granulomatosis with polyangiitis is the prototype of a severe systemic vasculitis requiring such a therapeutic approach (see below). Conversely, aggressive therapy should be avoided for vasculitic manifestations that rarely result in irreversible organ system dysfunction such as isolated idiopathic cutaneous vasculitis. Glucocorticoids should be initiated in those systemic vasculitides that cannot be specifically categorized or for which there is no established standard therapy, with other immunosuppressive agents being added if an adequate response does not result or if remission can only be achieved and maintained with an unacceptably toxic regimen of glucocorticoids. When remission is achieved, one should continually attempt to taper glucocorticoids and discontinue when possible. When using other immunosuppressive regimens, one should base the choice of agent upon the available therapeutic data supporting efficacy in that disease, the site and severity of organ involvement, and the toxicity profile of the drug.

Physicians should be thoroughly aware of the acute and long-term side effects associated with the agents that are commonly used to treat different forms of vasculitis (**Table 363-4**).

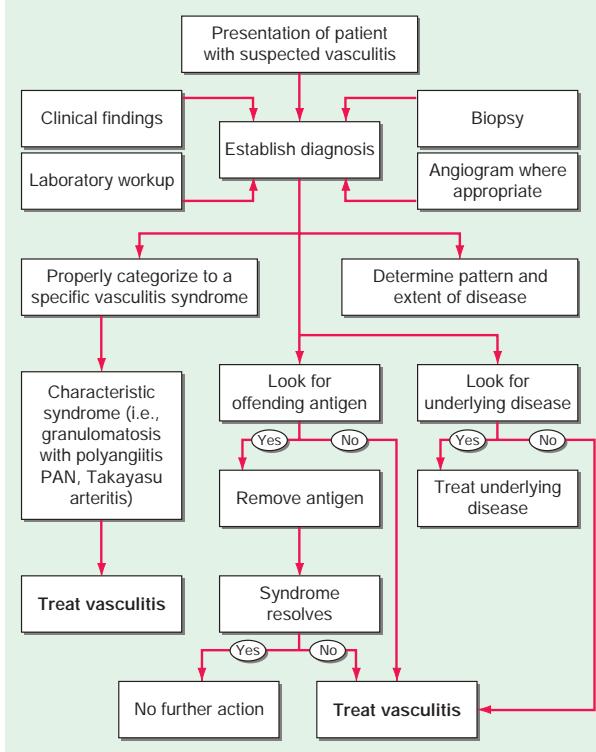


FIGURE 363-1 Algorithm for the approach to a patient with suspected diagnosis of vasculitis. PAN, polyarteritis nodosa.

Morbidity and mortality can occur as a result of treatment, and strategies to monitor for and prevent toxicity represent an essential part of patient care.

Addressing the risk of bone loss is important in all patients receiving glucocorticoids. Daily cyclophosphamide should be taken all at once in the morning with a large amount of fluid throughout the day to reduce the risk of bladder injury, and monitoring for bladder cancer should continue indefinitely.

Maintaining the white blood cell (WBC) count at $>3000/\mu\text{L}$ and the neutrophil count at $>1500/\mu\text{L}$ is essential to reduce the risk of life-threatening infections. Monitoring of the complete blood count every 1–2 weeks for as long as the patient receives cyclophosphamide can effectively prevent cytopenias. Methotrexate, azathioprine, and mycophenolate mofetil are also associated with bone marrow suppression, and complete blood counts should be obtained every 1–2 weeks for the first 1–2 months after their initiation and once a month thereafter. To lessen toxicity, methotrexate is often given together with folic acid, 1 mg daily, or folinic acid, 5–10 mg once a week 24 h following methotrexate. Methotrexate is eliminated by the kidney and contraindicated in renal insufficiency as this increases the risk for toxicity. Prior to initiation of azathioprine, thiopurine methyltransferase (TPMT), an enzyme involved in the metabolism of azathioprine, should be assayed because inadequate levels may result in severe cytopenia.

Rituximab can be associated with infusion reactions. In addition to administering this within a skilled infusion center, these reactions can be lessened by the use of premedications. There is a risk of hepatitis B reactivation with rituximab such that all patients should be screened for this infection prior to its use.

Tocilizumab is associated with cytopenias, hepatotoxicity, and hyperlipidemia. Laboratory monitoring for drug toxicity should be performed 4–8 weeks after start of therapy and every 3 months thereafter.

TABLE 363-4 Major Toxic Side Effects of Drugs Used in the Treatment of Vasculitis^a

CONVENTIONAL IMMUNOSUPPRESSIVE AGENTS

Glucocorticoids

Osteoporosis	Growth suppression in children
Cataracts	Hypertension
Glaucoma	Avascular necrosis of bone
Diabetes mellitus	Myopathy
Electrolyte abnormalities	Alterations in mood
Metabolic abnormalities	Psychosis
Severe and opportunistic infections	Pseudotumor cerebri
Cushingoid features	Peptic ulcer diathesis
	Pancreatitis

Cyclophosphamide

Bone marrow suppression	Hypogammaglobulinemia
Cystitis	Pulmonary fibrosis
Bladder carcinoma	Myelodysplasia
Gonadal suppression	Oncogenesis
Gastrointestinal intolerance	Teratogenicity
	Severe and opportunistic infections

Methotrexate

Gastrointestinal intolerance	Pneumonitis
Stomatitis	Teratogenicity
Bone marrow suppression	Severe and opportunistic infections
Hepatotoxicity (may lead to fibrosis or cirrhosis)	

Azathioprine

Gastrointestinal intolerance	Severe and opportunistic infections
Bone marrow suppression	Hypersensitivity
Hepatotoxicity	

Mycophenolate mofetil

Bone marrow suppression	Severe and opportunistic infections
Gastrointestinal intolerance	Teratogenicity

BIOLOGIC AGENTS

Rituximab (granulomatosis with polyangiitis and microscopic polyangiitis)

Infusion reactions	Severe and opportunistic infections
Progressive multifocal leuko-encephalopathy	Hepatitis B reactivation
Mucocutaneous reactions	Tumor lysis syndrome
Hypogammaglobulinemia	Late-onset neutropenia

Tocilizumab (giant cell arteritis)

Bone marrow suppression	Severe and opportunistic infections
Hepatotoxicity	Gastrointestinal perforation
Hyperlipidemia	Hypersensitivity reactions

Mepolizumab (eosinophilic granulomatosis with polyangiitis [Churg-Strauss])

Hypersensitivity reactions	Opportunistic infections: herpes zoster
----------------------------	---

Apremilast (Behcet's disease; see Chap. 364)

Diarrhea, nausea, and vomiting	Weight decrease
Depression	

^aConsult the drug package insert for a full listing of side effects.

Infection represents a significant toxicity for all vasculitis patients treated with immunosuppressive therapy. Infections with *Pneumocystis jirovecii* and certain fungi can be seen even in the face of WBCs that are within normal limits, particularly in patients receiving glucocorticoids. All vasculitis patients who are receiving daily glucocorticoids in combination with another immunosuppressive

agent should receive trimethoprim-sulfamethoxazole (TMP-SMX) or another prophylactic therapy to prevent *P. jirovecii* infection.

In recent years, national and regional organizations have published treatment guidelines that can provide additional direction to clinicians. It should be emphasized that each patient is unique and requires individual decision-making. Information provided through guideline documents as well as this chapter should serve as a framework for the application of evidence-based approaches; however, flexibility should be practiced to provide maximal therapeutic efficacy with minimal toxic side effects in each patient.

GRANULOMATOSIS WITH POLYANGIITIS

DEFINITION

Granulomatosis with polyangiitis is a distinct clinicopathologic entity characterized by granulomatous vasculitis of the upper and lower respiratory tracts together with glomerulonephritis. In addition, variable degrees of disseminated vasculitis involving both small arteries and veins may occur.

INCIDENCE AND PREVALENCE

Granulomatosis with polyangiitis is an uncommon disease with an estimated prevalence of 3 per 100,000. It is extremely rare in blacks compared with whites; the male-to-female ratio is 1:1. The disease can be seen at any age; ~15% of patients are <19 years of age, but only rarely does the disease occur before adolescence; the mean age of onset is ~40 years.

PATHOLOGY AND PATHOGENESIS

The histopathologic hallmarks of granulomatosis with polyangiitis are necrotizing vasculitis of small arteries and veins together with granuloma formation, which may be either intravascular or extravascular (Fig. 363-2). Lung involvement typically appears as multiple, bilateral, nodular cavitary infiltrates (Fig. 363-3), which on biopsy can reveal necrotizing granulomatous vasculitis. Upper airway lesions, particularly those in the sinuses and nasopharynx, typically reveal inflammation, necrosis, and granuloma formation, with or without vasculitis.

In its earliest form, renal involvement is characterized by a focal and segmental glomerulitis that may evolve into a rapidly progressive crescentic glomerulonephritis. Granuloma formation is only rarely seen on renal biopsy. In contrast to other forms of glomerulonephritis, evidence of immune complex deposition is not found in the renal lesion of granulomatosis with polyangiitis. In addition to the classic triad of

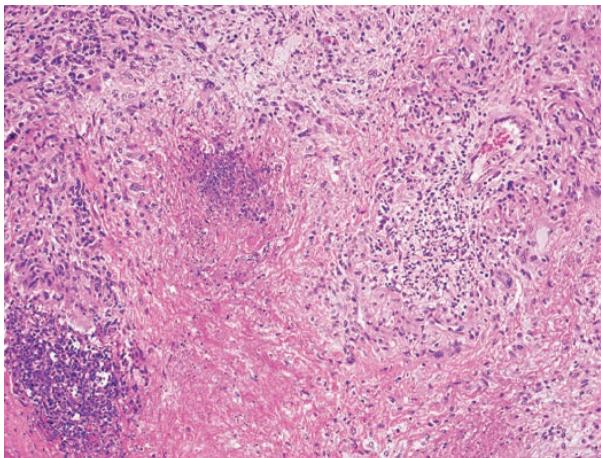


FIGURE 363-2 Lung histology in granulomatosis with polyangiitis. This area of geographic necrosis has a serpiginous border of histiocytes and giant cells surrounding a central necrotic zone. Vasculitis is also present with neutrophils and lymphocytes infiltrating the wall of a small arteriole (upper right). (Courtesy of William D. Travis, MD; with permission.)



FIGURE 363-3 Computed tomography scan of a patient with granulomatosis with polyangiitis. The patient developed multiple, bilateral, and cavitary infiltrates.

disease of the upper and lower respiratory tracts and kidney, virtually any organ can be involved with vasculitis, granuloma, or both.

The immunopathogenesis of this disease is unclear, although the involvement of upper airways and lungs with granulomatous vasculitis suggests an aberrant cell-mediated immune response to an exogenous or even endogenous antigen that enters through or resides in the upper airway. Chronic nasal carriage of *Staphylococcus aureus* has been reported to be associated with higher relapse rate of granulomatosis with polyangiitis; however, there is no evidence for a role of this organism in the pathogenesis of the disease.

Peripheral blood mononuclear cells obtained from patients with granulomatosis with polyangiitis manifest increased secretion of IFN- γ but not of IL-4, IL-5, or IL-10 compared to normal controls. In addition, TNF- α production from peripheral blood mononuclear cells and CD4+ T cells is elevated. Furthermore, monocytes from patients with granulomatosis with polyangiitis produce increased amounts of IL-12. These findings indicate an unbalanced T_H1-type T-cell cytokine pattern in this disease that may have pathogenic and perhaps ultimately therapeutic implications.

A high percentage of patients with granulomatosis with polyangiitis develop ANCA, and these autoantibodies may play a role in the pathogenesis of this disease (see above).

CLINICAL AND LABORATORY MANIFESTATIONS

Involvement of the upper airways occurs in 95% of patients with granulomatosis with polyangiitis. Patients often present with severe upper respiratory tract findings such as paranasal sinus pain and drainage and purulent or bloody nasal discharge, with or without nasal mucosal ulceration (Table 363-5). Nasal septal perforation may follow, leading to saddle nose deformity. Serous otitis media may occur as a result of eustachian tube blockage. Subglottic stenosis resulting from active disease or scarring occurs in ~16% of patients and may result in severe airway obstruction.

Pulmonary involvement (85–90% of patients) may be clinically expressed as cough, hemoptysis, dyspnea, and chest discomfort, or active disease may be asymptomatic in up to 30% of cases. Endobronchial disease, either in its active form or as a result of fibrous scarring, may lead to obstruction with atelectasis.

Eye involvement (52% of patients) may range from a mild conjunctivitis to dacryocystitis, episcleritis, scleritis, granulomatous sclerouveitis, ciliary vessel vasculitis, and retroorbital mass lesions leading to proptosis.

Skin lesions (46% of patients) appear as papules, vesicles, palpable purpura, ulcers, or subcutaneous nodules; biopsy reveals vasculitis, granuloma, or both. Cardiac involvement (8% of patients) manifests as pericarditis, coronary vasculitis, or, rarely, cardiomyopathy. Nervous system manifestations (23% of patients) include cranial neuritis, mononeuritis multiplex, or, rarely, cerebral vasculitis and/or granuloma.

Renal disease (77% of patients) generally dominates the clinical picture and, if left untreated, accounts directly or indirectly for most of the mortality rate in this disease. Although it may smolder in some cases as a mild glomerulitis with proteinuria, hematuria, and red blood cell casts, it is clear that once clinically detectable renal functional

TABLE 363-5 Granulomatosis with Polyangiitis: Frequency of Clinical Manifestations in 158 Patients Studied at the National Institutes of Health

MANIFESTATION	PERCENTAGE AT DISEASE ONSET	PERCENTAGE THROUGHOUT COURSE OF DISEASE
Kidney		
Glomerulonephritis	18	77
Ear/Nose/Throat	73	92
Sinusitis	51	85
Nasal disease	36	68
Otitis media	25	44
Hearing loss	14	42
Subglottic stenosis	1	16
Ear pain	9	14
Oral lesions	3	10
Lung	45	85
Pulmonary infiltrates	25	66
Pulmonary nodules	24	58
Hemoptysis	12	30
Pleuritis	10	28
Eyes		
Conjunctivitis	5	18
Dacryocystitis	1	18
Scleritis	6	16
Proptosis	2	15
Eye pain	3	11
Visual loss	0	8
Retinal lesions	0	4
Corneal lesions	0	1
Iritis	0	2
Other^a		
Arthralgias/arthritis	32	67
Fever	23	50
Cough	19	46
Skin abnormalities	13	46
Weight loss (>10% body weight)	15	35
Peripheral neuropathy	1	15
Central nervous system disease	1	8
Pericarditis	2	6
Hyperthyroidism	1	3

^aFewer than 1% had parotid, pulmonary artery, breast, or lower genitourinary (urethra, cervix, vagina, testicular) involvement.

Source: GS Hoffman et al: Ann Intern Med 116:488, 1992.

impairment occurs, rapidly progressive renal failure usually ensues unless appropriate treatment is instituted.

While the disease is active, most patients have nonspecific symptoms and signs such as malaise, weakness, arthralgias, anorexia, and weight loss. Fever may indicate activity of the underlying disease but more often reflects secondary infection, usually of the upper airway.

Characteristic laboratory findings include an elevated erythrocyte sedimentation rate (ESR) and/or C-reactive protein (CRP), mild anemia and leukocytosis, mild hypergammaglobulinemia (particularly of the IgA class), and mildly elevated rheumatoid factor. Thrombocytosis may be seen as an acute-phase reactant. Approximately 90% of patients with active granulomatosis with polyangiitis have a positive antiproteinase-3 ANCA. However, in the absence of active disease, the sensitivity drops to ~60–70%. A small percentage of patients with granulomatosis with polyangiitis may have antimyeloperoxidase rather than antiproteinase-3 antibodies, and up to 20% may lack ANCA.

Patients with granulomatosis with polyangiitis have been found to have an increased incidence of venous thrombotic events. Although routine anticoagulation for all patients is not recommended, a

heightened awareness for any clinical features suggestive of deep-vein thrombosis or pulmonary emboli is warranted.

DIAGNOSIS

The diagnosis of granulomatosis with polyangiitis can be established by the demonstration of necrotizing granulomatous vasculitis on tissue biopsy in a patient with compatible clinical features. Pulmonary tissue offers the highest diagnostic yield, almost invariably revealing granulomatous vasculitis. Biopsy of upper airway tissue usually reveals granulomatous inflammation with necrosis but may not show vasculitis. Renal biopsy can confirm the presence of pauci-immune glomerulonephritis.

The specificity of a positive antiproteinase-3 ANCA for granulomatosis with polyangiitis is very high, especially if active glomerulonephritis is present. However, the presence of ANCA should be viewed as adjunctive with tissue diagnosis being pursued when clinically inconsistent features are present or when ANCA is absent. False-positive ANCA has been reported in certain infectious and neoplastic diseases.

In its typical presentation, the clinicopathologic complex of granulomatosis with polyangiitis usually provides ready differentiation from other disorders. However, if all the typical features are not present at once, it needs to be differentiated from the other vasculitides, anti-glomerular basement membrane disease (Goodpasture's syndrome) (Chap. 314), relapsing polychondritis (Chap. 366), tumors of the upper airway or lung, and infectious diseases such as histoplasmosis (Chap. 212), endocarditis (Chap. 128), mucocutaneous leishmaniasis (Chap. 226), and rhinoscleroma (Chap. 218) as well as noninfectious granulomatous diseases.

Of particular note is the differentiation from other *midline destructive diseases*. These diseases lead to extreme tissue destruction and mutilation localized to the midline upper airway structures including the sinuses; erosion through the skin of the face commonly occurs, a feature that is extremely rare in granulomatosis with polyangiitis. Although blood vessels may be involved in the intense inflammatory reaction and necrosis, primary vasculitis is not seen. *Upper airway neoplasms* and specifically *extranodal natural killer (NK)/T-cell lymphoma (nasal type)* are important causes of midline destructive disease. These lesions are diagnosed based on histology, which reveals polymorphous atypical lymphoid cells with an NK cell immunophenotype, typically Epstein-Barr virus (Chap. 194). Such cases are treated based on their degree of dissemination, and localized lesions have responded to irradiation. Upper airway lesions should never be irradiated in granulomatosis with polyangiitis. Cocaine-induced tissue injury can be another important mimic of granulomatosis with polyangiitis in patients who present with isolated midline destructive disease. ANCA that target human neutrophil elastase can be found in patients with cocaine-induced midline destructive lesions and can complicate the differentiation from granulomatosis with polyangiitis. This has been further confounded by the high frequency of levamisole adulteration of cocaine, which can result in cutaneous infarction and serologic changes that may mimic vasculitis. Granulocytopenia is a common finding in levamisole-induced disease that would not be associated with granulomatosis with polyangiitis.

Granulomatosis with polyangiitis must also be differentiated from *lymphomatoid granulomatosis*, which is an Epstein-Barr virus-positive B-cell proliferation that is associated with an exuberant T-cell reaction. Lymphomatoid granulomatosis is characterized by lung, skin, CNS, and kidney involvement in which atypical lymphocytoid and plasma-celloid cells infiltrate nonlymphoid tissue in an angiocentric manner. In this regard, it clearly differs from granulomatosis with polyangiitis in that it is not an inflammatory vasculitis in the classic sense but an angiocentric perivascular infiltration of atypical mononuclear cells. Up to 50% of patients may develop a true malignant lymphoma.

TREATMENT

Granulomatosis with Polyangiitis

Prior to the introduction of effective therapy, granulomatosis with polyangiitis was universally fatal within a few months of diagnosis. Glucocorticoids alone led to some symptomatic improvement, with little effect on the ultimate course of the disease. The development

of treatment with cyclophosphamide dramatically changed patient outcome such that marked improvement was seen in >90% of patients, complete remission in 75% of patients, and 5-year patient survival was seen in >80%.

Despite the ability to successfully induce remission, 50–70% of remissions are later associated with one or more relapses. The determination of relapse should be based on objective evidence of disease activity, taking care to rule out other features that may have a similar appearance such as infection, medication toxicity, or chronic disease sequelae. Many patients who achieve remission continue to have a positive ANCA for years, and changes in ANCA should not be used as a measure of disease activity. Results from a large prospective study found that increases in ANCA were not associated with relapse and that only 43% of patients relapsed within 1 year of an increase in ANCA levels. Thus, a rise in ANCA by itself is not a harbinger of immediate disease relapse and should not lead to reinstitution or increase in immunosuppressive therapy. Reinduction of remission after relapse is almost always achieved; however, a high percentage of patients ultimately have some degree of damage from irreversible features of their disease, such as varying degrees of renal insufficiency, neurologic impairment, hearing loss, subglottic stenosis, saddle nose deformity, and chronic sinus dysfunction. Patients who developed irreversible renal failure but who achieved subsequent remission have undergone successful renal transplantation.

Treatment of granulomatosis with polyangiitis is currently viewed as having two phases: *induction*, where active disease is put into remission, followed by *maintenance*. The decision regarding which agents to use for induction and maintenance is guided by experience from published data, determination of disease severity, and individual patient factors that include contraindications, relapse history, and comorbidities.

Current induction regimens consist of glucocorticoids plus another immunosuppressive agent. For severe disease, glucocorticoids have historically been given as prednisone 1 mg/kg per day for the first month, followed by gradual tapering on an alternate-day or daily schedule. Recently, use of a reduced-dose glucocorticoid regimen was found to be noninferior to a standard-dose regimen in a randomized trial and was associated with a lower rate of serious infection. For patients with nonsevere disease, use of lower initial glucocorticoid doses can be considered.

In patients presenting with disease that is life-threatening, methylprednisolone 1000 mg daily for 3 days has been used. Adjunctive plasmapheresis was recently found to provide no added benefit in reducing the composite outcome of end-stage renal disease or death. Whether it may still play a role in selected patients with the most fulminant disease remains uncertain.

CYCLOPHOSPHAMIDE INDUCTION FOR SEVERE DISEASE

Daily cyclophosphamide combined with glucocorticoids was the first regimen proven to effectively induce remission and prolong survival. Cyclophosphamide is given in doses of 2 mg/kg per day orally, but because it is renally eliminated, dosage reduction should be considered in patients with renal insufficiency. Although we continue to favor the use of daily cyclophosphamide, some reports have indicated therapeutic success using IV cyclophosphamide. In a randomized trial, IV cyclophosphamide 15 mg/kg, three infusions given every 2 weeks, then every 3 weeks thereafter, was compared to cyclophosphamide 2 mg/kg daily given for 3 months followed by 1.5 mg/kg daily. Although IV cyclophosphamide was found to have a comparable rate of remission with a lower cumulative cyclophosphamide dose and occurrence of leukopenia, the use of a consolidation phase and an insufficient frequency of blood count monitoring may have negatively influenced the results in those who received daily cyclophosphamide. Of note in this study was that relapse occurred in 19% of those who received IV cyclophosphamide as compared to 9% who received daily oral administration.

RITUXIMAB INDUCTION FOR SEVERE DISEASE

Rituximab is a chimeric monoclonal antibody directed against CD20 present on normal and malignant B lymphocytes that is U.S.

Food and Drug Administration (FDA) approved for the treatment of granulomatosis with polyangiitis and microscopic polyangiitis. In two randomized trials that enrolled ANCA-positive patients with severe active granulomatosis with polyangiitis or microscopic polyangiitis, rituximab 375 mg/m² once a week for 4 weeks in combination with glucocorticoids was found to be as effective as cyclophosphamide with glucocorticoids for inducing disease remission. In the trial that also enrolled patients with relapsing disease, rituximab was found to be statistically superior to cyclophosphamide. Although rituximab does not have the bladder toxicity or infertility concerns, as can occur with cyclophosphamide, in both of the randomized trials, the rate of adverse events was similar in the rituximab and cyclophosphamide arms.

The decision about whether to utilize cyclophosphamide or rituximab for remission induction must be individually based. Factors to consider include the severity of the disease, whether the patient has newly diagnosed or relapsing disease, medication contraindications, and individual patient factors particularly including fertility concerns. In patients with rapidly progressive glomerulonephritis with a creatinine >4.0 mg/dL or pulmonary hemorrhage requiring mechanical ventilation, daily cyclophosphamide and glucocorticoids are favored.

REMISSION MAINTENANCE

When cyclophosphamide is given for induction, it should be stopped after 3–6 months and switched to another agent for remission maintenance. Medications used in this setting with which there has been published experience from randomized trials are rituximab, azathioprine, methotrexate, and mycophenolate mofetil. A lower rate of relapse was seen with rituximab given at 500 mg for two doses followed by 500 mg every 6 months when compared to azathioprine 2 mg/kg per day. In a randomized trial comparing methotrexate to azathioprine for remission maintenance, similar rates of toxicity and relapse were seen. Methotrexate is administered orally or subcutaneously at a starting not to exceed 15 mg/week, which is increased by 2.5 mg every 2 weeks up to a dosage of 20–25 mg/week. In patients who are unable to receive methotrexate or azathioprine or who have experienced relapse on such treatment, mycophenolate mofetil 1000 mg twice a day may also sustain remission, but it is associated with a higher rate of relapse compared to azathioprine.

For patients who receive rituximab for remission induction, a recent randomized trial found that rituximab 1000 mg given every 4 months had a lower rate of relapse compared to azathioprine.

The optimal duration of maintenance therapy is uncertain. With regard to glucocorticoids, it has been unclear whether maintaining patients on prednisone 5 mg/d has greater risks or benefits compared to discontinuation after 6–9 months. Maintenance therapy with azathioprine, methotrexate, or mycophenolate mofetil is usually given for a minimum of 2 years. Because there is evidence that the risk of relapse is higher once maintenance medication has been stopped, the decision is individualized regarding whether to continue treatment or taper these agents over a 6- to 12-month period until discontinuation. Patients with significant organ damage or a history of relapse may benefit from longer-term maintenance therapy. Although rituximab has been found to have a lower relapse rate, its long-term safety remains uncertain such that the decision for how long to continue this agent beyond 2 years must be weighed in each patient.

REMISSION INDUCTION OF NONSEVERE DISEASE

For patients whose disease is not immediately organ- or life-threatening, methotrexate or mycophenolate mofetil together with glucocorticoids may be given to induce and then maintain remission. Treatment with cyclophosphamide is rarely if ever justified for the treatment of nonsevere granulomatosis with polyangiitis.

OTHER BIOLOGIC AGENTS AND SMALL MOLECULE INHIBITORS

Abatacept (CTLA4-Ig) was examined in an open-label pilot study of nonsevere relapsing disease with favorable results, but further investigation is needed before application to clinical practice. Etanercept, a dimeric fusion protein containing the 75-kDa TNF

receptor bound to human IgG1, was not found to sustain remission when used adjunctively to standard therapy and should not be used in the treatment of granulomatosis with polyangiitis. Belimumab (anti-B lymphocyte stimulator) was examined as an adjunctive therapy to azathioprine for remission maintenance but showed no added benefit in reducing the risk of relapse.

Avacopan (a C5a receptor inhibitor) was recently investigated in a randomized trial as an alternative to glucocorticoids in patients receiving induction with either cyclophosphamide or rituximab. At 52 weeks, sustained remission was higher in those who received avacopan as compared to prednisone with a similar rate of serious adverse events. Although glucocorticoids were given within the first few weeks to some patients receiving avacopan, glucocorticoid exposure remained markedly less than those randomized to the prednisone treatment arm. Based on these findings, avacopan holds promise in being able to reduce the need for glucocorticoids in the treatment of ANCA-associated vasculitis.

TRIMETHOPRIM-SULFAMETHOXAZOLE

Although certain reports have indicated that TMP-SMX may be of benefit in the treatment of granulomatosis with polyangiitis isolated to the sinonasal tissues, it should never be used alone to treat active granulomatosis with polyangiitis involving other organs. In a study examining the effect of TMP-SMX on relapse, decreased relapses were shown only with regard to upper airway disease, and no differences in major organ relapses were observed.

ORGAN-SPECIFIC TREATMENT

Not all manifestations of granulomatosis with polyangiitis require or respond to immunosuppressive therapy, and differentiation of active disease from damage is necessary. As sinus disease can disrupt the mucociliary barrier, patients should be instructed on the use of local care with moisturization and humidification. Subglottic stenosis can often scar and responds optimally to nonmedical intervention with dilation and glucocorticoid injection.

MICROSCOPIC POLYANGIITIS

DEFINITION

The term *microscopic polyarteritis* was introduced into the literature by Davson in 1948 in recognition of the presence of glomerulonephritis in patients with polyarteritis nodosa. In 1992, the Chapel Hill Consensus Conference on the Nomenclature of Systemic Vasculitis adopted the term *microscopic polyangiitis* to connote a necrotizing vasculitis with few or no immune complexes affecting small vessels (capillaries, venules, or arterioles). Glomerulonephritis is very common in microscopic polyangiitis, and pulmonary capillaritis often occurs. The absence of granulomatous inflammation in microscopic polyangiitis is said to differentiate it from granulomatosis with polyangiitis.

INCIDENCE AND PREVALENCE

The incidence of microscopic polyangiitis is estimated to be 3–5/100,000. The mean age of onset is ~57 years, and males are slightly more frequently affected than females.

PATHOLOGY AND PATHOGENESIS

Microscopic polyangiitis has a predilection to involve capillaries and venules in addition to small- and medium-sized arteries. Immunohistochemical staining reveals a paucity of immunoglobulin deposition in the vascular lesion of microscopic polyangiitis, suggesting that immune-complex formation does not play a role in the pathogenesis of this syndrome. The renal lesion seen in microscopic polyangiitis is identical to that of granulomatosis with polyangiitis. Like granulomatosis with polyangiitis, microscopic polyangiitis is highly associated with ANCA, which may play a role in pathogenesis of this syndrome (see above).

CLINICAL AND LABORATORY MANIFESTATIONS

Because of its predilection to involve the small vessels, microscopic polyangiitis and granulomatosis with polyangiitis share similar clinical features. Disease onset may be gradual, with initial symptoms of fever,

weight loss, and musculoskeletal pain; however, it is often acute. Glomerulonephritis occurs in at least 79% of patients and can be rapidly progressive, leading to renal failure. Hemoptysis may be the first symptom of alveolar hemorrhage, which occurs in 12% of patients. Other manifestations include mononeuritis multiplex and gastrointestinal tract and cutaneous vasculitis. Upper airway disease and pulmonary nodules are not typically found in microscopic polyangiitis and, if present, suggest granulomatosis with polyangiitis.

Features of inflammation may be seen, including an elevated ESR and/or CRP, anemia, leukocytosis, and thrombocytosis. ANCA are present in 75% of patients with microscopic polyangiitis, with antimyeloperoxidase antibodies being the predominant antigen association.

DIAGNOSIS

The diagnosis is based on histologic evidence of vasculitis or pauci-immune glomerulonephritis in a patient with compatible clinical features of multisystem disease. Although microscopic polyangiitis is strongly ANCA-associated, tissue biopsy should continue to be pursued in patients who do not have a clinically compatible picture.

TREATMENT

Microscopic Polyangiitis

The 5-year survival rate for patients with treated microscopic polyangiitis is 74%, with disease-related mortality occurring from alveolar hemorrhage or gastrointestinal, cardiac, or renal disease. Studies on treatment have come from trials that have included patients with granulomatosis with polyangiitis or microscopic polyangiitis. Currently, the treatment approach for microscopic polyangiitis is the same as is used for granulomatosis with polyangiitis (see “Granulomatosis with Polyangiitis” for a detailed description of this therapeutic regimen). Disease relapse has been observed in at least 34% of patients. Treatment for such relapses would be based on site and severity of disease.

EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS (CHURG-STRAUSS)

DEFINITION

Eosinophilic granulomatosis with polyangiitis (Churg-Strauss) was described in 1951 by Churg and Strauss and is characterized by asthma, peripheral and tissue eosinophilia, extravascular granuloma formation, and vasculitis of multiple organ systems.

INCIDENCE AND PREVALENCE

Eosinophilic granulomatosis with polyangiitis (Churg-Strauss) is an uncommon disease with an estimated annual incidence of 1–3 per million. The disease can occur at any age with the possible exception of infants. The mean age of onset is 48 years, with a female-to-male ratio of 1.2:1.

PATHOLOGY AND PATHOGENESIS

The necrotizing vasculitis of eosinophilic granulomatosis with polyangiitis (Churg-Strauss) involves small- and medium-sized muscular arteries, capillaries, veins, and venules. A characteristic histopathologic feature of eosinophilic granulomatosis with polyangiitis (Churg-Strauss) is granuloma that may be present in the tissues or even within the walls of the vessels themselves. These are usually associated with infiltration of the tissues with eosinophils. This process can occur in any organ in the body; lung involvement is predominant, with skin, cardiovascular system, kidney, peripheral nervous system, and gastrointestinal tract also commonly involved. Although the precise pathogenesis of this disease is uncertain, its strong association with asthma and its clinicopathologic manifestations, including eosinophilia, granuloma, and vasculitis, point to aberrant immunologic phenomena.

CLINICAL AND LABORATORY MANIFESTATIONS

Patients with eosinophilic granulomatosis with polyangiitis (Churg-Strauss) often exhibit nonspecific manifestations such as fever, malaise,

anorexia, and weight loss, which are characteristic of a multisystem disease. The pulmonary findings in eosinophilic granulomatosis with polyangiitis (Churg-Strauss) dominate the clinical picture with severe asthmatic attacks and the presence of pulmonary infiltrates. Mononeuritis multiplex is the second most common manifestation and occurs in up to 72% of patients. Allergic rhinitis and sinusitis develop in up to 61% of patients and are often observed early in the course of disease. Clinically recognizable heart disease with myocarditis, pericarditis, endocarditis, or coronary vasculitis occurs in ~14% of patients and is an important cause of mortality. Skin lesions occur in ~51% of patients and include purpura in addition to cutaneous and subcutaneous nodules. The renal disease in eosinophilic granulomatosis with polyangiitis (Churg-Strauss) is less common and generally less severe than that of granulomatosis with polyangiitis and microscopic polyangiitis.

The characteristic laboratory finding in virtually all patients with eosinophilic granulomatosis with polyangiitis (Churg-Strauss) is a striking eosinophilia, which reaches levels >1000 cells/ μL in >80% of patients. Evidence of inflammation as evidenced by elevated ESR and/or CRP, fibrinogen, or α_2 -globulins can be found in 81% of patients. The other laboratory findings reflect the organ systems involved. Approximately 48% of patients with eosinophilic granulomatosis with polyangiitis (Churg-Strauss) have circulating ANCA that is usually antimyeloperoxidase.

DIAGNOSIS

Although the diagnosis of eosinophilic granulomatosis with polyangiitis (Churg-Strauss) is optimally made by biopsy in a patient with the characteristic clinical manifestations (see above), histologic confirmation can be challenging because the pathognomonic features often do not occur simultaneously. In order to be diagnosed with eosinophilic granulomatosis with polyangiitis (Churg-Strauss), a patient should have evidence of asthma, peripheral blood eosinophilia, and clinical features consistent with vasculitis.

TREATMENT

Eosinophilic Granulomatosis with Polyangiitis (Churg-Strauss)

The prognosis of untreated eosinophilic granulomatosis with polyangiitis (Churg-Strauss) is poor, with a reported 5-year survival of 25%. With treatment, prognosis is favorable, with one study finding a 78-month actuarial survival rate of 72%. Myocardial involvement is the most frequent cause of death and is responsible for 39% of patient mortality. Echocardiography should be performed in all newly diagnosed patients because this may influence therapeutic decisions.

Glucocorticoids alone appear to be effective in many patients. Dosage tapering is often limited by asthma, and many patients require low-dose prednisone for persistent asthma many years after clinical recovery from vasculitis. In patients who present with fulminant multisystem disease, particularly cardiac involvement, the treatment of choice is a combined regimen of daily cyclophosphamide and prednisone followed by azathioprine or methotrexate (see "Granulomatosis with Polyangiitis" for a detailed description of this therapeutic regimen).

Mepolizumab (anti-IL-5 antibody) 300 mg given subcutaneously once a month was studied in a randomized trial and found to be more effective than placebo. Patients with life-threatening eosinophilic granulomatosis with polyangiitis (Churg-Strauss) were excluded from the mepolizumab trial and should continue to be treated with cyclophosphamide and glucocorticoids. As mepolizumab is FDA approved for both eosinophilic granulomatosis with polyangiitis (Churg-Strauss) and severe eosinophilic asthma, it may have a particularly beneficial role in the setting of relapsing or resistant asthma requiring glucocorticoids.

Rituximab has been examined in retrospective series and may have a role in patients with active or relapsing vasculitis despite conventional agents or intolerance of these medications.

POLYARTERITIS NODOSA

DEFINITION

Polyarteritis nodosa was described in 1866 by Kussmaul and Maier. It is a multisystem, necrotizing vasculitis of small- and medium-sized muscular arteries in which involvement of the renal and visceral arteries is characteristic. Polyarteritis nodosa does not involve pulmonary arteries, although bronchial vessels may be involved; granulomas, significant eosinophilia, and an allergic diathesis are not observed.

INCIDENCE AND PREVALENCE

It is difficult to establish an accurate incidence of polyarteritis nodosa because previous reports have included polyarteritis nodosa and microscopic polyangiitis as well as other related vasculitides. Polyarteritis nodosa, as currently defined, is felt to be a very uncommon disease.

PATHOLOGY AND PATHOGENESIS

The vascular lesion in polyarteritis nodosa is a necrotizing inflammation of small- and medium-sized muscular arteries. The lesions are segmental and tend to involve bifurcations and branchings of arteries. They may spread circumferentially to involve adjacent veins. However, involvement of venules is not seen in polyarteritis nodosa and, if present, suggests microscopic polyangiitis (see below). In the acute stages of disease, polymorphonuclear neutrophils infiltrate all layers of the vessel wall and perivascular areas, which results in intimal proliferation and degeneration of the vessel wall. Mononuclear cells infiltrate the area as the lesions progress to the subacute and chronic stages. Fibrinoid necrosis of the vessels ensues with compromise of the lumen, thrombosis, infarction of the tissues supplied by the involved vessel, and, in some cases, hemorrhage. As the lesions heal, there is collagen deposition, which may lead to further occlusion of the vessel lumen. Aneurysmal dilations up to 1 cm in size along the involved arteries are characteristic of polyarteritis nodosa.

Multiple organ systems are involved, and the clinicopathologic findings reflect the degree and location of vessel involvement and the resulting ischemic changes. As mentioned above, pulmonary arteries are not involved in polyarteritis nodosa, and bronchial artery involvement is uncommon. The pathology in the kidney in polyarteritis nodosa is that of arteritis without glomerulonephritis. In patients with significant hypertension, typical pathologic features of glomerulosclerosis may be seen. In addition, pathologic sequelae of hypertension may be found elsewhere in the body.

The presence of a polyarteritis nodosa-like vasculitis in patients with hepatitis B together with the isolation of circulating immune complexes composed of hepatitis B antigen and immunoglobulin and the demonstration by immunofluorescence of hepatitis B antigen, IgM, and complement in the blood vessel walls strongly suggest the role of immunologic phenomena in the pathogenesis of this disease. A polyarteritis nodosa-like vasculitis has also been reported in patients with hepatitis C. Hairy cell leukemia can be associated with polyarteritis nodosa; the pathogenic mechanisms of this association are unclear.

A polyarteritis nodosa-like vasculitis has been described in conjunction with deficiency of adenosine deaminase type 2 (DADA2). Patients with DADA2 usually present in childhood with a variable pattern of clinical features and vascular pathology that is responsive to TNF inhibitors. As this differs from the usual treatment for polyarteritis nodosa, DADA2 should be considered in patients with suggestive clinical features, particularly those with early-onset disease.

CLINICAL AND LABORATORY MANIFESTATIONS

Nonspecific signs and symptoms are the hallmarks of polyarteritis nodosa. Fever, weight loss, and malaise are present in over one-half of cases. Patients usually present with vague symptoms such as weakness, malaise, headache, abdominal pain, and myalgias that can rapidly progress to a fulminant illness. Specific complaints related to the vascular involvement within a particular organ system may also dominate the presenting clinical picture as well as the entire course of the illness.

TABLE 363-6 Clinical Manifestations Related to Organ System Involvement in Polyarteritis Nodosa

ORGAN SYSTEM	PERCENT INCIDENCE	CLINICAL MANIFESTATIONS
Renal	60	Renal failure, hypertension
Musculoskeletal	64	Arthritis, arthralgia, myalgia
Peripheral nervous system	51	Peripheral neuropathy, mononeuritis multiplex
Gastrointestinal tract	44	Abdominal pain, nausea and vomiting, bleeding, bowel infarction and perforation, cholecystitis, hepatic infarction, pancreatic infarction
Skin	43	Rash, purpura, nodules, cutaneous infarcts, livedo reticularis, Raynaud's phenomenon
Cardiac	36	Congestive heart failure, myocardial infarction, pericarditis
Genitourinary	25	Testicular, ovarian, or epididymal pain
Central nervous system	23	Cerebral vascular accident, altered mental status, seizure

Source: Reproduced with permission from TR Cupps, AS Fauci: The vasculitides. Major Probl Intern Med 21:1, 1981.

(Table 363-6). In polyarteritis nodosa, renal involvement most commonly manifests as hypertension, renal insufficiency, or hemorrhage due to microaneurysms.

There are no diagnostic serologic tests for polyarteritis nodosa. In >75% of patients, the leukocyte count is elevated with a predominance of neutrophils. Eosinophilia is seen only rarely and, when present at high levels, suggests the diagnosis of eosinophilic granulomatosis with polyangiitis (Churg-Strauss). The anemia of chronic disease may be seen, and an elevated ESR and/or CRP is almost always present. Other common laboratory findings reflect the particular organ involved. Hypergammaglobulinemia may be present, and all patients should be screened for hepatitis B and C. ANCA are rarely found in patients with polyarteritis nodosa.

DIAGNOSIS

The diagnosis of polyarteritis nodosa is based on the demonstration of characteristic findings of vasculitis on biopsy material of involved organs. Biopsy of symptomatic organs such as nodular skin lesions, painful testes, and nerve/muscle provides the highest diagnostic yields. In the absence of easily accessible tissue for biopsy, the arteriographic demonstration of involved vessels, particularly in the form of aneurysms of small- and medium-sized arteries in the renal, hepatic, and visceral vasculature, is sufficient to make the diagnosis. This should consist of a catheter-directed dye arteriogram because magnetic resonance and computed tomography arteriograms do not have sufficient resolution at the current time to visualize the vessels affected in polyarteritis nodosa. Aneurysms of vessels are not pathognomonic of polyarteritis nodosa; furthermore, aneurysms need not always be present, and arteriographic findings may be limited to stenotic segments and obliteration of vessels.

TREATMENT

Polyarteritis Nodosa

The prognosis of untreated polyarteritis nodosa is extremely poor, with a reported 5-year survival rate between 10 and 20%. Death usually results from gastrointestinal complications, particularly bowel infarcts and perforation, and cardiovascular causes. Intracranial hypertension often compounds dysfunction in other organ systems, such as the kidneys, heart, and CNS, leading to additional late morbidity and mortality in polyarteritis nodosa. The combination of prednisone and cyclophosphamide has been found to significantly improve the survival rate (see “Granulomatosis with Polyangiitis” for a detailed description of this therapeutic regimen). In less severe cases of polyarteritis nodosa, glucocorticoids alone

have resulted in disease remission. In patients with hepatitis B or C who have a polyarteritis nodosa-like vasculitis, antiviral therapy represents an important part of management and has been used in combination with glucocorticoids and plasma exchange in some series. Careful attention to the treatment of hypertension can lessen the vascular complications of polyarteritis nodosa. Following successful treatment, relapse of polyarteritis nodosa has been estimated to occur in 10–20% of patients.

GIANT CELL ARTERITIS AND POLYMYALGIA RHEUMATICA

DEFINITION

Giant cell arteritis, historically referred to as *temporal arteritis*, is an inflammation of medium- and large-sized arteries. It characteristically involves one or more branches of the carotid artery, particularly the temporal artery. However, it is a systemic disease that can involve arteries in multiple locations, particularly the aorta and its main branches.

Giant cell arteritis is closely associated with *polymyalgia rheumatica*, which is characterized by stiffness, aching, and pain in the muscles of the neck, shoulders, lower back, hips, and thighs. Most commonly, polymyalgia rheumatica occurs in isolation, but it may be seen in 40–50% of patients with giant cell arteritis. In addition, ~10–20% of patients who initially present with features of isolated polymyalgia rheumatica later go on to develop giant cell arteritis. This strong clinical association together with data from pathophysiologic studies has increasingly supported that giant cell arteritis and polymyalgia rheumatica represent differing clinical spectrums of a single disease process.

INCIDENCE AND PREVALENCE

Giant cell arteritis occurs almost exclusively in individuals aged >50 years. It is more common in women than in men and is rare in blacks. The incidence of giant cell arteritis varies widely in different studies and in different geographic regions. A high incidence has been found in Scandinavia and in regions of the United States with large Scandinavian populations, compared to a lower incidence in southern Europe. The annual incidence rates in individuals aged ≥50 years range from 6.9 to 32.8 per 100,000 population. Familial aggregation has been reported, as has an association with HLA-DR4. In addition, genetic linkage studies have demonstrated an association of giant cell arteritis with alleles at the HLA-DRB1 locus, particularly HLA-DRB1*04 variants. In Olmsted County, Minnesota, the annual incidence of polymyalgia rheumatica in individuals aged ≥50 years is 58.7 per 100,000 population.

PATHOLOGY AND PATHOGENESIS

Although the temporal artery is most frequently involved in giant cell arteritis, patients often have a systemic vasculitis of multiple medium- and large-sized arteries, which may go undetected. Histopathologically, the disease is a panarteritis with inflammatory mononuclear cell infiltrates within the vessel wall with frequent giant cell formation. There is proliferation of the intima and fragmentation of the internal elastic lamina. Pathophysiologic findings in organs result from the ischemia related to the involved vessels.

Experimental data support that giant cell arteritis is an antigen-driven disease in which activated T lymphocytes, macrophages, and dendritic cells play a critical role in pathogenesis. Sequence analysis of the T-cell receptor of tissue-infiltrating T cells in lesions of giant cell arteritis indicates restricted clonal expansion, suggesting the presence of an antigen residing in the arterial wall. Giant cell arteritis is believed to be initiated in the adventitia where CD4+ T cells enter through the vasa vasorum, become activated, and orchestrate macrophage differentiation. T cells recruited to vasculitic lesions in patients with giant cell arteritis produce predominantly IL-2 and IFN-γ, and the latter has been suggested to be involved in the progression to arteritis. Laboratory-based data demonstrate that at least two separate lineages of CD4

CLINICAL AND LABORATORY MANIFESTATIONS

Giant cell arteritis is most commonly characterized clinically by the complex of fever, anemia, high ESR and/or CRP, and headaches in a patient aged >50 years. Other phenotypic manifestations include features of systemic inflammation, including malaise, fatigue, anorexia, weight loss, sweats, arthralgias, polymyalgia rheumatica, or large-vessel disease.

In patients with involvement of the cranial arteries, headache is the predominant symptom and may be associated with a tender, thickened, or nodular artery, which may pulsate early in the disease but may become occluded later. Scalp pain and claudication of the jaw and tongue may occur. A well-recognized and dreaded complication of giant cell arteritis, particularly in untreated patients, is ischemic optic neuropathy, which may lead to serious visual symptoms, including sudden blindness in some patients. However, most patients have complaints relating to the head or eyes before visual loss. Attention to such symptoms with institution of appropriate therapy (see below) lessens the risk of this complication. Other cranial ischemic complications include strokes and scalp or tongue infarction.

Up to one-third of patients can have large-vessel disease that can be the primary presentation of giant cell arteritis or can emerge at a later point in patients who have had previous cranial arteritis features or polymyalgia rheumatica. Manifestations of large-vessel disease can include subclavian artery stenosis that can present as arm claudication or aortic aneurysms involving the thoracic and to a lesser degree the abdominal aorta, which carry risks of rupture or dissection.

Characteristic laboratory findings in addition to the elevated ESR and/or CRP include a normochromic or slightly hypochromic anemia. Liver function abnormalities are common, particularly increased alkaline phosphatase levels. Increased levels of IgG and complement have been reported.

DIAGNOSIS

The diagnosis of giant cell arteritis can often be suggested clinically by the demonstration of the complex of fever, anemia, and high ESR and/or CRP with or without symptoms of polymyalgia rheumatica in a patient >50 years old. The diagnosis can be confirmed by biopsy of the temporal artery but may not be positive in all patients due to patchy histologic findings. Since involvement of the vessel may be segmental, positive yield is increased by obtaining a biopsy segment of 3–5 cm together with serial sectioning of biopsy specimens. Ultrasonography of the temporal artery has been reported to be helpful in diagnosis and has been increasingly used by some physicians. Therapy should not be delayed pending the performance of diagnostic studies. In this regard, it has been reported that temporal artery biopsies may show vasculitis even after ~14 days of glucocorticoid therapy. A dramatic clinical response to a trial of glucocorticoid therapy can further support the diagnosis.

Large-vessel disease may be suggested by symptoms and findings on physical examination such as diminished pulses or bruits. It is confirmed by vascular imaging, most commonly through magnetic resonance or computed tomography. Positron emission tomography has become increasingly investigated, although its role in diagnosis and monitoring remains unclear.

Isolated polymyalgia rheumatica is a clinical diagnosis made by the presence of typical symptoms of stiffness, aching, and pain in the muscles of the hip and shoulder girdle, an increased ESR and/or CRP, the absence of clinical features suggestive of giant cell arteritis, and a prompt therapeutic response to low-dose prednisone. Polymyalgia rheumatica can be associated with a peripheral arthritis that can mimic rheumatoid arthritis (**Chap. 358**). Rheumatoid factor and anti-cyclic citrullinated peptide (CCP) should be negative. In patients who develop a worsening pattern of peripheral arthritis, the potential for a seronegative rheumatoid arthritis or other inflammatory arthropathy

should be considered. Levels of enzymes indicative of muscle damage such as serum creatine kinase are not elevated.

TREATMENT

Giant Cell Arteritis and Polymyalgia Rheumatica

Acute disease-related mortality directly from giant cell arteritis is uncommon, with fatalities occurring from cerebrovascular events or myocardial infarction. However, patients are at risk of late mortality from aortic aneurysm rupture or dissection as patients with giant cell arteritis are 18 times more likely to develop thoracic aortic aneurysms than the general population.

The goals of treatment in giant cell arteritis are to reduce symptoms and, most importantly, to prevent visual loss. The treatment approach for cranial and large-vessel disease in giant cell arteritis is currently the same. Giant cell arteritis and its associated symptoms are responsive to glucocorticoid therapy. Treatment should begin with prednisone 40–60 mg/d for ~1 month, followed by a gradual tapering. When ocular signs and symptoms occur, consideration should be given for the use of methylprednisolone 1000 mg daily for 3 days to protect remaining vision. Although the optimal duration of glucocorticoid therapy has not been established, most series have found that patients require treatment for ≥2 years. Symptom recurrence during prednisone tapering develops in 60–85% of patients with giant cell arteritis, requiring a dosage increase. The ESR and/or CRP can serve as a useful indicator of inflammatory disease activity in monitoring and tapering therapy and can be used to judge the pace of the tapering schedule. However, minor increases in the ESR and/or CRP can occur as glucocorticoids are being tapered and do not necessarily reflect an exacerbation of arteritis, particularly if the patient remains symptom-free. Under these circumstances, the tapering should continue with caution. Glucocorticoid toxicity occurs in 35–65% of patients and represents an important cause of patient morbidity.

Tocilizumab (anti-IL-6 receptor) was found to be effective in giant cell arteritis in a randomized trial and is FDA approved for this indication. The recommended dose of tocilizumab is 162 mg given subcutaneously once every week or once every other week in combination with a tapering course of glucocorticoids. The decision about when to use tocilizumab in giant cell arteritis is individually based, taking into account patient comorbidities, potential for glucocorticoid toxicity, and the side effects of tocilizumab. By nature of its mechanism of action, tocilizumab impacts laboratory parameters of ESR and CRP, which will eliminate the ability to utilize these in disease activity assessment.

The use of methotrexate as a glucocorticoid-sparing agent has been examined in two randomized placebo-controlled trials that reached conflicting conclusions. It may be considered in select patients with glucocorticoid toxicity who are unable to take or intolerant of tocilizumab.

Abatacept (CTLA4-Ig) was examined in a small randomized trial in giant cell arteritis and demonstrated greater efficacy than glucocorticoids alone. Infliximab, a monoclonal antibody to TNF, was studied in a randomized trial and was not found to provide benefit.

Aspirin 81 mg daily has been found to reduce the occurrence of cranial ischemic complications in giant cell arteritis and should be given in addition to glucocorticoids in patients who do not have contraindications.

Patients with isolated polymyalgia rheumatica respond promptly to prednisone, which can be started at a lower dose of 10–20 mg/d. Similar to giant cell arteritis, the ESR and/or CRP can serve as a useful indicator in monitoring and prednisone reduction. Recurrent polymyalgia symptoms develop in the majority of patients during prednisone tapering. One study of methotrexate found that the use of this drug reduced the prednisone dose on average by only 1 mg and did not decrease prednisone-related side effects. A randomized trial in polymyalgia rheumatica did not find infliximab to lessen relapse or glucocorticoid requirements.

TAKAYASU ARTERITIS

DEFINITION

Takayasu arteritis is an inflammatory and stenotic disease of medium- and large-sized arteries characterized by a strong predilection for the aortic arch and its branches.

INCIDENCE AND PREVALENCE

Takayasu arteritis is an uncommon disease with an estimated annual incidence rate of 1.2–2.6 cases per million. It is most prevalent in adolescent girls and young women. Although it is more common in Asia, it is neither racially nor geographically restricted.

PATHOLOGY AND PATHOGENESIS

The disease involves medium- and large-sized arteries, with a strong predilection for the aortic arch and its branches; the pulmonary artery may also be involved. The most commonly affected arteries seen by arteriography are listed in Table 363-7. The involvement of the major branches of the aorta is much more marked at their origin than distally. The disease is a panarteritis with inflammatory mononuclear cell infiltrates and occasionally giant cells. There are marked intimal proliferation and fibrosis, scarring and vascularization of the media, and disruption and degeneration of the elastic lamina. Narrowing of the lumen occurs with or without thrombosis. The vasa vasorum are frequently involved. Pathologic changes in various organs reflect the compromise of blood flow through the involved vessels.

Immunopathogenic mechanisms, the precise nature of which is uncertain, are suspected in this disease. As with several of the vasculitis syndromes, circulating immune complexes have been demonstrated, but their pathogenic significance is unclear.

CLINICAL AND LABORATORY MANIFESTATIONS

Takayasu arteritis is a systemic disease with generalized as well as vascular symptoms. The generalized symptoms include malaise, fever, night sweats, arthralgias, anorexia, and weight loss, which may occur months before vessel involvement is apparent. These symptoms may merge into those related to vascular compromise and organ ischemia. Pulses are commonly absent in the involved vessels, particularly the subclavian artery. The frequency of arteriographic abnormalities and the potentially associated clinical manifestations are listed in Table 363-7. Hypertension occurs in 32–93% of patients and contributes to renal, cardiac, and cerebral injury.

Characteristic laboratory findings include an elevated ESR and/or CRP, mild anemia, and elevated immunoglobulin levels.

TABLE 363-7 Frequency of Arteriographic Abnormalities and Potential Clinical Manifestations of Arterial Involvement in Takayasu Arteritis

ARTERY	PERCENTAGE OF ARTERIOGRAPHIC ABNORMALITIES	POTENTIAL CLINICAL MANIFESTATIONS
Subclavian	93	Arm claudication, Raynaud's phenomenon
Common carotid	58	Visual changes, syncope, transient ischemic attacks, stroke
Abdominal aorta ^a	47	Abdominal pain, nausea, vomiting
Renal	38	Hypertension, renal failure
Aortic arch or root	35	Aortic insufficiency, congestive heart failure
Vertebral	35	Visual changes, dizziness
Coeliac axis ^a	18	Abdominal pain, nausea, vomiting
Superior mesenteric ^a	18	Abdominal pain, nausea, vomiting
Iliac	17	Leg claudication
Pulmonary	10–40	Atypical chest pain, dyspnea
Coronary	<10	Chest pain, myocardial infarction

^aArteriographic lesions at these locations are usually asymptomatic but may potentially cause these symptoms.

Source: G Kerr et al: Ann Intern Med 120:919, 1994.

DIAGNOSIS

The diagnosis of Takayasu arteritis should be suspected strongly in a young woman who develops a decrease or absence of peripheral pulses, discrepancies in blood pressure, and arterial bruits. The diagnosis is confirmed by the characteristic pattern on arteriography, which includes irregular vessel walls, stenosis, poststenotic dilation, aneurysm formation, occlusion, and evidence of increased collateral circulation. Complete imaging of the aorta and its major branches by magnetic resonance or computed tomography arteriography should be obtained to fully delineate the distribution and degree of arterial disease. Because of the involvement of the large vessels, tissue is rarely available as a means of diagnosis and obtained only if vascular surgery is necessary. IgG4-related disease (Chap. 368) is a potential cause of aortitis and periaortitis that is histologically differentiated from Takayasu arteritis by a dense lymphoplasmacytic infiltrate rich in IgG4-positive plasma cells, a storiform pattern of fibrosis, and obliterative phlebitis.

TREATMENT

Takayasu Arteritis

The long-term outcome of patients with Takayasu arteritis has varied widely between studies. Although two North American reports found overall survival to be ≥94%, the 5-year mortality rate from other studies has ranged from 0 to 35%. Disease-related mortality most often occurs from congestive heart failure, cerebrovascular events, myocardial infarction, aneurysm rupture, or renal failure. Even in the absence of life-threatening disease, Takayasu arteritis can be associated with significant morbidity. The course of the disease is variable, and although spontaneous remissions may occur, Takayasu arteritis is most often chronic and relapsing. Although glucocorticoid therapy in doses of 40–60 mg prednisone per day alleviates symptoms, there are no convincing studies that indicate that it increases survival. The combination of glucocorticoid therapy for acute signs and symptoms and an aggressive surgical and/or arterioplasty approach to stenosed vessels has markedly improved outcome and decreased morbidity by lessening the risk of stroke, correcting hypertension due to renal artery stenosis, and improving blood flow to ischemic viscera and limbs. Unless it is urgently required, surgical correction of stenosed arteries should be undertaken only when the vascular inflammatory process is well controlled with medical therapy.

In individuals who are refractory to or unable to taper glucocorticoids, methotrexate in doses up to 25 mg per week has yielded encouraging results. Results from retrospective series with anti-TNF therapies have been encouraging, but these agents have not been studied through randomized trials to determine efficacy.

Abatacept was examined in the first randomized trial to be conducted in Takayasu arteritis but did not demonstrate efficacy beyond glucocorticoids alone. Tocilizumab has been investigated in a randomized trial where it did not reach its primary efficacy endpoint. In this study, it was found to have secondary benefits and encouraging results have also been seen in retrospective studies such that the utility of this agent remains an active question.

IgA VASCULITIS (HENOCHE-SCHÖNLEIN)

DEFINITION

IgA vasculitis (Henoch-Schönlein) is a small-vessel vasculitis characterized by palpable purpura (most commonly distributed over the buttocks and lower extremities), arthralgias, gastrointestinal signs and symptoms, and glomerulonephritis.

INCIDENCE AND PREVALENCE

IgA vasculitis (Henoch-Schönlein) is usually seen in children ages 4–7 years; however, the disease may also be seen in infants and adults. It is not a rare disease; in one series, it accounted for between 5 and 24 admissions per year at a pediatric hospital. The male-to-female ratio is 1.5:1. A seasonal variation with a peak incidence in spring has been noted.

PATHOLOGY AND PATHOGENESIS

The presumptive pathogenic mechanism for IgA (Henoch-Schönlein) vasculitis is immune-complex deposition. A number of inciting antigens have been suggested including upper respiratory tract infections, various drugs, foods, insect bites, and immunizations. IgA is the antibody class most often seen in the immune complexes and has been demonstrated in the renal biopsies of these patients.

CLINICAL AND LABORATORY MANIFESTATIONS

In pediatric patients, palpable purpura is seen in virtually all patients; most patients develop polyarthralgias in the absence of frank arthritis. Gastrointestinal involvement, which is seen in almost 70% of pediatric patients, is characterized by colicky abdominal pain usually associated with nausea, vomiting, diarrhea, or constipation, and is frequently accompanied by the passage of blood and mucus per rectum; bowel intussusception may occur. Renal involvement occurs in 10–50% of patients and is usually characterized by mild glomerulonephritis leading to proteinuria and microscopic hematuria, with red blood cell casts in the majority of patients; it usually resolves spontaneously without therapy. Rarely, a progressive glomerulonephritis will develop. In adults, presenting symptoms are most frequently related to the skin and joints, while initial complaints related to the gut are less common. Although certain studies have found that renal disease is more frequent and more severe in adults, this has not been a consistent finding. However, the course of renal disease in adults may be more insidious and thus requires close follow-up. Myocardial involvement can occur in adults but is rare in children.

Laboratory studies generally show a mild leukocytosis, a normal platelet count, and occasionally eosinophilia. Serum complement components are normal, and IgA levels are elevated in about one-half of patients.

DIAGNOSIS

The diagnosis of IgA vasculitis (Henoch-Schönlein) is based on clinical signs and symptoms. Skin biopsy specimen can be useful in confirming leukocytoclastic vasculitis with IgA and C3 deposition by immunofluorescence. Renal biopsy is rarely needed for diagnosis but may provide prognostic information in some patients.

TREATMENT

IgA Vasculitis (Henoch-Schönlein)

The prognosis of IgA vasculitis (Henoch-Schönlein) is excellent. Mortality is exceedingly rare, and 1–5% of children progress to end-stage renal disease. Most patients recover completely, and some do not require therapy. When glucocorticoids are required, prednisone, 1 mg/kg per day and tapered according to clinical response, has been shown to be useful in decreasing tissue edema, arthralgias, and abdominal discomfort; however, it has not proved beneficial in the treatment of skin or renal disease and does not appear to shorten the duration of active disease or lessen the chance of recurrence. Patients with rapidly progressive glomerulonephritis have been anecdotally reported to benefit from glucocorticoids used in combination with another immunosuppressive agent. Disease recurrences have been reported in 10–40% of patients.

CRYOGLOBULINEMIC VASCULITIS

DEFINITION

Cryoglobulins are cold-precipitable monoclonal or polyclonal immunoglobulins. Cryoglobulinemia may be associated with a systemic vasculitis characterized by palpable purpura, arthralgias, weakness, neuropathy, and glomerulonephritis. The most common association has been with hepatitis C, although cryoglobulinemia can be observed in association with a variety of underlying disorders including multiple myeloma, lymphoproliferative disorders, connective tissue diseases, infection, and liver disease and can be idiopathic.

INCIDENCE AND PREVALENCE

The incidence of cryoglobulinemic vasculitis has not been established. It has been estimated that 5% of patients with chronic hepatitis C will develop cryoglobulinemic vasculitis.

PATHOLOGY AND PATHOGENESIS

Skin biopsies in cryoglobulinemic vasculitis reveal an inflammatory infiltrate surrounding and involving blood vessel walls, with fibrinoid necrosis, endothelial cell hyperplasia, and hemorrhage. Deposition of immunoglobulin and complement is common. Abnormalities of uninvolved skin including basement membrane alterations and deposits in vessel walls may be found. Membranoproliferative glomerulonephritis is responsible for 80% of all renal lesions in cryoglobulinemic vasculitis.

The association between hepatitis C and cryoglobulinemic vasculitis has been supported by the high frequency of documented hepatitis C infection, the presence of hepatitis C RNA and anti-hepatitis C antibodies in serum cryoprecipitates, evidence of hepatitis C antigens in vasculitic skin lesions, and the effectiveness of antiviral therapy. Current evidence suggests that in the majority of cases, cryoglobulinemic vasculitis occurs when an aberrant immune response to hepatitis C infection leads to the formation of immune complexes consisting of hepatitis C antigens, polyclonal hepatitis C-specific IgG, and monoclonal IgM rheumatoid factor. The deposition of these immune complexes in blood vessel walls triggers an inflammatory cascade that results in cryoglobulinemic vasculitis.

CLINICAL AND LABORATORY MANIFESTATIONS

The most common clinical manifestations of cryoglobulinemic vasculitis are cutaneous vasculitis, arthritis, peripheral neuropathy, and glomerulonephritis. Renal disease develops in 10–30% of patients. Life-threatening rapidly progressive glomerulonephritis or vasculitis of the CNS, gastrointestinal tract, or heart occurs infrequently.

The presence of circulating cryoprecipitates is the fundamental finding in cryoglobulinemic vasculitis. Rheumatoid factor is almost always found and may be a useful clue to the disease when cryoglobulins are not detected. Hypocomplementemia occurs in 90% of patients. An elevated ESR and/or CRP and anemia occur frequently. Evidence for hepatitis C infection must be sought in all patients by testing for hepatitis C antibodies and hepatitis C RNA.

TREATMENT

Cryoglobulinemic Vasculitis

Acute mortality directly from cryoglobulinemic vasculitis is uncommon, but the presence of glomerulonephritis is a poor prognostic sign for overall outcome. In such patients, 15% progress to end-stage renal disease, with 40% later experiencing fatal cardiovascular disease, infection, or liver failure. As indicated above, the majority of cases are associated with hepatitis C infection. In such patients, treatment with antiviral therapy ([Chap. 341](#)) is first-line therapy for hepatitis C-associated cryoglobulinemic vasculitis, particularly given the efficacy of current hepatitis C therapies. Clinical improvement with antiviral therapy is dependent on the virologic response. Patients who clear hepatitis C from the blood have objective improvement in their vasculitis along with significant reductions in levels of circulating cryoglobulins, IgM, and rheumatoid factor. While transient improvement can be observed with glucocorticoids, a complete response is seen in only 7% of patients. Plasmapheresis and cytotoxic agents have been used in anecdotal reports. These observations have not been confirmed, and such therapies carry significant risks. Randomized trials with rituximab in hepatitis C-associated cryoglobulinemic vasculitis have provided evidence of benefit such that this agent should be considered in patients with active vasculitis either in combination with antiviral therapy or alone in patients who have relapsed through, are intolerant to, or have contraindications to antiviral agents.

SINGLE-ORGAN VASCULITIS

Single-organ vasculitis has been defined as vasculitis in arteries or veins of any size in a single organ that has no features that indicate that it is a limited expression of a systemic vasculitis. Examples include isolated aortitis, testicular vasculitis, vasculitis of the breast, isolated cutaneous vasculitis, and primary CNS vasculitis. In some instances, this may be discovered at the time of surgery such as orchectomy for a testicular mass where there is concern for neoplasm that is found instead to be vasculitis. Some patients originally diagnosed with single-organ vasculitis may later develop additional manifestations of a more systemic disease. In instances where there is no evidence of systemic vasculitis and the affected organ has been removed in its entirety, the patient may be followed closely without immunosuppressive therapy. In other instances, such as primary CNS vasculitis or some patients with isolated cutaneous vasculitis, medical intervention is warranted.

IDIOPATHIC CUTANEOUS VASCULITIS

DEFINITION

The term *cutaneous vasculitis* is defined broadly as inflammation of the blood vessels of the dermis. Because of its heterogeneity, cutaneous vasculitis has been described by a variety of terms including *hypersensitivity vasculitis* and *cutaneous leukocytoclastic angitis*. However, cutaneous vasculitis is not one specific disease but a manifestation that can be seen in a variety of settings. In >70% of cases, cutaneous vasculitis occurs either as part of a primary systemic vasculitis or as a secondary vasculitis related to an inciting agent or an underlying disease (see “Secondary Vasculitis,” below). In the remaining 30% of cases, cutaneous vasculitis occurs idiopathically.

INCIDENCE AND PREVALENCE

Cutaneous vasculitis represents the most commonly encountered vasculitis in clinical practice. The exact incidence of idiopathic cutaneous vasculitis has not been determined due to the predilection for cutaneous vasculitis to be associated with an underlying process and the variability of its clinical course.

PATHOLOGY AND PATHOGENESIS

The typical histopathologic feature of cutaneous vasculitis is the presence of vasculitis of small vessels. Postcapillary venules are the most commonly involved vessels; capillaries and arterioles may be involved less frequently. This vasculitis is characterized by a *leukocytoclasia*, a term that refers to the nuclear debris remaining from the neutrophils that have infiltrated in and around the vessels during the acute stages. In the subacute or chronic stages, mononuclear cells predominate; in certain subgroups, eosinophilic infiltration is seen. Erythrocytes often extravasate from the involved vessels, leading to palpable purpura. *Cutaneous arteritis* can also occur, which involves slightly larger-sized vessels within the dermis.

CLINICAL AND LABORATORY MANIFESTATIONS

The hallmark of idiopathic cutaneous vasculitis is the predominance of skin involvement. Skin lesions may appear typically as palpable purpura; however, other cutaneous manifestations of the vasculitis may occur, including macules, papules, vesicles, bullae, subcutaneous nodules, ulcers, and recurrent or chronic urticaria. The skin lesions may be pruritic or painful, with a burning or stinging sensation. Lesions most commonly occur in the lower extremities in ambulatory patients or in the sacral area in bedridden patients due to the effects of hydrostatic forces on the postcapillary venules. Edema may accompany certain lesions, and hyperpigmentation often occurs in areas of recurrent or chronic lesions.

There are no specific laboratory tests diagnostic of idiopathic cutaneous vasculitis. A mild leukocytosis with or without eosinophilia is characteristic, as is an elevated ESR and/or CRP. Laboratory studies should be aimed toward ruling out features to suggest an underlying disease or a systemic vasculitis.

DIAGNOSIS

The diagnosis of cutaneous vasculitis is made by the demonstration of vasculitis on biopsy. An important diagnostic principle in patients with

cutaneous vasculitis is to search for an etiology of the vasculitis—be it an exogenous agent, such as a drug or an infection, or an endogenous condition, such as an underlying disease (Fig. 363-1). In addition, a careful physical and laboratory examination should be performed to rule out the possibility of systemic vasculitis. This should start with the least invasive diagnostic approach and proceed to the more invasive only if clinically indicated.

TREATMENT

Idiopathic Cutaneous Vasculitis

When an antigenic stimulus is recognized as the precipitating factor in the cutaneous vasculitis, it should be removed; if this is a microbe, appropriate antimicrobial therapy should be instituted. If the vasculitis is associated with another underlying disease, treatment of the latter often results in resolution of the former. In situations where disease is apparently self-limited, no therapy, except possibly symptomatic therapy, is indicated. When cutaneous vasculitis persists and when there is no evidence of an inciting agent, an associated disease, or an underlying systemic vasculitis, the decision to treat should be based on weighing the balance between the degree of symptoms and the risk of treatment. Some cases of idiopathic cutaneous vasculitis resolve spontaneously, whereas others remit and relapse. In patients with persistent vasculitis, a variety of therapeutic regimens have been tried with variable results. In general, the treatment of idiopathic cutaneous vasculitis has not been satisfactory. Fortunately, since the disease is generally limited to the skin, this lack of consistent response to therapy usually does not lead to a life-threatening situation. Agents with which there have been anecdotal reports of success include dapsone, colchicine, hydroxychloroquine, and nonsteroidal anti-inflammatory agents. Glucocorticoids are often used in the treatment of idiopathic cutaneous vasculitis. Therapy is usually instituted as prednisone 1 mg/kg per day, with rapid tapering where possible, either directly to discontinuation or by conversion to an alternate-day regimen followed by ultimate discontinuation. In cases that prove refractory to glucocorticoids, a trial of another immunosuppressive agent may be indicated. Patients with chronic vasculitis isolated to cutaneous venules rarely respond dramatically to any therapeutic regimen, and cytotoxic agents should be used only as a last resort in these patients. Methotrexate and azathioprine have been used in such situations in anecdotal reports. Although cyclophosphamide is the most effective therapy for the systemic vasculitides, it should almost never be used for idiopathic cutaneous vasculitis because of the potential toxicity.

PRIMARY CENTRAL NERVOUS SYSTEM VASCULITIS

Primary CNS vasculitis is an uncommon clinicopathologic entity characterized by vasculitis restricted to the vessels of the CNS without other apparent systemic vasculitis. The inflammatory process is usually composed of mononuclear cell infiltrates with or without granuloma formation.

Patients may present with headaches, altered mental function, and focal neurologic deficits. Systemic symptoms are generally absent. Devastating neurologic abnormalities may occur depending on the extent of vessel involvement. The diagnosis can be suggested by abnormal magnetic resonance imaging of the brain, an abnormal lumbar puncture, and/or demonstration of characteristic vessel abnormalities on arteriography (Fig. 363-4), but it is confirmed by biopsy of the brain parenchyma and leptomeninges. In the absence of a brain biopsy, care should be taken not to misinterpret as true primary vasculitis arteriographic abnormalities that might actually be related to another cause. An important entity in the differential diagnosis is reversible cerebral vasoconstrictive syndrome, which typically presents with “thunderclap” headache and is associated with arteriographic abnormalities that mimic primary CNS vasculitis that are reversible. Other diagnostic

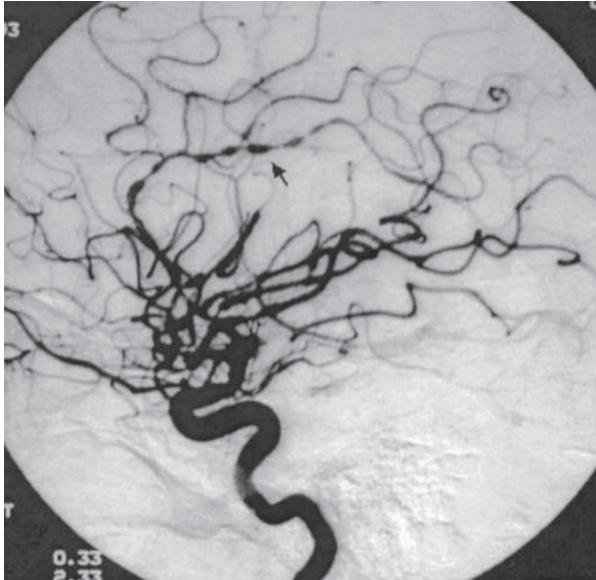


FIGURE 363-4 Cerebral arteriogram from a 32-year-old man with primary central nervous system vasculitis. Dramatic beading (arrow) typical of vasculitis is seen.

considerations include infection, atherosclerosis, emboli, connective tissue disease, sarcoidosis, malignancy, and drug-associated causes. The prognosis of granulomatous primary CNS vasculitis is poor; however, some reports indicate that glucocorticoid therapy, alone or together with cyclophosphamide administered as described above, has induced clinical remissions. Following disease remission, cyclophosphamide is switched to azathioprine or mycophenolate mofetil as these have good penetration into the CNS.

BEHÇET'S DISEASE

Behçet's disease is a clinicopathologic entity characterized by recurrent episodes of oral and genital ulcers, iritis, and cutaneous lesions. The underlying pathologic process is a leukocytoclastic venulitis, although vessels of any size and in any organ can be involved. **This disorder is described in detail in Chap. 364.**

COGAN'S SYNDROME

Cogan's syndrome is characterized by interstitial keratitis together with vestibuloauditory symptoms. It may be associated with a systemic vasculitis, particularly aortitis with involvement of the aortic valve. Glucocorticoids are the mainstay of treatment. Initiation of treatment as early as possible after the onset of hearing loss improves the likelihood of a favorable outcome.

KAWASAKI'S DISEASE

Kawasaki's disease is an acute, febrile, multisystem disease of children. Some 80% of cases occur prior to the age of 5, with the peak incidence occurring at ≤ 2 years. It is characterized by nonsuppurative cervical adenitis and changes in the skin and mucous membranes such as edema; congested conjunctivae; erythema of the oral cavity, lips, and palms; and desquamation of the skin of the fingertips. Although the disease is generally benign and self-limited, it is associated with coronary artery aneurysms in ~25% of cases, with an overall case-fatality rate of 0.5–2.8%. These complications usually occur between the third and fourth weeks of illness during the convalescent stage. Vasculitis of the coronary arteries is seen in almost all the fatal cases that have been autopsied and can cause complications into adulthood. There is typical intimal proliferation and infiltration of the vessel wall with mononuclear cells. Beadlike aneurysms and thromboses may be seen along the

artery. Other manifestations include pericarditis, myocarditis, myocardial ischemia and infarction, and cardiomegaly.

Apart from the up to 2.8% of patients who develop fatal complications, the prognosis of this disease for uneventful recovery is excellent. High-dose IV γ -globulin (2 g/kg as a single infusion over 10 h) together with aspirin (100 mg/kg/d for 14 days followed by 3–5 mg/kg per day for several weeks) has been shown to be effective in reducing the prevalence of coronary artery abnormalities when administered early in the course of the disease. Surgery may be necessary for Kawasaki disease patients who have giant coronary artery aneurysms or other coronary complications. Surgical treatment most commonly includes thromboendarterectomy, thrombus clearing, aneurysmal reconstruction, and coronary artery bypass grafting.

Multisystem inflammatory syndrome (MIS-C), a serious condition that may resemble Kawasaki's disease, has been observed with infections due to the novel coronavirus, SARS-CoV-2 (**Chap. 199**). Although clinical features consistent with Kawasaki's disease have been observed, these patients can also have manifestations atypical for Kawasaki's disease, including gastrointestinal symptoms, myocarditis, neurocognitive symptoms, and shock. Any patient who presents with a clinical picture suggestive of Kawasaki's disease should be tested for SARS-CoV-2 to guide care and management.

POLYANGIITIS OVERLAP SYNDROMES

Some patients with systemic vasculitis manifest clinicopathologic characteristics that do not fit precisely into any specific disease but have overlapping features of different vasculitides. The diagnostic and therapeutic considerations as well as the prognosis for these patients depend on the sites and severity of active vasculitis. Patients with vasculitis that could potentially cause irreversible damage to a major organ system should be treated as described under "Granulomatosis with Polyangiitis."

SECONDARY VASCULITIS

DRUG-INDUCED VASCULITIS

Vasculitis associated with drug reactions usually presents as palpable purpura that may be generalized or limited to the lower extremities or other dependent areas; however, urticarial lesions, ulcers, and hemorrhagic blisters may also occur (**Chap. 60**). Signs and symptoms may be limited to the skin, although systemic manifestations such as fever, malaise, and polyarthralgias may occur. Although the skin is the predominant organ involved, systemic vasculitis may result from drug reactions. Drugs that have been implicated in vasculitis include allopurinol, thiazides, gold, sulfonamides, phenytoin, and penicillin (**Chap. 60**).

An increasing number of drugs have been reported to cause vasculitis associated with ANCA. Of these, the best evidence of causality exists for hydralazine and propylthiouracil. The clinical manifestations in ANCA-positive drug-induced vasculitis can range from cutaneous lesions to glomerulonephritis and pulmonary hemorrhage. Outside of drug discontinuation, treatment should be based on the severity of the vasculitis. Patients with immediately life-threatening small-vessel vasculitis should initially be treated with glucocorticoids and cyclophosphamide as described for granulomatosis with polyangiitis. Following clinical improvement, consideration may be given for tapering such agents along a more rapid schedule.

SERUM SICKNESS AND SERUM SICKNESS-LIKE REACTIONS

These reactions are characterized by the occurrence of fever, urticaria, polyarthralgias, and lymphadenopathy 7–10 days after primary exposure and 2–4 days after secondary exposure to a heterologous protein (classic serum sickness) or a nonprotein drug such as penicillin or sulfa (serum sickness-like reaction). Most of the manifestations are not due to a vasculitis; however, occasional patients will have typical cutaneous venulitis that may progress rarely to a systemic vasculitis.

VASCULITIS ASSOCIATED WITH OTHER UNDERLYING DISEASES

Certain infections may directly trigger an inflammatory vasculitic process. For example, rickettsias can invade and proliferate in the endothelial cells of small blood vessels causing a vasculitis (**Chap. 187**). In addition, the inflammatory response around blood vessels associated with certain systemic fungal diseases such as histoplasmosis (**Chap. 212**) may mimic a primary vasculitic process. A leukocytoclastic vasculitis predominantly involving the skin with occasional involvement of other organ systems may be a minor component of many other infections. These include *subacute bacterial endocarditis*, *Epstein-Barr virus infection*, *HIV infection*, and a number of other infections.

Vasculitis can be associated with certain malignancies, particularly lymphoid or reticuloendothelial neoplasms. Leukocytoclastic venulitis confined to the skin is the most common finding; however, widespread systemic vasculitis may occur. Of particular note is the association of *hairy cell leukemia* (**Chap. 110**) with polyarteritis nodosa.

A number of connective tissue diseases have vasculitis as a secondary manifestation of the underlying primary process. Foremost among these are *systemic lupus erythematosus* (**Chap. 356**), *rheumatoid arthritis* (**Chap. 358**), *inflammatory myositis* (**Chap. 365**), *relapsing polychondritis* (**Chap. 366**), and *Sjögren's syndrome* (**Chap. 361**). The most common form of vasculitis in these conditions is the small-vessel venulitis isolated to the skin. However, certain patients may develop a fulminant systemic necrotizing vasculitis.

Secondary vasculitis has also been observed in association with *ulcerative colitis*, *congenital deficiencies of various complement components*, *sarcoidosis*, *primary biliary cirrhosis*, α_1 -*antitrypsin deficiency*, and *intestinal bypass surgery*.

FURTHER READING

- Buttgereit F et al: Polymyalgia rheumatica and giant cell arteritis: A systematic review. *JAMA* 315:2442, 2016.
- Fauci AS et al: Wegener's granulomatosis: Prospective clinical and therapeutic experience with 85 patients for 21 years. *Ann Intern Med* 98:76, 1983.
- Finkelman JD et al: Antiproteinase 3 antineutrophil cytoplasmic antibodies and disease activity in Wegener granulomatosis. *Ann Intern Med* 147:611, 2007.
- Guillemin L et al: Churg-Strauss syndrome. Clinical study and long-term follow-up of 96 patients. *Medicine (Baltimore)* 78:26, 1999.
- Hoffman GS et al: Wegener granulomatosis: An analysis of 158 patients. *Ann Intern Med* 16:488, 1992.
- Jayne D et al: A randomized trial of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoantibodies. *N Engl J Med* 349:36, 2003.
- Jayne DRW et al: Avacopan for the treatment of ANCA-associated vasculitis. *N Engl J Med* 18:599, 2021.
- Jennette JC et al: 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. *Arthritis Rheum* 65:1, 2013.
- Kerr GS et al: Takayasu arteritis. *Ann Intern Med* 120:919, 1994.
- Langford CA et al: A randomized, double-blind trial of abatacept (CTLA-4Ig) for the treatment of giant cell arteritis. *Arthritis Rheumatol* 69:837, 2017.
- Pagnoux C et al: Clinical features and outcomes in 348 patients with polyarteritis nodosa: A systematic retrospective study of patients diagnosed between 1963 and 2005 and entered into the French Vasculitis Study Group Database. *Arthritis Rheum* 62:616, 2010.
- Stone JH et al: Rituximab versus cyclophosphamide for ANCA-associated vasculitis. *N Engl J Med* 363:221, 2010.
- Stone JH et al: Trial of tocilizumab in giant-cell arteritis. *N Engl J Med* 377:317, 2017.
- Walsh M et al: Plasma exchange and glucocorticoids in severe ANCA-associated vasculitis. *N Engl J Med* 382:622, 2020.
- Wechsler ME et al: Mepolizumab or placebo for eosinophilic granulomatosis with polyangiitis. *N Engl J Med* 376:1921, 2017.
- Weyand CM, Goronzy JJ: Clinical practice. Giant-cell arteritis and polymyalgia rheumatica. *N Engl J Med* 371:50, 2014.

364

Behçet Syndrome

Yusuf Yazıcı



Behçet syndrome is a systemic vasculitis, first described by Hulusi Behçet, a Turkish dermatologist. It can present with skin and mucosal lesions, uveitis, arthritis, major arterial and venous vessel disease, and gastrointestinal and neurologic manifestations. These manifestations can be present in various combinations and sequences over time. Patients are most commonly from the Middle East, the Mediterranean region, and the Far East; it is most prevalent in Turkey, with a prevalence of 1 in 250 adults. It is relatively rare before the late teens and after age 50. Males and females are equally affected; however, males frequently have more severe disease and poorer outcomes. Some manifestations may show regional differences; for example, gastrointestinal involvement, rare in Turkey, is more common in Japan and is seen in ~30% of patients in the United States.

DIAGNOSIS

Behçet syndrome is diagnosed clinically. There are no specific laboratory, imaging, or histologic features that can help in the diagnosis of a patient with suggestive symptoms, and the diagnosis is based on a combination of clinical features in the setting of ruling out other potential causes. In this regard, some patients may require months to years to develop the array of symptoms that would lead to a definitive diagnosis, although a tentative diagnosis may be made well before. The most commonly used and best performing diagnostic criteria are the International Study Group (ISG) criteria (sensitivity ~95%, specificity ~96%); patients need to have recurrent oral ulcers plus two of the following four clinical manifestations: recurrent genital ulcers, skin lesions, eye lesions, or a positive pathergy test (**Table 364-1**). Additional clinical manifestations may involve various organ systems, including the gastrointestinal, vascular, pulmonary, and central nervous systems. Up to 50–60% of patients, depending on where they are from, can be positive for HLA B*51; however, it is not used as a diagnostic test because it is also found in up to 20% of the normal population.

PATHOGENESIS

The pathogenesis and etiology of Behçet syndrome are unknown. Family studies show a possible genetic predisposition, and increased inflammation and immunologic mechanisms play a role. Both innate and adaptive immune systems may be involved. Unlike other autoimmune diseases, however, Behçet syndrome is not typically associated with autoantibodies, Raynaud's phenomenon, Sjögren's syndrome, thrombocytopenia, hemolytic anemia, sun hypersensitivity, serosal involvement, or an increased risk for other autoimmune diseases. On the other hand, features that separate it from autoinflammatory

TABLE 364-1 International Study Group Criteria for the Diagnosis of Behçet Syndrome

CRITERIA	FREQUENCY	COMMENTS
Oral ulcers	~98%	3 times in a 12-month period
Plus 2 out of 4 from below:		
Recurrent genital ulcers	~80%	Usually scarring
Skin lesions	~80%	Erythema nodosum, pseudofolliculitis, papulopustular or acneiform nodules (postadolescent, not receiving corticosteroids)
Eye lesions	~50%	Anterior/posterior uveitis cells in vitreous or retinal vasculitis
Pathergy	~50%	24–48 h, after dermal insertion of a 20-gauge needle

conditions include tendency to abate with time, absence of mutations associated with autoinflammatory diseases, and higher prevalence than typical autoinflammatory diseases such as familial Mediterranean fever ([Chap. 369](#)). There is neutrophil hyperreactivity; however, it is not clear whether this is primary or secondary to cytokine-directed activation. There is also evidence from retrospective patient cohort analyses that there may be different clusters of disease presentation; for example, acne lesions are more commonly seen with arthritis and associated with enthesitis, and each of these clusters may have a different pathogenesis.

CLINICAL PRESENTATION

The most common symptoms are associated with mucocutaneous tissues. Oral ulcers are seen in virtually all patients and are commonly the first manifestation. Commonly, like ordinary cancer sores, they are usually multiple. They last around 10 days but recur unless treated. Only the uncommon, major ulcers tend to scar. Beneficial effects of dental and periodontal therapies suggest that decreased oral health is associated with disease severity.

Genital ulcers are the most specific lesions, most commonly occurring on the scrotum or labia. They are larger and deeper and take longer to heal than oral ulcers and tend to form scars.

Acne-like or papulopustular lesions are indistinguishable from acne vulgaris in appearance and pathology. They are seen both at the usual acne sites as well as at uncommon sites such as lower extremities. Other skin findings are the nodular lesions, which are of two types: erythema nodosum lesions due to panniculitis and superficial vein thromboses. Superficial thrombophlebitis often occurs in men and is associated with deep-vein thrombosis; it should trigger workup for other vascular involvement, including pulmonary artery aneurysms.

Pathergy reaction is a nonspecific hyperreactivity of the skin to trauma. Typically, a papule or pustule forms in 24–48 h after a needle prick. It is rather unique for Behçet syndrome and is part of the ISG diagnostic criteria.

Arthralgia or arthritis is seen in about half of patients; it is usually a mono- or oligoarthritis in the lower extremities and does not usually cause deformity or erosions.

Eye involvement is seen in half of all patients and in ~70% of males. It is most commonly a bilateral panuveitis. A hypopyon, seen in ~10% of patients with eye disease, is an intense inflammation in the anterior chamber and is quite specific for Behçet syndrome. Ocular involvement develops usually in the first 2 years after fulfillment of diagnostic criteria and is most severe during the first few years and then tends to abate. Male gender, posterior involvement, frequent attacks (>3 per year), strong vitreous opacity, and macular edema are poor prognostic factors.

Vascular disease is seen in up to 40% of patients. It is associated with intensive thrombosis and runs a relapsing course. Several well-defined venous vascular associations are seen, and superficial and deep-vein thrombosis, Budd-Chiari syndrome, inferior vena cava syndrome, pulmonary artery involvement, intracardiac thrombosis, and cerebral venous sinus thrombosis frequently cluster in various combinations. Pulmonary artery aneurysms carry a 5-year mortality rate of 20–25%.

Prevalence of neurologic involvement is ~5%, with about three-quarters of patients presenting with parenchymal involvement, while the remaining cases present with cerebral venous sinus thrombosis. These two forms only rarely occur together. Parenchymal involvement usually affects the telencephalic-diencephalic junction, brainstem, and spinal cord. Patients may present with a subacute onset of severe headache, cranial nerve palsy, dysarthria, ataxia, and hemiparesis.

Prevalence of gastrointestinal involvement changes significantly across different populations (up to 50% in the Far East but rare in the

Middle East). Clinical and endoscopic appearance of intestinal involvement can be similar to, and thus cannot easily be differentiated from, Crohn's disease. Ulcers tend to be single or less than five, are usually confined to the ileocecal area, are more likely to be deep and round, and are prone to perforate; perianal and rectal area involvement is rare. In practice, it is difficult to distinguish Behçet syndrome from Crohn's disease unless extraintestinal lesions are present.

TREATMENT

Behçet Syndrome

Treatment is guided by type and severity of involvement, with the goal of preventing long-term damage. Most new manifestations present within the first 5 years, and for most patients, the natural course is one of diminishing symptoms culminating in potential remission, frequently not requiring ongoing treatment with medications. Patient characteristics, such as being young and male, need to be kept in mind as these patients tend to have a worse prognosis. For most patients, tapering and/or stopping their medications in 2–3 years after the symptoms have improved should be attempted.

Oral ulcers can be managed with topical glucocorticoids and on an as-needed basis if mild. Lesions resistant to local measures may require systemic treatment with colchicine, oral glucocorticoids, immunosuppressants such as apremilast, azathioprine, or a tumor necrosis factor- α inhibitor such as infliximab. Apremilast has now been approved in the United States and Japan for the treatment of oral ulcers of Behçet syndrome. A similar treatment approach can be used for genital ulcers and other mucocutaneous manifestations. Patients may need a combination of medications, at least initially, to control disease activity.

Eye involvement, given its frequency and potential morbidity, requires early and aggressive treatment with brief courses of glucocorticoids and longer-term treatment with an immunosuppressant. Azathioprine is usually the preferred agent. Infliximab, adalimumab, or cyclosporine can also be used, in combination with systemic glucocorticoids and azathioprine, for control of disease activity. Monotherapy with interferon is another option. Glucocorticoids can be tapered in many patients after active disease has been controlled, whereas immunosuppressants are generally continued for at least 2 years.

Gastrointestinal involvement is treated with a glucocorticoid plus an immunosuppressant such as azathioprine alone or in combination with infliximab.

Venous thrombotic events are treated by controlling systemic inflammation with immunosuppressive medications (usually azathioprine or, for more severe cases, cyclophosphamide), rather than using anticoagulants. However, if venous thrombotic events occur, standard anticoagulation treatment can be given, provided there is a low risk of bleeding and there are no coexistent pulmonary artery aneurysms. For central nervous system involvement, the combination of azathioprine and a tumor necrosis factor inhibitor is usually the first choice.

FURTHER READING

- Hatemi G et al: 2018 update of the EULAR recommendations for the management of Behçet's syndrome. *Ann Rheum Dis* 77:808, 2018.
- Kural-Seyahi E et al: The long-term mortality and morbidity of Behçet syndrome: A 2-decade outcome survey of 387 patients followed at a dedicated center. *Medicine (Baltimore)* 82:60, 2003.
- Yazici H et al: Behçet syndrome: A contemporary view. *Nat Rev Rheumatol* 14:107, 2018.

This chapter focuses on the major types of inflammatory myopathies (IMs), including dermatomyositis (DM), polymyositis (PM), immune-mediated necrotizing myopathy (IMNM), antisynthetase syndrome (AS), and inclusion body myositis (IBM) (**Table 365-1**). Other IMs include those caused by infection, eosinophilic myositis, granulomatous myositis, and myositis triggered by checkpoint inhibitors. Of note, inflammatory cell infiltrates can also be occasionally seen in muscle biopsies in hereditary (e.g., muscular dystrophies, metabolic myopathies) and toxic myopathies.

Epidemiologic studies suggest that the incidence of IM grouped together is >4 cases per 100,000 with prevalence in the range of 14–32 per 100,000. Defining the actual incidence and prevalence of the individual myosites is limited, however, by the different diagnostic

criteria employed in various epidemiologic studies, increasing recognition of AS, and frequent misdiagnosis of IBM and IMNM. Idiopathic PM without signs of an overlap syndrome is quite rare, while DM, IBM, and IMNM occur in roughly similar frequencies. DM can occur in children (juvenile DM), while IBM always occurs in adults and is the most common cause of myopathy in those aged >50. DM, PM, and AS are more common in women, while IBM is more common in men.

DIAGNOSTIC APPROACH AND DIFFERENTIAL DIAGNOSIS

The approach to patients with suspected myopathy is detailed in **Chap. 449**. In any patient presenting with weakness, the first step is to localize the site of the lesion by history and clinical findings (**Chap. 24**). Weakness could be caused by a process in the cerebral hemispheres, spinal cord (**Chap. 442**), anterior horn cell (**Chap. 437**), peripheral nerve (**Chaps. 446–447**), neuromuscular junction (**Chap. 448**), or muscle (**Chap. 449**). Past medical history, medication use, and family history, combined with a detailed clinical examination and an appreciation for the pattern of muscle involvement (e.g., what muscles are weak and atrophic or hypertrophic as well as the presence of scapular winging, early contractures, sensory abnormalities, fasciculations, or rash), help

TABLE 365-1 Inflammatory Myopathies: Clinical and Laboratory Features

DISORDER	SEX	AGE OF ONSET	RASH	PATTERN OF WEAKNESS	LABORATORY FEATURES	MUSCLE BIOPSY	CELLULAR INFILTRATE	RESPONSE TO IS THERAPY	COMMON ASSOCIATED CONDITIONS
DM	F > M	Childhood and adult	Yes	Proximal > distal	Normal or increased CK (up to 50× normal or higher); various MSAs (anti-MDA5, anti-TIF1, anti-MI-2, anti-NXP2)	Perimysial and perivascular inflammation; IFN-1 regulated proteins (MHC-1, MxA), MAC deposition on capillaries	CD4+ dendritic cells; B cells; macrophages	Yes	Myocarditis, ILD, malignancy, vasculitis, other CTDs
PM	F > M	Adult	No	Proximal > distal	Increased CK (up to 50× normal or higher)	Endomysial and perivascular inflammation; ubiquitous expression of MHC-1	CD8+ T cells; macrophages; plasma cells	Yes	Myocarditis, ILD, other CTDs
NM	M = F	Children and adults	No	Proximal > distal	Elevated CK (>10× normal or higher); anti-HMGCR or anti-SRP antibodies	Necrotic muscle fibers; minimal inflammatory infiltrate	Macrophages in necrotic fibers undergoing phagocytosis	Yes	Malignancy, CTD, HMGCR antibody cases can be triggered by statin use
AS	F > M	Children and adults	Sometimes	Proximal > distal	Elevated CK (>10× normal or higher); antisynthetase antibodies	Perimysial and perivascular inflammation; perimysial fragmentation with alkaline phosphatase staining; perimysial muscle damage with necrosis	CD4+ dendritic cells; B cells; macrophages	Yes	Nonerosive arthritis, ILD, Raynaud's phenomenon, mechanic hands, and fever
IBM	M > F	Older adults (>50 years)	No	Proximal and distal; predilection for: finger/wrist flexors, knee extensors	Normal or mildly increased CK (usually <10× normal); anti-cN-1A antibodies; large granular lymphocytes on flow cytometry and reduced CD4/CD8 ratio with increased CD8 count	Endomysial and perivascular inflammation; ubiquitous expression of MHC-1; rimmed vacuoles; p62, LC3, TDP-43 aggregates; EM: 15–18 nm tubulofilaments; ragged red and COX-negative fibers	CD8+ T cells; macrophages; plasma cells; myeloid dendritic cells; large granular lymphocytes	None or minimal	Granular lymphocytic leukemia/lymphocytosis, sarcoidosis, sicca or Sjögren's syndrome

Abbreviations: CK, creatine kinase; cN-1A, cytosolic 5'-nucleotidase 1A; CTDs, connective tissue diseases; COX, cytochrome oxidase; DM, dermatomyositis; F, female; g, immunoglobulin; IBM, inclusion body myositis; IFN-1, type 1 interferon; ILD, interstitial lung disease; IS, immunosuppressive; M, male; MAC, membrane attack complex; MDA5, melanoma differentiation antigen; MHC-1, major histocompatibility antigen 1; MSA, myositis-specific autoantibodies; NCP2, nuclear matrix protein 2 (NXP2); NM, necrotizing myopathy; PM, polymyositis; TIF1, transcriptional intermediary factor 1.

Source: From AA Amato, JA Russell (eds): *Neuromuscular Disorders*, 2nd ed. New York, McGraw-Hill Education; 2016, Table 33-1, p. 824, with permission.

differentiate myopathies from other neuromuscular disorders and the different types of myopathies from each other (see Chap. 449). For example, atrophy with fasciculations suggests a neurogenic process such as amyotrophic lateral sclerosis, fatigable weakness on examination points to a neuromuscular junction defect such as myasthenia gravis, and concomitant sensory symptoms suggest a central process such as a spinal cord disorder or a polyneuropathy. Scapular winging, calf hypertrophy or atrophy, and early contractures before significant weakness develops would strongly suggest a muscular dystrophy, particularly if there is a positive family history. A heliotrope rash combined with Gottron papules and dilated nailfold capillaries is diagnostic for DM. The presence of atrophy and weakness of the flexor forearm muscles and quadriceps in a person aged >50 years is most likely IBM.

When the site of the lesion cannot be localized based on history and clinical examination alone, laboratory testing is required. Serum creatine kinase (CK) is the most sensitive laboratory marker of muscle destruction. Not all myopathies are associated with elevated CK levels, but a markedly elevated CK (e.g., >2000 U/L) is almost always due to a myopathy. A slightly elevated CK can also be seen in neurogenic disorders, however. Myositis-associated and myositis-specific antibodies (MSAs) help to distinguish subtypes of IM, as discussed below. Electromyography (EMG) and nerve conduction studies (NCS) are useful in localizing the site of the lesion but are less specific in helping to determine the actual cause of a myopathy. EMG can be useful at times in guiding what muscle to biopsy, especially if muscles typically biopsied are normal on clinical examination. Imaging skeletal muscle can be helpful in assessing muscle involvement and revealing fatty replacement, atrophy, or edema within muscle or surrounding fascia.

A muscle biopsy is usually required to definitively distinguish one myopathy from another. The different forms of IM can have distinctive histopathologic abnormalities as discussed below. In a patient with a

classic DM rash, a muscle or skin biopsy can be performed, but an argument can also be made that biopsy is unnecessary—particularly if the patient also has an MSA specific for DM. However, a muscle biopsy should be performed in every case of suspected PM to exclude IBM (if not clinically apparent) and other causes of myopathy. Diagnosis of IMNM is by definition based upon histologic findings. It is important to biopsy a muscle that is clinically affected but not too weak (e.g., Medical Research Council grade 4 out of 5 in strength); otherwise, one may just see end-stage muscle. A biopsy should always be coordinated with an experienced muscle histopathology laboratory.

Patients with severe muscle pain, subjective weakness, and fatigue with normal strength and function on examination are not likely to have an IM. Polymyalgia rheumatica should be considered in older individuals with an elevated erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) but normal CK and EMG. Fibromyalgia is likely in patients with a normal laboratory workup. In general, a muscle biopsy is not indicated unless there is objective weakness, an abnormal EMG, or elevated CK.

SPECIFIC DISORDERS

DERMATOMYOSITIS

Clinical Features DM manifests with symmetric, proximal greater than distal weakness along with a characteristic rash that includes the heliotrope rash (erythematous discoloration of eyelids with periorbital edema), Gottron sign (erythematous rash over the extensor surfaces of joints such as the knuckles, elbows, knees, and ankles), Gottron papules (raised erythematous rash over knuckles) (Fig. 365-1), V-sign (rash on the sun-exposed anterior neck and chest), shawl sign over the back of the neck and shoulders, nail bed telangiectasias, and subcutaneous calcium deposits. The weakness and rash usually accompany one another but can be separated by several months. Furthermore, there is a spectrum of involvement such that some patients continue to manifest only with a rash (amyopathic DM), while others may present mainly with weakness and little or no visible skin changes. Patients can also complain of myalgias, arthralgias, dysphagia, and dysarthria. Cutaneous disease activity is highly relevant in DM; in comparison to other debilitating skin diseases including cutaneous lupus erythematosus, psoriasis, and atopic dermatitis, skin symptoms in DM patients are associated with an overall reduction in life quality. Pruritus can be especially debilitating. Dyspnea can occur from ventilatory muscle weakness or intrinsic pulmonary problems including interstitial lung disease (ILD), bronchopneumonia, and alveolitis. Pulmonary manifestations are often associated with antisynthetase antibodies; myositis associated with the AS can be considered a distinct disorder (discussed below). DM can present in children (juvenile DM) or in adults. There is a higher risk for malignancy in adult-onset cases, ~15% within the first 2–3 years.

Laboratory Features Serum CK levels are elevated in 70–80% of patients; in 10% of those with normal CK, serum aldolase may be increased. Antinuclear antibodies can be positive but are a non-specific finding. DM is associated with several MSA targeting melanoma differentiation antigen 5 (MDA5), transcriptional intermediary factor 1 (TIF1), Mi-2, and



FIGURE 365-1 Cutaneous manifestations of dermatomyositis. **A.** Macular erythema plaques (Gottron sign) and erythematous papules (Gottron papules) on extensor surface of fingers and **B.** elbow. **C.** Macular erythema plaques over anterior neck and chest (V-sign) and **D.** the posterior neck, shoulder, and upper back (Shawl sign). **E.** Nail bed changes with dilated capillaries.

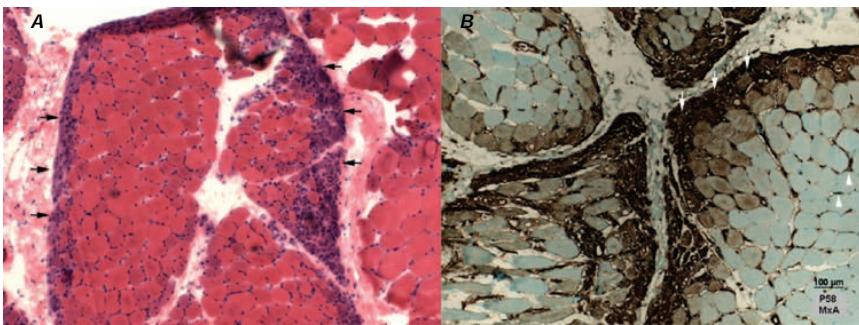


FIGURE 365-2 Perifascicular atrophy and myxovirus resistance protein A (MxA) expression in dermatomyositis. **A.** Perifascicular myofibers (black arrows) bordering on disrupted perimysial connective tissue are atrophic and basophilic on hematoxylin and eosin (H&E) stains. **B.** Perifascicular myofibers (white arrows) show intense staining for MxA protein along a gradient from superficial to deep; all capillaries show intense MxA expression (white arrowheads).

nuclear matrix protein 2 (NXP2). These antibodies are usually associated with characteristic clinical features. For example, anti-MDA5 antibodies are associated with amyopathic DM with severe palmar rash, digital ulcers, and rapidly progressive ILD. Anti-TIF1 (or p155) antibodies and anti-NXP2 antibodies are associated with an increased risk of cancer, while anti-Mi-2 antibodies are often associated with more benign DM and a favorable response to treatment.

EMG of weak muscles shows increased insertional and spontaneous activity in the form of positive sharp waves and fibrillation potentials, or complex repetitive discharges along with early recruitment of small amplitude, short duration, polyphasic motor units. These findings are nonspecific and can be seen in other myopathies. Skeletal muscle magnetic resonance imaging (MRI muscle) reveals edema in affected muscles and sometimes more specific findings of abnormalities of fascia suggesting fasciitis.

Histopathology and Pathogenesis The characteristic histopathologic abnormality on muscle biopsy is perifascicular atrophy (**Fig. 365-2A**); however, this is present in perhaps only 50% of patients. Immunohistochemical staining for myxovirus resistance protein A (MxA) is diagnostically more sensitive and highly specific (**Fig. 365-2B**). The inflammatory cell infiltrate is predominantly perivascular and located in the perimysium and is composed primarily of macrophages, B cells, and plasmacytoid dendritic cells (PDCs). Skin biopsies reveal cell-poor interface dermatitis, which is analogous to the perifascicular atrophy in that the basal layer of keratinocytes is most damaged; the inflammatory infiltrate is typically absent or minimal and, when present, is located mainly at the border zone of the dermis and epidermis.

The pathogenesis of DM was traditionally attributed to an antibody-mediated attack on endothelial cells, followed by complement-mediated destruction of capillaries and watershed ischemia of muscle fibers. However, recent studies suggest that this is not likely the case. Immunoglobulin deposition is largely absent on endothelial cells, and complement deposition may be a secondary phenomenon. There is increasing evidence that the microvasculopathy and skin and muscle damage associated with DM are primarily due to toxicity from type I interferon (IFN)-mediated pathways, most likely IFN- β .

Prognosis In the absence of malignancy, prognosis is generally favorable in patients with DM, with 5-year survival rates ranging from 70 to 93%. Poor prognostic features are increased age, associated ILD, cardiac disease, and late or previous inadequate treatment.

POLYMYOSITIS

Clinical Features PM is a heterogeneous group of disorders that usually presents with symmetric and proximal weakness that worsens over several weeks to months. As with DM, there can be associated heart, lung, and joint involvement as well as an increased risk of cancer. Some epidemiologic studies suggest that the risk of cancer in PM is less than that in DM, but these older series likely included patients with IBM and dystrophies with inflammation who were misdiagnosed as having PM.

Laboratory Features CK levels are always elevated in uncontrolled PM. A normal CK should alert clinicians to the possibility of IBM. As in DM, EMG and skeletal muscle imaging can be abnormal, but the findings are not specific (**Fig. 365-3**).

Histopathology and Pathogenesis Because PM is a heterogeneous category, muscle pathology varies substantially. Most often, patients with nonspecific inflammatory cells present in perimysial more often than endomysial locations have been categorized as PM. A small minority of patients have mononuclear inflammatory infiltrate that surrounds fibers with sarcolemmal major histocompatibility (MHC-I) expression (**Fig. 365-4**). There is debate as to whether true invasion of myofibers occurs in PM, or rather always indicates IBM. The inflammatory infiltrate predominantly consists of CD8+ T cells and macrophages located in the endomysial, perimysial, and perivascular regions. As PM is heterogeneous, its varied forms of pathogenesis are poorly understood.

Prognosis Most patients with PM improve with immunotherapies but usually require lifelong treatment. Some retrospective studies suggest that PM does not respond as well as DM to these therapies. However, many of these older series of “PM” likely included patients who actually had IMNM, IBM, or other myopathies (including muscular dystrophies) that do not respond to immunotherapies. As in DM, poor prognostic features are cancer, increased age, lung or cardiac involvement, and late or previously inadequate treatment.

OVERLAP SYNDROMES

The term *overlap syndrome* is applied when DM or PM is associated with other well-defined connective tissue diseases (CTDs) such as scleroderma, mixed connective tissue disease (MCTD), Sjögren's syndrome, systemic lupus erythematosus (SLE), or rheumatoid arthritis.

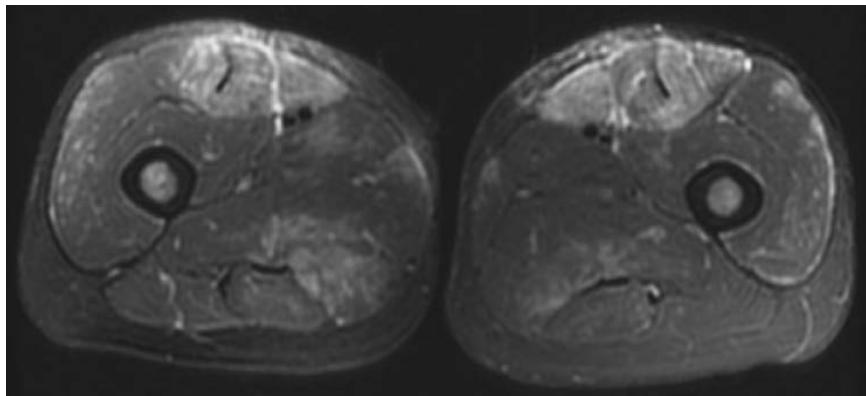


FIGURE 365-3 Skeletal muscle MRI with short T1 inversion recovery (STIR) imaging in polymyositis. MRI of the thigh demonstrates bright signal indicative of edema/inflammation, particularly in the rectus femoris muscle. This contrasts with MRI in IBM in which there is more selective involvement of the vastus lateralis and medialis with relative sparing of the rectus femoris (see Fig. 365-7F and G).

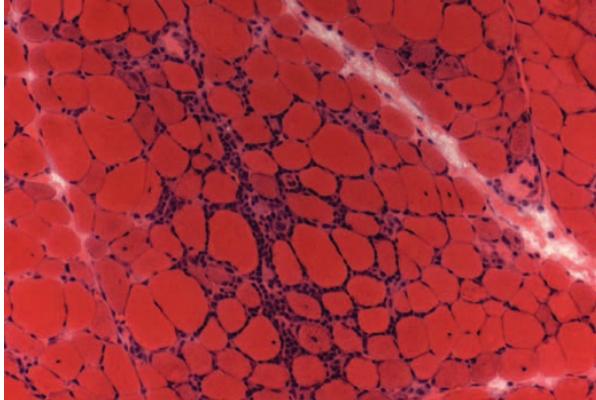


FIGURE 365-4 Pathology of polymyositis. Muscle biopsy demonstrates endomysial infiltrates surrounding nonnecrotic muscle fibers.

As in DM and PM, the myositis associated with these overlap syndromes is usually responsive to immunotherapies.

IMMUNE-MEDIATED NECROTIZING MYOPATHY

Clinical Features IMNM, or autoimmune necrotizing myopathy, is characterized by the acute or insidious onset of symmetric, proximal more than distal weakness. Dysphagia, dysarthria, or myalgia may occur. Patients may have an underlying CTD (usually scleroderma or MCTD) or cancer (paraneoplastic necrotizing myopathy), or the condition may be idiopathic. There are at least two distinct forms of IMNM associated with specific autoantibodies (anti-3-hydroxy-3-methyl-glutaryl-coenzyme reductase [HMGCR] and anti-signal recognition particle [SRP]). Anti-HMGCR myopathy can be seen in patients receiving statins, inhibitors of HMGCR, particularly in patients aged >50 years. However, anti-HMGCR myopathy can develop in children and young adults without a history of statin use and can mimic a limb girdle muscular dystrophy. Unlike the more common “toxic” myopathy associated with statin use, anti-HMGCR myopathy does not improve when statins are discontinued. Anti-SRP myopathies are notable for the presence of anti-SRP antibodies and a typically subacute, aggressive, and relatively refractory course.

Laboratory Features CK levels are markedly elevated (usually >10 × normal) in IMNM. As mentioned, IMNM can be associated with anti-HMGCR or anti-SRP antibodies. EMG often shows increased insertional and spontaneous activity, including myotonic discharges. Skeletal muscle imaging findings are nonspecifically abnormal.

Histopathology and Pathogenesis Muscle biopsies reveal multifocal necrotic and regenerating muscle fibers with a paucity of inflammatory cells (Fig. 365-5). However, some patients with anti-HMGCR myopathy have endomysial, macrophage-predominant infiltrates similar to what is seen in PM. Overexpression of MHC-I and membrane attack complex (MAC) may be evident on sarcolemma of nonnecrotic fibers and MAC deposition on capillaries. The pathogenesis of IMNM is not completely understood but may be complement mediated.

Prognosis IMNM is generally much more difficult to treat than either DM or PM, and aggressive immunotherapy is usually required. The progressive course despite immunotherapy and marked weakness with atrophy can lead to a misdiagnosis of a limb girdle muscular dystrophy. There may be an increased incidence of cancer in patients with anti-HMGCR myopathy; thus, patients should undergo a malignancy workup.

ANTISYNTHETASE SYNDROME

Clinical Features The presence of myositis, nonerosive arthritis, ILD, Raynaud's phenomenon, mechanic hands, and fever associated with antibodies against aminoacyl-tRNA synthetase constitute the AS. Some patients have an erythematous rash, and muscle biopsies share

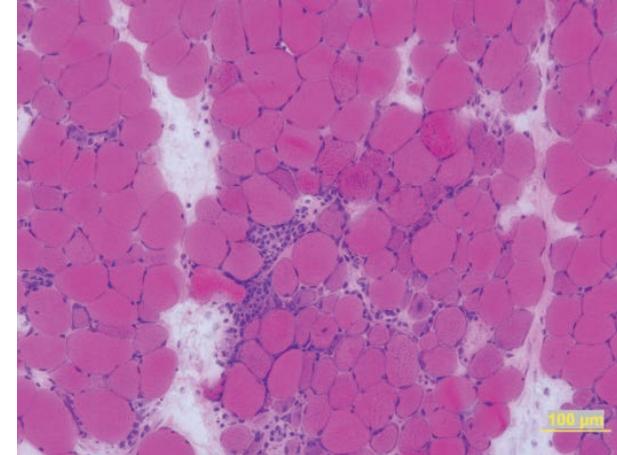


FIGURE 365-5 Pathology of immune-mediated necrotizing myopathy. Muscle biopsy demonstrates scattered necrotic fibers with inflammatory infiltrate confined to those fibers undergoing myophagocytosis along with a few regenerating fibers.

histopathologic features of DM, which likely accounts for many of these patients being classified as having DM.

Laboratory Features Antibodies against aminoacyl-tRNA synthetases are the most common MSA, present in 25–35% of patients with myositis. The most common aminoacyl-tRNA synthetase antibody is anti-Jo-1. CK is usually elevated in patients with AS and myositis. Those with ILD demonstrate reduced forced vital capacity and diffusion capacity on pulmonary function tests. Spiral chest CT scans are best at demonstrating the honeycomb pattern of ILD. Skeletal muscle MRI and EMG show abnormalities similar to DM, PM, and IMNM.

Histopathology and Pathogenesis Muscle biopsies demonstrate a predilection for perimysial damage including perimysial fragmentation and staining with alkaline phosphatase (Fig. 365-6), PDCs and macrophages in the perimysium and around blood vessels, and MAC deposition on capillaries. Also similar to DM, there is perifascicular muscle fiber damage, but with AS, there is more perifascicular muscle fiber necrosis compared to DM, in which perifascicular atrophy is more prominent. MHC-I and MAC deposits on muscle fibers may be seen on sarcolemma of perifascicular muscle fibers.

Prognosis Most patients respond to treatment, although responses are less complete than for DM and PM; ILD can be particularly refractory to treatment. Unlike DM, PM, and IMNM, there does not appear to be an increased risk of malignancy.

INCLUSION BODY MYOSITIS

Clinical Features IBM usually manifests in patients over the age of 50 years and is slightly more common in men than women. It is associated with slowly progressive weakness and muscle atrophy that has a predilection for early involvement of the wrist and finger flexors in the arms and quadriceps in the legs (Fig. 365-7). Weakness is often asymmetric. Dysphagia is common and rarely can be the presenting feature. These clinical features can help distinguish IBM from PM and other forms of myopathy. The mean duration from onset of symptoms to use of wheelchair or scooter is ~15 years. There is no known increased risk of malignancy.

Laboratory Features CK levels can be normal or only slightly elevated (usually <10 times normal). Antibodies targeting cytosolic 5'-nucleotidase 1A (cN-1A) are detected in the blood in a third to more than two-thirds of IBM patients and are a highly specific diagnostic biomarker for IBM among patients with myopathy. Other blood biomarkers for IBM include the presence of an abnormal population of large granular lymphocytes on flow cytometry and a reduced CD4/CD8 ratio with an increased CD8 count. Needle EMG may demonstrate large-amplitude, long-duration motor unit potentials that can be

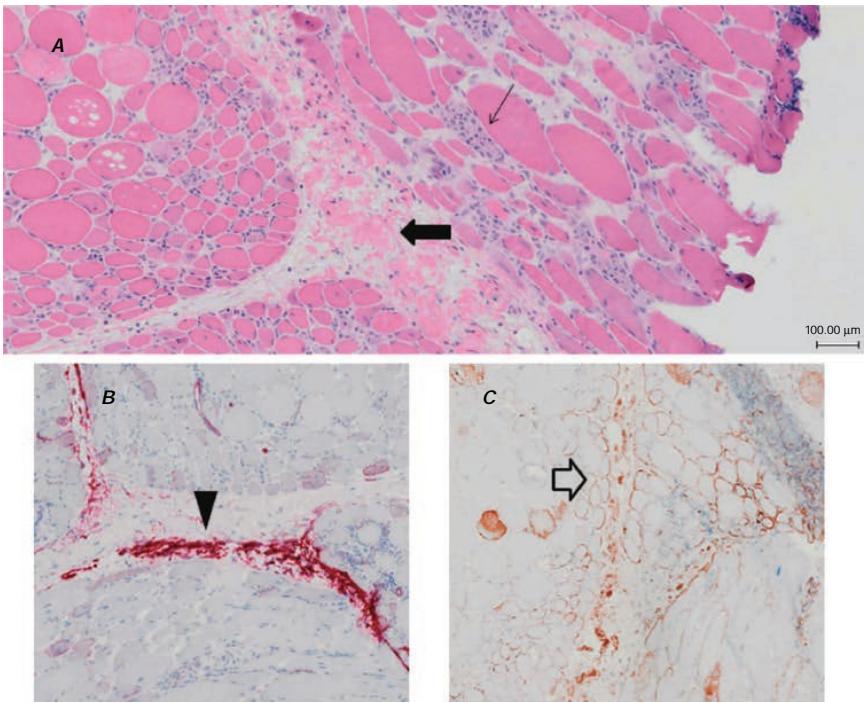


FIGURE 365-6 Pathology of myositis with anti-Jo-1 antibodies (antisynthetase syndrome). **A.** Perifascicular/perimysial muscle fiber atrophy and necrosis (thin arrow) associated with perimysial connective tissue is edematous and fragmented in appearance (thick arrow), hematoxylin and eosin stain. **B.** The perimysial connective tissue intensely stains red with alkaline phosphatase stain (arrowhead). **C.** Immunostaining demonstrates deposition of membrane attack complex (MAC) deposits on the sarcolemma of nonnecrotic perifascicular muscle fibers (open arrow).

misinterpreted as neurogenic but reflect the chronicity of the myopathy. Muscle MRI may show a predilection for involvement of the flexor digitorum profundus in the arms and the vastus medialis and lateralis muscles with sparing of the rectus femoris muscle.

Histopathology and Pathogenesis Muscle biopsies demonstrate endomysial inflammatory infiltrates predominantly composed of CD8+ T cells and macrophages surrounding and invading non-necrotic muscle fibers, MHC-1 expression on the sarcolemma, fibers

proteins including markers of endoplasmic reticulum (ER) stress and autophagy (e.g., p62 and LC3). Involvement of ER stress and autophagy has also been observed in other autoimmune diseases, such as primary biliary cholangitis (PBC), inflammatory bowel disease, and ankylosing spondylitis, some of which can be highly refractory to immunotherapy.

Prognosis The myopathy is slowly progressive and is not typically responsive to immunotherapies. Most patients require a scooter or wheelchair within 10–15 years of onset of symptoms.

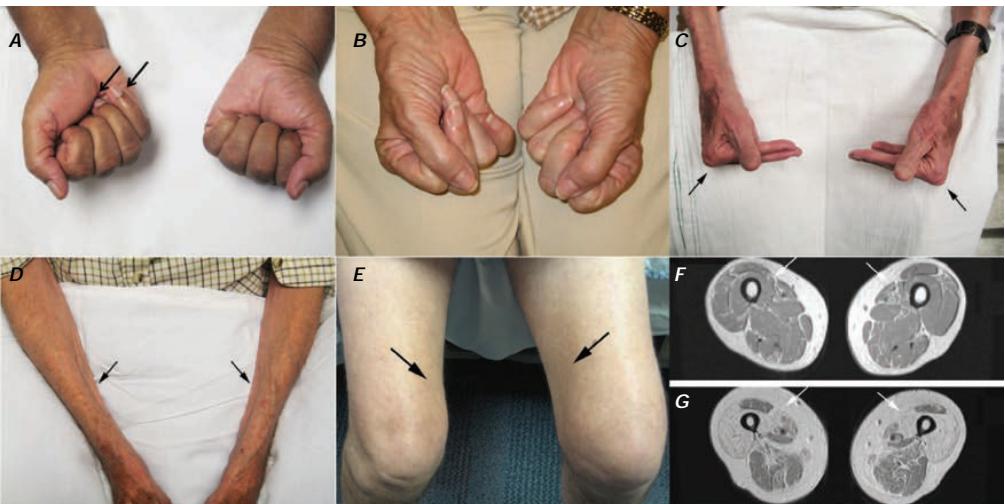


FIGURE 365-7 Muscle manifestations of inclusion body myositis (IBM; **A–C**). Finger flexor weakness can be (**A**) subtle and multifocal (black arrows), (**B**) moderate, or (**C**) severe. Note that even with complete paralysis of deep and superficial finger flexors, metacarpophalangeal joint flexion (arrows) is often maintained due to preservation of lumbricals. **D.** Ventral forearm atrophy (arrows). **E.** Atrophy of medial thighs due to loss of vastus medialis (arrows). **F.** Early IBM, with relatively preserved vastus medialis (arrows), in contrast to (**G**) advanced IBM with marked fibrous replacement of vastus medialis (arrows).

with rimmed vacuoles, cytochrome oxidase (COX)-negative fibers, and inclusions on light or electron microscopy (**Fig. 365-8**). The inclusions contain beta-sheet misfolded proteins (amyloid) but are difficult to appreciate with routine Congo red stain (they are seen on frozen but not paraffin sections). Immunostaining for p62 appears to be the most sensitive stain for detection of these inclusions. Importantly, rimmed vacuoles may not be seen in as many as 20–30% of muscle biopsies. In such cases, the presence of mitochondrial abnormalities (ragged red and COX-negative fibers) and immunostaining demonstrating p62 inclusions are helpful in distinguishing IBM from PM (aside from the clinical pattern of muscle weakness).

The pathogenesis of IBM is poorly understood. The marked adaptive immune system abnormalities related to T-cell inflammation and the presence of a relatively specific autoantibody against a muscle protein indicate an autoimmune attack on muscle. The chronic and highly inflammatory environment within muscles in IBM may alter protein synthesis and degradation pathways in part via aberrant immunoproteasome expression. Additional histologic features, typically referred to as “degenerative,” include aggregation of various

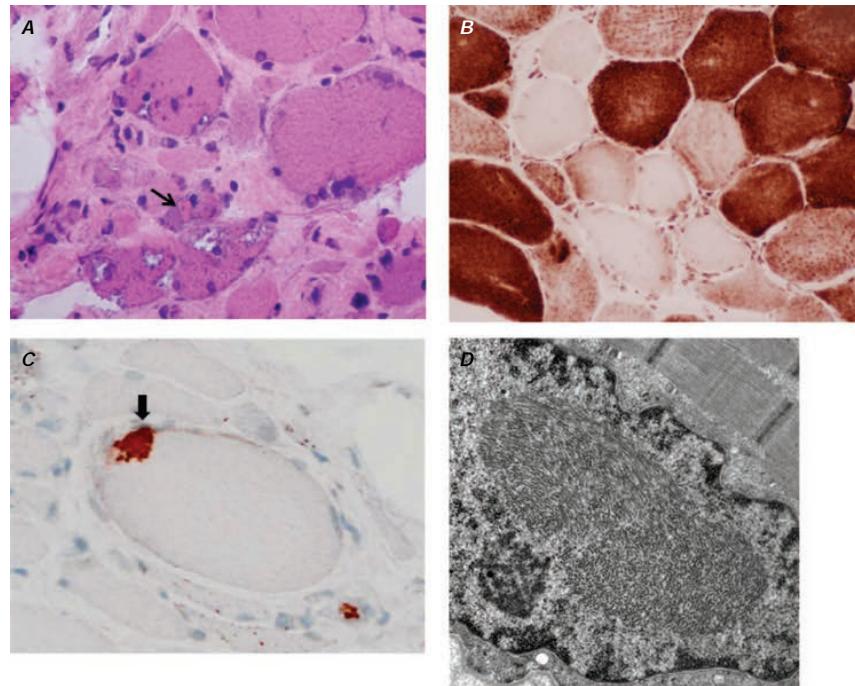


FIGURE 365-8 Pathology of inclusion body myositis. *A*, Scattered muscle fibers with rimmed vacuoles and rare fibers with eosinophilic inclusions (arrow), hematoxylin and eosin stain. *B*, Cytochrome oxidase stain demonstrates an increased number of pale-staining or COX-negative muscle fibers. *C*, Cytoplasmic inclusions stain positive with p62 within a muscle fiber (thick arrow). *D*, Electromicroscopy reveals 15- to 21-nm tubulofilamentous inclusions within a myonucleus.

TREATMENT OF THE IM (TABLE 365-2)

DM, PM, AS, and IMNM are typically responsive to immunotherapy. High-dose glucocorticoids (i.e., starting dose of prednisone 0.75–1.0 mg/kg per day) are considered the first-line treatment. There is uncertainty regarding when to start second-line agents (e.g., methotrexate, azathioprine, mycophenolate, immunoglobulin, or rituximab). The clinician must weigh with the patient the increased risks of immunosuppression versus possible benefits (e.g., faster improvement, steroid-sparing effect, and/or avoidance of the morbidities associated with long-term glucocorticoid use). We usually start a second-line agent (typically methotrexate) with glucocorticoids in patients with severe weakness or other organ system involvement (e.g., myocarditis, ILD), those with increased risk of steroid complications (e.g., diabetics, osteoporosis, or postmenopausal women), and patients with IMNM who are known to have difficult-to-treat myositis. In those in whom we initiate treatment with prednisone alone, a second-line agent is added in patients who fail to significantly improve after 2–4 months of treatment or in those who cannot be tapered to a low dose of prednisone.

Most patients with IMNM do not respond to prednisone alone or even prednisone plus a second-line agent in combination. Many require triple therapy with prednisone, methotrexate, and intravenous immunoglobulin (IVIG) and, if this fails, rituximab. Recent reports suggest that anti-HMGCR myopathy may respond to monotherapy with IVIG, and a large multicenter clinical trial to test this approach is underway. Additionally, muscle biopsies demonstrate deposition of membrane attack complexes on sarcolemma of nonnecrotic fibers in IMNM, suggesting that muscle destruction is complement mediated. In this regard, there is an ongoing international trial investigating the safety and efficacy of a complement inhibitor in anti-HMGCR and anti-SRP myopathies.

Unfortunately, IBM does not typically respond to any known immunotherapies. The mainstay of treatment is physical and occupational therapy to improve function and swallowing therapy (and sometimes esophageal dilation or cricopharyngeal myotomy) in those with dysphagia.

GENERAL GUIDELINES FOR USE OF SPECIFIC IMMUNOTHERAPIES

Glucocorticoids Treatment is initiated with prednisone (0.75–1.5 mg/kg up to 100 mg) administered as a daily morning single dose (the most common dose used in adults is 60 mg daily). In patients with severe weakness or comorbidities (e.g., ILD, myocarditis), treatment with a short course of intravenous methylprednisolone (1 g daily for 3 days) is recommended prior to starting oral glucocorticoids. Patients are generally maintained on high-dose prednisone until strength normalizes or until improvement in strength has reached a plateau (usually 3–6 months). Subsequently, prednisone can be tapered by 5 mg every 2–4 weeks. Once the dose is reduced to 20 mg every day or every other day, the taper is slowed to 2.5 mg every 2–4 weeks. The goal is to taper prednisone to ≤10 mg daily. Although most patients improve, the response may not be complete and many will require at least a small dose of prednisone or a second-line agent to have a sustained remission. Serum CK levels are monitored; however, dose adjustments of prednisone and other immunotherapies are primarily based on the objective clinical examination and not the CK levels or the patients' subjective response. When no response is noted after an adequate trial of high-dose prednisone, alternative diagnoses (e.g., IBM or an inflammatory muscular dystrophy) and a repeat muscle biopsy should be considered.

Relapse of the myositis needs to be distinguished from steroid myopathy. Features suggesting a steroid myopathy include weakness developing while on high dosage, a normal serum CK, clinical features of steroid excess such as ecchymoses and “moon facies,” and absence of muscle membrane irritability on EMG. By contrast, patients experiencing relapse of myositis may become weaker during the prednisone taper, have increasing serum CK levels, and display abnormal spontaneous activity on EMG.

SECOND-LINE THERAPIES

Methotrexate Methotrexate is usually the second-line treatment of choice because most authorities believe it works faster than other

TABLE 365-2 Immunotherapies for Inflammatory Myopathies

THERAPY	ROUTE	DOSE	SIDE EFFECTS	MONITOR
Prednisone	Oral	0.75–1.5 mg/kg per day to start	Hypertension, fluid and weight gain, hyperglycemia, hypokalemia, cataracts, gastric irritation, osteoporosis, infection, aseptic femoral necrosis	Weight, blood pressure, serum glucose/potassium, cataract formation
Methylprednisolone	Intravenous	1 g in 100 mL/normal saline over 1–2 h, daily or every other day for 3–6 doses	Arrhythmia, flushing, dysgeusia, anxiety, insomnia, fluid and weight gain, hyperglycemia, hypokalemia, infection	Heart rate, blood pressure, serum glucose/potassium
Azathioprine	Oral	2–3 mg/kg per day; single a.m. dose	Flu-like illness, hepatotoxicity, pancreatitis, leukopenia, macrocytosis, neoplasia, infection, teratogenicity	Blood count, liver enzymes
Methotrexate	Oral	7.5–20 mg weekly, single or divided doses; 1 day a week dosing	Hepatotoxicity, pulmonary fibrosis, infection, neoplasia, infertility, leukopenia, alopecia, gastric irritation, stomatitis, teratogenicity	Liver enzymes, blood count
	Subcutaneously	20–50 mg weekly; 1 day a week dosing	Same as oral	Same as oral
Cyclophosphamide	Oral Intravenous	1.5–2 mg/kg per day; single a.m. dose 0.5–1.0 g/m ² per month × 6–12 months	Bone marrow suppression, infertility, hemorrhagic cystitis, alopecia, infections, neoplasia, teratogenicity	Blood count, urinalysis
Cyclosporine	Oral	4–6 mg/kg per day, split into two daily doses	Nephrotoxicity, hypertension, infection, hepatotoxicity, hirsutism, tremor, gum hyperplasia, teratogenicity	Blood pressure, creatinine/BUN, liver enzymes, cyclosporine levels
Tacrolimus	Oral	0.1–0.2 mg/kg per day in two divided doses	Nephrotoxicity, hypertension, infection, hepatotoxicity, hirsutism, tremor, gum hyperplasia, teratogenicity	Blood pressure, creatinine/BUN, liver enzymes, tacrolimus levels
Mycophenolate mofetil	Oral	Adults (1–1.5 g BID) Children (600 mg/m ² per dose BID) (no >1 g/d in patients with renal failure)	Bone marrow suppression, hypertension, tremor, diarrhea, nausea, vomiting, headache, sinusitis, confusion, amblyopia, cough, teratogenicity, infection, neoplasia	Blood count
Intravenous immunoglobulin	Intravenous	2 g/kg over 2–5 days; then 1 g/kg every 4–8 weeks as needed	Hypotension, arrhythmia, diaphoresis, flushing, nephrotoxicity, headache, aseptic meningitis, anaphylaxis, stroke	Heart rate, blood pressure, creatinine/BUN
Rituximab	Intravenous	A course is typically 750 mg/m ² (up to 1 g) and repeated in 2 weeks Courses are then repeated usually every 6–18 months	Infusion reactions (as per IVIG), infection, progressive multifocal leukoencephalopathy	Some check B-cell count prior to subsequent courses (but this may not be warranted)

Abbreviations: BUN, blood urea nitrogen; IVIG, intravenous immunoglobulin.

Source: From AA Amato, JA Russell (eds): *Neuromuscular Disorders*, 2nd ed. New York, McGraw-Hill Education; 2016, Table 33-8, p. 859, with permission.

agents. An oral dose of 5 or 7.5 mg/week is initiated and then gradually increased as needed up to 25 mg/week. If there is no improvement after 1 month of 25 mg/week of oral methotrexate, a switch to weekly parenteral (usually subcutaneous) methotrexate is the next step, with dose escalation by 5 mg weekly; only rarely is a dose >35 mg/week used. The major side effects of methotrexate are alopecia, stomatitis, ILD, teratogenicity, oncogenicity, risk of infection, and pulmonary fibrosis, along with bone marrow, renal, and liver toxicity. Patients are concomitantly treated with folate or folic acid.

Azathioprine A recommended initial dose is 50 mg/d in adults, which can be increased by 50 mg every 2 weeks up to 2–3 mg/kg per day. Approximately 12% of patients develop a systemic reaction characterized by fever, abdominal pain, nausea, vomiting, and anorexia that requires discontinuation of the drug. The major practical limitation of azathioprine is that 6–18 months of treatment are usually required before benefit can be seen. Patients can be prescreened for thiopurine methyltransferase (TPMT) deficiency that is associated with severe bone marrow toxicity from this drug.

Mycophenolate Mofetil This drug inhibits the proliferation of T and B lymphocytes by blocking purine synthesis. It appears to be effective in different forms of myositis and is the second-line treatment of choice for myositis patients with ILD. The starting dose is 1.0 g twice daily and can be increased to 3 g daily in divided doses, if necessary. Mycophenolate is excreted through the kidneys; therefore, the dose should be decreased (no >1 g/d total dose) in patients with renal insufficiency. An advantage of mycophenolate compared to other immunosuppressive agents is the lack of renal or hepatic toxicity.

Intravenous Immunoglobulin IVIG is used in patients refractory to prednisone and at least one second-line immunosuppressive agent, although recent reports suggest that it may be the treatment of choice and effective as a monotherapy in anti-HMGCR myopathy. A dose of 2 g/kg is divided over 2–5 days, and repeat infusions are given at monthly intervals for at least 3 months. Subsequently, intervals can be lengthened or dosage decreased: 2 g/kg every 2 months or 1 g/kg per month.

Rituximab Rituximab is a monoclonal antibody directed against CD20+ B cells. A large randomized controlled trial found no benefit, but there were flaws in the study design. Most authorities feel that rituximab can be beneficial in some patients who are refractory to prednisone and at least one of the other second-line agents. The typical dosage is 750 mg/m² (up to 1 g) IV with a second infusion 2 weeks later and with repeat courses (375 mg/m² as a single infusion or with a second infusion 2 weeks apart) every 6–18 months as needed.

MYOSITIS ASSOCIATED WITH CHECKPOINT INHIBITORS

Autoimmune neurologic complications, including inflammatory neuropathy, myasthenia gravis, and myositis, can occur with use of immune checkpoint inhibitors (anti-CTLA-4, anti-PD-1, and anti-PD-L1) to treat various cancers (see Chaps. 447 and 448). Patients with myositis often develop muscle pain and weakness (axial musculature and proximal limbs) after one or two cycles. Myocarditis can also develop. Additionally, diplopia with extraocular weakness along with dysphagia and dysarthria suggesting the co-occurrence of myasthenia gravis (MG) may be present. In such cases, an elevated CK level helps support the diagnosis of myositis, while acetylcholine receptor antibodies or

decremental response on slow repetitive nerve stimulation can establish the diagnosis of MG. Endomysial inflammatory cell infiltrates composed of macrophages expressing PD-L1 and CD8+ lymphocytes expressing PD-1, overexpression of MHC-I on sarcolemma of muscle fibers, and scattered necrotic and regenerating fibers can be found on muscle biopsies.

The immune checkpoint inhibitor should be discontinued, but most patients require concurrent treatment with glucocorticoids or IVIG. Patients generally improve over several months, during which time immunotherapy can be tapered. There are rare reports of patients with mild myositis who were able to be successfully re-treated with an immune checkpoint inhibitor.

MYOSITIS ASSOCIATED WITH COVID-19 INFECTION

Early series of patients hospitalized with COVID-19 report that as many as 44% of patients experienced muscle pain or fatigue and 33% have elevated CK levels. Rare cases are complicated by myoglobinuria. Histopathology can demonstrate inflammatory cell infiltration and necrotic muscle fibers. A major concern during this pandemic is whether or not patients with inflammatory myopathies treated with various immunotherapies are more susceptible to infection with COVID-19 or at greater risk for severe complications. We strongly encourage our patients to wear masks and maintain social distancing.

GLOBAL ISSUES

There is a lack of epidemiologic data with regard to the incidence and prevalence of various subtypes of IM throughout the world. Complicating the issue is disease awareness and the inability to obtain and process muscle biopsies and MSAs, particularly in less developed countries. Nevertheless, each of these disorders occurs throughout the world. The specific environmental triggers and genetic risk factors are likely variable. Interestingly, a report from Japan found that 28% of IBM patients had evidence of exposure to hepatitis C, which was much higher than seen in the Western Hemisphere and also more common than seen in PM and healthy population controls in Japan. HIV-associated PM and IBM are more commonly encountered in areas endemic for HIV, and recent studies suggest most of these "PM" patients turn out to have IBM and can develop symptoms at an earlier age (e.g., in the 30s). Pyomyositis and parasitic myositis are clearly more common in the tropics. The prevalence of different types of cancers varies in different parts of the world, an important consideration with respect to paraneoplastic myositis seen in DM, PM, and IMNM. For example, nasopharyngeal cancer is particularly common in Asia; thus, assessment for this type of cancer should be considered in the workup of patients from high-risk regions.

FURTHER READING

- Amato AA, Russell JA (eds): *Neuromuscular Disorders*, 2nd ed. New York, McGraw-Hill Education, 2016, pp. 827–871.
- Aschman T et al: Association between SARS-CoV-2 infection and immune-mediated myopathy in patients who have died. *JAMA Neurol* 78(8):948–960, 2021.
- Beydon M et al: Myositis as a manifestation of SARS-CoV-2. *Ann Rheum Dis* 2020.
- Doughty CT, Amato AA: Toxic myopathies. *Continuum (Minneapolis Minn)* 25:1712, 2019.
- Greenberg SA: Inclusion body myositis: clinical features and pathogenesis. *Nat Rev Rheumatol* 15:257–272, 2019.
- Huard C et al: Correlation of cutaneous disease activity with type 1 interferon gene signature and interferon beta in dermatomyositis. *Br J Dermatol* 176:1224, 2017.
- Larman HB et al: Cytosolic 5'-nucleotidase 1A autoimmunity in sporadic inclusion body myositis. *Ann Neurol* 73:408, 2013.
- Lundberg IE et al: Diagnosis and classification of idiopathic inflammatory myopathies. *J Intern Med* 280:39, 2016.
- Mammen AL et al: Autoantibodies against 3-hydroxy-3-methylglutaryl-coenzyme A reductase in patients with statin-associated autoimmune myopathy. *Arthritis Rheum* 63:713, 2011.

Pluk H et al: Autoantibodies to cytosolic 5'-nucleotidase 1A in inclusion body myositis. *Ann Neurol* 73:397, 2013.

Puwanant A et al: Clinical spectrum of neuromuscular complications after immune checkpoint inhibition. *Neuromuscul Disord* 29:127, 2019.

Rose MR, Enmc IBM Working Group: 188th ENMC International Workshop: Inclusion Body Myositis, 2–4 December 2011, Naarden, The Netherlands. *Neuromuscul Disord* 23:1044, 2013.

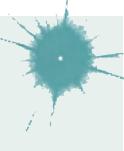
Suh J et al: Skeletal muscle and peripheral nerve histopathology in COVID-19. *Neurology* 97:e849–e885, 2021.

Watanabe Y et al: Clinical features and prognosis in anti-SRP and anti-HMGCR necrotising myopathy. *J Neurol Neurosurg Psychiatry* 87:1038, 2016.

366

Relapsing Polychondritis

Carol A. Langford



Relapsing polychondritis is an uncommon disorder of unknown cause characterized by inflammation of cartilage predominantly affecting the ears, nose, and laryngotracheobronchial tree. Multisystem disease occurs commonly and can also involve noncartilaginous tissues and organs. Relapsing polychondritis has been estimated to have an annual incidence of 3.5 per million. The peak age of onset is between 40 and 50 years, but the disease can be seen in all ages with both sexes being equally affected. Approximately 30% of patients with relapsing polychondritis will have another rheumatologic disorder, most frequently systemic vasculitis, rheumatoid arthritis, or systemic lupus erythematosus (SLE). Nonrheumatic disorders have also been associated with relapsing polychondritis (**Table 366-1**). In most cases, these disorders antedate the appearance of relapsing polychondritis, usually by months or years; however, in other instances, the onset of relapsing polychondritis can accompany disease presentation.

PATHOLOGY AND PATHOPHYSIOLOGY

The earliest abnormality of hyaline and elastic cartilage noted histologically is a focal or diffuse loss of basophilic staining indicating depletion of proteoglycan from the cartilage matrix. Inflammatory infiltrates are found adjacent to involved cartilage and consist predominantly of mononuclear cells and occasional plasma cells. In acute disease,

TABLE 366-1 Disorders Associated with Relapsing Polychondritis^a

- Systemic vasculitis
- Rheumatoid arthritis
- Systemic lupus erythematosus
- Overlapping connective tissue disease
- Spondyloarthritides
- Behcet's disease
- Polymyalgia rheumatica
- Primary biliary cirrhosis
- Pulmonary fibrosis
- Hashimoto's thyroiditis
- Graves' disease
- Crohn's disease
- Ulcerative colitis
- Myelodysplastic syndrome

^aSystemic vasculitis is the most common association, followed by rheumatoid arthritis and systemic lupus erythematosus.

Source: Modified from CJ Michet et al: Ann Intern Med 104:74, 1986.

polymorphonuclear white cells may also be present. Destruction of cartilage begins at the outer edges and advances centrally. There is lacunar breakdown and loss of chondrocytes. Degenerating cartilage is replaced by granulation tissue and later by fibrosis and focal areas of calcification. Small loci of cartilage regeneration may be present. Extracellular granular material observed in the degenerating cartilage matrix by electron microscopy has been interpreted to be enzymes, immunoglobulins, or proteoglycans.

The available data suggest that both humoral and cell-mediated immunity play an important role in the pathogenesis of relapsing polychondritis. Immunoglobulin and complement deposits are found at sites of inflammation. In addition, antibodies to type II collagen and to matrilin-1 and immune complexes are detected in the sera of some patients. The possibility that an immune response to type II collagen may be important in the pathogenesis is supported experimentally by the occurrence of auricular chondritis in rats immunized with type II collagen. Antibodies to type II collagen are found in the sera of these animals, and immune deposits are detected at sites of ear inflammation. Humoral immune responses to type IX and type XI collagen, matrilin-1, and cartilage oligomeric matrix protein have been demonstrated in some patients. Matrilin-1 is a noncollagenous protein present in the extracellular matrix in cartilage. It is present in high concentrations in the trachea and is also present in the nasal septum but not in articular cartilage. In one study, rats immunized with matrilin-1 were found to develop severe inspiratory stridor and swelling of the nasal septum but without involvement of the joint or ear cartilage. The rats had severe inflammation with erosions of the involved cartilage, which was characterized by increased numbers of CD4+ and CD8+ T cells in the lesions, and all had IgG antibodies to matrilin-1. A subsequent study demonstrated serum anti-matrilin-1 antibodies in ~13% of patients with relapsing polychondritis; ~70% of these patients had respiratory symptoms. Cell-mediated immunity may also be operative in causing tissue injury, since lymphocyte transformation can be demonstrated when lymphocytes of patients are exposed to cartilage extracts. T cells specific for type II collagen have been found in some patients, and CD4+ T cells have been observed at sites of cartilage inflammation. Genetic background may also play a role in disease development. A significantly higher frequency of HLA-DR4 has been found in patients with relapsing polychondritis than in healthy individuals, although a predominant subtype allele(s) was not found.

CLINICAL MANIFESTATIONS

The onset of relapsing polychondritis is frequently abrupt, with the appearance of one or two sites of cartilaginous inflammation. The pattern of cartilaginous involvement and the frequency of episodes vary widely among patients. Noncartilaginous presentations may also occur. Systemic inflammatory features such as fever, fatigue, and weight loss commonly occur and may precede other clinical signs. Relapsing polychondritis may go unrecognized for several months or even years in patients who only initially manifest intermittent joint pain and/or swelling or who have unexplained eye inflammation, hearing loss, valvular heart disease, or pulmonary symptoms. Recent studies have suggested that relapsing polychondritis may present in different subgroups that vary in time to diagnosis, clinical and radiologic characteristics, and disease-related complications. Although further investigation will be necessary to determine how these subgroups may impact treatment and outcome, recognition of disease patterns beyond cartilaginous involvement may facilitate diagnosis.

Auricular chondritis is the most frequent presenting manifestation of relapsing polychondritis, occurring in 40% of patients and eventually affecting ~85% of patients (**Table 366-2**). One or both ears are involved, either sequentially or simultaneously. Patients experience the sudden onset of pain, tenderness, and swelling of the cartilaginous portion of the ear. This typically involves the pinna of the ears, sparing the earlobes because they do not contain cartilage. The overlying skin has a beefy red or violaceous color. Prolonged or recurrent episodes lead to cartilage destruction and result in a droopy ear. Swelling may close off the eustachian tube or the external auditory meatus, either of

TABLE 366-2 Clinical Manifestations of Relapsing Polychondritis

CLINICAL FEATURE	PRESENTING	CUMULATIVE
	Frequency, %	
Auricular chondritis	43	89
Arthritis	32	72
Nasal chondritis	21	61
Ocular inflammation	18	59
Laryngotracheal symptoms	23	55
Reduced hearing	7	40
Saddle nose deformity	11	25
Cutaneous	4	25
Laryngotracheal stricture	15	23
Vasculitis	2	14
Elevated creatinine	7	13
Aortic or mitral regurgitation	0	12

Source: Reproduced with permission from PD Kent et al: Relapsing polychondritis. Curr Opin Rheumatology 16:56, 2004. <https://pubmed.ncbi.nlm.nih.gov/14673390/>.

which can impair hearing. Inflammation of the internal auditory artery or its cochlear branch produces hearing loss, vertigo, ataxia, nausea, and vomiting. Vertigo is almost always accompanied by hearing loss.

Approximately 61% of patients will develop nasal involvement, with 21% having this at the time of presentation. Patients may experience nasal congestion, rhinorrhea, and epistaxis. The bridge of the nose and surrounding tissue become red, swollen, and tender and may collapse, producing a saddle nose deformity (**Fig. 366-1**). In some patients, nasal deformity develops insidiously without overt inflammation. Saddle nose is observed more frequently in younger patients, especially in women.

Joint involvement is the presenting manifestation in relapsing polychondritis in approximately one-third of patients and may be present for several months before other features appear. Eventually, more than one-half of the patients will have arthralgias or arthritis. The arthritis

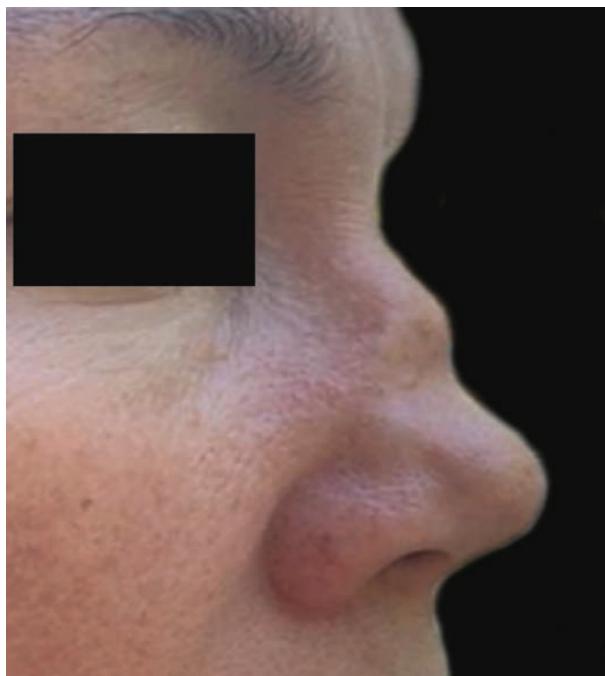


FIGURE 366-1 Saddle nose resulting from destruction and collapse of the nasal cartilage. (Image courtesy of Marcela Ferrada, MD)

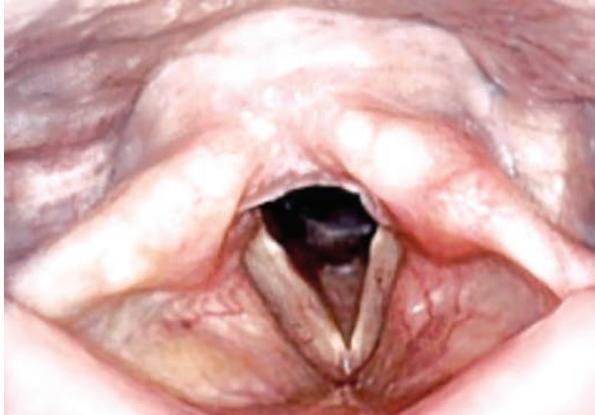


FIGURE 366-2 Narrowing of the subglottis occurring as a result of laryngotracheal involvement in relapsing polychondritis. (Image courtesy of Marcela Ferrada, MD)

is usually asymmetric and oligo- or polyarticular, and it involves both large and small peripheral joints. An episode of arthritis lasts from a few days to several weeks and resolves spontaneously without joint erosion or deformity. Attacks of arthritis may not be temporally related to other manifestations of relapsing polychondritis. Joint fluid has been reported to be noninflammatory. In addition to peripheral joints, inflammation may involve the costochondral, sternomanubrial, and sternoclavicular cartilages. Destruction of these cartilages may result in a pectus excavatum deformity or even a flail anterior chest wall.

Eye manifestations occur in more than one-half of patients and include conjunctivitis, episcleritis, scleritis, iritis, uveitis, and keratitis. Ocular inflammation can be severe and visually threatening. Other manifestations include eyelid and periorbital edema, proptosis, optic neuritis, extraocular muscle palsies, retinal vasculitis, and renal vein occlusion.

Laryngotracheobronchial involvement occurs in ~50% of patients and is among the most serious manifestations of relapsing polychondritis (**Fig. 366-2**). Symptoms include hoarseness, a nonproductive cough, and tenderness over the larynx and proximal trachea. Mucosal edema, strictures, and/or collapse of laryngeal or tracheal cartilage may cause stridor and life-threatening airway obstruction necessitating tracheostomy. Involvement can extend into the lower airways resulting in tracheobronchomalacia. Collapse of cartilage in bronchi leads to pneumonia and, when extensive, to respiratory insufficiency.

Cardiac valvular regurgitation occurs in ~5–10% of patients and is due to progressive dilation of the valvular ring or to destruction of the valve cusps. Aortic regurgitation occurs in ~7% of patients, with the mitral and other heart valves being affected less often. Other cardiac manifestations include pericarditis, myocarditis, coronary vasculitis, and conduction abnormalities. Aneurysms of the proximal, thoracic, or abdominal aorta may occur even in the absence of active chondritis and occasionally rupture.

Renal disease occurs in ~10% of patients. The most common renal lesions include mesangial expansion or segmental necrotizing glomerulonephritis, which often have small amounts of electron-dense deposits in the mesangium where there is also faint deposition of C3 and/or IgG or IgM. Tubulointerstitial disease and IgA nephropathy have also been reported.

Approximately 25% of patients have skin lesions, which can include purpura, erythema nodosum, erythema multiforme, angioedema/urticaria, livedo reticularis, and panniculitis.

Features of vasculitis are seen in up to 25% of patients and can affect any size vessel. Large vessel vasculitis may present with aortic aneurysms, and medium vessel disease may affect the coronary, hepatic, mesenteric, or renal arteries or vessel-supplying nerves. Cutaneous vasculitis can also occur. A variety of primary vasculitides have also been reported to occur in association with relapsing polychondritis (**Chap. 363**). One specific overlap is the “MAGIC” syndrome (mouth and genital ulcers

with inflamed cartilage) in which patients present with features of both relapsing polychondritis and Behcet’s disease (**Chap. 364**).

Relapsing polychondritis has also been found to be associated with VEXAS syndrome (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic). VEXAS syndrome should be considered in male patients with relapsing polychondritis who have hematologic abnormalities often in the spectrum of myelodysplastic syndrome, fevers, venous thrombotic events, pulmonary infiltrates, cutaneous lesions, or treatment resistant disease. VEXAS syndrome is strongly suggested by its clinical features and the finding of vacuoles within bone marrow precursor cells. It is proven by genetic testing for myeloid-restricted somatic missense mutations in UBA1, the major E1 enzyme that initiates ubiquitylation.

LABORATORY FINDINGS AND DIAGNOSTIC IMAGING

There are no laboratory features that are diagnostic for relapsing polychondritis. Mild leukocytosis and normocytic, normochromic anemia are often present. Eosinophilia is observed in 10% of patients. The erythrocyte sedimentation rate and C-reactive protein are usually elevated. Rheumatoid factor and antinuclear antibody tests are occasionally positive in low titers, and complement levels are normal. Antibodies to type II collagen are present in fewer than one-half of patients and are not specific. Circulating immune complexes may be detected, especially in patients with early active disease. Elevated levels of γ globulin may be present. Antineutrophil cytoplasmic antibodies (ANCA), either cytoplasmic (cANCA) or perinuclear (pANCA), are found in some patients with active disease. However, on target antigen-specific testing, there are only occasional reports of positive myeloperoxidase-ANCA, and proteinase 3-ANCA are very rarely found in relapsing polychondritis.

The upper and lower airways can be evaluated by imaging techniques such as computed tomography (CT) and magnetic resonance (MR). Dynamic inspiratory and expiratory CT imaging can be useful in assessing airway involvement. Bronchoscopy provides direct visualization of the airways but can be a high-risk procedure in patients with airway compromise. Pulmonary function testing with flow-volume loops can show inspiratory and/or expiratory obstruction.

Imaging can also be useful to detect extracartilaginous disease. Arteriography by CT or MR should be pursued if features are present suggesting aortic or other large vessel involvement. Electrocardiography and echocardiography can be useful in further evaluating for cardiac features of disease. A number of reports have described the use of positron emission tomography in relapsing polychondritis, but it is currently unclear if this is useful and for what features.

DIAGNOSIS

Diagnosis is based on recognition of the typical clinical features. Biopsies of the involved cartilage from the ear, nose, or respiratory tract can confirm the diagnosis but are only necessary when clinical features are not typical and may be difficult to obtain. Diagnostic criteria were suggested in 1976 by McAdam et al and included biopsy evidence combined with three of the following: (1) recurrent chondritis of both auricles; (2) nonerosive inflammatory arthritis; (3) chondritis of nasal cartilage; (4) inflammation of ocular structures, including conjunctivitis, keratitis, scleritis/episcleritis, and/or uveitis; (5) chondritis of the laryngeal and/or tracheal cartilages; and (6) cochlear and/or vestibular damage manifested by neurosensory hearing loss, tinnitus, and/or vertigo. In 1979, Damiani and Levine suggested that the diagnosis could be made when one or more of the above features and a positive biopsy were present, when two or more separate sites of cartilage inflammation were present that responded to treatment, or when three or more of the above features were present.

The differential diagnosis of relapsing polychondritis is centered around its sites of clinical involvement. Patients with granulomatosis with polyangiitis may have a saddle nose and tracheal involvement but can be distinguished by the primary inflammation occurring in the mucosa at these sites, the absence of auricular involvement, and the presence of pulmonary parenchymal disease. Patients with

Cogan's syndrome have interstitial keratitis and vestibular and auditory abnormalities, but this syndrome does not involve the respiratory tract or ears. Reactive arthritis may initially resemble relapsing polychondritis because of oligoarticular arthritis and eye involvement, but it is distinguished by the occurrence of urethritis and typical mucocutaneous lesions and the absence of nose or ear cartilage involvement. Rheumatoid arthritis may initially suggest relapsing polychondritis because of arthritis and eye inflammation, although the arthritis is erosive and symmetric. In addition, rheumatoid factor titers are usually high compared with those in relapsing polychondritis, and anti-cyclic citrullinated peptide is usually not seen. Bacterial infection of the pinna may be mistaken for relapsing polychondritis but differs by usually involving only one ear, including the earlobe. Auricular cartilage may also be damaged by trauma or frostbite. Nasal destructive disease and auricular abnormalities can also be seen in patients using cocaine adulterated with levamisole. Ear involvement in this setting differs from relapsing polychondritis by typically manifesting as purpuric plaques with necrosis extending to the earlobe, which does not contain cartilage.

TREATMENT

Relapsing Polychondritis

In patients with active chondritis, prednisone, 40–60 mg/d, is often effective in suppressing disease activity; it is tapered gradually once disease is controlled. In some patients, prednisone can be stopped, whereas in others, low doses in the range of 5–10 mg/d are required for continued suppression of disease. Other immunosuppressive drugs such as cyclophosphamide, methotrexate, azathioprine, mycophenolate mofetil, or cyclosporine should be used in patients who have severe organ-threatening disease, fail to respond to prednisone, or require high doses to control disease activity. There has been significant interest in the use of biologic agents to treat relapsing polychondritis. Tumor necrosis factor inhibitors have been the most widely examined therapies to date, and although benefit has been suggested, this has come solely from retrospective cases and series. Other agents with which there have been published reports include anakinra, rituximab, tocilizumab, and abatacept, but reports are too few in number to assess efficacy. Dapsone has also been used in selected settings but has largely been supplanted by other approaches and should not be used for severe disease. Heart valve replacement or repair of an aortic aneurysm may be necessary. When airway obstruction is severe, tracheostomy is required. Stents may be necessary in patients with tracheobronchial collapse.

PATIENT OUTCOME, PROGNOSIS, AND SURVIVAL

The course of relapsing polychondritis is highly variable. Some patients experience inflammatory episodes lasting from a few days to several weeks that then subside spontaneously or with treatment. Attacks may recur at intervals varying from weeks to months. In other patients, the disease has a chronic, smoldering course that may be severe. In one study, the 5-year estimated survival rate was 74%, and the 10-year survival rate was 55%. About one-half of the deaths could be attributed to relapsing polychondritis or complications of treatment. Airway complications accounted for 10% of all fatalities, although higher rates have been reported in other series. In general, patients with more widespread disease have a worse prognosis.

FURTHER READING

- Beck DB et al: Somatic mutations in UBA1 and severe adult-onset autoinflammatory disease. *N Engl J Med* 383:2628, 2020.
- Chopra R et al: Relapsing polychondritis. *Rheum Dis Clin North Am* 39:263, 2013.
- Ernst A et al: Relapsing polychondritis and airway involvement. *Chest* 135:1024, 2009.
- Ferrada M et al: Defining clinical subgroups in relapsing polychondritis: A prospective observational cohort study. *Arthritis Rheumatol* 72:1396, 2020.

Mouli G et al: Efficacy and safety of biologics in relapsing polychondritis: A French national multicentre study. *Ann Rheum Dis* 77:1172, 2018.

Vitale A et al: Relapsing polychondritis: An update on pathogenesis, clinical features, diagnostic tools, and therapeutic perspectives. *Curr Rheumatol Rep* 18:3, 2016.

367

Sarcoidosis

Robert P. Baughman, Elyse E. Lower



DEFINITION

Sarcoidosis is an inflammatory disease characterized by the presence of noncaseating granulomas. The disease is often multisystemic and requires the presence of involvement in two or more organs for a specific diagnosis. The finding of granulomas is not specific for sarcoidosis, and other conditions known to cause granulomas must be ruled out. These conditions include mycobacterial and fungal infections, malignancy, and environmental agents such as beryllium. Although sarcoidosis can affect virtually every organ of the body, the lung is most commonly affected. Other organs commonly affected are the liver, skin, and eye. The clinical outcome of sarcoidosis varies, with remission occurring in over one-half of patients within a few years of diagnosis; however, the remaining patients may develop chronic disease that lasts for decades.

ETIOLOGY

Despite multiple investigations, the cause of sarcoidosis remains unknown. Currently, the most likely etiology is an infectious or non-infectious environmental agent that triggers an inflammatory response in a genetically susceptible host. Among the possible infectious agents, careful studies have shown a much higher incidence of *Propionibacterium acnes* in the lymph nodes of sarcoidosis patients compared to controls. An animal model has shown that *P. acnes* can induce a granulomatous response in mice similar to sarcoidosis. Others have demonstrated the presence of a mycobacterial protein (*Mycobacterium tuberculosis* catalase-peroxidase [mKatG]) in the granulomas of some sarcoidosis patients. This protein is very resistant to degradation and may represent the persistent antigen in sarcoidosis. Immune response to this and other mycobacterial proteins has been documented by another laboratory. These studies suggest that a *Mycobacterium* similar to *M. tuberculosis* could be responsible for sarcoidosis. The mechanism exposure/infection with such agents has been the focus of other studies. Environmental exposures to insecticides and mold have been associated with an increased risk for disease. In addition, health care workers appear to have an increased risk. Also, sarcoidosis in a donor organ has occurred after transplantation into a sarcoidosis patient. Some authors have suggested that sarcoidosis is not due to a single agent but represents a particular host response to multiple agents. Some studies have been able to correlate environmental exposures to genetic markers. These studies have supported the hypothesis that a genetically susceptible host is a key factor in the disease.

INCIDENCE, PREVALENCE, AND GLOBAL IMPACT

Sarcoidosis is seen worldwide, with the highest prevalence reported in the Nordic population. In the United States, the disease has been reported more commonly in African Americans than whites, with the ratio of African Americans to whites ranging from 3:1 to 17:0. In the United States, women are more susceptible than men. The higher incidence in African Americans may have been influenced by the fact that African Americans seem to develop more extensive and chronic pulmonary disease. Because most sarcoidosis clinics are run

2830 by pulmonologists, a selection bias may have occurred. Worldwide, the prevalence of the disease varies from 20–60 per 100,000 for many groups such as Japanese, Italians, and American whites. Higher rates occur in Ireland and Nordic countries. In one closely observed community in Sweden, the lifetime risk for developing sarcoidosis was 3%.

Sarcoidosis often occurs in young, otherwise healthy adults. It is uncommon to diagnose the disease in someone aged <18 years. However, it has become clear that a second peak in incidence develops around age 60. In a study of nearly 30,000 sarcoidosis patients in the United States, the median age at diagnosis was 55.

Although most cases of sarcoidosis are sporadic, a familial form of the disease exists. At least 5% of patients with sarcoidosis will have a family member with sarcoidosis. Sarcoidosis patients who are Irish or African American seem to have a two to three times higher rate of familial disease.

PATOPHYSIOLOGY AND IMMUNOPATHOGENESIS

The granuloma is the pathologic hallmark of sarcoidosis. A distinct feature of sarcoidosis is the local accumulation of inflammatory cells. Extensive studies in the lung using bronchoalveolar lavage (BAL) have demonstrated that the initial inflammatory response is an influx of T helper cells. In addition, there is an accumulation of activated monocytes. **Figure 367-1** is a proposed model for sarcoidosis. Using the HLA-CD4 complex, antigen-presenting cells present an unknown antigen to the helper T cell. Studies have clarified that specific human leukocyte antigen (HLA) haplotypes such as HLA-DRB1*1101 are associated with an increased risk for developing sarcoidosis. In addition, different HLA haplotypes are associated with different clinical outcomes.

The macrophage/helper T-cell cluster leads to activation with the increased release of several cytokines. These include interleukin (IL) 2 released from the T cell and interferon γ and tumor necrosis factor (TNF) released by the macrophage. The T cell is a necessary part of the initial inflammatory response. In advanced, untreated HIV infection, patients who lack helper T cells rarely develop sarcoidosis. In contrast, several reports confirm that sarcoidosis becomes unmasked as HIV-infected individuals receive antiretroviral therapy, with subsequent restoration of their immune system. In contrast, treatment of established

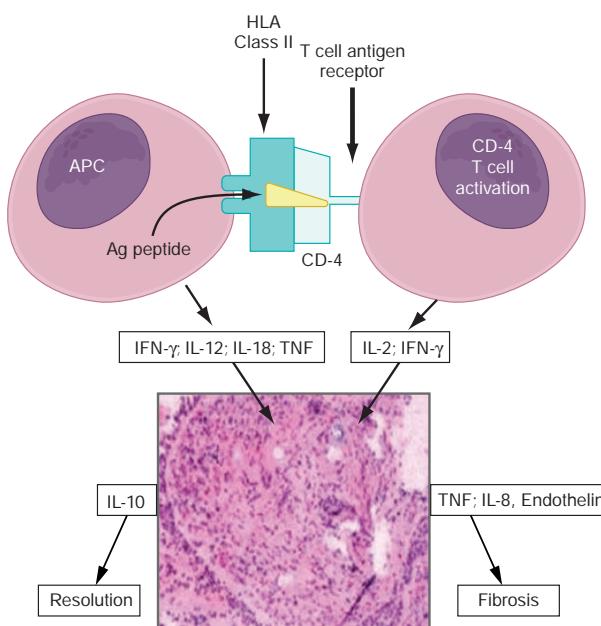


FIGURE 367-1 Schematic representation of initial events of sarcoidosis. The antigen-presenting cell and helper T-cell complex leads to the release of multiple cytokines. This forms a granuloma. Over time, the granuloma may resolve or lead to chronic disease, including fibrosis. APC, antigen-presenting cell; HLA, human leukocyte antigen; IFN, interferon; IL, interleukin; TNF, tumor necrosis factor.

pulmonary sarcoidosis with cyclosporine, a drug that downregulates helper T-cell responses, seems to have little impact on sarcoidosis.

The granulomatous response of sarcoidosis can resolve with or without therapy. However, in at least 20% of patients with sarcoidosis, a chronic form of the disease develops. This persistent form of the disease is associated with increased levels in blood and/or BAL of IL-8, IL-17, and CXCL9. Also, studies have reported that patients with this chronic form of disease release excessive amounts of TNF in areas of inflammation. Specific gene signatures have been associated with more severe disease, such as cardiac, neurologic, and fibrotic pulmonary disease.

At diagnosis, the natural history of the disease may be difficult to predict. One form of the disease, *Löfgren's syndrome*, consists of erythema nodosum and hilar adenopathy on chest roentgenogram. In some cases, periarthritis arthritis may be identified without erythema nodosum. Löfgren's syndrome is associated with a good prognosis, with >90% of patients experiencing disease resolution within 2 years. Recent studies have demonstrated that the HLA-DRB1*03 was found in two-thirds of Scandinavian patients with Löfgren's syndrome. More than 95% of those patients who were HLA-DRB1*03 positive had resolution of their disease within 2 years, whereas nearly one-half of the remaining patients had disease for >2 years. It remains to be determined whether these observations can be applied to a non-Scandinavian population.

CLINICAL MANIFESTATIONS

The presentation of sarcoidosis ranges from patients who are asymptomatic to those with organ failure. It is unclear how often sarcoidosis is asymptomatic. In countries where routine chest roentgenogram screening is performed, 20–30% of pulmonary cases are detected in asymptomatic individuals. The inability to screen for other asymptomatic forms of the disease would suggest that as many as one-third of sarcoidosis patients are asymptomatic.

Respiratory complaints including cough and dyspnea are the most common presenting symptoms. In many cases, the patient presents with a 2- to 4-week history of these symptoms. Unfortunately, due to the nonspecific nature of pulmonary symptoms, the patient may see physicians for up to a year before a diagnosis is confirmed. For these patients, the diagnosis of sarcoidosis is usually only suggested when a chest roentgenogram is performed.

Symptoms related to cutaneous and ocular disease are the next two most common complaints. Skin lesions are often nonspecific. However, because these lesions are readily observed, the patient and treating physician are often led to a diagnosis. In contrast to patients with pulmonary disease, patients with cutaneous lesions are more likely to be diagnosed within 6 months of symptoms.

Nonspecific constitutional symptoms include fatigue, fever, night sweats, and weight loss. Fatigue is perhaps the most common constitutional symptom that affects these patients. Given its insidious nature, patients are usually not aware of the association with their sarcoidosis until their disease resolves.

The overall incidence of sarcoidosis at the time of diagnosis and eventual common organ involvement are summarized in **Table 367-1**. Over time, skin, eye, and neurologic involvement seem more apparent. In the United States, the frequency of specific organ involvement appears to be affected by age, race, and gender. For example, eye disease is more common among African Americans. Under the age of 40, it occurs more frequently in women. However, in those diagnosed over the age of 40, eye disease is more common in men.

LUNG

Lung involvement occurs in >90% of sarcoidosis patients. The most commonly used method for detecting lung disease is still the chest roentgenogram. **Figure 367-2** illustrates the chest roentgenogram from a sarcoidosis patient with bilateral hilar adenopathy. Although the CT scan has changed the diagnostic approach to interstitial lung disease, it is not usually considered a monitoring tool for patients with sarcoidosis except for those with pulmonary fibrosis. **Figure 367-3** demonstrates some of the characteristic CT features, including peribronchial thickening and reticular nodular changes, which are predominantly

TABLE 367-1 Frequency of Common Organ Involvement and Lifetime Risk^a

	PRESENTATION, % ^b	FOLLOW-UP, % ^c
Lung	95	94
Skin	24	43
Eye	12	29
Extrathoracic lymph node	15	16
Liver	12	14
Spleen	7	8
Neurologic	5	16
Cardiac	2	3

^aPatients could have more than one organ involved. ^bFrom ACCESS study of 736 patients evaluated within 6 months of diagnosis. ^cFrom follow-up of 1024 sarcoidosis patients seen at the University of Cincinnati Interstitial Lung Disease and Sarcoidosis Clinic from 2002 to 2006.

subpleural. The peribronchial thickening seen on CT seems to explain the high yield of granulomas from bronchial biopsies performed for diagnosis.

Although the CT scan is more sensitive, the standard scoring system described by Scadding in 1961 for chest roentgenograms remains the preferred method of characterizing chest involvement. Stage 1 is hilar adenopathy alone (Fig. 367-2), often with right paratracheal involvement. Stage 2 is a combination of adenopathy plus infiltrates, whereas stage 3 reveals infiltrates alone. Stage 4 consists of fibrosis. Usually the infiltrates in sarcoidosis are predominantly an upper lobe process. Only in a few noninfectious diseases is an upper lobe predominance noted. In addition to sarcoidosis, the differential diagnosis of upper lobe disease includes hypersensitivity pneumonitis, silicosis, and Langerhans cell histiocytosis. For infectious diseases, tuberculosis and *Pneumocystis pneumonia* can often present as upper lobe diseases.

Lung volumes, mechanics, and diffusion are all useful in evaluating interstitial lung diseases such as sarcoidosis. The diffusion of carbon monoxide (DL_{CO}) is the most sensitive test for interstitial lung disease. Reduced lung volumes are a reflection of the restrictive lung disease seen in sarcoidosis. However, a third of the patients presenting with sarcoidosis still have lung volumes within the normal range, despite abnormal chest roentgenograms and dyspnea.

Approximately one-half of sarcoidosis patients present with obstructive disease, reflected by a reduced ratio of forced expiratory volume in 1 s to forced vital capacity (FEV₁/FVC). Cough is a very common symptom. Airway involvement causing varying degrees of obstruction underlies the cough in most sarcoidosis patients. Airway



FIGURE 367-3 High-resolution CT scan of the chest demonstrating patchy reticular nodularity, including areas of confluence.

hyperreactivity, as determined by methacholine challenge, will be positive in some of these patients. A few patients with cough will respond to traditional bronchodilators as the only form of treatment. In some cases, high-dose inhaled glucocorticoids alone are useful. Airway obstruction can be due to large airway stenosis, which can become fibrotic and unresponsive to anti-inflammatory therapy.

Pulmonary arterial hypertension is reported in at least 5% of sarcoidosis patients. Either direct vascular involvement or the consequence of fibrotic changes in the lung can lead to pulmonary arterial hypertension. In sarcoidosis patients with end-stage fibrosis awaiting lung transplant, 70% will have pulmonary arterial hypertension. This is a much higher incidence than that reported for other fibrotic lung diseases. In less advanced but still symptomatic patients, pulmonary arterial hypertension has been noted in up to 50% of cases. Because sarcoidosis-associated pulmonary arterial hypertension may respond to therapy, evaluation for this should be considered in persistently dyspneic patients.

SKIN

Skin involvement is eventually identified in over a third of patients with sarcoidosis. The classic cutaneous lesions include erythema nodosum, maculopapular lesions, hyper- and hypopigmentation, keloid formation, and subcutaneous nodules. A specific complex of involvement of the bridge of the nose, the area beneath the eyes, and the cheeks is referred to as *lupus pernio* (Fig. 367-4) and is diagnostic for a chronic form of sarcoidosis.

In contrast, erythema nodosum is a transient rash that can be seen in association with hilar adenopathy and uveitis (Löfgren's syndrome). Erythema nodosum is more common in women and in certain self-described demographic groups including whites and Puerto Ricans. In the United States, the other manifestations of skin sarcoidosis, especially lupus pernio, are more common in African Americans than whites.

The maculopapular lesions from sarcoidosis are the most common chronic form of the disease (Fig. 367-5). These are often overlooked by the patient and physician because they are chronic and not painful. Initially, these lesions are usually purplish papules and are often indurated. They can become confluent and infiltrate large areas of the skin. With treatment, the color and induration may fade. Because these lesions are caused by noncaseating granulomas, the diagnosis of sarcoidosis can be readily made by a skin biopsy.

EYE

The frequency of ocular manifestations for sarcoidosis varies depending on race. In Japan, >70% of sarcoidosis patients develop ocular disease, whereas in the United States, only 30% have eye disease, with



FIGURE 367-2 Posterior-anterior chest roentgenogram demonstrating bilateral hilar adenopathy, stage 1 disease.



FIGURE 367-4 Chronic inflammatory lesions around the nose, eyes, and cheeks, referred to as *lupus pernio*.

problems more common in African Americans than whites. Although the most common manifestation is anterior uveitis, over a quarter of patients will have inflammation at the posterior of the eye, including retinitis and pars planitis. Although symptoms such as photophobia, blurred vision, and increased tearing can occur, some asymptomatic patients still have active inflammation. Initially asymptomatic patients with ocular sarcoidosis can eventually develop blindness. Therefore, it is recommended that all patients with sarcoidosis receive a dedicated ophthalmologic examination. Sicca is seen in over one-half of chronic sarcoidosis patients. Dry eyes appear to be a reflection of prior lacrimal gland disease. Although the patient may no longer have active inflammation, dry eyes may require natural tears or other lubricants.

LIVER

Using biopsies to detect granulomatous disease, liver involvement can be identified in over one-half of sarcoidosis patients. However, using liver function studies, only 20–30% of patients will have evidence of liver involvement. The most common abnormality of liver function



FIGURE 367-5 Maculopapular lesions on the trunk of a sarcoidosis patient.

is an elevation of the alkaline phosphatase level, consistent with an obstructive pattern. In addition, elevated transaminase levels can occur. An elevated bilirubin level is a marker for more advanced liver disease. Overall, only 5% of sarcoidosis patients have sufficient symptoms from their liver disease to require specific therapy. Although symptoms can be due to hepatomegaly, more frequently symptoms result from extensive intrahepatic cholestasis leading to portal hypertension. In this case, ascites and esophageal varices can occur. It is rare that a sarcoidosis patient will require a liver transplant because even the patient with cirrhosis due to sarcoidosis can respond to systemic therapy.

BONE MARROW AND SPLEEN

One or more bone marrow manifestations can be identified in many sarcoidosis patients. The most common hematologic problem is lymphopenia, which is a reflection of sequestration of the lymphocytes into the areas of inflammation. Anemia occurs in 20% of patients, and leukopenia is less common. A bone marrow examination will reveal granulomas in about a third of patients. Although splenomegaly can be detected in 5–10% of patients, splenic biopsy reveals granulomas in 60% of patients. The CT scan can be relatively specific for sarcoidosis involvement of the spleen (**Fig. 367-6**). Both bone marrow and spleen involvement are more common in African Americans than whites. Although these manifestations alone are rarely an indication for therapy, on rare occasion, splenectomy may be indicated for massive symptomatic splenomegaly or profound pancytopenia. Nonthoracic lymphadenopathy can occur in up to 20% of patients.

CALCIUM METABOLISM

Hypercalcemia and/or hypercalcuria occur in ~10% of sarcoidosis patients. It is more common in whites than African Americans and in men. The mechanism of abnormal calcium metabolism is increased production of 1,25-dihydroxyvitamin D by the granuloma itself. The 1,25-dihydroxyvitamin D causes increased intestinal absorption of calcium, leading to hypercalcemia with a suppressed parathyroid hormone (PTH) level (**Chap. 410**). Increased exogenous vitamin D from diet or sunlight exposure may exacerbate this problem. Serum calcium should be determined as part of the initial evaluation of all sarcoidosis patients, and a repeat determination may be useful during the summer months with increased sun exposure. In patients with a history of renal calculi, a 24-h urine calcium measurement should be obtained. If a sarcoidosis patient with a history of renal calculi is to be placed on calcium supplements, a follow-up 24-h urine calcium level should be measured.



FIGURE 367-6 CT scan of the abdomen after oral and intravenous contrast. The stomach is compressed by the enlarged spleen. Within the spleen, areas of hypo- and hyperdensity are identified.

RENAL DISEASE

Direct kidney involvement occurs in <5% of sarcoidosis patients. It is associated with granulomas in the kidney itself and can lead to nephritis. However, hypercalcemia is the most likely cause of sarcoidosis-associated renal disease. In 1–2% of sarcoidosis patients, acute renal failure may develop as a result of hypercalcemia. Successful treatment of hypercalcemia with glucocorticoids and other therapies often improves but usually does not totally resolve renal dysfunction.

NERVOUS SYSTEM

Neurologic disease is reported in 5–10% of sarcoidosis patients and appears to be of equal frequency across all ethnic groups. Any part of the central or peripheral nervous system can be affected. The presence of granulomatous inflammation is often visible on MRI studies. MRI with gadolinium enhancement may demonstrate space-occupying lesions, but the MRI can be negative due to small lesions or the effect of systemic therapy in reducing the inflammation. Cerebral spinal fluid (CSF) findings include lymphocytic meningitis with a mild increase in protein. The CSF glucose level is usually normal but can be low. Certain areas of the nervous system are more commonly affected in neurosarcoidosis. These include cranial nerve involvement, basilar meningitis, myelopathy, and anterior hypothalamic disease with associated diabetes insipidus ([Chap. 381](#)). Seizures and cognitive changes also occur. Of the cranial nerves, seventh nerve paralysis can be transient and mistaken for Bell's palsy (idiopathic seventh nerve paralysis). Because this form of neurosarcoidosis often resolves within weeks and may not recur, it may have occurred prior to a definitive diagnosis of sarcoidosis. Optic neuritis is another cranial nerve manifestation of sarcoidosis. This manifestation is more chronic and usually requires long-term systemic therapy. It can be associated with both anterior and posterior uveitis. Differentiating between neurosarcoidosis and multiple sclerosis can be difficult at times. Optic neuritis can occur in both diseases. In some patients with sarcoidosis, multiple enhancing white matter abnormalities may be detected by MRI, suggesting multiple sclerosis. In such cases, the presence of meningeal enhancement or hypothalamic involvement suggests neurosarcoidosis, as does evidence of extraneurologic disease such as pulmonary or skin involvement, which also suggests sarcoidosis. Because the response of neurosarcoidosis to glucocorticoids and cytotoxic therapy is different from that of multiple sclerosis, differentiating between these disease entities is important.

CARDIAC

The presence of cardiac involvement is influenced by race. Although over a quarter of Japanese sarcoidosis patients develop cardiac disease, only 5% of sarcoidosis patients in the United States and Europe develop symptomatic cardiac disease. However, there is no apparent racial predilection between whites and African Americans. Cardiac disease, which usually presents as either congestive heart failure or cardiac arrhythmias, results from infiltration of the heart muscle by granulomas. Diffuse granulomatous involvement of the heart muscle can lead to profound dysfunction with left ventricular ejection fractions of <10%. Even in this situation, improvement in the ejection fraction can occur with systemic therapy. Arrhythmias can also occur with diffuse infiltration or with more patchy cardiac involvement. If the atrioventricular (AV) node is infiltrated, heart block can occur, which can be detected by routine electrocardiography. Ventricular arrhythmias and ventricular tachycardia are common causes of death. Arrhythmias are best detected using 24-h ambulatory monitoring, and electrophysiology studies may be negative. Other screening tests for cardiac disease include routine electrocardiography and echocardiography. The confirmation of cardiac sarcoidosis is usually performed with either MRI or positron emission tomography (PET) scanning. Because ventricular arrhythmias are usually multifocal due to patchy multiple granulomas in the heart, ablation therapy is not useful. Patients with significant ventricular arrhythmias should be considered for an implanted defibrillator, which appears to have reduced the rate of death in cardiac sarcoidosis. Although systemic therapy can be useful in treating arrhythmias, patients may still have malignant arrhythmias up to 6 months after starting successful treatment, and the risk for recurrent arrhythmias occurs whenever medications are tapered.

MUSCULOSKELETAL SYSTEM

Direct granulomatous involvement of bone and muscle can be documented by radiography (x-ray, MRI, PET scan [[Fig. 367-7](#)]), or gallium scan) or confirmed by biopsy in ~10% of sarcoidosis patients. However, a larger percentage of sarcoidosis patients complain of myalgia and arthralgia. These complaints are similar to those reported by patients with other inflammatory diseases, including chronic infections such as mononucleosis. Fatigue associated with sarcoidosis may be overwhelming for many patients. A link between fatigue and small peripheral nerve fiber disease in sarcoidosis has been described.

OTHER ORGAN INVOLVEMENT

Although sarcoidosis can affect any organ of the body, rarely does it involve the breast, testes, ovary, or stomach. Because of the rarity of involvement, a mass in one of these areas requires a biopsy to rule out other diseases, including cancer. For example, in a study of breast problems in female sarcoidosis patients, a breast lesion was more likely to be a granuloma from sarcoidosis than from breast cancer. However, findings on the physical examination or mammogram cannot reliably differentiate between these lesions. More importantly, as women with sarcoidosis age, breast cancer becomes more common. Therefore, it is recommended that routine screening including mammography be performed along with other imaging studies (ultrasound, MRI) or biopsy as clinically indicated.

COMPLICATIONS

Sarcoidosis is usually a self-limited, non-life-threatening disease. However, organ-threatening disease can occur. These complications can include blindness, paraplegia, or renal failure. Death from sarcoidosis occurs in ~5% of patients seen in sarcoidosis referral clinics. The usual causes of death related to sarcoidosis are from lung, cardiac, neurologic, or liver involvement. In respiratory failure, an elevation of the right atrial pressure is a poor prognostic finding. Lung complications can also include infections such as mycetoma, which can subsequently lead to massive bleeding. In addition, the use of immunosuppressive agents can increase the incidence of serious infections.

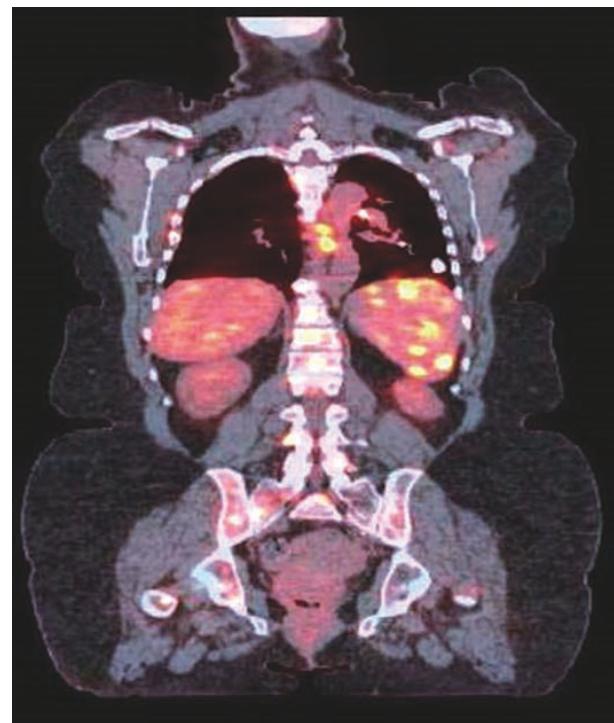


FIGURE 367-7 Positron emission tomography and CT scan merged, demonstrating increased activity in the spleen, ribs, and spine of a patient with sarcoidosis.

The chest roentgenogram remains the most commonly used tool to assess lung involvement in sarcoidosis. As noted above, the chest roentgenogram classifies involvement into four stages, with stages 1 and 2 having hilar and paratracheal adenopathy. The CT scan has been used increasingly in evaluating interstitial lung disease. In sarcoidosis, the presence of adenopathy and a nodular infiltrate is not specific for sarcoidosis. Adenopathy up to 2 cm can be seen in other inflammatory lung diseases such as idiopathic pulmonary fibrosis. However, adenopathy >2 cm in the short axis supports the diagnosis of sarcoidosis over other interstitial lung diseases.

The PET scan has increasingly replaced gallium-67 scanning to identify areas of granulomatous disease in the chest and other parts of the body (Fig. 367-7). Both tests can be used to identify potential areas for biopsy. Cardiac PET scanning has also proved useful in assessing cardiac sarcoidosis. The identification of hypermetabolic activity may be due to the granulomas from sarcoidosis and not to disseminated malignancy.

MRI has also proved useful in the assessment of extrapulmonary sarcoidosis. Gadolinium enhancement has been demonstrated in areas of inflammation in the brain, heart, and bone. MRI scans may detect asymptomatic lesions. Like the PET scan, MRI changes appear similar to those seen with malignancy and infection. In some cases, biopsy may be necessary to determine the cause of the radiologic abnormality.

Serum levels of angiotensin-converting enzyme (ACE) can be helpful in the diagnosis of sarcoidosis. However, the test has somewhat low sensitivity and specificity. Elevated levels of ACE are reported in 60% of patients with acute disease and only 20% of patients with chronic disease. Although there are several causes for mild elevation of ACE, including diabetes, elevations of >50% of the upper limit of normal are seen in only a few conditions including sarcoidosis, leprosy, Gaucher's disease, hyperthyroidism, and disseminated granulomatous infections such as miliary tuberculosis. Because the ACE level is determined by a biologic assay, the concurrent use of an ACE inhibitor such as lisinopril will lead to a very low ACE level.

DIAGNOSIS

The diagnosis of sarcoidosis requires both compatible clinical features and pathologic findings. Because the cause of sarcoidosis remains elusive, the diagnosis cannot be made with 100% certainty. Nevertheless, the diagnosis can be made with reasonable certainty based on history and physical features along with laboratory and pathologic findings.

Patients are usually evaluated for possible sarcoidosis based on two scenarios (Fig. 367-8). In the first scenario, a patient may undergo a biopsy revealing a noncaseating granuloma in either a pulmonary or an extrapulmonary organ. If the clinical presentation is consistent with sarcoidosis and there is no alternative cause for the granulomas identified, the patient is felt to have sarcoidosis.

In the second scenario, signs or symptoms suggesting sarcoidosis such as the presence of bilateral adenopathy may be present in an otherwise asymptomatic patient or a patient with uveitis or a rash consistent with sarcoidosis. At this point, a diagnostic procedure should be performed. For the patient with a compatible skin lesion, a skin biopsy should be considered. Other biopsies to consider could include liver, extrathoracic lymph node, or muscle. In some cases, a biopsy of the affected organ may not be easy to perform (such as a brain or spinal cord lesion). In other cases, such as an endomyocardial biopsy, the likelihood of a positive biopsy is low. Because of the high rate of pulmonary involvement in these cases, the lung may be easier to approach by bronchoscopy. During the bronchoscopy, a transbronchial biopsy, bronchial biopsy, or transbronchial needle aspirate can be performed. The endobronchial ultrasonography-guided (EBUS) transbronchial needle aspirate can assist in diagnosing sarcoidosis in patients with mediastinal adenopathy (stage 1 or 2 radiographic pulmonary disease), whereas transbronchial biopsy has a higher diagnostic yield for those with only parenchymal lung disease (stage 3). These tests are complementary and may be performed together.

If the biopsy reveals granulomas, an alternative diagnosis such as infection or malignancy must be excluded. Bronchoscopic washings can be sent for cultures for fungi and tuberculosis. For the pathologist,

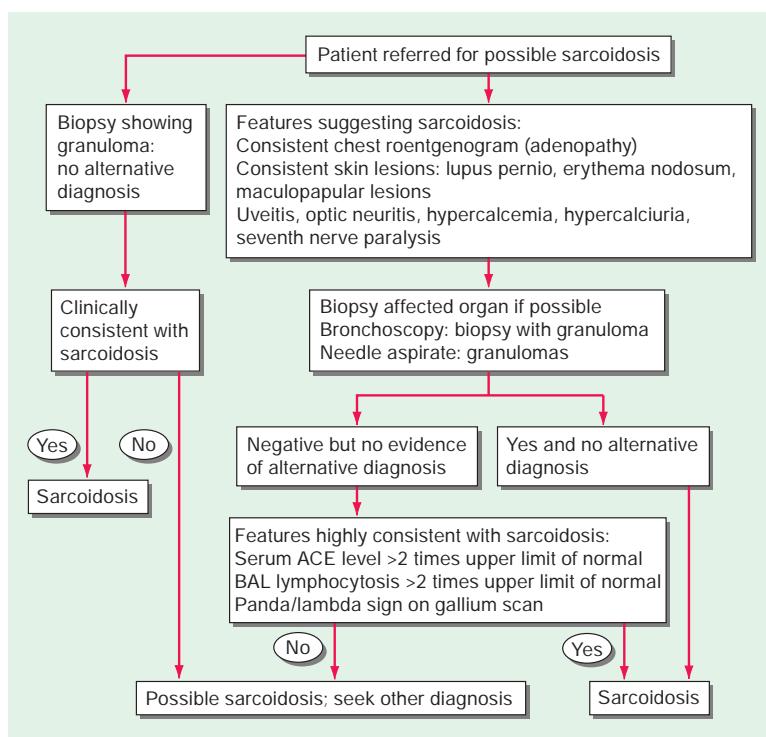


FIGURE 367-8 Proposed approach to management of a patient with possible sarcoidosis. Presence of one or more of the following features supports the diagnosis of sarcoidosis: uveitis, optic neuritis, hypercalcemia, hypercalciuria, seventh cranial nerve paralysis, and/or diabetes insipidus. ACE, angiotensin-converting enzyme; BAL, bronchoalveolar lavage.

the more tissue that is provided, the more comfortable is the diagnosis of sarcoidosis. A needle aspirate may be adequate in an otherwise classic case of sarcoidosis but may be insufficient in a patient in whom lymphoma or fungal infection is a likely alternative diagnosis. Because granulomas can be seen on the edge of a lymphoma, the presence of a few granulomas from a needle aspirate may not be sufficient to clarify the diagnosis. Mediastinoscopy provides a larger sample to confirm the presence or absence of lymphoma in the mediastinum. Alternatively, for most patients, evidence of extrathoracic disease (e.g., eye involvement) may further support the diagnosis of sarcoidosis.

For patients with negative pathology, positive supportive tests may increase the likelihood of the diagnosis of sarcoidosis. These tests include an elevated ACE level, which can also be elevated in other granulomatous diseases but not in malignancy. A positive PET scan can support the diagnosis if multiple organs are affected. BAL is often performed during the bronchoscopy. An increase in the percentage of lymphocytes supports the diagnosis of sarcoidosis. The lymphocyte markers CD4 and CD8 can be used to determine the CD4/CD8 ratio of these increased lymphocytes in the BAL fluid. A ratio of >3.5 is strongly supportive of sarcoidosis but is less sensitive than an increase in lymphocytes alone. Although in general an increase in BAL lymphocytes is supportive of the diagnosis, other conditions must be considered.

Supportive findings, when combined with commonly associated but nondiagnostic clinical features of the disease, improve the diagnostic probability of sarcoidosis. These clinical features include uveitis, renal stones, hypercalcemia, seventh cranial nerve paralysis, and erythema nodosum. A sarcoidosis diagnostic score has been developed that incorporates the cumulative information from multiorgan involvement and allows one to quantitate the likelihood of sarcoidosis.

Because the diagnosis of sarcoidosis can never be certain, over time, other features may arise that lead to an alternative diagnosis. Conversely, evidence for new organ involvement may eventually confirm the diagnosis of sarcoidosis.

PROGNOSIS

The risk of death or loss of organ function remains low in sarcoidosis. Poor outcomes usually occur in patients who present with advanced disease in whom treatment seems to have little impact. In these cases, irreversible fibrotic changes have frequently occurred. The overall mortality of sarcoidosis is approximately 5%. Mortality is associated with advanced pulmonary fibrosis ($>20\%$ fibrosis on chest CT scan and/or $\text{DL}_{\text{CO}} < 50\%$) and pulmonary hypertension. Over the past 20 years, the reported mortality from sarcoidosis has increased in the United States and England. Whether this is due to heightened

awareness of the chronic nature of this disease or to other factors such as more widespread immunosuppressive therapy usage remains unclear.

For the majority of patients, initial presentation occurs during the granulomatous phase of the disease, as depicted in Fig. 367-1. It is clear that many patients resolve their disease within 2–5 years. These patients are felt to have acute, self-limiting sarcoidosis. However, there is a form of the disease that does not resolve within the first 2–5 years. These chronic patients can be identified at presentation by certain risk factors at presentation such as fibrosis on chest roentgenogram, presence of lupus pernio, bone cysts, cardiac or neurologic disease (except isolated seventh nerve paralysis), and presence of renal calculi due to hypercalcemia. In several studies, patients who required glucocorticoids for any manifestation of their disease in the first 6 months of presentation had a $>50\%$ chance of having chronic disease. In contrast, $<10\%$ of patients who required no systemic therapy in the first 6 months required chronic therapy.

TREATMENT

Sarcoidosis

The decision to treat sarcoidosis is based on two indications: to avoid danger or improve quality of life. A dangerous outcome from sarcoidosis is the possibility of organ- or life-threatening disease, including disease involving the eye, heart, or nervous system. The patient with asymptomatic elevated liver function tests or an abnormal chest roentgenogram probably does not benefit from treatment. However, these patients should be monitored for evidence of progressive, symptomatic disease. Improvement of quality of life is an important indication to treat; however, one must be careful to avoid toxicity from therapy that is more problematic than the disease itself.

One approach to therapy is summarized in Figs. 367-9 and 367-10. We have divided the approach into treating acute versus chronic disease. For acute disease, no therapy remains a viable option for patients with no or mild symptoms. For symptoms confined to only one organ, topical therapy is preferable. For multiorgan disease or disease too extensive for topical therapy, an approach to systemic therapy is outlined. Glucocorticoids remain the drugs of choice for this disease. However, the decision to continue to treat with glucocorticoids or to add steroid-sparing agents depends on the tolerability, duration, and dosage of glucocorticoids. Table 367-2 summarizes the dosage and monitoring of several commonly used drugs. According to the available trials, evidence-based recommendations

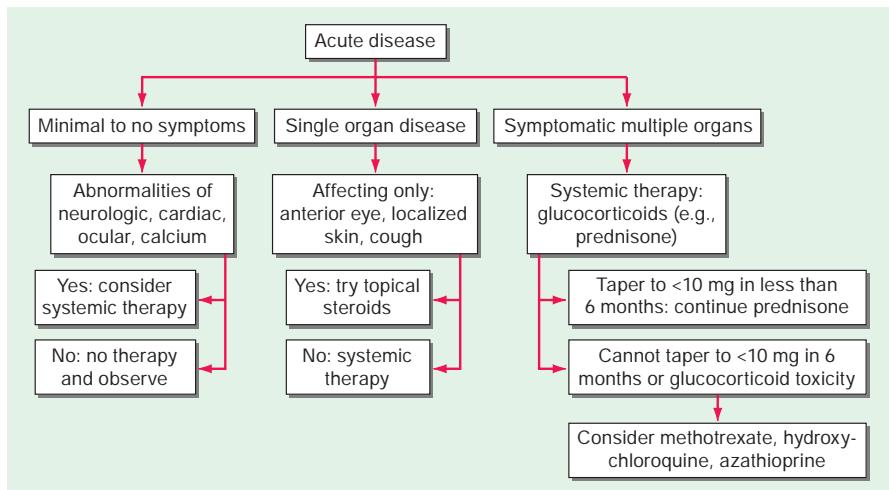


FIGURE 367-9 The management of acute sarcoidosis is based on level of symptoms and extent of organ involvement. In patients with mild symptoms, no therapy may be needed unless specified manifestations are noted.

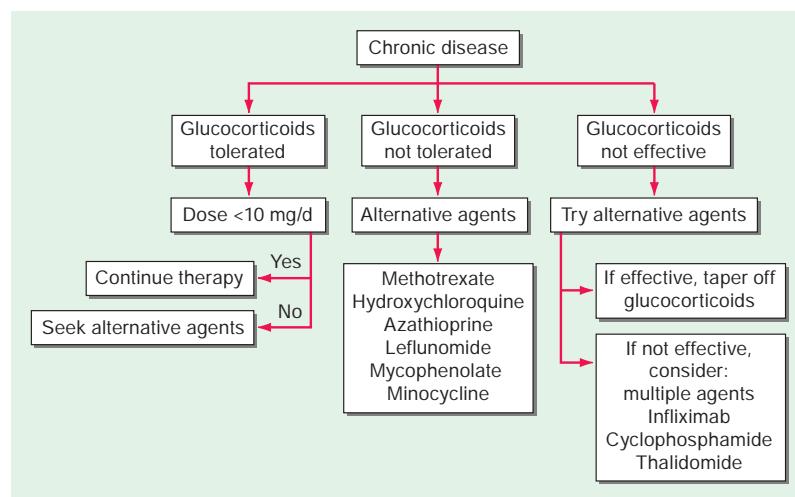


FIGURE 367-10 Approach to chronic disease is based on whether glucocorticoid therapy is tolerated or not.

are made. Most of these recommendations are for pulmonary disease because most of the trials were performed only in pulmonary disease. Treatment recommendations for extrapulmonary disease are usually similar with a few modifications. For example, the dosage of glucocorticoids is usually higher for neurosarcoidosis and lower for cutaneous disease. There was some suggestion that higher doses would be beneficial for cardiac sarcoidosis, but one study found that initial prednisone doses >40 mg/d were associated with a worse outcome because of toxicity.

Systemic therapies for sarcoidosis are usually immunosuppressive, including glucocorticoids, cytotoxics, or biologics. Although most patients receive glucocorticoids as their initial systemic therapy, toxicity associated with prolonged therapy often leads to steroid-sparing alternatives. The antimalarial drugs, such as hydroxychloroquine, are more effective for skin than pulmonary disease. Minocycline may also be useful for cutaneous sarcoidosis. For pulmonary and other extrapulmonary disease, cytotoxic agents that include methotrexate, azathioprine, leflunomide, mycophenolate, and cyclophosphamide are often used. The most widely studied cytotoxic agent has been methotrexate. This agent works in approximately two-thirds of sarcoidosis patients, regardless of the disease manifestation. In one retrospective study comparing

methotrexate with azathioprine, both drugs were equally effective. However, methotrexate was associated with significantly less toxicity. As noted in Table 367-2, specific guidelines for monitoring therapy have been recommended. Cytokine modulators such as thalidomide and pentoxifylline have also been used in a limited number of cases.

The biologic anti-TNF agents have recently been studied in sarcoidosis, with prospective randomized trials completed for etanercept, golimumab, and infliximab. Etanercept has a limited role as a steroid-sparing agent. Golimumab was not significantly different than placebo in treating chronic pulmonary disease. However, this may have been due to the relatively low dose of golimumab studied. Infliximab significantly improved lung function when administered to glucocorticoid and cytotoxic pretreated patients with chronic disease. The difference in response between etanercept and infliximab is similar to that observed in Crohn's disease, where infliximab is effective and etanercept is not. However, there is a higher risk for reactivation of tuberculosis with infliximab compared with etanercept. The differential response rate could be explained by differences in mechanism of action because etanercept is a TNF receptor antagonist and infliximab is a monoclonal antibody against TNF. In contrast to etanercept, infliximab also binds to TNF on the surface

TABLE 367-2 Commonly Used Drugs to Treat Sarcoidosis

DRUG	INITIAL DOSE	MAINTENANCE DOSE	MONITORING	TOXICITY	SUPPORT THERAPY ^a	SUPPORT MONITORING ^a
Prednisone	20–40 mg qd	Taper to 5–10 mg	Glucose, blood pressure, bone density	Diabetes, osteoporosis	A: Acute pulmonary D: Extrapulmonary	
Hydroxychloroquine	200–400 mg qd	400 mg qd	Eye examination q6–12 mo	Ocular	B: Some forms of disease	D: Routine eye examination
Methotrexate	10 mg qwk	2.5–15 mg qwk	CBC, renal, hepatic q2mo	Hematologic, nausea, hepatic, pulmonary	B: Steroid sparing C: Some forms chronic disease	D: Routine hematologic, renal, and hepatic monitoring
Azathioprine	50–150 mg qd	50–200 mg qd	CBC, renal q2mo	Hematologic, nausea	C: Some forms chronic disease	D: Routine hematologic monitoring
Infliximab	3–5 mg/kg q2wk for 2 doses	3–10 mg/kg q4–8 wk	Initial PPD	Infections, allergic reaction, carcinogen	A: Chronic pulmonary disease B: Caution in patients with latent tuberculosis or advanced congestive heart failure	

^aGrade A: supported by at least two double-blind randomized control trials; grade B: supported by prospective cohort studies; grade C: supported primarily by two or more retrospective studies; grade D: only one retrospective study or based on experience in other diseases.

Abbreviations: CBC, complete blood count; PPD, purified protein derivative test for tuberculosis.

Source: Reproduced with permission from RP Baughman, O Selroos: Evidence-based approach to treatment of sarcoidosis in PG Gibson et al (eds): Evidence-based respiratory medicine. Oxford, BMJ Books Blackwell, 2005.

of some cells that release TNF, which leads to cell lysis. This effect has been documented in Crohn's disease. Adalimumab is a humanized monoclonal anti-TNF antibody that also appears effective for sarcoidosis when dosed at higher strengths, as recommended for the treatment of Crohn's disease. The role of the newer therapeutic agents for sarcoidosis is still evolving. However, these targeted therapies confirm that TNF may be an important target, especially in the treatment of chronic disease. However, these agents are not a panacea because sarcoidosis-like disease has occurred in patients treated with anti-TNF agents for nonsarcoidosis indications.

FURTHER READING

- Baughman RP et al: Sarcoidosis in America. Analysis based on health care use. Ann Am Thorac Soc 13:1244, 2016.
- Bickett AN et al: Sarcoidosis diagnostic score: A systematic evaluation to enhance the diagnosis of sarcoidosis. Chest 154:1052, 2018.
- Broos CE et al: Granuloma formation in pulmonary sarcoidosis. Front Immunol 4:437, 2013.
- James WE, Baughman R: Treatment of sarcoidosis: Grading the evidence. Expert Rev Clin Pharmacol 11:677, 2018.
- Spagnolo P et al: Pulmonary sarcoidosis. Lancet Respir Med 6:389, 2018.

and submandibular glands, is one of the most common presentations of IgG4-RD.

CLINICAL FEATURES

The major organ lesions are summarized in **Table 368-1**. IgG4-RD usually presents subacutely, and even in the setting of multiorgan disease, most patients do not have fevers or high elevations of C-reactive protein levels. Some patients, however, experience substantial weight loss over periods of months, largely because of exocrine pancreatic failure. Failure of the endocrine pancreas, leading to diabetes mellitus, is also common. Clinically apparent disease can evolve over months, years, or even decades before the manifestations within a given organ become sufficiently severe to bring the patient to medical attention. Some patients have disease that is marked by the appearance and then resolution or temporary improvement in symptoms within a particular organ. Other patients accumulate new organ involvement as their disease persists in previously affected organs. Many patients with IgG4-RD are misdiagnosed as having other conditions, particularly malignancies, or their findings are attributed initially to nonspecific inflammation. The disorder is often identified incidentally through radiologic findings or unexpectedly in pathology specimens.

Multiorgan disease may be evident at diagnosis but can also evolve over months to years. Some patients have disease confined to a single organ for many years. Others have either known or subclinical organ involvement at the same time as the major clinical feature. Patients with type 1 AIP may have their major disease focus in the pancreas; however, thorough evaluations by history, physical examination, blood tests, and cross-sectional imaging may demonstrate lacrimal gland enlargement, sialadenitis, lymphadenopathy, a variety of pulmonary findings, tubulointerstitial nephritis, hepatobiliary disease, aortitis, retroperitoneal fibrosis, or other organ involvement.

Two common characteristics of IgG4-RD are allergic disease and the tendency to form tumefactive lesions that mimic malignancies (**Fig. 368-1**). Many IgG4-RD patients have allergic features such as atopy, eczema, asthma, nasal polyps, sinusitis, and modest peripheral eosinophilia. IgG4-RD also appears to account for a significant proportion of tumorous swellings—pseudotumors—in many organ systems (**Fig. 368-2**). Some patients undergo major surgeries (e.g., modified Whipple procedures or thyroidectomy) for the purpose of resecting malignancies before the correct diagnosis is identified.

IgG4-RD often causes major morbidity and can lead to organ failure; however, its general pattern is to cause damage in a subacute manner. Destructive bone lesions in the sinuses, head, and middle ear spaces that mimic granulomatosis with polyangiitis occur occasionally in IgG4-RD, but less aggressive lesions are the rule in most organs. In regions such as the retroperitoneum, substantial fibrosis often occurs before the diagnosis is established, leading to ureteral entrapment, hydronephrosis, postobstructive uropathy, and renal atrophy. Undiagnosed or undertreated IgG4-related sclerosing cholangitis can lead to hepatic failure within months. Similarly, IgG4-related aortitis can cause aneurysms and dissections. Substantial renal dysfunction and even renal failure can ensue from IgG4-related tubulointerstitial nephritis, and renal atrophy is a frequent sequel to this disease complication even following apparently effective immunosuppressive therapy. IgG4-related membranous glomerulonephropathy, a less common renal manifestation than tubulointerstitial nephritis, must be distinguished from idiopathic membranous glomerulonephropathy.

SEROLOGIC FINDINGS

The majority of patients with IgG4-RD have elevated serum IgG4 concentrations; however, the range of elevation varies widely. Serum concentrations of IgG4 as high as 30 or 40 times the upper limit of normal sometimes occur, usually in patients with disease that affects multiple organ systems simultaneously. Approximately 30% of patients have normal serum IgG4 concentrations despite classic histopathologic and immunohistochemical findings. Such patients tend to have disease that affects fewer organs. Patients with IgG4-related retroperitoneal fibrosis often have normal serum IgG4 concentrations, perhaps because the process has advanced to a fibrotic stage by the time the diagnosis is considered.

368

IgG4-Related Disease

John H. Stone



TABLE 368-1 Organ Manifestations of IgG4-Related Disease

ORGAN	MAJOR CLINICAL FEATURES
Orbits and periorbital tissues	Painless eyelid or periorcular tissue swelling; orbital pseudotumor; dacryoadenitis; dacryocystitis; orbital myositis; and mass lesions extending into the pterygopalatine fossa and infiltrating along the trigeminal nerve
Ears, nose, and sinuses	Allergic phenomena (nasal polyps, asthma, allergic rhinitis, peripheral eosinophilia); nasal obstruction, rhinorrhea, anosmia, chronic sinusitis; occasional bone-destructive lesions
Salivary glands	Submandibular and/or parotid gland enlargement (isolated bilateral submandibular gland involvement more common); minor salivary glands sometimes involved
Meninges	Headache, radiculopathy, cranial nerve palsies, or other symptoms resulting from spinal cord compression; tendency to form mass lesions; MRI shows marked thickening and enhancement of dura
Hypothalamus and pituitary	Clinical syndromes resulting from involvement of the hypothalamus and pituitary, e.g., anterior pituitary hormone deficiency, central diabetes insipidus, or both; imaging reveals thickened pituitary stalk or mass formation on the stalk, swelling of the pituitary gland, or mass formation within the pituitary
Lymph nodes	Generalized lymphadenopathy or localized disease adjacent to a specific affected organ; the lymph nodes involved are generally 1–2 cm in diameter and nontender
Thyroid gland	Riedel's thyroiditis; fibrosing variant of Hashimoto's thyroiditis
Lungs	Asymptomatic finding on lung imaging; cough, hemoptysis, dyspnea, pleural effusion, or chest discomfort; associated with parenchymal lung involvement, pleural disease, or both; four main clinical lung syndromes: inflammatory pseudotumor, paravertebral mass often extending over several vertebrae, central airway disease, localized or diffuse interstitial pneumonia; pleural lesions have severe, nodular thickening of the visceral or parietal pleura with diffuse sclerosing inflammation, sometimes associated with pleural effusion
Aorta	Asymptomatic finding on radiologic studies; surprise finding at elective aortic surgery; aortic dissection; clinicopathologic syndromes described include lymphoplasmacytic aortitis of thoracic or abdominal aorta, aortic dissection, periaortitis and periarteritis, and inflammatory abdominal aneurysm
Retroperitoneum	Backache, lower abdominal pain, lower extremity edema, hydronephrosis from ureteral involvement, asymptomatic finding on radiologic studies. Classic radiologic appearance is periaortic inflammation extending caudally to involve the iliac vessels.
Kidneys	Tubulointerstitial nephritis; membranous glomerulonephritis in a small minority; asymptomatic tumoral lesions, typically multiple and bilateral, are sometimes detected on radiologic studies; renal involvement strongly associated with hypocomplementemia
Pancreas	Type 1 autoimmune pancreatitis, presenting as mild abdominal pain; weight loss; acute, obstructive jaundice, mimicking adenocarcinoma of the pancreas (including a pancreatic mass); between 20 and 50% of patients present with acute glucose intolerance; imaging shows diffuse (termed "sausage-shaped pancreas") or segmental pancreatic enlargement, with loss of normal lobularity; a mass often raises the suspicion of malignancy
Biliary tree and liver	Obstructive jaundice associated with autoimmunity in most cases; weight loss; steatorrhea; abdominal pain; and new-onset diabetes mellitus; mimicker of primary sclerosing cholangitis and cholangiocarcinoma
Other organs involved	Gallbladder, liver (mass), breast (pseudotumor), prostate (prostatism), pericardium (constrictive pericarditis), mesentery (sclerosing mesenteritis), mediastinum (fibrosing mediastinitis), skin (erythematous or flesh-colored papules), peripheral nerve (perineurial inflammation)

Correlations between serum IgG4 concentrations, disease activity, and the need for treatment are imperfect. Serum IgG4 concentrations typically decline swiftly with the institution of therapy but often do not normalize completely. Patients can achieve clinical remissions yet have persistently elevated serum IgG4 concentrations. Following treatment and a disease response, however, steadily rising serum IgG4

concentrations are useful in identifying patients at risk for clinical flares who should be considered for re-treatment. Clinical relapses occur in some patients despite persistently normal IgG4 concentrations.

IgG4 concentrations in serum are usually measured by nephelometry assays. In the setting of extremely high serum IgG4 concentrations, these assays can generate spuriously low IgG4 values because of the



A



B

FIGURE 368-1 A major clinical feature of IgG4-related disease is its tendency to form tumefactive lesions. Shown here are mass lesions of the lacrimal glands (**A**) and the submandibular glands (**B**).

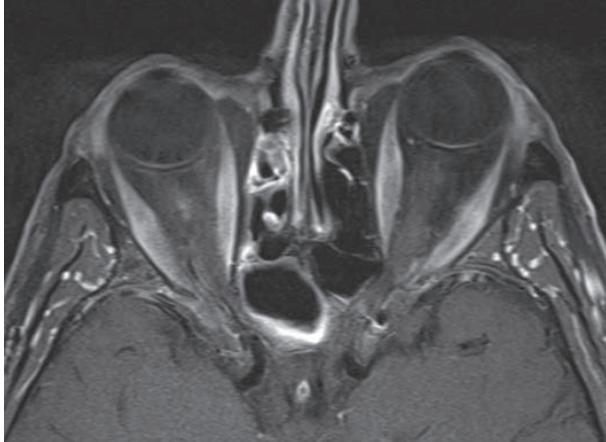
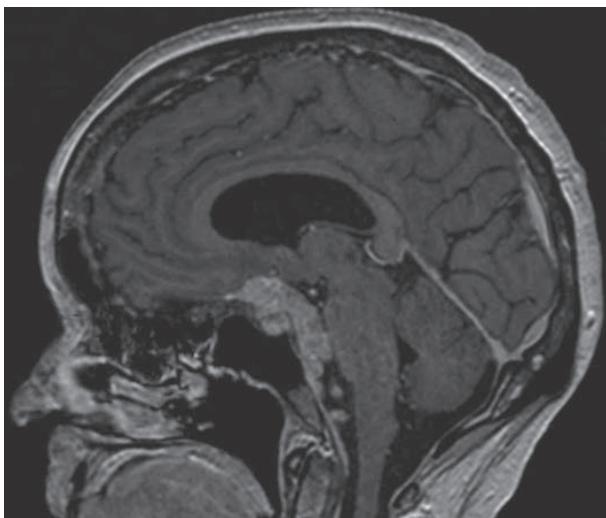
**A****B**

FIGURE 368-2 Thickening of extraocular muscles and meninges. **A.** Computed tomography scan of the orbits, showing enlargement of extraocular muscles in a patient with IgG4-related orbital disease. **B.** Computed tomography scan of the brain, showing thickening of the pachymeninges.

prozone effect. Failure to identify dramatic serum IgG4 elevations can have a substantial impact on patients because that subset of patients is at greatest risk for multiorgan disease and substantial end-organ injury. The prozone effect should be considered when the results of serologic testing for IgG4 concentrations are normal despite the presence of clinical features that strongly suggest IgG4-RD. This effect can be corrected by dilution of the serum sample in the laboratory.

EPIDEMIOLOGY

The typical patient with IgG4-RD is a middle-aged to elderly man. This epidemiology stands in stark contrast to that of many classic autoimmune conditions, which tend to affect young women. Studies of AIP patients in Japan indicate that the male-to-female ratio in that disease subset is on the order of 3:1. A striking male predominance has also been reported in IgG4-related tubulointerstitial nephritis and IgG4-related retroperitoneal fibrosis, but among IgG4-RD manifestations that involve organs of the head and neck—the orbits, lacrimal glands, and major salivary glands—the sex ratio may be closer to 1:1.

PATHOLOGY

The key histopathology characteristics of IgG4-RD are a dense lymphoplasmacytic infiltrate (**Fig. 368-3**) that is organized in a storiform

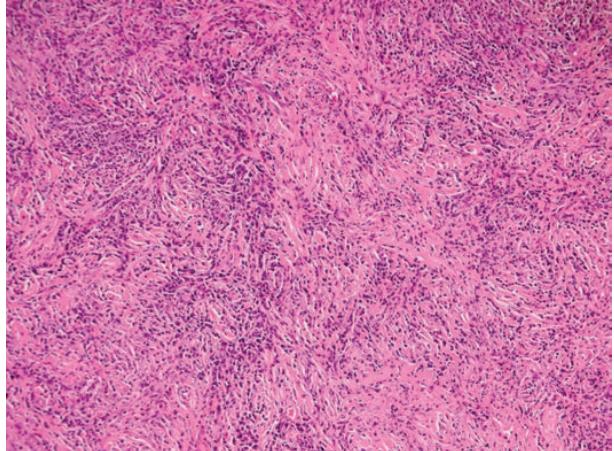


FIGURE 368-3 Hallmark histopathology characteristics of IgG4-related disease (IgG4-RD) are a dense lymphoplasmacytic infiltrate and a mild to moderate eosinophilic infiltrate. The cellular inflammation is often encased in a distinctive type of fibrosis termed "storiform," which often has a basket weave pattern. Abundant fibroblasts and strands of fibrosis accompany the lymphoplasmacytic infiltrate in this figure. This biopsy is from a patient with IgG4-related hypertrophic pachymeningitis. However, the findings are identical to the pathology found in the pancreas, kidneys, lungs, salivary glands, and other organs affected by IgG4-RD.

pattern, obliterative phlebitis, and a mild to moderate eosinophilic infiltrate. Lymphoid follicles and germinal centers are frequently observed. The infiltrate tends to aggregate around ductal structures when it affects glands. The inflammatory lesion often aggregates into tumefactive masses that destroy the involved tissue.

Obliterative arteritis is observed in some organs, particularly the lung; however, venous involvement is more common (and is indeed a hallmark of IgG4-RD). Several histopathology features are uncommon in IgG4-RD and, when detected, mitigate against the diagnosis of IgG4-RD. These include intense neutrophilic infiltration, leukocytoclasia, granulomatous inflammation, multinucleated giant cells, and fibrinoid necrosis.

The inflammatory infiltrate is composed of an admixture of B and T lymphocytes. B cells are typically organized in germinal centers. Plasma cells staining for CD19, CD138, and IgG4 appear to radiate from the germinal centers. In contrast, the T cells, usually CD4+, are distributed more diffusely throughout the lesion and generally represent the most abundant cell type. Fibroblasts, histiocytes, and eosinophils can all be observed in moderate numbers. Some biopsy samples are particularly enriched with eosinophils. In other samples, particularly from longstanding cases, fibrosis predominates.

The histologic appearance of IgG4-RD, although highly characteristic, requires immunohistochemical confirmation of the diagnosis with IgG4 immunostaining. IgG4-positive plasma cells predominate within the lesion, but plasma cells containing immunoglobulins from each subclass can be found. The number of IgG4-positive plasma cells can be quantified by either counting the number of cells per high-power field (HPF) or by calculating the ratio of IgG4- to IgG-bearing plasma cells. Tissue fibrosis predominates in the latter phases of organ involvement, and in this relatively acellular phase of inflammation, both the IgG4:total IgG ratio and the pattern of tissue fibrosis are more important than the number of IgG4-positive cells per HPF in establishing the diagnosis.

PATOPHYSIOLOGY

Despite the emphasis of IgG4 in the name of this disease, the IgG4 molecule is not believed to play a direct role in the pathophysiology of disease within most organs. The IgG4 molecule can undergo Fab exchange, a phenomenon in which the two halves of the molecule dissociate from each other and reassociate with hemi-molecules of different antigen specificity that have originated from other dissociated

IgG4 molecules. Partly as a result of this Fab exchange, IgG4 antibodies do not bind antigen tightly. Moreover, the molecules have low affinities for Fc receptors and C1q and are regarded generally as noninflammatory immunoglobulins. The low affinities for Fc receptors and C1q impair the ability of IgG4 antibodies to induce phagocyte activation, antibody-dependent cellular cytotoxicity, and complement-mediated damage. It is possible, therefore, that the role of IgG4 in this disease is actually as a counterregulatory mechanism rather than part of the primary inflammatory process.

Next-generation sequencing studies of CD4+ effector T cells have demonstrated a unique CD4+ cytotoxic T cell. This cell, also found in abundance at tissue sites of disease, makes interferon γ , T-cell growth factor- β , and interleukin-1, all of which may contribute to the storiform fibrosis found in this condition. The cells also elaborate perforin, granzyme A and B, and granulysin, products capable of inducing cytotoxicity. The pronounced oligoclonal expansion of this CD4+ cytotoxic T cell at tissue sites suggests that this cell is a major disease driver.

Oligoclonal expansions of plasmablasts are also present within the blood of patients with IgG4-RD. Continuous antigen presentation by B cells and plasmablasts may support this cell, which in turn produces profibrotic cytokines and other molecules, thereby directly mediating tissue injury.

TREATMENT

Vital organ involvement must be treated aggressively because IgG4-RD can lead to serious organ dysfunction and failure. Aggressive disease can lead quickly to end-stage liver disease, permanent impairment of pancreatic function, renal atrophy, aortic dissection or aneurysms, and destructive lesions in the sinuses and nasopharynx. Not every disease manifestation of IgG4-RD requires immediate treatment, however, because the disease may take an indolent form in some patients. IgG4-related lymphadenopathy, for example, can be asymptomatic for years, without evolution to other disease manifestations. Thus, watchful waiting is prudent in some cases, but monitoring is essential because serious organ involvement may evolve over time.

Glucocorticoids are the first line of therapy. Treatment regimens, extrapolated from experience with the management of type 1 AIP, generally begin with 40 mg/d of prednisone, with tapering to discontinuation or maintenance doses of 5 mg/d within 2 or 3 months. Although the clinical response to glucocorticoids is usually swift and striking, prolonged steroid-free remissions are uncommon and the risk of steroid-induced morbidity in this middle-aged to elderly patient population is high, particularly in those with baseline comorbidities and pancreatic involvement by IgG4-RD. Few data exist to support the utility of conventional steroid-sparing agents in this disease.

For patients with relapsing or glucocorticoid-resistant disease, B-cell depletion with rituximab is an excellent second-line therapy. Rituximab treatment (two doses of 1 g IV, separated by approximately 15 days) leads to a swift decline in serum IgG4 concentrations, suggesting that rituximab achieves its effects in part by preventing the repletion of short-lived plasma cells that produce IgG4. More important than its effects on IgG4 concentrations, however, may be the effect of B-cell depletion on T-cell function. Specific effects of rituximab on the CD4+ cytotoxic T cell described above have been documented in IgG4-RD. Rituximab may be an appropriate first-line therapy for some patients, particularly those at high risk for glucocorticoid toxicity and patients with immediately organ-threatening disease. The rapidly evolving understanding of the pathophysiology of IgG4-RD suggests several novel targeted approaches to treating the disease, some of which are in clinical trials. These novel strategies include inhibition of Bruton's tyrosine kinase, the depletion of CD19+ cells of the B lymphocyte lineage, and targeting of SLAM-F7, the molecule found on the surfaces of both B lymphocytes and the CD4+ cytotoxic T lymphocyte. Both of these cell types have been implicated in disease pathophysiology.

FURTHER READING

Perugino CA, Stone JH: IgG4-related disease: An update on pathophysiology and implications for clinical care. *Nat Rev Rheumatol* 16:702, 2020.

Perugino CA et al: CD4+ and CD8+ cytotoxic T lymphocytes may induce mesenchymal cell apoptosis in IgG₄-related disease. *J Allergy Clin Immunol* 147:368, 2021.

Wallace ZS et al: The 2019 American College of Rheumatology/European League Against Rheumatism classification criteria for IgG4-related disease. *Arthritis Rheumatol* 72:7, 2020.

Wallace ZS et al: The 2019 American College of Rheumatology/European League Against Rheumatism classification criteria for IgG4-related disease. *Ann Rheum Dis* 79:77, 2020.

Wallwork R et al: Rituximab for idiopathic and IgG4-related retroperitoneal fibrosis. *Medicine (Baltimore)* 97:e12631, 2018.

Zhang W, Stone JH: Management of IgG4-RD. *Lancet Rheumatol* 1:e55, 2019.

369

Familial Mediterranean Fever and Other Hereditary Autoinflammatory Diseases

Daniel L. Kastner



Familial Mediterranean fever (FMF) is the prototype of a group of inherited diseases (**Table 369-1**) that are characterized by recurrent episodes of fever with serosal, synovial, or cutaneous inflammation and, in some individuals, the eventual development of systemic AA amyloidosis (**Chap. 112**). Because of the relative infrequency of high-titer autoantibodies or antigen-specific T cells, the term *autoinflammatory* has been proposed to describe these disorders, rather than autoimmune. The innate immune system, with its myeloid effector cells and germline receptors for pathogen-associated molecular patterns and endogenous danger signals, plays a predominant role in the pathogenesis of the autoinflammatory diseases. Although the hereditary recurrent fevers comprise a major category of the autoinflammatory diseases, other inherited disorders of inflammation in which recurrent fever plays a less prominent role are now also considered to be autoinflammatory.

BACKGROUND AND PATHOPHYSIOLOGY

FMF was first recognized among Armenians, Arabs, Turks, and non-Ashkenazi (primarily North African and Iraqi) Jews. With the advent of genetic testing, FMF has been documented with increasing frequency among Ashkenazi Jews, Italians, and other Mediterranean populations, and occasional cases have been confirmed even in the absence of known Mediterranean ancestry. FMF is generally regarded as recessively inherited, but there is an increasing awareness of clear-cut clinical cases with only a single demonstrable genetic mutation, and for certain relatively rare FMF mutations, there is strong evidence for dominant inheritance. Particularly in countries where families are small, a positive family history can only be elicited in ~50% of cases. DNA testing demonstrates carrier frequencies as high as 1:10 among affected populations, most likely due to some selective advantage.

The FMF gene encodes a 781-amino-acid, ~95-kDa protein denoted *pyrin* that is expressed in granulocytes, eosinophils, monocytes, dendritic cells, and synovial and peritoneal fibroblasts. The N-terminal 92 amino acids of pyrin define a motif, the PYRIN domain, that mediates homotypic protein-protein interactions and has been found in several other proteins, including cryopyrin (NLRP3), which is mutated in three other recurrent fever syndromes. Through the interaction of its PYRIN domain with an intermediary adaptor protein, pyrin nucleates the formation of a macromolecular *pyrin inflammasome* to activate caspase-1 (interleukin [IL] 1 β -converting enzyme) and thereby IL-1 β

TABLE 369-1 The Hereditary Recurrent Fever Syndromes

	FMF	TRAPS	HIDS/MKD	MWS	FCAS	NOMID
Ethnicity	Jewish, Arab, Turkish, Armenian, Italian	Any ethnic group	Predominantly Dutch, northern European	Any ethnic group	Any ethnic group	Any ethnic group
Inheritance	Recessive or dominant ^a	Dominant	Recessive	Dominant	Dominant	Most commonly de novo mutations; somatic mosaicism in a significant minority
Gene/chromosome	<i>MEFV</i> 16p13.3	<i>TNFRSF1A</i> 12p13	<i>MVK</i> 12q24	<i>NLRP3</i> 1q44	<i>NLRP3</i> 1q44	<i>NLRP3</i> 1q44
Protein	Pyrin	p55 TNF receptor	Mevalonate kinase	<i>NLRP3</i> (cryopyrin)	<i>NLRP3</i> (cryopyrin)	<i>NLRP3</i> (cryopyrin)
Attack length	1–3 days	Often >7 days	3–7 days	1–2 days	Minutes–3 days	Continuous, with flares
Serosa	Pleurisy, peritonitis; asymptomatic pericardial effusions	Pleurisy, peritonitis, pericarditis	Abdominal pain, but seldom peritonitis; pleurisy, pericarditis uncommon	Abdominal pain; pleurisy, pericarditis rare	Rare	Rare
Skin	Erysipeloid erythema	Centrifugally migrating erythema	Diffuse maculopapular rash; oral ulcers	Diffuse urticaria-like rash	Cold-induced urticaria-like rash	Diffuse urticaria-like rash
Joints	Acute monoarthritis; chronic hip arthritis (rare)	Acute monoarthritis, arthralgia	Arthralgia, oligoarthritis	Arthralgia, large joint oligoarthritis	Polyarthralgia	Epiphyseal, patellar overgrowth, clubbing
Muscle	Exercise-induced myalgia common; protracted febrile myalgia rare	Migratory myalgia	Uncommon	Myalgia common	Sometimes myalgia	Sometimes myalgia
Eyes, ears	Uncommon	Periorbital edema, conjunctivitis, rarely uveitis	Uncommon	Conjunctivitis, episcleritis, optic disc edema; sensorineural hearing loss	Conjunctivitis	Conjunctivitis, uveitis, optic disc edema, blindness, sensorineural hearing loss
CNS	Aseptic meningitis rare	Headache	Headache	Headache	Headache	Aseptic meningitis, seizures
Amyloidosis	Most common in M694V homozygotes	~15% of cases, most often cysteine mutations, T50M	Sometimes associated with V377I/I268T MVK genotype	~25% of cases	Uncommon	Late complication
Treatment	Oral colchicine prophylaxis, IL-1 inhibitors for refractory cases	Glucocorticoids, IL-1 inhibitors, etanercept	NSAIDs for fever; IL-1 inhibitors	Canakinumab, rilonacept, anakinra	Canakinumab, rilonacept, anakinra	Anakinra

^aA substantial percentage of patients with clinical FMF have only a single demonstrable *MEFV* mutation on DNA sequencing.

Abbreviations: CNS, central nervous system; FCAS, familial cold autoinflammatory syndrome; FMF, familial Mediterranean fever; HIDS/MKD, hyperimmunoglobulinemia D with periodic fever syndrome, also known as mevalonate kinase deficiency; IL, interleukin; MWS, Muckle-Wells syndrome; NOMID, neonatal-onset multisystem inflammatory disease; NSAIDs, nonsteroidal anti-inflammatory drugs; TNF, tumor necrosis factor; TRAPS, TNF receptor-associated periodic syndrome.

and IL-18 secretion and gasdermin d-mediated cell death (pyroptosis). Certain bacterial toxins that block leukocyte cytoskeletal assembly by inactivating RhoA GTPase trigger pyrin inflammasome activation as a part of the normal host defense; in FMF patients, the threshold for pyrin inflammasome activation is reduced. Population genetic and immune functional studies support a role for bubonic plague pandemics in selecting for FMF founder mutations that had arisen in Biblical times in the Middle East.

ACUTE ATTACKS

Febrile episodes in FMF may begin even in early infancy; 90% of patients have had their first attack by age 20. Typical FMF episodes generally last 24–72 h, with arthritic attacks tending to last somewhat longer. In some patients, the episodes occur with great regularity, but more often, the frequency of attacks varies over time, ranging from as often as once every few days to remissions lasting several years. Attacks are often unpredictable, although some patients relate them to physical exertion, emotional stress, or menses; pregnancy may be associated with remission.

If measured, fever is nearly always present throughout FMF attacks. Severe hyperpyrexia and even febrile seizures may be seen in infants, and fever is sometimes the only manifestation of FMF in young children.

Over 90% of FMF patients experience abdominal attacks at some time. Episodes range in severity from dull, aching pain and distension with mild tenderness on direct palpation to severe generalized

pain with absent bowel sounds, rigidity, rebound tenderness, and air-fluid levels on upright radiographs. Computed tomography (CT) scanning may demonstrate a small amount of fluid in the abdominal cavity. If such patients undergo exploratory laparotomy, a sterile, neutrophil-rich peritoneal exudate is present, sometimes with adhesions from previous episodes. Ascites is rare.

Pleural attacks are usually manifested by unilateral, sharp, stabbing chest pain. Radiographs may show atelectasis and sometimes an effusion. If performed, thoracentesis demonstrates an exudative fluid rich in neutrophils. After repeated attacks, pleural thickening may develop.

FMF arthritis is most frequent among individuals homozygous for the M694V mutation, which is especially common in the non-Ashkenazi Jewish population. Acute arthritis in FMF is usually monoarticular, affecting the knee, ankle, or hip, although other patterns can be seen. Large sterile effusions rich in neutrophils are frequent, without commensurate erythema or warmth. Even after repeated arthritic attacks, radiographic changes are rare. Before the advent of colchicine prophylaxis, chronic arthritis of the knee or hip was seen in ~5% of FMF patients with arthritis. Chronic sacroiliitis can occur in FMF irrespective of the HLA-B27 antigen, even in the face of colchicine therapy. In the United States, FMF patients are much more likely to have arthralgia than arthritis.

The most characteristic cutaneous manifestation of FMF is erysipelas-like erythema, a raised erythematous rash that most commonly occurs on the dorsum of the foot, ankle, or lower leg alone or in combination with abdominal pain, pleurisy, or arthritis. Biopsy demonstrates perivascula-

infiltrates of granulocytes and monocytes. This rash is seen most often in M694V homozygotes and is relatively rare in the United States.

Exercise-induced (nonfebrile) myalgia is common in FMF, and a small percentage of patients develop a protracted febrile myalgia that can last several weeks. Symptomatic pericardial disease is rare, although small pericardial effusions may be noted on echocardiography. Unilateral acute scrotal inflammation may occur in prepubertal boys. Aseptic meningitis has been reported in FMF, but the causal connection is controversial. Vasculitis, including Henoch-Schönlein purpura and polyarteritis nodosa (**Chap. 363**), may be seen at increased frequency in FMF. The M694V FMF mutation has been shown to be a risk factor for Behcet's disease and ankylosing spondylitis.

Laboratory features of FMF attacks are consistent with acute inflammation and include an elevated erythrocyte sedimentation rate, leukocytosis, thrombocytosis (in children), and elevations in C-reactive protein, fibrinogen, haptoglobin, and serum immunoglobulins. Transient albuminuria and hematuria may also be seen.

AMYLOIDOSIS

Before the advent of colchicine prophylaxis, systemic amyloidosis was a common complication of FMF. It is caused by deposition of a fragment of serum amyloid A, an acute-phase reactant, in the kidneys, adrenals, intestine, spleen, lung, and testes (**Chap. 112**). Amyloidosis should be suspected in patients who have proteinuria between attacks; renal or rectal biopsy is used most often to establish the diagnosis. Risk factors include the M694V homozygous genotype, positive family history (independent of FMF mutational status), the SAA1 genotype, male gender, noncompliance with colchicine or IL-1 inhibitory therapy, and having grown up in the Middle East.

DIAGNOSIS

For typical cases, physicians experienced with FMF can often make the diagnosis on clinical grounds alone. Clinical criteria sets for FMF have been shown to have high sensitivity and specificity in parts of the world where the pretest probability of FMF is high. Genetic testing can provide a useful adjunct in ambiguous cases or for physicians not experienced in FMF. Most of the more severe disease-associated FMF mutations are in exon 10 of the gene. An updated list of mutations for FMF and other hereditary recurrent fevers can be found online at <http://fmf.igh.cnrs.fr/infevers/>.

Genetic testing has permitted a broadening of the clinical spectrum and geographic distribution of FMF and may be of prognostic value. Most studies indicate that M694V homozygotes have an earlier age of onset and a higher frequency of arthritis, rash, and amyloidosis. In contrast, the E148Q variant in exon 2 is quite common in certain Asian populations and is more likely to affect overall levels of inflammation than to cause clinical FMF. E148Q is sometimes found in *cis* with exon 10 mutations, which may complicate the interpretation of genetic test results. Only ~70% of patients with clinically typical FMF have two identifiable mutations in *trans*, consistent with the concept that FMF mutations are gain-of-function with regard to inflammasome activation, with a dosage effect. In those cases in which only a single mutation is identified, clinical judgment is very important, and sometimes a therapeutic trial of colchicine or an IL-1 inhibitor may help to confirm the diagnosis.

If a patient is seen during his or her first attack, the differential diagnosis may be broad, although delimited by the specific organ involvement. After several attacks, the differential diagnosis may include the other hereditary recurrent fever syndromes (Table 362-1); the syndrome of periodic fever with aphthous ulcers, pharyngitis, and cervical adenopathy (PFAPA); systemic-onset juvenile rheumatoid arthritis or adult Still's disease; porphyria; hereditary angioedema; inflammatory bowel disease; and, in women, gynecologic disorders.

TREATMENT

Familial Mediterranean Fever

The initial treatment of choice for FMF is daily oral colchicine, which decreases the frequency and intensity of attacks and prevents the development of amyloidosis in compliant patients. Intermittent

dosing at the onset of attacks is not as effective as daily prophylaxis and is of unproven value in preventing amyloidosis. The usual adult dose of colchicine is 1.2–1.8 mg/d, which causes substantial reduction in symptoms in two-thirds of patients and some improvement in >90%. Children may require lower doses, although not proportionately to body weight.

Common side effects of colchicine include bloating, abdominal cramps, lactose intolerance, and diarrhea. They can be minimized by starting at a low dose and gradually advancing as tolerated, splitting the dose, use of simethicone for flatulence, and avoidance of dairy products. If taken by either parent at the time of conception, colchicine may cause a small increase in the risk of trisomy 21 (Down's syndrome). Colchicine is usually continued during pregnancy, because the risk of miscarriage due to FMF attacks is thought to outweigh any effect of colchicine on fetal development. In elderly patients with renal insufficiency, colchicine can cause a myoneuropathy characterized by proximal muscle weakness and elevation of the creatine kinase. Cyclosporine inhibits hepatic excretion of colchicine by its effects on the multidrug resistance 1 (MDR1) transport system, sometimes leading to colchicine toxicity in patients who have undergone renal transplantation for amyloidosis. Intravenous colchicine should generally not be administered to patients already taking oral colchicine, because severe, sometimes fatal, toxicity has been observed in this setting.

For FMF patients who do not respond to colchicine or cannot tolerate therapeutic doses, injectable IL-1 inhibitors may be used. Based on a randomized placebo-controlled phase 3 trial, the monoclonal anti-IL-1 β antibody canakinumab received U.S. Food and Drug Administration (FDA) approval for this indication. In a small randomized placebo-controlled trial, weekly subcutaneous rilonacept, a recombinant IL-1 receptor fusion protein, significantly reduced the frequency of attacks. There is also substantial anecdotal experience with daily subcutaneous anakinra, a recombinant IL-1 receptor antagonist, in preventing the acute attacks of FMF and, in some cases, reducing established amyloid deposits. Bone marrow transplantation has been suggested for refractory FMF, but the risk-benefit ratio is currently regarded as unacceptable.

OTHER HEREDITARY RECURRENT FEVERS

TNF RECEPTOR-ASSOCIATED PERIODIC SYNDROME

Tumor necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS) is caused by dominantly inherited mutations in the extracellular domains of the 55-kDa TNF receptor (TNFR1, p55). Although originally described in a large Irish family (and hence the name *familial Hibernian fever*), TRAPS has a broad ethnic distribution. TRAPS episodes often begin in childhood. The duration of attacks ranges from 1 to 2 days to as long as several weeks, and in severe cases, symptoms may be nearly continuous. In addition to peritoneal, pleural, and synovial attacks similar to FMF, TRAPS patients frequently have ocular inflammation (most often conjunctivitis and/or periorbital edema), and a distinctive migratory myalgia with overlying painful erythema may be present. TRAPS patients generally respond better to glucocorticoids than to prophylactic colchicine. Untreated, ~15% develop amyloidosis. The diagnosis of TRAPS is based on the demonstration of a *TNFRSF1A* mutation in the presence of characteristic symptoms. Two particular variants, R92Q and P46L, are common in certain populations and may act more as functional polymorphisms than as disease-causing mutations. In contrast, pathogenic *TNFRSF1A* mutations, including a number of substitutions at highly conserved cysteine residues, are associated with intracellular TNFR1 misfolding, aggregation, and retention, with consequent ligand-independent kinase activation, mitochondrial reactive oxygen species production, and proinflammatory cytokine release. Etanercept, a TNF inhibitor, ameliorates TRAPS attacks, but the long-term experience with this agent has been less favorable. IL-1 inhibition has been beneficial in a large percentage of the patients in whom it has been used, and canakinumab recently

received FDA approval for the treatment of TRAPS. Monoclonal anti-TNF antibodies should be avoided, because they may exacerbate TRAPS attacks.

HYPERRIMNOGLOBULINEMIA D WITH PERIODIC FEVER SYNDROME (ALSO KNOWN AS MEVALONATE KINASE DEFICIENCY)

Hyperimmunoglobulinemia D with periodic fever syndrome (HIDS) is a recessively inherited recurrent fever syndrome found primarily in individuals of northern European ancestry. It is caused by mutations in mevalonate kinase (*MVK*), encoding an enzyme involved in the synthesis of cholesterol and nonsterol isoprenoids, including geranylgeranyl pyrophosphate. The latter compound is essential for proper localization of RhoA GTPase to the cell membrane, and the mislocalization of RhoA leads to its inactivation and the consequent activation of the pyrin inflammasome. HIDS attacks usually begin in infancy and last 3–5 days. Clinically distinctive features include painful cervical adenopathy, a diffuse maculopapular rash sometimes affecting the palms and soles, and aphthous ulcers; pleurisy is rare. Amyloidosis has been observed associated with the V377I/I268T *MVK* genotype. Although originally defined by the persistent elevation of serum IgD, disease activity is not related to IgD levels, and some patients with FMF or TRAPS may have modestly increased serum IgD. Moreover, occasional patients with *MVK* mutations and recurrent fever have normal IgD levels, while all patients with mutations have markedly elevated urinary mevalonate levels during their attacks. For these reasons, some have proposed renaming this disorder *mevalonate kinase deficiency* (MKD). Canakinumab was recently approved by the FDA for the treatment of HIDS/MKD.

NLRP3-ASSOCIATED AUTOINFLAMMATORY DISEASE (ALSO KNOWN AS THE CRYOPYRINOPATHIES OR CRYOPYRIN-ASSOCIATED PERIODIC SYNDROMES)

Three hereditary febrile syndromes, familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS), and neonatal-onset multisystem inflammatory disease (NOMID), are all caused by mutations in *NLRP3* (formerly known as *CIA1*), the gene encoding cryopyrin (or NLRP3), and represent a clinical spectrum of disease. FCAS patients develop chills, fever, headache, arthralgia, conjunctivitis, and an urticaria-like rash in response to generalized cold exposure. In MWS, an urticarial rash is noted, but it is not usually induced by cold; MWS patients also develop fevers, abdominal pain, limb pain, arthritis, conjunctivitis, and, over time, sensorineural hearing loss. NOMID is the most severe of the three disorders, with chronic aseptic meningitis, a characteristic arthropathy, and rash. Like the FMF protein pyrin, cryopyrin has an N-terminal PYRIN domain, allowing the formation of an *NLRP3* inflammasome that mediates caspase-1 activation, IL-1 β and IL-18 release, and pyroptosis. Peripheral blood leukocytes from patients with FCAS, MWS, and NOMID release increased amounts of IL-1 β upon in vitro stimulation, relative to healthy controls. Macrophages from cryopyrin-deficient mice exhibit decreased IL-1 β production in response to certain gram-positive bacteria, bacterial RNA, and monosodium urate crystals. Patients with all three cryopyrinopathies or cryopyrin-associated periodic syndromes (CAPS) show a dramatic response to injections of IL-1 inhibitors. Canakinumab and rilonacept are approved by the FDA for the treatment of FCAS and MWS, whereas anakinra is approved for the treatment of NOMID.

Approximately one-third of patients with clinical manifestations of NOMID do not have germline mutations in *NLRP3*, but they have been found to be mosaic for somatic *NLRP3* mutations. Such patients also respond dramatically to IL-1 inhibition. Somatic mosaicism in *NLRP3* has been reported rarely in Schnitzler's syndrome, which presents in middle age with recurrent fever, urticarial rash, elevated acute-phase reactants, monoclonal IgM gammopathy, and abnormal bone remodeling. IL-1 inhibition is the treatment of choice for Schnitzler's syndrome.

PERIODIC FEVER WITH APHTHOUS STOMATITIS, PHARYNGITIS, AND CERVICAL ADENITIS

Periodic fever with aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) is the most common periodic fever syndrome in children,

notable for the almost clock-like regularity of episodes and the tendency for resolution of attacks by early adulthood. PFAPA tends to run in families, but not in a Mendelian fashion. Recent studies indicate that common shared variants in the *IL12A*, *IL10*, *STAT4*, and *CCR1-CCR3* loci confer susceptibility for a spectrum of phenotypes ranging from common aphthous ulcers to PFAPA to Behcet's disease. Therapeutic options for PFAPA include intermittent glucocorticoids; daily oral colchicine, cimetidine, or apremilast; or tonsillectomy/adenoectomy.

OTHER INHERITED AUTOINFLAMMATORY DISEASES

There are a number of other Mendelian autoinflammatory diseases in which recurrent fevers are not a prominent clinical sign but that involve abnormalities of innate immunity. The syndrome of pyogenic arthritis with pyoderma gangrenosum and acne (PAPA) is a dominantly inherited disorder that presents with episodes of sterile pyogenic monoarthritis often induced by trauma, severe pyoderma gangrenosum, and severe cystic acne usually beginning in puberty. It is caused by mutations in *PSTPIP1*, which encodes a pyrin-binding protein, and the arthritic manifestations often respond to IL-1 inhibition. Dominantly inherited gain-of-function mutations in *NLRC4* lead to increased IL-1 and IL-18 production and potentially life-threatening recurrent macrophage activation syndrome.

Whereas the aforementioned disorders all involve mutations in IL-1-related molecules, other autoinflammatory diseases are caused by mutations in other components of innate immunity. *Blau's syndrome* is caused by mutations in *CARD15* (also known as *NOD2*), which regulates nuclear factor κ B activation. Blau's syndrome is characterized by granulomatous dermatitis, uveitis, and arthritis; distinct *CARD15* variants predispose to Crohn's disease. Recessive mutations in one or more components of the proteasome lead to excessive interferon signaling and a severe form of generalized panniculitis. De novo gain-of-function mutations in *TMEM173*, encoding the stimulator of interferon genes (STING), cause severe vasculopathy and pulmonary fibrosis. Recessive loss-of-function mutations in the gene encoding adenosine deaminase 2 (ADA2) cause a vasculopathy that can manifest as livedoid rash, early-onset lacunar strokes, or polyarteritis nodosa, often responsive to TNF inhibition. Mutations in the gene encoding the A20 ubiquitin-modifying enzyme cause a Behcet's-like monogenic illness ("HA20"), whereas mutations in a different deubiquitinase (OTULIN) cause a form of panniculitis ("otulipenia"). Mutations at the site where RIPK1 is inactivated by caspase-8 cause a condition manifesting recurrent fevers, painful lymphadenopathy, and organomegaly, denoted CRIA (cleavage-resistant RIPK1-induced autoinflammatory) syndrome, that may respond to IL-6 inhibition.

Finally, it should be noted that a number of common, genetically complex disorders are now sometimes considered autoinflammatory, because of evidence that components of the innate immune system, such as the inflammasome, may play a role in the pathogenesis. Two prominent examples are gout and atherosclerosis. Myeloid-restricted somatic mutations in an essential ubiquitylation enzyme have recently been implicated in a severe adult-onset autoinflammatory disease termed VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome, which can present as relapsing polychondritis, vasculitis, or myelodysplastic syndrome.

GLOBAL CONSIDERATIONS

All the disorders discussed in this chapter have been observed in multiple populations. However, as noted herein, FMF is most frequently observed in Mediterranean and Middle Eastern populations and HIDS in northern European populations, particularly the Dutch. A recessive founder mutation in *ADA2* is particularly common in the Georgian Jewish population and is associated with polyarteritis nodosa.

FURTHER READING

- Beck DB et al: Somatic mutations in *UBA1* and severe adult-onset autoinflammatory disease. *N Engl J Med* 383:2628, 2020.
- De Benedetti F et al: Canakinumab for the treatment of autoinflammatory recurrent fever syndromes. *N Engl J Med* 378:1908, 2018.

2844 Lal aoui N et al: Mutations that prevent caspase cleavage of RIPK1 cause autoinflammatory disease. *Nature* 577:103, 2020.

Manthiram K et al: The monogenic autoinflammatory diseases define new pathways in human innate immunity and inflammation. *Nat Immunol* 18:832, 2017.

Manthiram K et al: Common genetic susceptibility loci link PFAPA syndrome, Behcet's disease, and recurrent aphthous stomatitis. *Proc Natl Acad Sci USA* 117:14405, 2020.

Ombrellio AK et al: Treatment strategies for deficiency of adenosine deaminase 2. *N Engl J Med* 380:1582, 2019.

Park YH et al: Pyrin inflammasome activation and RhoA signaling in the autoinflammatory diseases FMF and HIDS. *Nat Immunol* 17:914, 2016.

Park YH et al: Ancient familial Mediterranean fever mutations in human pyrin and resistance to *Yersinia pestis*. *Nat Immunol* 21:857, 2020.

suspected by an acute onset and monarticular or focal musculoskeletal pain.

The majority of individuals with musculoskeletal complaints can be diagnosed with a thorough history and a comprehensive physical and musculoskeletal examination. The initial encounter should determine whether the musculoskeletal complaint signals a red flag condition (septic arthritis, gout, or fracture) or not. The evaluation should ascertain if the complaint is (1) *articular* or *nonarticular*, (2) *inflammatory* or *noninflammatory*, (3) *acute* or *chronic*, and (4) *localized* (*monarticular*) or *widespread* (*polyarticular*).

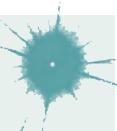
With this approach, the musculoskeletal presentation can be characterized (e.g., acute inflammatory monarthritis or a chronic noninflammatory, nonarticular widespread pain) to narrow the diagnostic possibilities. However, some patients will not fit immediately into an established diagnostic category. Many musculoskeletal disorders resemble each other at the outset, and some may take weeks or months (but not years) to evolve into a recognizable diagnostic entity. This consideration should temper the desire to establish a definitive diagnosis at the first encounter.

Section 3 Disorders of the Joints and Adjacent Tissues

370

Approach to Articular and Musculoskeletal Disorders

John J. Cush



Musculoskeletal complaints account for >315 million outpatient visits per year and >20% of all outpatient visits in the United States. The Centers for Disease Control and Prevention estimate that 58.5 million (or 1 in 4 adults) of the U.S. population has physician-diagnosed arthritis. While many patients will have self-limited conditions requiring minimal evaluation, reassurance, and symptomatic therapy, specific musculoskeletal presentations or their persistence may herald a more serious condition that requires further evaluation or laboratory testing to establish a diagnosis. The goal of the musculoskeletal evaluation is to formulate a differential diagnosis that leads to an accurate diagnosis and timely therapy, while avoiding excessive diagnostic testing and unnecessary treatment (Table 370-1). There are several urgent conditions that must be diagnosed promptly to avoid damage and morbidity. These "red flag" diagnoses include septic arthritis, acute crystal-induced arthritis (e.g., gout), and fracture. Each may be

TABLE 370-1 Evaluation of Patients with Musculoskeletal Complaints

Goals
Accurate diagnosis
Timely provision of therapy
Avoidance of unnecessary diagnostic testing
Identification of acute, focal/monarticular "red flag" conditions
Approach
Determine the chronology (acute vs chronic)
Determine the nature of the pathologic process (inflammatory vs noninflammatory)
Determine the extent of involvement (monarticular, polyarticular, focal, widespread)
Anatomic localization of complaint (articular vs nonarticular)
Consider the most common disorders first
Consider the need for diagnostic testing
Formulate a differential diagnosis

ARTICULAR VERSUS NONARTICULAR

The musculoskeletal evaluation must discriminate the anatomic origin(s) of the patient's complaint. For example, ankle pain can result from a variety of pathologic conditions involving disparate anatomic structures, including gouty arthritis, calcaneal fracture, Achilles tendinitis, plantar fasciitis, cellulitis, and peripheral or entrapment neuropathy. Distinguishing between articular and nonarticular conditions requires a careful and detailed examination. Articular structures include the synovium, synovial fluid, articular cartilage, intraarticular ligaments, joint capsule, and juxtaarticular bone. Nonarticular (or periarticular) structures, such as supportive extraarticular ligaments, tendons, bursae, muscle, fascia, bone, nerve, and overlying skin, may be involved in the pathologic process. Although musculoskeletal complaints are often ascribed to the joints, nonarticular disorders are more frequent and are often confused with arthritis. Distinguishing between articular and nonarticular (also called periarticular) pain may be challenging to the unskilled examiner. Articular disorders may be characterized by deep or diffuse pain, limited range of motion on active and passive movement, and swelling (caused by synovial proliferation, effusion, or bony enlargement), crepitus, instability, "locking," or deformity. By contrast, nonarticular disorders tend to be painful on active, but not passive (or assisted), range of motion. Periarticular conditions often demonstrate point or focal tenderness in regions adjacent to articular structures, may radiate or be elicited with a specific movement or position, and have physical findings remote from the joint capsule. Moreover, nonarticular disorders seldom demonstrate swelling, crepitus, instability, or deformity.

INFLAMMATORY VERSUS NONINFLAMMATORY DISORDERS

In the course of a musculoskeletal evaluation, the examiner should determine the nature of the underlying pathologic process and whether inflammatory or noninflammatory findings exist. Inflammatory disorders may be infectious (*Neisseria gonorrhoeae* or *Mycobacterium tuberculosis*), crystal-induced (gout, pseudogout), immune-related (rheumatoid arthritis [RA], systemic lupus erythematosus [SLE]), reactive (rheumatic fever, reactive arthritis), or idiopathic. Inflammatory disorders may be suggested by any of the four cardinal signs of inflammation (erythema, warmth, pain, or swelling), systemic symptoms (fatigue, fever, rash, weight loss), or laboratory evidence of inflammation (elevated erythrocyte sedimentation rate [ESR] or C-reactive protein [CRP], thrombocytosis, anemia of chronic disease, or hypoalbuminemia). Articular stiffness commonly accompanies chronic musculoskeletal disorders. The duration of stiffness may be prolonged (hours) with inflammatory disorders (such as RA or polymyalgia rheumatica [PMR]) and improves with activity. By contrast, intermittent stiffness (also known as gel phenomenon), typical of noninflammatory conditions (such as osteoarthritis [OA]), is shorter in duration (<60 min) and is exacerbated by activity. Fatigue may be

profound with inflammation (as seen in RA and PMR) but may also be a consequence of fibromyalgia (a noninflammatory disorder), chronic pain, poor sleep, depression, anemia, cardiac failure, endocrinopathy, or malnutrition.

Noninflammatory disorders may be related to trauma (rotator cuff tear), repetitive use (bursitis, tendinitis), degeneration or ineffective repair (OA), neoplasm (pigmented villonodular synovitis), or pain amplification (fibromyalgia). Noninflammatory disorders are often characterized by pain without synovial swelling or warmth, absence of inflammatory or systemic features, intermittent gel phenomena rather than prolonged morning stiffness, and normal (for age) or negative laboratory investigations.

With identification of the nature of the underlying process and the site of the complaint, the examiner can further categorize the musculoskeletal presentation (e.g., acute inflammatory monoarthritis, chronic noninflammatory, nonarticular widespread pain). By narrowing the diagnostic considerations, the examiner can assess the need for immediate diagnostic or therapeutic intervention or for continued observation. **Figure 370-1** presents an algorithmic approach to the evaluation of patients with musculoskeletal complaints. This approach relies on clinical and historic features, rather than laboratory testing, to diagnose many common rheumatic disorders.

A simpler, alternative approach would consider the most commonly encountered complaints first, based on frequency in younger versus

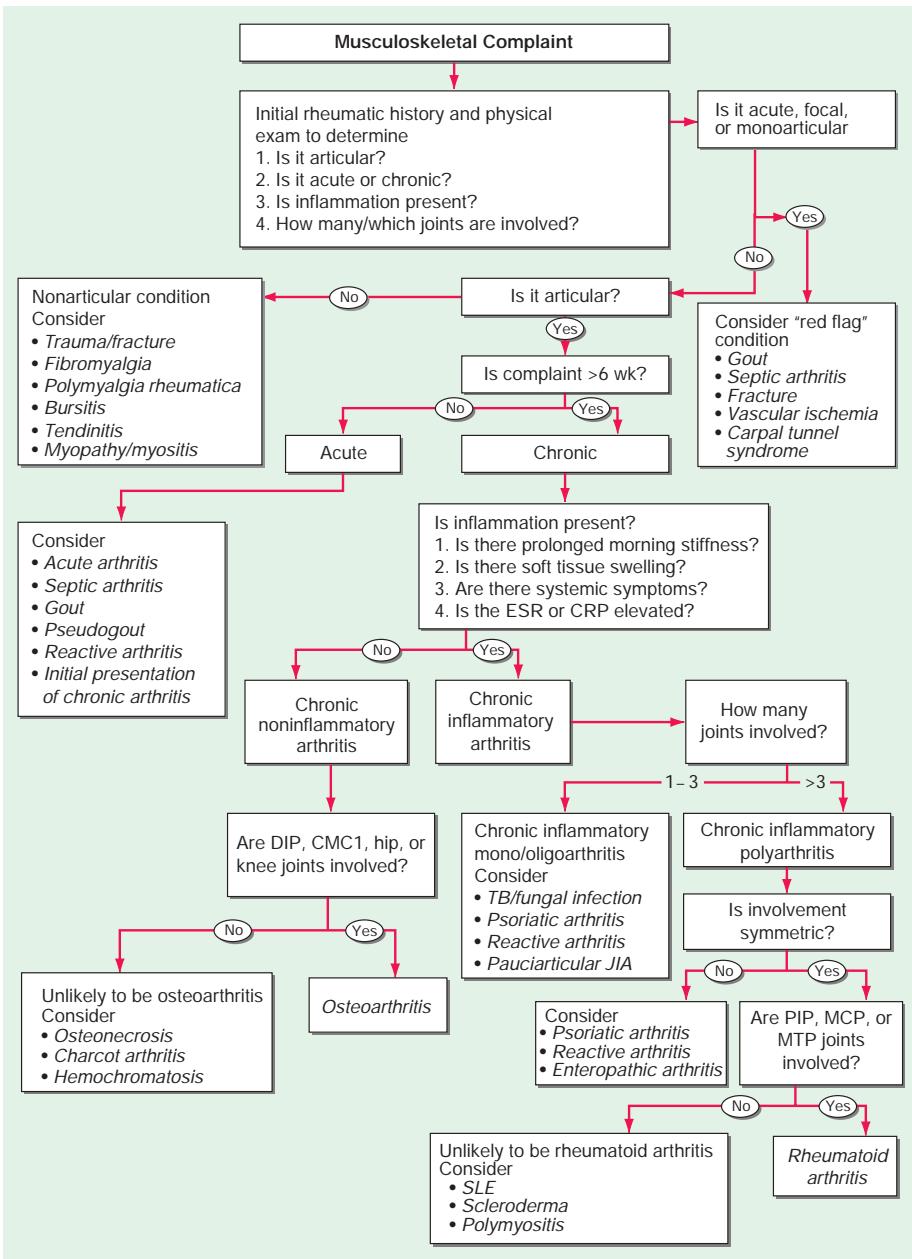


FIGURE 370-1 Algorithm for the diagnosis of musculoskeletal complaints. An approach to formulating a differential diagnosis (shown in italics). CMC, carpometacarpal; CRP, C-reactive protein; DIP, distal interphalangeal; ESR, erythrocyte sedimentation rate; JIA, juvenile idiopathic arthritis; MCP, metacarpophalangeal; MTP, metatarsophalangeal; PIP, proximal interphalangeal; PMR, polymyalgia rheumatica; SLE, systemic lupus erythematosus; TB, tuberculosis.

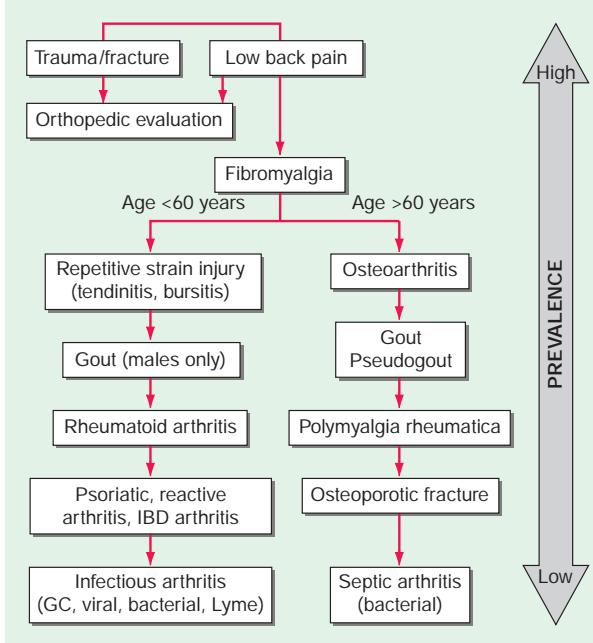


FIGURE 370-2 Algorithm for consideration of the most common musculoskeletal conditions. GC, gonococcal; IBD, inflammatory bowel disease.

older populations. The most prevalent causes of musculoskeletal complaints are shown in Fig. 370-2. Because trauma, fracture, overuse syndromes, and fibromyalgia are among the most common causes of musculoskeletal pain, these should be considered with each new encounter. If excluded, other frequently occurring disorders should be considered according to the patient's age. Hence, those aged <60 years are commonly affected by repetitive use/strain disorders, gout (men only), RA, spondyloarthritis, and uncommonly, infectious arthritis. Patients aged >60 years are frequently affected by OA, crystal (gout and pseudogout) arthritis, PMR, osteoporotic fracture, and uncommonly, septic arthritis. These conditions are between 10 and 100 times more prevalent than other serious autoimmune conditions, such as SLE, scleroderma, polymyositis, and vasculitis.

CLINICAL HISTORY

Historic features may reveal important clues to the diagnosis. Aspects of the patient profile, complaint chronology, extent of joint involvement, and precipitating factors can provide important information. Certain diagnoses are more frequent in different age groups. SLE and reactive arthritis occur more frequently in the young, whereas fibromyalgia and RA are frequent in middle age, and OA and PMR are more prevalent among the elderly. Diagnostic clustering is also evident when sex and race are considered. Gout, spondyloarthritis, and ankylosing spondylitis are more common in men, whereas RA, fibromyalgia, osteoporosis, and lupus are more frequent in women. Racial predilections may be evident. Thus, PMR, giant cell arteritis, and granulomatosis with polyangiitis (GPA; formerly called Wegener's granulomatosis) commonly affect whites, whereas sarcoidosis and SLE more commonly affect African Americans. Familial aggregation is unlikely for most arthropathies but may be seen with ankylosing spondylitis, gout, and Heberden's nodes of OA.

The chronology of the complaint is an important diagnostic feature and can be divided into the onset, evolution, and duration. The onset of disorders such as septic arthritis or gout tends to be abrupt, whereas OA, RA, and fibromyalgia may have more indolent presentations. The patients' complaints may evolve differently and be classified as chronic (OA), intermittent (crystal or Lyme arthritis), migratory (rheumatic

fever, gonococcal or viral arthritis), or additive (RA, psoriatic arthritis). Musculoskeletal disorders are typically classified as acute or chronic based on a symptom duration that is either <6 weeks or >6 weeks, respectively. Acute arthropathies tend to be infectious, crystal-induced, or reactive. Chronic conditions include noninflammatory or immunologic arthritides (e.g., OA, RA) and nonarticular disorders (e.g., fibromyalgia).

The extent or distribution of articular involvement is often informative. Articular disorders are classified based on the number of joints involved, as either *monarticular* (one joint), *oligoarticular* or *pauciarticular* (two or three joints), or *polyarticular* (four or more joints). Although crystal and infectious arthritis are often mono- or oligoarticular, OA and RA are usually polyarticular. Nonarticular disorders may be classified as either focal or widespread. Complaints secondary to tendinitis or carpal tunnel syndrome are typically focal, whereas weakness and myalgia, caused by polymyositis or fibromyalgia, are more widespread in their presentation. Joint involvement in RA tends to be symmetric and polyarticular. By contrast, spondyloarthritis, reactive arthritis, gout, and sarcoid are often asymmetric and oligoarticular. OA and psoriatic arthritis may be either symmetric or asymmetric and oligo- or polyarticular. The upper extremities are frequently involved in RA and OA, whereas lower extremity arthritis is characteristic of reactive arthritis and gout at their onset. Involvement of the axial skeleton is common in OA and ankylosing spondylitis but is infrequent in RA, with the notable exception of the cervical spine.

The clinical history should also identify precipitating events, such as trauma (osteonecrosis, meniscal tear), drug administration (Table 370-2), antecedent or intercurrent infection (reactive arthritis, hepatitis, chikungunya), or illnesses that may have contributed to the patient's complaint. Certain comorbidities may have musculoskeletal consequences. This is especially so for diabetes mellitus (carpal tunnel syndrome), renal insufficiency (gout), depression or insomnia (fibromyalgia), myeloma (spinal pain), cancer (myositis), and osteoporosis (fracture) or when using certain drugs such as glucocorticoids (osteonecrosis, septic arthritis), diuretics, or chemotherapy (gout) (Table 370-2).

Lastly, a thorough *rheumatic review of systems* may disclose useful diagnostic information. A variety of musculoskeletal disorders may be associated with systemic features such as fever (Still's disease, infection), rash (SLE, psoriatic arthritis), nail abnormalities (psoriatic or reactive arthritis), myalgias (fibromyalgia, statin- or drug-induced myopathy), or weakness (polymyositis, neuropathy). In addition, some conditions are associated with involvement of other organ systems including the eyes (Behcet's disease, sarcoidosis, spondyloarthritis), gastrointestinal tract (scleroderma, inflammatory bowel disease), genitourinary tract (reactive arthritis, gonococcemia), or nervous system (Lyme disease, vasculitis).

FIBROMYALGIA

Syphilis and tuberculosis have been called the "great masqueraders" as their protean symptoms and potential for multiorgan involvement may result in delays in diagnosis and treatment. In the modern era, other serious diagnoses (including lupus, sarcoidosis, vasculitis, and lymphoma) have also been labeled as great masqueraders. All of these are either uncommon or rare, compared to the more common masquerader of musculoskeletal complaints—fibromyalgia. Fibromyalgia (see Chap. 373) is a pain amplification disorder unified by sleep disturbance, exaggerated pain and sensitivity (owing to lowered pain thresholds), and a multiplicity of symptoms with a paucity of abnormalities on clinical examination or laboratory testing. Tender "trigger points" may be elicited over the epicondyles, trochanteric bursae, anserine bursae, and specific muscles (gluteal, trapezius, supraspinatus). Fibromyalgia is characterized by widespread aches and pains, even though presenting symptoms tend to be fewer or focal. Fibromyalgia coexists with numerous comorbidities including irritable bowel syndrome, dysmenorrhea, migraine, depression, anxiety, memory loss, nonanatomic paresthesia or dysesthesia, fatigue, myalgias, temporomandibular joint pain, hypermobility, and multiple chemical sensitivities. Fibromyalgia

TABLE 370-2 Drug-Induced Musculoskeletal Conditions**Arthralgias**

Quinidine, cimetidine, beta blockers, quinolones, chronic acyclovir, interferons, IL-2, nicardipine, vaccines, rifabutin, aromatase inhibitors, HIV protease inhibitors, DPP-4 inhibitors (sitagliptin, linagliptin, alogliptin), paclitaxel, checkpoint inhibitors (pilimumab, pembrolizumab, nivolumab, atezolizumab, durvalumab, cemiplimab)

Myalgias/myopathy

Glucocorticoids, penicillamine, hydroxychloroquine, AZT, lovastatin, simvastatin, atorvastatin, pravastatin, clofibrate, amiodarone, interferon, IL-2, alcohol, cocaine, paclitaxel, docetaxel, imatinib mesylate, colchicine, quinolones, cyclosporine, tacrolimus, protease inhibitors, checkpoint inhibitors

Tendon rupture/tendinitis

Quinolones, glucocorticoids, isotretinoin, statins, aromatase inhibitors, collagenase injections

Gout

Diuretics, aspirin, cytotoxics, cyclosporine, tacrolimus, alcohol, moonshine, ethambutol, fructose-containing soft drinks

Drug-induced lupus

Hydralazine, procainamide, quinidine, phenytoin, carbamazepine, methyldopa, isoniazid, chlorpromazine, lithium, penicillamine, tetracyclines, TNF inhibitors, ACE inhibitors, ticlopidine, terbinafine, aromatase inhibitors

Drug-induced subacute lupus

Proton pump inhibitors, calcium channel blockers (diltiazem), ACE inhibitors, TNF inhibitors, terbinafine, interferons (α and β -1a), paclitaxel, docetaxel, gemcitabine, capecitabine, aromatase inhibitors, HCTZ

Osteonecrosis/atypical fractures

Glucocorticoids, alcohol, radiation, bisphosphonates

Osteopenia

Glucocorticoids, chronic heparin, phenytoin, aromatase inhibitors, antiandrogen therapy, thiazolidinediones

Psoriasis

TNF inhibitors, beta blockers, lithium, hydroxychloroquine, chloroquine, minocycline, ACE inhibitors, terbinafine, checkpoint inhibitors.

Scleroderma

Vinyl chloride, bleomycin, baricitinib, pentazocine, organic solvents, carbidopa, tryptophan, rapeseed oil

Raynaud's phenomenon

Cisplatin, bleomycin, beta blockers, clonidine, bromocriptine, ergot alkaloids, cocaine, methylphenidate, dextroamphetamine, phentermine, interferon therapy

Vasculitis

Allopurinol, amphetamines, cocaine (often levamisole adulterated), cannabis, thiazides, penicillamine, propylthiouracil, montelukast, TNF inhibitors, hepatitis B vaccine, trimethoprim/sulfamethoxazole, minocycline, hydralazine

Abbreviations: ACE, angiotensin-converting enzyme; AZT, zidovudine; HCTZ, hydrochlorothiazide; IL-2, interleukin 2; TNF, tumor necrosis factor.

affects nearly 5 million Americans but is underrecognized or misdiagnosed as arthritis, lupus, multiple sclerosis, autoimmune disease, or other conditions. Early consideration of this very common disorder can avert needless investigation, therapy, and concern for those afflicted (Fig. 370-2).

RHEUMATOLOGIC EVALUATION OF THE ELDERLY

The incidence of rheumatic diseases rises with age, such that 58% of those >65 years will have joint complaints. Musculoskeletal disorders in elderly patients are often not diagnosed because the signs and symptoms may be insidious, overlooked, or overshadowed by comorbidities. These difficulties are compounded by the diminished reliability of laboratory testing in the elderly, who often manifest nonpathologic abnormal results. For example, the ESR may be misleadingly elevated, and low-titer positive tests for rheumatoid factor (RF) and antinuclear antibodies (ANAs) may be seen in up to 15% of elderly patients.

Although nearly all rheumatic disorders afflict the elderly, geriatric patients are particularly prone to OA, osteoporosis, osteoporotic fractures, gout, pseudogout, PMR, vasculitis, and drug-induced disorders (Table 370-2). The elderly should be approached in the same manner as other patients with musculoskeletal complaints, but with an emphasis on identifying the potential rheumatic consequences of medical comorbidities and therapies used in the elderly. The physical examination should identify the nature of the musculoskeletal complaint as well as coexisting diseases that may influence diagnosis and choice of treatment.

RHEUMATOLOGIC EVALUATION OF THE HOSPITALIZED PATIENT

Evaluation of a hospitalized patient with rheumatic complaints is often more complex owing to symptom severity, acute presentations, and greater interplay of comorbidities. Patients with rheumatic disorders tend to be admitted for one of several reasons: (1) acute onset of inflammatory arthritis (possibly gout or septic arthritis); (2) undiagnosed systemic or febrile illness; (3) musculoskeletal trauma; (4) exacerbation or deterioration of an existing musculoskeletal disorder (e.g., SLE); or (5) new medical comorbidities (e.g., thrombotic event, lymphoma, infection) arising in patients with an established rheumatic disorder. Notably, rheumatic patients are seldom if ever admitted because of widespread pain or serologic abnormalities or for the initiation of new therapies.

Acute monoarticular inflammatory arthritis is a “red flag” presentation (e.g., septic arthritis, gout, pseudogout) that may require arthrocentesis or hospitalization if infection is suspected. New-onset inflammatory polyarthritides has a wide differential diagnosis (e.g., RA, hepatitis-related arthritis, chikungunya arthritis, serum sickness, drug-induced lupus, SLE, polyarticular septic arthritis) and may require targeted laboratory investigations more so than synovial fluid analyses. Patients with febrile, multisystem disorders require exclusion of crystal, infectious, or neoplastic etiologies and an evaluation driven by the dominant symptom/finding with the greatest specificity. Conditions worthy of consideration may include gout or pseudogout, vasculitis (giant cell arteritis in the elderly or polyarteritis nodosa in younger patients), adult-onset Still's disease, SLE, antiphospholipid antibody syndrome, IgG4-related disease, and sarcoidosis. A preexisting rheumatic diagnosis (e.g., SLE, RA, ankylosing spondylitis) should be confirmed by careful history and examination and review of medical records, as this will influence the ensuing in-patient evaluation. Notably, when established rheumatic disease patients are admitted to the hospital, it is usually not for their autoimmune disease, but rather a comorbid medical problem or complication of drug therapy. Patients with chronic inflammatory disorders (e.g., RA, SLE, psoriasis) have an augmented risk of infection, cardiovascular events, pulmonary disorders, and neoplasia.

Certain conditions, such as acute gout, can be precipitated in hospitalized patients by surgery, dehydration, or medications and should be considered when hospitalized patients are evaluated for the acute onset of a musculoskeletal condition. Lastly, overly aggressive and unfocused laboratory testing will often yield abnormal findings that are better explained by the patient's preexisting condition (chronic lung, renal, or liver disease) rather than a new inflammatory or autoimmune disorder (lupus, vasculitis).

PHYSICAL EXAMINATION

The goal of the physical examination is to ascertain the structures involved, the nature of the underlying pathology, the functional consequences of the process, and the presence of systemic or extraarticular manifestations. A knowledge of topographic anatomy is necessary to identify the primary site(s) of involvement and differentiate articular from nonarticular disorders. The musculoskeletal examination depends largely on careful inspection, palpation, contralateral comparison, and a variety of specific physical maneuvers to elicit diagnostic signs (Table 370-3). Although most articulations of the appendicular skeleton can be examined in this manner, adequate inspection and

TABLE 370-3 Glossary of Musculoskeletal Terms**Crepitus**

A palpable (less commonly audible) vibratory or crackling sensation elicited with joint motion; fine joint crepitus is common and often insignificant in large joints; coarse joint crepitus indicates advanced cartilaginous and degenerative changes (as in osteoarthritis)

Subluxation

Alteration of joint alignment such that articulating surfaces incompletely approximate each other

Dislocation

Abnormal displacement of articulating surfaces such that the surfaces are not in contact

Range of motion

For diarthrodial joints, the arc of measurable movement through which the joint moves in a single plane

Contracture

Loss of full movement resulting from a fixed resistance caused either by tonic spasm of muscle (reversible) or by fibrosis of periarticular structures (permanent)

Deformity

Abnormal shape or size resulting from bony hypertrophy, malalignment of articulating structures, or damage to periarticular supportive structures

Enthesitis

Inflammation of the entheses (tendinous or ligamentous insertions on bone)

Epicondylitis

Infection or inflammation involving an epicondyle

periarticular process (e.g., tendinitis, tendon rupture, or myopathy) should be considered. *Contractures* may reflect antecedent synovial inflammation or trauma. Minor joint *crepitus* is common during joint palpation and maneuvers but may indicate significant cartilage degeneration as it becomes coarser (e.g., OA). Joint *deformity* usually indicates a long-standing or aggressive pathologic process. Deformities may result from ligamentous destruction, soft tissue contracture, bony enlargement, ankylosis, erosive disease, subluxation, trauma, or loss of proprioception. Examination of the musculature will document strength, atrophy, pain, or spasm. Appendicular muscle weakness should be characterized as proximal or distal. Muscle strength should be assessed by observing the patient's performance (e.g., walking, rising from a chair, grasping, writing). Strength may also be graded on a 5-point scale: 0 for no movement; 1 for trace movement or twitch; 2 for movement with gravity eliminated; 3 for movement against gravity only; 4 for movement against gravity and resistance; and 5 for normal strength. The examiner should assess for often overlooked nonarticular or periarticular involvement, especially when articular complaints are not supported by objective findings referable to the joint capsule. The identification of soft tissue or nonarticular pain will prevent unwarranted and often expensive additional evaluations. Specific maneuvers may reveal common nonarticular abnormalities, such as a carpal tunnel syndrome (which can be identified by Tinel's sign of Durkan's test). Other examples of soft tissue abnormalities include olecranon bursitis, epicondylitis (e.g., tennis elbow), enthesitis (e.g., Achilles tendinitis), and tender trigger points associated with fibromyalgia.

APPROACH TO REGIONAL RHEUMATIC COMPLAINTS

Although all patients should be evaluated in a logical and thorough manner, many focal musculoskeletal complaints are commonly caused by disorders that exhibit a predictable pattern of onset, evolution, and localization; they can often be easily diagnosed with limited historic information and selected maneuvers or tests. Although nearly every musculoskeletal complaint could be approached in this manner, the evaluation of four commonly involved anatomic regions—the hand, shoulder, hip, and knee—are reviewed here.

HAND PAIN

Focal or unilateral hand pain may result from trauma, overuse, infection, or a reactive or crystal-induced arthritis. By contrast, bilateral hand complaints commonly suggest a degenerative (e.g., OA), systemic, or inflammatory/immune (e.g., RA) etiology. The distribution or pattern of joint involvement is highly suggestive of certain disorders (Fig. 370-3). Thus, OA (or degenerative arthritis) may manifest as distal interphalangeal (DIP) and PIP joint pain and bony hypertrophy leading to Heberden's and Bouchard's nodes, respectively. Pain, with or without bony swelling, involving the base of the thumb (first carpometacarpal joint) is also highly suggestive of OA. By contrast, RA manifests as an additive, symmetric, polyarticular arthritis involving the PIP, MCP, intercarpal, and carpometacarpal joints (wrist) with pain and palpable synovial tissue hypertrophy. Psoriatic arthritis may mimic the pattern of joint involvement seen in OA (DIP and PIP joints) but can be distinguished by the presence of inflammatory signs (erythema, warmth, synovial swelling), with or without carpal involvement, nail pitting, or onycholysis. Whereas lateral or medial subluxations at the PIP or DIP joints are most likely due to inflammatory OA or psoriatic arthritis, dorsal or ventral deformities (swan neck or boutonnière deformities) are typical of RA. Hemochromatosis should be considered when degenerative changes (bony hypertrophy) are seen at the second and third MCP joints with associated radiographic chondrocalcinosis or episodic, inflammatory wrist arthritis.

Dactylitis manifests as soft tissue swelling of the whole digit and may have a sausage-like appearance. Common causes of dactylitis include psoriatic arthritis, spondyloarthritis, juvenile spondylitis, mixed connective tissue disease, scleroderma, sarcoidosis, and sickle cell disease. Soft tissue swelling over the dorsum of the hand and wrist may suggest an inflammatory extensor tendon tenosynovitis possibly caused by gonococcal infection, gout, or inflammatory arthritis (e.g.,

palpation are not possible for many axial (e.g., zygapophyseal) and inaccessible (e.g., sacroiliac or hip) joints. For such joints, there is a greater reliance on specific maneuvers and imaging for assessment.

Examination of involved and uninvolved joints will determine whether *pain*, *warmth*, *erythema*, or *swelling* is present. The locale and level of pain elicited by palpation or movement should be quantified. Examination of 28 easily palpated joints (proximal interphalangeals [PIPs], metacarpophalangeals [MCPs], wrists, elbows, shoulders, and knees) can quantify the number of tender or swollen joints (0–28) involved. Careful examination should distinguish between true articular swelling (caused by bony hypertrophy, synovial effusion or proliferation) and nonarticular (or periarticular) involvement, which usually extends beyond the normal joint margins. Cautious palpation can distinguish synovial effusion (fluctuant swelling) from synovial hypertrophy (grape-like compressibility) and bony hypertrophy (firm as a nut). Small to moderate knee effusions may be identified by the “bulge sign” or “ballottement of the patellae.” Bursal effusions (e.g., effusions of the olecranon or prepatellar bursa) are often focal and periarticular, overlie bony prominences, and are fluctuant with defined borders. Joint *stability* can be assessed by stabilizing the proximal joint and applying manual stress to the distal appendage in different planes. *Subluxation* or *dislocation*, which may be secondary to traumatic, mechanical, or inflammatory causes, can be assessed by inspection and palpation. Joint *swelling* or *volume* can be assessed by palpation. Distention of the articular capsule usually causes pain and evident enlargement or fluctuance. The patient will attempt to minimize the pain by maintaining the joint in the position of least intraarticular pressure and greatest volume (usually partial flexion), possibly leading to flexion contracture over time. Active and passive *range of motion* should be assessed in all planes, with contralateral comparison. A goniometer may be used to quantify the arc of movement. Each joint should be passively manipulated through its full range of motion (including, as appropriate, flexion, extension, rotation, abduction, adduction, lateral bending, inversion, eversion, supination, pronation, medial/lateral deviation, and plantar- or dorsiflexion). Extreme range of motion and connective tissue laxity may be seen with hypermobility syndrome, Ehlers-Danlos syndrome, or Marfan's syndrome. Limitation of motion or contractures are frequently caused by inflammation, effusion, pain, deformity, or neuromyopathic causes. If passive motion exceeds active motion, a

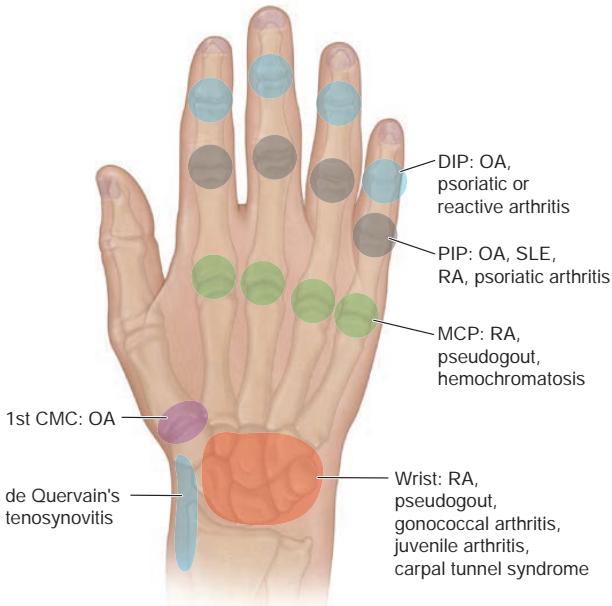


FIGURE 370-3 Sites of hand or wrist involvement and their potential disease associations. CMC, carpometacarpal; DIP, distal interphalangeal; MCP, metacarpophalangeal; OA, osteoarthritis; PIP, proximal interphalangeal; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus. (Reproduced with permission from JJ Cush et al [eds], *Evaluation of musculoskeletal complaints, in Rheumatology: Diagnosis and Therapeutics*, 2nd ed. Philadelphia, Lippincott Williams & Wilkins, 2005.)

RA). Tenosynovitis is suggested by localized warmth, swelling, or pitting edema and may be confirmed when the soft tissue swelling tracks with tendon movement during flexion and extension of fingers, or when pain is induced while stretching the extensor tendon sheaths (flexing the digits distal to the MCP joints and maintaining the wrist in a fixed, neutral position). Volar (palmar) tendon swellings may be from tenosynovitis, Dupuytren's contractures, tendon nodules, or synovial cysts.

Focal wrist pain localized to the radial aspect may be caused by de Quervain's tenosynovitis resulting from inflammation of the tendon sheath(s) involving the abductor pollicis longus or extensor pollicis brevis (Fig. 370-3). This commonly results from overuse or follows pregnancy and may be diagnosed with Finkelstein's test. A positive result is present when radial wrist pain is induced after the thumb is flexed and placed inside a clenched fist and the patient actively deviates the hand downward with ulnar deviation at the wrist. Carpal tunnel syndrome is another common disorder of the upper extremity and results from compression of the median nerve within the carpal tunnel. Manifestations include pain in the wrist that may radiate with paresthesia to the thumb, second and third fingers, and radial half of the fourth finger and, at times, atrophy of the thenar musculature. Carpal tunnel syndrome is commonly associated with pregnancy, edema, trauma, OA, inflammatory arthritis, and infiltrative disorders (e.g., amyloidosis). The diagnosis may be suggested by a positive Durkan's test or Tinel's sign. With each test, paresthesia in a median nerve distribution is induced or increased by 30 s of compression over the carpal tunnel (Durkan's test) or "thumping" the volar aspect of the wrist (Tinel's sign). The low sensitivity and moderate specificity of these tests may require nerve conduction velocity testing to confirm a suspected diagnosis.

SHOULDER PAIN

During the evaluation of shoulder disorders, the examiner should carefully note any history of trauma, fibromyalgia, infection, inflammatory

disease, occupational hazards, or previous cervical disease. In addition, the patient should be questioned as to the activities or movement(s) that elicit shoulder pain. While arthritis is suggested by pain on movement in all planes, pain with specific active motion suggests a periartricular (nonarticular) process. Shoulder pain may originate in the glenohumeral or acromioclavicular joints, subacromial (subdeltoid) bursa, periartricular soft tissues (e.g., fibromyalgia, rotator cuff tear/tendinitis), or cervical spine (Fig. 370-4). Shoulder pain is referred frequently from the cervical spine but may also be referred from intrathoracic lesions (e.g., a Pancoast tumor) or from gallbladder, hepatic, or diaphragmatic disease. These same visceral causes may also manifest as focal scapular pain. Fibromyalgia should be suspected when glenohumeral pain is accompanied by diffuse periartricular (i.e., subacromial, bicipital) pain, tender points (i.e., trapezius or supraspinatus), and a sleep disturbance. The shoulder should be put through its full range of motion both actively and passively (with examiner assistance): forward flexion, extension, abduction, adduction, and internal and external rotation. Manual inspection of the periartricular structures will often provide important diagnostic information. Glenohumeral involvement is best detected by placing the thumb over the glenohumeral joint just medial and inferior to the coracoid process and applying pressure anteriorly while internally and externally rotating the humeral head. Pain localized to this region is indicative of glenohumeral pathology. Synovial effusion or tissue is seldom palpable but, if present, may suggest infection, RA, amyloidosis, or an acute tear of the rotator cuff. The examiner should apply direct manual pressure over the subacromial bursa that lies lateral to and immediately beneath the acromion (Fig. 370-4). Subacromial bursitis is a frequent cause of shoulder pain. Anterior to the subacromial bursa, the bicipital tendon traverses the bicipital groove. This tendon is best identified by palpating it in its groove as the patient rotates the humerus internally and externally. Direct pressure over the tendon may reveal pain indicative of bicipital tendinitis. Palpation of the acromioclavicular joint may disclose local

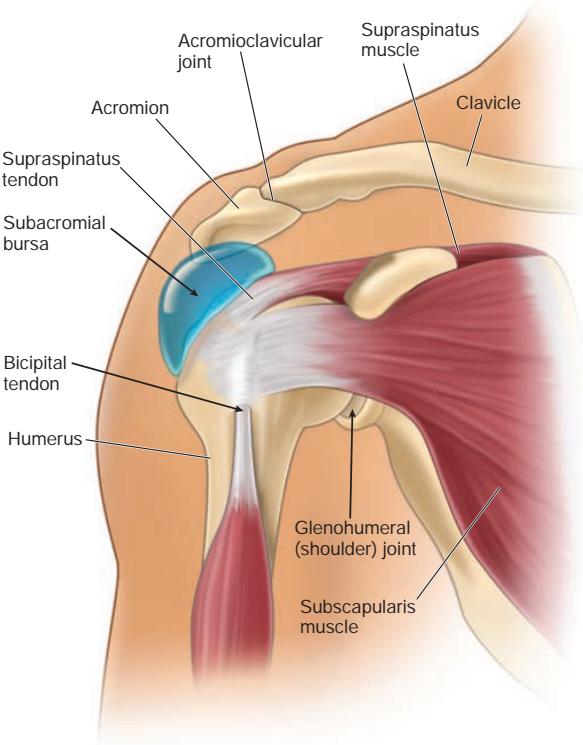


FIGURE 370-4 Origins of shoulder pain. The schematic diagram of the shoulder indicates, with arrows, the anatomic origins of shoulder pain.

pain, bony hypertrophy, or, uncommonly, synovial swelling. Whereas OA and RA commonly affect the acromioclavicular joint, OA seldom involves the glenohumeral joint, unless there is avascular necrosis or a traumatic or occupational cause.

Rotator cuff tendinitis or tear is a very common cause of shoulder pain. Nearly 30% of the elderly will have shoulder pain, with rotator cuff tendinitis or tear as a primary cause. The rotator cuff is formed by four tendons that attach the scapula to the proximal humerus (supraspinatus, infraspinatus, teres minor, and subscapularis tendons). Of these, the supraspinatus muscle is the most commonly damaged. Rotator cuff tendinitis is suggested by pain on active abduction (but not passive abduction), pain over the lateral deltoid muscle, night pain, and evidence of the impingement signs (pain with overhead arm activities). The Neer test for impingement is performed by the examiner raising the patient's arm into forced flexion while stabilizing and preventing rotation of the scapula. A positive sign is present if pain develops before 180° of forward flexion. Tear of the rotator cuff is common in the elderly and often results from trauma; it may manifest in the same manner as tendinitis. The drop arm test is abnormal with supraspinatus pathology and is demonstrated by passive abduction of the arm to 90° by the examiner. If the patient is unable to hold the arm up actively or unable to lower the arm slowly without dropping, the test is positive. Tendinitis or tear of the rotator cuff is best confirmed by magnetic resonance imaging (MRI) or ultrasound.

KNEE PAIN

Knee pain may result from intraarticular (OA, RA) or periarticular (anserine bursitis, collateral ligament strain) processes or be referred from hip pathology. A careful history should delineate the chronology of the knee complaint and whether there are predisposing conditions, trauma, or medications that might underlie the complaint. For example, patellofemoral disease (e.g., OA) may cause anterior knee pain that worsens with climbing stairs. Observation of the patient's gait is also important. The knee should be carefully inspected in the upright (weight-bearing) and supine positions for swelling, erythema, malalignment, visible trauma, muscle wasting, and leg length discrepancy. The most common malalignment in the knee is *genu varum* (bowlegs) or *genu valgum* (knock-knees) resulting from asymmetric cartilage loss medially or laterally, respectively. Bony swelling of the knee joint commonly results from hypertrophic osseous changes seen with disorders such as OA and neuropathic arthropathy. Swelling caused by hypertrophy of the synovium or synovial effusion may manifest as a fluctuant, ballotable, or soft tissue enlargement in the suprapatellar pouch (suprapatellar reflection of the synovial cavity) or regions lateral and medial to the patella. Synovial effusions may also be detected by balloting the patella downward toward the femoral groove or by eliciting a "bulge sign." With the knee extended, the examiner should manually compress, or "milk," synovial fluid down from the suprapatellar pouch and lateral to the patellae. The application of manual pressure lateral to the patella may cause an observable shift in synovial fluid (bulge) to the medial aspect. The examiner should note that this maneuver is only effective in detecting small to moderate effusions (<100 mL). Inflammatory disorders such as RA, gout, pseudogout, and psoriatic arthritis may involve the knee joint and produce significant pain, stiffness, swelling, or warmth. A popliteal or *Baker's cyst* may be palpated with the knee partially flexed and is best viewed posteriorly with the patient standing and knees fully extended to visualize isolated or unilateral popliteal swelling or fullness.

Anserine bursitis is an often-missed periarticular cause of knee pain in adults. The pes anserine bursa underlies the insertion of the conjoined tendons (sartorius, gracilis, semitendinosus) on the anteromedial proximal tibia and may be painful following trauma, overuse, or inflammation (bursitis). It is often tender in patients with fibromyalgia, obesity, and knee OA. Other forms of bursitis may also present as knee pain. The prepatellar bursa is superficial and is located over the inferior portion of the patella. The infrapatellar bursa is deeper and lies beneath the patellar ligament before its insertion on the tibial tubercle.

Internal derangement of the knee may result from trauma or degenerative processes. Damage to the meniscal cartilage (medial or lateral) frequently presents as chronic or intermittent knee pain. Such an injury should be suspected when there is a history of trauma, athletic activity, or chronic knee arthritis, and when the patient relates symptoms of "locking" or "giving way" of the knee. With the knee flexed 90° and the patient's foot on the table, pain elicited during palpation over the joint line or when the knee is stressed laterally or medially may suggest a meniscal tear. A positive McMurray test may also indicate a meniscal tear. To perform this test, the knee is first flexed at 90°, and the leg is then extended while the lower extremity is simultaneously torqued medially or laterally. A painful click during inward rotation may indicate a lateral meniscus tear, and pain during outward rotation may indicate a tear in the medial meniscus. Lastly, damage to the cruciate ligaments should be suspected with acute onset of pain, possibly with swelling, a history of trauma, or a synovial fluid aspirate that is grossly bloody. Examination of the cruciate ligaments is best accomplished by eliciting a drawer sign. With the patient recumbent, the knee should be partially flexed and the foot stabilized on the examining surface. The examiner should manually attempt to displace the tibia anteriorly or posteriorly with respect to the femur. If anterior movement is detected, then anterior cruciate ligament damage is likely. Conversely, significant posterior movement may indicate posterior cruciate damage. Contralateral comparison will assist the examiner in detecting significant anterior or posterior movement.

HIP PAIN

The hip is best evaluated by observing the patient's gait and assessing range of motion. The vast majority of patients reporting "hip pain" localize their pain unilaterally to the posterior gluteal musculature (**Fig. 370-5**) with radiation down the posterolateral aspect of the thigh, and the pain may be associated with complaints of low back pain. This presentation frequently results from degenerative arthritis of the lumbosacral spine or disks and commonly follows a dermatomal distribution with involvement of nerve roots between L4 and S1. Sciatica is caused by impingement of the L4, L5, or S1 nerve (i.e., from a herniated disk) and manifests as unilateral neuropathic pain extending from the gluteal region down the posterolateral leg to the foot. Some individuals instead localize their "hip pain" laterally to the area overlying the trochanteric bursa. Because of the depth of this bursa, swelling and warmth are usually absent. Diagnosis of trochanteric bursitis or enthesitis can be confirmed by inducing point tenderness over the trochanteric bursa. Gluteal and trochanteric pain are common findings in fibromyalgia. Range of movement may be limited by pain. Pain in the hip joint is less common and tends to be located anteriorly, over the inguinal ligament; it may radiate medially to the groin. Uncommonly, iliopsoas bursitis may mimic true hip joint pain. Diagnosis of iliopsoas bursitis may be suggested by a history of trauma or inflammatory arthritis. Pain associated with iliopsoas bursitis is localized to the groin or anterior thigh and tends to worsen with hyperextension of the hip; many patients prefer to flex and externally rotate the hip to reduce the pain from a distended bursa.

TELEHEALTH MUSCULOSKELETAL EVALUATION

Telemedicine has grown significantly in recent years as a means of remote patient assessment and providing remote clinical care. Engagement of patients via electronic telecommunication allows for virtual patient evaluations with a time, cost, and convenience advantage, but can be a technological disadvantage for the elderly or disadvantaged populations. Telemedicine is most efficient with quality audio and video connections and can be used for patient education, monitoring, and routine disease assessments. Patients evaluated by telemedicine should undergo the same medical history and inquiry as a routine clinic evaluation, but evaluation will differ in the scope of examination and maneuvers. The musculoskeletal televideo examination may be appropriate and effective in many, primarily by supplanting physical

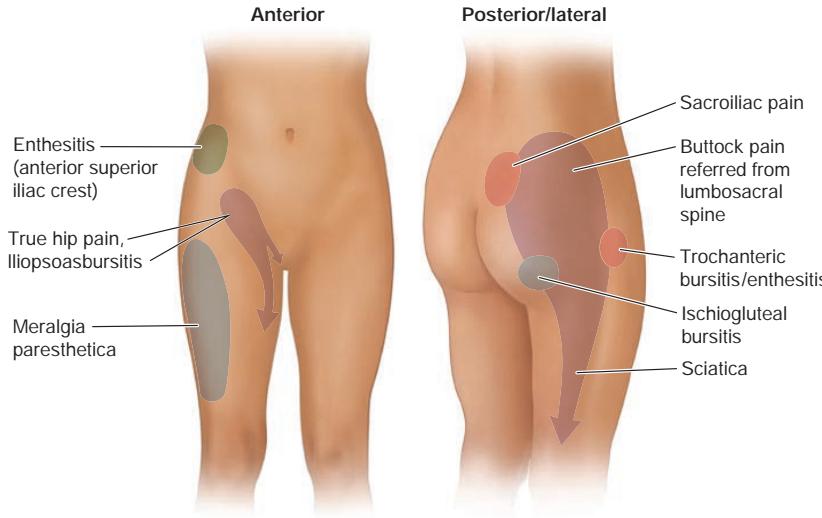


FIGURE 370-5 Origins of hip pain and dysesthesias. (Reproduced with permission from JJ Cush et al [eds], Evaluation of musculoskeletal complaints, in *Rheumatology: Diagnosis and Therapeutics*, 2nd ed. Philadelphia, Lippincott Williams & Wilkins, 2005.)

palpation with observation, range of motion, patient self-assessments, and contralateral comparison. Specifically, the televideo exam should assess the following: (1) patient gait (to assess lower extremity abnormalities); (2) rising from a seated position (to assess for weakness); (3) cervical range of motion (flexion, extension, lateral bending); (4) assessment by contralateral comparison (e.g., “praying hands,” “make a fist,” “flex wrists,” and “hands on ears, elbows out” to assess shoulder range of motion); and (5) side-by-side inspection of knees, ankles, and feet. Effective telehealth is contingent on clinical experience, knowledge of and familiarity with the patient, and training the patient on the use of technology and goals and limits of a televideo visit.

LABORATORY INVESTIGATIONS

The vast majority of musculoskeletal disorders can be logically diagnosed by a complete history and physical examination. An additional objective of the initial encounter is to determine whether additional investigations or immediate therapy is required. Laboratory evaluation is indicated with (1) monarticular conditions; (2) traumatic or inflammatory conditions; (3) the presence of neurologic findings; (4) systemic manifestations; or (5) chronic symptoms (>6 weeks) and a lack of response to symptomatic measures. The extent and nature of the additional investigation should be dictated by the clinical features and suspected pathologic process. Laboratory tests should be used to confirm a specific clinical diagnosis and not be used to screen or evaluate patients with vague rheumatic complaints. Indiscriminate use of broad batteries of diagnostic tests and radiographic procedures is rarely a useful or cost-effective means to establish a diagnosis.

Besides a complete blood count, including a white blood cell (WBC) and differential count, the routine evaluation should include a determination of an acute-phase reactant such as the ESR or CRP, which can be useful in discriminating inflammatory from noninflammatory disorders. Both are inexpensive, easily obtained, and may be elevated with infection, inflammation, autoimmune disorders, neoplasia, pregnancy, renal insufficiency, advanced age, or hyperlipidemia. Extreme elevation of the acute-phase reactants (CRP, ESR) is seldom seen without evidence of serious illness (e.g., sepsis, pleuropericarditis, PMR, giant cell arteritis, adult Still's disease).

Serum uric acid determinations are useful in the diagnosis of gout and in monitoring the response to urate-lowering therapy. Uric acid, the end product of purine metabolism, is primarily excreted in the urine. Serum values range from 238 to 516 µmol/L (4.0–8.6 mg/dL) in men; the lower values (178–351 µmol/L [3.0–5.9 mg/dL]) seen in

women are caused by the uricosuric effects of estrogen. Urinary uric acid levels are normally <750 mg per 24 h. Although hyperuricemia is associated with an increased incidence of gout and nephrolithiasis, levels may not correlate with the severity of articular disease. Uric acid levels (and the risk of gout) may be increased by inborn errors of metabolism (Lesch-Nyhan syndrome), disease states (renal insufficiency, myeloproliferative disease, psoriasis), or drugs (alcohol, cytotoxic therapy, thiazides). Although nearly all patients with gout will demonstrate hyperuricemia at some time during their illness, up to 50% of patients with an acute gouty attack will have normal serum uric acid levels. Monitoring serum uric acid is useful in assessing the response to urate-lowering therapy or chemotherapy, with the target goal being a serum urate <6 mg/dL.

Serologic tests for RF, cyclic anticitrullinated peptide (CCP) or ACPA antibodies, ANAs, complement levels, Lyme and antineutrophil cytoplasmic antibodies (ANCA), or anti-streptolysin O (ASO) titer should be carried out only when there is clinical evidence to specifically suggest a specific diagnosis because these have poor predictive value when used for screening, especially when the pretest probability is low. For most of these, there is no value to repeated or serial serologic testing. Although 4–5% of a healthy population will have positive tests for RF and ANAs, only 1% and <0.4% of the population will have RA or SLE, respectively. IgM RF (autoantibodies against the Fc portion of IgG) is found in 80% of patients with RA but is poorly specific as it may also be seen in low titers in patients with chronic infections (tuberculosis, leprosy, hepatitis); other autoimmune diseases (SLE, Sjögren's syndrome); and chronic pulmonary, hepatic, or renal disease. When considering RA, both serum RF and anti-CCP antibodies should be obtained as these are complementary. Both are comparably sensitive, but CCP antibodies are more specific than RF. In RA, the presence of high titers of anti-CCP or RF antibodies, or double positivity, may indicate a greater risk for more severe, erosive polyarthritis. ANAs are found in nearly all patients with SLE and may also be seen in patients with other autoimmune diseases (polymyositis, scleroderma, antiphospholipid syndrome, Sjögren's syndrome), drug-induced lupus (Table 370-2), chronic thyroid, liver or renal disorders, and advanced age. Positive ANAs are found in 5% of adults and in up to 14% of elderly or chronically ill individuals. The ANA test is very sensitive but poorly specific for lupus, as only 1–2% of all positive results will be caused by lupus alone up to 80% of patients with thyroid disease will be ANA positive. The interpretation of a positive ANA test may depend on the magnitude of the titer and the pattern observed by

TABLE 370-4 Antinuclear Antibody (ANA) Patterns and Clinical Associations

ANA PATTERN	ANTIGEN IDENTIFIED	CLINICAL CORRELATE
Diffuse	Deoxyribonucleoprotein Histones	Nonspecific Drug-induced lupus, lupus
Peripheral (rim)	ds-DNA	50% of SLE (specific)
Speckled	U1-RNP Sm Ro (SS-A) La (SS-B) Scl-70 (topoisomerase I) Jo-1 (histidyl t-RNA synthetase)	>90% of MCTD 30% of SLE (specific) Sjögren's 60%, SCLE, neonatal lupus, ANA(-) lupus 50% of Sjögren's, 15% lupus 40% of diffuse scleroderma PM with pneumonitis + arthritis
Nucleolar	RNA polymerase I, others	40% of PSS
Centromere	Kinetochoore	75% CREST (limited scleroderma), PBC, Sjögren's, thyroiditis

Abbreviations: CREST, calcinosis, Raynaud's phenomenon, esophageal involvement, sclerodactyly, and telangiectasia; MCTD, mixed connective tissue disease; PBC, primary biliary cirrhosis; PSS, progressive systemic sclerosis; SCLE, subacute cutaneous lupus erythematosus; SLE, systemic lupus erythematosus.

immunofluorescence microscopy (**Table 370-4**). Diffuse and speckled patterns are least specific, whereas a peripheral, or rim, pattern (related to autoantibodies against double-strand [native] DNA) is highly specific and suggestive of lupus. Centromeric patterns are seen in patients with limited scleroderma (calcinosis, Raynaud's phenomenon, esophageal involvement, sclerodactyly, telangiectasia [CREST] syndrome), primary biliary sclerosis, Sjögren's syndrome, or thyroiditis, and nucleolar patterns may be seen in patients with diffuse systemic sclerosis or inflammatory myositis.

Aspiration and analysis of synovial fluid are always indicated in acute monoarthritis or when an infectious or crystal-induced arthropathy is suspected. Synovial fluid may distinguish between noninflammatory and inflammatory processes by analysis of the appearance, viscosity, and cell count. Tests for synovial fluid glucose, protein, lactate dehydrogenase, lactic acid, or autoantibodies are not recommended as they have no diagnostic value. Normal synovial fluid is clear or a pale straw color and is viscous, primarily because of the high levels of hyaluronate. Noninflammatory synovial fluid is clear, viscous, and amber-colored, with a WBC count of <2000/ μ L and a predominance of mononuclear cells. The viscosity of synovial fluid is assessed by expressing fluid from the syringe one drop at a time. Normally, there is a stringing effect, with a long tail behind each synovial drop. Effusions caused by OA or trauma will have normal viscosity. Inflammatory fluid is turbid and yellow, with an increased WBC count (2000–50,000/ μ L) and a polymorphonuclear leukocyte predominance. Inflammatory fluid has reduced viscosity (no stringing), diminished hyaluronate, and little or no tail following each drop of synovial fluid. Such effusions are found in RA, gout, and other inflammatory arthritides. Septic fluid is opaque and purulent, with a WBC count usually >50,000/ μ L, a predominance of polymorphonuclear leukocytes (>75%), and low viscosity. Such effusions are typical of septic arthritis but may also occur with RA or gout. Lastly, hemorrhagic synovial fluid (hemarthrosis) may be seen with trauma (ligament or cartilage tears), osteochondral fracture, neuropathic arthritis, or coagulopathy. An algorithm for synovial fluid aspiration and analysis is shown in **Fig. 370-6**. Synovial fluid should be analyzed immediately for appearance, viscosity, and cell count. Monosodium urate crystals (observed in gout) are seen by polarized microscopy and are long, needle-shaped, negatively birefringent, and usually intracellular. In chondrocalcinosis and pseudogout, calcium pyrophosphate dihydrate crystals are usually short, rhomboid-shaped, and positively birefringent. Whenever infection is suspected, synovial fluid should be Gram stained and cultured appropriately. If gonococcal arthritis is suspected, nucleic acid amplification tests should be used

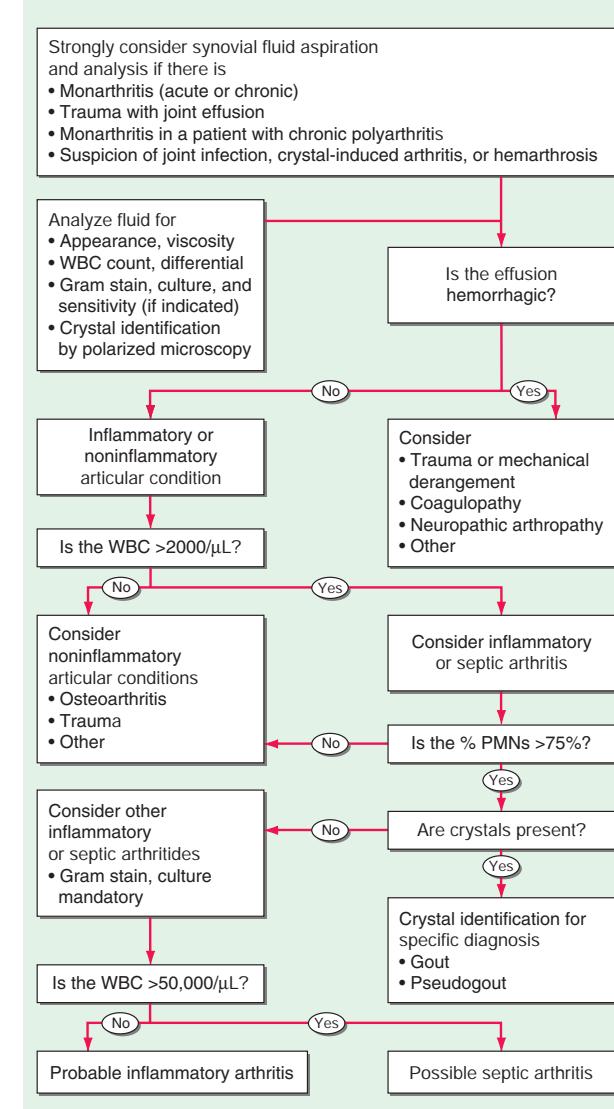


FIGURE 370-6 Algorithmic approach to the use and interpretation of synovial fluid aspiration and analysis. PMNs, polymorphonuclear (leukocytes); WBC, white blood cell count.

to detect either *Chlamydia trachomatis* or *N. gonorrhoeae* infection. Synovial fluid from patients with chronic monoarthritis should also be cultured for *M. tuberculosis* and fungi. Last, it should be noted that crystal-induced arthritis and septic arthritis occasionally occur together in the same joint.

DIAGNOSTIC IMAGING IN JOINT DISEASES

Conventional radiography has been valuable tool in the diagnosis and staging of articular disorders. Plain x-rays are most appropriate and cost effective when there is a history of trauma, suspected chronic infection, progressive disability, or monarticular involvement; when therapeutic alterations are considered; or when a baseline assessment is desired for what appears to be a chronic process. However, in acute inflammatory arthritis, early radiography is rarely helpful in establishing a diagnosis and may only reveal soft tissue swelling or juxtaarticular demineralization. As the disease progresses, calcification (of soft tissues, cartilage, or periarticular bone), joint space narrowing,

erosions, bony ankylosis, new bone formation (sclerosis, osteophytes, or periostitis), or subchondral cysts may develop and suggest specific clinical entities. Consultation with a radiologist will help define the optimal imaging modality, technique, or positioning to optimize interpretation and prevent the need for further studies.

Additional imaging techniques may possess greater diagnostic sensitivity and facilitate early diagnosis in a limited number of articular disorders and in selected circumstances and are indicated when conventional radiography is inadequate or nondiagnostic (**Table 370-5**). *Ultrasonography* is useful in the detection of soft tissue abnormalities (tendinitis, tenosynovitis, enthesitis, bursitis), crystal deposition, and entrapment neuropathies. Wider use, lower cost, better technology,

and enhanced site-specific transducers now allow for wider use and diagnostic specificity, especially when considering synovial (Baker's) cysts, rotator cuff tears, tendinitis and tendon injury, and crystal deposition on cartilage. Use of power Doppler allows for early detection of synovitis and bony erosions. *Radionuclide scintigraphy* is a very sensitive, but poorly specific, means of detecting inflammatory or metabolic alterations in bone or periarticular soft tissue structures (Table 370-5). Scintigraphy is best suited for total-body assessment (extent and distribution) of skeletal involvement (neoplasia, Paget's disease) and the assessment of patients with undiagnosed polyarthralgias, looking for occult arthritis. The use of scintigraphy has declined with greater use and declining cost of ultrasound and MRI. MRI has largely replaced scintigraphy in diagnosing osseous infection, neoplasia, inflammation, increased blood flow, bone remodeling, heterotopic bone formation, or avascular necrosis. Gallium scanning uses ^{67}Ga , which binds serum and cellular transferrin and lactoferrin and is preferentially taken up by neutrophils, macrophages, bacteria, and tumor tissue (e.g., lymphoma). As such, it is primarily used in the identification of occult infection or malignancy. Scanning with ^{111}In -labeled WBCs has been used to detect osteomyelitis and infectious or inflammatory arthritis. Despite their utility, ^{111}In -labeled WBC and ^{67}Ga scanning have largely been replaced by MRI, except when there is a suspicion of septic joint or prosthetic joint infections.

Computed tomography (CT) provides detailed visualization of the axial skeleton. Articulations previously considered difficult to visualize by radiography (e.g., zygapophyseal, sacroiliac, sternoclavicular, hip joints) can be evaluated using CT. CT has been demonstrated to be useful in the diagnosis of low back pain (e.g., spinal stenosis vs herniated disk), sacroilitis, osteoid osteoma, and stress fractures. Helical or spiral CT (with or without contrast angiography) is a novel technique that is rapid, cost effective, and sensitive in diagnosing pulmonary embolism or obscure fractures, often in the setting of initially equivocal findings. High-resolution CT can be advocated in the evaluation of suspected or established infiltrative lung disease (e.g., scleroderma or rheumatoid lung). The recent use of hybrid (positron emission tomography [PET] or single-photon emission CT [SPECT]) CT scans in metastatic evaluations has incorporated CT to provide better anatomic localization of scintigraphic abnormalities.

^{18}F -Fluorodeoxyglucose (FDG) is the most commonly used radiopharmaceutical in PET scanning. FDG-PET/CT scans are rarely indicated in septic or inflammatory arthritis but have been useful in the evaluation of patients with fever of unknown origin or suspected large vessel vasculitis. For instance, while FDG-PET is useful in assessing vascular inflammation/activity, MRI angiography can best define the extent of vascular damage. Dual-energy CT (DECT) scanning, developed in urology to identify urinary calculi, has been a highly sensitive and specific method used to identify and quantify uric acid deposition in tissues (**Fig. 370-7**).

MRI has significantly advanced the ability to image musculoskeletal structures. MRI has the advantages of providing multiplanar images with fine anatomic detail and contrast resolution (**Fig. 370-8**) that allows for the superior ability to visualize bone marrow and soft tissue periarticular structures. Although more costly with a longer procedural time than CT, the MRI has become the preferred technique when evaluating complex musculoskeletal disorders.

MRI can image fascia, vessels, nerve, muscle, cartilage, ligaments, tendons, pannus, synovial effusions, and bone marrow. Visualization of particular structures can be enhanced by altering the pulse sequence to produce either T1- or T2-weighted spin echo, gradient echo, or inversion recovery (including short tau inversion recovery [STIR]) images. Because of its sensitivity to changes in marrow fat, MRI is a sensitive but nonspecific means of detecting osteonecrosis, osteomyelitis, and marrow inflammation indicating overlying synovitis or osteitis (Fig. 363-8). Because of its enhanced soft tissue resolution, MRI is more sensitive than arthrography or CT in the diagnosis of soft tissue injuries (e.g., meniscal and rotator cuff tears); intraarticular derangements; marrow abnormalities (osteonecrosis, myeloma); and spinal cord or nerve root damage, synovitis, or cartilage damage or loss.

TABLE 370-5 Diagnostic Imaging Techniques for Musculoskeletal Disorders

METHOD	IMAGING TIME, H	COST ^a	CURRENT INDICATIONS
Ultrasound	<1	++	Synovial (Baker's) cysts Rotator cuff tears Bursitis, tendinitis, tendon injury Enthesitis Carpal tunnel syndrome Urate or calcium pyrophosphate deposition on cartilage Early detection of synovial inflammation or erosions Ultrasound-guided injection/arthrocentesis
Radionuclide scintigraphy			Metastatic bone survey Evaluation of Paget's disease Identifying occult arthritis in patients with undiagnosed polyarthralgia Acute infection Prosthetic infection Acute osteomyelitis Acute and chronic infection Acute osteomyelitis
$^{99\text{m}}\text{Tc}$	1–4	++	
^{111}In -WBC	24	+++	
^{67}Ga	24–48	++++	
Computed tomography (CT)	<1	+++	Herniated intervertebral disk Sacroilitis Spinal stenosis Spinal trauma Osteoid osteoma Stress fracture
Dual-energy CT	<1	NA	Uric acid deposition Tophus localization
Magnetic resonance imaging	1/2–2	++++	Avascular necrosis Osteomyelitis Septic arthritis, infected prosthetic joints Sacroilitis Intraarticular derangement and soft tissue injury Derangements of axial skeleton and spinal cord Herniated intervertebral disk Pigmented villonodular synovitis Inflammatory and metabolic muscle pathology

^aRelative cost for imaging study.

Abbreviations: NA, not commercially available; WBC, white blood cell.



FIGURE 370-7 Dual-energy computed tomography (DECT) scan from a 45-year-old woman with right ankle swelling around the lateral malleolus. Three-dimensional volume-rendered coronal reformatted DECT image shows that the mass is composed of monosodium urate (red) in keeping with tophus (arrow). (Reprinted from S Nicolaou et al: Dual-energy CT as a potential new diagnostic tool in the management of gout in the acute setting. *AJR Am J Roentgenol* 194:1072, 2010.)

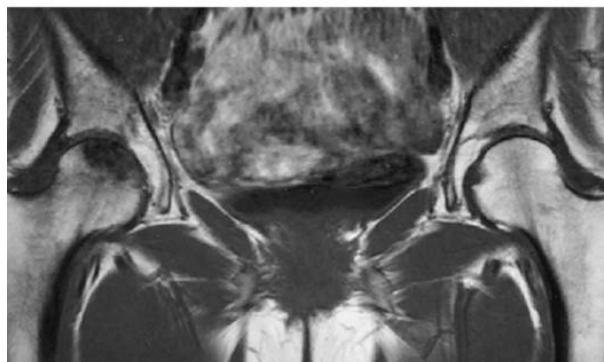


FIGURE 370-8 Superior sensitivity of magnetic resonance imaging (MRI) in the diagnosis of osteonecrosis of the femoral head. A 45-year-old woman receiving high-dose glucocorticoids developed right hip pain. Conventional x-rays (*top*) demonstrated only mild sclerosis of the right femoral head. T1-weighted MRI (*bottom*) demonstrated low-density signal in the right femoral head, diagnostic of osteonecrosis.

Acknowledgment

The author acknowledges the insightful contributions of Dr. Peter E. Lipsky to this chapter in previous editions.

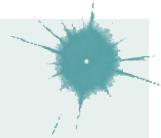
FURTHER READING

- Ali Y: Rheumatologic tests: A primer for family physicians. *Am Fam Physician* 98:164, 2018.
- Cush JJ et al: Evaluation of musculoskeletal complaints. Available from <http://www.rheumaknowledge.com/evaluation-of-musculoskeletal-complaints>. Accessed April 6, 2017.
- Hubbard MJ et al: Common soft tissue musculoskeletal pain disorders. *Prim Care* 45:289, 2018.
- Olsen NJ, Karp DR: Finding lupus in the ANA haystack. *Lupus Sci Med* 7:e000384, 2020.
- Rudwaleit M et al: How to diagnose axial spondyloarthritis early. *Ann Rheum Dis* 63:535, 2004.
- Simpfendorfer CS: Radiologic approach to musculoskeletal infections. *Infect Dis Clin North Am* 31:299, 2017.

371

Osteoarthritis

David T. Felson, Tuhina Neogi



Osteoarthritis (OA) is the most common type of arthritis. Its high prevalence, especially in the elderly, and its negative impact on physical function make it a leading cause of disability in the elderly. Because of the aging of Western populations and because obesity, a major risk factor, is increasing in prevalence, the occurrence of OA is on the rise.

OA affects certain joints, yet spares others (Fig. 371-1). Commonly affected joints include the hip, knee, and first metatarsal phalangeal

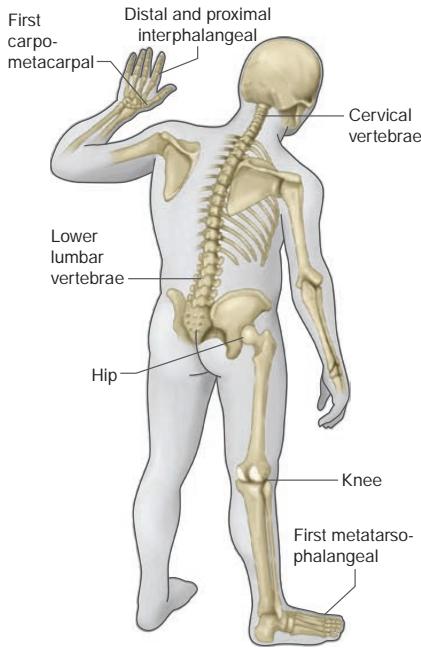


FIGURE 371-1 Joints commonly affected by osteoarthritis.

joint (MTP) and cervical and lumbosacral spine. In the hands, the distal and proximal interphalangeal joints and the base of the thumb are often affected. Usually spared are the wrist, elbow, and ankle. Our joints were designed, in an evolutionary sense, for brachiating apes, animals that still walked on four limbs. We thus develop OA in joints that were ill designed for human tasks such as pincer grip (OA in the thumb base) and walking upright (OA in knees and hips). Some joints, like the ankles, may be spared because their articular cartilage may be uniquely resistant to loading stresses.

OA can be diagnosed based on structural abnormalities or on the symptoms these abnormalities evoke. According to cadaveric studies, by elderly years, structural changes of OA are nearly universal. These include cartilage loss (seen as joint space loss on x-rays) and osteophytes. Many persons with x-ray evidence of OA have no joint symptoms, and although the prevalence of structural abnormalities is of interest in understanding disease pathogenesis, what matters more from a clinical perspective is the prevalence of symptomatic OA. Symptoms, usually joint pain, determine disability, visits to clinicians, and disease costs.

Symptomatic OA of the knee (pain on most days of a recent month plus x-ray evidence of OA in that knee) occurs in ~12% of persons age ≥ 60 in the United States and 6% of all adults age ≥ 30 . Symptomatic hip OA is roughly one-third as common as disease in the knee. Although radiographic hand OA and the appearance of bony enlargement in affected hand joints (Fig. 371-2) are extremely common in older persons, most affected persons have no pain. Even so, painful hand OA occurs in ~10% of elderly individuals and often produces measurable limitation in function.

The prevalence of OA rises strikingly with age, being uncommon in adults aged <40 and highly prevalent in those aged >60 . It is also a disease that, at least in middle-aged and elderly persons, is much more common in women than in men.

X-ray evidence of OA is common in the lower back and neck, but back pain and neck pain have not been tied to findings of OA on x-ray. Thus, back pain and neck pain are treated separately (Chap. 17).

GLOBAL CONSIDERATIONS

With the aging of the populations, both the prevalence of OA and the amount of disability worldwide related to OA have been increasing, especially in developed countries where many are living into old age. Hip



FIGURE 371-2 Severe osteoarthritis of the hands affecting the distal interphalangeal joints (Heberden's nodes) and the proximal interphalangeal joints (Bouchard's nodes). There is no clear bony enlargement of the other common site in the hands, the thumb base.

OA is rare in China and in immigrants from China to the United States. However, OA in the knees is at least as common, if not more so, in Chinese as in whites from the United States, and knee OA represents a major cause of disability in China, especially in rural areas. Anatomic differences between Chinese and white hips may account for much of the difference in hip OA prevalence, with white hips having a higher prevalence of anatomic predispositions to the development of OA.

DEFINITION

OA is joint failure, a disease in which all structures of the joint have undergone pathologic change, often in concert. The pathologic sine qua non of disease is hyaline articular cartilage loss, present in a focal and, initially, nonuniform manner. This is accompanied by increasing thickness and sclerosis of the subchondral bony plate, by outgrowth of osteophytes at the joint margin, by stretching of the articular capsule, by variable degrees of synovitis, and by weakness of muscles bridging the joint. In knees, meniscal degeneration is part of the disease. There are numerous pathways that lead to joint failure, but the initial step is often joint injury in the setting of a failure of protective mechanisms.

JOINT PROTECTIVE MECHANISMS AND THEIR FAILURE

Joint protectors include joint capsule and ligaments, muscle, sensory afferents, and underlying bone. Joint capsule and ligaments serve as joint protectors by providing a limit to excursion, thereby fixing the range of joint motion.

Synovial fluid reduces friction between articulating cartilage surfaces, thereby serving as a protector against friction-induced cartilage wear. This lubrication function depends on *hyaluronic acid* and on *lubricin*, a mucinous glycoprotein secreted by synovial fibroblasts whose concentration diminishes after joint injury and in the face of synovial inflammation.

The ligaments, along with overlying skin and tendons, contain mechanoreceptor sensory nerves. These mechanoreceptors fire at different frequencies throughout a joint's range of motion, providing feedback by way of the spinal cord to muscles and tendons. As a consequence, these muscles and tendons can assume the right tension at appropriate points in joint excursion to act as optimal joint protectors, anticipating joint loading.

Muscles and tendons that bridge the joint are key joint protectors. Focal stress across the joint is minimized by muscle contraction that decelerates the joint before impact and assures that when joint impact arrives, it is distributed broadly across the joint surface.

Failure of these joint protectors increases the risk of joint injury and OA. For example, in animals, OA develops rapidly when a sensory nerve to the joint is sectioned and joint injury induced. Similarly, in humans, Charcot's arthropathy, a severe and rapidly progressive OA, develops when minor joint injury occurs in the presence of posterior column

peripheral neuropathy. Another example of joint protector failure is rupture of ligaments, a well-known cause of the early development of OA.

CARTILAGE AND ITS ROLE IN JOINT FAILURE

In addition to being a primary target tissue for disease, cartilage also functions as a joint protector. A thin rim of tissue at the ends of two opposing bones, cartilage is lubricated by synovial fluid to provide an almost frictionless surface across which these two bones move. The compressive stiffness of cartilage compared to bone provides the joint with impact-absorbing capacity.

The earliest changes of OA may occur in cartilage, and abnormalities there can accelerate disease development. The two major macromolecules in cartilage are type 2 collagen, which provides cartilage its tensile strength, and aggrecan, a proteoglycan macromolecule linked with hyaluronic acid, which consists of highly negatively charged glycosaminoglycans. In normal cartilage, type 2 collagen is woven tightly, constraining the aggrecan molecules in the interstices between collagen strands, forcing these highly negatively charged molecules into close proximity. The aggrecan molecule, through electrostatic repulsion of its negative charges, gives cartilage its compressive stiffness. Chondrocytes, the cells within this avascular tissue, synthesize all elements of the matrix and produce enzymes that break it down (Fig. 371-3). Cartilage matrix synthesis and catabolism are in a dynamic equilibrium influenced by the cytokine and growth factor environment. Mechanical and osmotic stress on chondrocytes induces these cells to alter gene expression and increase production of inflammatory cytokines and matrix-degrading enzymes. While chondrocytes synthesize numerous enzymes, matrix metalloproteinases (MMPs; especially collagenases and ADAMTS-5) are critical enzymes in the breakdown of cartilage matrix.

Local inflammation accelerates the development and progression of osteoarthritis and increases the likelihood that an osteoarthritic joint will be painful. Some of this inflammation may be induced by mechanical stimuli, so called mechanoinflammation. The synovium, cartilage, and bone all influence disease development through cytokines, chemokines, and even complement activation (Fig. 371-3). These act on chondrocyte cell-surface receptors and ultimately have transcriptional effects. Matrix fragments released from cartilage stimulate synovitis. Inflammatory cytokines such as interleukin 1 β (IL-1 β) and tumor necrosis factor α (TNF- α) induce chondrocytes to synthesize prostaglandin E₂ and nitric oxide. At early stages in the matrix response to injury, the net effect of cytokine stimulation may be matrix synthesis, but ultimately, the combination of effects on chondrocytes triggers matrix degradation. Enzymes in the matrix are held in check by activation inhibitors, including tissue inhibitor of metalloproteinase (TIMP).

Growth factors are also part of this complex network, with bone morphogenetic protein 2 (BMP-2) and transforming growth factor β (TGF- β) playing prominent roles in stimulating the development of osteophytes. Whereas healthy articular cartilage is avascular in part due to angiogenesis inhibitors present in cartilage, disease is characterized by the invasion of blood vessels into cartilage from underlying bone. This is influenced by vascular endothelial growth factor (VEGF) synthesis in the cartilage and bone. With these blood vessels come nerves that may bring nociceptive innervation.

With aging, articular chondrocytes exhibit a decline in synthetic capacity, but they produce proinflammatory mediators and matrix-degrading enzymes, findings characteristic of a senescent secretory phenotype. These chondrocytes are unable to maintain tissue homeostasis (such as after insults of a mechanical or inflammatory nature). Thus, with age, cartilage is easily damaged by minor sometimes unnoticed injuries, including those that are part of daily activities.

OA cartilage is characterized by gradual depletion of aggrecan, an unfurling of the tightly woven collagen matrix, and loss of type 2 collagen. With these changes comes increasing vulnerability of cartilage, which loses its compressive stiffness.

RISK FACTORS

Joint vulnerability and joint loading are the two major factors contributing to the development of OA. On the one hand, a vulnerable joint whose protectors are dysfunctional can develop OA with minimal levels of loading, perhaps even levels encountered during everyday activities. On the other hand, in a young joint with competent protectors, a major acute injury or long-term overloading is necessary to precipitate disease. Risk factors for OA can be understood in terms of their effect either on joint vulnerability or on loading (Fig. 371-4).

SYSTEMIC RISK FACTORS THAT AFFECT JOINT VULNERABILITY

Age is the most potent risk factor for OA. Radiographic evidence of OA is rare in individuals aged <40; however, in some joints, such as the hands, OA occurs in >50% of persons aged >70. Aging increases joint vulnerability through several mechanisms. Whereas dynamic loading of joints stimulates matrix synthesis by chondrocytes in young cartilage, aged cartilage is less responsive to these stimuli. Partly because of this failure to synthesize matrix with loading, cartilage thins with age, and thinner cartilage experiences higher shear stress and is at greater risk of cartilage damage. Also, joint protectors fail more often with age. Muscles that bridge the joint become weaker with age and respond less quickly to oncoming impulses. Sensory nerve input slows with age, retarding the feedback loop of mechanoreceptors to muscles and

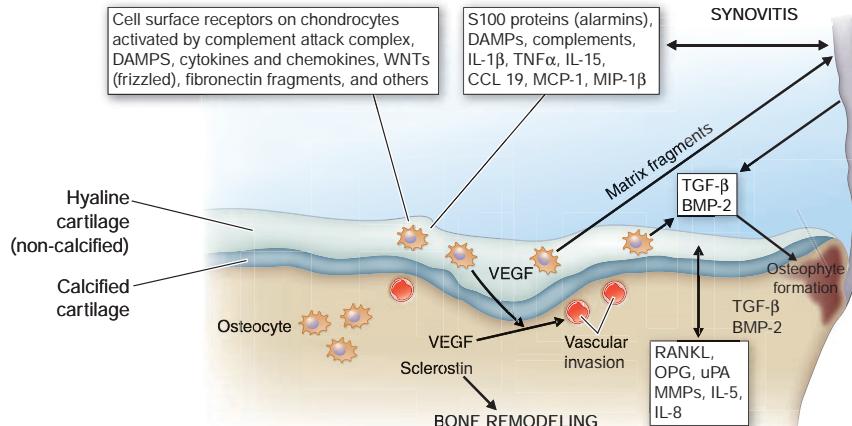


FIGURE 371-3 Selected factors involved in the osteoarthritic process including chondrocytes, bone, and synovium. Synovitis causes release of cytokines, alarmins, damage-associated molecular pattern (DAMP) molecules, and complement, which activate chondrocytes through cell-surface receptors. Chondrocytes produce matrix molecules (collagen type 2, aggrecan) and the enzymes responsible for the degradation of the matrix (e.g., ADAMTS-5 and matrix metalloproteinases [MMPs]). Bone invasion occurs through the calcified cartilage, triggered by vascular endothelial growth factor (VEGF) and other molecules. IL, interleukin; TGF, transforming growth factor; TNF, tumor necrosis factor. (Reproduced with permission from RF Loeser et al: Osteoarthritis: a disease of the joint as an organ. *Arthritis Rheum* 64:1697, 2012.)

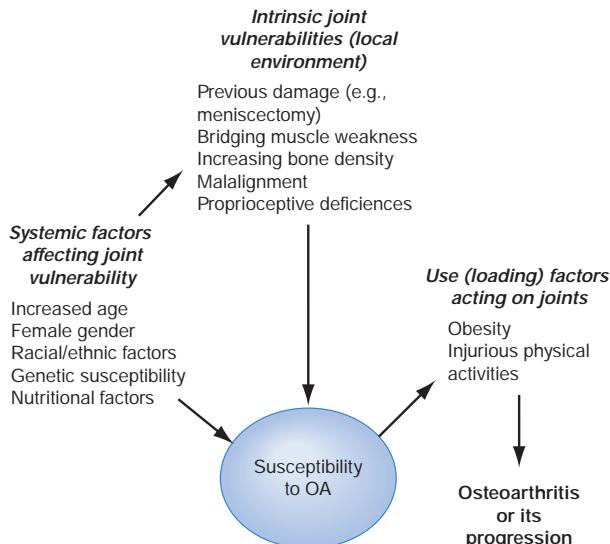


FIGURE 371-4 Risk factors for osteoarthritis (OA) either contribute to the susceptibility of the joint (systemic factors or factors in the local joint environment) or increase risk by the load they put on the joint. Usually, a combination of loading and susceptibility factors is required to cause disease or its progression.

tendons related to their tension and position. Ligaments stretch with age, making them less able to absorb impulses. These factors work in concert to increase the vulnerability of older joints to OA.

Older women are at high risk of OA in all joints, a risk that increases as women reach their sixth decade. Although hormone loss with menopause may contribute to this risk, there is little understanding of the unique vulnerability of older women versus men.

HERITABILITY AND GENETICS AND THEIR RELATION TO JOINT VULNERABILITY

 OA is a highly heritable disease, but its heritability is joint specific. Fifty percent of the hand and hip OA in the community is attributable to inheritance, that is, to disease present in other members of the family. However, the heritable proportion of knee OA is at most 30%, with some studies suggesting no heritability at all. Whereas many people with OA have disease in multiple joints, this “generalized OA” phenotype is rarely inherited and is more often a consequence of aging.

Emerging evidence has identified genetic mutations that confer a high risk of OA. The best replicated is a polymorphism within the growth differentiation factor 5 (GDF5) gene whose effect is to diminish the quantity of GDF5. GDF5 affects joint shape, which is likely to be the mechanism by which genes predisposing to OA increase risk of disease. Minor abnormalities in joint shape can make a joint vulnerable to damage if focal stresses across the joint increase.

RISK FACTORS IN THE JOINT ENVIRONMENT

Some risk factors increase vulnerability of the joint through local effects on the joint environment. With changes in joint anatomy, for example, load across the joint is no longer distributed evenly across the joint surface, but rather shows an increase in focal stress. In the hip, three uncommon developmental abnormalities occurring in utero or in childhood—congenital dysplasia, Legg–Perthes disease, and slipped capital femoral epiphysis—leave a child with distortions of hip joint anatomy that often lead to OA later in life. Girls are predominantly affected by acetabular dysplasia, a mild form of congenital dislocation, whereas the other abnormalities more often affect boys. Depending on the severity of the anatomic abnormalities, hip OA occurs either in young adulthood (severe abnormalities) or middle age (mild abnormalities). Femoroacetabular impingement can develop during adolescence. It is a clinical syndrome in which an outgrowth of bone at the femur's head/neck junction thought to develop during closure of

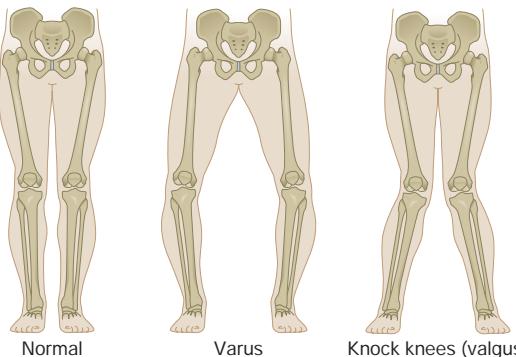


FIGURE 371-5 The two types of limb malalignment in the frontal plane: varus, in which the stress is placed across the medial compartment of the knee joint, and valgus, which places excess stress across the lateral compartment of the knee.

the growth plate results in abnormal contact between the femur and acetabulum, especially during hip flexion and rotation. This leads to cartilage and labral damage, to hip pain, and ultimately in later life, to an increased risk of hip OA.

Major injuries to a joint also can produce anatomic abnormalities that leave the joint susceptible to OA. For example, a fracture through the joint surface often causes OA in joints in which the disease is otherwise rare such as the ankle and the wrist. Avascular necrosis can lead to collapse of dead bone at the articular surface, producing anatomic irregularities and subsequent OA.

Tears of ligamentous and fibrocartilaginous structures that protect the joints, such as the meniscus in the knee and the labrum in the hip, can lead to premature OA. Meniscal tears increase with age and when chronic are often asymptomatic but lead to adjacent cartilage damage and accelerated OA. Even injuries in which the affected person never received a diagnosis may increase risk of OA. For example, in the Framingham Study subjects, men with a history of major knee injury, but no surgery, had a 3.5-fold increased risk for subsequent knee OA.

Another source of anatomic abnormality is malalignment across the joint (**Fig. 371-5**). This factor has been best studied in the knee. Varus (bowlegged) knees with OA are at exceedingly high risk of cartilage loss in the medial or inner compartment of the knee, whereas valgus (knock-kneed) malalignment predisposes to rapid cartilage loss in the lateral compartment. Malalignment causes this effect by increasing stress on a focal area of cartilage, which then breaks down; it also causes damage to bone underlying the cartilage, producing bone marrow lesions seen on magnetic resonance imaging (MRI). Malalignment in the knee often produces such a substantial increase in focal stress within the knee (as evidenced by its destructive effects on subchondral bone) that severely malaligned knees may be destined to progress regardless of the status of other risk factors.

Weakness in the quadriceps muscles bridging the knee increases the risk of the development of painful OA in the knee.

The role of bone in serving as a shock absorber for impact load is not well understood, but persons with increased bone density are at high risk of OA. Those with high bone density have an increased risk of osteophytes at the joint margin.

LOADING FACTORS

Obesity Three to six times body weight is transmitted across the knee during single-leg stance. Any increase in weight may be multiplied by this factor to reveal the excess force across the knee in overweight persons during walking. Obesity is a well-recognized and potent risk factor for the development of knee OA and, less so, for hip OA. Obesity precedes the development of disease and is not just a consequence of the inactivity present in those with disease. It is a stronger risk factor for disease in women than in men, and for women, the relationship of weight to the risk of disease is linear, so that with each pound increase in weight, there is a commensurate increase in risk. Weight loss in women lowers the risk of developing symptomatic disease. Not only is

obesity a risk factor for OA in weight-bearing joints, but obese persons have more worse pain from the disease.

Obesity's effect on the development and progression of disease is mediated mostly through the increased loading in weight-bearing joints that occurs in overweight persons and more severe joint pain in obese persons.

Repeated Use of Joint and Exercise There are two categories of repetitive joint use: occupational use and leisure time physical activities. Workers performing repetitive tasks as part of their occupations for many years are at high risk of developing OA in the joints they use repeatedly. For example, farmers are at high risk for hip OA, and miners have high rates of OA in knees and spine. Workers whose jobs require regular knee bending or lifting or carrying heavy loads have a high rate of knee OA. One reason why workers may get disease is that during long days at work, their muscles may gradually become exhausted, no longer serving as effective joint protectors.

It is widely recommended for people to adopt an exercise-filled lifestyle, and long-term studies of exercise suggest no consistent association of exercise with OA risk in most persons. However, persons who already have injured joints may put themselves at greater risk by engaging in certain types of exercise. For example, persons who have already sustained major knee injuries are at increased risk of progressive knee OA as a consequence of running. In addition, compared to nonrunners, elite runners (professional runners and those on Olympic teams) have high risks of both knee and hip OA. Lastly, although recreational runners are not at increased risk of knee OA, studies suggest that they have a modest increased risk of disease in the hip.

PATHOLOGY

The pathology of OA provides evidence of the involvement of many joint structures in disease. Cartilage initially shows surface fibrillation and irregularity. As disease progresses, focal erosions develop there, and these eventually extend to the subjacent bone. With further progression, cartilage erosion down to bone expands to involve a larger proportion of the joint surface, even though OA remains a focal disease with nonuniform loss of cartilage.

After an injury to cartilage, chondrocytes undergo mitosis and clustering. Although the metabolic activity of these chondrocyte clusters is high, the net effect of this activity is to promote proteoglycan depletion in the matrix surrounding the chondrocytes. This is because the catabolic activity is greater than the synthetic activity. As disease develops, collagen matrix becomes damaged, the negative charges of proteoglycans get exposed, and cartilage swells from ionic attraction to water molecules. Because in damaged cartilage proteoglycans are no longer forced into close proximity, cartilage does not bounce back after loading as it did when healthy, and cartilage becomes vulnerable to further injury. Chondrocytes at the basal level of cartilage undergo apoptosis.

With loss of cartilage comes alteration in subchondral bone. Stimulated by growth factors and cytokines, osteoclasts and osteoblasts in the bony plate just underneath cartilage become activated. Bone formation produces a thickening of the subchondral plate that occurs even before cartilage ulcerates. Trauma to bone during joint loading may be the primary factor driving this bone response, with healing from injury (including microcracks) inducing remodeling. Small areas of osteonecrosis usually exist in joints with advanced disease. Bone death may also be caused by bone trauma with shearing of microvasculature, leading to a cutoff of vascular supply to some bone areas.

At the margin of the joint, near areas of cartilage loss, osteophytes form. These start as outgrowths of new cartilage, and with neurovascular invasion from the bone, this cartilage ossifies. Osteophytes are an important radiographic hallmark of OA.

The synovium produces lubricating fluids that minimize shear stress during motion. In healthy joints, the synovium consists of a single discontinuous layer filled with fat and containing two types of cells, macrophages and fibroblasts, but in OA, it can sometimes become edematous and inflamed. There is a migration of macrophages from the periphery into the tissue, and cells lining the synovium proliferate. Inflammatory cytokines and alarmins secreted by the synovium activate chondrocytes to produce enzymes that accelerate destruction of matrix.

Additional pathologic changes occur in the capsule, which stretches, becomes edematous, and can become fibrotic.

The pathology of OA is not identical across joints. In hand joints with severe OA, for example, there are often cartilage erosions in the center of the joint probably produced by bony pressure from the opposite side of the joint.

Basic calcium phosphate and calcium pyrophosphate dihydrate crystals are present microscopically in most joints with end-stage OA. Their role in osteoarthritic cartilage is unclear, but their release from cartilage into the joint space and joint fluid likely triggers synovial inflammation, which can, in turn, produce release of cytokines and trigger nociceptive stimulation.

SOURCES OF PAIN

Because healthy cartilage is aneural, cartilage loss alone in a joint is not accompanied by pain. Thus, pain in OA likely arises from structures outside the cartilage. Innervated structures in the joint include the synovium, ligaments, joint capsule, muscles, and subchondral bone. Most of these are not visualized by x-ray, and the severity of x-ray changes in OA correlates poorly with pain severity. However, in later stages of OA, loss of cartilage integrity accompanied by neurovascular invasion may contribute to pain.

Based on MRI studies in osteoarthritic knees comparing those with and without pain and on studies mapping tenderness in unanesthetized joints, likely sources of pain include synovial inflammation, joint effusions, and bone marrow edema. Modest synovitis develops in many but not all osteoarthritic joints. The presence of synovitis on MRI is correlated with the presence and severity of knee pain, and potentially with pain sensitization. Capsular stretching from fluid in the joint stimulates nociceptive fibers there, inducing pain. Increased focal loading as part of the disease not only damages cartilage but probably also injures the underlying bone. As a consequence, bone marrow edema appears on the MRI; histologically, this edema signals the presence of microcracks and scar, which are the consequences of trauma. These lesions may stimulate bone nociceptive fibers. Pain may arise from outside the joint also, including bursae near the joints. Common sources of pain near the knee are anserine bursitis and iliotibial band syndrome.

Much of the pain experienced in OA occurs when nociceptors in the joint are stimulated during weight-bearing activities. However, the pain may eventually become more constant and present at rest, and this suggests other mechanisms contribute to the pain experience. The pathologic changes of OA may lead to alterations in nervous system signaling (**Chap. 17**). Specifically, peripheral nociceptors can become more responsive to sensory input, known as peripheral sensitization, and there can also be an increase in facilitated central ascending nociceptive signaling, known as central sensitization. Individuals with OA may also have insufficient descending inhibitory modulation. Some individuals may be genetically predisposed to becoming sensitized; however, regardless of the etiology, these nervous system alterations are associated with more severe pain severity, contribute to the presence of allodynia and hyperalgesia in patients with OA, and may predispose to development of chronic pain. Obesity increases the severity of joint pain. This is probably because adipose tissue produces adipokines and other hormones which act on the nervous system to enhance pain sensitivity.

CLINICAL FEATURES

Joint pain from OA is primarily activity-related in the early stages of the disease. Pain comes on either during or just after joint use and then gradually resolves. Examples include knee or hip pain with going up or down stairs, pain in weight-bearing joints when walking, and, for hand OA, pain when cooking. Early in disease, pain is episodic, triggered often by overactive use of a diseased joint, such as a person with knee OA taking a long run and noticing a few days of pain thereafter. As disease progresses, the pain becomes continuous and even begins to be bothersome at night. Stiffness of the affected joint may be prominent, but morning stiffness is usually brief (<30 min).

In knees, buckling may occur, in part, from weakness of muscles crossing the joint. Mechanical symptoms, such as buckling, catching, or locking, could also signify internal derangement, like an anterior cruciate ligament or meniscal tear; however, these symptoms, which

are common in persons with knee OA, need to be further evaluated only if they develop after an acute knee injury. In the knee, pain with activities requiring knee flexion, such as stair climbing and arising from a chair, often emanates from the patellofemoral compartment of the knee, which does not actively articulate until the knee is bent ~35°.

OA is the most common cause of chronic knee pain in persons aged >45, but the differential diagnosis is long. Inflammatory arthritis is likely if there is prolonged morning stiffness and many other joints are affected. Bursitis occurs commonly around knees and hips. A physical examination should focus on whether tenderness is over the joint line (at the junction of the two bones around which the joint is articulating) or outside of it. Anserine bursitis, medial and distal to the knee, is an extremely common cause of chronic knee pain that may respond to a glucocorticoid injection. Prominent nocturnal pain in the absence

of end-stage OA merits a distinct workup. For hip pain, OA can be detected by loss of internal rotation on passive movement, and pain isolated to an area lateral to the hip joint usually reflects the presence of trochanteric bursitis.

No blood tests are routinely indicated for workup of patients with OA unless symptoms and signs suggest inflammatory arthritis. Examination of the synovial fluid is often more helpful diagnostically than an x-ray. If the synovial fluid white count is >1000/ μL , inflammatory arthritis or gout or pseudogout is likely, the latter two being also identified by the presence of crystals.

Neither x-rays nor magnetic resonance imaging are indicated in the workup of OA. They should be ordered only when joint pain and physical findings are not typical of OA or if pain persists after inauguration of treatment effective for OA. In OA, imaging findings (Fig. 371-6) correlate poorly with the presence and severity of pain. Further, in both

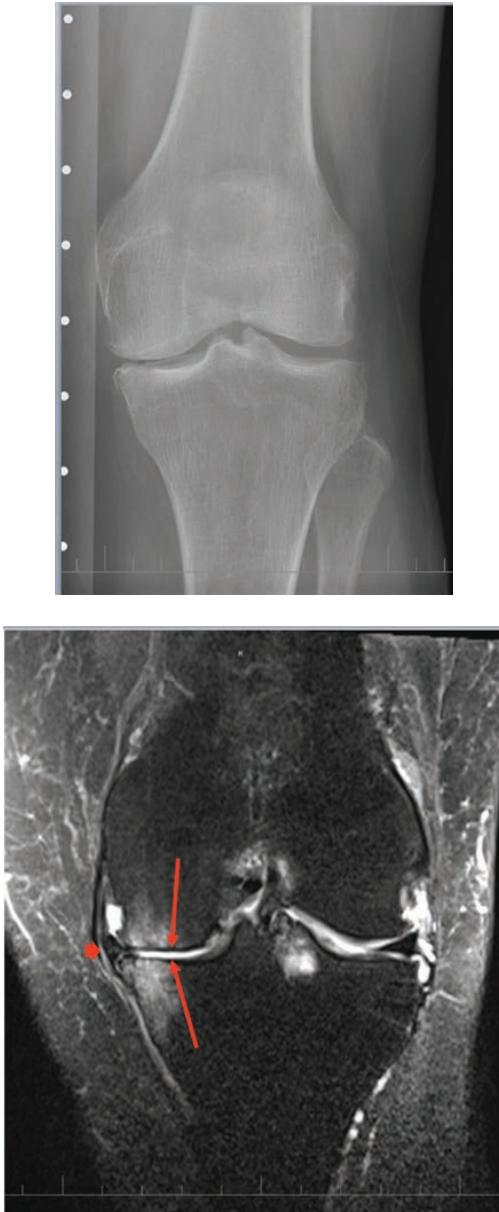


FIGURE 371-6 X-ray and MRI of knee with medial osteoarthritis. X-ray shows osteophytes at the medial and lateral tibia and femur and joint space narrowing of the medial tibiofemoral joint. Coronal intermediate-weighted fat-suppressed MRI confirms the presence of medial and lateral osteophytes and the medial tibiofemoral joint space narrowing. There is diffuse denuded area with no cartilage remaining at the weight-bearing medial tibiofemoral joint (arrows). There is also a severe medial meniscus extrusion (arrowhead). Bone marrow lesions, which provide evidence of bone injury, are present at medial tibia, medial femur, and intraspinous tibial region. Cartilage focal defects are also seen at the lateral weight-bearing femur and tibia.

knees and hips, radiographs may be normal in early disease as they are insensitive to cartilage loss and other early findings.

Although MRI may reveal the extent of pathology in an osteoarthritic joint, it is not indicated as part of the diagnostic workup. Findings such as meniscal tears and cartilage and bone lesions occur not only in most patients with OA in the knee, but also in most older persons without joint pain. MRI findings almost never warrant a change in therapy.

TREATMENT

Osteoarthritis

The goals of the treatment of OA are to alleviate pain and minimize loss of physical function. To the extent that pain and loss of function are consequences of inflammation, of weakness across the joint, and of laxity and instability, the treatment of OA involves addressing each of these impairments. Comprehensive therapy consists of a multimodality approach including physical modalities and pharmacologic elements.

Patients with mild and intermittent symptoms may need only symptomatic management and/or treatments aimed at weight loss, physical activity, exercise, and self-management strategies. Patients with ongoing, disabling pain are likely to need both physical modalities and pharmacotherapy.

Treatments for knee OA have been more completely evaluated than those for hip and hand OA or for disease in other joints. Thus, although the principles of treatment are identical for OA in all joints, we shall focus below on the treatment of knee OA, noting specific recommendations for disease in other joints, especially when they differ from those for the knee.

PHYSICAL MANAGEMENT MODALITIES

Because OA is a mechanically driven disease, the mainstay of treatment involves altering loading across the painful joint and improving the function of joint protectors, so they can better distribute load across the joint. Ways of lessening focal load across the joint include:

1. Avoiding painful activities as these are usually activities that overload the joint
2. Improving the strength and conditioning of muscles that bridge the joint to optimize their function
3. Unloading the joint, either by redistributing load within the joint with a brace or a splint or by unloading the joint during weight bearing with a cane or a crutch

The simplest treatment for many patients is to avoid activities that precipitate pain. For example, for the middle-aged patient whose long-distance running brings on symptoms of knee OA, a less demanding form of weight-bearing activity may alleviate all symptoms. For an older person whose daily walks up and down hills bring on knee pain, routing these away from hills might eliminate symptoms.

Weight loss is a central strategy, particularly for knee OA. Each pound of weight loss may have a multiplier effect, unloading both knees and hips and probably relieving pain in those joints.

In hand joints affected by OA, splinting, by limiting motion, often minimizes pain for patients with involvement especially in the base of the thumb. Weight-bearing joints such as knees and hips can be unloaded by using a cane in the hand opposite the affected joint for partial weight bearing. A physical therapist can help teach the patient how to use the cane optimally, including ensuring that its height is optimal for unloading. Crutches or walkers can serve a similar beneficial function.

Exercise Osteoarthritic pain in knees or hips during weight bearing results in lack of activity and poor mobility, and because OA is so common, the inactivity that results increases the risk of cardiovascular disease and obesity. Aerobic capacity is poor in most elders with symptomatic knee OA, worse than others of the same age.

Weakness in muscles that bridge osteoarthritic joints is multifactorial in etiology. First, there is a decline in strength with age. Second, with limited mobility comes disuse muscle atrophy. Third, patients with painful knee or hip OA alter their gait to lessen loading across the affected joint, and this further diminishes muscle use. Fourth, "arthrogenous inhibition" may occur, whereby contraction of muscles bridging the joint is inhibited by a nerve afferent feedback loop emanating in a swollen and stretched joint capsule; this prevents attainment of voluntary maximal strength. Because adequate muscle strength and conditioning are critical to joint protection, weakness in a muscle that bridges a diseased joint makes the joint more susceptible to further damage and pain. The degree of weakness correlates strongly with the severity of joint pain and the degree of physical limitation. One of the cardinal elements of the treatment of OA is to improve the functioning of muscles surrounding the joint.

Trials in knee and hip OA have shown that exercise lessens pain and improves physical function. Most effective exercise regimens consist of aerobic and/or resistance training, the latter of which focuses on strengthening muscles across the joint. Exercises are likely to be effective especially if they train muscles for the activities a person performs daily. Activities that increase pain in the joint should be avoided, and the exercise regimen needs to be individualized to optimize effectiveness. Range-of-motion exercises, which do not strengthen muscles, and isometric exercises that strengthen muscles, but not through range of motion, are unlikely to be effective by themselves. Low-impact exercises, including water aerobics and water resistance training, are often better tolerated by patients than exercises involving impact loading, such as running or treadmill exercises. A patient should be referred to an exercise class or to a therapist who can create an individualized regimen. In addition to conventional exercise regimens, tai chi may be effective for knee OA. However, there is no strong evidence that patients with hand OA benefit from therapeutic exercise.

Adherence over the long term is the major challenge to an exercise prescription. In trials involving patients with knee OA who were engaged in exercise treatment, from a third to over half of patients stopped exercising by 6 months. Less than 50% continued regular exercise at 1 year. The strongest predictor of a patient's continued exercise is a previous personal history of successful exercise. Physicians should reinforce the exercise prescription at each clinic visit, help the patient recognize barriers to ongoing exercise, and identify convenient times for exercise to be done routinely. Mobile health and wearable technologies are increasingly being used to encourage adherence to exercise. The combination of exercise with calorie restriction and weight loss is especially effective in lessening pain.

Correction of Malalignment Malalignment in the frontal plane (varus-valgus) markedly increases the stress across the joint, which can lead to progression of disease and to pain and disability (Fig. 371-5). Correcting varus-valgus malalignment, either surgically or with bracing, may relieve pain in persons whose knees are malaligned. However, correcting malalignment is often very challenging. Fitted braces that straighten varus knees by putting valgus stress across the knee can be effective. Unfortunately, many patients are unwilling to wear a realigning knee brace; in addition, in patients with obese legs, braces may slip with usage and lose their realigning effect. Braces are indicated for willing patients who can learn to put them on correctly and on whom they do not slip. Shoes modified with rubber hemispheres on the sole that alter alignment of the proximal knee have shown efficacy in trials especially if used over several months.

Pain from the patellofemoral compartment of the knee can be caused by tilting of the patella or patellar malalignment with the patella riding laterally in the femoral trochlear groove. Using a patellar brace to realign the patella, or tape to pull the patella back into the trochlear sulcus or reduce its tilt, has been shown in controlled trials to lessen patellofemoral pain. However, patients may

find it difficult to apply tape, and skin irritation from the tape is common, and like realigning braces, patellar braces may slip.

Although their effect on malalignment is questionable, neoprene sleeves pulled up to cover the knee lessen pain and are easy to use and popular among patients. The explanation for their therapeutic effect on pain is unclear.

In patients with knee OA, acupuncture produces modest pain relief compared to placebo needles and may be an adjunctive treatment, though placebo effect is likely high. In patients with refractory joint pain from OA, radiofrequency ablation of the nerves innervating the joint has been shown to provide prolonged pain relief, although long-term safety is unknown.

PHARMACOTHERAPY

Although approaches involving physical modalities constitute its mainstay, pharmacotherapy serves an important adjunctive role in OA treatment for symptom management. Available drugs are administered using oral, topical, and intraarticular routes. To date, there are no available drugs that alter the disease process itself.

Acetaminophen, Nonsteroidal Anti-Inflammatory Drugs (NSAIDs), and Cyclooxygenase-2 (COX-2) Inhibitors NSAIDs are the most popular drugs to treat osteoarthritic pain. They can be administered either topically or orally. In clinical trials, oral NSAIDs produce ~30% greater improvement in pain than high-dose acetaminophen. Occasional patients treated with NSAIDs experience dramatic pain relief, whereas others experience little improvement. Initially, NSAIDs should be administered topically or taken orally on an “as-needed” basis because side effects are less frequent with low intermittent doses. If occasional medication use is insufficiently effective, then daily treatment may be indicated, with an anti-inflammatory dose selected (Table 371-1). Patients should be reminded to take low-dose aspirin and ibuprofen or naproxen at different times to eliminate a drug interaction.

NSAIDs taken orally have substantial and frequent side effects, the most common of which is upper gastrointestinal (GI) toxicity, including dyspepsia, nausea, bloating, GI bleeding, and ulcer disease. Thirty to forty percent of patients experience upper GI side effects so severe as to require discontinuation of medication. To minimize the risk of nonsteroidal-related GI side effects, patients should take NSAIDs after food; if risk is high, patients should take a gastroprotective agent, such as a proton pump inhibitor. Certain oral agents are safer to the stomach than others, including non-acetylated salicylates and nabumetone. Major NSAID-related GI side effects can occur in patients who do not complain of upper GI symptoms. In one study of patients hospitalized for GI bleeding, 81% had no premonitory symptoms.

Because of the increased rates of cardiovascular events associated with conventional NSAIDs such as diclofenac, many of these drugs are not appropriate long-term treatment choices for older persons with OA, especially those at high risk of heart disease or stroke. The American Heart Association has identified COX-2 inhibitors as putting patients at high risk, although low doses of celecoxib (≤ 200 mg/d) are not associated with an elevation of risk. The only conventional NSAIDs that appear safe from a cardiovascular perspective are naproxen and low-dose celecoxib, but they do have GI toxicity.

There are other common side effects of NSAIDs, including the tendency to develop edema because of prostaglandin inhibition of afferent blood supply to glomeruli in the kidneys and, for similar reasons, a predilection toward reversible renal insufficiency. Blood pressure may increase modestly in some NSAID-treated patients. Oral NSAIDs should not be used in patients with stage IV or V renal disease and should be used with caution in those with stage III disease.

NSAIDs can be placed into a gel or topical solution with another chemical modality that enhances penetration of the skin barrier creating a topical NSAID. When absorbed through the skin, plasma concentrations are an order of magnitude lower than with the same amount of drug administered orally or parenterally. However, when these drugs are administered topically in proximity to a superficial joint

TABLE 371-1 Pharmacologic Treatment for Osteoarthritis

TREATMENT	DOSAGE	COMMENTS
Oral NSAIDs and COX-2 inhibitors		Take with food. Increased risk of myocardial infarction and stroke for some NSAIDs.
Naproxen	375–500 mg bid	High rates of gastrointestinal side effects, including ulcers and bleeding, occur.
Salsalate	1500 mg bid	Patients at high risk for gastrointestinal side effects should also take either a proton pump inhibitor or misoprostol. ^a There is an increase in gastrointestinal side effects or bleeding when taken with acetylsalicylic acid. Can also cause edema and renal insufficiency.
Ibuprofen	600–800 mg 3–4 times a day	
Celecoxib	100–200 mg qd	
Topical NSAIDs		Rub onto joint. Few systemic side effects. Skin irritation common.
Diclofenac Na 1% gel	4 g qid (for knees, hands)	
Acetaminophen	Up to 1 g tid	Of limited efficacy and only conditionally recommended
Opiates	Various	Common side effects include dizziness, sedation, nausea or vomiting, dry mouth, constipation, urinary retention, and pruritis. Addiction risk. Less efficacious than oral NSAIDs
Capsaicin	0.025–0.075% cream 3–4 times a day	Can irritate mucous membranes.
Intraarticular injections		
Steroids		
Hyaluronans	Varies from 3 to 5 weekly injections depending on preparation	Mild to moderate pain at injection site. Controversy exists regarding efficacy.

^aPatients at high risk include those with previous gastrointestinal events, persons >60 years, and persons taking glucocorticoids. Trials have shown the efficacy of proton pump inhibitors and misoprostol in the prevention of ulcers and bleeding. Misoprostol is associated with a high rate of diarrhea and cramping; therefore, proton pump inhibitors are more widely used to reduce NSAID-related gastrointestinal symptoms.

Abbreviations: COX-2, cyclooxygenase-2; NSAIDs, nonsteroidal anti-inflammatory drugs.

Source: From DT Felson: Osteoarthritis of the Knee. N Engl J Med 354:841, 2006. Copyright © 2006 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

(knees, hands, but not hips), the drug can be found in joint tissues such as the synovium and cartilage. Trial results have varied but generally have found that topical NSAIDs are slightly less efficacious than oral agents, but have far fewer GI and systemic side effects. Unfortunately, topical NSAIDs often cause local skin irritation where the medication is applied, inducing redness, burning, or itching (see Table 371-1).

The treatment effect of acetaminophen (paracetamol) in OA is small and not considered clinically meaningful (Table 371-1). However, for a minority of patients, it is adequate to control symptoms, in which case more toxic drugs such as NSAIDs can be avoided.

Intraarticular Injections: Glucocorticoids and Hyaluronic Acid Because synovial inflammation is likely to be a major cause of pain in patients with OA, local anti-inflammatory treatments administered intraarticularly may be effective in ameliorating pain, for up to 3 months. Glucocorticoid injections provide such efficacy, but response is variable. While some patients having little relief of pain, most experience pain relief lasting up to several months. Synovitis, a major cause of joint pain in OA, may abate after an injection, and this correlates with the reduction in knee pain severity. Glucocorticoid injections are useful to get patients over acute flares of pain. Repeated injections may cause minor amounts of cartilage loss with probably unimportant clinical consequences.

Hyaluronic acid injections can be given for treatment of symptoms in knee and hip OA, but most evidence suggests no efficacy versus placebo (Table 371-1).

Other Classes of Drugs and Nutraceuticals Opioids have only modest short-term efficacy in treating pain in hip or knee OA with unclear benefit over the long-term and, given concerns about opioid dependency, should be avoided. If NSAIDs are ineffective, one option is the use of duloxetine, which has modest efficacy in OA and may be efficacious especially when knee pain is part of a syndrome of widespread pain.

Recent guidelines recommend against the use of glucosamine or chondroitin for OA. Large publicly supported trials have failed to show that, compared with placebo, these compounds relieve pain in persons with disease.

Optimal pharmacologic therapy for OA is often achieved by trial and error, with each patient having idiosyncratic responses to specific treatments. Placebo (or contextual) effects may account for 50% of more of treatment effects in OA, and certain modes of treatment delivery including intraarticular injections have greater contextual effects than others such as pills. When medical therapies have failed and the patient has an unacceptable reduction in their quality of life and ongoing pain and disability, then at least for knee and hip OA, total joint arthroplasty is indicated.

SURGERY

Based on data from randomized trials, the efficacy of arthroscopic debridement and lavage in persons with OA is no greater than that of sham surgery for relief of pain or disability. Further, if a meniscal tear is present, as is often the case in persons with knee OA, trials have shown that arthroscopic meniscectomies do not relieve knee pain or improve function long-term nor do they reduce catching or locking symptoms.

On the other hand, for patients with knee OA isolated to the medial compartment, operations to realign the knee to lessen medial loading can relieve pain. These include a high tibial osteotomy, in which the tibia is broken just below the tibial plateau and realigned to load the lateral, nondiseased compartment, or a unicompartmental replacement with realignment. Each surgery may provide the patient with years of pain relief before a total knee replacement is required.

Ultimately, when the patient with knee or hip OA has failed nonsurgical treatments with limitations of pain or function that compromise their quality of life, patients with reasonable expectations and readiness for surgery should be referred for total knee or hip arthroplasty. These are highly efficacious operations that relieve pain and improve function in the vast majority of patients, although pain elimination occurs in almost all patients getting a hip replacement but only ~80% of those undergoing knee replacement. Currently, failure rates from loosening or infection for both are ~1% per year, with higher rates in obese patients. The chance of surgical success is greater in centers where at least 25 such operations are performed yearly or with surgeons who perform multiple operations annually. The timing of knee or hip replacement is critical. If the patient suffers for many years until their functional status has declined substantially, with considerable muscle weakness, postoperative functional status may not improve to a level achieved by others who underwent operation earlier in their disease course.

Cartilage Regeneration Chondrocyte transplantation has not been found to be efficacious in OA, perhaps because OA includes pathology of joint mechanics, which is not corrected by chondrocyte transplants. Similarly, abrasion arthroplasty (chondroplasty) has not been well studied for efficacy in OA, but it produces fibrocartilage in place of damaged hyaline cartilage. Both surgical attempts to regenerate and reconstitute articular cartilage are more likely to be efficacious early in disease when joint malalignment and many of the other noncartilage abnormalities that characterize OA have not yet developed.

FURTHER READING

Felson D: Safety of nonsteroidal antiinflammatory drugs. *N Engl J Med* 375:2595, 2016.

Glyn-Jones S et al: Osteoarthritis. *Lancet* 386:376, 2015.

Kolasinski SL et al: 2019 American College of Rheumatology/Arthritis Foundation Guideline for the management of osteoarthritis of the hand, hip, and knee. *Arthritis Rheumatol* 72:220, 2020.

McAlindon TE et al: Effect of intra-articular triamcinolone vs saline on knee cartilage volume and pain in patients with knee osteoarthritis: A randomized clinical trial. *JAMA* 317:1967, 2017.

372

Gout and Other Crystal-Associated Arthropathies

Hyon K. Choi



The use of polarizing light microscopy during synovial fluid analysis in 1961 by McCarty and Hollander and the subsequent application of other crystallographic techniques, such as electron microscopy, energy-dispersive elemental analysis, and x-ray diffraction, have allowed investigators to identify the pathogenic roles of different microcrystals, including monosodium urate (MSU), calcium pyrophosphate (CPP), calcium apatite (apatite), and calcium oxalate (CaOx), in inducing acute or chronic arthritis or periarthritis (**Table 372-1**). The clinical manifestations that result from these crystals have substantial similarities but also have notable differences. Given their therapeutic implications, the need to perform synovial fluid analysis to distinguish the type of crystal involved should be emphasized. Polarized light microscopy alone can identify most typical crystals, except for apatite. Aspiration and analysis of effusions are also important to assess the possibility of infection. Crystal shedding from inert deposits triggered by certain factors is considered a key process behind episodic manifestation of acute inflammation (gout or pseudogout) involving activation of inflammasome and potent proinflammatory cytokines such as interleukin (IL) 1 β . Furthermore, physical, inflammatory, and catalytic effects (involving metalloproteinase, collagenase, or prostaglandin E $_2$) of crystal deposits on the cartilage and other joint structures can lead to chronic erosive or destructive changes in the articular structures.

GOUT

PATHOGENESIS

Gout is a hyperuricemic metabolic condition, typically manifested by episodic inflammatory arthritis with disabling pain, among middle-aged to elderly men and postmenopausal women. It stems from an increased

TABLE 372-1 Musculoskeletal Manifestations of Crystal-Induced Arthritis

Acute arthritis (episodic)

Mono-, oligo-, or polyarthritis

Periarticular inflammation

Bursitis

Tendinitis

Enthesitis

Tophaceous deposits

Chronic arthropathy

Destructive arthropathies

Chronic inflammatory arthritis

Peculiar type of osteoarthritis

Spinal arthritis

Carpal tunnel syndrome

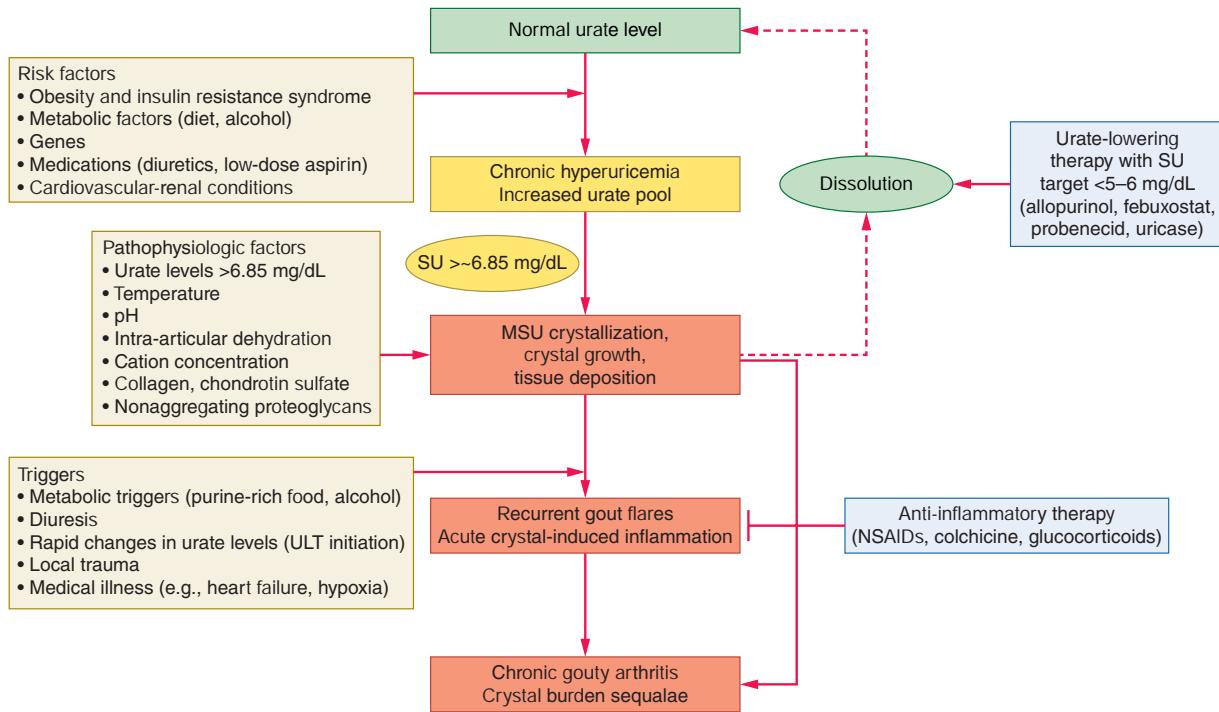


FIGURE 372-1 Pathogenesis of gout and therapeutic targets. Metabolic and some genetic factors contribute to the development of chronic hyperuricemia. Gout stems from an increased body pool of urate due to chronic hyperuricemia, leading to supersaturation and crystal formation and deposition of monosodium urate (MSU; tophi) within the joints and connective tissue. Synovial tophi are usually walled off, but certain triggers may loosen them from the organic matrix, leading to crystal shedding and interaction with synovial cell lining and resident inflammatory cells, initiating an acute gout flare. In some individuals, growing MSU crystal deposition leads to chronic gouty arthritis with subcutaneous tophi. Anti-inflammatory therapy targets the downstream process of crystal-induced inflammation, whereas ultimate control of gout requires correction of the underlying central cause, chronic hyperuricemia with increased urate pool. NSAIDs, nonsteroidal anti-inflammatory drugs; SU, sodium urate; ULT, urate-lowering therapy.

body pool of urate due to chronic hyperuricemia, leading to supersaturation and crystal formation and deposition of MSU within the joints and connective tissue (Fig. 372-1). If left untreated, gout can progress to chronic gouty arthritis, frequently with low-grade persistent synovitis and erosive deformities due to growing deposition of MSU crystals. Humans are the only mammals known to develop gout spontaneously as they often develop hyperuricemia with their evolutionary species-wide loss of uricase, which converts urate into the highly water-soluble compound allantoin. Although chronic hyperuricemia is a prerequisite for the development of gout, other factors influence MSU deposition and pathogenic reactions to the crystals (Fig. 372-1); a minority of hyperuricemic individuals develop gout during their lifetime. At physiologic pH, uric acid exists largely as urate, the ionized form, given its weak acidic property (pK_a , 5.8). Considered as a part of the insulin resistance syndrome, hyperuricemia and gout are associated with multiple cardiovascular-metabolic comorbidities, including obesity, hypertension, type 2 diabetes, myocardial infarction, stroke, and urate nephrolithiasis (Chap. 417); modifiable risk factors include obesity, Western diet, alcohol, sedentary lifestyle, and diuretics (Fig. 372-1).

CLINICAL MANIFESTATIONS

Early clinical manifestation of gout is characterized by acute recurrent gout flares. Usually, only one joint is affected initially, although oligo- and polyarticular gout flares can develop over time. The metatarsophalangeal joint of the first toe is involved in 70–90% of cases (podagra), followed by tarsal joints, ankles, and knees. Finger, wrist, and elbow joints can also be involved, although more often in elderly patients or in advanced disease. The gout flares often begin at night to early morning, constituting one of the most painful conditions experienced by humans. The affected joints rapidly become warm, red, tender, and substantially swollen with a clinical appearance that often mimics

cellulitis (pseudocellulitis). Typical flares tend to subside spontaneously within 1–2 weeks, and most patients have intervals of varying length with no residual symptoms until the next episode (intercritical gout). Triggers of gout flares include purine-rich food, alcohol, diuretic use, initial introduction of urate-lowering therapy, local trauma, and medical illnesses such as congestive heart failure and respiratory hypoxic conditions (Fig. 372-1).

Usually after years of gout flares without treatment, chronic gouty arthritis can develop, often associated with ongoing synovitis, subcutaneous tophi, deformity, and bony destruction. Less commonly, chronic gouty arthritis will be the only manifestation, and more rarely, gout can manifest only as tophi. Women represent only 5–20% of all patients with gout. Most women with gout are postmenopausal and elderly; tend to have osteoarthritis, hypertension, or mild renal insufficiency; and usually are receiving diuretics. Premenopausal gout is rare, although kindreds of precocious gout in young women caused by decreased renal urate clearance and renal insufficiency have been described.

DIAGNOSIS

Laboratory Diagnosis Even if characteristic clinical features strongly suggest gout, the presumptive diagnosis ideally should be confirmed by needle aspiration of involved joints or tophaceous deposits. Acute septic arthritis, other crystal-associated arthropathies, palindromic rheumatism, and psoriatic arthritis can mimic clinical presentations of gout. During acute gout flares, needle-shaped MSU crystals typically are present both intracellularly and extracellularly (Fig. 372-2). Under compensated polarized light, these crystals show bright, negative birefringence. Synovial fluid appears cloudy due to the increased numbers of leukocytes (e.g., from 5000–75,000/ μ L). Large amounts of crystals occasionally produce a thick, pasty, chalky joint fluid or drainage from distended tophi. Because bacterial infection

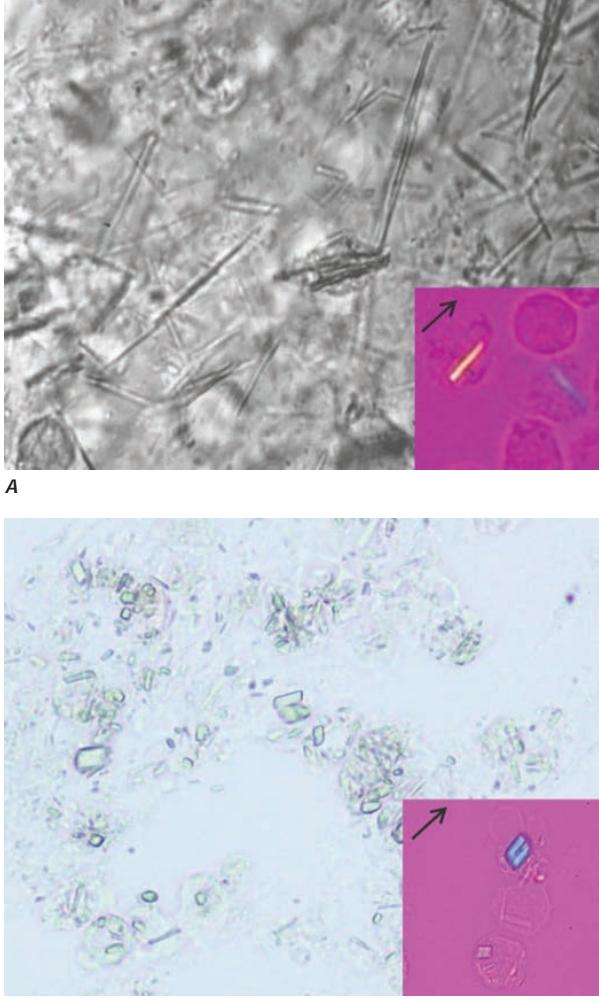


FIGURE 372-2 **A.** Extracellular and intracellular monosodium urate crystals, as seen in a fresh preparation of synovial fluid, illustrate needle- and rod-shaped crystals (400 \times). These crystals are strongly negative birefringent crystals under compensated polarized light microscopy. (Inset 400 \times , provided by Eliseo Pascual.) **B.** Intracellular and extracellular calcium pyrophosphate (CPP) crystals, as seen in a fresh preparation of synovial fluid, illustrate rectangular, rod-shaped, and rhomboid crystals (400 \times). These crystals are weakly positively or nonbirefringent crystals under compensated polarized light microscopy (inset 600 \times). (Images provided by Eliseo Pascual.)

can coexist with MSU crystals in synovial fluid, joint fluid is often stained and cultured for potential septic arthritis. MSU crystals also can often be demonstrated in the first metatarsophalangeal joint and in knees not acutely involved with gout, making arthrocentesis of these joints useful for the diagnosis of gout between flares.

While chronic hyperuricemia is a prerequisite in the pathogenesis of gout, serum urate levels can be normal or low at the time of an acute flare, as inflammatory cytokines' uricosuric property (e.g., IL-6) can lower the level by ~2 mg/dL. This tends to limit the value of serum urate testing in the setting of an acute flare. Nevertheless, serum urate levels are almost always elevated at some time in a gout patient's lifetime, and thus, it is important to seek historical or postflare serum urate values as a diagnostic clue or therapeutic target to urate-lowering therapy. Serum creatinine, liver function tests, hemoglobin, white blood cell (WBC) count, hemoglobin A_{1c}, and serum lipids are usually obtained at baseline to assess possible risk factor and comorbidities requiring treatment or monitored for potential adverse effects of gout treatments.

Radiographic Features In plain radiography, cystic changes, well-defined erosions with sclerotic margins (often with overhanging bony edges), and soft tissue masses are characteristic features of advanced gout with tophaceous deposits, although these findings are typically absent in earlier stages of gout. Musculoskeletal ultrasound can timely aid earlier diagnosis by revealing a double-contour sign overlying the articular cartilage (signifying MSU deposition). Similarly, dual-energy computed tomography (CT) that utilizes two different energy beams and identifies MSU based on its chemical composition can indicate specific presence of MSU crystals.

TREATMENT

Acute Gout Care

Although nonpharmacologic measures, such as ice pack application and rest of the involved joints, can be helpful, the mainstay of acute gout care is the administration of anti-inflammatory drugs such as nonsteroidal anti-inflammatory drugs (NSAIDs), colchicine, and glucocorticoids (Fig. 372-1). The choice of these options largely depends on the patients' comorbidities, concurrent medications, and previous response if recurrent flares. Early initiation of anti-inflammatories helps abort or reduce the severity of flares. Thus, for recurrent flares in established gout patients, patients can be provided a supply of their medications ready to start at the first sign of a flare. NSAIDs are used most often in individuals without complicating comorbidities; NSAIDs given in full anti-inflammatory doses are effective in the vast majority of patients (e.g., indomethacin, 25–50 mg tid; naproxen, 500 mg bid; ibuprofen, 800 mg tid; and celecoxib, 800 mg followed by 400 mg 12 h later, then 400 mg bid). Oral colchicine is also effective, particularly if used early in a gout flare. A low-dose regimen (1.2 mg with the first sign of a flare, followed by 0.6 mg in 1 h and subsequent-day dosing depending on response) is as effective as, and better tolerated than, the formerly used higher-dose regimens. Colchicine is eliminated from the body through P-glycoprotein (also known as MDR1) in the liver, small intestine, and kidneys as well as via enteric and hepatic cytochrome P450 3E4 (CYP3A4). As such, the dose, particularly for prolonged use, is reduced among patients with renal disease or when used with P-glycoprotein or CYP3A4 inhibitors such as clarithromycin or tacrolimus; additional caution is warranted among patients with hepatorenal impairment.

Glucocorticoids given as an intramuscular injection or orally (e.g., prednisone, 30–50 mg/d as the initial dose and gradually tapered with the resolution of the attack) can be effective even in polyarticular gout. For a single joint or a few involved joints, intraarticular glucocorticoid injection is effective and well tolerated. With the central role of the inflammasome and IL-1 β in gout flares, anakinra is a useful option when other treatments are contraindicated or have failed.

URATE-LOWERING THERAPY

Ultimate control of gout requires correction of the underlying chronic hyperuricemia, the central cause for gout. Attempts to normalize serum urate to a subsaturation point (typically, <300–360 μ mol/L [5.0–6.0 mg/dL]) to prevent recurrent gout flares and eliminate tophi are critical and entail a commitment to urate-lowering regimens that are required usually for life (Fig. 372-1). Urate-lowering drug therapy should be considered when, as in most patients, the hyperuricemia cannot be corrected by risk factor interventions (control of body weight, healthy diet, limitation of alcohol use, decreased consumption of fructose-rich foods and beverages, and avoidance of thiazide and loop diuretics). The decision to initiate urate-lowering drug therapy usually is made considering the number of gout flares (urate lowering may be cost-effective with more than two attacks yearly), severity and duration of flares, quality of life, or the patient's willingness to commit to lifelong therapy. Urate-lowering therapy should be initiated in any patient who already has subcutaneous tophi or chronic gouty arthritis or known uric acid stones.

Allopurinol, a xanthine oxidase inhibitor, is the first-line urate-lowering drug among gout patients. Allopurinol can be given in a single morning dose, starting at 100 mg daily or less and titrating up (to 800 mg daily) to achieve a target serum urate level <5–6 mg/dL (i.e., a subsaturation point of MSU crystals). In patients with chronic kidney disease (CKD), the starting allopurinol dose should be lowered depending on the CKD levels; for example, with an estimated glomerular filtration rate of 30–45 mL/min, one would start at 50 mg daily and titrate up slowly. Starting at a low dose and titrating up reduces the risk of severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome and toxic epidermal necrolysis, as well as the risk of gout flares associated with rapid serum urate reduction due to introduction of urate-lowering therapy (Fig. 372-1). Allopurinol is generally well tolerated, but mild cutaneous reactions can develop in ~2% of users. SCARs to allopurinol are rare but can be life-threatening, and thus, appropriate precaution is advised. Presence of CKD, higher allopurinol initial dosing (e.g., >100 mg daily in CKD patients), and *HLA-B 5801* carriage are important risk factors; older age and female sex are also associated with a higher risk of SCARs. As the *HLA-B 5801* carriage rate is substantially higher among Southeast Asians (except for Japanese descendants), Pacific Islanders/Native Hawaiians, and blacks than whites or Hispanics (leading to racial disparity in the risk of SCARs), screening for *HLA-B 5801* should be performed before starting allopurinol in those Asians and blacks. If patients carry the *HLA-B 5801* allele, an alternative urate-lowering agent should be administered. Febuxostat is a newer xanthine oxidase inhibitor that is predominantly metabolized by glucuronide formation and oxidation in the liver and considered to not require dose adjustment in moderate to severe chronic kidney disease. It has also been used in patients who carry the *HLA-B 5801* allele.

Uricosuric agents such as probenecid are considered second-line urate-lowering therapies for gout and can be used in patients with good renal function either alone or in combination with xanthine oxidase inhibitors such as allopurinol. Probenecid can be started at a dose of 250 mg twice daily and increased gradually as needed up to 3 g/d to achieve and maintain a target serum urate level. Probenecid is generally not effective in patients with serum creatinine levels >177 µmol/L (2 mg/dL). Benzboromarone (not available in the United States) is another uricosuric drug that is more effective in patients with CKD. In contrast to thiazide and loop diuretics, which increase serum urate levels and trigger gout attacks, other drugs used to treat common comorbidities of gout can also help lower serum urate levels, including losartan, amlodipine, fenofibrate, and sodium-glucose cotransporter-2 inhibitors. Pegloticase is a pegylated uricase that is available for patients who do not tolerate or fail full doses of other treatments.

Urate-lowering drugs are generally not initiated during active ongoing gout flares, given the potential worsening of the flare by acutely lowering serum urate levels. However, urate-lowering therapy can be started during the resolution phase of or after a gout flare, together with anti-inflammatory prophylaxis (e.g., colchicine 0.6 mg one to two times daily or naproxen 250 mg twice daily) to reduce the risk of the flares that often occur with the initiation of urate-lowering therapy. These paradoxical flares are presumed to be inflammatory reactions to MSU crystals shed from dissolution of organized MSU deposits (synovial tophi) induced by rapid serum urate reduction (Fig. 372-1). As such, faster urate reduction has been associated with higher risk of flares in clinical trials of urate-lowering drugs. Continuing concomitant anti-inflammatory prophylaxis is usually recommended until the patient is normouricemic and without gouty attacks for 3–6 months or tophi disappear.

CALCIUM PYROPHOSPHATE DEPOSITION DISEASE

CPP deposition (CPPD) predominately affects the elderly, with a doubling prevalence of CPPD in articular tissues with each decade >60 years of age (e.g., prevalence of nearly 50% for those >85 years old).

TABLE 372-2 Factors and Conditions Associated with Calcium Pyrophosphate Crystal Deposition Disease

Aging	
Osteoarthritis	
Postmeniscectomy or joint trauma	
Familial-genetic	
Endocrine-metabolic conditions	
Primary hyperparathyroidism	
Hemochromatosis	
Hypophosphatasia	
Hypomagnesemia	
Certain drugs: thiazide and loop diuretics, potentially proton pump inhibitors	
Malabsorption	
Gitelman's syndrome	
Gout	
X-linked hypophosphatemic rickets	
Familial hypocalciuric hypercalcemia	

In most cases, this process is asymptomatic with uncertain underlying etiology, although it is likely that biochemical changes in aging or diseased cartilage favor CPP crystal nucleation. Increased levels of inorganic pyrophosphate in cartilage matrix are thought to be a central pathogenic process in patients with CPPD arthritis, analogous to hyperuricemia in gout. This pyrophosphate can combine with calcium to form CPP crystals in cartilage matrix vesicles or on collagen fibers. Most inorganic pyrophosphate in cartilage matrix originates from breakdown of extracellular ATP. The ATP efflux (and thus the levels of inorganic pyrophosphate) is tightly regulated by a multipass membrane protein, ANKH. As such, mutations in the *ANKH* gene, as described in both familial and sporadic cases, have been found to increase elaboration and extracellular transport of pyrophosphate. The increase in pyrophosphate production is also related to enhanced activity of ATP pyrophosphohydrolase and 5'-nucleotidase, which catalyze the reaction of ATP to adenosine and pyrophosphate. Decreased levels of cartilage glycosaminoglycans and increased activities of transglutaminase enzymes may contribute to the deposition of CPP crystals.

Similar to MSU crystals, release of CPP crystals into the joint space is followed by the phagocytosis of those crystals by monocyte-macrophages and neutrophils, which respond by releasing chemotactic and inflammatory substances and activating the inflammasome.

A minority of patients with CPPD arthropathy have metabolic abnormalities or hereditary CPPD (Table 372-2). As such, the presence of CPPD arthritis in individuals aged <50 years should lead to consideration of these metabolic disorders and inherited forms of disease, including those identified in a variety of ethnic groups. Included among endocrine-metabolic conditions are hyperparathyroidism, hemochromatosis, hypophosphatasia, and hypomagnesemia. These associations suggest that a variety of different metabolic products may enhance CPP crystal deposition either by directly altering cartilage or by inhibiting inorganic pyrophosphatases. Investigation of younger patients with CPPD should include inquiry for evidence of familial aggregation and evaluation of serum calcium, phosphorus, alkaline phosphatase, magnesium, iron, and transferrin.

CLINICAL MANIFESTATIONS

Acute CPP crystal arthritis, originally termed *pseudogout* by McCarty and co-workers, often mimics acute gout flares with similar articular findings of substantial inflammation. There are several clinical clues that suggest CPP crystal arthritis. The knee is the joint most commonly affected, followed by the wrist, while the first metatarsophalangeal joint (podagra) is rarely affected. Other affected joints include the shoulder, ankle, elbow, and hands. Also, initial episodes of acute attacks tend to last longer than typical gout flares, even up to weeks to months. Acute attacks present sometimes with systemic signs such as fever, chills, and elevated acute-phase reactants. Acute CPP crystal arthritis may be precipitated by trauma, severe medical illness, or surgery, especially

parathyroidectomy, as it leads to rapid diminution of serum calcium and magnesium levels, causing dissolution and shedding of crystal.

Chronic CPP crystal arthritis has several patterns; the most common form is a polyarticular arthritis resembling osteoarthritis (pseudoosteosteoarthritis). The clinical picture mimics that of progressive osteoarthritis, characterized by unusually severe joint damage in atypical joints for osteoarthritis, such as metacarpophalangeal, wrist, elbow, shoulder, or ankle joints. Other less common forms include chronic symmetric synovitis that is clinically similar to rheumatoid arthritis, severe destructive disease that may radiographically mimic neuropathic arthritis, intervertebral disk and ligament calcification with restriction of spine mobility, the crowned dens syndrome, spinal stenosis (most commonly seen in the elderly), and rarely, tumoral deposits of CPP crystals in soft tissues.

If radiographs or ultrasound reveal punctate and/or linear radiodense deposits within fibrocartilaginous joint menisci or articular hyaline cartilage (*chondrocalcinosis*), the diagnostic likelihood of CPPD disease is further increased. *Definitive diagnosis* requires demonstration of typical rhomboid or rodlike crystals (generally weakly positively birefringent or nonbirefringent with polarized light) in synovial fluid or articular tissue (Fig. 372-2). In the absence of joint effusion or indications to obtain a synovial biopsy, chondrocalcinosis is presumptive of CPPD. One exception is chondrocalcinosis due to CaOx in some patients with chronic renal failure.

In as many as 50% of cases, episodes of CPP crystal-induced inflammation are associated with low-grade fever and, on occasion, temperatures as high as 40°C (104°F). In such cases, synovial fluid analysis with microbial cultures is essential to rule out the possibility of infection. In fact, infection in a joint with any microcrystalline deposition process can lead to crystal shedding and subsequent synovitis from both crystals and microorganisms. The leukocyte count in synovial fluid in acute CPPD can range from several thousand cells to 100,000 cells/ μ L, with the mean being ~24,000 cells/ μ L and the predominant cell being the neutrophil. CPP crystals may be seen inside tissue fragments and fibrin clots and in neutrophils (Fig. 372-2). CPP crystals may coexist with MSU and apatite in some cases.

TREATMENT

CPPD Disease

Anti-inflammatory treatment for acute CPP crystal arthritis is largely adapted from that for gout flares, including ice pack applications with rest, joint fluid aspiration and glucocorticoid injection, oral colchicine, NSAIDs, and systemic glucocorticoids. Severe polyarticular attacks can also be treated with the IL-1 β antagonist anakinra. For patients with frequent recurrent attacks, prophylactic treatment with daily colchicine can be helpful. For chronic CPP crystal arthritis, there is no effective way to remove CPP crystal deposits from cartilage and synovium (unlike urate-lowering agents in gout). Limited studies suggest that NSAIDs (with a gastric protective agent if required), colchicine, low-dose glucocorticoids, hydroxychloroquine, or methotrexate may be helpful for chronic synovitis. Patients with progressive destructive large-joint arthropathy may require joint replacement.

CALCIUM APATITE DEPOSITION DISEASE

PATHOGENESIS

Apatite is the primary mineral of normal bone and teeth. Abnormal accumulation of basic calcium phosphates, largely carbonate substituted apatite, can occur in areas of tissue damage (dystrophic calcification), hypercalcemic or hyperparathyroid states (metastatic calcification), connective tissue diseases (calcinosis), and other conditions (Table 372-3). In chronic renal failure, hyperphosphatemia can contribute to extensive apatite deposition both in and around joints (tumoral calcinosis, calciphylaxis). Familial aggregation is rarely seen. Synovial lining cell or fibroblast cultures exposed to apatite (or CPP)

TABLE 372-3 Clinical Manifestations of Apatite Crystal Deposition

Periarticular

Calcific periartthritis (e.g., supraspinatus tendon apatite deposit rupture)

Bursitis and tendinitis

Hydroxyapatite pseudopodagra

Polyarticular involvement

Asymptomatic deposition

Articular

Hemorrhagic shoulder effusions in the elderly (Milwaukee shoulder)

Chronic destructive arthropathy

Chronic erosive monoarthritis (resembling erosive osteoarthritis)

Acute synovitis

Association with osteoarthritis

Secondary apatite crystal deposition

Tumoral calcinosis

Hyperparathyroidism

Calciphylaxis (renal failure/long-term dialysis)

Connective tissue diseases (e.g., systemic sclerosis, dermatomyositis)

Heterotopic calcification after neurologic catastrophes (e.g., stroke, spinal cord injury)

Fibrodysplasia ossificans progressiva

crystals can undergo mitosis and markedly increase the release of prostaglandin E₂, various cytokines, and collagenases and neutral proteases, underscoring the destructive potential of abnormally stimulated synovial lining cells.

Although the true incidence of apatite arthritis is not known, 30–50% of patients with osteoarthritis have apatite microcrystals in their synovial fluid. Such crystals frequently can be identified in clinically stable osteoarthritic joints, but they are more likely to come to attention in persons experiencing acute or subacute worsening of joint pain and swelling.

CLINICAL MANIFESTATIONS

Periarticular or articular deposits can present with acute reversible inflammation and/or chronic damage to the joint capsule, tendons, bursa, or articular surfaces (Table 372-3). The most common sites of apatite deposition include bursae and tendons in and/or around the knees, shoulders, hips, and fingers. These deposits can also be asymptomatic radiographic abnormalities.

Apatite aggregates are often present in synovial fluid in an extremely destructive chronic arthropathy of the elderly that occurs most often in the shoulders (Milwaukee shoulder) and in a similar process in hips, knees, and erosive osteoarthritis of fingers (Table 372-3). Joint destruction is associated with damage to cartilage and supporting structures, leading to instability and deformity. Progression tends to be indolent. Symptoms range from minimal to severe pain and disability that may lead to joint replacement surgery.

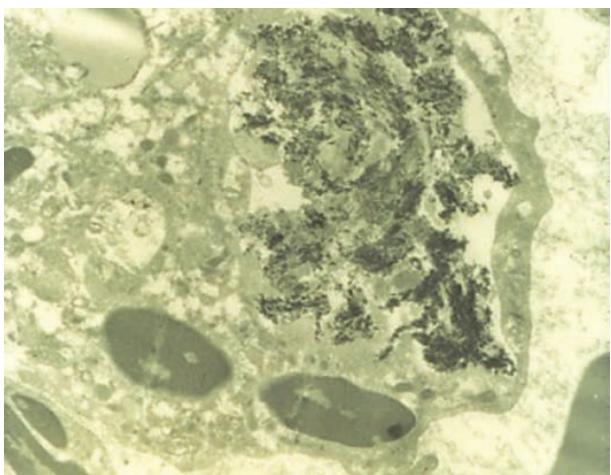
DIAGNOSIS

Intra- and/or periarticular calcifications with or without erosive, destructive, or hypertrophic changes may be seen on radiographs (Fig. 372-3). They should be distinguished from the linear calcifications typical of CPPD.

The synovial fluid leukocyte count in apatite arthritis is usually low (<2000/ μ L) despite dramatic symptoms, with predominance of mononuclear cells. Definitive diagnosis of apatite arthropathy, also called basic calcium phosphate disease, depends on identification of crystals from synovial fluid or tissue (Fig. 372-3). Individual crystals are very small and can be seen only by electron microscopy. Clumps of crystals may appear as 1- to 20- μ m shiny intra- or extracellular nonbirefringent globules or aggregates that stain purplish with Wright's stain and bright red with alizarin red S. Absolute identification depends on electron microscopy with energy-dispersive elemental analysis, x-ray diffraction, infrared spectroscopy, or Raman microspectroscopy, but these techniques usually are not required in clinical diagnosis.



A



B

FIGURE 372-3 **A.** Radiograph showing calcification due to apatite crystals surrounding an eroded joint. **B.** An electron micrograph demonstrates dark needle-shaped apatite crystals within a vacuole of a synovial fluid mononuclear cell (30,000 \times).

TREATMENT

Calcium Apatite Deposition Disease

Treatment of apatite arthritis or periarthritis is nonspecific. Acute attacks of bursitis or synovitis may be self-limiting, resolving in days to several weeks. Aspiration of effusions and the use of either NSAIDs or oral colchicine for 2 weeks or intra- or periaricular injection of a depot glucocorticoid appear to shorten the duration and intensity of symptoms. Periaricular apatite deposits may be resorbed with resolution of attacks. Agents to lower serum phosphate levels may lead to resorption of deposits in renal failure patients receiving hemodialysis. In patients with underlying severe destructive articular changes, response to medical therapy is usually less rewarding.

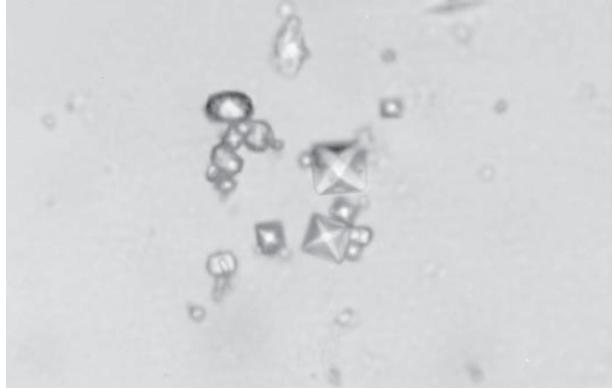


FIGURE 372-4 Bipyramidal and small polymorphic calcium oxalate crystals from synovial fluid are a classic finding in calcium oxalate arthropathy (ordinary light microscopy; 400 \times).

CaOx DEPOSITION DISEASE

PATHOGENESIS

In chronic renal disease, CaOx deposits have long been recognized in visceral organs, blood vessels, bones, and cartilage and are now known to be one of the causes of arthritis in chronic renal failure. Thus far, reported patients have been dependent on long-term hemodialysis or peritoneal dialysis (**Chap. 312**), and many had received ascorbic acid supplements. Ascorbic acid is metabolized to oxalate, which is inadequately cleared in uremia and by dialysis. Such supplements and foods high in oxalate content usually are avoided in dialysis programs because of the risk of enhancing hyperoxalosis and its sequelae.

CaOx aggregates can be found in bone, articular cartilage, synovium, and periarticular tissues. From these sites, crystals may be shed, causing acute synovitis. Persistent aggregates of CaOx can, like apatite and CPP crystals, stimulate synovial cell proliferation and enzyme release, resulting in progressive articular destruction. *Primary oxalosis* is a rare hereditary metabolic disorder (**Chap. 420**) that can lead to acute or chronic CaOx arthritis, periarthritis, and bone disease during later years of illness.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Clinical features of acute CaOx arthritis may not be distinguishable from those due to MSU, CPP, or apatite. Deposits have been documented in fingers, wrists, elbows, knees, ankles, and feet. Radiographs may reveal chondrocalcinosis or soft tissue calcifications. CaOx-induced synovial effusions are usually noninflammatory, with <2000 leukocytes/ μ L, or mildly inflammatory. Neutrophils or mononuclear cells can predominate. CaOx crystals have a variable shape and variable birefringence to polarized light. The most easily recognized forms are bipyramidal, have strong birefringence (**Fig. 372-4**), and stain with alizarin red S.

TREATMENT

Calcium Oxalate Deposition Disease

Treatment of CaOx arthropathy with NSAIDs, colchicine, intraarticular glucocorticoids, and/or an increased frequency of dialysis has produced only slight improvement. In primary oxalosis, liver transplantation has induced a significant reduction in crystal deposits (**Chap. 420**).

Acknowledgment

The chapter is an updated version of the chapter on this subject written by H. Ralph Schumacher and Lan X. Chen in previous editions of this textbook.

FURTHER READING

- Choi HK et al: Pathogenesis of gout. Ann Intern Med 143:499, 2005.
- Dalbeth N et al: Gout. Nat Rev Dis Primers 5:69, 2019.
- Rosenthal AK, Ryan LM: Calcium pyrophosphate deposition disease. N Engl J Med 374:2575, 2016.



DEFINITION

Fibromyalgia (FM) is characterized by chronic widespread musculoskeletal pain and tenderness. Although FM is defined primarily as a pain syndrome, patients also commonly report associated neuropsychological symptoms of fatigue, unrefreshing sleep, cognitive dysfunction, anxiety, and depression. Patients with FM have an increased prevalence of other syndromes associated with pain and fatigue, including myalgic encephalitis/chronic fatigue syndrome (Chap. 450), temporomandibular disorder, chronic headaches, irritable bowel syndrome, interstitial cystitis/painful bladder syndrome, and other pelvic pain syndromes. Available evidence implicates the central nervous system as key to maintaining pain and other core symptoms of FM and related conditions. The presence of FM is associated with substantial negative consequences for physical and social functioning.

EPIDEMIOLOGY

Worldwide prevalence is ~2%, with a prevalence of ~4% in women and <1% in men. There is some variability depending on the method of ascertainment; however, the prevalence data are similar across world regions and socioeconomic classes. Cultural factors may play a role in determining whether patients with FM symptoms seek medical attention; however, even in cultures in which secondary gain is not expected to play a significant role, the prevalence of FM remains in this range. In clinical settings, a diagnosis of FM is far more common in women than in men, with a ratio of ~9:1.

CLINICAL MANIFESTATIONS

Pain and Tenderness At presentation, patients with FM most commonly report “pain all over.” These patients have pain that is typically both above and below the waist on both sides of the body and involves the axial skeleton (neck, back, or chest). The pain attributable to FM is poorly localized, difficult to ignore, severe in its intensity, and associated with a reduced functional capacity. For a diagnosis of FM,

pain should have been present most of the day on most days for at least 3 months.

The pain of FM is associated with tenderness and increased evoked pain sensitivity. In clinical practice, this elevated sensitivity may be identified by pain induced by the pressure of a blood pressure cuff or skin roll tenderness. More formally, an examiner may complete a tender-point examination in which the examiner uses the thumbnail to exert pressure of ~4 kg/m² (or the amount of pressure leading to blanching of the tip of the thumbnail) on well-defined musculotendinous sites (Fig. 373-1). Previously, the classification criteria of the American College of Rheumatology required that 11 of 18 sites be perceived as painful for a diagnosis of FM. In practice, tenderness is a continuous variable, and strict application of a categorical threshold for diagnostic specifics is not necessary. Newer criteria eliminate the need for identification of tender points and focus instead on clinical symptoms of widespread or multisite pain and neuropsychological symptoms. The newer criteria perform well in a clinical setting in comparison to the older, tender-point criteria. However, it appears that when the new criteria are applied to populations, the result is an increase in prevalence of FM and a change in the sex ratio (see “Epidemiology,” earlier).

Patients with FM often have peripheral pain generators that are thought to serve as triggers for the more widespread pain attributed to central nervous system factors. Potential pain generators such as arthritis, bursitis, tendinitis, neuropathies, and other inflammatory or degenerative conditions should be identified by history and physical examination. More subtle pain generators may include joint hypermobility and scoliosis. In addition, patients may have chronic myalgias triggered by infectious, metabolic, or psychiatric conditions that can serve as triggers for the development of FM. These conditions are often identified in the differential diagnosis of patients with FM, and a major challenge is to distinguish the ongoing activity of a triggering condition from FM that is occurring as a consequence of a comorbid condition and that should itself be treated.

Neuropsychological Symptoms In addition to widespread pain, FM patients typically report fatigue, stiffness, sleep disturbance, cognitive dysfunction, anxiety, and depression. These symptoms are present to varying degrees in most FM patients but are not present in every patient or at all times in a given patient. Relative to pain,

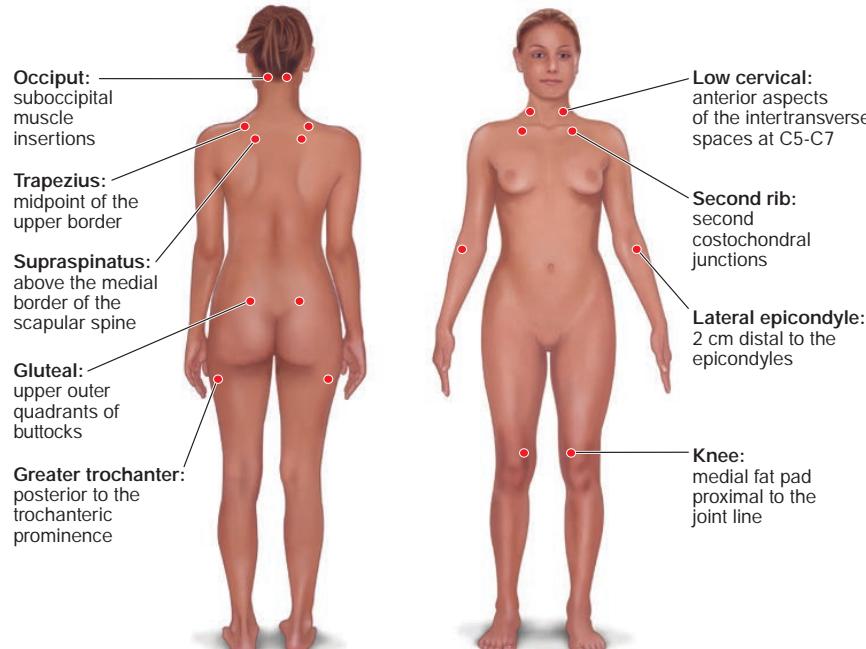


FIGURE 373-1 Tender-point assessment in patients with fibromyalgia. (Figure created using data from F Wolfe et al: Arthritis Care Res 62:600, 2010.)

such symptoms may, however, have an equal or even greater impact on function and quality of life. Fatigue is highly prevalent in patients under primary care who ultimately are diagnosed with FM. Pain, stiffness, and fatigue often are worsened by exercise or unaccustomed activity. The sleep complaints include difficulty falling asleep, difficulty staying asleep, and early-morning awakening. Regardless of the specific complaint, patients awake feeling unrefreshed. Patients with FM may meet criteria for restless legs syndrome and sleep-disordered breathing; frank sleep apnea can also be documented. Cognitive issues are characterized as difficulties with attention or concentration, problems with word retrieval, and short-term memory loss. Studies have demonstrated altered cognitive function in these domains in patients with FM, although speed of processing is age appropriate. Symptoms of anxiety and depression are common, and the lifetime prevalence of mood disorders in patients with FM approaches 80%. Although depression is neither necessary nor sufficient for the diagnosis of FM, it is important to screen for major depressive disorders by querying for depressed mood and anhedonia. Analysis of genetic factors that are likely to predispose to FM reveals shared neurobiologic pathways with mood disorders, providing the basis for comorbidity (see later in this chapter).

Overlapping Syndromes FM is considered as part of a group of conditions called “chronic overlapping pain syndromes” because of the propensity to coexist with other syndromes that may share underlying mechanisms. Review of systems often reveals headaches, facial/jaw pain, regional myofascial pain particularly involving the neck or back, and arthritis. Visceral pain involving the gastrointestinal tract, bladder, and pelvic or perineal region is often present as well. It is important for patients to understand that shared pathways may mediate symptoms and treatment strategies effective for one condition may help with global symptom management.

Comorbid Conditions FM is often comorbid with chronic musculoskeletal, infectious, metabolic, or psychiatric conditions. Whereas FM affects only ~2% of the general population, it occurs in ~10–30% of patients with degenerative or inflammatory rheumatic disorders, likely because these conditions serve as peripheral pain generators to alter central pain-processing pathways. Similarly, chronic infectious, metabolic, or psychiatric diseases associated with musculoskeletal pain can mimic FM and/or serve as a trigger for the development of FM. It is particularly important for clinicians to be sensitive to pain management of these comorbid conditions so that when FM emerges—characterized by pain outside the boundaries of what could reasonably be explained by the triggering condition, development of neuropsychological symptoms, or tenderness on physical examination—treatment of central pain processes will be undertaken as opposed to a continued focus on treatment of peripheral or inflammatory causes of pain.

Psychosocial Considerations Symptoms of FM often have their onset and are exacerbated during periods of perceived stress. This pattern may reflect an interaction among central stress physiology, vigilance or anxiety, and central pain-processing pathways. An understanding of current psychosocial stressors will aid in patient management, as many factors that exacerbate symptoms cannot be addressed by pharmacologic approaches. Furthermore, there is a high prevalence of exposure to previous interpersonal and other forms of violence in patients with FM and related conditions. If posttraumatic stress disorder is an issue, the clinician should be aware of it and consider treatment options.

Functional Impairment It is crucial to evaluate the impact of FM symptoms on function and role fulfillment. In defining the success of a management strategy, improved function is a key measure. Functional assessment should include physical, mental, and social domains. Recognition of the ways in which role functioning falls short will be helpful in establishing treatment goals.

DIFFERENTIAL DIAGNOSIS

Because musculoskeletal pain is such a common complaint, the differential diagnosis of FM is broad. **Table 373-1** lists some of the more

TABLE 373-1 Common Conditions in the Differential Diagnosis of Fibromyalgia

Inflammatory
Polymyalgia rheumatica
Inflammatory arthritis: rheumatoid arthritis, spondyloarthritides
Connective tissue diseases: systemic lupus erythematosus, Sjögren's syndrome
Infectious
Hepatitis C
HIV infection
Lyme disease
Parvovirus B19 infection
Epstein-Barr virus infection
Noninflammatory
Degenerative joint/spine/disk disease
Myofascial pain syndromes
Bursitis, tendinitis, repetitive strain injuries
Endocrine
Hypo- or hyperthyroidism
Hyperparathyroidism
Neurologic Diseases
Multiple sclerosis
Neuropathic pain syndromes
Psychiatric Disease
Major depressive disorder
Drugs
Statins
Aromatase inhibitors

common conditions that should be considered. Patients with inflammatory causes for widespread pain should be identifiable on the basis of specific history, physical findings, and laboratory or radiographic tests.

LABORATORY OR RADIOGRAPHIC TESTING

Routine laboratory and radiographic tests yield normal results in FM without comorbidities. Thus, diagnostic testing is focused on identification of other diagnoses and evaluation for pain generators or comorbid conditions (**Table 373-2**). Most patients with new chronic widespread pain should be assessed for the most common entities in the differential diagnosis. Radiographic testing should be used very sparingly and only for diagnosis of inflammatory arthritis. After the patient has been evaluated thoroughly, repeat testing is discouraged unless the symptom complex changes. Particularly to be discouraged is magnetic resonance imaging (MRI) of the spine unless there are features suggesting inflammatory spine disease or neurologic symptoms.

TABLE 373-2 Laboratory and Radiographic Testing in Patients with Fibromyalgia Symptoms

Routine
Erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP)
Complete blood count (CBC)
Thyroid-stimulating hormone (TSH)
Guided by History and Physical Examination
Complete metabolic panel
Antinuclear antibody (ANA)
Anti-SSA (anti-Sjögren's syndrome A) and anti-SSB
Rheumatoid factor and anti-cyclic citrullinated peptide (anti-CCP)
Creatine phosphokinase (CPK)
Viral (e.g., hepatitis C, HIV) and bacterial (e.g., Lyme) serologies
Spine and joint radiographs

Source: LM Arnold et al: J Women's Health 21:231, 2012; MA Fitzcharles et al: J Rheumatol 40:1388, 2013.

 As in most complex diseases, it is likely that a number of genes contribute to vulnerability to the development of FM. To date, these genes appear to be in pathways controlling pain and stress responses. Some of the genetic underpinnings of FM are shared across other chronic pain conditions. Genes associated with metabolism, transport, and receptors of serotonin and other monoamines have been implicated in FM and overlapping conditions. Genes associated with other pathways involved in pain transmission have also been described as vulnerability factors for FM. Taken together, the pathways in which polymorphisms have been identified in FM patients further implicate central factors in mediation of the physiology that leads to the clinical manifestations of FM.

Psychophysical testing of patients with FM has demonstrated altered sensory afferent pain processing and impaired descending noxious inhibitory control leading to hyperalgesia and allodynia. Functional MRI and other research imaging procedures clearly demonstrate activation of the brain regions involved in the experience of pain in response to stimuli that are innocuous in study participants without FM. Pain perception in FM patients is influenced by the emotional and cognitive dimensions, such as catastrophizing and perceptions of control, providing a solid basis for recommendations for cognitive and behavioral treatment strategies.

Studies have indicated that some patients meeting criteria for FM may have a small fiber neuropathy. Other studies have identified alterations in expressed gene or metabolic signatures in peripheral blood. These early studies raise the possibility that confirmatory diagnostic testing could be developed in the future to assist in the diagnosis of FM.

APPROACH TO THE PATIENT

Fibromyalgia

FM is common and has an extraordinary impact on the patient's function and health-related quality of life. Optimal management requires prompt diagnosis and assessment of pain, function, and psychosocial context. Physicians and other health professionals can be helpful in managing some of the symptoms and impact of FM. Developing a partnership with patients is essential for improving the outcome of FM, with a goal of understanding the factors involved, implementing a treatment strategy, and choosing appropriate nonpharmacologic and pharmacologic treatments.

TREATMENT

Fibromyalgia

NONPHARMACOLOGIC TREATMENT

Patients with chronic pain, fatigue, and other neuropsychological symptoms require a framework for understanding the symptoms that have such an important impact on their function and quality of life. Explaining the genetics, triggers, and physiology of FM can be an important adjunct in relieving associated anxiety and in reducing the overall cost of health care resources. In addition, patients must be educated regarding expectations for treatment. The physician should focus on improved function and quality of life rather than elimination of pain. Illness behaviors, such as frequent physician visits, should be discouraged and behaviors that focus on improved function strongly encouraged.

Treatment strategies should include physical conditioning, with encouragement to begin at low levels of aerobic exercise and to proceed with slow but consistent advancement. Physical activity and exercise are consistently found to be the most helpful strategies.

TABLE 373-3 Pharmacologic Agents Effective for Treatment of Fibromyalgia

Muscle relaxant

Cyclobenzaprine

Antidepressants: balanced serotonin–norepinephrine reuptake inhibitors

Amitriptyline^a

Duloxetine^{b,c}

Milnacipran^{b,c}

Anticonvulsants: ligand of the alpha-2-delta subunit of voltage-gated calcium channels

Pregabalin^b

Analgesic

Tramadol

^aRA Moore et al: Cochrane Database Syst Rev 12:CD008242, 2012. ^bApproved by the U.S. Food and Drug Administration. ^cW Hauser et al: Cochrane Database Syst Rev 1: CD010292, 2013.

Source: GJ Macfarlane et al: EULAR revised recommendations for the management of fibromyalgia. Ann Rheum Dis 76:318, 2017.

Patients who have been physically inactive may do best in supervised or water-based programs at the start. Strength training may be recommended after patients reach their aerobic goals. Transcutaneous electric nerve stimulation (TENS) reduces movement-evoked pain and fatigue. Meditative movement therapies, such as qigong, yoga, or Tai Chi, may also be helpful. Other defined physical therapies such as acupuncture or hydrotherapy may also be considered. Exercise programs are helpful in reducing tenderness and enhancing self-efficacy. Cognitive-behavioral strategies to improve sleep hygiene and reduce illness behaviors can also be helpful in management.

PHARMACOLOGIC APPROACHES

It is essential for the clinician to treat any comorbid triggering condition and to clearly delineate for the patient the treatment goals for each medication. For example, glucocorticoids or nonsteroidal anti-inflammatory drugs may be useful for management of inflammatory triggers but are not effective against FM-related symptoms. At present, the treatment approaches that have proved most successful in FM patients target afferent or descending pain pathways. **Table 373-3** lists the drugs with demonstrated effectiveness. It should be emphasized that strong opioid analgesics are to be avoided in patients with FM. These agents have no demonstrated efficacy in FM and are associated with adverse effects that can worsen both symptoms and function. Tramadol, an opioid with mild serotonin–noradrenaline reuptake inhibitor activity, has been studied in this population with indication of efficacy. Use of single agents to treat multiple symptom domains is strongly encouraged. For example, if a patient's symptom complex is dominated by pain and sleep disturbance, use of an agent that exerts both analgesic and sleep-promoting effects is desirable. These agents include cyclobenzaprine, sedating antidepressants such as amitriptyline, and alpha-2-delta ligands such as gabapentin and pregabalin. For patients whose pain is associated with fatigue, anxiety, or depression, drugs that have both analgesic and antidepressant/anxiolytic effects, such as duloxetine or milnacipran, may be the best first choice.

FURTHER READING

Clauw DJ: Fibromyalgia: A clinical review. JAMA 311:1547, 2014.

Macfarlane GJ et al: EULAR revised recommendations for the management of fibromyalgia. Ann Rheum Dis 76:318, 2017.

Wolf F et al: 2016 Revisions to the 2010/2011 fibromyalgia diagnostic criteria. Semin Arthritis Rheum 46:319, 2016.

Carol A. Langford, Brian F. Mandell

ARTHRITIS ASSOCIATED WITH SYSTEMIC DISEASE

ARTHROPATHY OF ACROMEGALY

Acromegaly is the result of excessive production of growth hormone by an adenoma in the anterior pituitary gland (*Chap. 383*). The excess of growth hormone along with insulin-like growth factor I stimulates proliferation of cartilage, periarticular connective tissue, and bone, resulting in several musculoskeletal problems, including osteoarthritis, back pain, muscle weakness, and carpal tunnel syndrome.

Osteoarthritis is a common feature, most often affecting the knees, shoulders, hips, and hands. Single or multiple joints may be affected. Hypertrophy of cartilage initially produces radiographic widening of the joint space. The newly synthesized cartilage is abnormally susceptible to fissuring, ulceration, and destruction. Ligamentous laxity of joints further contributes to the development of articular discomfort and osteoarthritis. Cartilage degrades, the joint space narrows, and subchondral sclerosis and osteophytes may develop. Joint examination reveals crepitus and laxity. Joint fluid is noninflammatory. Calcium pyrophosphate dihydrate crystals are found in the cartilage in some cases of acromegaly arthropathy and, when shed into the joint, can elicit attacks of pseudogout (calcium pyrophosphate arthropathy). Chondrocalcinosis may be observed on radiographs. Back pain is extremely common, perhaps as a result of spine hypermobility. Spine radiographs show normal or widened intervertebral disk spaces, hypertrophic anterior osteophytes, and ligamentous calcification. The latter changes are similar to those observed in patients with diffuse idiopathic skeletal hyperostosis. Dorsal kyphosis in conjunction with elongation of the ribs contributes to the development of the barrel chest seen in acromegalic patients. The hands and feet become enlarged as a result of soft tissue proliferation. The fingers are thickened and have spadelike distal tufts. One-third of patients have a thickened heel pad. Approximately 25% of patients exhibit Raynaud's phenomenon. Carpal tunnel syndrome occurs in about half of patients. The median nerve may become compressed by excess connective tissue in the carpal tunnel. Patients with acromegaly may develop proximal muscle weakness, which is thought to be caused by the effect of growth hormone on muscle. Serum muscle enzyme levels and electromyographic findings are normal. Muscle biopsy specimens contain muscle fibers of varying size without inflammation.

ARTHROPATHY OF HEMOCHROMATOSIS

Hemochromatosis is a disorder of iron storage. Absorption of excessive amounts of iron from the intestine leads to iron deposition in parenchymal cells, which results in impairment of organ function (*Chap. 414*). Symptoms of hemochromatosis usually begin between the ages of 40 and 60 but can appear earlier. Arthropathy, which occurs in 20–40% of patients, usually begins after the age of 50 and may be the first clinical feature of hemochromatosis. The arthropathy is an osteoarthritis-like disorder affecting the small joints of the hands and later the larger joints, such as knees, ankles, shoulders, and hips. The second and third metacarpophalangeal joints of both hands are often the first and most prominent joints affected; this clinical picture may provide an important clue to the possibility of hemochromatosis because these joints are not predominantly affected by primary osteoarthritis. Patients experience some morning stiffness and pain with use of involved joints. The affected joints are enlarged and mildly tender. Hand pain in patients with hemochromatosis generally is milder, starts at an earlier age, and causes less disability than in patients with primary osteoarthritis.

Radiographs show narrowing of the joint space, subchondral sclerosis, subchondral cysts, and juxtaarticular proliferation of bone. Hook-like osteophytes are seen in up to 20% of patients; although they are regarded as a characteristic feature of hemochromatosis, they are not disease specific. However, dominant radiographic and clinical findings in the second and third metacarpophalangeal joints, even if modest in degree, warrants evaluation of ferritin and iron/total iron-binding capacity levels. The more typical radiographic changes of primary osteoarthritis in the proximal interphalangeal, distal interphalangeal, and first carpometacarpal joint are often not present. The synovial fluid is noninflammatory. The synovium shows mild to moderate proliferation of iron-containing lining cells, fibrosis, and some mononuclear cell infiltration. In approximately half of patients, there is evidence of calcium pyrophosphate deposition disease, and some patients late in the course of disease experience episodes of acute calcium pyrophosphate arthritis (*Chap. 372*). An early diagnosis is suggested by high serum transferrin saturation, which is more sensitive than ferritin elevation.

Iron may damage the articular cartilage in several ways. Iron catalyzes superoxide-dependent lipid peroxidation, which may play a role in joint damage. In animal models, ferric iron has been shown to interfere with collagen formation and increase the release of lysosomal enzymes from cells in the synovial membrane. Iron inhibits synovial tissue pyrophosphatase *in vitro* and therefore may inhibit pyrophosphatase *in vivo*, resulting in chondrocalcinosis.

TREATMENT

Arthropathy of Hemochromatosis

The treatment of hemochromatosis is repeated phlebotomy. Unfortunately, this treatment has little effect on established arthritis, which, along with chondrocalcinosis, may progress. Symptom-based treatment of the arthritis consists of administration of acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs), as tolerated. Acute calcium pyrophosphate arthropathy flares are treated with high doses of an NSAID or a short course of glucocorticoids. Low-dose colchicine may have efficacy in limiting the number of flares. Hip or knee total joint replacement has been successful in advanced disease.

HEMOPHILIC ARTHROPATHY

Hemophilia is a sex-linked recessive genetic disorder characterized by the absence or deficiency of factor VIII (hemophilia A, or classic hemophilia) or factor IX (hemophilia B, or Christmas disease) (*Chap. 116*). Hemophilia A constitutes 85% of cases. Spontaneous hemarthrosis is a common problem with both types of hemophilia and can lead to a deforming arthritis. The frequency and severity of hemarthrosis are related to the degree of clotting factor deficiency. Hemarthrosis is not common in other disorders of coagulation such as von Willebrand disease, factor V deficiency, warfarin therapy, or thrombocytopenia.

Hemarthrosis occurs after 1 year of age, when a child begins to walk and run. In order of frequency, the joints most commonly affected are the knees, ankles, elbows, shoulders, and hips. Small joints of the hands and feet are occasionally involved.

In the initial stage of arthropathy, hemarthrosis produces a warm, tensely swollen, and painful joint. The patient holds the affected joint in flexion and guards against any movement. Blood in the joint remains liquid because of the absence of intrinsic clotting factors and the absence of tissue thromboplastin in the synovium. The synovial blood is resorbed over a period of ≥ 1 week, with the precise interval depending on the size of the hemarthrosis. Joint function usually returns to normal or baseline in ~ 2 weeks. Low-grade temperature elevation may accompany hemarthrosis, but a fever $>38.3^{\circ}\text{C}$ (101°F) warrants concern about infection.

Recurrent hemarthrosis may result in chronic, noninflammatory, fibrotic arthropathy. The involved joints remain swollen, and flexion deformities impacting function develop. Restricted joint motion or laxity with subluxation is a feature of end-stage disease.

Bleeding into muscle and soft tissue also causes musculoskeletal dysfunction. When bleeding into the iliopsoas muscle occurs, the hip is held in flexion because of the pain, resulting in a hip flexion contracture. Rotation of the hip is preserved, which distinguishes this problem from hemarthrosis or other causes of hip synovitis. Expansion of the hematoma may place pressure on the femoral nerve, resulting in femoral neuropathy. Hemorrhage into a closed compartment space, such as the calf or the volar compartment in the forearm, can result in muscle necrosis, neuropathy, and flexion deformities of the ankles, wrists, and fingers. When bleeding involves periosteum or bone, a painful pseudotumor forms. These pseudotumors occur distal to the elbows or knees in children and improve with treatment of hemophilia. Surgical removal is indicated if the pseudotumor continues to enlarge. In adults, pseudotumors develop in the femur and pelvis and are usually refractory to treatment. When bleeding occurs in muscle, cysts may develop within the muscle. Needle aspiration of a cyst is contraindicated because this procedure can induce further bleeding; however, if the cyst becomes secondarily infected, drainage may be necessary (after factor repletion).

Septic arthritis is rare in hemophilia but is difficult to distinguish from acute hemarthrosis on physical examination. If there is serious suspicion of an infected joint, the joint should be aspirated immediately, the fluid cultured, and treatment with broad-spectrum antibiotics administered, with coverage for microorganisms including *Staphylococcus*, until culture results become available. Clotting factor deficiency should be corrected before arthrocentesis to minimize the risk of traumatic bleeding. Notably, low-grade fever can occur in the setting of acute hemarthrosis.

Radiographs of joints reflect the stage of disease. In early stages, there is capsule distention; later, juxtaarticular osteopenia, marginal erosions, and subchondral cysts develop. Late in the disease, the joint space is narrowed, and there is bony overgrowth similar to that in osteoarthritis.

TREATMENT

Hemarthrosis

The treatment of musculoskeletal bleeding is initiated with the immediate infusion of factor VIII or IX at the first sign of joint or muscle hemorrhage. Patients who have developed factor inhibitors are at elevated risk for joint damage and may benefit from receiving recombinant activated factor VII or activated prothrombin complex concentrate. The joint should be rested in a position of forced extension, as tolerated, to avoid contracture. Analgesia should be provided; nonselective NSAIDs, which can diminish platelet function, should be avoided. Selective cyclooxygenase-2 inhibitors do not interfere with platelet function, although cardiovascular and gastrointestinal risks must still be weighed. Synovectomy—open or arthroscopic—may be attempted in patients with chronic symptomatic synovial proliferation and recurrent hemarthrosis, although hypertrophied synovium is highly vascular and subject to bleeding. Both types of synovectomy reduce the number of hemarthroses. Open surgical synovectomy, however, is associated with some loss of range of motion. Both require aggressive prophylaxis against bleeding. Radiosynovectomy with either yttrium-90 silicate or phosphorus-31 colloid has been effective and may be attempted when surgical synovectomy is not practical. Total joint replacement is indicated for severe joint destruction and incapacitating pain.

ARTHROPATHIES ASSOCIATED WITH HEMOGLOBINOPATHIES

Sickle Cell Disease Sickle cell disease (Chap. 98) is associated with several musculoskeletal abnormalities (Table 374-1). Children aged <5 years may develop diffuse swelling, tenderness, and warmth of the hands and feet lasting 1–3 weeks. This condition, referred to as *sickle cell dactylitis* or *hand-foot syndrome*, has also been observed in sickle cell thalassemia. Dactylitis is believed to result from infarction

TABLE 374-1 Musculoskeletal Abnormalities in Sickle Cell Disease

Sickle cell dactylitis	Avascular necrosis
Joint effusions in sickle cell crises	Bone changes secondary to marrow hyperplasia
Osteomyelitis	Septic arthritis
Infarction of bone	Gouty arthritis
Infarction of bone marrow	Synovial infarction

of the bone marrow and cortical bone leading to periostitis and soft tissue swelling. Radiographs show periosteal elevation, subperiosteal new bone formation, and areas of radiolucency and increased density involving the metacarpals, metatarsals, and proximal phalanges. These bone changes disappear after several months. The syndrome leaves little or no residual damage. Because hematopoiesis ceases in the small bones of the hands and feet with age, the syndrome is rarely seen after age 5.

Sickle cell crisis is associated with periarthritis pain and occasionally with joint effusions. The joint and periarthritis area are warm and tender. Knees and elbows are most often affected, but other joints can be involved. Joint effusions are usually noninflammatory. Acute synovial infarction can cause a sterile effusion with high neutrophil counts in synovial fluid. Synovial biopsies have shown mild lining-cell proliferation and microvascular thrombosis with infarctions. Scintigraphic studies have shown decreased marrow uptake adjacent to the involved joint. The treatment for sickle cell crisis is detailed in Chap. 98.

Patients with sickle cell disease are predisposed to osteomyelitis, which commonly involves the long tubular bones (Chap. 131); *Salmonella* is a particularly common cause (Chap. 165). Radiographs of the involved site initially show periosteal elevation, with subsequent disruption of the cortex. Treatment of the infection results in healing of the bone lesion. In addition, bone infarction resulting from vasoocclusion secondary to the sickling of red cells can occur and is the cause of the bone pain in sickle cell crisis. Bone infarction also occurs in hemoglobin sickle cell disease and sickle cell thalassemia (Chap. 98). In children, infarction of the epiphyseal growth plate interferes with normal growth of the affected extremity. Radiographically, infarction of the bone cortex results in periosteal elevation and irregular thickening of the bone cortex. Infarction in the bone marrow leads to lysis, fibrosis, and new bone formation. Clinical distinction between osteomyelitis and bone infarctions can be difficult; imaging can be helpful.

Avascular necrosis of the head of the femur occurs in ~5% of patients. It also occurs in the humeral head and less commonly in the distal femur, tibial condyles, distal radius, vertebral bodies, and other juxtaarticular sites. Irregularity of the femoral head and other articular surfaces often results in degenerative joint disease. Radiographs may show patchy radiolucency and density followed by flattening of the bone. MRI is a sensitive technique for detecting early avascular necrosis as well as bone infarction elsewhere. Total hip replacement and placement of prostheses in other joints may improve function and relieve joint pain in these patients.

Septic arthritis is occasionally encountered in sickle cell disease (Chap. 130). Multiple joints may be infected. Joint infection may result from bacteremia due to splenic dysfunction or from contiguous osteomyelitis. The more common microorganisms include *Staphylococcus aureus*, *Streptococcus*, and *Salmonella*. *Salmonella* does not cause septic arthritis as frequently as it causes osteomyelitis. Acute gouty arthritis is uncommon in sickle cell disease, even though 40% of patients are hyperuricemic. However, it may occur in patients generally not expected to get gout (young patients, female patients). Hyperuricemia is due to overproduction of uric acid secondary to increased red cell turnover as well as suboptimal renal excretion. Attacks may be polyarticular, and diagnostic arthrocentesis should be performed to distinguish infection from gout or synovial infarction.

The bone marrow hyperplasia in sickle cell disease results in widening of the medullary cavities, thinning of the cortices, and coarse trabeculations and central cupping of the vertebral bodies. These changes are also seen to a lesser degree in hemoglobin sickle cell disease and sickle cell thalassemia. In normal individuals, red marrow is located

mostly in the axial skeleton, but in sickle cell disease, red marrow is found in the bones of the extremities and even in the tarsal and carpal bones. Vertebral compression may lead to dorsal kyphosis, and softening of the bone in the acetabulum may result in protrusio acetabuli.

Thalassemia A congenital disorder of hemoglobin synthesis, β thalassemia is characterized by impaired production of β chains (Chap. 98). Bone and joint abnormalities occur in β thalassemia, being most common in the major and intermedia groups. In one study, ~50% of patients with β thalassemia had evidence of symmetric ankle arthropathy with onset in the second or third decade of life. The degree of ankle pain in these patients varied. Some patients experienced self-limited ankle pain that occurred only after strenuous physical activity and lasted several days or weeks, while others had chronic ankle pain that became worse with walking. Compression of the ankle, calcaneus, or forefoot was painful in some patients. Synovial fluid from two patients was noninflammatory. Radiographs of the ankle showed osteopenia, widened medullary spaces, thin cortices, and coarse trabeculations as a result of bone marrow expansion. The joint space was preserved. Specimens of bone from three patients revealed osteomalacia, osteopenia, and microfractures. Increased numbers of osteoblasts as well as increased foci of bone resorption were present on the bone surface. Iron staining was found in the bone trabeculae, in osteoid, and in the cement line. Synovium showed hyperplasia of lining cells, which contained deposits of hemosiderin. This arthropathy was considered to be related to the underlying bone pathology. The role of iron overload or abnormal bone metabolism in the pathogenesis of this arthropathy is not known. The arthropathy was treated with analgesics and splints. Patients also received transfusions to decrease hematopoiesis and bone marrow expansion.

In patients with β -thalassemia major and β -thalassemia intermedia, other joints are also involved, including the knees, hips, and shoulders. Acquired hemochromatosis with arthropathy has been described in a patient with thalassemia. Gouty arthritis and septic arthritis can occur. Avascular necrosis is not a feature of thalassemia because there is no sickling of red cells leading to thrombosis and infarction.

β Thalassemia minor (also known as *thalassemia trait*) is likewise associated with joint manifestations. Chronic seronegative oligoarthritis affecting predominantly ankles, wrists, and elbows has been described; the affected patients had mild persistent synovitis without large effusions or joint erosions. Recurrent episodes of acute asymmetric arthritis have also been reported; episodes last <1 week and may affect the knees, ankles, shoulders, elbows, wrists, and metacarpophalangeal joints. The mechanism underlying this arthropathy is unknown. Treatment with NSAIDs is not particularly effective.

MUSCULOSKELETAL DISORDERS ASSOCIATED WITH HYPERLIPIDEMIA

(See also Chap. 407) Musculoskeletal or cutaneous manifestations may be the first clinical indication of a specific hereditary disorder of lipoprotein metabolism. Patients with familial hypercholesterolemia (previously referred to as *type II hyperlipoproteinemia*) may have recurrent migratory polyarthritides involving the knees and other large peripheral joints and, to a lesser degree, peripheral small joints. Pain ranges from moderate to incapacitating. The involved joints can be warm, erythematous, swollen, and tender. Arthritis usually has a sudden onset, lasts from a few days to 2 weeks, and does not cause joint damage. Synovial fluid from involved joints is not inflammatory and contains few white cells and no crystals. Joint involvement may actually represent inflammatory periarthritis or peritendinitis and not true arthritis. The recurrent, transient nature of the arthritis may suggest acute gout or rheumatic fever, especially because patients with hyperlipoproteinemia may have an elevated erythrocyte sedimentation rate and elevated antistreptolysin O titers (the latter being quite common). Attacks of tendinitis, including the large Achilles and patellar tendons, may come on gradually and last only a few days or may be acute, as described above. Patients may be asymptomatic between attacks. Achilles tendinitis and other joint manifestations often precede the appearance of xanthomas and may be the first clinical indication

of hyperlipoproteinemia. Attacks of tendinitis may follow treatment with a lipid-lowering drug. Over time, patients may develop tendinous xanthomas in the Achilles, patellar, and extensor tendons of the hands and feet. Xanthomas have also been reported in the peroneal tendon, the plantar aponeurosis, and the periosteum overlying the distal tibia where they are located within tendon fibers. Tuberous xanthomas are soft subcutaneous masses located over the extensor surfaces of the elbows, knees, and hands as well as on the buttocks. They appear during childhood in homozygous patients and after the age of 30 in heterozygous patients. Patients with elevated plasma levels of very-low-density lipoprotein (VLDL) and triglycerides (previously referred to as *type IV hyperlipoproteinemia*) may also have a mild inflammatory arthritis affecting large and small peripheral joints, usually in an asymmetric pattern, with only a few joints involved at a time. The onset of arthritis is typically between the age of 40 and 65 years. Arthritis may be persistent or recurrent, with episodes lasting a few days or weeks. Severe joint pain and tenderness, morning stiffness, and periarthritis hyperesthesia may also be present, as may synovial thickening. Joint fluid is usually noninflammatory and without crystals but may have increased white blood cell counts with predominantly mononuclear cells. Radiographs may show juxtaarticular osteopenia and cystic lesions. Large bone cysts have been noted in a few patients. Xanthoma and bone cysts are also observed in other lipoprotein disorders. The pathogenesis of arthritis in patients with familial hypercholesterolemia or with elevated levels of VLDL and triglycerides is not well understood. NSAIDs or analgesics usually provide adequate relief of symptoms when used on an as-needed basis.

Patients may improve clinically as they are treated with lipid-lowering agents; however, patients treated with an HMG-CoA reductase inhibitor may experience myalgias, and a few patients develop myopathy, myositis, or even rhabdomyolysis. Patients who develop myositis during statin therapy may be susceptible to this adverse effect because of an underlying muscle disorder and should be reevaluated after discontinuation of the drug. Testing for anti-3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR) autoantibodies in patients with elevated muscle enzymes on treatment may identify patients with statin-induced necrotizing autoimmune myopathy. Myositis has also been reported with the use of niacin (Chap. 365) but is less common than myalgias.

Musculoskeletal syndromes have not clearly been associated with the more common mixed hyperlipidemias seen in general practice.

OTHER ARTHRITIDES

NEUROPATHIC JOINT DISEASE

Neuropathic joint disease (Charcot joint) is a progressive destructive arthritis associated with loss of pain sensation, proprioception, or both. Normal muscular reflexes that modulate joint movement are impaired. Without these protective mechanisms, joints are subjected to repeated trauma, resulting in progressive cartilage and bone damage. Today, diabetes mellitus is the most frequent cause of neuropathic joint disease (Fig. 374-1). A variety of other disorders are associated with neuropathic arthritis, including tabes dorsalis, leprosy, yaws, syringomyelia, meningomyelocele, congenital indifference to pain, peroneal muscular atrophy (Charcot-Marie-Tooth disease), and amyloidosis. An arthritis resembling neuropathic joint disease has been reported in patients who have received intraarticular glucocorticoid injections, but this is a rare complication and was not observed in one series of patients with knee osteoarthritis who received intraarticular glucocorticoid injections every 3 months for 2 years. The distribution of joint involvement depends on the underlying neurologic disorder (Table 374-2). In tabes dorsalis, the knees, hips, and ankles are most commonly affected; in syringomyelia, the glenohumeral joint, elbow, and wrist; and in diabetes mellitus, the tarsal and tarsometatarsal joints.

PATHOLOGY AND PATHOPHYSIOLOGY

The pathologic changes in the neuropathic joint are similar to those found in the severe osteoarthritic joint. There is fragmentation and eventual loss of articular cartilage with eburnation of the underlying bone. Osteophytes are found at the joint margins. With more advanced



FIGURE 374-1 Charcot arthropathy associated with diabetes mellitus. Lateral foot radiograph demonstrating complete loss of the arch due to bony fragmentation and dislocation in the midfoot. (Courtesy of Andrew Neckers, MD, and Jean Schils, MD; with permission.)

disease, erosions are present on the joint surface. Fractures, devitalized bone, intraarticular loose bodies, and microscopic fragments of cartilage and bone may be present.

At least two underlying mechanisms are believed to be involved in the pathogenesis of neuropathic arthritis. An abnormal autonomic nervous system is thought to be responsible for the dysregulated blood flow to the joint with subsequent resorption of bone. Loss of bone, particularly in the diabetic foot, may be the initial finding. With the loss of deep pain, proprioception, and protective neuromuscular reflexes, the joint is subjected to repeated microtrauma, resulting in ligamentous tears and bone fractures. The injury that follows frequent intraarticular glucocorticoid injections is thought to be due to the analgesic effect of glucocorticoids, leading to overuse of an already damaged joint; the result is accelerated cartilage damage, although steroid-induced cartilage damage is more common in some other animal species than in humans. It is not understood why only a few patients with neuropathy develop clinically evident neuropathic arthritis.

CLINICAL MANIFESTATIONS

Neuropathic joint disease usually begins in a single joint and then becomes apparent in other joints, depending on the underlying neurologic disorder. The involved joint becomes progressively enlarged as a result of bony overgrowth and synovial effusion. Loose bodies may be palpated in the joint cavity. Joint instability, subluxation, and crepitus occur as the disease progresses. Neuropathic joints may develop rapidly, and a totally disorganized joint with multiple bony fragments may evolve within weeks or months. The amount of pain experienced by the patient is less than would be anticipated from the degree of joint damage. Patients may experience sudden joint pain from intraarticular fractures of osteophytes or condyles.

Neuropathic arthritis is encountered most often in patients with diabetes mellitus, with an incidence of ~0.5%. The onset of disease usually comes at an age of ≥50 years in a patient who has had diabetes for several years, but exceptions occur. The tarsal and tarsometatarsal joints are most often affected, with the metatarsophalangeal and talotibial joints next most commonly involved. The knees and spine are occasionally involved. Patients often attribute the onset of foot pain to antecedent trauma such as twisting of the foot. Neuropathic changes may develop rapidly after a foot fracture or dislocation. The foot and ankle are often swollen. Downward collapse of the tarsal bones leads to convexity of the sole, referred to as a "rocker foot." Large osteophytes may protrude from the top of the foot. Calluses frequently form over

the metatarsal heads and may lead to infected ulcers and osteomyelitis. The value of protective inserts and orthotics, as well as regular foot examination, cannot be overstated. Radiographs may show resorption and tapering of the distal metatarsal bones. The term *Lisfranc fracture-dislocation* is sometimes used to describe the destructive changes at the tarsometatarsal joints.

DIAGNOSIS

The diagnosis of neuropathic arthritis is based on the clinical features and characteristic radiographic findings in a patient with underlying sensory neuropathy. The differential diagnosis of neuropathic arthritis depends upon the severity of the process and includes osteomyelitis, avascular necrosis, advanced osteoarthritis, stress fractures, and calcium pyrophosphate deposition disease. Radiographs in neuropathic arthritis initially show changes of osteoarthritis with joint space narrowing, subchondral bone sclerosis, osteophytes, and joint effusions; marked destructive and hypertrophic changes follow later. The radiographic findings of neuropathic arthritis may be difficult to differentiate from those of osteomyelitis, especially in the diabetic foot. The joint margins in a neuropathic joint tend to be distinct, while in osteomyelitis, they are blurred. Imaging studies may be helpful, but cultures of tissue from the joint are often required to exclude osteomyelitis. MRI and bone scans using indium-111-labeled white blood cells or indium-111-labeled immunoglobulin G, which will show increased uptake in osteomyelitis but not in a neuropathic joint, may be useful. A technetium bone scan will not distinguish osteomyelitis from neuropathic arthritis, as increased uptake is observed in both. The joint fluid in neuropathic arthritis is noninflammatory; it may be xanthochromic or even bloody and may contain fragments of synovium, cartilage, and bone. The finding of calcium pyrophosphate dihydrate crystals supports the diagnosis of crystal-associated arthropathy. In the absence of such crystals, an increased number of leukocytes may indicate osteomyelitis.

TREATMENT

Neuropathic Joint Disease

The primary focus of treatment is to stabilize the joint. Treatment of the underlying disorder, even if successful, does not usually affect established joint disease. Braces and splints are helpful. Their use requires close surveillance, because patients may be unable to appreciate pressure from a poorly adjusted brace. In the diabetic patient, early recognition of Charcot foot and its treatment—prohibition of weight bearing by the foot for at least 8 weeks—may possibly prevent severe disease from developing. Fusion of an unstable joint may improve function and reduce pain, but nonunion is frequent, especially when immobilization of the joint is inadequate.

HYPERTROPHIC OSTEOARTHROPATHY AND CLUBBING

Hypertrophic osteoarthropathy (HOA) is characterized by clubbing of digits and, in more advanced stages, by periosteal new bone formation and synovial effusions. HOA may be primary or familial and may begin in childhood. Secondary HOA is associated with intrathoracic malignancies, suppurative and some hypoxic lung diseases, congenital heart disease, and a variety of other disorders. Clubbing is almost always a feature of HOA but can also occur as an isolated finding (Fig. 374-2). The presence of clubbing in isolation may be congenital or represent either an early stage or one element in the spectrum of HOA. Isolated acquired clubbing has the same clinical significance as clubbing associated with periostitis.

Pathology and Pathophysiology of Acquired HOA In HOA, bone changes in the distal extremities begin as periostitis followed by new bone formation. At this stage, a radiolucent area may be observed between the new periosteal bone and the subjacent cortex. As the process progresses, multiple layers of new bone are deposited and become contiguous with the cortex, with consequent cortical thickening. The outer portion of the bone is laminated in appearance, with an irregular

TABLE 374-2 Disorders Associated with Neuropathic Joint Disease

Diabetes mellitus	Amyloidosis
Tabes dorsalis	Leprosy
Meningomyelocele	Congenital indifference to pain
Syringomyelia	Peroneal muscular atrophy



FIGURE 374-2 Clubbing of the fingers. (Photo contributor Alan B. Storrow, MD).

surface. Initially, the process of periosteal new bone formation involves the proximal and distal diaphyses of the tibia, fibula, radius, and ulna and, less frequently, the femur, humerus, metacarpals, metatarsals, and phalanges. Occasionally, scapulae, clavicles, ribs, and pelvic bones are also affected. The adjacent interosseous membranes may become ossified. The distribution of bone manifestations is usually bilateral and symmetric. The soft tissue overlying the distal third of the arms and legs may be thickened. Proliferation of connective tissue occurs in the nail bed and volar pad of digits, giving the distal phalanges a clubbed appearance. Small blood vessels in the clubbed digits are dilated and have thickened walls. In addition, the number of arteriovenous anastomoses is increased.

Several theories have been suggested for the pathogenesis of HOA, but many have been disproved or have not explained the condition's development in all clinical disorders with which it is associated. Previously proposed neurogenic and humoral theories are no longer considered likely explanations for HOA. Studies have suggested a role for platelets in the development of HOA. It has been observed that megakaryocytes and large platelet particles present in the venous circulation are fragmented in their passage through normal lung. In patients with cyanotic congenital heart disease and in other disorders associated with right-to-left shunts, these large platelet particles bypass the lung and reach the distal extremities, where they can interact with endothelial cells. Platelet–endothelial cell activation in the distal portion of the extremities may result in the release of platelet-derived growth factor (PDGF) and other factors leading to the proliferation of connective tissue and periosteum. Stimulation of fibroblasts by PDGF and transforming growth factor β results in cell growth and collagen synthesis. Elevated plasma levels of von Willebrand factor antigen have been found in patients with both primary and secondary forms of HOA, indicating endothelial activation or damage. Abnormalities of collagen synthesis have been demonstrated in the involved skin of patients with primary HOA. Other factors are undoubtedly involved in the pathogenesis of HOA, and further studies are needed to elucidate this disorder.

Clinical Manifestations Primary or familial HOA, also referred to as *pachydermoperiostosis* or *Touraine-Solente-Golé syndrome*, usually begins insidiously at puberty. In a smaller proportion of patients, the onset comes in the first year of life. The disorder is inherited as an autosomal dominant trait with variable expression and is nine times more common among boys than among girls. Approximately one-third of patients have a family history of primary HOA.

Primary HOA is characterized by clubbing, periostitis, and unusual skin features. A small number of patients with this syndrome do not express clubbing. The skin changes and periostitis are prominent features of this syndrome. The skin becomes thickened and coarse. Deep nasolabial folds develop, and the forehead may become furrowed. Patients may have heavy-appearing eyelids and ptosis. The skin is often greasy, and there may be excessive sweating of the hands and feet. Patients may also experience acne vulgaris, seborrhea, and folliculitis. In a few patients, the skin over the scalp becomes very thick and

corrugated, a feature that has been descriptively termed *cutis verticis gyrrata*. The distal extremities, particularly the legs, become thickened as a consequence of the proliferation of new bone and soft tissue; when the process is extensive, the distal lower extremities resemble those of an elephant. The periostitis usually is not painful, which it can be in secondary HOA. Clubbing of the fingers may be extensive, producing large, bulbous deformities, and clumsiness. Clubbing also affects the toes. Patients may experience articular and periarticular pain, especially in the ankles and knees, and joint motion may be mildly restricted by periarticular bone overgrowth. Noninflammatory effusions occur in the wrists, knees, and ankles. Synovial hypertrophy is not found. Associated abnormalities observed in patients with primary HOA include hypertrophic gastropathy, bone marrow failure, female escutcheon, gynecomastia, and cranial suture defects. In patients with primary HOA, the symptoms disappear when adulthood is reached.

HOA secondary to an underlying disease occurs more frequently than primary HOA. It accompanies a variety of disorders and may precede clinical features of the associated disorder by months. Clubbing is more frequent than the full syndrome of HOA in patients with associated illnesses. Because clubbing evolves over months and is usually asymptomatic, it is often recognized first by the physician and not the patient. Patients may experience a burning sensation in their fingertips. Clubbing is characterized by widening of the fingertips, enlargement of the distal volar pad, convexity of the nail contour, and the loss of the normal 15° angle between the proximal nail and cuticle. The thickness of the digit at the base of the nail is greater than the thickness at the distal interphalangeal joint. An objective measurement of finger clubbing can be made by determining the diameter at the base of the nail and at the distal interphalangeal joint of all 10 digits. Clubbing is present when the sum of the individual digit ratios is >10. At the bedside, clubbing can be appreciated by having the patient place the dorsal surface of the distal phalanges of the fourth fingers together with the nails opposing each other. Normally, an open area is visible between the bases of the opposing fingernails; when clubbing is present, this open space is no longer visible. The base of the nail feels spongy when compressed, and the nail can be easily rocked on its bed. When clubbing is advanced, the finger may have a drumstick appearance, and the distal interphalangeal joint can be hyperextended. Periosteal involvement in the distal extremities may produce a burning or deep-seated aching pain. The pain, which can be quite incapacitating, is aggravated by dependency and relieved by elevation of the affected limbs. Pressure applied over the distal forearms and legs or gentle percussion of distal long bones like the tibia may be quite painful.

Patients may experience joint pain, most often in the ankles, wrists, and knees. Joint effusions may be present but are usually noninflammatory. The small joints of the hands are rarely affected. Severe joint or long bone pain may be the presenting symptom of an underlying lung malignancy and may precede the appearance of clubbing. In addition, the progression of HOA tends to be more rapid when associated with malignancies, most notably bronchogenic carcinoma. Noninflammatory but variably painful knee effusions may occur prior to the onset of clubbing and symptoms of distal periostitis. Unlike primary HOA, secondary HOA does not commonly include excessive sweating and oiliness of the skin or thickening of the facial skin.

HOA occurs in 5–10% of patients with intrathoracic malignancies, the most common being bronchogenic carcinoma and pleural tumors (**Table 374-3**). Lung metastases infrequently cause HOA. HOA is also seen in patients with intrathoracic infections, including lung abscesses, empyema, and bronchiectasis, but is uncommon in pulmonary tuberculosis. HOA may accompany chronic interstitial pneumonitis, sarcoidosis, and cystic fibrosis. In cystic fibrosis, clubbing is more common than the full syndrome of HOA. Other causes of clubbing include congenital heart disease with right-to-left shunts, bacterial endocarditis, Crohn's disease, ulcerative colitis, sprue, and neoplasms of the esophagus, liver, and small and large bowel. In patients who have congenital heart disease with right-to-left shunts, clubbing alone occurs more often than the full syndrome of HOA.

Unilateral clubbing has been found in association with aneurysms of major extremity arteries, with infected arterial grafts, and with

TABLE 374-3 Disorders Associated with Hypertrophic Osteoarthropathy

Pulmonary
Bronchogenic carcinoma and other neoplasms
Lung abscesses, empyema, bronchiectasis
Chronic interstitial pneumonitis
Cystic fibrosis
Sarcoidosis
Gastrointestinal
Inflammatory bowel disease
Sprue
Neoplasms: esophagus, liver, bowel
Cardiovascular
Cyanotic congenital heart disease
Subacute bacterial endocarditis
Infected arterial grafts ^a
Aortic aneurysm ^b
Aneurysm of major extremity artery ^a
Patent ductus arteriosus ^b
Arteriovenous fistula of major extremity vessel ^a
Thyroid (thyroid acropachy)
Hyperthyroidism (Graves' disease)

^aUnilateral involvement. ^bBilateral lower-extremity involvement.

arteriovenous fistulas of brachial vessels. Clubbing of the toes but not the fingers has been associated with an infected abdominal aortic aneurysm and patent ductus arteriosus. Clubbing of a single digit may follow trauma and has been reported in tophaceous gout and sarcoidosis. While clubbing occurs more commonly than the full syndrome in most diseases, periostitis in the absence of clubbing has been observed in the affected limb of patients with infected arterial grafts.

Hyperthyroidism (Graves' disease), treated or untreated, is occasionally associated with clubbing and periostitis of the bones of the hands and feet. This condition is referred to as *thyroid acropachy*. Periostitis may be asymptomatic and occurs in the midshaft and diaphyseal portion of the metacarpal and phalangeal bones. Significant hand-joint pain may occur, which may respond to successful therapy for thyroid dysfunction. The long bones of the extremities are seldom affected. Elevated levels of long-acting thyroid stimulator are found in the sera of these patients.

Laboratory Findings The laboratory abnormalities reflect the underlying disorder. The synovial fluid of involved joints has <500 white cells/ μ L, and the cells are predominantly mononuclear. Radiographs show a faint radiolucent line beneath the new periosteal bone along the shaft of long bones at their distal end. These changes are observed most frequently at the ankles, wrists, and knees. The ends of the distal phalanges may show osseous resorption. Radionuclide studies show pericortical linear uptake along the cortical margins of long bones that may precede any radiographic changes.

TREATMENT

Hypertrophic Osteoarthropathy

The treatment of HOA aims to identify and treat the associated disorder. The symptoms and signs of HOA may disappear completely with removal of or effective chemotherapy for a tumor or with antibiotic therapy for a chronic pulmonary infection and drainage of the infected site. Vagotomy or percutaneous block of the vagus nerve leads to symptomatic relief in some patients. NSAIDs or analgesics may help control symptoms of HOA.

COMPLEX REGIONAL PAIN SYNDROME

The reflex sympathetic dystrophy syndrome is now referred to as *complex regional pain syndrome, type 1*, according to the new classification

system of the International Association for the Study of Pain. This syndrome is characterized by pain and swelling, usually of a distal extremity, accompanied by vasomotor instability, trophic skin changes, and the rapid development of bony demineralization. Complex regional pain syndrome, including its treatment, is covered in greater detail in **Chap. 440**.

TIETZE SYNDROME AND COSTOCHONDROITIS

Tietze syndrome is manifested by painful swelling of one or more costochondral articulations. The age of onset is usually before 40, and both sexes are affected equally. In most patients, only one joint is involved, usually the second or third costochondral joint. The onset of anterior chest pain may be sudden or gradual. The pain may radiate to the arms or shoulders and is aggravated by sneezing, coughing, deep inspirations, or twisting motions of the chest. The term *costochondritis* is often used interchangeably with *Tietze syndrome*, but some restrict the former term to pain of the costochondral articulations without swelling. Costochondritis is observed in patients aged >40 years; it tends to affect the third, fourth, and fifth costochondral joints, and occurs more often in women. Both syndromes may superficially mimic cardiac or upper abdominal causes of pain. Rheumatoid arthritis, ankylosing spondylitis, and reactive arthritis may involve costochondral joints but are distinguished easily by their other clinical features. Other skeletal causes of anterior chest wall pain are xiphoidalgia and the slipping rib syndrome, which usually involves the tenth rib and causes reproducible pain below the rib cage. Malignancies such as breast cancer, prostate cancer, plasma cell myeloma, and sarcoma can invade the ribs, thoracic spine, or chest wall and produce symptoms suggesting Tietze's syndrome. Patients with osteomalacia may have significant rib pain, with or without documented microfractures. These conditions should be distinguishable by radiography, bone scanning, vitamin D measurement, or biopsy. Analgesics, NSAIDs, and local glucocorticoid injections usually relieve symptoms of costochondritis/Tietze's syndrome. Care should be taken to avoid overdiagnosing these syndromes in patients with acute chest pain syndromes.

MYOFASCIAL PAIN SYNDROME

Myofascial pain syndrome is characterized by multiple areas of localized musculoskeletal pain and tenderness in association with tender points. The pain is deep and aching and may be accompanied by a burning sensation. Myofascial pain may be regional and follow trauma, overuse, or prolonged static contraction of a muscle or muscle group, which may occur when an individual is reading or writing at a desk or working at a computer. In addition, this syndrome may be associated with underlying osteoarthritis of the neck or low back. Pain may be referred from tender points to defined areas distant from the area of original tenderness. Palpation of the tender point reproduces or accentuates the pain. The tender points are usually located in the center of a muscle belly, but they can occur at other sites such as costosternal junctions, the xiphoid process, ligamentous and tendinous insertions, fascia, and fatty areas. Tender point sites in muscle have been described as feeling indurated and taut, and palpation may cause the muscle to twitch. These findings, however, have been shown not to be unique to myofascial pain syndrome: in a controlled study, they were also present in some "normal" subjects. Myofascial pain most often involves the posterior neck, low back, shoulders, and chest. Chronic pain in the muscles of the posterior neck may involve referral of pain from a tender point in the erector spinae muscle or upper trapezius to the head, leading to persistent headaches that may last for days. Tender points in the paraspinal muscles of the low back may refer pain to the buttock. Pain may be referred down the leg from a tender point in the gluteus medius and can mimic sciatica. A tender point in the infraspinatus muscle may produce local and referred pain over the lateral deltoid and down the outside of the arm into the hand. Injection of a local anesthetic such as 1% lidocaine into the tender point site often results in transient pain relief. Another useful technique is first to spray an agent such as ethyl chloride from the tender point toward the area of referred pain and then to stretch the muscle. This maneuver may need to be repeated several times. Massage and application of ultrasound to

the affected area also may be beneficial. Patients should be instructed in methods to prevent muscle stresses related to work and recreation. The prognosis in most patients is good. In some patients, regionally localized myofascial pain syndrome may evolve into more generalized fibromyalgia (**Chap. 373**). Nonrestorative sleep is a common accompaniment in these patients and may need to be specifically addressed.

NEOPLASIAS AND ARTHRITIS

Primary tumors and tumor-like disorders of synovium are uncommon but should be considered in the differential diagnosis of monarticular joint disease. In addition, metastases to bone and primary bone tumors adjacent to a joint may produce joint symptoms.

Pigmented villonodular synovitis (PVNS), likely the same process causing tenosynovial giant cell tumors, is characterized by the slowly progressive, benign proliferation of tenosynovial tissue. This usually involves a single large joint or tendon. The most common age of onset is in the third decade, and women are affected slightly more often than men. The proliferating tissue usually displays clonal chromosomal translocations; most of these aberrations appear to involve the colony stimulating factor-1 (CSF-1) pathway, which influences the proliferation and maturation of mononuclear cells and macrophages.

The synovium has a brownish color and numerous large, fingerlike villi that fuse to form pedunculated nodules. There is marked hyperplasia of synovial cells in the stroma of the villi. Hemosiderin and lipids are found in the cytoplasm of macrophages and in the interstitial tissue. Multinucleated giant cells may be present. The proliferative synovium may behave as a simple mass or as a more diffuse invasive tissue growing into the adjacent cartilage and bone.

The clinical picture of PVNS is characterized by the insidious onset of progressive swelling and pain in affected joints or tendons, most commonly the knee or flexor tendons of the hand. Other commonly affected joints include the hips, ankles, calcaneocuboid joints, elbows, and small joints of the fingers or toes; multifocal form is less common. Tendon sheaths in the wrist, ankle, or foot may be involved. Symptoms of pain, a catching sensation, or stiffness may initially be mild and intermittent and may be present for years before the patient seeks medical attention. Radiographs may show joint space narrowing, erosions, and subchondral cysts. The diagnosis of PVNS is strongly suggested by gradient echo MRI, which reveals a synovial mass lesion of low signal intensity typical of tissue containing hemosiderin (**Fig. 374-3**). The joint fluid contains blood and is dark red or almost black in color. Lipid-containing macrophages may be present in the fluid. The joint fluid may be clear if hemorrhage has not occurred.

The treatment for PVNS, if needed, is complete open or arthroscopic synovectomy. Irradiation of the involved joint has been successful in some patients but may cause a delayed malignant transformation.



FIGURE 374-3 Pigmented villonodular synovitis. MRI gradient echo sagittal image showing a mass that abuts the neck of the talus with marked low signal typical of tissue containing hemosiderin. (Courtesy of Donald Flemming, MD; with permission.)

Treatment directed at inhibiting the CSF-1 pathway activated kinase has demonstrated efficacy.

Synovial chondromatosis is a disorder characterized by multiple focal metaplastic growths of normal-appearing cartilage in the synovium or tendon sheath. Segments of cartilage break loose and continue to grow as loose bodies. When calcification and ossification of loose bodies occur, the disorder is referred to as *synovial osteochondromatosis*. The disorder is usually monarticular and affects young to middle-aged individuals. The knee is most often involved, followed by hip, elbow, and shoulder. Symptoms are pain, swelling, and decreased motion of the joint. Radiographs may show several rounded calcifications within the joint cavity. Treatment is synovectomy; however, as in PVNS, the growths may recur.

Synovial sarcoma is a malignant neoplasm often found near a large joint of both upper and lower extremities, being more common in the lower extremity. It seldom arises within the joint itself. Synovial sarcomas constitute 10% of soft tissue sarcomas. The tumor is believed to arise from primitive mesenchymal tissue that differentiates into epithelial cells and/or spindle cells. Small foci of calcification may be present in the tumor mass. Synovial sarcoma occurs most often in young adults and is more common in men. The tumor presents as a slowly growing deep-seated mass near a joint, without much pain. The area of the knee is the most common site, followed by the foot, ankle, elbow, and shoulder. Other primary sites include the buttocks, abdominal wall, retroperitoneum, and mediastinum. The diagnosis is made by biopsy and must be distinguished from PVNS. Treatment consists of wide resection of the tumor, including adjacent muscle and regional lymph nodes, followed by chemotherapy and radiation therapy. Amputation of the involved distal extremity may be required. Chemotherapy may be beneficial in some patients with metastatic disease. Isolated sites of pulmonary metastasis can be surgically removed. The 5-year survival rate with treatment depends on the staging of the tumor, ranging from ~25% to ≥60%. Synovial sarcomas tend to recur locally and metastasize to regional lymph nodes, lungs, and skeleton.

In addition to the rare direct metastases of solid cell tumors to the highly vascular synovium, neoplasia arising from nonarticular organ sites can affect joints in other ways. Acute leukemias in children can mimic juvenile systemic inflammatory arthritis with severe joint pain and fever. In adults, chronic and acute myeloid leukemia rarely infiltrate the synovium. Hairy cell leukemia has a peculiar tendency to cause episodic inflammatory oligoarthritis and tenosynovitis; these episodes are dramatic and mimic acute gout flares. They respond to potent anti-inflammatory therapy with glucocorticoids; with remission of the leukemia, they may abate. Lymphomas, usually of T-cell origin, may also involve the synovium.

Carcinomas can be associated with several paraneoplastic articular syndromes, including HOA (discussed above). Acute palmar fasciitis with polyarthritis is a well-described but rare condition associated with certain cancers, mainly adenocarcinomas. Clinically, this syndrome is abrupt in onset, with pain in the metacarpophalangeal and proximal interphalangeal joints of the hands and rapidly evolving contractures of the fingers due to thickening of the palmar (flexor) tendons. A similar syndrome, although less dramatic in onset, can occur in diabetics. Paraneoplastic arthritis has been described and may occur in several patterns: asymmetric disease predominantly affecting the lower extremity joints and symmetric polyarthritis with hand joint involvement. Tumors are often found after the onset of the arthritis, and many patients have a preceding period of malaise or weight loss. The onset is often acute, and patients tend to be older men. These features should raise the question of an underlying malignancy as the cause of the arthritis. In one series, the symptoms resolved with successful therapy for the malignancy and did not recur with relapse of the malignancy. Dermatomyositis has a well-described association with neoplasms and may include joint pain and arthritis. Malignancy-associated arthritis may be responsive to NSAIDs and to treatment of the primary neoplasm.

Immune checkpoint inhibitors, increasingly used to treat various malignancies, are now well recognized to frequently elicit severe autoimmune, inflammatory, organ-targeted reactions including myositis, polymyalgia rheumatica, and polyarthritis.

- Aguilar C et al: Bone and joint disease in sickle cell disease. *Hematol Oncol Clin North Am* 19:929, 2005.
- Botek G et al: Charcot neuroarthropathy: An often overlooked complication of diabetes. *Cleve Clin J Med* 77:593, 2010.
- Dallos T et al: Idiopathic hand osteoarthritis vs haemochromatosis arthropathy: A clinical, functional and radiographic study. *Rheumatology* 52:910, 2013.
- Guggenbuhl P et al: Miscellaneous non-inflammatory musculoskeletal conditions. Haemochromatosis: The bone and the joint. *Best Pract Res Clin Rheumatol* 25:649, 2011.
- Kedar E, Gardner GC: Lipid-associated rheumatologic syndromes. *Rheum Dis Clin North Am* 39:481, 2013.
- Killinger Z et al: Arthropathy in acromegaly. *Rheum Dis Clin North Am* 36:713, 2010.
- Pineda C, Martínez-Lavín M: Hypertrophic osteoarthropathy: What a rheumatologist should know about this uncommon condition. *Rheum Dis Clin North Am* 39:383, 2013.
- Stephan SR et al: Pigmented villonodular synovitis. A comprehensive review and proposed treatment algorithm. *JBJS Rev* 4:1, 2016.
- Vanderhave KL et al: Musculoskeletal care of the hemophiliac patient. *J Am Acad Orthop Surg* 20:553, 2012.

375

Periarticular Disorders of the Extremities

Carol A. Langford

Periarticular disorders are common musculoskeletal abnormalities that can affect people throughout a wide range of ages. This chapter discusses some of the more common periarticular disorders.

BURSITIS

Bursitis is inflammation of a bursa, which is a thin-walled sac lined with synovial tissue. The function of the bursa is to facilitate movement of tendons and muscles over bony prominences. Excessive frictional forces from overuse, trauma, systemic disease (e.g., rheumatoid arthritis, gout), or infection may cause bursitis. *Subacromial bursitis* (subdeltoid bursitis) is the most common form of bursitis. The subacromial bursa, which is contiguous with the subdeltoid bursa, is located between the undersurface of the acromion and the humeral head and is covered by the deltoid muscle. Bursitis often accompanies rotator cuff tendinitis. Another frequently encountered form is *trochanteric bursitis*, which involves the bursa around the insertion of the gluteus medius onto the greater trochanter of the femur. Patients experience pain over the lateral aspect of the hip and upper thigh and have tenderness over the posterior aspect of the greater trochanter. External rotation and resisted abduction of the hip elicit pain, as will direct pressure applied to the bursa. *Olecranon bursitis* occurs over the posterior elbow and, when the area is acutely inflamed, infection or gout should be excluded by aspirating the bursa and performing a Gram stain and culture on the fluid as well as examining the fluid for urate crystals. *Achilles bursitis* involves the bursa located above the insertion of the tendon to the calcaneus and results from overuse and wearing tight shoes. *Retrocalcaneal bursitis* involves the bursa that is located between the calcaneus and posterior surface of the Achilles tendon. The pain is experienced at the back of the heel, and swelling appears on the medial and/or lateral side of the tendon. It occurs in association with spondyloarthritides, rheumatoid arthritis, gout, or trauma. *Ischial bursitis* affects the bursa separating the gluteus medius from the ischial tuberosity and develops from prolonged sitting and pivoting on hard surfaces. *Iliopsoas bursitis* affects the bursa that lies between the iliopsoas muscle and hip joint

and is lateral to the femoral vessels. Pain is experienced over this area and is made worse by hip extension and flexion. *Anserine bursitis* is an inflammation of the sartorius bursa located over the medial side of the tibia just below the knee and under the conjoint tendon and is manifested by pain on climbing stairs. Tenderness is present over the insertion of the conjoint tendon of the sartorius, gracilis, and semitendinosus. *Prepatellar bursitis* occurs in the bursa situated between the patella and overlying skin and is caused by kneeling on hard surfaces. Gout or infection may also occur at this site. Bursitis is typically diagnosed by history and physical examination, but visualization by ultrasound may play a useful role in selected instances for diagnosis and directed guidance of glucocorticoid injection. Treatment of bursitis consists of prevention of any aggravating situation, rest of the involved part, administration of a nonsteroidal anti-inflammatory drug (NSAID) where appropriate for an individual patient, or local glucocorticoid injection.

ROTATOR CUFF TENDINITIS AND IMPINGEMENT SYNDROME

Tendinitis of the rotator cuff is the major cause of a painful shoulder and is currently thought to be caused by inflammation of the tendon(s). The rotator cuff consists of the tendons of the supraspinatus, infraspinatus, subscapularis, and teres minor muscles, and inserts on the humeral tuberosities. Of the tendons forming the rotator cuff, the supraspinatus tendon is the most often affected, probably because of its repeated impingement (*impingement syndrome*) between the humeral head and the undersurface of the anterior third of the acromion and coracohumeral ligament above as well as the reduction in its blood supply that occurs with abduction of the arm (Fig. 375-1). The tendon of the infraspinatus and that of the long head of the biceps are less commonly involved. Subacromial bursitis also accompanies this syndrome. Symptoms can appear without a triggering cause or after injury or overuse, especially with activities involving elevation of the arm with some degree of forward flexion. Impingement syndrome occurs in persons participating in baseball, tennis, swimming, or occupations that require repeated elevation of the arm. Those aged >40 years are particularly susceptible. Patients complain of a dull aching in the shoulder, which may interfere with sleep. Severe pain is experienced when the arm is actively abducted into an overhead position. The arc between 60° and 120° is especially painful. Tenderness is present over the lateral aspect of the humeral head just below the acromion. NSAIDs, local glucocorticoid injection, and physical therapy may relieve symptoms. Surgical decompression of the subacromial space may be necessary in patients refractory to conservative treatment.

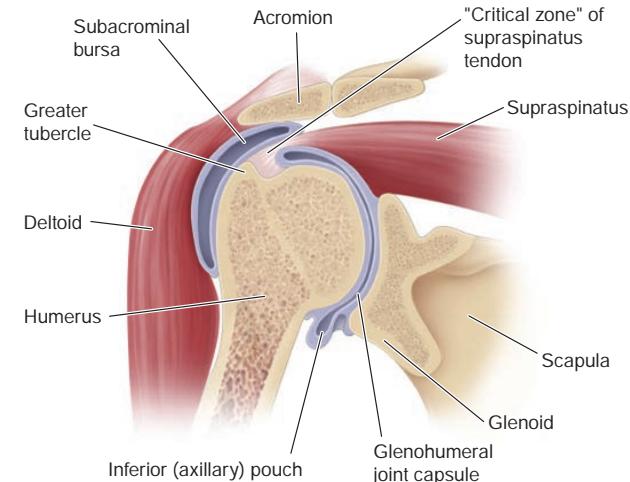


FIGURE 375-1 Coronal section of the shoulder illustrating the relationships of the glenohumeral joint, the joint capsule, the subacromial bursa, and the rotator cuff (supraspinatus tendon). (Reproduced with permission from F Kozin, in WJ Koopman [ed]: *Arthritis and Allied Conditions*, 13th ed, Baltimore, Williams & Wilkins, 1997.)

Patients may tear the supraspinatus tendon acutely by falling on an outstretched arm or lifting a heavy object. Symptoms are pain along with weakness of abduction and external rotation of the shoulder. Atrophy of the supraspinatus muscles develops. The diagnosis is established by ultrasound, magnetic resonance imaging (MRI), or arthrogram. Surgical repair may be necessary in patients who fail to respond to conservative measures. In patients with moderate-to-severe tears and functional loss, surgery is indicated.

CALCIFIC TENDINITIS

This condition is characterized by deposition of calcium salts, primarily hydroxyapatite, within a tendon. The exact mechanism of calcification is not known but may be initiated by ischemia or degeneration of the tendon. The supraspinatus tendon is most often affected because it is frequently impinged on and has a reduced blood supply when the arm is abducted. The condition usually develops after age 40. Calcification within the tendon may evoke acute inflammation, producing sudden and severe pain in the shoulder. However, it may be asymptomatic or not related to the patient's symptoms. Diagnosis of calcific tendonitis can be made by ultrasound or radiograph. Most cases are self-limited and respond to conservative therapy with physical therapy and/or NSAIDs. A subset of patients is refractory and requires ultrasound-guided percutaneous needle aspiration and lavage or surgery.

BICIPITAL TENDINITIS AND RUPTURE

Bicipital tendinitis, or tenosynovitis, is produced by friction on the tendon of the long head of the biceps as it passes through the bicipital groove. When the inflammation is acute, patients experience anterior shoulder pain that radiates down the biceps into the forearm. Abduction and external rotation of the arm are painful and limited. The bicipital groove is very tender to palpation. Pain may be elicited along the course of the tendon by resisting supination of the forearm with the elbow at 90° (Yergason's supination sign). Acute rupture of the tendon may occur with vigorous exercise of the arm and is often painful. In a healthy and active patient, it should be repaired surgically as soon as possible after the rupture occurs. Rupture of the tendon in an older person may be associated with little or no pain and is recognized by the presence of persistent swelling of the biceps produced by the retraction of the long head of the biceps. Surgery is usually not necessary in this setting.

DE QUERVAIN'S TENOSYNOVITIS

In this condition, inflammation involves the abductor pollicis longus and the extensor pollicis brevis as these tendons pass through a fibrous sheath at the radial styloid process. The usual cause is repetitive twisting of the wrist. It may occur in pregnancy, and it also occurs in mothers who hold their babies with the thumb outstretched. Patients experience pain on grasping with their thumb, such as with pinching. Swelling and tenderness are often present over the radial styloid process. The Finkelstein sign is positive, which is elicited by having the patient place the thumb in the palm and close the fingers over it. The wrist is then ulnarly deviated, resulting in pain over the involved tendon sheath in the area of the radial styloid. Treatment consists initially of splinting the wrist and an NSAID. When severe or refractory to conservative treatment, glucocorticoid injections can be very effective.

PATELLAR TENDINITIS

Tendinitis involves the patellar tendon at its attachment to the lower pole of the patella. Patients may experience pain when jumping during sports, going up stairs, or doing deep knee squats. Tenderness is noted on examination over the lower pole of the patella. Treatment consists of rest, icing, and NSAIDs, followed by strengthening and increasing flexibility.

DRUG-INDUCED TENDINOPATHIES

With the broadening range of available pharmacologic agents, the potential for drug-induced tendinopathies has become increasingly recognized. The drug classes most associated with tendinopathies include quinolones, glucocorticoids, aromatase inhibitors, and statins.

Although any tendon can be affected, the tendons of the lower extremities are most often impacted, particularly the Achilles tendon. The pathophysiologic mechanisms responsible for drug-induced tendinopathies remain unknown. Presenting features include pain and potentially swelling over the tendon, although some patients may first present with tendon rupture. Ultrasound and MRI can provide information on tendon structure and integrity in support of the diagnosis. When suspected, the potential agent should be withdrawn and not reintroduced where possible. Tendon ruptures may require surgery.

ILIOTIBIAL BAND SYNDROME

The iliotibial band is a thick connective tissue that runs from the ilium to the fibula. Patients with iliotibial band syndrome most commonly present with aching or burning pain at the site where the band courses over the lateral femoral condyle of the knee; pain may also radiate up the thigh, toward the hip. Predisposing factors for iliotibial band syndrome include a varus alignment of the knee, excessive running distance, poorly fitted shoes, or continuous running on uneven terrain. Treatment consists of rest, NSAIDs, physical therapy, and addressing risk factors such as shoes and running surface. Glucocorticoid injection into the area of tenderness can provide relief, but running must be avoided for at least 2 weeks after the injection. Surgical release of the iliotibial band has been helpful in rare patients for whom conservative treatment has failed.

ADHESIVE CAPSULITIS

Often referred to as "frozen shoulder," adhesive capsulitis is characterized by pain and restricted movement of the shoulder, usually in the absence of intrinsic shoulder disease. Adhesive capsulitis most often develops in the setting of reduced arm mobility following bursitis or tendinitis of the shoulder, fractures, or recovery from surgery but can occur without an antecedent event. It has been associated with systemic disorders such as diabetes mellitus, chronic pulmonary disease, myocardial infarction, and thyroid disease. Pathologically, the capsule of the shoulder is thickened, and a mild chronic inflammatory infiltrate and fibrosis may be present.

Adhesive capsulitis occurs more commonly in women aged >50 years. Pain and stiffness usually develop gradually but progress rapidly in some patients. Night pain is often present in the affected shoulder, and pain may interfere with sleep. The shoulder is tender to palpation, and both active and passive movements are restricted. Radiographs of the shoulder show osteopenia. The diagnosis is typically made by physical examination but can be confirmed if necessary by arthrography, in that only a limited amount of contrast material, usually <15 mL, can be injected under pressure into the shoulder joint.

In most patients, the condition improves spontaneously 1–3 years after onset. While pain usually improves, many patients are left with some limitation of shoulder motion. Early mobilization of the arm following an injury to the shoulder may prevent the development of this disease. Physical therapy provides the foundation of treatment for adhesive capsulitis. Local injections of glucocorticoids and NSAIDs may also provide relief of symptoms. Slow but forceful injection of contrast material into the joint may lyse adhesions and stretch the capsule, resulting in improvement of shoulder motion. Manipulation under anesthesia may be helpful in some patients.

LATERAL EPICONDYLITIS

Lateral epicondylitis, also known as tennis elbow, is a painful condition involving the soft tissue over the lateral aspect of the elbow. The pain originates at or near the site of attachment of the common extensors to the lateral epicondyle and may radiate into the forearm and dorsum of the wrist. The pain usually appears after work or recreational activities involving repeated motions of wrist extension and supination against resistance. Most patients with this disorder injure themselves in activities other than tennis, such as pulling weeds, carrying suitcases or briefcases, or using a screwdriver. The injury in tennis usually occurs when hitting a backhand with the elbow flexed. Shaking hands and opening doors can reproduce the pain. Striking the lateral elbow against a solid object may also induce pain.

The treatment is usually rest along with administration of an NSAID. Ultrasound, icing, and friction massage may also help relieve pain. When pain is severe, the elbow is placed in a sling or splinted at 90° of flexion. When the pain is acute and well localized, injection of a glucocorticoid using a small-gauge needle may be effective. Following injection, the patient should be advised to rest the arm for at least 1 month and avoid activities that would aggravate the elbow. Once symptoms have subsided, the patient should begin rehabilitation to strengthen and increase flexibility of the extensor muscles before resuming physical activity involving the arm. A forearm band placed 2.5–5.0 cm (1–2 in.) below the elbow may help to reduce tension on the extensor muscles at their attachment to the lateral epicondyle. The patient should be advised to restrict activities requiring forcible extension and supination of the wrist. Improvement may take several months. The patient may continue to experience mild pain but, with care, can usually avoid the return of debilitating pain. Occasionally, surgical release of the extensor aponeurosis may be necessary.

MEDIAL EPICONDYLITIS

Medial epicondylitis is an overuse syndrome resulting in pain over the medial side of the elbow with radiation into the forearm. The cause of this syndrome is considered to be repetitive resisted motions of wrist flexion and pronation, which lead to microtears and granulation tissue at the origin of the pronator teres and forearm flexors, particularly the flexor carpi radialis. This overuse syndrome is usually seen in patients aged >35 years and is much less common than lateral epicondylitis. It occurs most often in work-related repetitive activities and also occurs with recreational activities such as swinging a golf club or throwing a baseball. On physical examination, there is tenderness just distal to the medial epicondyle over the origin of the forearm flexors. Pain can be reproduced by resisting wrist flexion and pronation with the elbow extended. Radiographs are usually normal. The differential diagnosis of patients with medial elbow symptoms includes tears of the pronator teres, acute medial collateral ligament tear, and medial collateral ligament instability. Ulnar neuritis has been found in 25–50% of patients with medial epicondylitis and is associated with tenderness over the ulnar nerve at the elbow as well as hypesthesia and paresthesia on the ulnar side of the hand.

The initial treatment of medial epicondylitis is conservative, involving rest, NSAIDs, friction massage, ultrasound, and icing. Some patients may require splinting. Injections of glucocorticoids at the painful site may also be effective. Patients should be instructed to rest for at least 1 month. Also, patients should start physical therapy once the pain has subsided. In patients with chronic debilitating medial epicondylitis that remains unresponsive after at least a year of treatment, surgical release of the flexor muscle at its origin may be necessary and is often successful.

PLANTAR FASCIITIS

Plantar fasciitis is a common cause of foot pain in adults, with the peak incidence occurring in people between the ages of 40 and 60 years. The pain originates at or near the site of the plantar fascia attachment to the medial tuberosity of the calcaneus. Several factors that increase the risk of developing plantar fasciitis include obesity, pes planus (flat foot or absence of the foot arch when standing), pes cavus (high-arched foot), limited dorsiflexion of the ankle, prolonged standing, walking on hard surfaces, and faulty shoes. In runners, excessive running and a change to a harder running surface may precipitate plantar fasciitis.

The diagnosis of plantar fasciitis can usually be made on the basis of history and physical examination alone. Patients experience severe pain with the first steps on arising in the morning or following inactivity during the day. The pain usually lessens with weight-bearing activity only to increase with continued activity. Pain is made worse on walking barefoot or up stairs. On examination, maximal tenderness is elicited on palpation over the inferior heel corresponding to the site of attachment of the plantar fascia.

Imaging studies may be indicated when the diagnosis is not clear. Plain radiographs may show heel spurs, which are of little diagnostic significance. Ultrasonography in plantar fasciitis can demonstrate thickening of the fascia and diffuse hypoechoicity, indicating edema at the attachment of the plantar fascia to the calcaneus. MRI is a sensitive method for detecting plantar fasciitis, but it is usually not required for establishing the diagnosis.

Resolution of symptoms occurs within 12 months in >80% of patients with plantar fasciitis. Initial treatment consists of ice, heat, massage, stretching, and eliminating inciting activities. Orthotics provide medial arch support and can be effective. Some patients may benefit from foot strapping or taping or by wearing a night splint designed to keep the ankle in a neutral position. A short course of NSAIDs can be given to patients when the benefits outweigh the risks. Local glucocorticoid injections have also been shown to be efficacious but may carry an increased risk for plantar fascia rupture. Plantar fasciotomy is reserved for those patients who have failed to improve after at least 6–12 months of conservative treatment.

FURTHER READING

- Buchbinder R: Plantar fasciitis. *N Engl J Med* 350:2159, 2004.
- Greis AC et al: Evaluation and nonsurgical management of rotator cuff calcific tendinopathy. *Orthop Clin North Am* 46:293, 2015.
- Harrison AK, Flatow EL: Subacromial impingement syndrome. *J Am Acad Orthop Surg* 19:701, 2011.
- Kirchgesner T et al: Drug-induced tendinopathy: From physiology to clinical applications. *Joint Bone Spine* 81:485, 2014.
- Neviaser AS, Neviaser RJ: Adhesive capsulitis of the shoulder. *J Am Acad Orthop Surg* 19:536, 2011.