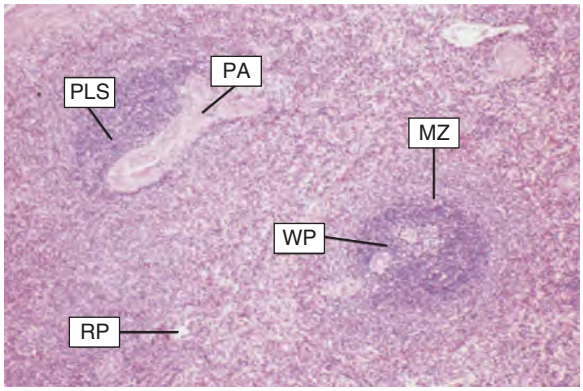

FIG. 311.1 Normal splenic architecture in the adult human. Hematoxylin and eosin stain. *MZ,* Marginal zone; *PA,* penicilliary arteriole; *PLS,* periarterial lymphatic sheath; *RP,* red pulp made up of vascular cords and venous sinuses; *WP,* white pulp. *(From Opal SM. Splenectomy and splenic dysfunction. In: Cohen J, Powderly WG, eds.* Infectious Diseases. *3rd ed. St. Louis: Mosby; 2010.)*

zones, where antigen-presenting cells, bacterial antigens, and T and B lymphocytes are in close proximity, are sites of considerable importance in the coordinated immune response to circulating antigens.[5]

FUNCTION OF THE SPLEEN

The contribution of the spleen to controlling overwhelming infection was first recognized in 1952 by King and Schumacker,[6] who reported life-threatening bacterial infections in splenectomized infants. Since then, the mechanisms by which the spleen combats bacterial infection, such as filtration, phagocytosis, and opsonization of bacteria, as well as regulation of inflammatory responses, have been carefully elucidated. The percentage of $CD8^+$ T cells is higher in the spleen than in the peripheral blood, leading to an inverse splenic CD4/CD8 ratio. Further, both CD4 and CD8 cell populations in the spleen show a higher number of activated cells, and the splenic $CD8^+$ T cells show a more differentiated cytotoxic $CD27^-CD45RA^+$ memory phenotype.[7] The multiple types of immune cells in close approximation within the spleen engage in complex interactions; are subject to the varied effects of autocrine and paracrine signaling; and migrate into, within, and out of the spleen—all contributing to the extraordinary repertoire of innate and adaptive immune responses important in protecting the host against bacterial and parasitic infections.

Regulation of Inflammation

The impact of the spleen on inflammation is evident by the increased production of proinflammatory cytokines during sepsis, which is, in part, mediated by nicotinic acetylcholine receptors in the spleen. This inflammatory response can be dampened by vagal nerve stimulation or the administration of nicotine.[8] In normal mice, administration of nicotine protected from polymicrobial sepsis by decreasing production of the proinflammatory mediator, high mobility group box-1 (HMGB1),[9] but in splenectomized mice, administration of nicotine failed to reduce HMGB1 levels and decreased survival during sepsis.[8] Similarly, although vagal nerve stimulation suppresses tumor necrosis factor (TNF) production in response to endotoxin administration in intact mice, no decrease was noted in splenectomized mice. This decrease in TNF production after vagal nerve stimulation occurs through stimulation of splenic acetylcholine-producing T cells by norepinephrine.[10] These findings suggest that loss of control of inflammation through this newly appreciated inflammatory reflex pathway may play a role in the inflammatory storm seen during postsplenectomy sepsis. Further, cytokines produced by splenic macrophages appear to modulate the febrile response to bacterial components, including lipopolysaccharide.[11]

Filtration and Clearance

The red pulp serves as a filter that provides grooming (antibody removal), pitting (intracellular material removal), and culling (cell destruction) functions to clear the blood of debris. As peripheral blood percolates through the splenic sinusoids, damaged cellular elements, senescent erythrocytes, cell-associated antibodies, circulating unopsonized bacteria, erythrocytes harboring malarial or babesial parasites, and foreign particles are removed, and platelets, erythrocytes, and iron are sequestered. The major defect associated with infectious risk of patients with asplenia or hyposplenia is impaired clearance of poorly opsonized particulate antigens, such as bacteria.[12]

Adaptive Immunity

After exposure of the host to microbial antigens (e.g., through vaccination or bacteremia), T cell–dependent B-cell activation in the spleen begins through antigen interactions with T-helper lymphocytes, stimulating B lymphocytes to rapidly differentiate into either antigen-presenting cells or immunoglobulin M (IgM)-producing plasma cells. After activation in the marginal zone, B and T cells, along with dendritic cells, are attracted to the periarteriolar lymphoid sheath of the splenic white pulp by cell-specific chemokines, where they facilitate T cell–dependent B-cell responses. Activated B cells undergo further maturation and clonal expansion in the splenic germinal centers, where, through contact with activated T cells, they undergo isotype switching into plasma cells capable of producing high-affinity antibodies or switched memory B cells.[13] Antigen-specific plasma cells that have differentiated in the white pulp lodge in the red pulp in close proximity to macrophages, where antigenic sampling occurs. This process is mediated by upregulation of CXC-chemokine receptor 4 (CXCR4), which binds CXC-chemokine ligand 12 (CXCL12) expressed in the red pulp.[14] Generation of IgM and IgG2 antibodies against polysaccharide antigens, which represent largely T-cell–independent responses, occurs in the marginal zone of the spleen and is profoundly compromised by splenectomy.[15]

Innate Immunity

The marginal zone of the spleen is responsible for trapping and processing circulating antigens in the course of peripheral blood circulating through its rich beds of macrophages. Marginal zone macrophages are proficient in processing carbohydrate antigens through lectin receptors on their surfaces and through their scavenger activities. Unlike other B-cell lineages, marginal zone B cells, characterized as IgM^+IgD^+CD27 memory cells, develop during ontogeny and mutate their immunoglobulin receptors during the first years of life without prior engagement in an immune response. On stimulation with thymus-independent polysaccharide antigens expressed by encapsulated bacteria, the prediversified IgM memory B cells of the marginal zone do not differentiate into switched memory cells, but, rather, represent an immediate innate immune defense, as opposed to a memory-dependent adaptive defense, against invading pathogens.[16,17] Thus, in asplenic hosts, this polysaccharide-specific immune function is lost, placing the patients at increased risk of infection with polysaccharide-encapsulated bacteria.

Hematopoiesis/Hemostasis

During the second trimester of fetal life, hematopoiesis actively occurs in the spleen and then wanes in the third trimester, although hematopoietic stem cells remain in the spleen through adult life. In the face of bone marrow failure, such as myelofibrosis, extramedullary hematopoiesis may occur in the spleen with the appearance of erythroid and megakaryocytic, and, to a lesser extent, myeloid precursors. Further, the spleen contributes to hemostasis through the production of factor VIII and von Willebrand factor.[18]

TYPES OF ASPLENIA

Congenital Asplenia

Congenital asplenia is rarely seen as an isolated clinical entity. It is, however, more commonly associated with many types of cyanotic congenital heart disease with heterotaxy, previously known as *Ivemark syndrome,* and is characterized by bilateral right-sidedness in which the liver is central, both lungs have three lobes, and the spleen is reduced in size or absent.[19] The degree of splenic function is variable in these children, dependent on the amount of splenic tissue present. It was traditionally believed that bilateral left-sidedness, characterized by polysplenia, dextrocardia, and other congenital cardiac defects, was not associated with splenic dysfunction, but a recent review of the available

literature suggests that patients exhibiting this defect are also at increased risk for bacteremia.[20]

Acquired Asplenia

The most dramatic and predictable loss of splenic function occurs after surgical splenectomy or splenic infarction secondary to sickled erythrocytes, which progressively develops over the first few years of life,[21] or to other embolic or thrombotic events in the splenic vasculature. Surgical splenectomy may be indicated in patients with severe splenic trauma, patients with intractable immune-mediated thrombocytopenia or anemia, patients with spherocytosis, or to relieve the effects of hypersplenism in patients with splenomegaly. Accessory spleens, present in up to 15% of patients at autopsy, may contribute to persistent immune cytopenias after splenectomy. Partial splenectomy, with retention of splenic immune function, may be an option in some patients with splenic trauma,[22] such as those who are hemodynamically stable and require fewer than two units of erythrocytes for resuscitation. The ability of either accessory spleens or residual splenic tissue to protect against severe infections in splenectomized patients is unclear, although overwhelming infections have been reported in both patients with accessory spleens and those with various amounts of residual splenic tissue.[23] In patients with hemoglobinopathies the greatest splenic dysfunction, which ultimately leads to splenic atrophy and asplenia, occurs in those with homozygous sickle cell anemia, followed sequentially by hemoglobin S/β-thalassemia major disease, hemoglobin SC disease, and hemoglobin S/β-thalassemia intermedia.

Acquired Hyposplenia

Functional hyposplenism related to impaired function of the splenic macrophage-associated Fc receptors may be associated with a variety of immunologic, rheumatologic, and inflammatory disorders (Table 311.1).[24,25] Those at particular risk include patients with graft-versus-host disease after bone marrow/stem cell transplantation, patients with human immunodeficiency virus (HIV) infection, and those with celiac disease. In the late stages of HIV–acquired immunodeficiency syndrome, atrophy of lymphoid follicles and T-cell depletion contribute to hyposplenism. Approximately a third of patients with celiac disease demonstrate impaired splenic function, and increased susceptibility to severe pneumococcal infection is seen among those with premalignant or malignant complications, concomitant autoimmune disorders, or thromboembolism, and among the elderly.[26] Further, splenic function is also compromised by a variety of medical therapies.[27] For example, corticosteroid treatment impairs the affinity of Fc receptors on splenic macrophages for opsonized IgG to a greater extent than hepatic, pulmonary, and bone marrow macrophages. Further, intravenous (IV) immune globulin decreases the phagocytic function of the spleen temporarily by binding to Fc receptors and impeding its recognition of opsonized particles. Although ionizing radiation does not affect phagocytic cells, it has a particularly profound, albeit transient, dose-dependent effect on T and B cells.

ASSESSMENT FOR SPLENIC FUNCTION

Splenic function is most simply assessed by examination of a peripheral smear for presence of the particulates normally filtered by the spleen. Such findings include red cells containing Howell-Jolly bodies (basophilic DNA remnants of red cell precursors), Pappenheimer bodies (abnormal iron granules), or presence of pitted or pocked red cells by phase-contrast microscopy (Fig. 311.2). The percentages of both pocked and pitted cells have been used to predict splenic function; normally, individuals possess less than 2% of these cells, but splenectomized patients possess up to 60%, and hyposplenic patients have intermediate values.[28,29] Percentages of red cells possessing Howell-Jolly bodies, which are present when the spleen is largely nonfunctional, is somewhat less sensitive than percentages of pocked or pitted cells.[28] With further validation, the number of IgM memory B cells, which correlates with functional splenic volume, may be a valuable parameter to assess splenic function.[16,30]

A variety of imaging studies may be useful in defining the presence, size, and, occasionally, function of the spleen. Abdominal ultrasonography and computed tomography scans can describe the size and position of the spleen, whereas radionuclide scintigraphy, which assesses phagocytic uptake of technetium-99m sulfur colloid, assesses anatomic features and correlates with phagocytic and immunologic function.[30,31] In a study using radionuclide scintigraphy in patients older than 18 years, all patients homozygous for sickle cell disease were asplenic, and heterozygous patients showed increased anatomic splenic volumes but decreased functional splenic volumes. In patients with splenosis (i.e., ectopic splenic tissue implanted in the abdomen after traumatic splenic rupture) or patients with accessory spleens that were retained after splenectomy, the immunologic defects related to splenic dysfunction are difficult to access, and overwhelming sepsis has been described in patients with documented residual splenic tissue.[23]

The immunologic defects associated with asplenia or hyposplenia reflect impairment of the many normal immunologic functions of the spleen, including compromised clearance of circulating bacteria, decreased opsonization of bacteria, impaired phagocytosis, and dysregulation of inflammatory responses (Table 311.2).

Epidemiology and Risk Factors of Sepsis in Asplenic Patients

Although sepsis related to reduced splenic function is relatively rare, when it occurs it often progresses rapidly to overwhelming, severe sepsis and may result in a fatal outcome. Risk factors for severe infection in asplenic patients include age (both very young and old age); indication for, and time since, splenectomy; underlying diseases or medical conditions; and vaccine status (Tables 311.3 to 311.5). In a large Danish

TABLE 311.1 Medical Conditions Associated With Functional Hyposplenism

MEDICAL CONDITION	PREVALENCE OF HYPOSPLENISM	DEGREE OF HYPOSPLENISM	STRENGTH OF EVIDENCE FOR RISK OF SEPSIS
Sickle cell anemia	100%	Severe	+++
Graft-versus-host disease	15%–40%	Moderate to severe	+++
Celiac disease	33%–76%	Moderate to severe	+++
Human immunodeficiency virus–acquired immunodeficiency syndrome	36%	Moderate to severe	+++
Alcoholic liver disease	37%–100%	Moderate to severe	+++
Inflammatory bowel disease Ulcerative colitis Crohn disease	 35%–45% 9%–37%	 Moderate Mild	++
Primary amyloidosis	28%	Moderate	++
Systemic lupus erythematosus	5%–7%	Mild to moderate	++

++, Moderate evidence; *+++*, strong evidence.
Modified from Di Sabatino A, Carsetti R, Corazza GR. Post-splenectomy and hyposplenic states. Lancet. *2011;378:86–97.*

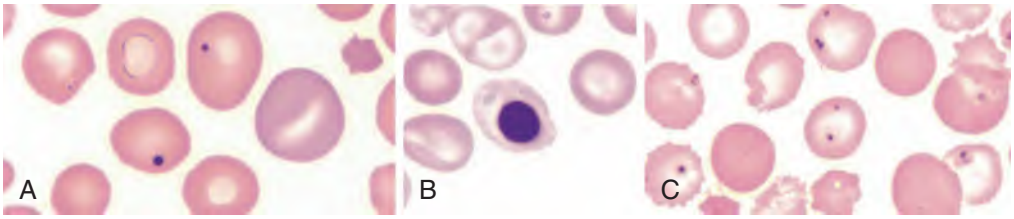

FIG. 311.2 Red cell findings in hyposplenism. (A) Red blood cells with Howell-Jolly bodies, which are cytoplasmic inclusions composed of nuclear remnants, as seen in patients with hyposplenism. (B) Nucleated red blood cell that occurs during red cell maturation but is typically cleared by a normal spleen. (C) Red blood cells with Pappenheimer bodies, which are siderotic granules that are irregular in shape and frequently multiple within a cell. *(From Connell NT, Shurin SB, Schiffman FJ. The spleen and its disorders. In: Hoffman R, Benz EJ Sr, Silberstein LE, eds.* Hematology: Basic Principles and Practice. *6th ed. Philadelphia: Saunders; 2012:2259.)*

TABLE 311.2 Immunologic Defects After Splenectomy

DEFECT	MECHANISM
Decreased clearance of unopsonized bacteria	Depleted red pulp macrophages
Decreased clearance of cell-associated antibodies	Depleted red pulp macrophages
Decreased clearance of erythrocytes harboring malarial or babesial parasites	Depleted red pulp macrophages
Decreased processing of carbohydrate antigens	Depleted marginal zone macrophages
Decreased B-cell activation	Depleted marginal zone T cells
Decreased IgG2 and IgM antibodies	Depleted B cells in the germinal centers
Decreased CXC-chemokine ligand 12	Depleted CXC-chemokine receptor 4
Increased tumor necrosis factor	Depleted splenic nicotinic acetylcholine–producing T cells
Decreased recognition of pathogen-associated molecular patterns	Decreased Toll-like receptor networks in marginal zone macrophages
Decreased macrophage scavenger function	Decreased macrophage receptor with collagenous structure in marginal zone macrophages

CXC, Cysteine-X-cysteine (motif); *IgG2,* immunoglobulin G2; *IgM,* immunoglobulin M.

TABLE 311.3 Risk Factors for Hyposplenia/ Postsplenectomy Sepsis

RISK FACTOR	MECHANISM
Young age	Immune immaturity and naïveté
Old age	Immune senescence, comorbidities
Time since splenectomy	Risk at 0–90 days > 91–365 days > more than 1 year
Indication for splenectomy: splenectomy 2° to immune cytopenias > 2° to trauma > 2° to incidental	Unknown immune dysfunction associated with immune cytopenias
Hemoglobinopathies	Splenic infarction
Lack of appropriate vaccines	Impaired acquired immunity
Immunosuppressive drugs	Immunosuppression
Human immunodeficiency virus–acquired immunodeficiency virus	Immunosuppression
Amyloidosis/sarcoidosis	Splenic infiltration
Autoimmune diseases	Innate immunosuppression
Splenic radiation	Impaired splenic function

TABLE 311.4 Rates of Postsplenectomy Infection Requiring Hospitalization

SUBJECTS	INFECTIONS PER 100 PERSON-YEARS (95% CI)
Adults + children	7 (6.3–7.78)[a]
0–16 yr	2.94 (1.74–4.96)
17–29 yr	2.66 (1.82–3.88)
30–49 yr	5.35 (4.11–6.97)
50–59 yr	7.46 (5.84–9.49)
60–69 yr	11.07 (8.89–13.80)
70+ yr	13.85 (11.24–17.07)
Male	6.48 (5.61–7.48)
Female	7.72 (6.63–8.90)

[a]Infections >28 days after splenectomy.
CI, Confidence interval.
Modified from Kyaw MH, Holmes EM, Toolis F, et al. Evaluation of severe infection and survival after splenectomy. Am J Med. *2006;119:276.e1–276.e7.*

National Patient Registry[32] the overall rate of any infection requiring hospital care among splenectomized patients was 7.7 per 100 person-years compared with 2 per 100 person-years in the general population. The relative frequency of sepsis associated with hyposplenism or splenectomy among various groups of patients, however, is difficult to accurately assess, because the many studies include patients of different ages, vaccination status, indications for splenectomy, and underlying diseases leading to hyposplenism. Nevertheless, the risk of sepsis is clearly dependent on the age of the patient (see Table 311.4). Overall, children younger than 16 years have the same risk of sepsis associated with splenectomy or asplenia as young adults, although infants are at higher risk. Among patients with hemoglobinopathies the risk is greater for children than adults. In splenectomized adults the risk for severe infection increases among patients older than 50 years, with the highest risk among those older than 70 years.[33] The risk of sepsis is also dependent on the underlying disease associated with hyposplenism and with the indication for splenectomy (see Table 311.5).[2,32,34] Posttraumatic splenectomy is associated with a lower rate of sepsis than splenectomy due to hematologic abnormalities,[33] possibly due to regeneration of splenic tissue after posttraumatic splenectomy. Such regenerated splenic tissue, however, is histologically and functionally different from normal spleen tissue, and its ability to protect against sepsis may be limited.[35]

TABLE 311.5 Relative Risk of Postsplenectomy Infection Requiring Hospitalization by Indication

CLINICAL INDICATION FOR SPLENECTOMY AND DAYS SINCE SPLENECTOMY	RELATIVE RISK (95% CI) VERSUS GENERAL POPULATION	RELATIVE RISK (95% CI) VERSUS NONSPLENECTOMIZED CONTROLS
Any Indication		
<90 days	18.1 (14.8–22.1)	1.7 (1.5–2.1)
91–365 days	4.6 (3.8–5.5)	1.5 (1.2–1.8)
>365 days	2.5 (2.2–2.8)	1.2 (1.1–1.4)
Idiopathic Thrombocytopenic Purpura		
<90 days	14.8 (5.1–43.2)	2.6 (1.3–5.1)
91–365 days	14.2 (4.3–46.1)	1 (0.5–2)
>365 days	4 (2.8–5.6)	1.4 (1–2)
Hereditary Hemolytic Anemia		
<90 days	31.5 (6.4–153.7)	3.6 (1.1–12.5)
91–365 days	4.3 (1.4–13.4)	1 (0.4–2.6)
>365 days	4.0 (2.3–7.2)	1.1 (0.6–1.9)
Trauma		
<90 days	21.2 (12.8–35.1)	0.8 (0.5–1.2)
91–365 days	3.4 (2–5.9)	1.4 (0.6–2.9)
>365 days	2.5 (2–3.3)	1.3 (0.9–1.9)

CI, Confidence interval.
Modified from Thomsen RW, Schoonen WM, Farkas DK, et al. Risk for hospital contact with infection in patients with splenectomy: a population-based cohort study. Ann Intern Med. *2009;151:546–555.*

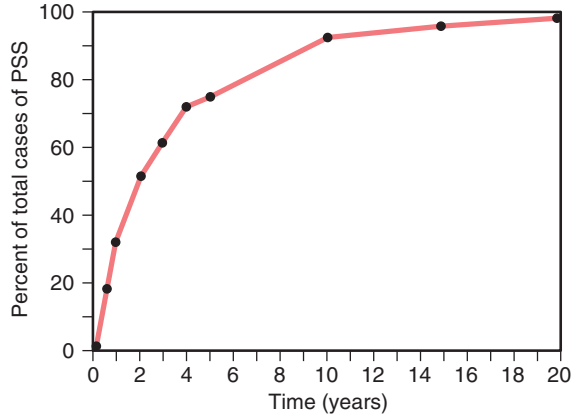

FIG. 311.3 Cumulative incidence of first severe infection after splenectomy. *PSS,* Postsplenectomy sepsis. *(Data from Kyaw MH, Holmes EM, Toolis F, et al. Evaluation of severe infection and survival after splenectomy.* Am J Med. *2006;119:276.e1–276.e7.)*

Hemoglobinopathy imparts a relatively high risk of sepsis, and patients with sickle cell anemia or thalassemia major are three to four times more likely to experience sepsis episodes compared with patients with splenectomy secondary to trauma.[34] Comorbidities among patients with hemoglobinopathies, such as decreased complement activation, immunoglobulin deficiency, cardiopulmonary illnesses, and hemochromatosis, may further increase their risk of infection.[36,37] The risk of subsequent episodes of postsplenectomy sepsis increases after each episode, with the risk of a second episode 6-fold higher than the first and the risk of a third episode 14-fold higher than the first.[33] The risk of sepsis is greatest during the first 3 years after splenectomy, with greatest rates during the first 3 months, and decreases significantly beyond 8 to 10 years after splenectomy (Fig. 311.3).[32,38] In general, young age predicts a shorter interval between splenectomy/hyposplenism and sepsis, but these data may be confounded by different reasons for splenic failure.

Although the incidence of overwhelming infection in asplenic/hyposplenic patients is low, the mortality rate is high, reportedly up to 50% and 70%.[34,38,39] Most recent data suggest that children are overall at lower risk of sepsis-associated death (<5% cumulative over 10 years) than older patients,[33] likely because of the impact of pneumococcal and *Haemophilus influenzae* type b (Hib) vaccines and advanced intensive care support in children, and because of increased comorbid conditions in older adults. Kyaw and colleagues[33] showed overall cumulative 1- and 5-year mortality rates of 10% to 40% and 20% to 70%, respectively, in adult splenectomized patients, with increased mortality rates in patients at increased age at the time of splenectomy. Recent data from Denmark documented the overall adjusted relative risk of death during the first 90 days after splenectomy to be 30-fold higher than in the general population.[40] This high mortality rate nearly disappeared, however, when controlled for morbidities associated with clinically similar patients who did not undergo splenectomy, suggesting that most of the mortality risk is associated with the indication for splenectomy rather than the splenectomy itself.

As in all postoperative patients, those undergoing splenectomy are at risk of immediate postoperative infections of the respiratory and urinary tracts or at operative sites. Patients requiring incidental splenectomy are at reduced risk of immediate postsplenectomy sepsis than those with splenectomy related to trauma because of the increased rate of postoperative infections, in general, among patients after severe trauma.[41] Because of the additive risks of spleen removal and general surgical infection, patients who undergo spleen-sparing management after splenic trauma may have lower rates of infection than those undergoing splenectomy.[42,43]

CLINICAL PRESENTATION OF SEPSIS SECONDARY TO ASPLENIA

In light of the important role the spleen plays in several immune pathways, patients with asplenia or hyposplenia are at risk of fulminating, severe, and sometimes fatal bacterial infections. Infected asplenic patients generally exhibit higher fevers than infected eusplenic patients,[44] so fever in splenectomy patients, irrespective of specific symptoms localized to the skin or respiratory or gastrointestinal tracts, must be assumed to represent bacterial systemic infection until proven otherwise. In splenectomized patients, decreased opsonization and phagocytosis of bacteria allows the microbes to proliferate to a level that exceeds the rate of removal, thus promoting and sustaining intravascular infections.[12] Because of dysregulation of the innate and adaptive immune systems,

low-level bacteremia may rapidly (over several hours) lead to high-level bacteremia with acute onset of high fever, rigors, acute respiratory distress, hypotension, coagulation defects, cardiovascular collapse, or a combination of these. Kyaw and colleagues[33] showed that 3% of splenectomized patients developed at least one episode of overwhelming infection, and more than a third of those had two or more subsequent severe infections. Endovascular damage related to overwhelming sepsis may lead to purpura fulminans with resulting gangrene of the extremities. In a study from the United Kingdom, 78 (68%) of the 114 deaths from postsplenectomy sepsis occurred within 24 hours of the onset of symptoms, and a further 13 (22%) patients died within 48 hours of the first symptoms.[38] Among patients who died of postsplenectomy sepsis, adrenal hemorrhage was seen in 39%, and disseminated intravascular coagulation (DIC) was seen in 14.6%. After bacteremia, metastatic sites of infection in asplenic patients may occur, such as septic arthritis, pericarditis, or meningitis, and are more prevalent in young children.

MICROBIAL AGENTS CAUSING POSTSPLENECTOMY SEPSIS

Bacteria

The specific immunologic defects that reduce the formation of antibodies to polysaccharide antigens in asplenic or hyposplenic patients place them at greatest risk of infection with encapsulated bacteria, historically *Streptococcus pneumoniae,* Hib, and *Neisseria meningitidis*. Infections with nontypeable and non-b encapsulated *H. influenzae* strains (i.e., types a and c–f) are not reported to be increased among splenectomy patients. The amount of polysaccharide capsule expressed by the bacteria may contribute to the risk of infection, as noted by the case of a splenectomized adult infected with a strain of *H. influenzae* possessing six copies of the *cap b* gene locus[45]; most type b strains possess two copies of the locus. No specific capsular serotype appears to predominate among *S. pneumoniae* strains associated with postsplenectomy sepsis.[46] *Neisseria meningitidis* has classically been listed as an important cause of sepsis in splenectomized patients, but this assertion has been questioned because few cases have been reported and, in one study, none of 10 splenectomized pediatric patients with meningococcemia had received splenectomy secondary to trauma, suggesting that previously reported meningococcal infections may have been related to the underlying illnesses, necessitating splenic removal rather than splenectomy itself.[47] Experimental data in mice supported this conclusion.[47]

Most data on the bacteria associated with severe infections in asplenic or hyposplenic patients were obtained before widespread use of prophylactic antibiotics or conjugated vaccines against these agents. More recent data obtained from 1998–2006 in Australia and from 1973–2009 in Israel [48,49] report that gram-negative bacilli and *Staphylococcus aureus* were the most common causes of postsplenectomy infections. These findings may depend on vaccination rates in the studied population, for in a recent prospective study from Germany, *S. pneumoniae* remained the major cause of overwhelming postsplenectomy infections, but, the reported vaccination rate was only 42% in this population (21% within the prior 5 years).[50] Thus the current increasing use of *S. pneumoniae* vaccines among adults, as well as the widespread use of protein-conjugated *S. pneumoniae* and *H. influenzae* vaccines in children in the United States, may modulate both the rates of postsplenectomy sepsis and the spectrum of the implicated bacteria.

Unusual gram-negative bacteria have also been associated with infections in asplenic or hyposplenic patients. Splenectomy is a strong risk factor for infections caused by *Capnocytophaga canimorsus,* the bacteria previously known as Centers for Disease Control and Prevention (CDC) group DF2 and associated with dog bites or scratches.[51] Between 20% and 39% of infected patients had undergone splenectomy.[52,53] Among patients with *Bordetella holmesii* bacteremia, 85% were anatomically asplenic.[54] Severe *Salmonella* infection is associated with hyposplenism secondary to splenic infarction in patients with sickle cell anemia but is not associated with overwhelming postsplenectomy sepsis. Postoperative infection after incidental splenectomy is usually caused by *S. aureus,* group A streptococci, or enteric gram-negative bacteria, as is reported in postoperative infections in general. A large number of other organisms have been implicated in postsplenectomy sepsis by single-case reports, but the true meaning of these associations is unclear.

Protozoa

The human spleen plays an important role in the clearance of parasite-infected red blood cells (RBCs) by filtering erythrocytes that are poorly deformable. Although classically transmitted by ticks, *Babesia microti,* which is endemic in the northeastern and upper midwestern regions of the United States, has been transmitted to asplenic patients through blood transfusion.[55] Asplenic patients with babesiosis experience high-grade parasitemia and develop more severe disease associated with significant hemolysis.[56] Similarly, in splenectomized patients with *Plasmodium falciparum* primary infection, parasitemia levels are higher, mature forms circulate more frequently, and disease severity and death rates are increased[57] compared with malaria in nonsplenectomized patients. In addition, cerebral malaria is frequent after splenectomy and likely reflects poor parasite clearance. In splenectomized patients who are immune to malaria (by nature of living in highly endemic areas), however, antibodies to the surface adhesins of mature parasites impede the sequestration of infected erythrocytes in the microcirculation, thereby preventing severe complications of malarial infection. During acute malaria in otherwise healthy people, previously parasitized erythrocytes that no longer contain a malarial parasite, the so-called ring-infected erythrocyte surface antigen (RESA)-RBCs that result after cleansing of the infected cells by the spleen, are found in the circulation. In splenectomized patients with falciparum malaria, however, these forms are not present, which highlights the importance of the filtration function of the spleen in clearing malarial-infected erythrocytes.[58] Acute *P. falciparum* malaria has been described in a chronic malaria carrier no longer exposed to *P. falciparum* and was attributed to loss of splenic clearance of adhesin-defective malarial variants, resulting in an acute clinical attack. Even in the face of adequate antimalarial treatment, parasite clearance was significantly delayed in a splenectomized patient, whose parasite burden of 63% decreased to only 30% after 13 days of treatment.[59] In addition to those infected with red cell parasites, asplenic patients infected with *Anaplasma phagocytophilum* (the causative agent of human granulocytic ehrlichiosis) exhibit recurrent, prolonged, or severe infections.[60]

DIAGNOSIS OF POSTSPLENECTOMY SEPSIS

The single most valuable diagnostic test in evaluating a patient with suspected postsplenectomy sepsis is the blood culture (Table 311.6). As a result of impaired bacterial clearance in the absence of normal splenic function, the bacterial burden in the blood of asplenic patients can be so high that organisms may be seen on blood smear or on Gram stain of the buffy coat. The blood cultures usually become positive quickly, often within hours of incubation. Antimicrobial susceptibility analysis of organisms isolated on blood culture is important for choosing the most appropriate antibiotics for definitive treatment. Bacterial culture of purpuric skin lesion aspirates may also yield positive results, and the complete blood count offers important immediate information on the risk of bacterial infection. The neutrophil count in the peripheral blood may be elevated or depressed during postsplenectomy sepsis, dependent on the ability of the infected host to adequately mount a white cell response in the face of overwhelming sepsis. The differential count often shows a high prevalence of band forms or other immature cells, such as myelocytes or metamyelocytes, indicating massive demargination and recruitment of developing neutrophils from the bone marrow. Peripheral white cells may show toxic granulations or Döhle bodies, or both. Peripheral red cells often show manifestations of reduced filtration of damaged erythrocytes, such as Howell-Jolly bodies, and pitted or pocked red cells. Thrombocytopenia is a sign of DIC from serious infection, as is the presence of schistocytes on the peripheral smear.

Other laboratory abnormalities associated with postsplenectomy sepsis and indicative of multiorgan failure include coagulation abnormalities associated with DIC, elevated creatinine, and elevated aminotransferases. Hypoxemia, hypocarbia, and mixed metabolic acidosis and respiratory alkalosis may be seen on blood gas analysis. Cerebrospinal fluid analysis may reveal leukocytosis indicative of bacterial meningitis, although bacteria may be present in early, rapid-onset meningitis before leukocytosis is evident.

TABLE 311.6 Diagnostic Tools to Assess Asplenic Patients for Infection

TEST	RESULT
Blood culture	Positive, often within hours, in the absence of prior antibiotic therapy
Culture of purpuric skin lesions	May be positive
White blood cell count	Elevated or depressed, with a marked shift to the left. Cells may show toxic granulations or Döhle bodies
Peripheral smear	Evidence of asplenia (Howell-Jolly bodies, pitted or pocked red cells). Circulating bacteria may be seen
Lumbar puncture	Elevated white blood cell count indicates meningitis. Culture is positive in the absence of prior antibiotic therapy
Chest radiograph	May show evidence of myocarditis or pneumonia
Coagulation studies	May support DIC
Platelet count	May be depressed with overwhelming sepsis and DIC
Creatinine	May be elevated with multiorgan failure
Hepatic enzymes	May be elevated with multiorgan failure
Blood gases	May indicate metabolic acidosis or respiratory alkalosis, or both

DIC, Disseminated intravascular coagulation.

TABLE 311.7 Antibiotic Management Options for Sepsis in Asplenic Patients

CLINICAL SITUATION	DRUGS, ADULT DOSES
Empirical: patient self-administered at onset of fever (before immediate visit to an emergency facility)	Amoxicillin-clavulanate 875 mg PO (q12h) *or* Cefuroxime 500 mg PO (q12h) *or* Levofloxacin 750 mg PO (q24h) *or* Moxifloxacin 400 mg PO (q24h)
Empirical: physician's office (before immediate visit to an emergency facility)	Ceftriaxone 2 g IM or IV *or* Levofloxacin 750 mg PO or IV *or* Moxifloxacin 400 mg PO or IV
Empirical: emergency medical facility	Vancomycin 15-20 mg/kg IV q12h *plus* Ceftriaxone 2 g IV q12h *or* Levofloxacin 750 mg IV q24h *or* Ciprofloxacin 400 mg IV q12h
Definitive: pathogen recovered	Appropriate antibiotic based on culture and antibiotic susceptibility testing

IM, Intramuscular; *IV,* intravenous; *PO,* orally.

MANAGEMENT OF POSTSPLENECTOMY SEPSIS

Because of the potential for rapidly developing severe and sometimes fatal infections in patients with asplenia or hyposplenia, such patients must be counseled to seek immediate medical attention at the first signs of infection, such as fever and chills, and to communicate their asplenic status to the medical personnel (Table 311.7). The risk of rapidly progressive systemic infection in these patients has led some experts to recommend patient-administered, empirical, high-dose oral antibiotics at the onset of fever, especially in the first several years after splenectomy, with the strong recommendation that the patient proceed immediately to an urgent care medical facility. Suggested antibiotics, kept in the patient's home, include amoxicillin-clavulanate, cefuroxime, or extended-spectrum fluoroquinolones. Prescriptions for these empirical antibiotics must be renewed annually to prevent outdating of the drugs.

If an asplenic/hyposplenic patient presents to a physician's office with symptoms of suspected sepsis, the patient should receive intramuscular or IV third-generation cephalosporin or, if β-lactam allergic, oral or IV extended-spectrum fluoroquinolone. Ideally, these drugs should be administered after a blood culture is obtained, but if blood culture is not immediately feasible, the drugs should be administered anyway to prevent delay in initiating antibiotic treatment.

Asplenic/hyposplenic patients with suspected sepsis should be evaluated at a full-service emergency medical facility as soon as the symptoms of a possible infection are recognized. Blood cultures should be obtained and empirical antibiotic therapy begun immediately, even before obtaining other diagnostic tests. Effective antibiotics include vancomycin plus either a third-generation cephalosporin, such as ceftriaxone, or an extended-spectrum fluoroquinolone. Fluoroquinolones may be used in children of all ages when indicated. The patient should then be hospitalized for continued antibiotic treatment and should be carefully monitored for evidence of vascular collapse and multiorgan failure. Blood culture and antibiotic susceptibility results will guide subsequent antibiotic choice. If the patient does not appear to respond to the antimicrobial treatment, an empirical change in antibiotic or initiation of an additional antibiotic may be warranted, although the poor clinical response may be due to uncontrolled sepsis with vascular collapse and multiorgan failure rather than antibiotic failure. Supportive care may require inotropic support and mechanical ventilation. Adjunctive dexamethasone therapy has been shown to reduce neurologic complications and case fatality rates when given early in treatment of adults with *S. pneumoniae* meningitis,[61,62] but no data are available to support its use in postsplenectomy sepsis without meningitis. Other adjunctive therapies targeting host immune responses have been studied in patients with sepsis in general, and to date none have been shown to be effective and without significant side effects.

Patients with documented accessory spleens or residual splenic tissue after partial splenectomy may remain at risk of overwhelming sepsis and should be managed similarly to other asplenic patients. Absence of Howell-Jolly bodies in their peripheral smears does not predict protection by the remaining splenic tissue against infection.

PREVENTION OF POSTSPLENECTOMY SEPSIS

Because the outcome of sepsis in asplenic/hyposplenic patients may be devastating, preventing such infections is paramount to good medical care (Tables 311.8 and 311.9). Recent studies have shown that spleen-sparing approaches to splenic injury, such as surgical repair, may be successful in patients with grades 1 to 3 blunt splenic trauma,[63] and this approach led to no difference in risk of immediate postoperative sepsis (18.3%) compared with similar patients who underwent total splenectomy(18.5%).[43] The risk of sepsis outside the immediate postoperative period is not, however, well defined for patients undergoing partial splenectomy, so sepsis prevention strategies should be the same for this group of patients as those undergoing total removal of the spleen. Overwhelming sepsis in patients with documented splenosis after traumatic spleen injury has been documented.[23]

Prophylactic Antibiotics

Daily oral antibiotics have been shown to reduce the incidence of sepsis in children with all-cause splenectomy by 47% and the incidence of mortality by 88%.[64] Further, daily oral penicillin reduced the incidence of *S. pneumoniae* bacteremia by 85% in children with sickle cell anemia and functional hyposplenism.[65] It should be noted that these studies were conducted before the recent increase in penicillin resistance in *S. pneumoniae* and before widespread use of conjugated pneumococcal vaccines. Nevertheless, children with asplenia or hyposplenia should receive oral antibiotic prophylaxis with penicillin VK (125 mg, twice a day, for children younger than 3 years and 250 mg, twice a day, for children 3 years old and older) or amoxicillin (20–40 mg/kg/day). Experts in the United States recommend daily prophylaxis with β-lactam antibiotics in children with sickle cell anemia up to 5 years of age and for at least 1 year after

TABLE 311.8 General Strategies to Prevent Specific Severe Infections and Sepsis in Splenectomized Patients

STRATEGY	COMMENTS
Avoid splenectomy	Spleen-sparing approaches to splenic trauma are being increasingly considered
Educate patients of their risks	Should be reinforced at each medical encounter
Create warnings of sepsis risk in the medical record	Should be readily available to all health care providers
Medic-Alert bracelet	Should be considered in all patients, especially those who travel
Antibiotic prophylaxis	Used in children primarily
Empirical self-administered antibiotic therapy in the home	Needs to be represcribed annually to avoid outdated drugs
Immunization	Should be discussed at each medical encounter and boosters given as recommended

TABLE 311.9 Specific Strategies to Prevent Severe Infections in Splenectomized Patients

INFECTION/AGENT	PREVENTION STRATEGY
Bacteria	Antibiotic prophylaxis (penicillin VK or amoxicillin) in children <age 5 yr; survivors of previous sepsis; immunosuppressed patients
Streptococcus pneumoniae	*Infants:* PCV13 at 2, 4, 6, and 12–15 mo; influenza vaccine annually ≥6 mo of age *Children:* PPSV23 at ≥2 yr, with revaccination after 5 yr; if nonvaccinated, PCV13 one dose 8 wk before PPSV23; influenza vaccine annually *Adults*: PCV13 followed in 8 wk by PPSV23, with one-time PPSV23 revaccination after 5 yr; influenza vaccine annually
Haemophilus influenzae	*Infants:* Hib vaccine at 2, 4, (6), and 12–15 mo *Children:* Hib vaccine 1 dose 2 wk presplenectomy *Adults:* Hib vaccine 1 dose 2 wk presplenectomy
Neisseria meningitidis	*Infants (6 wk–18 mo):* Men-ACYW-CRM at 2, 4, 6, and 12–15 mo. MenACYW 3 yr after completion of infant schedule. *Children >2 yr and adults* MenACYW two doses, revaccinate every 5 yr. MenACYW-D must be given at least 4 weeks after PCV-13 administration. *Children and adults 10–25 yr:* MenB, two or three doses
Babesiosis	Vector avoidance in endemic regions
Malaria	Vector avoidance in endemic regions, malaria prophylaxis
Human granulocytic ehrlichiosis	Vector avoidance in endemic regions
Capnocytophaga canimorsus	Avoidance of dog bites and scratches

Hib, Haemophilus influenzae type b; *Men,* meningococcal; *MPSV4,* meningococcal polysaccharide vaccine 4; *PCV13,* pneumococcal conjugate vaccine 13; *PPSV23,* plain polysaccharide vaccine 23.

splenectomy.[66] Asplenic and highly immunocompromised patients, as well as those with thalassemia and previous episodes of sepsis, may benefit from prophylaxis until age 18 years or for life. Patients with penicillin allergies manifested by nonurticarial rash and without anaphylaxis may be given first-generation oral cephalosporins, and children older than 8 years of age and adults may receive doxycycline. Other options are less attractive and less well studied but include oral clindamycin or oral fluoroquinolones; *S. pneumoniae* are increasingly resistant to macrolides and trimethoprim-sulfamethoxazole, but erythromycin (250 mg, twice a day) continues to be recommended by many experts.[66]

Patients and their families must be counseled to the limitations of prophylactic antibiotics in preventing infections in asplenic patients because of possible antibiotic resistance. The value of prophylactic antibiotics may also be compromised by poor compliance. Only 40% of splenectomized patients who received prescriptions for prophylactic penicillin demonstrated penicillin in their urine,[67] so additional prevention strategies and reinforcement of the implemented strategies are necessary to reduce the risk of postsplenectomy sepsis.

Antibiotics are indicated for dental prophylaxis in children after splenectomy[68] but are controversial in adults because of lack of strong supporting evidence.[69]

Vaccines

Vaccination against encapsulated bacteria is a mainstay of prevention against overwhelming sepsis in asplenia/hyposplenia patients. These vaccines should be administered at least 14 days before planned splenectomy to assure an adequate immune response, although they may be of some value when given shortly after splenectomy.[70] In patients receiving immunosuppressive chemotherapy or radiation therapy, the vaccines should be delayed until at least 3 months after completion of the treatment to assure optimal efficacy.[71]

Two vaccines targeting *S. pneumoniae* are available in the United States (see also Chapter 316). Plain polysaccharide vaccine (PPSV23) contains 23 pneumococcal capsular polysaccharides and is immunogenic in adults and children older than 2 years. Pneumococcal conjugate vaccine 13 (PCV13) contains the 13 pneumococcal polysaccharides most common in invasive *S. pneumoniae* infections in the United States conjugated to protein carriers, thus theoretically improving the magnitude and duration of immunoprotection. PCV13 is immunogenic in children older than 6 weeks of age and is routinely recommended for all children in the United States at 2, 4, 6, and 12 to 15 months.

All young children, including those with asplenia or hyposplenia, should receive the four-dose series of PCV13 beginning at age 2 months as routinely recommended.[72] For inadequately immunized children younger than 6 years who have not received the full routine vaccine series, catch-up vaccination should follow the recommendations of the American Academy of Pediatrics and the Advisory Committee on Immunization Practices (ACIP) of the CDC,[71] which are updated annually (www.cdc.gov/vaccines/acip/index.html). In addition, asplenic and hyposplenic children 6 to 18 years of age who have not received pneumococcal immunization should receive one dose of PCV13. To extend protection against an increased number of *S. pneumoniae* serotypes, asplenic and hyposplenic children should also receive a dose of PPSV23 at 2 years of age or older and at least 8 weeks after the last dose of PCV13. Because antibodies against PPSV23 are not as enduring as those induced by PCV13, children should be revaccinated with PPSV23 5 years after their first PPSV23 vaccine. Children who received PCV7 (an earlier vaccine formulation containing seven pneumococcal serotypes) as their primary series should receive a supplemental dose of PCV13 at least 8 weeks after receiving the PCV7.

All asplenic and hyposplenic adults previously unimmunized against *S. pneumoniae* should receive PCV13 followed by, at least 8 weeks later, PPSV23. Adults previously immunized with PPSV23 should receive a single dose of PCV13 at least 1 year after the most recent dose of PPSV23 because lower opsonophagocytic antibody responses were seen in persons who received PCV13 less than 1 year after PPSV23.[73] Adults up to age 65 years should be revaccinated with PPSV23 5 years after their first vaccine. In addition, asplenic adults 65 years of age and older should be reimmunized with PPSV23 if they were vaccinated more than 5 years earlier and at a time when they were younger than 65 years.[74]

A history of *S. pneumoniae* sepsis is not a contraindication for receipt of subsequent PCV13 or PPSV23 vaccines. Asplenic children and adults who experience *S. pneumoniae* infection should receive subsequent vaccines as recommended for all asplenic individuals.

Vaccines against Hib contain the type b polysaccharide conjugated to carrier proteins and are routinely recommended for all children in

the United States at 2, 4, (6), and 12 to 15 months of age, dependent on the vaccine formulation.[66] Children older than 5 years and adults are assumed to be naturally immune to Hib. Nevertheless, fully immunized children and adults should receive one dose of Hib vaccine at least 14 days before undergoing elective splenectomy.[67,72] Inadequately immunized children should receive catch-up Hib vaccines per the recommendations of the American Academy of Pediatrics and ACIP, which are updated annually (www.cdc.gov/vaccines/acip/index.html).

Quadrivalent vaccines that protect against *N. meningitidis* serogroups A, C, Y, and W135 contain four polysaccharides conjugated to the carrier protein diphtheria toxin (MenACYW-D) or CRM (MenACYW-CRM).[75]

Asplenic/hyposplenic infants younger than 24 months of age should receive Men-ACYW-CRM at 2, 4, 6, and 12 to 15 months. Nonimmunized children between the ages of 19 months and 2 years should receive two doses of MenACYW-CRM, 3 months apart. A blunted response to PCV-7 was noted in patients who received MenACYW-D simultaneously with PCV.[75] For this reason, children with asplenia should not receive MenACYW-D before the age of 2 years. In children older than 2 years, MenACYW-D should follow PCV-13 vaccination by at least 4 weeks. Children who received the primary series before age 2 years should receive a booster dose of Men-ACYW three years after its completion, followed by revaccination every 5 years. Asplenic individuals older than age 2 who have not been previously vaccinated against meningococcal disease should receive two doses of MenACYW at least 3 months apart, with revaccination every 5 years. Two meningococcal serogroup B vaccines (MenB) that contain factor H–binding protein with or without three additional bacterial proteins are licensed by the US Food and Drug Administration for individuals 10 to 25 years of age and given as either a two- or three-dose series, dependent on the vaccine.[76] These vaccines are not interchangeable, and the entire series must be completed with the same vaccine product.

Influenza infection increases the risk of pneumococcal infection among healthy individuals and likely is an additional risk for splenectomized individuals. Routine influenza vaccine is now recommended for all children older than 6 months and for all adults. Asplenic or hyposplenic individuals should be specifically encouraged to receive seasonal influenza vaccine annually.

Patient Education

Optimal medical care of asplenic/hyposplenic patients is contingent on the patient's knowledge of all aspects of the condition.[77] Basic information on asplenia and its risks, as well as sepsis prevention and management strategies, with repeated reinforcement and updating, is the responsibility of all health care providers (Table 311.10). Even in the face of good patient education, patient retention of the information may be limited,[78] and compliance with recommendations may be suboptimal.[79] A few professional organizations and health care institutions have prepared educational materials for postsplenectomy patients, and these can be useful as a base on which more detailed disease and patient-specific information is built.[80–82] Use of a patient registry to assist in delivering vaccines, antibiotic prophylaxis, and patient education in Australia proved cost-effective in terms of reduced mortality rates and reduced postsplenectomy infection rates.[63] Further, education of asplenic patients about travel-related risks may reduce the rate of postsplenectomy infection.[79]

TABLE 311.10 Important Educational Information for Asplenic Patients

INFORMATION CATEGORY	INFORMATION CONTENT
Spleen	Basic information on splenic anatomy and function
Splenectomy	Operative procedure, complications, alternatives
Sepsis—what is it?	Signs and symptoms of infection
Sepsis—who gets it?	Risk assessment, risk of parasites based on geography
Sepsis—what to do about fever?	Self-administered empirical antibiotics, need for immediate medical attention
Sepsis—how to prevent it	Prophylactic antibiotics for children, immunizations for all ages, insect vector avoidance
Sepsis—how to treat it	Basics of antibiotics and supportive care
What about traveling?	Update immunizations, empirical self-administered antibiotics, malaria prophylaxis, insect vector avoidance

Modified from Pasternack MS. Patient Information: Preventing Severe Infection After Splenectomy (Beyond the Basics). *http://www.uptodate.com/contents/preventing-severe-infection-after-splenectomy-beyond-the-basics. Accessed February 19, 2013.*

Key References

The complete reference list is available online at Expert Consult.

2. Rodeghiero F, Ruggeri R. Short- and long-term risks of splenectomy for benign haematological disorders: should we revisit the indications? *Br J Haematol.* 2012;158:16–29.
6. King H, Shumacker HB Jr. Splenic studies. I. Susceptibility to infection after splenectomy performed in infancy. *Ann Surg.* 1952;136:239–242.
14. Hargreaves DC, Hyman PL, Lu TT, et al. A coordinated change in chemokine responsiveness guides plasma cell movements. *J Exp Med.* 2001;194:45–56.
15. Breukels MA, Zandvoort A, van Den Dobbelsteen GP, et al. Pneumococcal conjugate vaccines overcome splenic dependency of antibody response to pneumococcal polysaccharides. *Infect Immun.* 2001;69:7583–7587.
17. Weller S, Braun MC, Tan BK, et al. Human blood IgM "memory" B cells are circulating splenic marginal zone B cells harboring a prediversified immunoglobulin repertoire. *Blood.* 2004;104:3647–3654.
18. Crary SE, Buchanan GR. Vascular complications after splenectomy for hematologic disorders. *Blood.* 2009;114:2861–2868.
22. Uranues S, Grossman D, Ludwig L, et al. Laparoscopic partial splenectomy. *Surg Endosc.* 2007;21:57–60.
23. Connell NT, Brunner AM, Kerr CA, et al. Splenosis and sepsis: the born-again spleen provides poor protection. *Virulence.* 2011;2:4–11.
24. Di Sabatino A, Carsetti R, Corazza GR. Post-splenectomy and hyposplenic states. *Lancet.* 2011;378:86–97.
26. Di Sabatino A, Brunetti L, Carnevale Maffe G, et al. Is it worth investigating splenic function in patients with celiac disease? *World J Gastroenterol.* 2013;19:2313–2318.
27. Connell NT, Shurin SB, Schiffman FJ. The spleen and its disorders. In: Hoffman R, Benz B, Silberstein H, et al, eds. *Hematology: Basic Principles and Practice.* Philadelphia: Churchill Livingstone; 2012:2252–2265.
30. Lammers AJ, de Porto AP, Bennink RJ, et al. Hyposplenism: comparison of different methods for determining splenic function. *Am J Hematol.* 2012;87:484–489.
31. de Porto AP, Lammers AJ, Bennink RJ, et al. Assessment of splenic function. *Eur J Clin Microbiol Infect Dis.* 2010;29:1465–1473.
32. Thomsen RW, Schoonen WM, Farkas DK, et al. Risk for hospital contact with infection in patients with splenectomy: a population-based cohort study. *Ann Intern Med.* 2009;151:546–555.
33. Kyaw MH, Holmes EM, Toolis F, et al. Evaluation of severe infection and survival after splenectomy. *Am J Med.* 2006;119:276.e1–276.e7.
34. Bisharat N, Omari H, Lavi I, et al. Risk of infection and death among post-splenectomy patients. *J Infect.* 2001;43:182–186.
38. Holdsworth RJ, Irving AD, Cuschieri A. Postsplenectomy sepsis and its mortality rate: actual versus perceived risks. *Br J Surg.* 1991;78:1031–1038.
40. Yong M, Thomsen RW, Schoonen WM, et al. Mortality risk in splenectomised patients: a Danish population-based cohort study. *Eur J Intern Med.* 2010;21:12–16.
41. Malangoni MA, Dillon LD, Klamer TW, et al. Factors influencing the risk of early and late serious infection in adults after splenectomy for trauma. *Surgery.* 1984;96:775–783.
42. Demetriades D, Scalea TM, Degiannis E, et al. Blunt splenic trauma: splenectomy increases early infectious complications: a prospective multicenter study. *J Trauma Acute Care Surg.* 2012;72:229–234.
43. Heuer M, Taeger G, Kaiser GM, et al. No further incidence of sepsis after splenectomy for severe trauma: a multi-institutional experience of the trauma registry of the DGU with 1,630 patients. *Eur J Med Res.* 2010;15:258–265.
44. Meekes I, van der Staak F, van Oostrom C. Results of splenectomy performed on a group of 91 children. *Eur J Pediatr Surg.* 1995;5:19–22.
46. Alanee SR, McGee L, Jackson D, et al. Association of serotypes of *Streptococcus pneumoniae* with disease severity and outcome in adults: an international study. *Clin Infect Dis.* 2007;45:46–51.
47. Loggie BW, Hinchey EJ. Does splenectomy predispose to meningococcal sepsis? An experimental study and clinical review. *J Pediatr Surg.* 1986;21:326–330.
48. Sakran W, Levin C, Kenes Y, et al. Clinical spectrum of serious bacterial infections among splenectomized patients with hemoglobinopathies in Israel: a 37-year follow-up study. *Infection.* 2012;40:35–39.
49. Yapp AR, Lindeman R, Gilroy N, et al. Infection outcomes in splenectomized patients with hemoglobinopathies in Australia. *Int J Infect Dis.* 2009;13:696–700.
52. Brenner DJ, Hollis DG, Fanning GR, et al. *Capnocytophaga canimorsus* sp. nov. (formerly CDC group DF-2), a cause of septicemia following dog bite, and *C. cynodegmi* sp. nov., a cause of localized wound infection following dog bite. *J Clin Microbiol.* 1989;27:231–235.
53. Hicklin H, Verghese A, Alvarez S. Dysgonic fermenter 2 septicemia. *Rev Infect Dis.* 1987;9:884–890.
54. Shepard CW, Daneshvar MI, Kaiser RM, et al. *Bordetella holmesii* bacteremia: a newly recognized clinical entity among asplenic patients. *Clin Infect Dis.* 2004;38:799–804.
56. Krause PJ, Gewurz BE, Hill D, et al. Persistent and relapsing babesiosis in immunocompromised patients. *Clin Infect Dis.* 2008;46:370–376.

57. Buffet PA, Safeukui I, Deplaine G, et al. The pathogenesis of *Plasmodium falciparum* malaria in humans: insights from splenic physiology. *Blood*. 2011;117:381–392.
58. Chotivanich K, Udomsangpetch R, McGready R, et al. Central role of the spleen in malaria parasite clearance. *J Infect Dis*. 2002;185:1538–1541.
60. Rabinstein A, Tikhomirov V, Kaluta A, et al. Recurrent and prolonged fever in asplenic patients with human granulocytic ehrlichiosis. *QJM*. 2000;93:198–201.
63. Woolley I, Jones P, Spelman D, et al. Cost-effectiveness of a post-splenectomy registry for prevention of sepsis in the asplenic. *Aust N Z J Public Health*. 2006;30:558–561.
64. Jugenburg M, Haddock G, Freedman MH, et al. The morbidity and mortality of pediatric splenectomy: does prophylaxis make a difference? *J Pediatr Surg*. 1999;34:1064–1067.
65. Gaston MH, Verter JI, Woods G, et al. Prophylaxis with oral penicillin in children with sickle cell anemia. A randomized trial. *N Engl J Med*. 1986;314:1593–1599.
66. Committee on Infectious Diseases American Academy of Pediatrics. *Haemophilus influenzae* infections. In: Kimberlin DW, Brady MT, Jackson MA, et al, eds. *Red Book: 2018 Report of the Committee on Infectious Diseases*. Elk Grove Village, IL: American Academy of Pediatrics; 2018:367–375.
67. Keenan RD, Boswell T, Milligan DW. Do post-splenectomy patients take prophylactic penicillin? *Br J Haematol*. 1999;105:509–510.
68. Council on Clinical Affairs, Guideline on antibiotic prophylaxis for dental patients at risk for infection. *Pediatr Dent*. 2011;30(suppl 7):215–218.
69. de Montalembert M, Lenoir G. Antibiotic prevention of pneumococcal infections in asplenic hosts: admission of insufficiency. *Ann Hematol*. 2004;83:18–21.
71. Nuorti JP, Whitney CG, Centers for Disease Control and Prevention. Prevention of pneumococcal disease among infants and children—use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine—recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2010;59(RR–11):1–18.
72. Committee on Infectious Diseases American Academy of Pediatrics. Immunocompromised children. In: Kimberlin DW, Brady MT, Jackson MA, et al, eds. *Red Book: 2018 Report of the Committee on Infectious Diseases*. Elk Grove Village, IL: American Academy of Pediatrics; 2018:89–90.
73. Centers for Disease Control and Prevention. Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine for adults with immunocompromising conditions: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep*. 2012;61:816–819.
75. Cohn AC, MacNeil JR, Clark TA, et al; Centers for Disease Control and Prevention. Prevention and control of meningococcal disease: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2013;62(RR02):1–22. https://www.cdc.gov/mmwr/preview/mmwrhtml/rr6202a1.htm.
77. Davies JM, Lewis MP, Wimperis J, et al. Review of guidelines for the prevention and treatment of infection in patients with an absent or dysfunctional spleen: prepared on behalf of the British Committee for Standards in Haematology by a working party of the Haemato-Oncology task force. *Br J Haematol*. 2011;155:308–317.
79. Boeddha C, de Graaf W, Overbosch D, et al. Travel health preparation and travel-related morbidity of splenectomised individuals. *Travel Med Infect Dis*. 2012;10:197–200.
80. Cleveland Clinic. Diseases and Conditions: Splenectomy. my.clevelandclinic.org/services/splenectomy. Accessed February 19, 2013.
81. Pasternack MS Patient Information: Preventing Severe Infection after Splenectomy (Beyond the Basics). September 28, 2012. http://www.uptodate.com/contents/preventing-severe-infection-after-splenectomy-beyond-the-basics. Accessed April 30, 2014.
82. Platelet Disorder Support Association. Splenectomy. http://www.pdsa.org/component/k2/item/101.html?ltemid=123. Accessed February 19, 2013.

References

1. Wilkins B. The spleen. *Br J Haematol*. 2002;117:265–274.
2. Rodeghiero F, Ruggeri R. Short- and long-term risks of splenectomy for benign haematological disorders: should we revisit the indications? *Br J Haematol*. 2012;158:16–29.
3. Brown AR. Immunological functions of splenic B-lymphocytes. *Crit Rev Immunol*. 1992;11:395–417.
4. Peters AM, Walport MJ, Bell RN, et al. Methods of measuring splenic blood flow and platelet transit time with In-111-labeled platelets. *J Nucl Med*. 1984;25:86–90.
5. Eichner ER. Splenic function: normal, too much and too little. *Am J Med*. 1979;66:311–320.
6. King H, Shumacker HB Jr. Splenic studies. I. Susceptibility to infection after splenectomy performed in infancy. *Ann Surg*. 1952;136:239–242.
7. Langeveld M, Gamadia LE, ten Berge IJ. T-lymphocyte subset distribution in human spleen. *Eur J Clin Invest*. 2006;36:250–256.
8. Huston JM, Ochani M, Rosas-Ballina M, et al. Splenectomy inactivates the cholinergic antiinflammatory pathway during lethal endotoxemia and polymicrobial sepsis. *J Exp Med*. 2006;203:1623–1628.
9. Wang H, Liao H, Ochani M, et al. Cholinergic agonists inhibit HMGB1 release and improve survival in experimental sepsis. *Nat Med*. 2004;10:1216.
10. Rosas-Ballina M, Olofsson PS, Ochani M, et al. Acetylcholine-synthesizing T cells relay neural signals in a vagus nerve circuit. *Science (New York)*. 2011;334:98–101.
11. Felder C, Perlik V, Tang Y, et al. Putative antihyperpyretic factor induced by LPS in spleen of guinea pigs. *Am J Physiol Regul Integr Comp Physiol*. 2005;289:R680–R687.
12. Hosea SW, Brown EJ, Hamburger MI, et al. Opsonic requirements for intravascular clearance after splenectomy. *N Engl J Med*. 1981;304:245–250.
13. Rajewsky K. Clonal selection and learning in the antibody system. *Nature*. 1996;381:751–758.
14. Hargreaves DC, Hyman PL, Lu TT, et al. A coordinated change in chemokine responsiveness guides plasma cell movements. *J Exp Med*. 2001;194:45–56.
15. Breukels MA, Zandvoort A, van Den Dobbelsteen GP, et al. Pneumococcal conjugate vaccines overcome splenic dependency of antibody response to pneumococcal polysaccharides. *Infect Immun*. 2001;69:7583–7587.
16. Kruetzmann S, Rosado MM, Weber H, et al. Human immunoglobulin memory B cells controlling *Streptococcus pneumoniae* infections are generated in the spleen. *J Exp Med*. 2003;197:939–945.
17. Weller S, Braun MC, Tan BK, et al. Human blood IgM "memory" B cells are circulating splenic marginal zone B cells harboring a prediversified immunoglobulin repertoire. *Blood*. 2004;104:3647–3654.
18. Crary SE, Buchanan GR. Vascular complications after splenectomy for hematologic disorders. *Blood*. 2009;114:2861–2868.
19. Moller JH, Nakib A, Anderson RC, et al. Congenital cardiac disease associated with polysplenia. A developmental complex of bilateral "left-sidedness.". *Circulation*. 1967;36:789–799.
20. Loomba RS, Geddes GC, Basel D, et al. Bacteremia in patients with heterotaxy: a review and implications for management. *Congenit Heart Dis*. 2016;11:537–547.
21. Pearson HA, Gallagher D, Chilcote R, et al. Developmental pattern of splenic dysfunction in sickle cell disorders. *Pediatrics*. 1985;76:392–397.
22. Uranues S, Grossman D, Ludwig L, et al. Laparoscopic partial splenectomy. *Surg Endosc*. 2007;21:57–60.
23. Connell NT, Brunner AM, Kerr CA, et al. Splenosis and sepsis: the born-again spleen provides poor protection. *Virulence*. 2011;2:4–11.
24. Di Sabatino A, Carsetti R, Corazza GR. Post-splenectomy and hyposplenic states. *Lancet*. 2011;378:86–97.
25. William BM, Corazza GR. Hyposplenism: a comprehensive review, Part I. Basic concepts and causes. *Hematology*. 2007;12:1–13.
26. Di Sabatino A, Brunetti L, Carnevale Maffe G, et al. Is it worth investigating splenic function in patients with celiac disease? *World J Gastroenterol*. 2013;19:2313–2318.
27. Connell NT, Shurin SB, Schiffman FJ. The spleen and its disorders. In: Hoffman R, Benz B, Silberstein H, et al, eds. *Hematology: Basic Principles and Practice*. Philadelphia: Churchill Livingstone; 2012:2252–2265.
28. Corazza GR, Ginaldi L, Zoli G, et al. Howell-Jolly body counting as a measure of splenic function. A reassessment. *Clin Lab Haematol*. 1990;12:269–275.
29. Buchanan G, Holtkamp C, Horton J. Formation and disappearance of pocked erythrocytes: studies in human subjects and laboratory animals. *Am J Hematol*. 1987;25:243–251.
30. Lammers AJ, de Porto AP, Bennink RJ, et al. Hyposplenism: comparison of different methods for determining splenic function. *Am J Hematol*. 2012;87:484–489.
31. de Porto AP, Lammers AJ, Bennink RJ, et al. Assessment of splenic function. *Eur J Clin Microbiol Infect Dis*. 2010;29:1465–1473.
32. Thomsen RW, Schoonen WM, Farkas DK, et al. Risk for hospital contact with infection in patients with splenectomy: a population-based cohort study. *Ann Intern Med*. 2009;151:546–555.
33. Kyaw MH, Holmes EM, Toolis F, et al. Evaluation of severe infection and survival after splenectomy. *Am J Med*. 2006;119:276.e1–276.e7.
34. Bisharat N, Omari H, Lavi I, et al. Risk of infection and death among post-splenectomy patients. *J Infect*. 2001;43:182–186.
35. Clayer MT, Drew PA, Leong AS, et al. IgG-mediated phagocytosis in regenerated splenic tissue. *Clin Exp Immunol*. 1994;97:242–247.
36. Constantoulakis M, Trichopoulos D, Avgoustaki O, et al. Serum immunoglobulin concentrations before and after splenectomy in patients with homozygous beta-thalassaemia. *J Clin Pathol*. 1978;31:546–550.
37. Koren A, Haasz R, Tiatler A, et al. Serum immunoglobulin levels in children after splenectomy. A prospective study. *Am J Dis Child*. 1984;138:53–55.
38. Holdsworth RJ, Irving AD, Cuschieri A. Postsplenectomy sepsis and its mortality rate: actual versus perceived risks. *Br J Surg*. 1991;78:1031–1038.
39. Styrt B. Infection associated with asplenia: risks, mechanisms, and prevention. *Am J Med*. 1990;88:33N–42N.
40. Yong M, Thomsen RW, Schoonen WM, et al. Mortality risk in splenectomised patients: a Danish population-based cohort study. *Eur J Intern Med*. 2010;21:12–16.
41. Malangoni MA, Dillon LD, Klamer TW, et al. Factors influencing the risk of early and late serious infection in adults after splenectomy for trauma. *Surgery*. 1984;96:775–783.
42. Demetriades D, Scalea TM, Degiannis E, et al. Blunt splenic trauma: splenectomy increases early infectious complications: a prospective multicenter study. *J Trauma Acute Care Surg*. 2012;72:229–234.
43. Heuer M, Taeger G, Kaiser GM, et al. No further incidence of sepsis after splenectomy for severe trauma: a multi-institutional experience of the trauma registry of the DGU with 1,630 patients. *Eur J Med Res*. 2010;15:258–265.
44. Meekes I, van der Staak F, van Oostrom C. Results of splenectomy performed on a group of 91 children. *Eur J Pediatr Surg*. 1995;5:19–22.
45. Cerquetti M, Cardines R, Giufre M, et al. Detection of six copies of the capsulation b locus in a *Haemophilus influenzae* type b strain isolated from a splenectomized patient with fulminant septic shock. *J Clin Microbiol*. 2006;44:640–642.
46. Alanee SR, McGee L, Jackson D, et al. Association of serotypes of *Streptococcus pneumoniae* with disease severity and outcome in adults: an international study. *Clin Infect Dis*. 2007;45:46–51.
47. Loggie BW, Hinchey EJ. Does splenectomy predispose to meningococcal sepsis? An experimental study and clinical review. *J Pediatr Surg*. 1986;21:326–330.
48. Sakran W, Levin C, Kenes Y, et al. Clinical spectrum of serious bacterial infections among splenectomized patients with hemoglobinopathies in Israel: a 37-year follow-up study. *Infection*. 2012;40:35–39.
49. Yapp AR, Lindeman R, Gilroy N, et al. Infection outcomes in splenectomized patients with hemoglobinopathies in Australia. *Int J Infect Dis*. 2009;13:696–700.
50. Theilacker C, Ludewig K, Serr A, et al. Overwhelming postsplenectomy infection: a prospective multicenter cohort study. *Clin Infec Dis*. 2016;62:871–878.
51. Martone WJ, Zuehl RW, Minson GE, et al. Postsplenectomy sepsis with DF-2: report of a case with isolation of the organism from the patient's dog. *Ann Intern Med*. 1980;93:457–458.
52. Brenner DJ, Hollis DG, Fanning GR, et al. *Capnocytophaga canimorsus* sp. nov. (formerly CDC group DF-2), a cause of septicemia following dog bite, and *C. cynodegmi* sp. nov., a cause of localized wound infection following dog bite. *J Clin Microbiol*. 1989;27:231–235.
53. Hicklin H, Verghese A, Alvarez S. Dysgonic fermenter 2 septicemia. *Rev Infect Dis*. 1987;9:884–890.
54. Shepard CW, Daneshvar MI, Kaiser RM, et al. *Bordetella holmesii* bacteremia: a newly recognized clinical entity among asplenic patients. *Clin Infect Dis*. 2004;38:799–804.
55. Wudhikarn K, Perry EH, Kemperman M, et al. Transfusion-transmitted babesiosis in an immunocompromised patient: a case report and review. *Am J Med*. 2011;124:800–805.
56. Krause PJ, Gewurz BE, Hill D, et al. Persistent and relapsing babesiosis in immunocompromised patients. *Clin Infect Dis*. 2008;46:370–376.
57. Buffet PA, Safeukui I, Deplaine G, et al. The pathogenesis of *Plasmodium falciparum* malaria in humans: insights from splenic physiology. *Blood*. 2011;117:381–392.
58. Chotivanich K, Udomsangpetch R, McGready R, et al. Central role of the spleen in malaria parasite clearance. *J Infect Dis*. 2002;185:1538–1541.
59. White NJ, Krishna S. Treatment of malaria: some considerations and limitations of the current methods of assessment. *Trans R Soc Trop Med Hyg*. 1989;83:767–777.
60. Rabinstein A, Tikhomirov V, Kaluta A, et al. Recurrent and prolonged fever in asplenic patients with human granulocytic ehrlichiosis. *QJM*. 2000;93:198–201.
61. Greenwood BM. Corticosteroids for acute bacterial meningitis. *N Engl J Med*. 2007;357:2507–2509.
62. Tunkel AR, Hartman BJ, Kaplan SL, et al. Practice guidelines for the management of bacterial meningitis. *Clin Infect Dis*. 2004;39:1267–1284.
63. Woolley I, Jones P, Spelman D, et al. Cost-effectiveness of a post-splenectomy registry for prevention of sepsis in the asplenic. *Aust N Z J Public Health*. 2006;30:558–561.
64. Jugenburg M, Haddock G, Freedman MH, et al. The morbidity and mortality of pediatric splenectomy: does prophylaxis make a difference? *J Pediatr Surg*. 1999;34:1064–1067.
65. Gaston MH, Verter JI, Woods G, et al. Prophylaxis with oral penicillin in children with sickle cell anemia. A randomized trial. *N Engl J Med*. 1986;314:1593–1599.
66. Committee on Infectious Diseases American Academy of Pediatrics. *Haemophilus influenzae* infections. In: Kimberlin DW, Brady MT, Jackson MA, et al, eds. *Red Book: 2018 Report of the Committee on Infectious Diseases*. Elk Grove Village, IL: American Academy of Pediatrics; 2018:367–375.
67. Keenan RD, Boswell T, Milligan DW. Do post-splenectomy patients take prophylactic penicillin? *Br J Haematol*. 1999;105:509–510.
68. Council on Clinical Affairs, Guideline on antibiotic prophylaxis for dental patients at risk for infection. *Pediatr Dent*. 2011;30(suppl 7):215–218.
69. de Montalembert M, Lenoir G. Antibiotic prevention of pneumococcal infections in asplenic hosts: admission of insufficiency. *Ann Hematol*. 2004;83:18–21.
70. Shatz DV, Schinsky MF, Pais LB, et al. Immune responses of splenectomized trauma patients to the 23-valent pneumococcal polysaccharide vaccine at 1 versus 7 versus 14 days after splenectomy. *J Trauma*. 1998;44:760–765, discussion 5–6.
71. Nuorti JP, Whitney CG, Centers for Disease Control and Prevention. Prevention of pneumococcal disease among infants and children—use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine—recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2010;59(RR–11):1–18.
72. Committee on Infectious Diseases American Academy of Pediatrics. Immunocompromised children. In: Kimberlin DW, Brady MT, Jackson MA, et al, eds. *Red Book: 2018 Report of the Committee on Infectious Diseases*. Elk Grove Village, IL: American Academy of Pediatrics; 2018:89–90.
73. Centers for Disease Control and Prevention. Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine for adults with immunocompromising conditions: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep*. 2012;61:816–819.
74. Centers for Disease Control and Prevention. Recommended adult immunization schedule: United States, 2019. *Ann Intern Med*. 2019;170:182–192.
75. Cohn AC, MacNeil JR, Clark TA, et al; Centers for Disease Control and Prevention. Prevention and control of meningococcal disease: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2013;62(RR02):1–22.
76. Patton ME, Stephens D, Moore K, et al. Updated recommendations for use of MenB-FHbp serogroup b meningococcal vaccine—Advisory Committee on Immunization Practices, 2016. *MMWR Morb Mortal Wkly Rep*. 2017;66:509–513.
77. Davies JM, Lewis MP, Wimperis J, et al. Review of guidelines for the prevention and treatment of infection in patients with an absent or dysfunctional spleen: prepared on behalf of the British Committee for Standards in Haematology by a working party of the Haemato-Oncology task force. *Br J Haematol*. 2011;155:308–317.
78. Rutherford EJ, Livengood J, Higginbotham M, et al. Efficacy and safety of pneumococcal revaccination after splenectomy for trauma. *J Trauma*. 1995;39:448–452.
79. Boeddha C, de Graaf W, Overbosch D, et al. Travel health preparation and travel-related morbidity of splenectomised individuals. *Travel Med Infect Dis*. 2012;10:197–200.
80. Cleveland Clinic. Diseases and Conditions: Splenectomy. my.clevelandclinic.org/services/splenectomy. Accessed February 19, 2013.
81. Pasternack MS Patient Information: Preventing Severe Infection after Splenectomy (Beyond the Basics); September 28, 2012. http://www.uptodate.com/contents/preventing-severe-infection-after-splenectomy-beyond-the-basics. Accessed April 30, 2014.
82. Platelet Disorder Support Association. Splenectomy. http://www.pdsa.org/component/k2/item/101.html?Itemid=123. Accessed February 19, 2013.

312 Infections in Injection Drug Users

Donald P. Levine and Patricia Brown

SHORT VIEW SUMMARY

HOST DEFENSES

- Direct effects of opioids on the immune system include impairment of chemotaxis, phagocytosis, cytokine and chemokine production, natural killer cell activity, lymphocyte proliferation in response to mitogens, and antigen presentation by B lymphocytes. Indirect effects through the neuroendocrine system and the autonomic nervous system are also postulated.
- Immunoglobulin M (IgM) and IgG levels are often elevated, giving rise to a high frequency of autoantibodies as well as antibodies against various microorganisms; this may cause diagnostic confusion (e.g., in interpretation of syphilis serology).
- Morphine-mediated depression of monocyte functions important to antiviral defense may contribute to the high efficiency of transmission of viruses such as hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV).

SKIN AND SOFT TISSUE INFECTIONS

- Location of infection is related to the preferred location of injection; abscesses are most common, followed by cellulitis and skin ulcers.
- Infection with *Staphylococcus aureus* (particularly community-acquired methicillin-resistant *S. aureus* [MRSA]) is most common, followed by streptococci, either alone or in combination with other pathogens; infection with *Eikenella corrodens* occurs in injection drug users (IDUs) who lick their needles or contaminate their drugs with saliva; anaerobes and gram-negative bacilli are found in mixed infections.
- Incision and drainage is the mainstay of therapy for abscesses; for cellulitis, antibiotic selection and need for hospitalization must be individualized based on severity of illness; a high index of suspicion for necrotizing fasciitis should be maintained in the setting of severe pain or severe signs of systemic toxicity or both.

BONE AND JOINT INFECTIONS

- These infections are common, mainly affect the axial skeleton, and occur by the hematogenous route; contiguous spread from adjacent skin and soft tissue infection also occurs.
- Bacterial infection with *S. aureus* is most common; infection with *Pseudomonas* is reported; infection with *Eikenella* occurs in IDUs who lick their needles; and infection with *Candida* spp. is increasingly reported.
- Joint infections typically involve the extremities (most commonly the knee), although involvement of unusual sites (costochondral and sternoclavicular joints, pubic symphysis) is frequent; there is a high incidence of cervical spine involvement in individuals with vertebral osteomyelitis.
- Microbiologic diagnosis should be confirmed in all cases; the use of high bioavailability oral antibiotic therapy for prolonged treatment is increasing.

INFECTIVE ENDOCARDITIS

- Incidence among IDUs appears to be increasing, perhaps owing to increased methamphetamine use (increased number of injections); IDUs with HIV are at even higher risk for infective endocarditis (IE).
- Infection with *S. aureus* is most common (the incidence of MRSA is increasing), followed by groups A, B, and G streptococci; outbreaks of gram-negative IE (caused by *Serratia* or *Pseudomonas*) are well described; and infection with *Candida* spp. (mainly species other than *C. albicans*) have been reported.
- Tricuspid valve IE is associated with injection drug use, but the incidence of left-sided IE now exceeds that of right-sided infection in some series; multiple valves may be involved; infection of the pulmonary valve is rare.
- IDUs tend to present acutely in the first week of illness; diagnosis is usually easy to make based on clinical signs and symptoms and supported by the results of blood cultures and cardiac imaging.
- Initial empirical therapy should be directed against *S. aureus* (with vancomycin or nafcillin in settings where MRSA is known to be rare); optimal therapy for MRSA isolates with vancomycin minimal inhibitory concentration of 2.0 µg/mL is not yet defined; many experts recommend daptomycin.
- Cefepime plus high-dose tobramycin has been used successfully to treat pseudomonal IE; surgical therapy along with amphotericin plus flucytosine is the standard recommendation for candidal IE; the role of azoles and echinocandins is not yet defined; indefinite suppressive therapy with oral azoles is recommended if the patient is not a candidate for surgery.

NONCARDIAC VASCULAR INFECTIONS

- Infection with *S. aureus* is most common; infection with *Pseudomonas* is also reported; polymicrobial infections are common.
- Septic thrombophlebitis manifests as local pain, swelling, and fever, with bacteremia and sepsis; septic pulmonary emboli may occur; antibiotic therapy should be given for at least 4 weeks; the role of anticoagulation remains controversial—short-term anticoagulation while the patient is hospitalized may be sufficient.
- Mycotic aneurysms frequently involve the femoral veins and manifest as a tender, enlarging, and pulsatile mass; Doppler ultrasonography, computed tomography (CT), or magnetic resonance angiography (MRA) can be used for diagnosis; surgical management is required, along with antibiotic therapy for 4 to 6 weeks.

PULMONARY INFECTIONS

- Community-acquired pneumonia caused by common respiratory pathogens is most common; patients are at risk for bacteremia, parapneumonic effusions, and empyema.
- Pulmonary tuberculosis is a major problem among IDUs, especially IDUs infected with HIV; treatment for latent tuberculous infection is challenging; material incentives and directly observed therapy can increase adherence.

HEPATITIS

- Cocaine, methamphetamine, and buprenorphine (injected or sublingual) can be hepatotoxic; heroin is not.
- IDUs are at risk for HBV infection and should be vaccinated if nonimmune; spontaneous reactivation of infection can occur.
- In nonendemic areas such as the United States, hepatitis delta virus (HDV) occurs almost exclusively in IDUs; although the overall prevalence of HDV has decreased, the prevalence among individuals with chronic HBV infection has increased.
- Superinfection of HDV on chronic HBV is most common; however, simultaneous infection occurs in IDUs and can result in fulminant hepatitis.
- IDUs account for most HCV infections in the United States. The seroprevalence of HCV infection among IDUs in the United States was decreasing; however, the current opioid epidemic has reversed this trend. HCV

SHORT VIEW SUMMARY—cont'd

treatment is challenging in IDUs and should be linked to treatment for addiction.
- IDUs are at increased risk for infection with hepatitis A virus, but socioeconomic factors rather than drug use are the larger risk; nonimmune IDUs should be vaccinated.

SPLENIC ABSCESS
- Splenic abscess occurs most commonly as a complication of IE; secondary infection of a cocaine-induced splenic infarct or infection occurring after trauma also is reported; staphylococci and streptococci are the most common causative agents.
- Ultrasonography, CT, and magnetic resonance imaging all can be used for diagnosis; although splenectomy is generally considered the management of choice, especially in the setting of IE necessitating valve replacement, there is an increasing role for percutaneous drainage.

CENTRAL NERVOUS SYSTEM INFECTION
- Infection of the central nervous system occurs most commonly as a complication of IE (e.g., meningitis, brain abscess, mycotic aneurysms).
- Mycotic aneurysm may be diagnosed by CT, CT angiography, or MRA; optimal management is not defined; many aneurysms heal with antibiotic therapy; ruptured aneurysms require surgery or an endovascular procedure.
- The differential diagnosis of brain abscess is broad, especially in IDUs with HIV infection; microbiologic diagnosis should always be confirmed.
- Spinal epidural abscess should be suspected in IDUs who present with back pain accompanied by radicular symptoms or neurologic findings; *S. aureus* is the most common etiologic agent.
- IDUs are at increased risk for tetanus and wound botulism.

OCULAR INFECTIONS
- Bacterial and fungal endophthalmitis are seen frequently as a complication of IE; *Aspergillus* endophthalmitis is also reported.
- Intravitreal antimicrobial agents with or without pars plana vitrectomy may be required.

HUMAN IMMUNODEFICIENCY VIRUS INFECTION
- Incidence of HIV infection among IDUs in the United States has steadily declined, although the current opioid epidemic may threaten this trend; however, injection drug use remains a major risk factor for HIV acquisition in other parts of the world.
- Safe syringe programs are effective at reducing HIV transmission but should ideally be coupled with access to voluntary counseling and testing, opioid substitution therapy, and combination antiretroviral therapy (ART) for individuals already infected. IDUs can benefit from preexposure prophylaxis with antiretroviral agents.
- Injection drug use is associated with an increased risk of nonadherence to ART; periods of incarceration are associated with virologic failure, but the prevalence of drug resistance is no higher than in non-IDUs. IDUs are less likely to be on ART compared with other risk groups.

SEXUALLY TRANSMITTED DISEASES
- Injection drug use is associated with high-risk sexual behavior, and reduction in risky sexual behavior is more difficult to achieve than reductions in risky injection behavior.
- Although there have been conflicting studies, research suggests that the prevalence of common sexually transmitted infections is higher in IDUs than in the general population.

According to the 2017 World Drug Report, an estimated 250 million people worldwide used illicit drugs at least once in 2015. Of these, 11.8 million injected drugs.[1] Since the early 2000s, prescription opioid injection increased dramatically in the United States, particularly in rural areas.[2] The 2014 National Survey on Drug Use and Health Estimated that 4.3 million people were nonmedical users of prescription pain relievers. Frequently this type of use is a precursor to injection drug use.[3] Ultimately these users were 40 times more likely than the general population to use heroin or other injecting drugs. By 2015 more than one-third of adults in the United States were prescription opioid users, many of whom reported misuse and use disorders.[5] In the United States the use of heroin almost doubled between 2006 and 2013 with more than 680,000 active users, most of whom were young adults who found the drug less expensive and easier to obtain than prescription medications.[6] In addition to heroin and prescription opioids, cocaine and methamphetamines are commonly injected.

The impact of this drug use is substantial because the mortality rate among injection drug users (IDUs) younger than 30 years of age is 10 times the rate in the general population. Although this rate is mostly attributed to overdose, infection exacts a substantial toll on the population.[7] IDUs have higher rates of bacterial, viral, and fungal infections than the general population, and infection is undoubtedly the major reason for contact between an illicit drug user and the health care system. The social circumstances of many addicts, including living in shelters or crowded conditions, increase the risk for pulmonary tuberculosis (TB) including multidrug-resistant infections. Moreover, the reluctance of IDUs to seek medical attention and their failure to adhere to treatment regimens are responsible for the further spread of infection. Malnutrition contributes to altered host defenses, making infection more likely. Poor hygiene that frequently accompanies the drug use habit may exacerbate the risk for infection due to commensal organisms. In addition, IDUs have a higher rate of nasal and skin colonization with potential pathogens than do nonusers. Frequent injection into heavily colonized sites such as the groin region likely increases the risk for infection with enteric flora. Among addicts in San Francisco, 22.8% were found to have nasal colonization with *Staphylococcus aureus,* 12% of which was community-acquired methicillin-resistant *S. aureus* (CA-MRSA).[8] Indeed, the major risk factor among illicit drug users for colonization with *S. aureus* was ever injecting drugs, and, among illicit drug users who are colonized, "ever using" was associated with colonization by MRSA. The fact that addicts have frequent hospitalizations and exposure to antibiotics secondary to complications of injection drug use leads to an increased risk for MRSA colonization and infection.

Certain practices that are unique to IDUs, such as crushing capsules or tablets in the mouth before injection of the drug, may be responsible for infections caused by oral flora. Some addicts lick their needles to make the injection easier, a practice that doubles the risk for cellulitis or abscess caused by oral streptococci or anaerobes.[9] The use of "speedball" (a mixture of heroin and cocaine) or the practice of "booting" (repeatedly withdrawing small amounts of blood into the injection equipment before administering the complete contents) have also been associated with an increased risk for infection. "Speedball" use leads to tissue necrosis, with the formation of abscesses, and injection by using poor technique or sclerosing substances causes a loss of usable veins, which may lead the addict to resort to "skin popping," or injection directly into the skin or muscle, leading to an increase in the odds of wound botulism.

IDUs tend to experiment with a variety of substances, each with a unique set of complications. Different drugs are more or less popular, depending on the region. Methamphetamine use is widely popular, and in at least one study it was demonstrated to be associated with syringe sharing and an increased risk for human immunodeficiency virus (HIV) acquisition.[10] In Tennessee, several IDUs developed thrombotic thrombocytopenic purpura after injecting Opana ER, a newly reformulated extended-release form of oxymorphone.[11] Xylazine, a horse tranquilizer, has become popular in Puerto Rico. This agent is typically mixed with "speedball" and is associated with skin ulceration and local abscesses in up to 35% who inject this substance.[12] Fentanyl and fentanyl analogues have become popular drugs of abuse in the United States[13]; solvent injection has become popular in Canada,[14] in the United Kingdom, mephedrone use has been associated with high-risk behaviors,[15] and a mixture of opioids, benzodiazepines, and antihistamines called "South Asian Cocktail" has become prevalent.[16] Buprenorphine, which is a heroin substitute intended to be used as an oral or sublingual preparation,

has also become a drug of abuse and was associated with severe soft tissue injury in 31% of users in one study.[17,18]

Although early studies failed to detect pathogenic bacteria contaminating the illicit drugs, more recent evidence demonstrating a connection between the use of black tar heroin and severe *Clostridium* infection indicates that certain substances or practices enhance the growth of particular organisms and account for infections that are unique to the drug-using population. Failure to adequately clean the injection paraphernalia and sharing of equipment are also responsible for transmission of infection. The close contact among addicts may also be responsible for outbreaks of severe infections in certain locales. An outbreak of infection caused by *Clostridium novyi* in 2000 was associated with severe infection and a high mortality rate and appeared to be secondary to close contact in the IDU social network and use of shared substances and needles.[19] A brief increase of group A *Streptococcus* M nontypeable strains between 1999 and 2001appears to have resolved.[19]

Ultimately, infection drives a need for care in both the outpatient and the inpatient environment. There are few differences between IDUs and non-IDUs when they present to an emergency department with infection. Both groups have similar rates of fever and bacteremia. However, IDUs are more likely to have hyponatremia and thrombocytopenia.[20] In the British health care system, IDUs infected with HIV are less likely than others to use outpatient services but are more likely to have frequent and prolonged hospitalizations.[21] Substance abuse treatment programs can have a major impact on the use of health care services. The mortality rate among IDUs who are not enrolled in formal substance treatment programs is three times higher than the rate for IDUs in treatment programs, mostly secondary to the high incidence of infection, although trauma also plays a role. The type of program also makes a difference. Addicts who continue to inject but who are enrolled in needle exchange programs are six times more likely to have injection-related infection than addicts enrolled in methadone maintenance programs.[21] Despite the availability of needle exchange programs, young adults are more likely than their older counterparts to practice unsafe injection practices.[22,23] Several reasons explain some of this behavior. In many cases these programs are located outside of areas where drug use is frequent. In addition, criminalization of illicit drug use leads to reluctance of users to carry sterile drug paraphernalia for fear of being caught and arrested. In the United States, high arrest rates for illicit drug use are colocated with syringe exchange programs, with African Americans and Latinos most adversely affected.[24] Decreased access to syringe exchange programs is associated with risky behaviors, and the need for a "fix" outweighs concerns for HIV and hepatitis C virus (HCV) infection.[25,26] There are also differences in drug use based on the particular substance used. Methamphetamine users tend to inject in groups, making sharing of needles and syringes more likely. They are also less likely to frequent neighborhoods where open drug use is common, perceiving them as too dangerous. However, those are the precise neighborhoods where the exchange programs tend to be located.[27] In addition, the frequency of infection increases with the number of injections per day, from a rate of 1.8% for drug users who do not inject, 3.5% for users with single daily injections, 6.1% for users who inject twice daily, to 11.4% for users who inject three or more times per day.[21]

Infection in IDUs is not just a problem for persons in that population; infections may spread to other members of the community in many cases. Examples of infections that can spread beyond the group of drug injectors include infections with HIV, hepatitis B virus (HBV), and HCV and resistant organisms such as MRSA. As noted earlier, opiate maintenance programs have been demonstrated to significantly reduce the infection rate among drug users and can play a major role in reducing the spread of infection to nonusers.[28] Programs that include counseling and psychosocial services as well as medical care to methadone maintenance programs can decrease drug use and, secondarily, the spread of infection.

An effort to decrease infections in IDUs requires multiple strategies but begins with an understanding of the issues leading to drug abuse. Among young adults, as noted previously, a history of receiving a prescription for legal narcotics, tranquilizers, or stimulants precedes misuse and a transition to injection drug use.[29] Early initiation into drug injecting is also associated with high-risk behavior and infectious consequences and emphasizes the need for comprehensive prevention programs and early intervention efforts targeting youth at risk.[30] Education programs designed to teach addicts safe injecting techniques can prevent local disease as well as the spread of infection to others.[31] Among noninjecting heroin users, risky sexual behavior often accompanies a transition to injecting and with it the risk for acquiring HIV and other infections. Thus a strategy to reduce HIV and other infections associated with injection drug use would incorporate behavioral interventions as well as efforts aimed at risk reduction such as needle and syringe exchange programs and easy access to sterile syringes in pharmacies.[32] Pharmacies have also been proposed as providers of expanded health services for people who inject drugs, which could reduce the need for clinic and hospital care. However, most pharmacies are involved only in syringe exchange programs. Users could be treated in pharmacies for simple abscesses and receive vaccinations, and pharmacies could be a source for needle disposal. Nevertheless, they seldom serve these roles for a variety of reasons, not the least of which is that people who inject drugs frequently are deterred by what they view as being held in contempt by employees of these facilities.[33] Needle exchange programs have reduced the incidence of abscesses but are not available in many locales. In addition, making methadone or other opiate substitution programs more accessible can have the overall effect of improving the health status of addicts, while decreasing their use of illegal substances and participating in illegal activity. When successful, these programs prevent the spread of HIV and other bloodborne pathogens, as well as skin abscesses and cellulitis.

The infections associated with injection drug use are frequently the consequence of the illegal status of street drugs. Heroin reduction programs, safer injecting facilities, and opiate substitution programs can reduce the incidence of many infections among addicts.[28,34] It has also been found that the route drug users employ to ingest heroin is influenced by the purity and ease of use of the drug available, as well as the locale. Powdered forms of heroin, which are common in South America and Asia, are uncommon in Texas, whereas "white" heroin is more likely to be available on the East Coast of the United States. Some forms are easier to dissolve, making intravenous use practical. "Black tar" heroin, which is common in the western regions of the United States, is difficult to get into solution, and most users resort to skin popping, which is highly likely to lead to local ulcerations and abscesses. Because many heroin users initiate their drug use by inhalation, which is associated with far fewer complications than injection, a goal would be to maintain that form of use and prevent the transition to injection, a goal that most likely requires early intervention in a treatment program.[35]

The cities of Vancouver and Victoria in Canada have developed highly successful programs aimed at risk reduction. Vancouver implemented the first medically supervised injection facility in North America, a center where previously obtained drugs can be injected under the supervision of health care professionals. This center is designed to reduce the incidence of overdose and bloodborne virus transmission while improving access to health care.[36] It is likely that the incidence of injection-related infections could be even further reduced if health care providers were permitted to perform the injections rather than serve only as a resource to supervise the injections. Thus users still frequently resort to unsafe practices in other environments.[37] Nevertheless, these services allow safer injection, are associated with decreased overdoses, facilitate early access to clinic or hospital health care for patients in need of treatment for abscesses and other infections, increase referrals for drug treatment, and benefit public order.[38] When the Victoria site was shut down owing to pressure from the local community, there was an increase in sharing of needles from less than 10% in 2008 to more than 20% in 2010, whereas the rate was unchanged in Vancouver.[39] Along with increased needle sharing is the expectation of an increase in bloodborne and injection-related infections. After examining published data showing that the Vancouver supervised injection facility did not increase public disorder, crime, or drug use and recognizing that addiction is a public health matter, the Supreme Court of Canada affirmed the legality of the center and recognized the rights of people with addictions to the security of their persons under the Charter of Rights and Freedoms.[40] In a similar effort, a group of IDUs established an injection

support team in 2005. By assisting IDUs in their own settings, which may be the street or "shooting galleries," the injection support team successfully increased awareness of safer injection techniques among addicts.[40]

Despite these advances there remains a strong reluctance to deal with addiction as a health care–related issue rather than as a crime. In the United States the 1988 ban on syringe exchange programs was reversed in 2010, allowing federal funds to be used to support such programs.[41] These programs, which have been responsible for a reduction in HIV transmission and probably for a reduction in the transmission of HCV as well, have the potential to provide additional risk prevention services. Still, as noted earlier, even where needle exchange programs are legal, IDUs who take advantage of such facilities frequently are harassed by police.[24,42,43] Hence there is an increase in sharing of needles and syringes and an increased risk for HIV and other bloodborne infections. IDUs persist with unhealthy habits, and efforts to reduce risky behavior will remain sporadic despite demonstrated success.[44]

As a consequence of these many risky behaviors, IDUs are admitted to the hospital significantly more often than the general population. Once an IDU is admitted, a frequent sequence of events occurs, starting with admission to an emergency department, followed by an inpatient stay and all too frequently a discharge against medical advice, followed often by readmission for the same or a related problem.[45] One of the problems is the failure to commit sufficient resources to the management of these patients, often with the goal of keeping costs down. This may be shortsighted and only amplifies the amount of money spent to treat any given individual.[46] Part of the problem is the failure of health care providers to recognize the need to adequately treat pain in this population and the prison-like environment drug users are often subjected to. Furthermore, although in many hospital settings many providers who have expertise dealing with the addiction problem are available, as are medications aimed at decreasing the drug cravings, all too often they overlooked, and the patient goes without.[47] There is also a dilemma associated with the need for prolonged hospitalization, as many of the infections acquired by this population require prolonged parenteral therapy. Physicians are almost uniformly reluctant to allow people who inject drugs to be treated in the outpatient setting with antibiotics that necessitate an intravenous catheter for fear the addict will resort to use of the line to inject illicit drugs. Ho and colleagues[48] used a security seal placed over a peripherally inserted catheter to successfully treat drug users in the outpatient setting. The greatest likelihood for success is to carefully select patients whose drug use is somewhat remote and to avoid antibiotics with a relatively high side-effect profile.[49] An alternative approach taking into consideration the psychosocial needs of IDUs in a community care setting has been successful at keeping the patients in a care setting and is associated with completion of care.[50]

HOST DEFENSES

Although it has been recognized for more than a century that opioid abuse is associated with an increased risk for infectious complications, a clear understanding of the effects of opioids on the immune system is still lacking. Studies have examined the effects of in vivo opioid exposure on the function of cells of the immune system isolated from drug users, the effects of in vitro exposure to opioids on immune cells isolated from healthy nonaddicts, and the effects of in vivo and in vitro exposure to opioids in animal models. The results of studies performed after the beginning of the HIV epidemic but before the availability of a serologic test may be confounded by the effects of immunodeficiency caused by unrecognized HIV infection. Previously, it was believed that immunologic dysfunction played a relatively minor role in the pathogenesis of infection in IDUs compared with the repeated parenteral introduction or injection of nonsterile material and lifestyle factors associated with injection drug use. However, there is clear evidence of a direct effect of opioids on immune system function. These effects have been reviewed and summarized elsewhere.[51–53]

Immune Changes

Opiates have been demonstrated to reduce chemotaxis, phagocytosis, and production of cytokines and chemokines. Both heroin and morphine (a major metabolite of heroin) have been shown to decrease natural killer cell activity and decrease lymphocyte proliferation in response to phytohemagglutinin and other mitogens. Morphine has also been shown to impair antigen presentation by B lymphocytes. In addition to their direct effects on cells of the immune system (which have been demonstrated to have opiate receptors), opiates affect the immune system indirectly through the neuroendocrine system (mainly via the hypothalamic-pituitary-adrenal axis). Immunosuppression mediated through effects on the autonomic nervous system is also suggested. Despite the depressed cell-mediated immunity demonstrated in IDUs, opportunistic infections characteristic of T-cell deficiency were rarely reported before the HIV epidemic. In the lung, heroin appears to reduce the activity of inducible nitric oxide synthase, which may increase susceptibility to pulmonary infections.[54,55] Methamphetamine increases the expression and production of metalloproteinase-2, leading to host collagen degradation and diminished wound healing, thereby at least partially explaining the prevalence of *S. aureus* in wounds of IDUs. It also impairs the function of phagocytic cells, further increasing susceptibility of users to infection.[56]

Prolonged methadone maintenance has been shown to reverse some of the immunosuppressive effects of heroin.[57–59] Buprenorphine, which is increasingly used as substitution therapy, also appears to allow a reversal of the immunosuppressive effects associated with heroin addiction.[59]

Active IDUs have substantial humoral immunity dysregulation that is associated with increased systemic inflammation.[60] IDUs who resist HCV infection despite repeated risky activity have significantly elevated levels of immunoglobulin G (IgG) and IgM against viral envelope glycoproteins as well as alterations of natural killer cells compared with healthy control subjects.[61,62] Increased immunoglobulin levels tend to normalize after prolonged opiate withdrawal. Elevated immunoglobulin concentrations are accompanied by a high frequency of autoantibodies such as rheumatoid factor, as well as those directed against various microorganisms. The latter phenomenon often manifests as a biologic false-positive Venereal Disease Research Laboratory test result, which may create diagnostic confusion in IDUs who are at high risk for acquiring sexually transmitted diseases (STDs). Mixed cryoglobulinemia is also seen and increases with the duration of drug use.[63] Hypergammaglobulinemia resulting from polyclonal B-cell activation may be the result of recurrent immunologic stimulation by injected foreign antigens as well as associated chronic liver disease and chronic infections with other pathogens. Regardless of HIV infection, injection drug use is associated with an increase in peripheral blood and mucosal cells. Interestingly, sharing injection paraphernalia also leads to the same increase in immune activation.[64]

It has been shown that morphine may depress the monocyte functions essential for antiviral defense.[65] These alterations could contribute to the high efficiency of transmission of certain viral pathogens in IDUs, including HBV, HCV, and HIV. In vitro, morphine has been shown to enhance HIV infection of human mononuclear cells through the downregulation of β-chemokine production and the upregulation of CCR5 receptor expression.[66] More recent evidence shows that microRNAs involved in the processing of HCV are altered in IDUs and at least partially explain the innate anti-HCV immunity among drug users.[67]

SKIN AND SOFT TISSUE INFECTIONS

Skin and soft tissue infections are the most common reason for IDUs to be admitted to the hospital. There is evidence that skin and soft tissue infections are increasing in this population. Among IDUs in England, between 1997 and 2004 there was a 566% increase in the number of patients admitted for abscesses of the trunk or groin and a 469% increase in patients with cellulitis of the trunk or groin.[68] Based on the aggregate of reports, the lifetime prevalence among addicts varies between 6% and 69%. Risk factors vary, but there is much commonality among users. It is not unusual for IDUs to spend time in jail or prison. Many chronic wound infections first appear in IDUs during incarceration, most likely related at least in part to policies that create an unhealthy environment.[69] Women appear to be more likely than their male counterparts to develop abscesses and skin ulcers, perhaps due to smaller veins making them more likely to resort to skin popping.[70] Intramuscular

and subcutaneous injection carry significantly greater risk of skin infections. The prevalence of soft tissue infections also increases with increased injection frequency and most likely the duration of injection drug use.

Age alone also has an impact on the nature of chronic soft tissue infections. Some data suggest there is a growing population of older IDUs. With this population is an expanding pool of subjects who have chronic wounds. It has been suggested that older IDUs (≥45 years old) find themselves in a different stage of life having survived years of drug use and may have learned to cope with their chronic health conditions better than younger IDUs. IDUs with chronic wounds, regardless of age, have an injection history of at least 15 years. That duration invariably leads to injection in the lower extremity with resultant venous insufficiency and the chronic ulcers and infections that tend to follow. Older IDUs with chronic wound infection are less likely to engage in risky injection behaviors than both their peers who have no wounds and younger IDUs.[71] Compared with their peers who do not have chronic wounds, they are more likely to be African American and to inject in the leg. Compared with younger IDUs who have chronic wounds, older IDUs with chronic wounds, although more likely to inject in the leg, are more likely to clean the injection site with alcohol before injecting. Most importantly, they appear to be more receptive to engaging in therapeutic relationships that address their addiction and health issues.

As noted earlier in this chapter, intramuscular injection and greater frequency of injection are common risk factors, especially with heroin or the heroin-cocaine combination known as speedball. These IDUs tend to have a longer history of drug use that has led to sclerosis of accessible veins. As a consequence, their injection time is prolonged as they seek to find a way to administer the drug. It is believed that this prolonged exposure is responsible for an increase in local infection. An emphasis on skin cleansing may help reduce the number of these infections. Education of the patient thus becomes important and should not be considered hopeless. Phillips and colleagues[44] noted that most often IDUs had limited access to supplies that would help reduce infection. They also found a gap between the knowledge of the patients and their practices; although they recognized bleach cleaning of needles and cleaning their skin would likely prevent infection, IDUs often did not practice such behavior. With this information, they used an information-motivation-behavioral skills model with some success in a pilot program. This program and others designed to reduce infections in this population can make an impact not only on the patients but also on the utilization of health care resources because these common skin and soft tissue infections account for a substantial proportion of emergency department encounters in urban medical centers. In Vancouver, the presence of nurses in safe injection facilities leads to treatment there of minor infections, with referral of only more serious cases to emergency departments and a shorter length of stay in the hospital than for other IDUs who were not part of the supervised injection facility program. Further development of such facilities may prove to be very effective at reducing the burden on emergency departments.[72,73] Elsewhere, San Francisco General Hospital established the Integrated Soft Tissue Infection (ISIS), an outpatient facility at which patients can receive care for lesions that would otherwise be treated in the emergency department. Over a 3-year period, 6156 patients were seen for a total of 12,012 visits.[74] Of the patients, 58% were IDUs.

Infection Sites

The distribution of soft tissue lesions varies with the sites used for injection and reflects both the duration of drug use and the local practices among drug users. Typically, IDUs go through a progression of injection sites, starting with the upper extremity in the antecubital fossa, followed after approximately 2 years by the forearm. After about 4 years of use, users switch to injecting into the veins of the hand, and approximately 6 years after first injecting, they switch the veins of the neck, feet, and leg. By the 10th year of drug use, IDUs resort to the groin and peripheral digits.[20] The groin becomes a favored site after other injection sites have been exhausted, although in some cases femoral injection is preferred for convenience and ease of use or as a means of ensuring immediate blood levels of the drug rather than facing the risk for the reduced euphoric effect associated with skin popping, that is, either intended or accidental injection of drugs into the skin and subcutaneous tissues.[75]

After repeated injections into a site, frequently without benefit of sterile technique, local ischemia or necrosis develops, and the tissues become susceptible to infection. In addition, the substances injected frequently contain materials added as diluents that commonly cause norepinephrine release and vasospasm or local damage to the vascular intima. This leads to thrombosis and further compromise of the soft tissues. Cocaine use may be associated with vascular thrombus at sites distant from injections and may cause muscle and skin infections even after inhalational use.[76,77] Opiates also have immunosuppressive properties that may predispose to infection.[78] In addition, among methamphetamine users, there are substantial differences based on the color of the drug they inject. Depending on the type of adulterant added to the drug the color may be clear, white, yellow, or pink. IDUs injecting a colored drug were more likely to develop an abscess compared with IDUs using the clear substance.[79] HIV infection is now recognized as an important risk factor for skin abscesses. Women are at greater risk, presumably because of the difficulty they have accessing veins and the consequent injury to skin and subcutaneous tissues.[80] In one British study, in addition to female sex, all of the following were associated with an injection site infection: being at least 25 years of age; having injected into the legs, groin, and hands over the last year; injecting on 14 or more days in the last 4 weeks; reusing needles and injecting crack cocaine; having HIV infection; and having previously received a prescribed substitute drug. The cost of such infections was estimated conservatively to be between £19.2 million and £30.5 million.[81] It is also very common for IDUs to attempt self-management of their wounds by using a variety of manipulations, including applying heat or a rag soaked in salt water, squeezing out pus with their fingers or doing incision and drainage with a knife or syringe, or taking antibiotics orally or by applying crushed antibiotics to the wound. Although many of these behaviors may increase the risk for spread of the infection, in at least one study the infection healed in 89% of patients. Only 12% ended up going to a hospital, and most waited 5 days before doing so.[82,83]

Abscess

Abscesses are the most common form of soft tissue infection, followed closely by cellulitis and skin ulcers.[84] Cleaning the skin with alcohol before injection protects against abscess and offers a potential intervention to reduce disease and hospital admissions.[85] Original optimism that needle exchange programs might reduce the incidence of abscesses has not been fully realized. In Vancouver, despite having a supervised injection facility program, 21.5% of IDUs had an abscess in the previous 6 months.[86] However, other investigators demonstrated that for every 1000 needles exchanged, there was one less abscess; for every eight visits to the needle exchange program, one additional abscess was prevented. When the funding for the program was reduced, the prevalence of abscesses increased.[87] With conflicting data, it may be that either complete cessation from injecting or scrupulous attention to sterile technique is the only effective measure to eliminate abscesses in IDUs.

The location of lesions depends on the sites injected. They are found commonly in both upper and lower extremities depending on where the user most frequently injects. In at least one comparison between IDUs and nonusers, IDUs were more likely to have abscesses in the groin, whereas the hand was a more common location in nonusers.[88] Addicts also tended to present later and ended up having a longer hospital stay, with treatment costing almost 2.5 times more. Although abscesses occur with injection of heroin as a single drug, they are also found frequently in addicts who inject a mixture of heroin and cocaine and are more likely in IDUs with a long history of drug use and skin popping.[85] Booting is also an independent risk factor for abscess formation.[85] Additional risk factors for abscesses are female sex (odds ratio [OR], 1.7; $P = .002$), recent incarceration (OR, 1.7; $P = .001$), involvement in sex trade (OR, 1.4; $P = .030$), frequent cocaine use (OR, 1.5; $P = .002$), and being seropositive for HIV (OR, 1.5; $P = .003$).[86]

Abscesses may spread to adjacent tissues, frequently with disastrous consequences. Mediastinitis may result from the extension of a cervical abscess, whereas lesions in the carotid triangle can erode into the carotid arteries resulting in massive hemorrhage. Thrombosis of the internal

jugular vein has been reported as a complication of a deep neck abscess, as has acute vocal cord paralysis.[89,90] This can lead to acute, severe airway obstruction and may necessitate immediate tracheostomy. Local venous thrombosis or extension to the retroperitoneal space may result from abscess in the femoral triangle.

Microbiology of Abscesses

Blood cultures from IDUs have low yield and are recommended only for patients with signs and symptoms of systemic toxicity, especially fever. Likewise, wound cultures should be done only for patients who have moderate-to-severe purulent infections.[91] When the decision is made to culture, a useful approach is to first débride the wound of any obviously necrotic tissue. After cleaning the skin with saline or wound cleaner, either swab or tissue cultures yield the same results detecting most of the usually anticipated organisms, although the swab technique had a higher yield of anaerobes.[92] Although *S. aureus* is the most common pathogen found in non-IDUs, streptococci and anaerobes were found more frequently among IDUs in at least one more recent study.[93] MRSA was detected equally in both groups. Methamphetamine was found to be a risk factor for MRSA infection in IDUs presenting to emergency departments in Georgia. Unsterile injection practices did not appear to be a risk factor because only 12.5% of patients injected the drug compared with 62.5% who either smoked or inhaled. The most significant risk factor among methamphetamine users was a skin infection within the previous 3 months (adjusted OR, 7.92). The authors noted that methamphetamine use causes formication, a sensation of something crawling on the skin. This sensation prompts the user to pick at the skin, which can lead to skin breakdown and subsequently serves as a focus for infection.[94] Among the staphylococci, MRSA has become the predominant strain, particularly CA-MRSA. Disease caused by CA-MRSA is most often a single lesion in an extremity, although multiple furuncles are also seen. Recurrences are common.[95] Coagulase-negative staphylococci and α-hemolytic streptococci are also seen. Among the latter, the *Streptococcus anginosus (milleri)* group is most important, especially in addicts in Scotland, who inject tablets of buprenorphine and temazepam after crushing them between their teeth.[96,97] Other oral flora have been reported, in particular, *Eikenella corrodens,* which in some centers has become the third most common pathogen. IDUs who lick their needles or contaminate their drugs with saliva are particularly prone to this infection. The pneumococcus is also occasionally found in this setting. Gram-negative bacilli are found with variable frequency. In the past, anaerobes were found infrequently, particularly in upper extremity infection. In one study, 39% of isolates from IDUs contained both aerobes and anaerobes compared with only 27% of isolates from nonusers. In addition, anaerobes, either alone or as part of a mixed flora, were detected more frequently in drug users than in nonusers (44% vs. 35%).[98]

Diagnosis of Abscess

The diagnosis of an abscess can be difficult. Patients typically have single lesions. The signs and symptoms are similar to patients with cellulitis alone. Indeed, most patients will also have an area of adjacent cellulitis. Less than half of patients are febrile. Erythema, pain, and tenderness of the affected site are common, but fluctuance is absent in approximately 25%.[99] Deep abscesses may be particularly difficult to detect.[100] Computed tomography (CT) is useful for locating cervical abscesses[101] and is probably effective for detecting abscesses in the groin and femoral region. Magnetic resonance imaging (MRI) is also useful, particularly in infection of the extremities.[102] Ultrasonography has been reported to be useful but is of variable accuracy, particularly when diagnosing lesions in the groin. Bedside ultrasound has been used in an emergency department setting with a high degree of accuracy. These machines are portable, have the advantage of being available while the patient is in the emergency department, can be completed in less than 1 minute, and are comfortable for the patient. In one large study in an emergency department, abscesses were found in 37% of addicts who were tested. There were only five false-positive studies, two of which were determined to be hematomas rather than abscesses. The sensitivity of ultrasound was 98% compared with only 86% for clinical examination alone. The specificity was 85%, with a positive predictive value of 93% and a negative predictive value of 97%. An unanticipated but important additional benefit of ultrasonography is that pseudoaneurysms that otherwise might have been misidentified as abscesses were also detected, thus avoiding a dangerous attempted incision and drainage.[103]

Management of Soft Tissue Infections

The first decision in the management of patients with soft tissue infections is whether the patient should be admitted to a hospital. This can be a difficult decision, but it depends on the severity of the illness. Eron and colleagues[104] recommend an approach in which patients are assigned to one of four classes. Class 1 patients have no signs of systemic toxicity and have no uncontrolled comorbid conditions. These patients usually respond to topical or oral therapy. Class 2 patients either have evidence of systemic illness but without any unstable, comorbid conditions or are systemically well but have one or more comorbid conditions that may complicate the outcome. Class 3 patients are toxic or are not toxic but have unstable comorbid conditions that may interfere with the response to therapy. Class 4 patients have sepsis syndrome or a serious life-threatening infection such as necrotizing fasciitis. Predictors of severe infection are hypotension, tachycardia, temperature lower than 35°C (95°F) or higher than 40°C (104°F), confusion, or a depressed level of consciousness. Patients with two or more of these findings have a blunted response to antibiotics and poor outcome. In terms of the decision whether to admit the patient to the hospital, class 1 patients most likely will do well if managed as outpatients. Class 2 patients may benefit from a period of observation; patients who respond quickly can be treated as outpatients, but others will require hospital admission. Patients in classes 3 and 4 should be treated as inpatients.

Determining the appropriate antibiotic is the next decision. Class 1 patients usually respond to oral antibiotics, as do some in class 2. Initial therapy with parenteral agents with rapid switch to oral agents may be preferable for class 2 patients. Patients with more serious illness should be treated with parenteral therapy, at least until they respond satisfactorily. Data from randomized trials to guide the duration of therapy are insufficient. In most cases, 1 to 2 weeks of treatment is adequate, but infection may recur in up to 20%; thus prevention of future infections cannot be ignored.[104] Empirical therapy aimed at the usual pathogens is usually adequate, although in at least one medical center, patients with hand abscesses were found to be 11 times more likely to be infected with a clindamycin-resistant MRSA than other patients.[105] Thus it may be important to be aware of local resistance patterns before initiating empirical treatment.

As with other patients, incision and drainage remains the mainstay of treatment of abscesses in IDUs. Infection in the deltoid region is a consequence of skin popping and subsequent necrosis of the underlying fascia. In these cases, drainage may be facilitated by ultrasound-guided aspiration, even in the emergency department setting.[106] Regardless of location, cure rates for drainage alone may approach 80%; however, the addition of trimethoprim-sulfamethoxazole for 7 days is associated with a significantly higher cure rate and is effective at preventing many secondary complications such as need for repeat drainage or metastatic spread of infection.[107]

Antibiotic therapy is directed at the organisms recovered from the blood or purulent material. In uncomplicated cellulitis, cultures are seldom helpful. In such cases, therapy is empirical and is based on the pathogens most commonly encountered in that geographic location. Prolonged antibiotic treatment is frequently required.[108] As noted previously, early surgical drainage of abscesses is essential; because of the tendency of these lesions to spread to adjacent or distant regions, multiple drainage procedures may be required.[109] Deep infections of the hand are far more common in IDUs than in non-IDUs, and they mandate a unique approach. The microbiology of such infections varies depending on the injected substances. Patients who primarily inject cocaine have a high frequency of mixed anaerobic infection,[99] whereas heroin users are more likely to harbor streptococci and staphylococci.[110] In either case, surgical débridement is far more likely to be required in IDUs than in non-IDUs.[48] Some caution is indicated before incising a lesion in the vicinity of blood vessels because a mycotic pseudoaneurysm can easily be misdiagnosed as an abscess. Inadvertent entry into such a lesion can have disastrous consequences. Inadvertent intraarterial injection of crushed tablets leading to hand swelling mimicking infection

has also been reported. Failure to make the correct diagnosis may lead to loss of digits due to extreme ischemia.[111]

Skin Ulcers

Skin ulcers are extremely common in IDUs. They are found at every conceivable site but are particularly common below the knee, close to the ankle.[112] They arise from tissue damage caused by repeated nonsterile injection into the same site with associated thrombosis and infection. Synergy between streptococcal infection and cocaine-induced tissue ischemia may lead to large necrotic ulcerations and extensive tissue loss.[97] Alternatively, skin ulcerations may result from necrosis induced by the illicit substance injected. Skin ulcers may persist for years and are a frequent reason for hospitalization. Typically, they have ragged edges and seropurulent drainage. Patients experience severe pain, and it is often the pain, rather than the ulcer itself, that brings the patient to medical attention. The microbiology of these lesions is similar to that of other soft tissue infections in addicts, although they more frequently contain more than one organism. *S. aureus* and β-hemolytic streptococci remain the most common isolates, with gram-negative bacilli—most often *Klebsiella, Pseudomonas, Escherichia coli,* and *Proteus*—playing an important role. Skin ulcers present particularly difficult management problems when they involve the hands and feet, and they may ultimately lead to loss of function.

Treatment of skin ulcers requires administration of systemic antibiotics and prolonged local wound care, including gentle washing, wet-to-dry dressings, and application of topical antibacterial creams. Elevation of the leg to reduce edema is an important component of the therapy and plays a role in pain management.[113] Generally, parenteral antibiotics are continued until the wound is covered by granulation tissue. Very large lesions may require skin grafting or muscle flaps, but these are effective only after all necrotic tissue has been removed and the wound is clean and granulating. An important adjuvant treatment is the application of compression dressings, such as Unna boots, which, when properly applied, serve to reduce edema as well as to promote wound healing.[114] With time, most skin ulcers heal completely, leaving circular, punched-out scars.

The most important complication is contiguous osteomyelitis, which may be difficult to diagnose because radiologic evidence frequently indicates periosteal reaction in bones immediately beneath large ulcers. When there is still a question of osteomyelitis, a triple-phase bone scan or MRI may be helpful. Ultimately a diagnosis of osteomyelitis may be impossible without a bone biopsy, which may be difficult to obtain without traversing infected superficial tissues. In such cases, prolonged parenteral antibiotic therapy directed at the organism cultured from the ulcer and careful radiographic follow-up may be the best approach. A combination of codeine tablets cooked with a solvent (gasoline, lighter fluid, or paint thinner) creates a drug called desomorphine, known as krokodil because of the scaly green patches that develop at the injection sites. Ultimately these lesions may ulcerate, and underlying osteomyelitis is known to occur. As with similar ulcers, a team approach and local care are required for resolution.[115]

Paradoxically, IDUs may wish to prevent healing of these ulcers because once well-vascularized granulation tissue forms, the ulcers become an excellent location in which to inject. These lesions are referred to as "shooter's patches." They may be successfully managed by use of a well-vascularized muscle flap, providing even better access to the circulation. The competing goals of the clinicians and the IDU are a source of continued frustration for the health care team.[116]

Necrotizing Fasciitis

Necrotizing fasciitis, without or with myositis, is the single infection in IDUs that is most likely to need immediate and appropriate treatment. In one institution the prevalence increased significantly in the period 2009–2010 solely due to an increase in admissions of IDUs.[117] However, the clinical picture is subtle and rarely elicits the emergency response required. At San Francisco General Hospital, 1% of IDUs in need of incision and drainage for soft tissue infection were found to have necrotizing infection requiring extensive débridement. The classic findings of high fever, bullae, crepitance, and skin necrosis are usually absent initially, and the impression may be that of mild cellulitis.[110] In some cases, the true nature of the disease may be so subtle as to be missed during a procedure to débride an abscess or cellulitis. Alternatively, infection may spread after an apparently effective incision and drainage.[118] The major indication of the true nature of the infection is the fact that signs and symptoms, such as pain and hemodynamic instability, are disproportionate to the apparent extent of the local process.[110] However, this can be misleading because the clinical presentation may be no different from routine cellulitis, with no more than erythema of the involved area, providing no clue to the serious underlying pathologic process.[119] Also, because addicts are frequently viewed as drug-seeking complainers, patients with excessive complaints for what appears to be a minor disease may be interpreted as exhibiting narcotic-seeking behavior. This misperception can further delay recognition of the need for aggressive and rapid action. In one study the correct diagnosis was made in only 59% of patients who presented to an emergency department, and many were initially admitted to a nonsurgical service.[120] Others argue that the best results are achieved by admission directly to a vascular surgery service.[121] Regardless of the admitting service, it is clear that a high index of suspicion is required so as not to miss the correct diagnosis. Additional clues to the serious nature of the problem are hemodynamic instability, increased creatinine level, local anesthesia, rapid progression of inflammation, or the presence of blue or hemorrhagic bullae. Crepitance is an important clue when present. Although a rapid test is not yet available, the finding of the proinflammatory cytokine interleukin-1 receptor antagonist with markedly elevated white blood cell count has been associated with fatal outcome in patients with necrotizing fasciitis, especially in the absence of fever.[122] Finally, a slow response to appropriate antibiotic treatment suggests a deeper underlying problem. MRI and CT may be useful diagnostic tools. Characteristic findings include asymmetrical fascial thickening and fat stranding, followed by gas tracking along fascial planes. Abscesses may also be seen.[123] CT scans may be misleading because both false-positive and false-negative results have been reported, and contrast enhancement contributes no additional information. The only definitive test is surgical exploration, which is both diagnostic and therapeutic. The finding of necrosis is characteristic; however, it may be necessary to explore more than one area. A negative biopsy result from one location does not preclude the diagnosis in adjacent tissues.[124]

As with most infections in IDUs, gram-positive organisms are usually found. However, β-hemolytic streptococci predominate in approximately 50% of cases, followed by *S. aureus,* α-hemolytic streptococci, and coagulase-negative staphylococci. Gram-negative organisms are infrequent and are usually represented by enteric pathogens, especially *E. coli, Klebsiella, Proteus mirabilis, Pseudomonas,* and *Enterobacter.* Anaerobes are recovered in 12% of cases, including *Clostridium sordellii* in one series of black tar heroin users[125]; yeasts (*Candida* spp.) are uncommon. Polymicrobial infection is common.[126] Cultures are imperative, as occasionally unusual organisms are detected, as in the case of IDUs with *C. novyi* as the sole cause of necrotizing fasciitis.[127]

Management of necrotizing fasciitis by antibiotics alone leads to progression of the infection in 75% of patients. Parenteral antibiotics and aggressive surgery coupled with reexploration at 24 hours and as often as necessary afterward to ensure complete removal of all necrotic tissue offer the best prognosis. In one study, IDUs required an average of 3.4 débridements for necrotizing fasciitis.[126] Aggressive nutritional support and early coverage of the soft tissue defect have been shown to improve the outcome.[128] Even with aggressive treatment, the mortality rate is high, ranging from 10% to 23%, and amputation is required in up to 10% of patients. Patients with group A streptococcal infection and streptococcal sepsis appear to have the worst prognosis.[126,129] The best results are achieved with the use of vacuum-assisted therapy in addition to extensive débridement.[130] Addicts, who tend to be young and relatively healthy, have the best outcome of any patient group with this disease.

Pyomyositis

Pyomyositis, a less serious infection involving the musculature, occurs frequently in IDUs. Direct inoculation of bacteria into the musculature has been implicated. Hematogenous spread also occurs, occasionally as a complication of endocarditis.[131] Most patients who have pyomyositis

present with pain and swelling of the affected area. Lesions have been reported in the deltoid, psoas, biceps, gastrocnemius, gluteal, and quadriceps muscles. Ultrasound, CT, or MRI shows the underlying defect within the muscle. *S. aureus* is the most common pathogen; infection with viridans streptococci, infection with aerobic gram-negative bacilli, and mixed infection with anaerobes have also been reported. Patients respond well to drainage and antibiotic therapy. A rare but related condition, uterine pyomyoma, has also been reported. The cause appears to be hematogenous dissemination to an infarcted leiomyoma.[132]

Just as needle exchange programs reduce HIV infection among IDUs, combining needle exchange programs with a wound and abscess clinic may substantially reduce the cost of care (to as low as $5.00 per patient) and the number of visits to emergency departments. Widespread implementation of such clinics could have a major impact on the management of skin and soft tissue infections among IDUs.[133]

Injection Anthrax

Over the past several years a cluster of cases of injection anthrax have been identified among IDUs in the United Kingdom and Germany. The first recognized case occurred in a skin popper who was diagnosed in 2000. After a lull, additional cases were seen between December 2009 and December 2010. There were 54 confirmed cases, and 18 deaths occurred. Sporadic cases still occur.[134] In contrast to classic cutaneous anthrax, cases do not manifest as an eschar. These patients typically present with severe tissue swelling and evidence of soft tissue infection occurring 1 to 10 days after injecting heroin. The injection was frequently in the subcutaneous tissues. Initially the lesions were often similar to typical soft tissue infections seen in IDUs; however, blood cultures were often positive for *Bacillus anthracis.* Other diagnoses were also confirmed via polymerase chain reaction (PCR) assay of tissue from wounds. Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry was also used successfully in several cases.[135] Cultures of *B. anthracis* can be easily misidentified as *Bacillus cereus.* In suspected anthrax cases, special techniques should be used to verify the identification of the isolate.

Patients in this outbreak were treated with a variety of different antibiotic regimens. Empirical therapy, including ciprofloxacin and clindamycin with additional antibiotics combined into a five-drug regimen, is recommended. In addition, aggressive surgical débridement with or without fasciotomy is considered necessary, and repeat débridement may be required.

The epidemiology of this outbreak is currently unclear, but it is most likely related to the transportation of heroin from Afghanistan, the site of origin, to Western Europe and the United Kingdom hidden in goat skins. It appears these goat skins were likely contaminated with anthrax spores that germinated once injected into the warm tissues of the patients.[136]

BONE AND JOINT INFECTIONS

Epidemiology of Skeletal Infections

Skeletal infections are common in IDUs, most occurring via hematogenous seeding by bacteria or fungi.[137] Target sites for infection are determined by the blood supply and predominantly involve the axial skeleton. The original source of these infections may not be apparent, or the infections may represent metastatic complications of endocarditis. Injection drug use has been identified as a risk factor for osteoarticular infection in patients with endocarditis.[138] In addition, bone and joint infections frequently result from contiguous spread from adjacent, often neglected, areas of infection in skin and soft tissues. IDUs with hematogenous infection often have multiple sites involved simultaneously, and blood cultures frequently are negative at the time of presentation. IDUs with HIV infection do not appear to be at increased risk for osteoarticular infections, and when these infections do occur, they are most frequently caused by the usual bacterial pathogens, not opportunistic pathogens.[139,140]

IDUs with skeletal infection tend to be young and otherwise healthy. Clinical findings include constitutional manifestations and local signs and symptoms depending on the site involved. Patients with osteomyelitis often have a paucity of findings, presenting with local pain and tenderness only. Lack of signs and symptoms frequently results in delay in diagnosis. Fever is absent in one-third of patients.[141] Similarly, signs of sepsis and leukocytosis and radiologic signs may be absent in patients with osteomyelitis.

Pyogenic infections predominate, with almost 90% being bacterial in origin, although virtually any organism can cause skeletal infections. The predominant pathogen isolated is *S. aureus,* with one large series finding almost one-fifth of cases due to coagulase-negative staphylococci (half associated with hardware).[142] Gram-negative bacilli are responsible for one-fifth of cases, with about half of these due to *Pseudomonas aeruginosa*. Polymicrobial infections are reported in 46% of osteomyelitis cases but only 15% of septic arthritis cases.[142] Anaerobes are isolated from as many as one-fifth of bone infections but rarely cause septic arthritis. IDUs who lick their needles or the skin surface before injection may develop osteomyelitis or septic arthritis with *E. corrodens* ("needle licker's osteomyelitis").[143] *Candida* spp. have been increasingly recognized as a possible etiology of skeletal infections in IDUs, particularly spondylodiscitis and vertebral osteomyelitis.[144] A characteristic form of systemic candidiasis has been reported among IDUs who inject heroin that includes folliculitis, usually of the scalp and beard; endophthalmitis; and bone and joint lesions, most often costochondritis. Lastly, *Mycobacterium tuberculosis* should always be considered among the possible causes of skeletal infection in IDUs, particularly vertebral osteomyelitis.[145] As many as 20% of infections are culture negative. Because the microbiologic differential diagnosis is broad, nucleic acid amplification techniques should be used in these cases in an attempt to confirm the microbial etiology of the infection.

Site of Skeletal Infection

Joint infections usually involve the extremities, most commonly affecting the knee. The incidence of left-sided knee arthritis exceeds right-sided knee arthritis, possibly because of the tendency of right-handed IDUs to inject into the left groin veins; this suggests a relationship between site of injection and infection.[141] IDUs are particularly susceptible to vertebral osteomyelitis. IDUs with vertebral osteomyelitis are more likely to present with symptoms of a shorter duration and have more profound neurologic deficits, likely owing to the higher incidence of cervical spine involvement compared with non-IDUs.[146] Primary sternal osteomyelitis, often associated with an antecedent history of blunt trauma to the sternum, is reported in IDUs. This group is also prone to septic arthritis in unusual sites such as the sternoclavicular and costochondral joints and the pubic symphysis. Other sites frequently involved include wrist, shoulder, hip, and sacroiliac joints. Vertebral osteomyelitis may extend into the subdural or epidural spaces and may cause formation of an abscess, with consequent cord compression and paraplegia. In addition, lumbosacral vertebral osteomyelitis may be associated with psoas abscess.

Diagnosis and Management of Skeletal Infections

Because of the wide spectrum of organisms that may be involved, diagnostic needle aspiration for smear and culture is necessary in all cases. Even when blood cultures are positive, invasive diagnostic steps are advised because skeletal and bloodstream infection may represent two separate processes, and infections may be polymicrobial. Frequent arthrocentesis, arthroscopic or open drainage, and débridement of nonviable bone are also advised if clinically indicated. Antibiotic therapy is required for 4 to 6 weeks, with the selection of drug based on the identity of the responsible microorganisms and susceptibility data. Increasingly, oral antimicrobial agents with high bioavailability and good bone penetration are used for at least a portion of the therapeutic course.[147,148]

Overall, with early diagnosis, the immediate prognosis of bone and joint infection in IDUs is excellent, but long-term follow-up data are lacking.[141] Many IDUs present late in the clinical course, and delays in diagnosis and institution of therapy are accompanied by a high likelihood of chronic osteomyelitis and late relapse of disease. Also contributing to this late but frequent complication is the problem of nonadherence. IDUs tend to leave the hospital against medical advice when confronted with prolonged intravenous antibiotic therapy in a skilled nursing facility, and many physicians are reluctant to consider outpatient parenteral

antibiotic therapy in patients who are active IDUs. A tendency for medical personnel to underappreciate and undertreat the pain associated with skeletal infection may also lead to patients leaving the hospital before discharge planning can be completed. A retrospective review of discharge to a residential addiction treatment facility to complete parenteral antibiotics showed high rates of success and substantial cost savings for the health system.[149]

BACTEREMIA AND INFECTIVE ENDOCARDITIS

Epidemiology

Bacteremia is common in IDUs, often with resultant infective endocarditis (IE). In the Detroit Medical Center, 74 of 180 addicts with bacteremia had endocarditis.[150] In North Carolina, there was more than a 12-fold increase in the number of hospitalizations for injection drug use–related IE from 0.2 to 2.7 per 100,000 per year between 2010 and 2015.[4] The associated hospital costs during the same period increased from $1.1 million in 2010 to $22.2 million in 2015. At the same time there was a remarkable shift in the prevalence of IE from urban to rural populations in North Carolina and elsewhere.[2] The increase occurred while the use of heroin remained stable and was largely the result of the dramatic increase in the use of prescription opioid medications. This transformation from primarily urban to rural populations forced to handle this new influx of addiction-related endocarditis has major implications for the overall health care system. In one setting, a single patient who had multiple episodes of IE was responsible for the institutional cost of $380,000, not counting the cost of providers and eventual cardiac surgery that was performed elsewhere. In part, this was due to a system unwilling to pay for drug rehabilitation services that may have prevented subsequent admissions.[46] In contrast to the United States and with some exceptions, in Western Europe the prevalence of IE among IDUs has decreased, leading to a corresponding decrease in hospital admissions for right-sided endocarditis; serious cases of left-sided IE are still seen.[151] In Central and Eastern Europe, there has been an increase in injection drug use and, in contrast to the West where polymicrobial IE has decreased, there has been an apparent increase in IE.[151] In Scotland the injection of a new psychoactive substance referred to a "burst" (variably butylone, methiopropamine, or ethylphenidate) led to a dramatic increase in IE and necrotizing pneumonia cases, all of which were associated with *S. aureus* infection.[152] A Swedish referral center saw an increase of cases of addiction-related IE but experienced a lower mortality rate, perhaps due to the implementation of a multidisciplinary team to handle these infections.[153]

HIV infection also has had an effect on the epidemiology of IE among IDUs. The rate in this population now appears to be similar to the rate of prosthetic valve infection, approximately 1% per year. The incidence of IE is higher among IDUs with HIV than among seronegative IDUs (24.8 vs. 3.9 cases/10,000 person-years). With the widespread adoption of antiretroviral therapy (ART), the overall incidence has decreased.[154] An inverse relationship between IE and $CD4^+$ lymphocyte count (OR for 200–499 cells/mm^3, 2.01; OR for <200 cells/mm^3, 3.61) had been reported and undoubtedly still exists among patients with advanced disease.[155]

In most early studies, men were affected more often than women (5.4:1 in the Detroit Medical Center, 2:1 in Chicago), and men with IE were older than women and had significantly longer histories of drug use (10.2 years vs. 7.1 years). However, among addicts with HIV infection, women had an increased risk (OR, 3.26), a rate that was similar to addicts with increased injection frequency. The reason for this difference is unclear, but it may be due to women having smaller veins, making it more difficult to inject, which might lead to more local infections and subsequent bacteremia. Greater risk-taking behavior may also be a factor. HCV infection was an associated factor in 100% of IDUs with IE in Taiwan. Injection drug use is also a risk factor for relapsing (≤41%) and polymicrobial (8%) IE.[156] Among patients with recurrent disease, the median interval between episodes is far shorter in addicts than in nonaddicts.[157] In areas where buprenorphine lacks the inhibitor compound that is active only when injected, such as in Singapore, addicts have turned to injection, with the consequence of an increased rate of IE.[158] Cocaine use is an additional risk factor. In contrast, alcohol consumption confers protection against endocarditis, perhaps by inducing an inhibitory effect on platelet function.[155]

Microbiology

S. aureus remains the most common pathogen, affecting the tricuspid or pulmonary valve in approximately 90% of cases. Coagulase-negative staphylococci are an uncommon cause of endocarditis in IDUs. Streptococci, particularly groups A, B, and G, are the second most common pathogens.[150,159] These two organisms account for up to 75% of cases.[150] Ruppen and colleagues[160] found *Streptococcus dysgalactiae* to be common over a 10-year period, 2006–15, with a predominance among female addicts. *Enterococcus* played a major role in the past, but its prevalence is decreasing.[150,159] Gram-negative organisms are infrequent causes. Intermittent epidemics of *P. aeruginosa* endocarditis have occurred in Detroit and Chicago. The most recent epidemic occurred in Detroit during the years 2006–08. There were 10 cases, all in HIV-negative patients. Five were left-sided, three of which occurred on prosthetic valves. Four patients had tricuspid infection alone, and one had aortic and tricuspid disease. In one case, *Pseudomonas* was combined with *Candida parapsilosis*.[161] *Serratia marcescens* was responsible for a sustained epidemic in the Oakland, California, area[162,163] and occurs sporadically.[164] Gram-negative endocarditis in IDUs is not common outside the HACEK group (*Haemophilus* spp., *Aggregatibacter* spp., *Cardiobacterium hominis, E. corrodens,* and *Kingella* spp.). In one report, only 2 of 49 cases of gram-negative endocarditis occurred in IDUs.[165]

Among the fungi, *Candida* endocarditis (typically non–*C. albicans*) is most common. In one series of *Candida* endocarditis, 9 of 30 cases were in IDUs: 3 of *C. parapsilosis;* 3 of *C. albicans;* and 1 each of *C. tropicalis, C. guilliermondii,* and *C. pelliculosa.* All patients had left-sided infection, but the mortality risk was lower among IDUs (OR, 0.12; 95% confidence interval [CI], 0.02–0.7; $P = .03$). One death occurred at day 4 owing to a brain embolism, and the others occurred remotely: one at 3 months from an unknown cause and one at 1 year due to *S. aureus* IE.[166] *Aspergillus* endocarditis in addicts has also been reported.[167] Two of three patients were HIV infected. Duration of symptoms ranged from 2 weeks to 1 month before detection. Blood cultures were negative, but there were large vegetations and peripheral embolization. *Aspergillus* frequently contaminates illicit drugs, but whether the inoculum associated with injection is sufficient to cause endocarditis is unclear. That two of three patients were HIV positive is of interest and may indicate that altered immune status played a role.

Polymicrobial endocarditis is observed with increasing frequency among drug users. Usually only a few organisms are involved, but rarely there may be numerous pathogens. In such cases, standard laboratory techniques may be inadequate to isolate and identify the full microbial spectrum, placing a burden on the clinician to suspect polymicrobial endocarditis caused by salivary contamination of needles or injection sites whenever uncommon oropharyngeal organisms are cultured from the blood.[168] *E. corrodens* is often found in polymicrobial IE, frequently in association with *Streptococcus constellatus.* These organisms may be a synergistic combination, owing to coinciding metabolic niches. They coaggregated during in vitro growth, and in animal models, *E. corrodens* produced endocarditis only if injected with streptococci.[156] Among the fastidious organisms, in addition to *Eikenella* there are reports of endocarditis caused by anaerobes such as *Fusobacterium* spp. and *Clostridium.* Sporadic reports document the occurrence of *B. cereus* bacteremia in IDUs, who, in contrast to immunocompromised patients infected with this pathogen, tend to have uncomplicated infections that may even resolve without therapy.[169] In addition, numerous reports describe endocarditis in IDUs caused by a variety of organisms that are frequently considered nonpathogens. These infections may be related to altered host immunity resulting from HIV infection[170] or to unusual practices among addicts such as licking needles before use or "cleaning" the injection site with saliva. Given the proclivity of addicts to experiment with novel substances to inject, almost any microorganism can be found in the blood of IDUs, as exemplified by the isolation of *Paenibacillus larvae,* an organism that lives in honey and causes severe disease in honeybees, in the blood of addicts. These IDUs injected methadone that had been previously mixed with honey to make it too viscous to inject.[171]

Pathophysiology

The pathophysiology of endocarditis in addicts is poorly understood. The organism is most often part of the patient's own flora,[150,172] although injection paraphernalia have been implicated in the case of *P. aeruginosa* endocarditis. Environmental contamination was also considered in the initial outbreak of *Serratia* endocarditis in California when it was learned that years earlier *Serratia* had been sprayed into the air to study wind currents. However, these strains were not the same ones that caused disease, and the regional predilection for this infection remains unknown. It is also unclear why certain valves are affected in IDUs with endocarditis. It is known that, in contrast to native valve endocarditis in nonaddicts, the affected cardiac valve is almost always previously normal.[150,173,174] In an autopsy study of addicts who died of endocarditis, Dressler and Roberts[173] reported that 81% of the valves were normal, including all right-sided valves. Early reports of endocarditis in addicts noted a predominance of tricuspid valve involvement. Left-sided involvement predominates in some recent studies, and multiple valves are frequently involved.[159,175] Pulmonary involvement remains rare and may be misdiagnosed as pneumonia.[176] Nevertheless, tricuspid valve involvement is seen almost exclusively in IDUs.

No single hypothesis explains the prevalence of right-sided involvement in IDUs. Potential explanations include damage to right-sided endothelium by repeated exposure to injected particulate matter; vasospasm caused by injected diluents or illicit drugs, particularly cocaine; or drug-induced thrombus formation and subsequent bacterial aggregation. The fact that endocarditis caused by *Enterococcus* and *Serratia* is primarily a left-sided phenomenon suggests that other mechanisms must be important. Mitral valve prolapse has been proposed to explain the predilection for mitral valve endocarditis in female IDUs, but studies showing equal numbers of men and women with mitral involvement make this explanation unlikely. Specific surface properties of the common infecting pathogens, especially *S. aureus,* might favor attachment to extracellular matrix proteins that may have greater expression on right-sided valves. *S. aureus* is also phagocytized by endothelial cells, where it is protected from host defenses. This may activate the clotting system, leading to vegetation formation. The production of coagulase by *S. aureus* may further promote clotting and vegetation formation. Cytokines produced after phagocytosis may enhance immune complex deposition that leads to valvulitis, thereby creating a lesion that is susceptible to vegetation formation and bacterial seeding. Finally, endothelial differences between the right and left sides of the heart might contribute to the predilection for tricuspid valve involvement. Additional hypotheses invoke an association between large, directly injected bacterial inocula and immune abnormalities that may contribute to sustained bacteremia and valvulitis[177] or even drug-induced pulmonary hypertension leading to increased right-sided turbulence.[178] Which, if any, of these mechanisms proves to be responsible for the preponderance of right-sided involvement depends on future studies. There are differences in the involved valve that appear to be related to the drug the IDU injects. Heroin use is far more likely to lead to tricuspid valve infection than use of methamphetamines or cocaine.[179] One potential explanation is that heroin leads to elevated pulmonary pressure due to respiratory suppression, which in turn causes tricuspid regurgitation, abnormal blood flow with eddy currents, and subsequent IE. In contrast, methamphetamines and cocaine cause a dramatic increase in systemic afterload that leads to mitral and aortic valve regurgitation and ultimately a higher risk for endocarditis. Whatever the reason, *S. aureus* predominantly affects the tricuspid valve but may also involve the mitral or aortic valves. *S. marcescens, Streptococcus pyogenes,* and enterococci affect left-sided valves almost exclusively.[163,180,181]

Clinical Manifestations

In contrast to nonaddicts, who generally present with symptoms of longer than 2 weeks' duration,[182] most addicts with IE present within the first week of illness with signs indicative of severe, acute infection.[150,159,183] Typically, they have acute onset of fever, chills, and dyspnea. Chest pain, often pleuritic in nature and associated with hemoptysis due to septic pulmonary emboli, occurs in up to 75% of cases of tricuspid endocarditis. Any IDU presenting with unrelenting spiking fever, bacteremia, and pulmonary symptoms such as cough and hemoptysis should be considered to have right-sided IE.[184] At presentation, more than 50% of chest x-rays reveal multiple pulmonary infiltrates, often with central cavitation, compatible with septic pulmonary emboli.[184] CT reveals the same findings but often to a greater extent. These lesions typically are more plentiful in the lower lobes, perhaps due to the effect of gravity, and frequently increase for several days despite the initiation of effective antimicrobial therapy. Pneumothorax, occasionally bilateral, is a complication of septic pulmonary embolism.[185] Involvement of other organ systems is similar to that observed in endocarditis in nonaddicts. Initially, central nervous system (CNS) involvement may be confused with toxic effects of illicit drugs, but the diagnosis usually becomes rapidly apparent when blood cultures become positive.

The overall severity of the clinical picture depends on the valve or valves involved and whether there is any associated damage to the heart itself such as valve ring abscess or valve rupture or metastatic infection involving other organs. In our study, IDUs with endocarditis who required admission to an intensive care unit had severe sepsis and shock (36%) or respiratory failure (33%) or had neurologic deterioration (18%). *S. aureus* was the etiologic agent in 94%, although polymicrobial infection was found in 15%. Most patients had septic emboli to one or more organs, including the lung in 36% and the CNS in 21%. Independent risk factors for mortality were a previous history of IE and an increased Acute Physiology and Chronic Health Evaluation (APACHE II) score.[186]

Osler nodes and Janeway lesions are rare in addicts. Splenomegaly occurs in only 10% to 15%, and heart murmurs are found with variable frequency. When the infection is confined to the tricuspid valve, the presence of murmurs ranges from 35% to 72%.[150]

Because of the high-grade bacteremia and acute nature of endocarditis in addicts, every organ is affected to some degree. Complications involving the heart, although infrequent, may be life threatening. When cardiac problems dominate the clinical picture, which is most likely with mitral or aortic valve infections, the prognosis is poor, especially if congestive heart failure develops. As noted earlier, recurrent IE is common in addicts. Most patients survive the first episode but with such severely damaged valves that dysfunction occurs in almost 70%. Previous valve damage predisposes to subsequent episodes, which frequently are fatal. Additional cardiac lesions include left ventricular abscesses, which are multifocal and are found in conjunction with clusters of bacteria in intramural arteries, and myocardial infarction. Valve ring abscesses and, rarely, focal, acute interstitial myocarditis are also found.[173,187] Cardiac abscesses may also lead to further serious complications such as a pseudoaneurysm of the heart, which can be demonstrated by MRI and color Doppler ultrasound evaluation.[188] As with nonaddicts, left-sided infection predisposes to systemic emboli and acute pericarditis. Certain organisms, especially *Serratia* and *Candida,* are notable for their tendency to induce large, systemic emboli. Their isolation in a patient with endocarditis should alert the clinician to the probability of left-sided infection and the likelihood of a serious embolic event. CNS complications of endocarditis are similar to those in non-IDUs and include mycotic aneurysms, brain abscess, stroke, meningitis, and epidural abscess. Splenic abscesses are seen, especially with *S. aureus* infection, and should be assessed before cardiac surgery to avoid valve replacement in a patient likely to remain bacteremic from a noncardiac source. Drug users are more likely than nonusers to develop bone and joint infection, particularly vertebral osteomyelitis, secondary to endocarditis.[189]

Diagnosis

The diagnosis of endocarditis in IDUs is often easily made on the basis of the characteristic clinical picture, yet IDUs with right-sided IE, even due to *S. aureus,* frequently have very limited clinical findings.[190] The modified Duke criteria effectively classify IDUs with either definite or possible endocarditis and can be used in difficult cases, particularly when difficult therapeutic decisions must be made.[191] Despite the utility of this schema, it should be noted that the Duke criteria were validated for endocarditis caused by bacteria and may not be an accurate assessment for patients with fungal infection. Patients with definite IE frequently have no obvious focus of infection and are more likely to have vascular phenomena and multiple opacities on chest radiographs.[192] However, in the emergency department setting, the absence of signs specific for endocarditis and the limited information available make the diagnosis

particularly difficult.[193] At the time of the initial presentation, there are no differences in age, sex, maximum temperature, or leukocyte count between addicts with and without endocarditis. Addicts with endocarditis account for only 13% of addicts admitted for infection; positive echocardiogram findings, pulmonary or systemic emboli, and bacteremia distinguish patients with endocarditis from patients without endocarditis.[194]

Rothman and colleagues[195] further modified the Duke criteria in an effort to improve diagnostic accuracy in an urban emergency department. Major criteria are the same as the Duke criteria, although an echocardiogram performed on arrival at the hospital is added, and only data available in the first 24 hours are used. Minor criteria are unchanged. The definition of definite endocarditis is the same as in the Duke system; possible endocarditis requires either one major and two minor criteria or four minor criteria. The diagnosis is rejected if these criteria are not met. The results were almost identical to published results that used the standard Duke criteria, but the investigators were able to make admission and therapeutic decisions much earlier than was otherwise possible. The same investigators also evaluated the contribution to diagnosis of transthoracic echocardiography (TTE) in the emergency department. The addition of TTE proved diagnostic for nearly 70% of patients who failed to meet major culture criteria.[196] In another attempt to arrive at earlier diagnosis, investigators used PCR assay to detect universal 16S ribosomal RNA. They found a sensitivity and specificity of only 86.7% and 86.9%, respectively, but accurately identified all eight patients with blood culture–positive endocarditis.[197] If validated, this method may provide an additional diagnostic tool for the emergency department clinician.

Chung-Esaki and colleagues[198] evaluated a prediction rule to assist in the diagnosis of IDUs in the emergency department setting. In their model, patients with tachycardia, cardiac murmur, and absence of skin infection had a sensitivity of 100% (95% CI, 82%–100%) but, perhaps more importantly, a negative predictive value of 100% (95% CI, 88%–100%). Although by using this model in their study they were able to rule out IE in only 12% of cases, given the difficulty of excluding IE by other means, such an approach may prove useful in the emergency department setting.

The most sensitive indicator of endocarditis in IDUs is a blood culture, which is positive in 80% to 100% of cases. However, because many addicts take oral antibiotics before admission, initial cultures may be negative. Subsequent blood cultures reveal the pathogen.[199] Even after several days of appropriate parenteral therapy, blood cultures are still likely to be positive.[200,201] Because culture-negative IE is rare in IDUs, negative blood cultures suggest an alternative diagnosis.

Additional blood studies are not of particular benefit in diagnosing endocarditis. Anemia is common in IDUs as a result of the continual blood loss associated with the act of injecting. An elevated white blood cell count, usually with a left shift, is also common, although neutropenia and thrombocytopenia are occasionally found. Hyponatremia of 125 to 133 mEq/L is found in approximately 40% of cases immediately after admission and predicts prolonged fever and greater morbidity.[150] The etiology is unclear, and the abnormality corrects immediately after fluid administration. Additional laboratory abnormalities reflect the high-grade bacteremia associated with endocarditis and routinely normalize soon after bacteremia clears. The cerebrospinal fluid (CSF) level is abnormal in many cases, with increased white blood cells and protein level in patients showing no overt CNS symptoms or signs.[202] Echocardiography is routinely performed in patients suspected to have IE. However, results can be misleading because normal right-sided structures may mimic vegetations. In IDUs with right-sided IE, the low pressure in the pulmonary circulation often permits the growth of large vegetations, making the diagnostic yield of TTE comparable to transesophageal echocardiography (TEE).[184] Caution is still required, as a high percentage of IDUs who have no evidence of IE still have abnormalities on the tricuspid valve.[203] Abnormalities in an IDU must be considered in the context of the clinical setting. In a study comparing TTE and TEE in veterans with *S. aureus* bacteremia suspected to have IE, Sekar and colleagues[204] determined that TEE was superior, even for patients with right-sided disease. However, there were only 3 IDUs in the study population, and details of the nature of their infections were not provided. In the absence of more compelling data, if IE is strongly suspected, TTE may be performed first, and if it is negative, TEE may be ordered.[190] Alternatively, TEE may be reserved for patients believed to have left-sided involvement or patients with perivalvular lesions such as valve ring abscess or perforation or a vestigial eustachian valve.[205] It is important to recognize that negative TEE does not rule out endocarditis. Several newer modalities may confirm the diagnosis in patients with suspected IE who have negative TEE and/or TTE. In such patients, three-dimensional echocardiography may be useful, especially in cases with confusing artifacts on traditional tests. In addition, there is increasing evidence supporting the use of combined ^{18}F-fluorodeoxyglucose positron emission tomography/CT to identify infected cardiac vegetations.[184] Cardiac MRI is also effective at identifying vegetations, and PCR can be diagnostic in patients when blood and tissue cultures are negative.[190]

Therapy

Addicts with IE who are stable and only moderately ill can be observed safely without antibiotic therapy while the results of blood cultures are awaited. Transient fever and bacteremia occur in this population, and because bacteremia is the most sensitive indicator of endocarditis, a commitment to therapy before the nature of the septic condition is documented can lead to unnecessary and prolonged hospitalization for administration of antibiotics. Even when the patient is acutely ill, several blood cultures should be obtained before antibiotic therapy is initiated.

Complete recommendations for antimicrobial treatment of IE were published in 2015 by the American Heart Association and will not be repeated here.[190] As a routine, when empirical treatment is initiated, it is based in part on knowledge of the organisms most likely to cause endocarditis in that geographic location. In most settings, coverage is directed against *S. aureus*. The prevalence of MRSA is decreasing; however, it may be prudent to cover for it until finalization of culture results.[206] Accumulating information indicates that infections due to MRSA that have a vancomycin minimal inhibitory concentration of 2.0 μg/mL have a poor outcome, and in such cases an alternative regimen is recommended. Daptomycin at a dose of 8 or 10 mg/kg has been suggested by some experts.[190]

Trimethoprim-sulfamethoxazole has been used for both methicillin-sensitive *S. aureus* and MRSA soft tissue infections, but its efficacy in treating endocarditis is questionable, and it is not recommended. Traditionally, endocarditis in IDUs was treated with 4- to 6-week courses of parenteral antibiotics. However, some patients with uncomplicated right-sided endocarditis may be successfully treated for 2 weeks with nafcillin plus an aminoglycoside[207] or even cloxacillin alone.[208] When quinolones are used, therapy may consist entirely of oral medication.[209] The addition of an aminoglycoside for treatment of native valve right-sided staphylococcal IE is no longer recommended.[190] In a recent *Pseudomonas* outbreak, patients were treated with a variety of regimens, but the most successful included cefepime, 4 to 6 g/day, plus high-dose tobramycin, 8 mg/kg/day, as a single dose, aiming for a peak serum concentration of 18 to 22 μg/mL and trough levels of less than 1 μg/mL.[161] Quinolones also have utility against *Pseudomonas,* but the data are insufficient to permit a recommendation for their use.[210]

The management of enterococcal endocarditis is evolving along with the increasing prevalence of vancomycin-resistant strains and new data evaluating novel antimicrobial regimens. Double β-lactam combinations appear to be very effective and avoid potentially toxic regimens including aminoglycosides.[190]

The management of fungal endocarditis is also in a state of evolution, although surgery is still required in many cases. Accumulating evidence indicates that treatment with a lipid formulation amphotericin B with or without 5-fluorocytosine, followed by step-down therapy to fluconazole if the organism is susceptible and blood cultures are negative, may be very effective and obviate the need for surgery.[211] Echinocandins at doses higher than used for treatment of candidemia (caspofungin at 50–150 mg daily, micafungin at 100–150 mg daily, or anidulafungin at 100–200 mg daily) may be considered alternatives. Even among patients with prosthetic valve endocarditis including a large number of IDUs, successful outcome was achieved by medical management alone.[212] Valve replacement is still strongly recommended; but if valve replacement is not possible, lifelong suppressive therapy is recommended.[190,213]

The role of surgery in the management of IE, particularly right-sided IE in IDUs, has long been controversial. Although the operative risk tends to be lower in IDUs with endocarditis, the long-term outcome is often compromised by resumption of illicit drug use.[214] The increase in drug use by itself will undoubtedly increase the pool of patients in need of some kind of procedure. Some authors advocated complete removal of the valve, whereas others argue for repair or replacement with a new mechanical or bioprosthetic valve.

Although not specific for IDU endocarditis, the American Heart Association guidelines offer the following surgical indications for right-sided ID:[190] Severe tricuspid regurgitation causing right-sided heart failure poorly responsive to medical treatment; sustained infection, particularly with a difficult-to-treat organism; lack of response to appropriate antibiotics; tricuspid vegetations larger than 20 mm; and recurrent pulmonary embolism despite appropriate antimicrobial therapy. Finally, whenever possible, valve repair, rather than valve replacement, is recommended especially in IDUs. Regardless of the invasive approach employed, a strong case can be made for performing CT angiography even in young IDUs, as this population has been identified to have a high incidence of coronary vascular disease. Being aware of coronary vascular disease before operating gives the surgeon additional options for approaching the patient.[215] In addition, three-dimensional TEE has been proposed as a preoperative test to help identify lesions that were not visible by other modalities.[216]

A recently developed vacuum device that has been shown to remove vegetations via a percutaneous approach has been used successfully in several IDUs who had severe tricuspid endocarditis and may prove to be an alternative to open heart surgery in this difficult population.[217] Unless or until this device is proven effective and gains approval, the decision to operate will remain an economic and ethical dilemma. In theory, the same complications leading to a recommendation for surgery in nonaddicts should apply to IDUs. One difference is that despite large vegetations in right-sided IE, medical management alone is usually effective. Mortality is more likely predicted by a high sepsis score, such as the Pittsburgh Bacteremia Score.[218] Another difference is that medical management alone is highly likely to be successful despite numerous septic pulmonary emboli.[184] In cases where surgery for right-sided endocarditis is required, valve repair or even valvectomy may be considered. The greatest difficulty relates to the ethical question of performing open heart surgery and potentially inserting a prosthetic valve into a patient who is likely to continue to inject drugs, making reinfection of a prosthetic valve likely.[219,220] The use of time, funds, and materials for such a patient in resource-limited settings is major cause for concern. In one study, the presence of active injection drug use was an independent predictor of not having valve surgery.[153] Early results show that IDUs have acceptable 2-year and 5-year postoperative results, although the number of reinfections is high among individuals who continue to use drugs.[221] It becomes an even greater problem when an IDU presents with a second or third episode of endocarditis after having previously received valve surgery. To help deal with this issue, several authors developed an ethical decision-making model that takes into consideration the problem itself, the objectives, the classic four principles (beneficence, nonmaleficence, autonomy, and justice), any relevant ethical theories, and the competence of the patient.[222] Others used similar ethical considerations to conclude that these patients should receive the same treatment as other patients, regardless of whether drug use was likely to continue after the surgery.[223]

Prognosis

In most cases of IE in IDUs, the survival rate is good using antibiotics alone, despite complications and prolonged fever.[224] Septic emboli frequently occur after the initiation of therapy but do not affect the prognosis and are not necessarily an indication for removal or replacement of the infected valve.[150,224] The relationship between vegetation size, as determined by echocardiography, and the likelihood of an embolus is controversial. However, vegetations larger than 2 cm are associated with a 33% mortality rate compared with 1.3% for patients with vegetations smaller than 2 cm ($P < .001$).[224] Hence some clinicians consider large vegetations as an indication for surgery. In general, the indications for surgery and the final result are the same in IDUs with endocarditis as in the general population. Although surgery carries substantial risk, the mortality rate in patients who fail medical management approaches 100%, so surgical treatment is indicated and clearly improves survival.[225] The patient's HIV-1 status is a significant prognostic indicator. The $CD4^+$ cell count decreases after cardiopulmonary bypass, which may lead to an acceleration of the progress toward acquired immunodeficiency syndrome (AIDS).[226] Addicts with HIV-1 infection whose IE is poorly controlled at the time of cardiac surgery and those with advanced AIDS also have a poor prognosis.[227] The major problem after cardiac surgery for endocarditis in IDUs is their propensity to continue illicit drug use. In one study, only 4 of 57 addicts remained drug-free, and the 10-year survival rate was only 10%.[227] Hence some investigators advocate excision of the tricuspid valve or repair of the left-sided valves rather than replacement for IDUs needing surgical intervention.[228] Prognosis is not affected by the duration of symptoms before initiation of therapy, antibiotic use before admission, right-sided heart failure, pulmonary embolism, or results of the following laboratory tests: leukocyte count, hemoglobin, and serum creatinine concentration.[224]

NONCARDIAC VASCULAR INFECTIONS

Septic Thrombophlebitis

As arm and leg veins become thrombosed, sclerosed, and unusable, femoral, axillary, and neck vessels are increasingly selected for injection. Vessels used frequently for injection become injured or infected, leading to the formation of hematomas, thrombosis, septic thrombophlebitis, mycotic aneurysm, or traumatic arteriovenous fistula.[229,230] As the quest for injection sites expand, may IDUs resort to neck injection, leading in at least one case to classic Lemierre syndrome due to *Fusobacterium necrophorum*.[231] *S. aureus* has been associated with Lemierre syndrome, emphasizing the importance of cultures.[232]

More recent evidence demonstrates that various samples of heroin have widely different degrees of acidity, with some far more likely to lead to vessel injury than others.[233] Buprenorphine itself appears to be highly toxic to vasculature.[234] The predominant pathogens are gram-positive cocci, usually *S. aureus,* although gram-negative pathogens, particularly *P. aeruginosa,* are not infrequently found. Polymicrobial infection is common. Findings with septic thrombophlebitis include local pain, swelling, and fever together with bacteremia and sepsis. Local signs of infection may be masked when deep vessels are involved. Infection or sclerosis of proximal large veins is frequently complicated by venous stasis and supervening thrombosis. Septic pulmonary embolization follows and closely resembles right-sided bacterial endocarditis.[150] The management of septic thrombophlebitis, which most frequently involves the femoral veins, remains controversial. Parenteral antimicrobial therapy is standard, but the value of anticoagulant use has not been established. Furthermore, hemorrhagic complications from unrecognized coexistent femoral and cerebral mycotic aneurysms may occur. Difficulty performing venography in IDUs precludes controlled studies evaluating efficacy and complications of anticoagulant use. Some experienced clinicians believe the risks of short-term anticoagulation are outweighed by the risk for major pulmonary emboli. In one trial, all patients were treated successfully by a 2- to 3-week course of intravenous therapy followed by therapy with oral antibiotics to complete a mean of 28 days of total treatment. In 91.7% of patients in that series, anticoagulation therapy was initiated while the patient was hospitalized but was stopped on discharge owing to compliance concerns.[235]

Mycotic Aneurysm

A major vascular complication in IDUs is the formation of mycotic aneurysms, most frequently involving femoral and, less commonly, neck vessels. Mycotic aneurysms of the superior mesenteric artery are also seen; some predict increasing incidence due to the expanding population of IDUs.[236] True aneurysms, involving all three layers of the arterial wall, are rare. In the IDU, frequent direct trauma to peripheral vessels produces damage to the vessel wall and an initial sterile perivascular hematoma. Injection of chemical agents in illicit drugs also causes tissue necrosis. The vascular wall usually becomes infected by contiguous spread from adjacent subcutaneous abscesses or areas of cellulitis, although embolization from a distant focus, such

as endocarditis, also may be involved.[237] Infection causes liquefaction of the central portion of the hematoma in communication with the arterial or, less commonly, the venous wall, forming a secondary (false) pseudoaneurysm.[230,238] The common femoral artery is the most frequent location, followed by the deep femoral and superficial femoral arteries.[239] Because most IDUs are right-handed, left-sided groin infections and aneurysms are more common. Primary mycotic aneurysms in which the damaged vessel wall is infected secondary to unrelated bacteremia are rare and are more likely to involve cerebral vessels as a complication of endocarditis. Pathogenesis includes septic embolization from valvular vegetations to the vasa vasorum of smaller vessels, such as the middle or posterior cerebral and visceral intraabdominal arteries, which are more frequently involved than the aorta. Occasionally, septic emboli arising from a groin abscess causing a pulmonary artery mycotic aneurysm and hemoptysis mimicking tricuspid endocarditis occurs, often with disastrous consequences.[240] Arteriovenous fistula has also been known to occur.[241]

Clinical manifestations of a mycotic aneurysm include a painful, often enlarging, tender, and frequently pulsatile mass, accompanied by variable constitutional symptoms. Pain, swelling, and erythema are common, occurring in 94%, 82%, and 76.5% in one series.[239] These lesions are predisposed to hemorrhage. Distal embolism may cause ischemia, leading to limb loss. Nerve compression is often present, and detection of a bruit or thrill over the mass strongly supports the diagnosis. Lesions of the subclavian artery are frequently associated with injury to the brachial plexus, with resultant neurologic symptoms.[237] Often addicts report "hitting the pinky," indicating unintended arterial injection. Bleeding from an injection site may be evidence of an aneurysm. Because drug abusers usually present with cellulitis and accompanying edema and induration, the pulsatile mass may be masked, obscuring the aneurysm. When rupture of the aneurysm occurs, it is usually preceded by severe pain that may be misdiagnosed as thrombophlebitis or soft tissue abscess. In contrast to an aneurysm in the lower limb, distal ischemia in the upper extremity (hand) from induced arterial spasm occurs commonly.

Anemia, leukocytosis, and an elevated erythrocyte sedimentation rate, although frequently present, are of limited diagnostic value. A high index of suspicion together with angiographic confirmation is essential because misdiagnosis is common, and cellulitis, abscess, or infected hematoma may mimic or mask an aneurysm (Fig. 312.1). Duplex ultrasound is an extremely useful noninvasive diagnostic tool that has high sensitivity and specificity for diagnosing pseudoaneurysms and should be the first diagnostic study performed.[237] CT, especially with injected contrast material, is extremely useful and delineates the pathologic process in the adjacent soft tissues. Color Doppler ultrasound may confirm the diagnosis, especially in the extremities, but may not define the vascular anatomy clearly.[242] Thus angiography remains the definitive diagnostic procedure, not only for delineating the lesion but also for planning the approach to surgery, and digital subtraction angiography may replace traditional arteriography in diagnosing femoral and other peripheral aneurysms.[243] Magnetic resonance angiography (MRA) may prove to be helpful in the diagnosis of mycotic aneurysms. Unintentional invasion of an aneurysm after incision and drainage of a lesion mistakenly believed to be an abscess can lead to catastrophic bleeding.

Successful management of a mycotic aneurysm requires early diagnosis before rupture occurs. Surgery is almost always required. Various procedures have been used, including simple ligation of the artery with excision of the involved segment. IDUs who have a relatively brief history of illicit injection drug use frequently develop claudication after ligation, whereas IDUs who have been using for more than 5 years are likely to have built up a number of collaterals, which prevents subsequent symptoms.[244] An approach involving resection of the infected segment with débridement of the wound bed and in-line arterial reconstruction employing an autologous vein graft has been used with success.[239] In other cases a polytetrafluoroethylene graft may be used if suitable graft material cannot be found. Others rely on stent placement in emergency situations.[245] Surgical treatment should not be delayed, because rupture is frequent. Vascular reconstruction as a delayed procedure is recommended only in patients who develop ischemia after

FIG. 312.1 Arteriogram demonstrating a mycotic aneurysm of the right common iliac artery in an injection drug user.

excision of the aneurysm, and then only when a graft can be positioned through an uninfected tissue plane. Some authors argue that the presence of extensive tissue necrosis or necrotizing fasciitis is a contraindication to any attempt at revascularization; amputation may be required.[246] Thrombectomy of the distal artery facilitates collateral circulation and improves the long-term outcome among patients who undergo ligation and excision.[247] Postoperative complications are common. Complete débridement of the infected artery is essential, and failure to achieve complete débridement is associated with anastomotic dehiscence. The addition of a well-vascularized muscle flap for coverage minimizes the risk for anastomotic failure due to infection.[239]

In the absence of an agreed-on approach to mycotic aneurysm in IDUs, a variety of different approaches have proved successful. Several authors have proposed treatment algorithms that take into consideration the presence of significant hemorrhage at the time of diagnosis, the urgency for surgery, and the likelihood of success of different surgical procedures.[246,248] In any case, given the high mortality associated with these lesions, some form of surgery based on the location and nature of the aneurysm seems a requirement.[249]

Because *S. aureus* is the most common pathogen, initial empirical antibiotic therapy should include a β-lactamase–resistant penicillin such as nafcillin. When MRSA is prominent, vancomycin should be started. An aminoglycoside is added initially if there is suspicion or evidence of gram-negative bacilli on Gram staining of sanguinopurulent drainage. As with other infections in IDUs, any bacterium or even occasionally fungus may be responsible, making culture imperative.[250] Subsequent cultures obtained from blood and local exudate influence antibiotic selection. Recommended therapy is intravenous and lasts for 4 to 6 weeks.

PULMONARY INFECTIONS

Pathophysiology

Pulmonary manifestations are extremely common in IDUs. The lung is the target of numerous infectious and noninfectious insults. The latter include bronchospasm, airflow obstruction, diffusion impairment, emphysema, and pulmonary hypertension in heroin users.[251] Pulmonary hypertension and alveolar hemorrhage are associated with injection of

cocaine [251] Alveolar hemorrhage due to vasculitis is also associated with levamisole, a common cocaine adulterant.[252] Levamisole contamination of heroin is now increasingly reported. An increased prevalence of pulmonary hypertension, independent of the presence of septic pulmonary emboli, has been reported in individuals who inject buprenorphine.[253] Heroin overdose may be associated with pulmonary edema; however, this complication of heroin overdose is now reported much less frequently than in older series.[254] Granulomatous lesions occur in reaction to particles of cotton (used to filter the drug before injection) and fillers (mainly from injection of crushed pills). Starch can cause mild transient pulmonary granuloma formation, whereas cotton fibers and talc (used as a filler) can cause permanent intravascular and perivascular granulomas in pulmonary arteries and arterioles.[255] The injection of crushed oral tablets can result in a constellation of clinical and radiographic findings due to a foreign-body reaction in the pulmonary arterioles related to the fillers present in tablets (excipients).[256] The resultant baseline abnormalities of chest radiographs and blood gases may cause diagnostic confusion in febrile IDUs. IDUs have a 10-fold increased risk for pneumonia compared with the risk for non-IDUs.[257] Among patients with HIV infection on ART, bacterial pneumonia was more common in patients who were IDUs.[258] The incidence of pneumonia is increased in IDUs for a number of reasons, including impaired clearance of secretions, aspiration, increased exposure, decreased immune function, and higher prevalence of HIV infection. In a series of pulmonary complications of injection drug use, septic pulmonary emboli were the most common complication, followed by community-acquired pneumonia and *M. tuberculosis* infection.[259]

Clinical Patterns

Most pulmonary infections are community-acquired episodes of pneumonia caused by common respiratory pathogens. In an older series of febrile IDUs, pneumonia was the most common cause of fever[260]; in a second series, pneumonia was second only to cellulitis as a cause of fever in IDUs.[261] A more recent series also found pneumonia second only to skin and soft tissue infections as a reason for hospital admission among IDUs.[20] Bacterial pneumonia must be distinguished from septic emboli originating from right-sided endocarditis or more distal thrombophlebitis and resultant pulmonary infarcts. Septic emboli result in multiple round or wedge-shaped lesions that may cavitate (Fig. 312.2). Pleural involvement is common in both conditions and results in chest pain, pleural effusion, or empyema. Recurrent pulmonary emboli may also result in pulmonary hypertension. Injection drug use was found to be an independent risk factor for complicated parapneumonic effusion and empyema in patients with community-acquired pneumonia.[262] The usual pathogens in bacterial pneumonia include *Streptococcus pneumoniae* and oral anaerobes by the bronchogenic route and *S. aureus* or, less commonly, *P. aeruginosa* by the hematogenous route. One study of the etiology of community-acquired pneumonia in an urban public hospital emphasized the importance of aspiration pneumonia in this patient population, particularly among patients with pneumonia necessitating admission to the intensive care unit.[263] Injection drug use has been identified as a risk factor for bacteremia in patients with community-acquired pneumococcal pneumonia.[264] Lung abscesses may arise from aspiration pneumonia, necrotizing pneumonitis, or septic emboli. Opportunistic pulmonary infections, especially *Pneumocystis jirovecii* pneumonia, must also be considered in febrile IDUs.

Tuberculosis in Injection Drug Users

Pulmonary TB is a major problem in both HIV-infected and non–HIV-infected drug users throughout the world; the prevalence of latent TB infection among IDUs globally is reported to be between 10% and 67%.[265] Homelessness and nonadherence to medication regimens further complicate the problem. The risk for TB is still substantial in HIV-positive individuals taking ART.[266] In a study from San Diego, one-quarter of IDUs were infected with TB.[265] In this study, 95% of IDUs had been previously tested for TB infection; however, only 60% of those who reported having a previous diagnosis of latent TB infection were ever treated. TB in IDUs with AIDS is more frequently extrapulmonary, and patients present with less cavitary pulmonary disease and fewer acid-fast bacillus–positive organisms in sputum than other patients with TB. Coughing induced by the use of marijuana or crack cocaine and injection in shooting galleries or other cramped spaces may increase the transmission of TB. IDUs may be screened for latent TB infection by either tuberculin skin test (TST) or an interferon-γ release assay. An interferon-γ release assay is preferred for testing in IDUs because they are less likely to return for skin test readings.[267] IDUs should receive therapy for latent TB infection if the TST is 10 mm or larger. IDUs with HIV infection should receive therapy for latent TB infection as recommended for other HIV-infected patients, that is, if the TST is 5 mm or larger or if the patient is a close contact of a person who has active TB, regardless of skin test results or previous courses of therapy for latent TB infection.[268] The US Centers for Disease Control and Prevention (CDC) recommends four different regimens for the treatment of latent TB infection. Isoniazid daily or twice weekly (as directly observed therapy) may be given for 6 or 9 months; 9 months is preferred for HIV-infected patients. Isonazid and rifapentine may be given once weekly for 12 doses as directly observed therapy; however, this regimen is not recommended for HIV-infected patients on ART. Lastly, rifampin daily for 4 months can be used; this regimen is least preferred but may be an option for individuals at high risk for hepatotoxicity. The potential risk for isoniazid-induced hepatotoxicity in IDUs, who have a higher frequency of background hepatitis and who may also be abusing other hepatotoxic agents such as alcohol and cocaine, is a concern. However, a study of isoniazid therapy in IDUs with an HCV seroprevalence of 95% found that the risks for hepatotoxicity and isoniazid discontinuation were similar to risks reported for populations with a lower prevalence of HCV.[269] Material incentives have been shown to be effective in increasing the return rates for TST reading and promoting adherence to a program of directly observed latent TB infection therapy and treatment of TB in IDUs.[270]

A febrile IDU with pulmonary infiltrates constitutes an enormous diagnostic challenge given the wide differential diagnosis, which includes noninfectious causes. Accordingly, initial treatment often involves multiple therapeutic agents to cover several pathogens. Empirical coverage for TB may be needed in critically ill patients.

FIG. 312.2 Anteroposterior chest radiograph demonstrating pleural effusion and multiple cavitating nodular infarcts resulting from septic emboli in a patient with tricuspid endocarditis.

HEPATITIS

Risk Factors

Hepatitis has long been recognized as a complication of injection drug use. A significant number of IDUs also report hazardous alcohol use.[271] The combination of alcohol use plus HBV or HCV infection results in more severe liver disease than either factor alone and is associated with more rapid acceleration to cirrhosis. Heroin itself is not known to be hepatotoxic, but cocaine can cause severe liver injury. Hepatotoxicity can also occur secondary to methamphetamine abuse. Buprenorphine, which is used as a substitution drug in the treatment of opiate addiction, has been reported to cause hepatitis, both when diverted and injected and when used sublingually.[272,273] IDUs have been demonstrated to have significantly less knowledge regarding risks and transmission of viral hepatitis than regarding risks and transmission of HIV.[133] Syringe services programs have been shown to be less effective at preventing the transmission of HCV and HBV than HIV.[274–276] The validity of self-reported serostatus of hepatitis A, B, and C and HBV vaccination status by IDUs is poor.[277,278]

Hepatitis B

Injection drug use remains an important risk factor for HBV infection in the United States. Although the overall incidence of acute HBV infection has remained stable since 2006, beginning in 2009 more cases of acute HBV infection have been reported from nonurban areas than urban areas.[279] The changing epidemiology of injection drug use related to the current opioid epidemic is likely responsible for this shift. A study of acute HBV infection in three Appalachian states documented an increase in infection among non-Hispanic whites 30 to 39 years of age, most of whom reported injection drug use as a risk factor.[279] Clinically apparent HBV infection is uncommon, and many IDUs end up with a serologic pattern indicative of naturally acquired immunity. In the United States 60% to 80% of IDUs have serum antibody against hepatitis B surface antigen; however, only 5% to 10% become chronic carriers.[280–282] Spontaneous reactivation of chronic HBV infection has been described in IDUs, but the diagnosis may be difficult because the clinical presentation is indistinguishable from that of acute hepatitis, anti-HBV core IgM may increase during a reactivation, and information on the patient's previous serologic status usually is unknown.[283,284] HIV-infected patients with HBV infection are more likely to become chronic carriers.[285] In addition, a high prevalence of occult HBV infection has been reported in IDUs with HIV infection.[286] The CDC Advisory Committee on Immunization Practices has recommended HBV vaccination for IDUs since 1991, yet current vaccine coverage rates for HBV among adults ≥19 years of age are low.[287] Although there is a tendency toward a decreased antibody response to immunization in HIV-positive and HIV-negative IDUs, there is not convincing evidence of decreased protection from infection, and all susceptible IDUs should be offered vaccination.[288] The incorporation of HBV vaccination into syringe services programs may be cost-effective and improve coverage rates.[289] IDUs with isolated anti-HBV core antibody have been shown to have strong resistance to reinfection and do not need vaccination.[290] These individuals are at risk for occult, chronic HBV infection, although the clinical significance of this entity remains unclear.[286] Guidelines for the treatment of chronic HBV infection are available, but they do not specifically address the issue of treatment of active IDUs, in contrast to guidelines for the treatment of HCV.[291]

Delta Virus

Hepatitis delta virus (HDV) is a defective RNA virus that can replicate and cause hepatitis only in the presence of active HBV infection. HDV may be acquired along with HBV as a primary coinfection or as a superinfection in people who are carriers of HBV. Because of the interdependent nature of the two viruses, immunity to HBV provides protection against HDV. In some areas where HBV is prevalent, HDV is also seen with relatively high frequency. In nonendemic areas such as the United States, HDV infection is confined almost exclusively to particular high-risk groups, including IDUs.[292,293] A significant decrease in the prevalence of HDV infection has been reported in nonendemic countries with universal HBV vaccination.[294,295] A serologic study of IDUs in Baltimore found a decrease in the overall prevalence of HDV from 15% in 1988–89 to 11% in 2005–06; however, there was a significant increase in the prevalence of HDV in individuals with chronic HBV infection from 29% to 50%.[296] Attendance at a shooting gallery was shown to be a strong correlate of HDV infection in this study. The association of injection drug use with HBV and HDV was clarified in a study comparing the transmission and carriage of each agent in two populations known to be at risk: IDUs and men who have sex with men (MSM).[297] Among 372 IDUs, 52.4% had evidence of current or past HBV infection; of these, 8.7% were chronic carriers of HBV. Among the chronic carriers, 70.6% were also chronic carriers of HDV. In contrast, only 27.4% of MSM had serologic evidence of HBV infection (current or remote), of whom 7.9% were chronic carriers. Only a third of these chronic HBV carriers had evidence of HDV infection, which was a significant difference from the IDUs, demonstrating that injection drug use is a much more efficient means of transmission of HDV infection than sexual contact.

Superinfection of HDV on previous HBV infection is the most common pattern of dual infection. Simultaneous acquisition of both viruses is more common among IDUs and is more likely to result in fulminant infection.[293] IDUs who experience coinfection frequently have a biphasic illness.[297] The initial phase of the disease is caused by HDV, and the second phase is caused by HBV.[298] The closer the proximity of the biphasic peaks, the greater the risk for a fatal outcome. IDUs who survive such an illness usually have a complete recovery and clear both viruses.[299] HDV can be prevented by vaccination of IDUs against HBV.

Hepatitis C

Injection drug use is a major risk factor for HCV infection. The seroprevalence of anti-HCV antibody among IDUs in four US cities decreased between 1994 and 2004 from 65% to 35%; this decrease was thought to be due to safer injection practices as a result of risk reduction targeted toward HIV transmission.[300] From 2004 to 2014, there was a reversal of this trend, which has been clearly linked to the opioid epidemic occurring in the United States at the present time.[301] In 2014, more than 80% of individuals with acute HCV infection with an identified risk factor reported injection drug use, confirming that injection drug use is the primary mode of HCV transmission in the United States. Maternal drug use, independent of HIV coinfection, has been identified as a risk factor for perinatal transmission of HCV, but this finding was not confirmed in a more recent study.[302,303] Studies of HCV seroconversion among young IDUs have identified sharing of needles and drug preparation equipment, pooling money with another IDU to purchase drugs, requiring assistance to inject, and injecting more than once daily as independent risk factors for the acquisition of HCV.[304–306] Injection of prescription opioid analgesics has been identified as an additional risk factor for HCV infection.[307] In an outbreak of HIV infection in rural Indiana linked to injection oxymorphone use, coinfection with HCV was diagnosed in 84.4% of individuals with newly diagnosed HIV infection.[308] Although injection drug use is more efficient at transmitting HCV infection than sexual activity, exchanging sex for money and having a sexual partner who uses injection drugs are also risk factors for seroconversion. Recent work has shown that sharing of equipment used to prepare drugs for injection does not directly result in HCV transmission but is a surrogate for infection that results from sharing drugs.[309] Studies from the mid-1980s and 1990s showed that HCV infection was acquired after a very brief interval of IDU; subsequent work demonstrated a longer time to seroconversion.[300] The average time to seroconversion among HCV-negative IDUs in Seattle was 3.4 years—long enough to justify the allocation of resources to try to reduce risky injection practices.[304] More current data regarding time to seroconversion are needed. There may be other benefits to reducing risky injection practices beyond the reduction of infection with bloodborne viral infections. IDUs without HCV infection who were enrolled in an HCV risk reduction program had a lower risk for bacterial infections than other IDU cohorts.[310] The receipt of opioid substitution therapy has been shown to decrease the risk of HCV seroconversion among IDUs.[311] It has been shown that IDUs who successfully cleared HCV infection in the past are less likely to develop persistent HCV viremia despite continued exposure, and this appears to correlate with T-cell responses to HCV.[312–314]