**Approach to the adult with recurrent infections**

**Author**  
Mark S Pasternack, MD

**Section Editor**  
E Richard Stiehm, MD

**Deputy Editor**  
Anna M Feldweg, MD

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**INTRODUCTION** — Adult patients who present with recurrent infections pose a dilemma to the generalist. In most cases, there is a secondary cause, such as an anatomic abnormality. However, secondary immune defects due to other medical disorders are sometimes identified, while primary immune defects presenting in adults are rare. The initial approach to an adult patient with recurrent infections is discussed here, with a discussion of the nonimmunologic disorders that should be considered in the evaluation of recurrent infection at specific anatomic sites and a brief overview of immunodeficiency in adults. The laboratory tests that are used to evaluate the various components of the immune system are reviewed separately. (See "Laboratory evaluation of the immune system".)

**OVERVIEW OF ETIOLOGIES** — In adults, recurrent infections are usually due to an anatomic lesion, a functional disorder, or to a secondary cause of immunosuppression.

It is helpful to consider the following broad categories of etiologies when evaluating an adult with recurrent infections:

●Anatomic lesions, whether congenital or acquired, and disorders affecting the function of specific organs are important causes of recurrent infections in adults (table 1).

●Secondary immune disorders due to other medical conditions or treatments for these conditions are a much more common cause of recurrent infections than primary immunodeficiencies (table 2). (See 'Secondary immunodeficiency' below.)

●Most congenital (primary) immunodeficiencies do not present in adulthood, but rather are diagnosed in infancy or childhood because patients with these disorders often require repeated hospitalizations for serious infections at an early age and may develop growth retardation from chronic and recurrent illnesses [[1-4](https://www.uptodate.com/contents/approach-to-the-adult-with-recurrent-infections/abstract/1-4)]. However, the number of recognized immunodeficiencies has expanded dramatically in recent decades, and primary immunodeficiency is probably not as rare as previously thought. In addition, there are increasing reports of milder phenotypes of disorders that were previously recognized only in the most severe forms (eg, DiGeorge syndrome). (See 'Primary immunodeficiency' below.)

**CLINICAL EVALUATION** — The evaluation of an adult with recurrent infections begins with a complete history and thorough physical examination.

**History and documentation of infections** — The clinical history should include a careful review of past medical problems and their treatments, surgeries, accidental injuries, and medications. Culture information and imaging studies documenting the presence of infections and types of organisms should be retrieved or obtained for past and current infections, whenever possible. The etiology and subsequent approach varies according to the type and pattern of infections present.

**Physical examination** — The physical examination of a patient with a history of recurrent infections may reveal anatomic abnormalities or signs and stigmata of significant underlying disorders (eg, venous insufficiency). Patients with longstanding immune defects may display low body mass index (BMI), sequelae of recurrent infection in the form of scarring (of tympanic membranes or skin), signs of chronic lung disease (chronic cough, absent gag reflex, clubbing, crackles, or wheezing to suggest bronchiectasis), or ongoing infection (signs of chronic sinusitis, oral thrush, warts, or dermatophyte infections). Lymphadenopathy and/or hepatosplenomegaly can be seen with antibody deficiencies, as can arthritic changes.

**Family history** — A detailed family history is important for the detection of primary immunodeficiencies. Severe and/or recurrent febrile illnesses or infections or childhood deaths in relatives may suggest an X-linked or autosomal recessive immune disorder. Consanguinity increases the likelihood that a rare autosomal recessive condition could be expressed. Multiple family members with autoimmune diseases or malignancies should also raise the suspicion of a familial immune disorder.

**CONSIDERATIONS BY SITE OF INFECTION** — Patients will sometimes present with recurrent infections of one type. In this setting, there are specific nonimmunologic conditions which should be considered before an immune evaluation is undertaken.

**Skin infections** — Skin infections, in isolation, are not usually indicative of an underlying primary immunodeficiency.

**Cellulitis** — Cellulitis is likely to recur in the setting of lymphatic stasis (lymphedema) and/or breaches in the skin barrier (eg, dermatophyte infections or trauma). (See "Cellulitis and skin abscess: Clinical manifestations and diagnosis".)

●Lymphedema can be classified as primary (congenital) or secondary (acquired) disease. Lymphedema in adults is most often due to axillary or inguinal lymph node dissection and/orradiation, and such patients have an increased risk of cellulitis. Patients from endemic areas may present with lymphedema as a sequela of filariasis. (See "Clinical features and diagnosis of peripheral lymphedema" and "Cellulitis following pelvic lymph node dissection" and "Breast cellulitis and other skin disorders of the breast".)

●A previous episode of cellulitis itself can lead to lymphatic scarring and impaired lymphatic drainage, thereby promoting the development of recurrent cellulitis. This has been best described after saphenous venectomy for coronary artery bypass graft surgery. (See "Early noncardiac complications of coronary artery bypass graft surgery", section on 'Post-venectomy cellulitis'.)

●Dermatophyte infections can predispose patients to recurrent cellulitis, especially when tinea pedis develops after saphenous venectomy. The dermatophyte infection provides a portal of entry for bacteria, most often streptococci or staphylococci, and predisposes to the development of cellulitis. The frequency of infections in these patients is often reduced by treatment of dermatophyte infections and other primary dermatologic conditions, meticulous podiatric care, and consideration of antibiotic prophylaxis. (See "Early noncardiac complications of coronary artery bypass graft surgery", section on 'Post-venectomy cellulitis'.)

●Chronic edema also increases the risk of recurrent cellulitis. Venous insufficiency, congestive heart failure, hepatic disease, and nephrotic syndrome are all causes of chronic edema that predispose patients to recurrent cellulitis. These underlying diagnoses should be considered during the evaluation of recurrent cellulitis in patients with unexplained edema. (See "Pathophysiology and etiology of edema in adults".)

●Peripheral arterial disease with ischemia is associated with an increased risk of recurrent skin infection in the affected limbs. The presence of ischemic ulcers provides a ready portal of entry for progressive local infection, exacerbated by poor arterial inflow and delivery of granulocytes and antibiotics. (See "Clinical features and diagnosis of lower extremity peripheral artery disease".)

●Obesity has also been reported as a risk factor for recurrent cellulitis. It is possible that lower extremity venous stasis and/or lymphatic stasis due to hydrostatic issues in these individuals is responsible for their increased risk of infection [[5,6](https://www.uptodate.com/contents/approach-to-the-adult-with-recurrent-infections/abstract/5,6)]. (See "Clinical evaluation of the obese child and adolescent".)

**Abscess** — Recurrent abscess formation in the same anatomic location often arises from a local defect, such as a congenital branchial cleft cyst, pilonidal or urachal cyst, hidradenitis suppurativa, or a retained foreign body. In these situations, recurrent infection is limited to the neck, axilla, groin, umbilicus, or site of previous trauma, and there is no need to suspect a generalized susceptibility to infection [[7](https://www.uptodate.com/contents/approach-to-the-adult-with-recurrent-infections/abstract/7)].

●Crohn disease may rarely lead to inguinal and/or perianal abscesses complicating enteric fistula and intraabdominal abscess formation. Inflammatory bowel disease occasionally coexists with antibody deficiencies [[8](https://www.uptodate.com/contents/approach-to-the-adult-with-recurrent-infections/abstract/8)]. (See "Clinical manifestations, diagnosis and prognosis of Crohn disease in adults".)

●Patients with risk factors for acquired immunosuppressive conditions predisposing to infection (such as diabetes or human immunodeficiency virus [HIV] infection) should undergo screening for these conditions. (See "Screening for type 2 diabetes mellitus" and "Screening and diagnostic testing for HIV infection".)

●Multiple or recurrent abscesses in a variety of locations may be the result of autoinoculation in the setting of drug abuse (subcutaneous drug injection or "skin-popping") or Munchausen syndrome [[9,10](https://www.uptodate.com/contents/approach-to-the-adult-with-recurrent-infections/abstract/9,10)]. Qualitative granulocyte disorders rarely present with recurrent abscesses in adults, but acquired quantitative granulocyte disorders (myelofibrosis and other causes of progressive marrow failure) may develop in this population. (See "Factitious disorder imposed on self (Munchausen syndrome)".)

●The epidemic of community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA) infection involving strains related to clone USA300 has led to a striking increase in the number of individuals with recurrent superficial skin abscesses. These patients are otherwise well, and immunologic evaluation can generally be restricted to those with recurrent deep infections (pyomyositis, skeletal infection, necrotizing pneumonia, etc). Preventive measures for reducing the spread of staphylococci may be helpful for reducing the risk for recurrent skin infection and are discussed in detail separately. (See "Methicillin-resistant Staphylococcus aureus (MRSA) in adults: Prevention and control".)

**Recurrent herpes simplex** — Patients with frequent and/or severe oral, cutaneous, or genital herpes infections are often referred for formal infectious disease consultation.

●The hallmark of herpes group virus infections is persistent (latent) neuronal viral infection, with the risk of recurrent regional disease throughout life. The frequency of recurrence varies widely among different individuals (from one or two episodes over a lifetime to approximately one episode monthly) and is likely determined by multiple factors, including age at the time of primary infection, age at the time of recurrence (immunologic immaturity in infancy, waning immune protection in advanced age), viral strain variations, inflammatory triggers in the distribution of the latently-infected neurons, and underlying host diseases. (See "Clinical manifestations and diagnosis of herpes simplex virus type 1 infection", section on 'Recurrent infection'.)

●Patients with occasional recurrences respond well to episodic treatment with antiviral therapies, self-administered at the first sign of recurrence. Patients with very frequent recurrences, a problem seen during the first few years after primary infection in some individuals, may be offered maintenance suppression therapy. (See "Treatment of herpes simplex virus type 1 infection in immunocompetent patients", section on 'Recurrent infections' and "Treatment of genital herpes simplex virus infection", section on 'Treatment strategies for recurrent disease'.)

●Immunocompetent individuals usually experience satisfactory control with episodic or maintenance suppression. In contrast, immunodeficient patients may develop refractory or progressive primary infection or very frequent relapses despite appropriate antiviral therapy. Investigation of these individuals for underlying T or natural killer (NK) cell dysfunction is indicated, although in many instances the underlying immunologic disorders are known at the time of presentation with severe herpes simplex. (See 'Initial immunologic evaluation' below.)

In patients with recurrent or severe outbreaks, it is important to confirm the diagnosis of herpes simplex, preferably by direct immunofluorescence, viral culture, or serology, depending upon available laboratory resources. Two disorders that may mimic recurrent herpes simplex are nonherpetic aphthous ulcers, which often respond to topical corticosteroids, and recurrent herpes zoster, which may become less frequent following administration of the zoster vaccine. (See "Clinical manifestations and diagnosis of herpes simplex virus type 1 infection", section on 'Diagnosis' and "Oral lesions", section on 'Treatment' and "Clinical manifestations of varicella-zoster virus infection: Herpes zoster".)

**Recurrent herpes zoster** — More than one episode of herpes zoster is uncommon, but not rare, in an immunocompetent individual. In a population-based study, Mayo Clinic investigators demonstrated a recurrence rate of 5.7 percent over an eight-year follow-up of immunocompetent patients [[11](https://www.uptodate.com/contents/approach-to-the-adult-with-recurrent-infections/abstract/11)]. In contrast, zoster can be recurrent in patients with HIV infection. Herpes simplex occurring outside of the mouth, lips, and genitals can also be mistaken for herpes zoster, so it is important to confirm the type of infection. Recurrent zoster is reviewed separately. (See "Clinical manifestations of varicella-zoster virus infection: Herpes zoster", section on 'Recurrent zoster'.)

**Initial immunologic evaluation** — Immunologic evaluation would be appropriate in patients with recurrent cellulitis or abscesses affecting **different** sites who do not have predisposing lymphatic or venous abnormalities or associated dermatologic conditions.

●Neutropenia should be excluded as a risk factor by routine differential white blood cell count. (See "Approach to the adult with unexplained neutropenia".)

●A variety of functional defects in phagocytes should also be considered. These disorders are rare in general and present with combinations of skin and respiratory tract infections. Tissue and organ focal infections (phlegmon, granuloma, or abscess) also occur. Other frequent manifestations include abnormal wound healing, dermatitis/eczema, and stomatitis. Referral to an allergist/immunologist or infectious disease specialist would be prudent to help guide further testing. (See 'Referral' below and "Primary disorders of phagocytic function: An overview".)

●In patients with recurrent simplex despite appropriate suppressive therapies or in patients with recurrent herpes zoster, testing for HIV as well as T and NK cell quantitation are indicated. Occasionally, NK cell functional assessment is performed, although this should be done in consultation with an immunology specialist. (See "Laboratory evaluation of the immune system", section on 'Flow cytometry for cell populations' and "NK cell deficiency syndromes: Clinical manifestations and diagnosis".)

**Respiratory tract infections** — Recurrent respiratory infections are extremely common, and most patients do not have an underlying immune defect or suffer from other more serious infections. However, recurrent respiratory tract infections in combination with more serious infections are a classic presentation of antibody deficiencies.

**Sinusitis** — Recurrent sinusitis in isolation is rarely associated with an immunodeficiency state and more likely reflects underlying allergic rhinitis, inadequate antibiotic therapy, or a local anatomic defect (eg, nasal polyposis or structural abnormalities due to a deviated nasal septum, narrowed sinus ostia, or past facial trauma). However, recurrent sinusitis in isolation is occasionally seen in the less severe antibody deficiencies, including specific antibody deficiency, immunoglobulin G (IgG) subclass deficiency, and selective immunoglobulin A (IgA) deficiency.

Inadequate antibiotic therapy is a common cause of apparent recurrent sinusitis and may arise from treatment that is either too brief or too narrow in its spectrum of antimicrobial activity. Patients may report multiple episodes of sinusitis over the course of several months, but on careful questioning, the clinician can detect a pattern of improvement on antibiotics, with gradual return of symptoms within the first two weeks after completing therapy and then worsening to the point that another course of antibiotics was prescribed. This pattern suggests a single relapsing infection rather than multiple new infections.

In contrast, adult patients with recurrent or chronic sinus infections, in combination with lower respiratory tract infections or recurrent otitis media, may have a defect in antibody production or function, such as common variable immunodeficiency, IgG subclass deficiencies, or specific antibody deficiency with polysaccharide nonresponsiveness. A quantitative or qualitative granulocyte disorder or a deficiency of complement proteins are other possible explanations. (See "Clinical manifestations, epidemiology, and diagnosis of common variable immunodeficiency in adults" and "IgG subclass deficiency" and "Specific antibody deficiency" and "Primary disorders of phagocytic function: An overview".)

**Pharyngitis** — Recurrent streptococcal pharyngitis usually reflects inadequacy of therapy to eradicate pharyngeal carriage of group A beta-hemolytic streptococci rather than immunodeficiency. Molecular analyses of symptomatic patients show persistence of individual isolates rather than serial infection by independent strains. Once adequate medication adherence is ensured, symptomatic patients with recurrent pharyngitis often benefit from the use of a beta-lactamase-resistant agent. In some individuals, beta-lactamase production by oral flora is associated with penicillin failure [[12](https://www.uptodate.com/contents/approach-to-the-adult-with-recurrent-infections/abstract/12)].

Some patients are (noninvasive) carriers of pharyngeal group A streptococci and have positive throat cultures for group A streptococci when they are cultured in the setting of viral respiratory tract infections. Antibody screening for anti-streptococcal antibodies (anti-streptolysin O [ASLO] and anti-DNase B) may be helpful, since carriers of group A streptococci typically have low antibody titers. (See "Treatment and prevention of streptococcal tonsillopharyngitis", section on 'Treatment' and "Treatment and prevention of streptococcal tonsillopharyngitis", section on 'Carriers'.)

**Pneumonia** — Patients with recurrent pneumonia often fall into one of two categories:

●Patients with recurrent pneumonia limited to a particular anatomic region (eg, right middle lobe), who generally have a local anatomic abnormality.

●Patients with sequential infections involving different regions of the lung, who are more likely to have an underlying systemic process rather than a local anatomic defect. Patients with recurrent pneumonia in association with other infections, such as sinusitis, otitis media, or bronchitis, are most likely to have an underlying immunodeficiency.

Patients with recurrent pneumonia limited to a particular anatomic region should be evaluated for an anatomic abnormality. This may be extrinsic to the trachea and bronchi (eg, bronchial compression by mediastinal adenopathy, neoplasm, or vascular anomaly) or intrinsic to the bronchus or alveoli (eg, retained foreign body, bronchiectasis, bronchomalacia, bronchial stenosis, tracheobronchial fistula, bronchial sequestration, or cyst) [[13,14](https://www.uptodate.com/contents/approach-to-the-adult-with-recurrent-infections/abstract/13,14)]. Patients with tracheal disorders, such as tracheobronchomegaly [[15](https://www.uptodate.com/contents/approach-to-the-adult-with-recurrent-infections/abstract/15)] or tracheomalacia, may have recurrent infections in a limited or more generalized pattern. (See "Tracheomalacia and tracheobronchomalacia in adults" and "Airway foreign bodies in adults".)

Other underlying conditions that predispose to recurrent pneumonia in a particular anatomic area include recurrent aspiration due to seizures, ethanol or other drug use, dysphagia, reflux, Zenker's diverticulum, or achalasia. These disorders can cause recurrent pneumonitis restricted to the lung bases and posterior segments. In such cases, a barium swallow or other appropriate gastroenterologic studies should be considered.

In contrast, patients with sequential infections involving different regions of the lung are more likely to have an underlying systemic process rather than a local anatomic defect. Examples include:

●Prominent sinopulmonary disease may be seen in patients with cystic fibrosis and immotile cilia syndrome [[16-20](https://www.uptodate.com/contents/approach-to-the-adult-with-recurrent-infections/abstract/16-20)]. It is important to screen young adults with recurrent pneumonia and sinusitis for these processes, especially if symptoms suggestive of cystic fibrosis are present, as this may present in adulthood, and de novo mutations may be responsible for illness despite a negative family history. (See "Cystic fibrosis: Clinical manifestations and diagnosis" and "Primary ciliary dyskinesia (immotile-cilia syndrome)".)

●Noninfectious processes, particularly pulmonary vasculitis or bronchiolitis obliterans organizing pneumonia (BOOP), can sometimes mimic recurrent infectious pneumonitis. If serologic testing (eg, antineutrophil cytoplasmic antibodies [ANCA]) is negative, flexible fiberoptic bronchoscopy and transbronchial biopsy can be valuable in establishing a diagnosis. (See "Pulmonary manifestations of systemic lupus erythematosus in adults", section on 'Other disorders' and "Cryptogenic organizing pneumonia".)

●A secondary immunodeficiency, including HIV infection, hemoglobinopathy, multiple myeloma, or chronic lymphocytic leukemia, can lead to recurrent pneumonia [[21,22](https://www.uptodate.com/contents/approach-to-the-adult-with-recurrent-infections/abstract/21,22)]. HIV testing, hemoglobin electrophoresis, and serum and urine electrophoresis for multiple myeloma may be indicated. (See "Secondary immunodeficiency due to underlying disease states, environmental exposures, and miscellaneous causes".)

**Initial immunologic evaluation** — Primary immunodeficiency should be suspected in adults with recurrent infections of the lung in association with other infections, such as sinusitis, otitis media, or bronchitis [[23-26](https://www.uptodate.com/contents/approach-to-the-adult-with-recurrent-infections/abstract/23-26)]. A defect in antibody production or function, such as common variable immunodeficiency or one of several other antibody defects, or a milder variant of chronic granulomatous disease are possible explanations. (See "Clinical manifestations, epidemiology, and diagnosis of common variable immunodeficiency in adults" and "Primary humoral immunodeficiencies: An overview" and "Primary disorders of phagocytic function: An overview".)

Serum levels of immunoglobulin G (IgG), immunoglobulin A (IgA), immunoglobulin M (IgM), and immunoglobulin E (IgE) are screening tests for antibody defects. A screening test for chronic granulomatous disease is also reasonable, since flow cytometric testing utilizing dihydrorhodamine is widely available. (See "Primary humoral immunodeficiencies: An overview" and "Chronic granulomatous disease: Pathogenesis, clinical manifestations, and diagnosis", section on 'Diagnosis'.)

Two of the most common forms of antibody defects in adults are associated with normal levels of total IgG, IgA, IgM, and IgE:

●IgG subclass deficiency – This is often studied at the same time as quantitative immunoglobulin levels to expedite clinical evaluation. (See "IgG subclass deficiency".)

●Specific antibody deficiency (also called polysaccharide nonresponse) – This assessment requires quantitative evaluation of antipolysaccharide antibody levels against encapsulated pathogens (eg, a panel of *Streptococcus pneumoniae* serotypes) and, if low, the response following the administration of pneumococcal polysaccharide vaccine. (See "Specific antibody deficiency".)

Interpretation of immunoglobulin levels and further testing for antibody defects are reviewed separately. (See "Laboratory evaluation of the immune system", section on 'Antibody deficiency and defects'.)

**Urinary tract infections** — Isolated recurrent urinary tract infections, in the absence of infections in other organ systems, are not a typical presentation of immunodeficiency. Instead, local anatomic abnormalities are a more likely underlying cause. However, recurrent urinary tract infections are also a common problem in sexually active women without any identifiable predisposing condition.

●Anatomic abnormalities resulting in obstruction, stasis, reflux of urinary flow, and functional abnormalities, such as overactive bladder and incontinence [[27](https://www.uptodate.com/contents/approach-to-the-adult-with-recurrent-infections/abstract/27)], all predispose toward recurrent urinary infections. (See "Bacterial adherence and other virulence factors for urinary tract infection".)

●Recurrent urinary tract infections are a common problem in sexually active women in the absence of an identifiable structural abnormality. Sexual activity may cause local irritation of the urethral meatus and lead to cystitis ("honeymoon cystitis"). Women with frequent recurrences often benefit from prevention strategies, including antibiotic prophylaxis that is given after intercourse. (See "Recurrent urinary tract infection in women", section on 'Prevention strategies'.)

●Older men can develop recurrent urinary tract infections with increasing frequency, largely due to obstructive and/or neurogenic abnormalities. Neurogenic abnormalities leading to hypotonic bladder result in urine stasis and an increased risk of infection. In about one-half of men with recurrent urinary tract infections, the prostate is the source of infection. (See "Acute bacterial prostatitis", section on 'Risk factors' and "Chronic bacterial prostatitis", section on 'Antimicrobial penetration into prostatic tissue'.)

●Intraluminal (indwelling bladder catheter, calculi, neoplasms), intramural (ureteral stenosis, urethral strictures, prostatic obstruction), and extramural lesions (paravesical inflammatory mass, neoplasm, or fibrosis) all may predispose to recurrent urinary infection. (See "Catheter-associated urinary tract infection in adults".)

**Gastrointestinal infections**

●Recurrent focal infections, such as cholangitis, are due to local anatomic considerations, such as biliary tract obstruction (calculi, strictures) or reflux (postoperative Roux-en-Y anastomosis). Recurrent diverticulitis is common among individuals with severe diverticular disease. Patients experiencing these focal infections are generally immunologically normal and do not require investigation for immunodeficiency.

●Relapsing and/or recurrent *Clostridium difficile* colitis is increasingly common among immunologically normal individuals, attributable to the increasing use of broad spectrum antibiotics (particularly in patients receiving multiple courses of antibiotic therapy for recurrent extraintestinal infections) and the enhanced virulence of circulating epidemic strains of NAP1 *C. difficile*. It is rarely a presentation of immunodeficiency. (See "Clostridium difficile in adults: Treatment", section on 'Recurrent disease' and "Clostridium difficile in adults: Epidemiology, microbiology, and pathophysiology", section on 'Hypervirulent strain: NAP1/BI/027'.)

Immunocompromised patients appear to be at increased risk for *C. difficile* colitis [[28](https://www.uptodate.com/contents/approach-to-the-adult-with-recurrent-infections/abstract/28)]. Underlying disorders, such as HIV, malignancy, or neutropenia are usually known at the time of *C. difficile*diagnosis.

●Relapsing, recurrent, and/or progressive enterocolitis due to common enteropathogens, such as *Giardia*, enteroviruses, cytomegalovirus, and campylobacter, are associated with underlying hypogammaglobulinemia and/or T cell immunodeficiency. In addition, refractory bouts of enterocolitis due to unusual pathogens, such as *Microsporidia*, *Cyclospora*, or *Isospora*, should also raise the possibility of underlying immunodeficiency.

**Initial immunologic evaluation** — It is reasonable to consider immunologic investigation for underlying neutropenia and T cell immunodeficiency in patients who experience severe primary *C. difficile* disease requiring hospitalization or refractory disease despite appropriate therapy when a clinical explanation is lacking. Granulocyte and lymphocyte assessment by complete blood count and differential white blood cell count, screening immunoglobulin levels (IgG, IgA, IgM), and T and B cell subset quantitation by flow cytometry, are appropriate in patients with unusually severe gastrointestinal disease without apparent clinical explanation.

**Meningitis** — Recurrences can occur with bacterial, viral, and noninfectious causes of meningitis.

**Bacterial meningitis** — The epidemiology of recurrent bacterial meningitis was evaluated in a review of 493 episodes in 445 adults seen at a single center in Boston from 1962 to 1988 [[29](https://www.uptodate.com/contents/approach-to-the-adult-with-recurrent-infections/abstract/29)]. Among 275 patients with community-acquired meningitis, 17 (6.2 percent) had more than one episode of community-acquired disease and 10 had three or more episodes.

●Recurrent bacterial meningitis can result from a breach in the cranial vault. Defects in the cribriform plate, sphenoid or other sinuses, or temporal bone may be congenital or acquired (post-traumatic or post-neurosurgical, especially in the setting of cerebrospinal fluid [CSF] rhinorrhea or other CSF leak). Recurrent meningitis also occurs with the use of indwelling medical devices (eg, Ommaya reservoirs, ventricular shunts, and cochlear implants) placed into the central nervous system. (See "Infections of cerebrospinal fluid shunts and other devices".)

A bony cranial defect can usually be detected by high-resolution computed tomography (HRCT) scanning [[30](https://www.uptodate.com/contents/approach-to-the-adult-with-recurrent-infections/abstract/30)]. Lumbar puncture and instillation of fluorescein or radionuclides for localizing a CSF leak are rarely necessary.

Abnormalities in both complement and opsonizing antibodies have also been associated with recurrent bacterial meningitis:

●Deficiency of one or more of the terminal complement components (C5, C6, C7, C8, C9) has been associated with recurrent *Neisseria meningitidis* meningitis. Low complement levels may be due to either congenital complement deficiency or acquired diseases, such as systemic lupus erythematosus. (See "Inherited disorders of the complement system".)

●Immunoglobulin deficiency disorders or impaired reticuloendothelial function resulting from splenectomy or hemoglobinopathy are associated with an increased risk of bacteremia and therefore meningitis, due to encapsulated pathogens. Recurrent enteroviral (aseptic) meningitis has been associated with agammaglobulinemia [[31](https://www.uptodate.com/contents/approach-to-the-adult-with-recurrent-infections/abstract/31)]. (See "Primary humoral immunodeficiencies: An overview" and "Clinical features and management of sepsis in the asplenic patient".)

**Mollaret's meningitis** — Mollaret's meningitis is a form of benign recurrent aseptic (ie, nonbacterial) meningitis that is almost always due to herpes simplex type 2 (HSV-2) infection [[32](https://www.uptodate.com/contents/approach-to-the-adult-with-recurrent-infections/abstract/32)], although genital lesions are usually absent at the time of presentation. Aseptic meningitis has also been observed in patients with occult craniopharyngiomas [[33](https://www.uptodate.com/contents/approach-to-the-adult-with-recurrent-infections/abstract/33)], where episodic discharge of squamous debris triggers recurrent symptoms and inflammation of the CSF. In cases where HSV-2 does not appear to be the cause of illness based on negative cultures, the absence of viral material on polymerase chain reaction (PCR), negative serology, CSF examination for birefringent material, and cranial imaging may be quite helpful, as discussed separately. (See "Aseptic meningitis in adults", section on 'Management'.)

**Noninfectious meningitis** — Noninfectious meningitides that can recur include Behçet's syndrome, chemical meningitis, neoplastic meningitis, Vogt-Koyanagi-Harada syndrome, and the hypersensitivity meningitis syndromes occasionally triggered by certain medications (eg, sulfonamides, azathioprine, nonsteroidal anti-inflammatory drugs [NSAIDs], and intravenous immunoglobulin). (See "Aseptic meningitis in adults".)

**Initial immunologic evaluation** — In patients with recurrent meningitis and in those recovering from an initial episode of meningococcal meningitis, screening complement testing with C3, C4, and CH50 should be performed. A complete deficiency of any one of the terminal components (C5-9) gives an undetectable CH50 value, with the exception of C9 deficiency, which gives a low, but detectable CH50 titer. If these initial tests are abnormal, further individual testing of the terminal complement components (C5 through C9) is warranted. In addition, levels of IgG, IgA, and IgM should be measured.

**Brain abscess** — Anatomic factors are almost always responsible for the development of parenchymal brain abscesses. Although most brain abscesses result from direct extension from adjacent foci of infection, such as sinusitis or mastoiditis, a variety of remote abnormalities may be important in selected patients.

As an example, shunting of venous blood to the systemic circulation may occur through intracardiac right-to-left or bidirectional shunts, anomalous pulmonary arteries, or extracardiac vascular malformations (eg, Rendu-Osler-Weber syndrome). In addition, extracranial infections that can seed the systemic arterial supply, such as lung abscesses and rarely subacute infective endocarditis, may predispose patients to the development of brain abscesses.

**Severe periodontitis** — Adults with diabetes mellitus have an increased risk of periodontitis. Necrotizing ulcerative periodontitis is an especially severe form of the periodontitis that is seen in patients with a variety of underlying immunodeficiency states, most commonly HIV infection or low CD4 counts due to other disorders, as well as in patients undergoing chemotherapy for malignancies [[34,35](https://www.uptodate.com/contents/approach-to-the-adult-with-recurrent-infections/abstract/34,35)]. (See "Gingivitis and periodontitis in adults: Classification and dental treatment", section on 'Manifestation of systemic disease'.)

**Bacteremia and sepsis** — Patients with isolated deficiency or dysfunction of mannose-binding lectin, a component of the innate immune system that is involved in complement activation, may be at higher risk for bacteremia and sepsis despite normal complement levels. (See "Mannose-binding lectin deficiency".)

Deficiency of C3 has also been associated with bacteremia due to encapsulated pathogens, such as *S. pneumoniae* and *Haemophilus influenzae*, as well as by enteropathogens, such as *Salmonella* species. (See "Inherited disorders of the complement system", section on 'C3 deficiency'.)

**IMMUNODEFICIENCY IN ADULTS**

**Secondary immunodeficiency** — Secondary immune disorders are far more prevalent than primary immunodeficiencies and should be considered in the presence of underlying disease states, medications, or previous surgical procedures (table 2):

●Diabetes mellitus

●Human immunodeficiency virus (HIV) infection

●Cirrhosis

●Nephrotic syndrome

●Other protein-losing states, such as enteropathies, severe exudative skin disease including burn injury, and peritoneal dialysis

●Malnutrition

●Hemoglobinopathy

●Inflammatory bowel disease or rheumatoid arthritis receiving immunosuppressive therapies (particularly tumor necrosis factor [TNF] inhibitors)

●Neurologic disease

●Autoimmune disease

●Splenectomy

●Malignancy

●Radiation therapy

●Immunosuppressive agents, such as glucocorticoids and others

●Immunomodulatory agents, such as rituximab, etanercept, and others

Categories of secondary immune defects are reviewed elsewhere. (See "Secondary immunodeficiency induced by biologic therapies" and "Secondary immunodeficiency due to underlying disease states, environmental exposures, and miscellaneous causes".)

**Primary immunodeficiency** — A study published in 2007 estimated the prevalence of well-defined primary immunodeficiency disorders at 1 in approximately 1200 people in the United States, which is 10-fold higher than earlier estimates [[36](https://www.uptodate.com/contents/approach-to-the-adult-with-recurrent-infections/abstract/36)]. Some of these disorders, particularly some antibody defects, are of mild or moderate clinical severity (eg, specific antibody deficiency, immunoglobulin G [IgG] subclass deficiencies, selective immunoglobulin A [IgA] deficiency) and routinely escape detection until adulthood [[37,38](https://www.uptodate.com/contents/approach-to-the-adult-with-recurrent-infections/abstract/37,38)].

**What is an excessive number of infections?** — The number of infections experienced by an otherwise healthy adult can vary tremendously from year to year, depending on multiple factors, such as exposure to children, variations in the incidence and virulence of common respiratory viruses, stress levels, and other transient fluctuations in health status.

"Warning signs" of primary immunodeficiency in adults have been developed to help patients and clinicians recognize excessive infections [[39,40](https://www.uptodate.com/contents/approach-to-the-adult-with-recurrent-infections/abstract/39,40)]. Primary immunodeficiency should be considered when an adult has experienced **any one** of the following:

●Four or more infections requiring antibiotics within one year (eg, sinusitis, bronchitis, pneumonia, otitis media, especially with perforation).

●Recurring infections or infection requiring or not responding to prolonged antibiotic therapy and requiring intravenous antibiotic therapy.

●Two or more severe bacterial infections (osteomyelitis or septic arthritis, meningitis, septicemia, cellulitis).

●Two or more radiologically proven pneumonias within three years (particularly if severe enough to require hospitalization and/or intravenous antibiotics or associated with slow recovery, intrathoracic spread of infection, or necrotizing pneumonia).

●Infection with unusual localization or unusual pathogen.

●Recurrent deep abscesses of the skin, lymph nodes, or internal organs.

●Chronic diarrhea with weight loss, especially due to campylobacter or cryptosporidiosis.

●Persistent thrush especially in the absence of recently administered antibiotics.

●Recurrent prolonged and unexplained fevers.

●A family history of primary immunodeficiency.

In addition to these warning signs, several other health problems are more common in patients with immunodeficiency, such as poor wound healing (may be seen with neutropenia) and unexplained bronchiectasis [[41](https://www.uptodate.com/contents/approach-to-the-adult-with-recurrent-infections/abstract/41)]. (See "Wound healing and risk factors for non-healing" and "Clinical manifestations and diagnosis of bronchiectasis in adults", section on 'Etiologies'.)

Patients who have two or more warning signs or other history to suggest an immune problem should still be evaluated for secondary immune disorders and anatomic causes of recurrent infections, because the latter categories of illness are more common than primary immunodeficiency. If neither of these problems is identified, then an evaluation for primary immunodeficiency is appropriate.

**Noninfectious manifestations of immunodeficiency** — In addition to infections, many immune disorders are associated with autoimmune disease and a higher risk of malignancies. A fundamental function of the immune system is to distinguish "self" from "non-self." This capacity is critical not only for defense against invading micro-organisms, but also for the prevention of autoimmune disease and detection and destruction of malignant cells. Some immunodeficiencies are also associated with higher rates of allergic disease, which is another manifestation of immune dysregulation.

Autoimmune disorders that are seen in patients with immunodeficiencies include autoimmune thyroiditis, autoimmune hemolytic anemia, thrombocytopenia, or neutropenia, pernicious anemia, celiac disease, and vitiligo [[41](https://www.uptodate.com/contents/approach-to-the-adult-with-recurrent-infections/abstract/41)]. Inflammatory diseases, such as arthritis, inflammatory bowel disease, pyoderma granuloma, and connective tissue disorders are also seen with increased frequency.

Thus, the clinician's threshold for initiating an evaluation of the immune system should be lower in a patient with disorders in one or more of these categories of disease.

**PATTERNS OF INFECTION** — Patients with immunodeficiency typically experience stereotypic patterns of recurrent infection, which provide clues regarding which portion of the immune system is affected. The laboratory evaluation of each of these components of the immune system is reviewed separately. (See "Laboratory evaluation of the immune system".)

**Defects in immunoglobulins and/or complement proteins** — Recurrent sinopulmonary infections, chronic gastrointestinal infections, bacteremia, and/or meningitis are associated with defects in immunoglobulins and/or complement proteins. Common pathogens include the encapsulated bacteria, *S. pneumoniae*, *H. influenzae* type b, and *N. meningitidis*, as well as *Giardia*, *Cryptosporidia*, and *Campylobacter*. (See "Primary humoral immunodeficiencies: An overview" and "Inherited disorders of the complement system".)

**Granulocyte (neutrophil) defects** — Recurrent invasive skin and soft tissue infections, especially focal abscesses requiring incision and drainage, are associated with granulocyte (neutrophil) defects. Characteristic organisms include catalase-positive organisms, such as S*. aureus*, gram-negative bacilli, *Aspergillus*, and *Nocardia*. (See "Primary disorders of phagocytic function: An overview".)

**Defects in cell-mediated immunity** — Progressive infections with ordinarily "benign" viruses, opportunistic intracellular pathogens, or fungi suggest defective cell-mediated immunity, particularly defects of T cells. Typical micro-organisms include cytomegalovirus, Epstein-Barr virus or other herpes viruses, mycobacteria, and fungi (*Candida*, *Cryptococcus*, and *Pneumocystis*). Natural killer (NK) cell defects also present with severe and fulminant herpes virus infections, although these conditions are rare. (See "Severe combined immunodeficiency (SCID): An overview" and "Combined immunodeficiencies" and "NK cell deficiency syndromes: Clinical manifestations and diagnosis".)

**Other disorders** — Some disorders cause recurrent infections that do not fit into one of these simple patterns. As examples:

●Leukocyte-adhesion deficiency (LAD) results in both lymphocyte and phagocyte dysfunction. As a result, both bacterial infections and life-threatening viral infections may recur early in life. Patients with milder phenotypes of LAD-I can survive into adulthood. (See "Leukocyte-adhesion deficiency".)

●Deficiency of mannose-binding lectin, a complement-like protein that confers innate immunity to a variety of pathogens, has been described in adults as well as in children and is associated with skin abscesses, cryptosporidiosis, pneumonia, and meningococcal sepsis. (See "Mannose-binding lectin deficiency".)

Hyperimmunoglobulin E syndrome (Job syndrome), classically a multisystem disorder resulting from defects in intracellular signaling pathways, should be suspected in adults with infected eczema, pneumatoceles, mucocutaneous candidiasis, recurrent cutaneous and respiratory tract bacterial infections, and marked elevation of serum immunoglobulin E (IgE). (See "Autosomal dominant hyperimmunoglobulin E syndrome".)

**REFERRAL** — Referral to a variety of specialists may be needed, depending upon the expertise and interest of the generalist, as well as the availability of specialists.

●For patients with recurrent infections that may be due to an underlying anatomic abnormality or may not actually be infectious in nature, such as sinusitis or urinary tract infection, referral to a specialist in that organ system may be most helpful (eg, otolaryngologist, urologist/urogynecologist).

●Referral to an infectious disease specialist is appropriate for patients with underlying disorders, such as human immunodeficiency virus (HIV) infection, or for those in whom there may be an issue of chronic bacterial colonization or carriage (recurrent pharyngitis). The infectious disease clinician usually has the most experience in formulating antibiotic strategies for acute therapy and prophylaxis that may minimize morbidity.

●For suspected primary or secondary immunodeficiency, an allergist/immunologist is likely to be most helpful, and referral should be considered before advanced immunologic testing is undertaken [[42](https://www.uptodate.com/contents/approach-to-the-adult-with-recurrent-infections/abstract/42)].

**SUMMARY**

●The vast majority of adults presenting with recurrent infections, especially localized to one organ system, have an anatomic abnormality or underlying condition that predisposes to infections, (such as allergic rhinitis causing recurrent sinusitis or saphenous venectomy causing recurrent cellulitis) rather than an immune defect (table 1). (See 'Overview of etiologies' above and 'Considerations by site of infection' above.)

●When an immune defect is suspected in an adult, secondary causes of immunodeficiency (eg, diabetes, immune-altering medications) are more common than primary immunodeficiencies (table 2). (See 'Overview of etiologies' above and 'Immunodeficiency in adults' above.)

●Primary immunodeficiency occasionally presents for the first time in adulthood. Affected patients may also have autoimmune disease and suffer higher rates of malignancies, as these disorders are also manifestations of abnormal immune function. A history of one or more of these types of disorders in a patient with recurrent infections should raise suspicion of an underlying immunodeficiency. (See 'Noninfectious manifestations of immunodeficiency' above.)

●Referral to a variety of different specialists may be needed, depending upon the expertise and interest of the generalist, as well as the availability of specialists. Referral to an allergist/immunologist is best pursued before extensive immunologic testing is initiated. (See 'Referral' above.)

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