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Approach to adult patients with recurrent infections

■ KEY POINTS:

HIV testing should always be considered if the clinical situation is at all compatible with HIV infection, even if the patient has no identifiable HIV risk factors.

Factitious disorders are more common than most clinicians realize, but are difficult to document firmly.

Common predisposing conditions for cellulitis include chronic venous insufficiency, lymphedema, and previous episodes of cellulitis; these sometimes coexist.

In general, recurrent uncomplicated upper respiratory infections rarely denote a serious underlying disorder.

Recurrent central nervous system infections are less common than recurrent soft tissue infections and respiratory infections, but may be the indication of an underlying systemic disorder.

■ **ABSTRACT:** Recurrent infections often reflect underlying abnormalities, either anatomic or immunologic. In this paper we review how to recognize the underlying disorders in a variety of recurrent infections.

Although patients with recurrent infections are frequently referred to infectious disease subspecialists,¹ internists should be familiar with the evaluation and management of the most common types of recurrent infection. A primary care clinician who monitors and coordinates the patient's care is often important in such cases, as patients may receive fragmented care as they move from specialist to specialist, receiving many different opinions. This fragmentation of care can hinder the evaluation and may generate unnecessary repetition of laboratory and radiographic tests.

More important, a primary care relationship can help the patient develop strategies for living with a chronic condition (if one is discovered) and can lead to the most effective management of recurrences if they occur, with the assistance of subspecialists when appropriate.

■ GENERAL APPROACH TO EVALUATION

The challenge in evaluating recurrent infections is to distinguish those due to common medical problems (such as chronic obstructive pulmonary disease) from those due to more unusual conditions that may require specific therapy.

What underlying conditions are likely?

In some cases, recurrent infections may be the first sign of an underlying condition. Examples include:

Acquired immunodeficiencies: human immunodeficiency virus (HIV) infection, some forms of hypogammaglobulinemia, plasma cell dyscrasias, some rheumatologic, endocrinologic, and oncologic conditions.

Anatomic abnormalities, foreign bodies, or other unusual local factors.



Rare congenital immunodeficiencies (ie, chronic granulomatous disease), which may occasionally come to light for the first time in adulthood.²

Are specialized tests necessary?

Because many of the tests used to diagnose these underlying conditions are costly and time-consuming, the clinician should have a clear idea of the expected benefits before embarking on an extensive evaluation. Will testing lead to meaningful therapeutic intervention? Will it provide a satisfying answer to the patient?

HIV testing, on the other hand, should always be considered if the clinical situation is at all compatible with HIV infection, even if the patient has no identifiable HIV risk factors. Patients with recurrent infection frequently are concerned about HIV and may be afraid to mention it unless the clinician does so first.

Many clinicians routinely offer HIV testing, with appropriate counseling, in any unusual or otherwise unexplained infection. Testing occasionally uncovers unsuspected HIV infection and leads to changes in management, but more often reassures the patient.

The initial history

The initial history should specify:

- Any pertinent family history.
- The patient's medical history.
- Any underlying primary disease such as diabetes mellitus, chronic lung disease, cirrhosis, nephrotic syndrome, autoimmune disease, hemoglobinopathy, or cancer.
- Any risk factors for HIV infection, including substance abuse, which may itself predispose to infections.
- The age at onset and pattern of recurrent infections.
- The anatomic location of recurrent focal infections.
- All medications taken (to rule out exogenous immunosuppression).
- Any environmental factors or unusual exposures.

Clues to types of immune deficiencies

If clues from the medical history suggest a pri-

mary problem with the immune system,³ the clinician should consider where the defect likely resides: in nonspecific humoral and cellular factors (complement, phagocytic cell function⁴), or in the specific immune response to particular pathogens (immunoglobulin abnormalities,⁵ cell-mediated immunity).

Age at onset. Congenital or early-onset immunodeficiencies usually become evident well before adulthood, but may occasionally escape detection. Abnormalities of immunoglobulins and of cell-mediated immunity are acquired rather than congenital in many patients.

Immunoglobulin deficiency states, including common variable hypogammaglobulinemia and acquired hematologic conditions such as multiple myeloma and splenectomy, may first become symptomatic when an adult experiences recurrent infection. Selective IgA deficiency, the most common of the immunoglobulin deficiencies (though frequently asymptomatic), is particularly important to identify, as patients with it should not be given immunoglobulin replacement therapy because of the risk of anaphylaxis.⁵

Recurrent sinopulmonary infections, bacteremia, and meningitis should, in general, raise the question of antibody or complement deficiencies.⁶

Recurrent invasive skin infections may reflect defects in phagocyte function, although there are many other causes.

Progressive infection with opportunistic pathogens or protracted atypical viral syndromes suggest possible cell-mediated immunodeficiency.

■ SKIN AND SOFT TISSUE INFECTIONS

Recurrent cellulitis and soft tissue abscesses are common in primary care practice. Some factors predispose to cellulitis, others to formation of abscesses, and some factors can cause either problem.

Cellulitis: predisposing factors

Common predisposing conditions for cellulitis include chronic venous insufficiency, lymphedema, and previous episodes of cellulitis

Recurrent infections may be the first sign of an underlying problem

(TABLE 1); these sometimes coexist.⁷

Lymphedema alters the lymphatic drainage of the extremity and predisposes to infection; it may be either congenital or acquired. Familial lymphedema (Milroy's disease) and sporadic primary congenital lymphedema are uncommon. More common causes of lymphedema are streptococcal infection and, in developing countries, filariasis. Surgical procedures, such as mastectomy, lymph node dissection, and saphenous vein harvesting for coronary artery bypass grafting,⁸ may alter local anatomy and increase the risk for infection, as can radiation therapy.

Trauma to an extremity or a digit, chronic or acute ulcerations, chronic skin conditions such as tinea pedis, and self-induced injuries (which may be inadvertent, such as during shaving of the legs, or factitious, ie, intentional) can all provide entry for organisms that then invade the soft tissues.

Factitious disorders are more common than most clinicians realize, but are difficult to document firmly. There are a wide variety of manifestations, including recurrent bacteremia. The patient is frequently knowledgeable about the health care system. If a factitious disorder is suspected, it is important to rule out any other possible contributing organic conditions. Some clinicians favor confronting the patient, but the management is controversial. The assistance of a psychiatrist or psychologist familiar with these disorders is crucial.

Diabetes, arterial insufficiency due to atherosclerosis or vasculitis, and scleroderma can all predispose to poor healing and chronic alteration in skin integrity.⁹

Congenital or acquired neutropenia can lead to soft tissue infection that may rapidly progress and may lack characteristic inflammatory findings on physical examination.

Foreign bodies such as surgically placed hardware or prostheses have important implications for diagnosis and therapy, as recurrent or persistent infections may be difficult if not impossible to eradicate with these materials in place. In trauma patients who subsequently contract recurrent focal infections or a deep abscess, an unsuspected foreign body may provide the missing piece in the clinical puzzle.

Therapy for recurrent cellulitis

Therapy depends on the underlying factors and the frequency and pattern of recurrences. Patients with frequent or debilitating recur-

TABLE 1
CAUSES OF RECURRENT SKIN AND SOFT TISSUE INFECTIONS
Chronic venous insufficiency
History of cellulitis
Lymphedema (acquired or congenital)
Trauma
Surgery
Skin ulcer or ulcers
Chronic skin conditions
Self-induced injury
Foreign body or prosthesis
Diabetes mellitus
Arterial insufficiency
Deep infection with sinus tract
Vasculitis
Scleroderma
Others
Branchial cleft cyst
Pilonidal cyst
Ulcerative colitis with pyoderma gangrenosum
Defects in granulocyte function (rare)

rent cellulitis may be candidates for long-term oral antimicrobial prophylaxis, usually with agents effective against streptococci (such as penicillin twice daily), unless their previous cultures indicate otherwise.

Predisposing factors for all types of soft tissue infections

In addition to recurrent cellulitis, recurrent soft tissues abscesses may be seen.

Local factors include branchial cleft cysts, pilonidal cysts or sinus tracts, and retained foreign bodies.¹⁰ The area of abscess formation, whether one area or many are involved, and the organisms isolated are important. A history of hidradenitis suppurativa or other skin conditions should be sought. Autoinoculation, either factitious or due to substance abuse (ie, subcutaneous injection or "skin-popping"), should always be in the differential diagnosis.

Systemic diseases, such as Crohn's disease with sinus tract formation, ulcerative colitis with pyoderma gangrenosum, or systemic lupus erythematosus with cutaneous vasculitis, may occasionally play a role.

An unsuspected foreign body may provide the missing piece in the clinical puzzle



An illustrative case: soft tissue infections

A 35-year-old man had chronic drainage from his left foot for 10 years, with episodes of redness and swelling over the medial malleolus.¹¹ He underwent six surgical procedures without success. Magnetic resonance imaging, indium and bone scans, computed tomography, and plain films failed to reveal a cause. A contrast study through the sinus tract demonstrated a probable fluid collection between the first and second metatarsals; a foreign body was suspected. At operation a thorn-like object was excised. The patient recalled a possible thorn injury 23 years previously. After this procedure and antibiotic therapy, the draining sinus healed.

Tracheal
disease may
present with
recurrent
pneumonia

Causes of all types of soft tissue infections

Immunodeficiency. Of the immunodeficiencies that can lead to recurrent soft tissue infections, defects in granulocyte or complement function are most likely. Defects in granulocyte function may be quantitative or qualitative.

Chronic granulomatous disease usually manifests itself in early childhood, but may be first diagnosed in adulthood,² perhaps representing a variant of the disease. The major defect involves impaired oxidative killing of organisms such as bacteria (*Staphylococcus aureus*), some gram-negative bacilli, and *Aspergillus*. The nitroblue tetrazolium dye reduction test is used to screen for this condition.

Job's syndrome (hyperimmunoglobulin E with impaired chemotaxis), a rare cause of recurrent soft tissue infections, presents with eczema and recurrent "cold" abscesses.

Nasal colonization. Most patients with recurrent soft tissue infections do not have such esoteric diseases. A much more common cause is chronic staphylococcal nasal colonization, especially in frequently hospitalized patients or health care workers. A trial of intranasal mupirocin therapy and antibacterial hand washes can interrupt the cycle of colonization and reinfection, though colonization can later recur.

Unusual pathogens such as mycobacteria, actinomycetes, fungi (endemic mycoses such as blastomycosis; agents of mycetoma), or *Leishmania* (if the patient has traveled to an area where this is endemic) may be present in nonhealing or progressive soft tissue infections, with or without known immunocompromise. A skin biopsy or surgical debridement and appropriate cultures may establish the diagnosis; the clinician should alert the microbiology and pathology laboratories if an unusual pathogen is suspected.

■ RESPIRATORY INFECTIONS

In general, recurrent uncomplicated upper respiratory infections rarely denote a serious underlying disorder.

Sinusitis

Predisposing factors. Isolated recurrent sinusitis does not generally imply an immunodeficiency, although sinusitis is common in patients with HIV infection or immunoglobulin deficiencies. Recurrent sinusitis is more often due to environmental allergens, inadequate antibiotic therapy for an initial episode of sinusitis, or impaired sinus drainage. Occasionally, unusual conditions such as fungal infection or Wegener's granulomatosis come to light (TABLE 2).

Therapy. An adequate trial (at least 2 weeks) of broad-spectrum antibiotics or suppressive antibiotic therapy and, possibly, endoscopic surgery to improve ostial drainage may be indicated for some patients with recurrent or refractory sinusitis.

Pharyngitis

Predisposing factors. Recurrent pharyngitis, in particular due to infection with group A beta-hemolytic streptococci, may result from inadequate compliance with therapy, inadequate dosing, or reinfection among family members or close contacts. Some patients continue to carry streptococci in the pharynx despite appropriate therapy and resolution of symptoms; in general such carriers do not require retreatment.

Therapy. For symptomatic recurrence,

some clinicians prescribe a course of alternate therapy such as a beta-lactamase-resistant antibiotic. However, recent evidence suggests that higher doses of penicillin or amoxicillin (40 mg/kg/day) are more effective than standard doses. Penicillin in higher doses appears preferable to broad-spectrum antibiotics because it is cheaper and helps prevent antimicrobial resistance.¹²

Routine throat cultures, obtained to verify cure after symptoms have abated, are often confusing because they cannot distinguish antibiotic failure from a benign carrier state. Such cultures are most useful for patients in whom symptoms persist after therapy for streptococcal infection. If family members appear to be reinfecting one another repeatedly, a course of clindamycin for the entire family may help to eradicate colonization.¹³

For severe and frequent recurrences, long-term suppression with penicillin is an option. Frequent symptomatic recurrences are rarely associated with a tonsillar abscess; selected patients with frequent and severe recurrent unilateral exudative pharyngitis should undergo evaluation by an otolaryngologist. Tonsillectomy is rarely necessary for adults with recurrent streptococcal pharyngitis without associated airway obstruction or abscess formation.

Lower respiratory tract infections

If a patient has recurrent lower respiratory tract infections, it is important to determine if the infections always recur in a particular region of the lung, or in different regions. A recurrent localized infection may indicate an endobronchial lesion (neoplasm, foreign body, broncholithiasis) or extrinsic bronchial compression by a neoplasm or mediastinal adenopathy. Infections that occur in different regions may indicate a more generalized abnormality of local or systemic host defense.

Congenital disorders to consider include cystic fibrosis, a milder variant of which may present in adulthood.¹⁴ Hemoglobinopathies may produce recurrent pulmonary infiltrates that may be difficult to distinguish from recurrent pneumonia. Kartagener's (immotile cilia) syndrome consists of bronchiectasis, sinusitis, and dextrocardia; incomplete forms with recurrent infection in the absence of dextrocardia may be seen. Tracheal disease, including tracheoesophageal fistula, may present with recurrent pneumonia. Bronchial disease, including sequestration of the lung and bronchial cysts, may also present in this fashion.

TABLE 2

CAUSES OF RECURRENT SINOPULMONARY INFECTIONS

Sinusitis

- Environmental allergens
- Inadequate initial antibiotic therapy (efficiency, dose, and/or duration)
- Inadequate drainage
- Less common: fungal or unusual pathogen
- HIV infection
- Wegener's granulomatosis
- Lymphoma
- Humoral immunodeficiency

Pulmonary or sinopulmonary

- Tobacco abuse
- Chronic obstructive pulmonary disease
- Obstructive endobronchial lesion
- Extrinsic bronchial compression
- Recurrent aspiration
- Bronchiectasis
- HIV infection
- Cystic fibrosis
- Hemoglobinopathies
- Kartagener's syndrome
- Tracheal disease (eg, tracheoesophageal fistula)
- Bronchial disease (bronchial cyst, sequestration)
- Immunoglobulin deficiencies (class or subclass)
- Multiple myeloma and other plasma cell dyscrasias
- Chronic lymphocytic leukemia
- Asplenia (anatomic or functional)

Conditions that may mimic recurrent sinopulmonary infection

- Pulmonary vasculitis
- Hypersensitivity pneumonitis
- Allergic bronchopulmonary aspergillosis

Routine throat cultures often cannot distinguish antibiotic failure from a benign carrier state

Acquired disorders include chronic bronchitis (especially related to tobacco abuse), emphysema, bronchiectasis, and recurrent aspiration (from neurogenic mechanisms, use of ethanol or other sedating drugs, or esophageal diseases such as reflux, Zenker's diverticulum, or achalasia).

Respiratory infections and the immune system

Recurrent sinusitis, bronchitis, and pneumonia may indicate an underlying humoral immunodeficiency and an inability to handle encapsulated pathogens adequately. Systemic disorders include congenital immunoglobulin



An illustrative case: respiratory infections

A 23-year-old man had several episodes of sinusitis, bronchitis, and pneumonia every year for several years. His total IgG level was slightly low (IgG1 415 mg/dL, IgG3 41 mg/dL). A serum immune survey performed before and after immunization with pneumococcal polysaccharide vaccine and *Hemophilus influenzae* type B conjugate vaccine demonstrated adequate responses to vaccination.

After discussion, his physicians decided that his immunodeficiency was not profound enough to warrant immunoglobulin replacement therapy. Antibiotic prophylaxis during viral respiratory tract infections should be considered in this situation to prevent bacterial superinfection. (Note: the type of vaccine and the particular kind of subclass deficiency affect the response to vaccinations. Polysaccharides such as pneumococcal vaccine elicit IgG2 and IgG4 responses; however, the *H influenzae* type B conjugate vaccine elicits IgG1 and IgG3 responses because of the protein conjugate.)

Recurrent lung infections in different areas may indicate an immune deficiency

deficiencies (both class and subclass)⁶ and acquired defects. Recurrent sinopulmonary infections are a hallmark of IgA deficiency in some patients, though most have no symptoms, and symptomatic patients may have associated IgG subclass deficiency. Other humoral abnormalities that may turn up in primary care practice include common variable hypoglobulinemia, multiple myeloma, chronic lymphocytic leukemia, anatomic or functional asplenia, and HIV infection.

Many patients infected with HIV contract multiple bacterial infections before the manifestations of AIDS appear, as the polyclonal hyperglobulinemia and poor specific B-cell response occur well before the patient becomes susceptible to opportunistic pathogens. Noninfectious processes may mimic recurrent infection in pulmonary vasculitis, hypersensitivity pneumonitis, and eosinophilic pneumonia. Allergic bronchopulmonary aspergillosis should be suspected in a patient with chronic pulmonary infiltrates and high IgE level.

If recurrent sinopulmonary infections

appear more frequent and severe than can be explained by known factors such as cigarette smoking, it may be advisable to check quantitative IgG, IgA, and IgM levels. IgG subclass deficiency is uncommon but may occur with or without diminished total IgG levels, and IgG subclass levels should be checked if the suspicion of humoral immunodeficiency is strong. If multiple myeloma or another plasma cell dyscrasia is suspected, especially in an older patient, serum and urine immunoelectrophoresis should be performed to detect a possible monoclonal gammopathy.

■ CENTRAL NERVOUS SYSTEM INFECTIONS

Recurrent central nervous system infections are less common than recurrent soft tissue infections and respiratory infections. However, these may be the key to an underlying systemic disorder, and should be thoroughly evaluated.

Recurrent meningitis: predisposing conditions

Local factors, such as congenital lesions in the cribriform plate, sphenoid, or other sinuses, can lead to sequential episodes of meningitis with different pathogens or pathogens of decreased virulence (TABLE 3). Acquired lesions include posttraumatic and postsurgical abnormalities, particularly those involving a persistent cerebrospinal fluid leak.¹⁵ In the latter, pneumococcal infections are particularly common, although other pathogens may also be seen.

Systemic factors associated with recurrent meningitis include splenectomy or functional asplenia, hemoglobinopathy, complement deficiencies, and hypogammaglobulinemia. Congenital deficiencies of the late complement components predispose to infection with *Neisseria meningitidis* and *N gonorrhoeae*, and screening for such complement deficiencies in patients with meningococcal infection is helpful. Acquired hypocomplementemia, which may occur in systemic lupus erythematosus and other vasculitides, may also predispose to bacterial meningitis. Agammaglobulinemic patients can be sub-

TABLE 3**CAUSES OF RECURRENT CENTRAL NERVOUS SYSTEM INFECTIONS OR NONINFECTIOUS MENINGITIS**

Anatomic abnormality or cerebrospinal fluid leak
Dermoid cyst with chemical meningitis
Behçet's disease
Neoplastic meningitis
Sarcoidosis
Vogt-Koyanagi-Harada syndrome
Mollaret's meningitis
Medications
Nonsteroidal anti-inflammatory drugs
Muromonab-CD3 (OKT3)
Azathioprine
Asplenia
Complement deficiencies (especially if <i>Neisseria</i>)
Systemic lupus erythematosus
Hypogammaglobulinemia

ject to recurrent and refractory enteroviral meningitis.

Noninfectious disorders that may mimic recurrent infectious meningitis include:

- Chemical meningitis. For example, periodic release of inflammatory material from a central nervous system dermoid cyst¹⁶ may cause recurrent pleocytosis that resembles repeated episodes of bacterial meningitis.
- Behçet's disease, in which central nervous system manifestations may predominate.
- Vogt-Koyanagi-Harada syndrome (uveitis, vitiligo, and meningitis).
- Neoplastic meningitis.
- Sarcoidosis.
- Systemic lupus erythematosus.¹⁷

Mollaret's meningitis features recurrent self-limited febrile episodes, pleocytosis, and characteristic "Mollaret cells" in the cerebrospinal fluid. At least some cases are due to herpes simplex virus.¹⁸

Medications, including nonsteroidal anti-inflammatory drugs, trimethoprim-sulfamethoxazole, azathioprine, and muromonab-CD3 (OKT3), can also cause recurrent meningitis, in which polymorphonuclear leukocytes often predominate in the cerebrospinal fluid.

Brain abscesses

Brain abscesses do not often recur, as any

**An illustrative case:
central nervous system infections**

A young man presented with hepatitis and pancreatitis after a second episode of aseptic meningitis. He had a history of recurrent joint inflammation (diagnosed previously as gout), sacroiliac pain, abdominal pain, oral ulcerations (during his first episode of aseptic meningitis), recurrent ocular inflammation suggestive of uveitis, and an episode of genital ulcerations several years earlier. An exhaustive diagnostic evaluation that excluded other conditions led to the diagnosis of Behçet's disease.

underlying condition is usually diagnosed during the initial episode. Uncorrected problems such as chronic sinusitis or mastoiditis, traumatically introduced or neurosurgically placed foreign bodies, right-to-left cardiac shunts, lung abscess, and recurrent infectious endocarditis could potentially lead to recurrence.

GENITOURINARY TRACT INFECTIONS

Recurrent urinary tract infection has been extensively reviewed,^{19–21} but the following is a brief overview of possible causes.

Common predisposing factors

Urinary tract obstruction, stasis, or reflux, due to either congenital or acquired factors (TABLE 4), can predispose to infection. A variety of congenital lesions may alter urine flow, but these are generally diagnosed before adulthood.

Anatomic and local factors predominate as causes of recurrent urinary tract infection, rather than immunodeficiencies. However, underlying conditions such as diabetes mellitus or exogenous immunosuppression may increase the number of infections and their severity and the variety of pathogens.

Instrumentation (eg, Foley catheterization) is a common cause of infections.

Intraluminal problems such as calculi or neoplasms, or intramural lesions such as ureteral stenosis or other intrinsic ureteral abnormalities, may be a factor. The latter may arise from surgery, radiation therapy, trauma, or infections such as tuberculosis or with *Schistosoma haematobium*.

Prostatic and urethral obstruction and incomplete bladder emptying frequently predispose to infections. Extramural lesions such as compression by intra-abdominal inflamma-

Screen for late complement deficiencies in patients with meningococcal infection



An illustrative case: genitourinary tract infections

A diabetic woman with end-stage renal failure was transferred from another hospital in septic shock. She had a history of staghorn calculi and recurrent urinary tract infections, had undergone a right nephrectomy, and was on hemodialysis. An abdominal computed tomographic scan showed an extensive abscess involving the entire left kidney, which also contained a staghorn calculus. Percutaneous aspiration of the abscess revealed *Proteus mirabilis*, coagulase-negative staphylococci, and anaerobic gram-positive cocci.

tory masses, tumors, or retroperitoneal fibrosis are occasional factors.

Recurrent urinary tract infections in women. About one in five young women with cystitis develops recurrent episodes, most without any demonstrable anatomic abnormalities.¹⁹ Proposed explanations include increased vaginal colonization with *Escherichia coli* in relation to diaphragm and spermicide use, and specific adherence properties of the uroepithelium. Stamm and Hooton¹⁹ recommend one of three strategies: patient-initiated therapy, postcoital therapy, or continuous prophylaxis. Postmenopausal women may have alterations in the normal vaginal flora and may benefit from topical estrogen therapy.¹⁹

CONCLUSION

A variety of factors, local and systemic, may predispose to the development of recurrent infections. The general internist has an important role in the diagnosis and management of

TABLE 4

CAUSES OF RECURRENT URINARY TRACT INFECTIONS

Urinary tract obstruction or foreign body (calculi, neoplasm)
Anatomic abnormalities
Reflux
Congenital or postoperative lesions
Radiation therapy
Neurogenic bladder
Diabetes mellitus
Prostate enlargement
Instrumentation
Specific adherence properties of uroepithelium
Postcoital or contraceptive-related (eg, diaphragm)
Estrogen deficiency

these conditions, though the involvement of subspecialists is often helpful. In any case, a careful history with attention to past medical and surgical conditions, family history, travel and environmental exposures, and possible host factors provides an essential background for evaluating and treating any recurrent infection. Documentation of previous episodes, provided by other hospitals and physicians previously consulted, may provide essential clinical clues. Often, the detection of a correctable underlying condition or institution of appropriate prophylaxis may greatly benefit the patient. ■

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In urinary tract infections, anatomic and local factors predominate, rather than immuno-deficiencies

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