TABLE 24. Diseases Caused by Nontuberculous Mycobacteria

Clinical Disease	Microbe	Risk Factors	Comments
Pulmonary	MAC *M. kansasii* *M. abscessus* *M. fortuitum* *M. xenopi* *M. malmoense* *M. szulgai* *M. simiae* *M. asiaticum*	Older persons with or without underlying lung disease; cystic fibrosis MAC most common cause of pulmonary NTM infection in U.S., followed by *M. kansasii* and *M. abscessus* Municipal water sources (*M. kansasii*, *M. xenopi*) Aspiration (*M. fortuitum*)	All organisms ubiquitous in the environment Possible person-to-person transmission of *M. abscessus* among patients with cystic fibrosis has been reported, but mechanism of transmission is unclear; otherwise, no evidence of human-to-human transmission
Lymphadenitis	MAC *M. abscessus* *M. fortuitum* *M. scrofulaceum* *M. malmoense*	More commonly seen in children	MAC most common: surgical excision results in >90% cure rate
Skin and soft tissue	*M. marinum* *M. ulcerans* *M. abscessus* RGM	Exposure to fish tanks (*M. marinum*) Surgical-site infections (RGM) Whirlpool footbaths, tattoo ink (RGM) Buruli[a] ulcer, an extensive disabling ulcer with central necrosis; tropics, not U.S. (*M. ulcerans*)	Results from direct inoculation
Catheter-related bloodstream infections	RGM	Long-term catheterization; immunocompromise	
Disseminated	MAC (in persons with AIDS and CD4 cell count <50/μL) *M. kansasii* *M. chimaera* RGM	Immunocompromise, especially persons with AIDS or those taking tumor necrosis factor-α inhibitors (MAC, *M. kansasii*) Heater-cooler devices in cardiac surgery (*M. chimaera*)	Clinical presentation: fever, night sweats, weight loss Prosthetic valve endocarditis months to years after surgery (*M. chimaera*); diagnosis requires multiple mycobacterial blood cultures

MAC = *Mycobacterium avium* complex; NTM = nontuberculous mycobacteria; RGM = rapidly growing mycobacteria; U.S. = United States.

[a]Named for the Buruli district in Uganda, where initial cases were described.

Mycobacterium kansasii

M. kansasii infection mimics pulmonary tuberculosis with cavitary lung disease. Predisposing conditions include underlying lung disease, alcoholism, and immunocompromised status.

Rapidly Growing Mycobacteria

Rapidly growing NTM have been implicated in NTM outbreaks. The most common rapidly growing mycobacterial species include *M. abscessus*, *M. chelonae*, and *M. fortuitum*.

M. abscessus is the most common. Considering its intrinsic drug resistance and increased prevalence, it is one of the most difficult to treat. Most of these mycobacteria are associated with chronic pulmonary infections and nonhealing ulcers unresponsive to appropriate antibiotic therapy.

KEY POINTS

- *Mycobacterium avium* complex is a common cause of chronic lung infection worldwide, causing cavitary lung disease.
- *Mycobacterium abscessus*, *Mycobacterium chelonae*, and *Mycobacterium fortuitum* can produce lung disease, adenitis, skin and soft tissue infections, surgical site infections, and catheter-related bloodstream infections.

Fungal Infections

The incidence of fungal infections is increasing because of the increased recognition of these infections and an increase in the population at risk worldwide. Most commonly encountered infections in North America are caused by *Candida*

species (73%) followed by *Aspergillus* species (14.8%), other yeast (such as *Cryptococcus* species; 6.2%), and mucormycetes (including *Rhizopus* and *Mucor* species; 1.7%).

Systemic Candidiasis

Candida species are the fourth most commonly isolated organisms in bloodstream infections and are associated with a mortality rate of 30% to 40%.

Candidemia can present as an isolated fever or septic shock. Signs and symptoms of focal infection depend on the site involved. Meningitis, septic arthritis, and endocarditis are other forms of invasive infection. The presence of yeast in the respiratory or urinary tract (often in the presence of an indwelling catheter) generally represents colonization, not infection; whereas *Candida* isolated in blood cultures should never be considered a contaminant.

Diagnosing invasive candidiasis is challenging because only 40% to 60% of patients with infection have positive blood cultures. Recognizing risk factors (**Table 25**) for candidiasis is essential to avoid delays in initiating antifungal therapy and increased mortality. Nonculture methods, such as the T2 magnetic resonance assay of blood, provide rapid (within hours) diagnosis of invasive candidal infections and can be performed after antifungal therapy initiation. The β-D-glucan assay may also be used to support the diagnosis of invasive fungal infections, including candidiasis, particularly among patients with negative blood cultures; however, false-positive results may occur. These assays are particularly useful in patients at high risk who are receiving antimicrobial agents and are not responding to therapy.

When *Candida* is identified from a sterile site, identifying species and susceptibilities are necessary. Fewer than 15 of more than 160 known *Candida* species commonly produce disease. Additionally, several *Candida* species (e.g., *C. glabrata*, *C. krusei*, and *C. auris*) have low susceptibility or intrinsic resistance to antifungal agents. *C. auris* is an emerging species that presents a serious global threat. It is difficult to identify microbiologically, is often resistant to azoles and polyenes and occasionally to echinocandins, and has been associated with numerous health care outbreaks.

TABLE 25. Risk Factors for Systemic Candidiasis

Central venous catheters
Broad-spectrum antimicrobial agents
Neutropenia
ICU stay for more than 3 days
Total parenteral nutrition
General surgery (especially of the gastrointestinal tract)
Burns
Trauma
Mechanical ventilation for more than 3 days
Transplantation (hematopoietic stem cell/solid organ)
Hemodialysis-associated catheters
Severe acute pancreatitis

Initial treatment of candidemia and invasive candidiasis should include an echinocandin (caspofungin, micafungin, or anidulafungin) and intravascular device removal (if present/possible). However, because echinocandins have poor penetration into the central nervous system (CNS) and the eye, patients with CNS and eye infections should be treated with amphotericin B or an azole; treatment may also require additional agents depending on host factors and disease extent. For all invasive candidal infections, prompt treatment initiation is critical, and follow-up blood cultures are required to document clearance. A dilated funduscopic examination is also necessary to exclude endophthalmitis. Speciation, sensitivities, and follow-up blood culture results guide de-escalation therapy. Antifungal therapy duration for candidemia should be 14 days from the first negative blood culture result in patients with uncomplicated candidemia or 14 to 42 days in patients with invasive candidal infections.

KEY POINTS

- Only 40% to 60% of patients with invasive candidal infection have positive blood culture results, so recognizing risk factors of candidiasis is essential to avoid delays in initiating effective antifungal therapy.
- Nonculture methods (T2 magnetic resonance and β-D-glucan assays) may provide a rapid diagnosis of invasive candidal infections, particularly in patients with negative blood cultures.
- *Candida* species obtained from the respiratory or urinary tract usually represents colonization; treatment is not indicated unless clinical infection is suspected.
- Initial management of candidemia and invasive candidiasis should include an echinocandin and intravascular device removal (if possible); central nervous system and ocular infections require amphotericin B or an azole and potentially additional agents depending on host factors and disease extent.

Aspergillosis

Aspergillus fumigatus is the most common species causing disease in humans, followed by *A. flavus*, *A. niger*, and the amphotericin-resistant *A. terreus*. *Aspergillus* produces disease after inhalation of airborne spores (90%) and occasionally by traumatic skin inoculation.

Invasive aspergillosis most often occurs in immunosuppressed patients with neutropenia or who are hematopoietic stem cell transplant recipients (**Table 26**). This type of aspergillosis usually begins in the respiratory tract and then enters the circulatory system (angioinvasion) (**Figure 18**). The most common manifestation is pulmonary (60%), but

TABLE 26. Risk Factors for Invasive Aspergillosis

Major	Minor
Neutropenia	COPD treated with glucocorticoids
Graft-versus-host disease	Cirrhosis
Cytomegalovirus infection/ reactivation	Following influenza
Hematopoietic stem cell transplantation	Burns
Solid organ transplantation	Solid organ malignancies
Systemic glucocorticoids (>1 mg/kg/d) or inhaled steroids	Immunosuppressants
Hematologic malignancies	Cyclosporine
	Methotrexate
	Cyclophosphamide
	Advanced HIV with CD4 cell count <50/μL
	Injection drug use (rare)
	Gram-negative bacterial pneumonia

Fever[a]
Pulmonary findings
Pleuritic chest pain, pleural rub
Dry cough
Dyspnea
Hemoptysis: usually minor but occasionally catastrophic
Chest radiograph: potentially normal in early disease; infiltrates, infarction, nodules, and cavitation in late disease
Focal neurologic deficits
Multiorgan dysfunction
Hemorrhagic skin lesions

[a]Frequently the only feature present.

sinusitis, brain abscess, and disseminated infection may also occur. Timely diagnosis is essential to decrease morbidity and mortality. However, symptoms and signs are nonspecific (**Table 27**), and blood culture results are generally negative. Therefore, when invasive pulmonary aspergillosis is suspected, bronchoscopy, bronchoalveolar lavage, and, if possible, tissue biopsy are recommended to establish the diagnosis. Early CT of the chest, along with the bronchoalveolar lavage and serum galactomannan assay results, can be useful in establishing a diagnosis of invasive infection; septic emboli (nodules, often with a "halo sign") (**Figure 19**), thromboembolic pulmonary infarction (wedge-shaped peripheral densities), or necrosis with cavitation (air-crescent sign) are typical findings, especially in neutropenic patients and hematopoietic stem cell transplant recipients.

First-line treatment of invasive aspergillosis is voriconazole; alternative agents include liposomal amphotericin B, isavuconazole, or other lipid formulations of amphotericin B. When possible, reversing immunosuppression improves treatment response.

Chronic necrotizing aspergillosis is a semi-invasive, indolent form of infection that does not typically disseminate and may occur in patients who have lesser degrees of immunosuppression (such as those who take chronic glucocorticoids) or chronic pulmonary disease. Treatment is similar to that for invasive pulmonary aspergillosis.

Allergic bronchopulmonary aspergillosis results from hypersensitivity to *Aspergillus* species colonizing the respiratory tract. This disorder is seen primarily in patients with cystic fibrosis and occasionally in those with asthma (see MKSAP 19 Pulmonary and Critical Care Medicine for more information). Because allergic bronchopulmonary aspergillosis represents a hypersensitivity response, systemic glucocorticoids are the mainstay of treatment (sometimes supplemented by antifungal therapy with an azole).

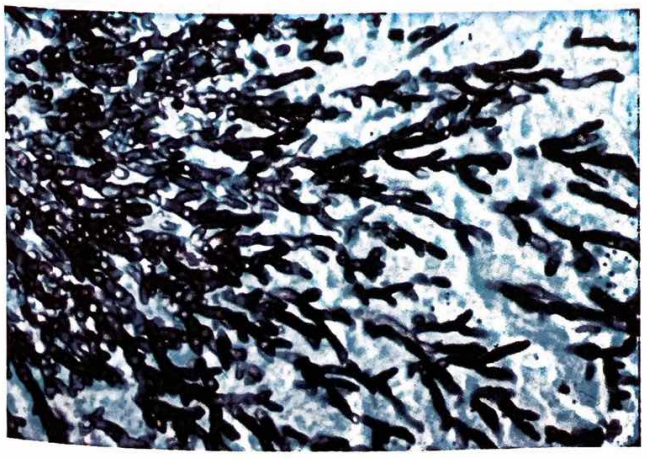

FIGURE 18. Aspergillus in lung tissue; methenamine silver stain. Organisms appear as septate hyaline hyphae with dichotomous acute angle (45°) branching.

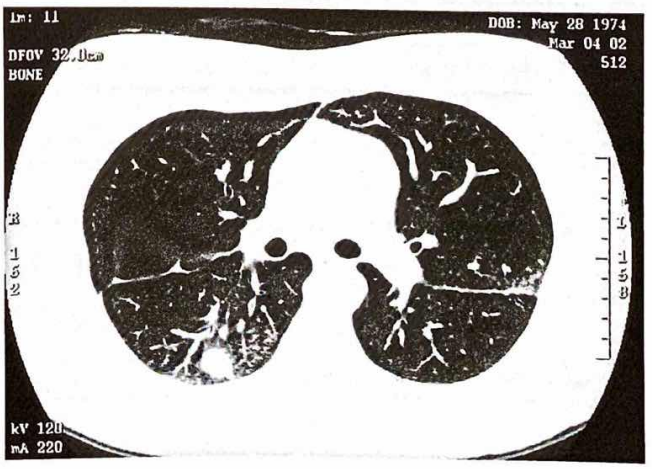

FIGURE 19. CT scan showing typical findings suggesting aspergillosis with a "halo sign," which is an area of low attenuation surrounding a pulmonary nodule that reflects hemorrhage into the adjacent tissues.

KEY POINTS

- *Aspergillus* infection can manifest in various ways, including invasive pulmonary aspergillosis, chronic necrotizing pulmonary aspergillosis, and allergic bronchopulmonary aspergillosis.
- Tissue biopsy is frequently necessary to establish a definitive diagnosis of invasive aspergillosis; however, early chest CT, the serum or bronchoalveolar lavage, and galactomannan assay results are typically used to establish a presumptive diagnosis in patients at high risk of infection.
- Voriconazole is first-line treatment for invasive or chronic pulmonary *Aspergillus* infection.

Cryptococcosis

Cryptococcus is an encapsulated yeast that is ubiquitous in the environment. Patients with immune suppression, such as AIDS, neutropenia, cirrhosis, or organ transplantation are most commonly infected, but it can occur in healthy persons. *C. neoformans* is the most commonly identified species, but *C. gattii* is seen with increasing frequency in the Pacific Northwest region of North America and appears to be spreading southward. Pathogenesis of cryptococcosis involves inhalation of spores into the respiratory tract, followed by dissemination into susceptible tissues, especially the CNS.

Cryptococcal infection most commonly manifests in the CNS, and cryptococcosis is the most common cause of fungal meningitis worldwide. Clinical manifestations are listed in **Table 28**, and indicators of poor prognosis are provided in **Table 29**. Because patients with cryptococcosis-related increased intracranial pressure (ICP) may develop sudden blindness, deafness, or coma, opening pressure should always be documented during initial lumbar puncture. Cerebrospinal fluid analysis is essential to diagnose CNS involvement; classic findings include an increased leukocyte count (mainly lymphocytes), an increased protein level, a low to normal glucose level, and the presence of cryptococcal antigen. Serum cryptococcal antigen is positive in greater than 95% of infected patients. Occasionally, blood culture results are positive, indicating disseminated disease.

TABLE 28. Clinical Features of Cryptococcosis

Signs and Symptoms of Meningeal Infection (% Affected)
Fever (60%-90%)
Headache (80%-90%)
Nausea/vomiting (~50%)
Meningism (30%)
Altered mental status (20%-30%)
Extrameningeal Infection Sites
Lung
Bone marrow
Skin
Prostate (can be a cryptic reservoir of infection)

TABLE 29. Indicators of Poor Prognosis in Cryptococcal Meningitis

Altered mental state
Visual abnormalities
CSF leukocyte count less than 20/μL (20×10^6/L)
CSF cryptococcal antigen assay greater than 1:10,000
No previous antiretroviral therapy in those with HIV infection

CSF = cerebrospinal fluid.

Symptoms of increased ICP may be improved by cerebrospinal fluid removal through sequential lumbar punctures or insertion of a shunt. Aggressive ICP reduction decreases early morbidity and mortality. Amphotericin B plus flucytosine is the treatment of choice for induction therapy and is effective in more than 90% of patients. After at least 2 weeks of successful induction therapy, consolidation therapy with fluconazole may be initiated, continuing for at least 8 weeks. HIV-infected patients require maintenance (suppressive) therapy with fluconazole for at least 1 year after successful treatment and until they have maintained their CD4 cell counts greater than 100/μL for a minimum of 3 months and have an undetectable viral load.

KEY POINTS

- In patients with suspected cryptococcal infection, cerebrospinal fluid (CSF) analysis and documentation of the CSF opening pressure are necessary; CSF and serum cryptococcal antigen are highly sensitive for identifying infection.
- Amphotericin B plus flucytosine is effective in more than 90% of patients; for those with elevated intracranial pressure (ICP), cerebrospinal fluid removal through sequential lumbar punctures or shunt insertion can reduce ICP, thus reducing morbidity and mortality.

Histoplasmosis

Histoplasma capsulatum is one of the most common endemic mycoses in the world. Acquired by inhalation of conidia, this organism primarily produces asymptomatic pulmonary infection. It is distributed along the Mississippi River Valley (Ohio, Missouri, Indiana, Mississippi) in the United States, in Central and South America, the Caribbean, and in regions of Africa, Australia, and India.

Histoplasmosis most commonly presents with acute respiratory symptoms. Other presentations include disseminated infections (immunosuppressed host), chronic pulmonary symptoms, rheumatologic symptoms, pericarditis, and sclerosing mediastinitis.

The *Histoplasma* urinary antigen assay has a sensitivity and specificity of greater than 85% in acute and disseminated infection but less than 50% in chronic infection. Identification by tissue culture can be a lengthy process but is indicated for

suspected cases in which the serum antibody and urinary antigen assay result is negative.

Asymptomatic and mild pulmonary histoplasmosis typically resolve without treatment. Antifungal therapy is recommended for severe or disseminated disease. Itraconazole is the agent of choice; therapy duration is 6 to 12 weeks for acute infection and 12 months for chronic cavitary pulmonary infection. For severe lung disease and disseminated infection, liposomal amphotericin B should be used initially, followed by de-escalation to oral itraconazole.

KEY POINTS

- *Histoplasma* urinary antigen assay has a sensitivity and specificity of greater than 85% in acute and disseminated infection but less than 50% in chronic infection.
- Itraconazole is the antifungal agent of choice for most patients with histoplasmosis; liposomal amphotericin B should be used initially for patients with severe lung disease and disseminated infection.

Coccidioidomycosis

Coccidioides is a dimorphic fungus that exists as a mold in the environment. There are two species: *C. immitis* refers to isolates from California, and *C. posadasii* refers to isolates from all other endemic areas, including Arizona, New Mexico, western Texas, northern Mexico, and parts of Central and South America. In endemic areas, the annual risk of infection is approximately 3% for most persons, although the risk of infection (and dissemination) is greater in those who are pregnant, younger than 5 years or older than 50 years, or of African, Filipino (and possibly other Asian), and Native American ancestry.

Infection is usually acquired by inhalation of aerosolized arthroconidia; the fungus then begins its dimorphic change in the lungs and becomes a yeast cell. Several clinical syndromes are seen in coccidioidomycosis and may manifest as acute or chronic pulmonary infection, cutaneous infection (~40%), or meningitis (~33%).

Diagnosis is straightforward in endemic areas and usually is based on clinical manifestations and confirmatory testing by a mycologic culture of affected tissue, histopathologic evaluation of tissue, and serology for *Coccidioides* antibodies.

Fluconazole is the first-line treatment for symptomatic infection. In patients with meningitis, fluconazole is continued for life. In patients who do not respond to azoles, intrathecal amphotericin B may be an alternative.

KEY POINTS

- Coccidioidomycosis should be suspected clinically in endemic areas and may be confirmed by a mycologic culture of affected tissues, histopathologic evaluation of tissue, or serology for *Coccidioides* antibodies.
- Fluconazole is first-line treatment for symptomatic coccidioidomycosis infection.

Blastomycosis

Blastomyces dermatitidis is a dimorphic, round, budding yeast. In the United States, blastomycosis is found primarily along the Mississippi and Ohio River valleys but can be found as far north as Wisconsin and Minnesota and as far south as Florida. Infection occurs by inhalation of conidia and manifests initially as a primary pulmonary infection (acute or chronic pneumonia). Occasionally, a chest radiograph shows a spiculated nodular appearance that may be mistaken for lung cancer. Rarely, dissemination occurs and produces extrapulmonary disease (osteomyelitis or skin infection).

Diagnosis can be made by direct fungal stain of clinical specimens (sputum, tissue, or purulent material) and confirmed by culture or serology for *Blastomyces* antibodies. Urinary antigen testing is also available. The preferred treatment for mild to moderate infection is itraconazole. Liposomal amphotericin B is recommended for CNS, severe pulmonary, and disseminated infections.

KEY POINTS

- Blastomycosis occurs by inhalation of *Blastomyces dermatitidis* conidia and manifests initially as a primary pulmonary infection; diagnosis is made by direct fungal stain of clinical specimens and confirmed by culture, urinary antigen testing, or serology for *Blastomyces* antibodies.
- The preferred treatment for mild to moderate blastomycosis is itraconazole, with liposomal amphotericin B used for central nervous system, severe pulmonary, and disseminated infections.

Sporotrichosis

Sporothrix schenckii is a dimorphic fungus found most often in soil, plants, or plant debris. Although found worldwide, most reported infections are from North and South America and Japan. Infection occurs after direct contact with plants, such as roses and sphagnum moss. Direct inoculation of the organism into the skin or subcutaneous tissue manifests as fixed, "plaque-like" cutaneous sporotrichosis or as lymphocutaneous sporotrichosis. Extracutaneous infection (osteoarticular, pulmonary, ocular, or disseminated) can occur in patients who are immunocompromised.

Diagnosis requires culture of the organism from affected tissues. Treatment is with itraconazole.

KEY POINTS

- Sporotrichosis is an infection of cutaneous and lymphocutaneous tissues usually caused by direct contact with plants; extracutaneous infection can occur in immunocompromised persons.
- Itraconazole is the preferred treatment for cutaneous and lymphocutaneous sporotrichosis.

Mucormycosis

Mucormycosis (formerly zygomycosis) is the third most frequent cause of invasive fungal infections in immunocompromised persons. Patients with diabetes mellitus, neutropenia, and iron overload states (including deferoxamine administration) are particularly at risk. The most common mucormycetes are *Rhizopus arrhizus* and *Mucor* species. These fungi are commonly found in the environment on decaying organic debris and soil.

Infection is acute and rapidly fatal, even with early diagnosis and treatment. Major blood vessels are invaded, with ensuing ischemia, necrosis, and infarction of adjacent tissues. Mucormycosis has five major clinical forms: (1) rhinocerebral (**Figure 20**); (2) pulmonary; (3) abdominal, pelvic, gastric, gastrointestinal; (4) primary cutaneous; and (5) disseminated.

Because laboratory studies are nonspecific, diagnosis relies on a high index of suspicion in a host with appropriate risk factors and evidence of tissue invasion. Serologic tests and blood cultures offer no diagnostic benefit.

Treatment requires reversal of any predisposing conditions, extensive surgical removal of affected tissue, and early antifungal therapy. Initial treatment is high-dose liposomal amphotericin B, with de-escalation to posaconazole or isavuconazole. If amphotericin B is not tolerated, initial therapy with one of the azoles is warranted. Mortality rates remain as high as 60% to 80%, even with therapy.

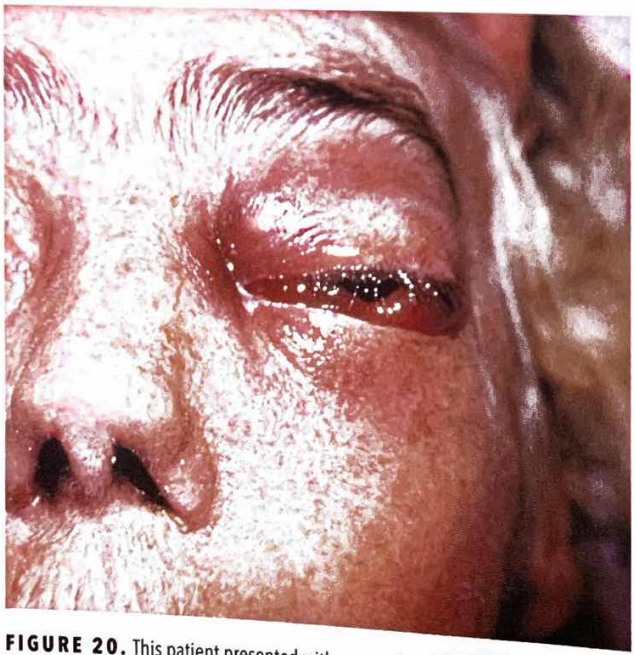

FIGURE 20. This patient presented with a case of a periorbital fungal infection known as mucormycosis, a dangerous invasive fungal infection frequently occurring in patients with uncontrolled diabetes in ketoacidosis or severely immunocompromised patients such as solid organ or hematopoietic stem cell transplantation recipients. The most common form of infection tends to affect the regions of the eye and nose, with penetration into the central nervous system (rhinocerebral form).

KEY POINTS

- Because laboratory studies are nonspecific, diagnosing mucormycosis relies on a high index of suspicion in a host with appropriate risk factors and evidence of tissue invasion.
- Treatment of mucormycosis requires reversing any predisposing condition, extensive surgical removal of affected tissue, and initial antifungal therapy with high-dose liposomal amphotericin B.

Sexually Transmitted Infections

Introduction

Sexually transmitted infections (STIs) occur most commonly in adolescents, young adults, and men who have sex with men (MSM). Most infections are asymptomatic, so a detailed sexual history, including sexual practices, is imperative to understanding individual risk. STI risk factors include a new partner, more than one current partner, a partner with an STI, or a partner who has concurrent partners. Particularly high-risk populations include persons attending STI clinics and MSM. The U.S. Preventive Services Task Force (USPSTF) recommends behavioral counseling to reduce the likelihood of acquiring STIs in sexually active adolescents and in adults at increased risk.

Unrecognized or inadequately treated STIs are a preventable cause of infertility in women. The World Health Organization and the CDC provide evidence-based guidelines for the evaluation and management of STIs; the CDC guidelines are recommended for use in the United States. Any patient diagnosed with an STI should be evaluated for other STIs, including HIV, and receive risk reduction counseling.

Chlamydia trachomatis Infection

Chlamydia trachomatis is the most commonly reported bacterial STI in the United States. Screening of all sexually active women younger than 25 years is recommended. Women aged 25 years and older should be screened if they have STI risk factors. The USPSTF concluded that evidence is insufficient to support routine screening in men; the CDC recommends screening men in settings or populations with high prevalence or burden of disease (MSM, STI clinics).

Nucleic acid amplification testing (NAAT) is preferred for screening and diagnosis. First-catch urine (for men and women) and endocervical (for women) or urethral (for men) swabs can be used. NAAT of urine samples for *C. trachomatis* and *Neisseria gonorrhoeae* has been shown to have a sensitivity and specificity nearly identical to tests obtained from urethral and endocervical samples. Chlamydia may cause oropharyngeal and rectal infection, and these sites should be