253 *Nocardia* Species

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SHORT VIEW SUMMARY

Definition

- Nocardiosis results from infection by members of the genus *Nocardia,* which are ubiquitous environmental saprophytes that cause localized or disseminated disease in humans and animals.

Microbiology and Epidemiology

- Microscopically, *Nocardia* appear as gram-positive, beaded, weakly acid-fast, branching rods.
- Molecular speciation has revolutionized taxonomy by identifying several new species and reassigning species, especially from the commonest pathogenic group, the former *Nocardia asteroides* complex.
- Infection arises by direct inoculation through the skin or by inhalation.
- Mycetomas from *Nocardia* spp., most often caused by *N. brasiliensis,* primarily affect immunocompetent hosts in tropical countries.
- Immunocompromise, alcoholism, and certain lung diseases predispose patients to pulmonary and disseminated nocardiosis, most often due to *N. cyriacigeorgica, N. nova,* or *N. farcinica.*

Clinical Manifestations

- Primary skin infection may be manifested as superficial cellulitis or pyogenic abscess(es), lymphocutaneous (spirotrichoid) infection, or chronically progressive, destructive disease with sinus tract formation (mycetoma), usually on a distal limb.
- Presentation of lung disease may be subacute or chronic, with productive or nonproductive cough, dyspnea, hemoptysis, and fever, and other systemic symptoms. Cavity formation within the pneumonia or spread to the central nervous system (CNS), or both, are suggestive of nocardiosis. Isolated CNS lesions also occur, and their presentation can be insidious.

Diagnosis

- Cerebral imaging, preferably magnetic resonance imaging, should be performed in all cases of pulmonary and disseminated nocardiosis to rule out insidious CNS disease.
- The microbiology laboratory should be informed of suspected nocardiosis because it may not be detected by routine laboratory methods. Respiratory secretions, skin biopsies, or aspirates from deep collections are the most useful diagnostic specimens and are typically positive on Gram stain. Modified acid-fast stain of sputum or pus is helpful in suggesting the diagnosis. Growth of *Nocardia* spp. may take 48 hours to several weeks but usually 3 to 5 days.
- Species identification may be predictive of antimicrobial susceptibility; it often requires molecular identification based on nucleic acid technology (NAT, DNA sequencing).
- Recently, mass spectrometry analysis using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry has been reported to be a reliable and more rapid alternative to NAT, but species identification is contingent on a reliable mass spectral database.

Therapy and Follow-Up

- Trimethoprim-sulfamethoxazole (TMP-SMX) is the mainstay of treatment, and monotherapy is usually successful in patients with isolated skin infection or mycetomas that are not extensive (see Table 253.3).
- In infection spread beyond the lung, speciation and/or susceptibility testing results should guide definitive combination therapy. TMP-SMX is usually included in initial therapy.
- Empirical therapy with TMP-SMX plus amikacin (with imipenem or meropenem) is recommended in immunocompromised patients or those with disseminated disease but no brain involvement.
- For isolated cerebral disease, empirical TMP-SMX plus imipenem or meropenem are suitable.
- When additional sites are involved or the patient has life-threatening disease, empirical three-drug regimens, such as TMP-SMX, meropenem or imipenem, and amikacin (or ceftriaxone in patients with renal failure), are preferred. Initial adjunctive therapy with linezolid is an option, especially if one of these classes of drug is contraindicated.
- Clinical improvement is generally evident within 3 to 5 days or, at the most, 7 to 10 days after initiation of appropriate therapy.
- Prolonged therapy is necessary to prevent relapse.
- Surgical excision or drainage of pus may be required, depending on the extent and site of the lesions or the response to medical therapy, or both.
- Patients with deep-seated infection should be monitored clinically and radiologically during and for up to 12 months after cessation of therapy.

Nocardia is a genus of aerobic actinomycetes responsible for localized or disseminated infections in animals and humans. The genus is named after Edmond Nocard, who in 1888 described the isolation of an aerobic actinomycete from cattle with bovine farcy. The first human case of nocardiosis was reported by Eppinger in 1890. Cases of human disease have increased substantially in the past 2 decades, in association with an increasing population of immunocompromised hosts and improved methods for detection and identification of *Nocardia* spp. in the clinical laboratory. In parallel, an increasing number of novel species of *Nocardia* has been recognized as human pathogens.

CLASSIFICATION

The aerobic actinomycetes are a large and diverse group of gram-positive bacteria[1] that appear on microscopy as branching, filamentous cells. Members of the group are often only distantly related phylogenetically. A subgroup, classified in the suborder Corynebacterineae, is the most important cause of human and veterinary infection and includes the genera *Mycobacterium, Corynebacterium, Nocardia, Rhodococcus, Gordonia,* and *Tsukamurella.*[1] All members of the group have cell walls containing meso-diaminopimelic acid, arabinose, galactose (type IV cell wall[1]), and mycolic acids of various chain lengths. The latter are

responsible for varying degrees of acid fastness on modified acid-fast staining. In this chapter the genus *Nocardia* is discussed in the context of human infection.

Previous taxonomic classifications have relied on traditional phenotypic methods to assign nocardiae to both genus and species. *Nocardia* spp. are characterized by an ability to form aerial hyphae and to grow in media containing lysozyme and by an inability to grow at 50°C.[1,2] Speciation using biochemical reactions has been largely superseded due to their frequent inability to distinguish between species, especially those that are phylogenetically closely related.[1,2]

Molecular Identification and Taxonomy

Molecular techniques are now preferred for accurate species determination. In addition, matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) has proven useful for identification of clinically relevant *Nocardia* spp.[3,4]

The application of molecular methods[2,5,6] has greatly expanded the spectrum of pathogenic nocardiae and has led to significant taxonomic changes and species reassignment within the genus. This is particularly evident among isolates formerly assigned to the *Nocardia asteroides* complex.[2] More than 100 *Nocardia* spp. have now been identified (National Center for Biotechnology Information—taxonomy for *Nocardia:* www.ncbi.nlm.nih.gov/Taxonomy/, and www.bacterio.net/nocardia.html), many of which have been implicated in human disease (Table 253.1).[2,6,7] The nomenclature of isolates formerly in the *N. asteroides* complex is summarized in Table 253.2 and includes *Nocardia cyriacigeorgica,*[8] *Nocardia abscessus,*[9] the *Nocardia nova* complex, and the *Nocardia transvalensis* complex. Other major human pathogens include *Nocardia*

TABLE 253.1 Current Classifiable *Nocardia* Species Names

NOCARDIA SPECIES[a]	FREQUENCY[b]	*NOCARDIA* SPECIES[a]	FREQUENCY[b]
Nocardia abscessus	22	*Nocardia donostiensis*	
Nocardia acidovorans		*Nocardia elegans*	12
Nocardia africana		*Nocardia endophytica*	
Nocardia alba		*Nocardia exalbida*	4
Nocardia alboflava		*Nocardia farcinica*	160
Nocardia altamirensis		*Nocardia flavorosea*	
Nocardia amamiensis		*Nocardia fluminea*	
Nocardia amikacinitolerans		*Nocardia fusca*	
Nocardia anaemiae		*Nocardia gamkensis*	
Nocardia aobensis	5	*Nocardia globerula*	
Nocardia araoensis	1	*Nocardia goodfellowii*	
Nocardia argentinensis		*Nocardia grenadensis*	
Nocardia arizonensis		*Nocardia harenae*	
Nocardia artemisiae		*Nocardia heshunensis*	
Nocardia arthritidis	4	*Nocardia higoensis*	1
Nocardia asiatica	21	*Nocardia ignorata*	
Nocardia asteroides	2	*Nocardia inohanensis*	1
Nocardia beijingensis	24	*Nocardia interforma*	
Nocardia bhagyanarayanae		*Nocardia iowensis*	
Nocardia blacklockiae		*Nocardia jejuensis*	
Nocardia boironii		*Nocardia jiangxiensis*	
Nocardia brasiliensis	71	*Nocardia jinanensis*	
Nocardia brevicatena		*Nocardia kruczakiae*	
Nocardia caishijiensis		*Nocardia lasii*	
Nocardia callitridis		*Nocardia levis*	
Nocardia camponoti		*Nocardia lijiangensis*	
Nocardia canicruria		*Nocardia lillensis*	
Nocardia carnea	3	*Nocardia mexicana*	
Nocardia casaurinae		*Nocardia mikamii*	
Nocardia caverna		*Nocardia miyunensis*	
Nocardia cerradoensis		*Nocardia neocaledoniensis*	
Nocardia coeliaca		*Nocardia niigatensis*	4
Nocardia concava	3	*Nocardia ninae*	
Nocardia coubleae		*Nocardia niwae*	
Nocardia crassostreae		*Nocardia nova*	81
Nocardia cummidelens		*Nocardia novocastrensa*	
Nocardia cyriacigeorgica	60	*Nocardia otitidiscaviarum*	14
Nocardia devorans		*Nocardia paucivorans*	1

TABLE 253.1 Current Classifiable *Nocardia* Species Names—cont'd

NOCARDIA SPECIES[a]	FREQUENCY[b]	*NOCARDIA* SPECIES[a]	FREQUENCY[b]
Nocardia pigrifrangens		*Nocardia takedensis*	
Nocardia pneumoniae		*Nocardia tartaricans*	
Nocardia polyresistens		*Nocardia tenerifensis*	
Nocardia pseudobrasiliensis	2	*Nocardia tengchongensis*	
Nocardia pseudosporangifera		*Nocardia terpenica*	1
Nocardia pseudovaccinii		*Nocardia testacea*	2
Nocardia puris	4	*Nocardia thailandica*	1
Nocardia rayongensis		*Nocardia thraciensis*	
Nocardia rhamnosiphila		*Nocardia transvalensis*	13
Nocardia rhizosphaerae		*Nocardia uniformis*	
Nocardia rhizosphaerihabitans		*Nocardia vaccinii*	
Nocardia roseoalba		*Nocardia vermiculata*	
Nocardia salmonicida		*Nocardia veterana*	3
Nocardia salmonicolor		*Nocardia vinacea*	3
Nocardia seriolae		*Nocardia violaceofusca*	
Nocardia shimofusensis		*Nocardia vulneris*	
Nocardia sienata	1	*Nocardia wallacei*	10
Nocardia soli		*Nocardia xestospongiae*	
Nocardia speluncae		*Nocardia xishanensis*	
Nocardia strombolensis		*Nocardia yamanashiensis*	
Nocardia sungurluensis		*Nocardia zapadnayensis*	
Nocardia sylvodorifera			

[a]Species names in http://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi. Accessed January 22, 2018.
[b]Frequency of classifiable isolates at Chiba University, Medical Mycology Center, 1999–2007.
Data from Mikami U. [Recent progress in taxonomic studies on pathogenic Nocardia *and usefulness of the bacteria for the studies on secondary metabolites and antibiotic resistant mechanisms].* Nihon Ishinkin Gakkai Zasshi. *2010;51:179–192 [in Japanese].*

TABLE 253.2 *Nocardia asteroides* Complex: Major Changes in Taxonomic Categories

FORMER SPECIES OR SPECIES GROUP ASSIGNMENT	CURRENT SPECIES GROUP DESIGNATION	CURRENT SPECIES DESIGNATION
N. asteroides drug pattern I	—	*N. abscessus*
N. asteroides drug pattern II	*N. paucivorans*/*N. brevicatena* complex	*N. paucivorans*[b] *N. brevicatena*[b]
N. asteroides drug pattern III	*N. nova* complex[c]	*N. nova* sensu stricto, *N. africana* *N. aobensis* *N. elegans*, *N. kruczakiae*, *N. veterana*
N. asteroides drug pattern IV[d]	*N. transvalensis* complex	*N. wallacei*, *N. transvalensis* sensu stricto, *N. blacklockiae*
N. asteroides drug pattern V		*N. farcinica*
N. asteroides drug pattern VI		*N. cyriacigeorgica*

[a]*N. brevicatena* and *N. paucivorans* are not new species names; they have been reclassified.
[b]*N. asteroides* sensu stricto is rarely pathogenic.
[c]It is uncertain to which species the former *N. asteroides* drug pattern III isolates now correspond.
[d]Only *N. wallacei* is designated as the former "*N. asteroides* drug pattern IV." The other members of the *N. transvalensis* complex are previously either separate as "*N. asteroides* complex" or are recently identified species.
Data from Conville PS, Witebsky FG. Nocardia, Rhodococcus, Gordonia, Actinomadura, Streptomyces*, and other aerobic actinomycetes. In: Jorgensen JH, Pfaller MA, Carroll KC, et al., eds.* Manual of Clinical Microbiology. *Washington, DC: American Society for Microbiology Press; 2015.*

otitidiscaviarum, Nocardia farcinica, and *Nocardia brasiliensis.*[2] Some more recently described or reclassified species have been reported to cause human infection. They include *Nocardia paucivorans* (*Nocardia brevicatena/paucivorans* complex[2,10]), *Nocardia africana,*[11] *Nocardia veterana*[12] (*N. nova* complex[2]), *Nocardia wallacei*, and *Nocardia blacklockiae* (*N. transvalensis* complex).[13] The terminology "*N. asteroides* spp. complex" is no longer used because it encompasses such a heterogenous group of organisms.

ECOLOGY AND EPIDEMIOLOGY

Nocardia spp. are ubiquitous environmental saprophytes, occurring in soil, organic matter, and aquatic habitats, including in waste-water systems.[1,2] Human infection usually arises from direct inoculation of the skin or soft tissues or by inhalation. *N. brasiliensis* is the commonest cause of mycetoma due to nocardial infection in immunocompetent hosts reported from tropical regions of the southern United States, Mexico, Central and South America, and Australia. Worldwide, respiratory and disseminated infections occur predominately in immunosuppressed hosts, and although species distribution varies with geographic region, infections are most often due to *N. cyriacigeorgica*, *N. nova, N, abscessus*, *N. brasiliensis,* and *N. farcinica.*[1,2,14,15]

Nocardia spp. are well-recognized causes of infection in animals, with bovine mastitis being the most common.[2] There are no reports of animal-to-human transmission nor of person-to-person transmission. However, clusters of invasive nocardiosis acquired by patients in oncology and transplantation units, presumed to be associated with inhalation of contaminated air or dust, have been described.[2] Transmission via the hands of staff or contaminated fomites appeared likely in one outbreak.[2] Hospital construction work may have been a risk factor in separate clusters of postsurgical wound infections due to *Nocardia* spp.[2,16] Cases of indwelling intravenous (IV) line–associated bloodstream

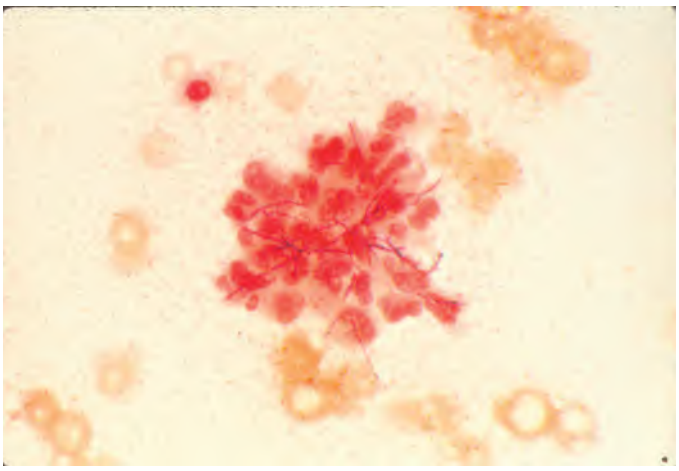

FIG. 253.1 Pulmonary nocardiosis. Photomicrograph of direct Gram-stained smear from a patient with pulmonary nocardiosis, showing typical branching rods.

infection, mostly due to members of the *N. asteroides* spp. complex or *N. nova,* have been reported occasionally in immunosuppressed patients.[17] A community cluster of *N. cyriacigeorgica* infection associated with unlicensed cosmetic procedures has also been described.[18] In a recent study, hospital environmental reservoirs of *Nocardia*, including dust on window frames and equipment and potable water sources were described.[19] Pulsed-field gel electrophoresis,[16] random amplification of polymorphic DNA fingerprinting,[20] and multilocus sequence typing[18] have been used to confirm clusters and define common sources.

PATHOLOGY

Sections of tissues infected with *Nocardia* usually show an acute pyogenic inflammatory reaction. Gram stains (Fig. 253.1) of specimens may reveal branching, beaded, filamentous bacteria, similar to those seen in smears taken from cultures, within abscesses. "Sulfur granules" (bacterial macrocolonies), similar to those seen in actinomycosis, may be found in nocardial mycetomas. *Nocardia* spp. usually stain acid-fast in tissue sections if a method such as that of Fite-Faraco is used, whereas *Actinomyces* spp. do not.[1]

PATHOGENESIS

Disease manifestations of nocardiosis are determined by the portal of entry, tissue tropism, growth rates in vivo, ability to survive phagocyte attack, the nature of the host immune reaction, and the characteristics of the infecting strain.

Immune Response to *Nocardia* Infection

After IV inoculation into mice, virulent *Nocardia* are cleared from the blood within a few hours and localize in a number of organs (lung, brain, kidneys, liver, and spleen). Innate immune function is important in the initial response to infection. In an intranasal mouse model of pulmonary nocardiosis, effective clearance was dependent on early neutrophil recruitment initiated by interleukin-17 (IL-17) production by γδT lymphocytes.[21] Early neutrophil mobilization appears to retard the process until lymphocyte-mediated cytotoxicity and activated macrophages effect a definitive response.[22,23] In human infection *Nocardia*-induced granulocyte-macrophage colony-stimulating factor (GM-CSF) production may also be a key cytokine response mediator.[24] Protective immune responses to *Nocardia* spp. are primarily T-cell–mediated. Nocardiosis is more problematic in patients with impaired cell-mediated immunity, eliciting little in the way of an effective humoral response.[22] Healing is associated with strong, sustained rises in interferon-γ (IFN-γ) in animal models, and IFN-γ may have a therapeutic role in humans with chronic granulomatous disease.[25]

Specific Virulence Determinants

The nocardial envelope of the Corynebacterineae suborder, which includes *Mycobacterium* spp. and *Nocardia* spp., is an asymmetrical bilayer composed of inner-leaflet mycolic acids and assorted noncovalently bound outer-layer glycolipids. A substantial proportion of the cell wall mass is composed of peptidoglycan.[26] Mycolic acid polymers are found in many actinomycetes, including *Nocardia* spp., and are associated with virulence.[27] Outer-layer lipids induce production of proinflammatory cytokines IL-1β and IL-6 by macrophages and are likely to be responsible for the powerful granulomatous reaction to *N. brasiliensisis* infection,[28] but they are also implicated in the immunosuppressive microenvironment generated later.[29]

Nocardia spp. contain no cell wall lipopolysaccharide, exopolysaccharide capsule, or surface fimbriae. Strain-dependent specific adhesins and invasive properties influence the outcome of infection in animal models.[30,31] Specific toxins, including hemolysins and proteases, have been identified, but these are not thought to be widespread or particularly significant virulence factors.[22,32,33] Highly pathogenic members of the *N. asteroides* complex secrete superoxide dismutase into growth media, whereas nonpathogenic *Nocardia* spp. do not.[34] Catalases, superoxide dismutase, and two types of putative determinants of mammalian cell entry, secreted siderophores and toxins, are present in the genomes of pathogenic *Nocardia*.[35]

Host Cell–*Nocardia* Interactions

Virulent strains of *N. asteroides* are relatively resistant to neutrophil-mediated killing.[36] Patients with specific defects in the phagocyte oxidative burst (e.g., chronic granulomatous disease)[14,25] or with anti–GM-CSF neutralizing antibodies in their serum may be more vulnerable to this infection.[24]

Virulent *Nocardia* inhibit phagosome-lysosome fusion more successfully in vitro,[37] giving rise to cell wall–deficient forms (L-forms) that persist within macrophages.[38] Such forms ("filterable *Nocardia*") are readily cultured from in vitro broth filtrates, especially when supplemented with erythrocytes,[39] and L-forms have been isolated from animal infections.[40,41]

Ciliated epithelia appear relatively resistant to invasion by *Nocardia* spp. However, a range of susceptible lung- and airway-associated cell types has been observed in rat models.[31] Tropism for cerebral tissue is evident experimentally, but neuroinvasiveness and macrophage penetration vary significantly between strains. Electron microscopic studies of infected macrophage and astrocytoma-derived or astrocytoma-related cell lines suggest that the penetration competence of invasive *N. asteroides* spp. complex is localized to the bacterial apex.[32] Specific lectins have been shown to determine site specificity in the murine brain,[32] intrinsic differences in expression of which may contribute to variations in host susceptibility.[42]

Biofilms

Although IV catheter–associated bloodstream infections are rare in clinical practice, nocardiae promote heavy growth of biofilms, both on the surface of central venous catheter segments in vitro and in a biofilm model.[17] When embedded in such a matrix, the organisms are resistant to antimicrobial drugs unless exposed to very high local concentrations, such as can be achieved with intraluminal antimicrobial lock therapy.[17]

CLINICAL EPIDEMIOLOGY

Nocardia Species and Disease Associations

Members of the former *N. asteroides* spp. complex are responsible for about 80% of noncutaneous invasive disease and for most systemic and central nervous system (CNS) disease.[22,43] *N. farcinica* is also an important pathogen, notable for its relatively greater resistance to antibiotics. There is also evidence from mouse models that it may be more virulent than other *Nocardia* spp.[44] *N. brasiliensis* is the most often reported cause of cutaneous and lymphocutaneous disease, particularly in tropical areas. *N. pseudobrasiliensis,* a species now separated from *N. brasiliensis,* appears to be associated with disseminated, including CNS, infections.[1,45] Pulmonary disease is the most frequent presentation of nocardiosis caused by the less common pathogens *N. transvalensis*[46] and *N. otitidiscavarum,*[22] although both may cause severe cutaneous infection.[47] Superficial nocardiosis after implantation is not necessarily

associated with compromised cell-mediated immunity but may progress to disseminated disease in that setting.[47]

Immunocompromise as a Risk Factor for Nocardiosis

Immunocompromise is a well-established risk factor for nocardiosis. *Nocardia* spp. may therefore be considered as opportunistic pathogens, which cause serious and disseminated disease in settings such as organ transplantation and lymphoreticular neoplasia. The relative risk for progressive disease reflects the level of immunosuppression. A compilation of more than 1000 randomly selected cases from the literature in the early 1990s showed that greater than 60% of all reported cases of nocardiosis were associated with preexisting immune compromise, ranging from alcoholism and diabetes to chronic granulomatous disease, organ transplantation, and acquired immunodeficiency syndrome (AIDS).[22] In a recent northern Australian study, greater than one-third (36%) of patients with nocardiosis were immuncompromised.[43] Among recipients of solid-organ transplants with nocardiosis, significant risk factors include receipt of high-dose corticosteroids at time of onset, cytomegalovirus disease within the preceding 6 months, high serum trough levels of calcineurin inhibitors within the preceding 30 days, use of tacrolimus, patient age, and length of stay in the intensive care unit postoperatively.[15,48] Use of low-dose trimethoprim-sulfamethoxazole (TMP-SMX) for *Pneumocystis* prophylaxis, such as one double-strength tablet twice a week, did not prevent nocardiosis in either solid-organ or hematopoietic stem cell transplant (HSCT) recipients.[48–50] Breakthrough nocardiosis remains susceptible to TMP-SMX.[49] The use of anti–tumor necrosis factor-α agents has been associated with disseminated nocardial infections.[51,52] Although cases of nocardiosis have been described in patients with AIDS, the overall incidence is low and not fully explained by the use of sulfonamide prophylaxis against *Pneumocystis jirovecii* pneumonia.[53]

Chronic Lung Disease as a Risk Factor for Nocardiosis

Persons with chronic lung disorders, such as pulmonary alveolar proteinosis, and almost any condition requiring long-term corticosteroid use are also at risk. Other chronic airway conditions that may predispose to colonization with *Nocardia,* with the potential, albeit low, for subsequent infection include cystic fibrosis (CF) and non-CF bronchiectasis. In one study the incidence of nocardiosis among patients with bronchiectasis rose significantly between 1996 and 2013.[54]

CLINICAL MANIFESTATIONS

Primary Cutaneous Nocardiosis

Primary cutaneous nocardiosis may manifest as superficial cellulitis or abscess, lymphocutaneous (spirotrichoid) infection, or mycetoma. Unlike other forms of nocardiosis, this usually develops in immunocompetent hosts.[55] Superficial infection often follows relatively trivial inoculation injuries (Fig. 253.2), which may vary from insect and animal bites to puncture wounds and contaminated abrasions. The lymphocutaneous form includes a rare variant, cervicofacial nocardiosis, which is associated with prominent localized lymphadenitis.[56] Members of the former *N. asteroides* complex more commonly cause superficial infections, whereas *N. brasiliensis* is the most common cause of progressive cutaneous and lymphocutaneous disease.[22] Because the initial response to *Nocardia* is pyogenic, localized skin lesions may initially be treated as staphylococcal or streptococcal in origin; however, nocardial disease is usually more indolent. In advanced disease a mycetoma can develop with sinus tract formation. Mycetomas are a chronically progressive, destructive disease, occurring days to months after inoculation, and are typically located distally on the limbs. Eumycetoma (of fungal etiology) and actinomycetoma (due to actinomycetes) are equally prominent in the literature, the epidemiology varying with geographic location (see Chapter 261). Overall, *Streptomyces* and *Actinomadura* spp. appear to be of equal or greater importance than *Nocardia* spp. as causative agents of actinomycetoma. Suppurative granulomas, progressive fibrosis and necrosis, sinus formation with destruction of adjacent structures, and macroscopically visible infective granules (grains) are regular features of nocardial mycetoma.

FIG. 253.2 Skin lesions. Nocardial skin lesions due to direct inoculation in an immunosuppressed landscape gardener.

Pulmonary Disease

Pulmonary disease is the predominant clinical presentation of nocardiosis and is acquired through inhalation of organisms from the environment.[15,22] Any species may cause lung infection, although the most common are *N. cyriacigeorgica*, *N. nova,* and *N. farcinica*. Onset of symptoms may be subacute or chronic and include one or more of productive or nonproductive cough, dyspnea, hemoptysis, and fever and other systemic symptoms. In patients with malignancy, radiologically evident pulmonary infiltrates commonly herald the presence of nocardiosis.[57] Established infection may include endobronchial inflammatory masses, pneumonia, lung abscess, and cavitary disease with contiguous extension to surface and deep structures, including effusion and empyema.

Radiologic Manifestations of Pulmonary Nocardiosis

These include irregular nodules (usually cavitating when large), reticulonodular or diffuse pneumonic infiltrates, and pleural effusions (Fig. 253.3). High-resolution computed tomography (CT) of pulmonary lesions most often shows them to be dense, well-circumscribed nodules or masses, often with central cavitation. Interlobar septal thickening around the lesion or ground-glass infiltrates may also be seen.[58] The "halo sign," considered characteristic of aspergillosis in neutropenic patients, has been described. Progressive fibrotic disease may develop in the immunocompetent host, and diagnosis is often difficult. Pulmonary nocardiosis may occasionally complicate advanced human immunodeficiency virus (HIV) infection (most commonly when the CD4 count is <200/mm^3), where it often presents with alveolar infiltrates that progress during therapy rather than as cavitary disease.[59]

Differential Diagnosis of Pulmonary Nocardiosis

Nocardiosis should always be considered in the differential diagnosis of indolent pulmonary disease, particularly in the setting of cellular immune compromise, along with other actinomycetes (e.g., mycobacteria, *Actinomyces* spp.) and fungi (e.g., *Cryptococcus neoformans, Aspergillus* spp.). Pneumonia may have subacute presentation, resembling staphylococcal pneumonia. Clues to a nocardial etiology include spread to contiguous structures, especially with soft tissue swelling or external fistulae, and to the CNS. Invasive diagnostic procedures, including bronchoalveolar lavage for pneumonia, should be considered early in the immunocompromised host because disease may be rapidly progressive; in patients with severe immunodeficiency, coexisting pathology with similar clinical characteristics (e.g., aspergillosis, tuberculosis, malignancy) is well documented.[60]

Central Nervous System Nocardiosis

CNS involvement was recognized in greater than 44% of cases of all systemic nocardiosis in an early survey[22] compared with 4% to 33% in

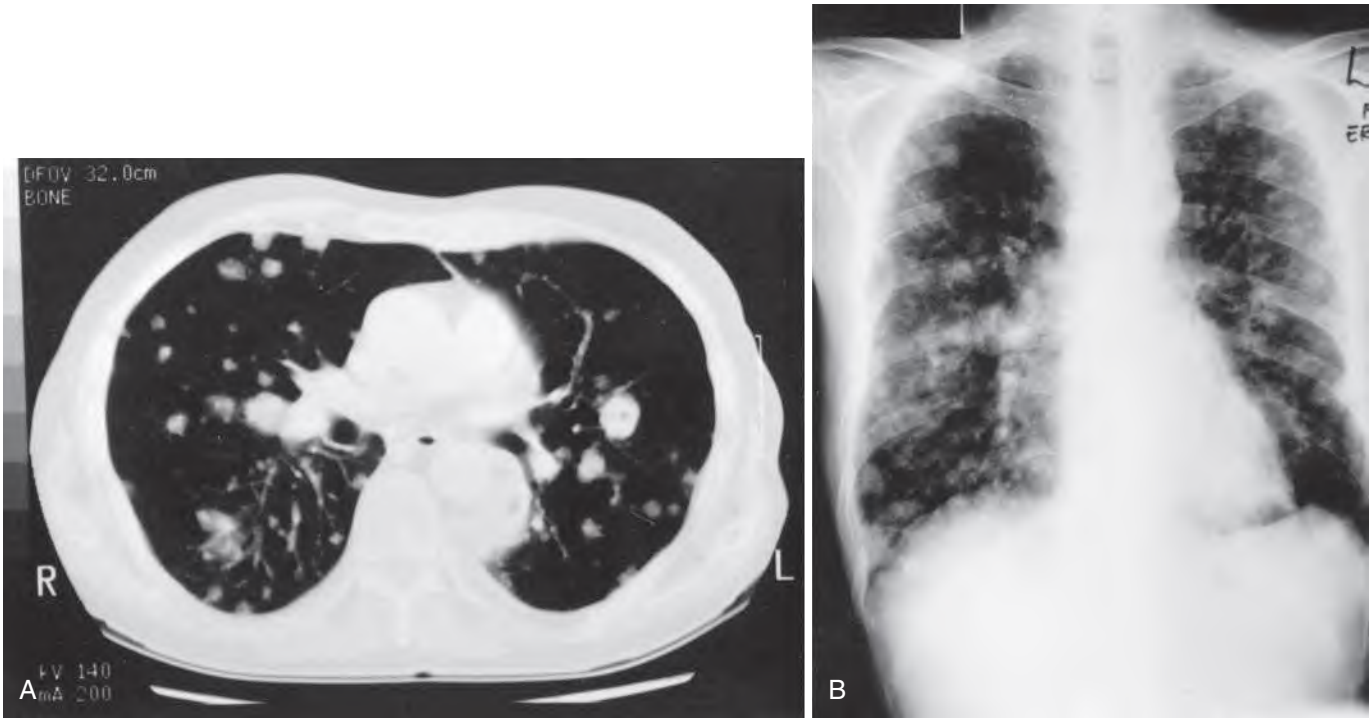

FIG. 253.3 Pulmonary nodules. Multiple pulmonary nodules, demonstrated by computed tomography (A) and chest radiograph (B), in an immunosuppressed patient with disseminated nocardiosis.

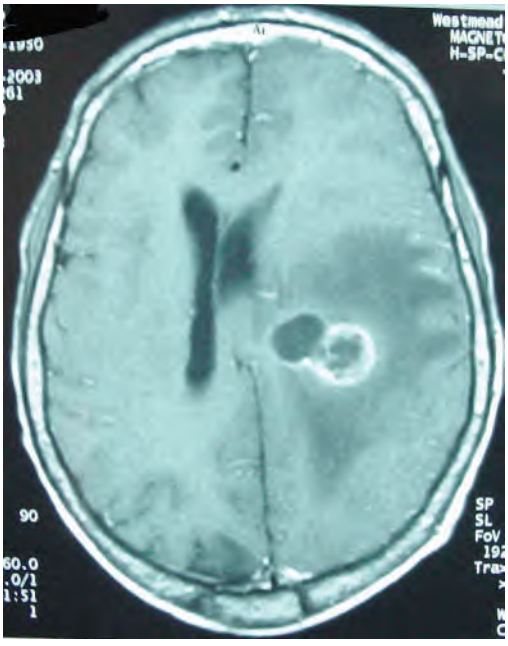

FIG. 253.4 Brain abscess. Magnetic resonance image showing *Nocardia* brain abscess.

FIG. 253.5 Skin lesion. Skin lesion from disseminated *Nocardia farcinica* infection.

more recent series.[48,57,61] Clinical manifestations usually result from local effects of granulomas or abscesses in the brain and, less commonly, the spinal cord or meninges (Fig. 253.4). These include headache, focal neurologic signs, seizures, confusion, and depressed consciousness. Multiple brain lesions are common. CNS nocardiosis should always be considered in patients with pulmonary or disseminated disease. Indeed, clinically silent brain abscess is sufficiently common that cerebral imaging, preferably magnetic resonance imaging (MRI), should be performed routinely in such cases.[48,49] Isolated CNS disease can also occur.[17,62,63] Insidious presentations are often mistaken for neoplasia because of the paucity of clinical and laboratory signs of inflammation; silent invasion and persistence make diagnosis and management more difficult.[14,22] Tissue diagnosis of a cerebral mass in the setting of proven pulmonary nocardiosis is not always necessary.[14] However, cerebral biopsy or aspiration should be considered early in the immunocompromised patient because of the higher incidence of serious coexisting pathology and a more aggressive course than that ascribed traditionally to cerebral nocardiosis. *N. farcinica* has a particular association with CNS (and skin) disease.[48,57]

Disseminated Nocardiosis

Disseminated infection is characterized by sites widespread abscess formation. The most commonly reported sites include the CNS (see earlier) and eye (particularly the retina), skin and subcutaneous tissues, kidneys, joints, bone, and heart (Fig. 253.5). Occasional cases of IV catheter–associated bacteremia have also been reported. Bacteremia is uncommon. *N. nova* was the predominant bloodstream pathogen in cancer patients and recipients of HSCT.[49,57]

Keratitis

Nocardia keratitis is well described in Asia and has been reported in travelers returning from Asia.[62,64] Although uncommon in most parts of the world, the entity is increasingly recognized, largely due to the availability of molecular diagnostic methods in many laboratories (see later). It is an aggressive ocular infection, typically after corneal trauma or minor surgical procedures to the eye. If the diagnosis is delayed, the infection can lead to corneal scarring.[62] Although the most commonly identified agents are from the former *N. asteroides* complex and *N. brasiliensis*, a broad range of species have now been implicated.[63] With appropriate therapy, keratitis resolves with good visual outcomes.[62]

Colonization

Occasional instances of transient colonization of the respiratory tract and skin by *Nocardia* spp. have been reported and appear to represent aerosol contamination or soil-derived contamination. Colonization of the sputum may be found in patients with underlying pulmonary pathology (e.g., bronchiectasis) or cystic fibrosis who are not receiving steroid therapy and requires no specific therapy. To be considered significant, *Nocardia* should be visible on Gram or modified acid-fast stain, produce a pure or predominant growth in culture, and be isolated repeatedly from clinical specimens. However, the extent to which spontaneously resolving or subclinical pulmonary infection occurs in the population is ill-defined, and at least one leading authority warns against dismissing positive sputum cultures as harmless.[22] The isolation of *Nocardia* from any site in an immunocompromised patient must never be ignored and should prompt appropriate investigations for invasive infection.

LABORATORY DIAGNOSIS

Nocardia spp. are most frequently isolated from respiratory secretions, abscess aspirates, and biopsy specimens. In pulmonary nocardiosis the diagnostic yield is increased by testing repeated sputum specimens, bronchoalveolar lavage, and biopsies.[1] For cutaneous nocardiosis, tissue biopsies are preferred for culture.[1] Specimens should be transported in sterile containers, and the microbiology laboratory should always be informed when nocardiosis is suspected, as the diagnosis may be missed by routine laboratory methods.

Direct smears from such specimens typically show gram-positive, beaded, fine, right-angled branching filaments (<1 µm diameter). Filaments may fragment to form rods and cocci of varying sizes. They are characteristically acid fast by methods such as the modified Kinyoun technique.[2] *Nocardiae* can be identified directly from clinical specimens using nucleic acid tests,[65,66] which may be particularly useful when there has been preexisting antimicrobial therapy or when biopsy specimens have been embedded in paraffin for histopathology.

Standard blood culture media support the growth of nocardiae, but prolonged incubation (up to 2 weeks) and blind subcultures may be required for their detection.[1] Bacteremia, as demonstrated by positive blood cultures, is rare in patients with nocardiosis.[2] In general, *Nocardia* spp. will grow on nonselective media used routinely for culture of bacteria, fungi, and mycobacteria. However, in specimens containing mixed flora (e.g., respiratory secretions), *Nocardia* colonies are easily obscured by those of more rapidly growing bacteria, and the yield is increased by use of selective media, such as Thayer-Martin agar with antibiotics[67] or paraffin agar.[68] Buffered charcoal-yeast extract medium, which is commonly used for selective growth of *Legionella* spp., may also be used for the isolation of *Nocardia* spp. from respiratory specimens.[69] Decontamination methods used for mycobacterial culture are too harsh for *Nocardia* spp. and may substantially reduce the numbers of viable organisms present in the specimen.[70]

Growth of *Nocardia* spp. on solid media take 48 hours to 14 days, but typical colonies are usually seen after 3 to 5 days. They appear as either buff or pigmented, waxy, cerebriform colonies (Fig. 253.6) or have a dry, chalky-white appearance if aerial hyphae are produced.[1] They have a characteristic earthy odor. Smears from cultures often show greater fragmentation of filaments than direct smears from clinical specimens.

Presumptive *Nocardia* isolates were previously classified on the basis of biochemical tests that were relatively expensive, slow, and limited by their inability to differentiate between members of the *N. asteroides* and *N. nova* complexes or to identify newly described species.[1,2] Molecular testing and MALDI-TOF MS can be used to identify *Nocardia* to a genus or species level and, where necessary, isolates should be referred to a reference laboratory.

FIG. 253.6 Culture. Typical colonies of *Nocardia* spp. growing on selective media.

Identification of *Nocardia* Species

Molecular techniques can provide definitive identification of most *Nocardia* isolates and recognize new species. An accurate species identification allows the prediction of antimicrobial susceptibilities in many cases.[1] Polymerase chain reaction–amplified DNA can be characterized, analyzed, and compared with archived sequences. Although sequencing of the first 500 to 606 base pairs (bp) of the 5′ end of the 16S ribosomal RNA (rRNA) gene contains sufficient sequence variability for species identification,[2,5,6] sequence analysis of longer gene fragments (e.g., 999–1400 bp) is necessary to distinguish between closely related species, most notably *N. abscessus*/*N. asiatica*/*N. arthritidis, N. africana*/*N. elegans,* and *N. veterana*.[5] Although guidelines of the Clinical and Laboratory Standards Institute (CLSI) recommend that greater than 99.6% similarity is needed for species identification, Conville and associates[1,71] recommend greater than 99.8% homology to differentiate between some species, including those within the *N. nova* complex.

Although housekeeping gene sequences, such as *hsp65, secA1, gyrB, rpoB,* and *sodA,* can improve phylogenetic resolution,[1,72,73] the accuracy of species identification is also dependent on the quality of sequences in gene repositories,[74] and inaccuracies have been found in public databases.[75] Thus comparison with sequences of well-characterized type strains of a species and/or with those in a curated database (e.g., the SmartGene [SmartGene GMbH, Zug, Switzerland]) is necessary for correct identification. Errors may also arise because multiple but different 16S rRNA genes are present in certain *Nocardia* spp., such as *N. nova*.[74–76] Multiple copies of the *gyrB* and *rpoB* genes have also been identified.[77]

Multilocus sequence analysis (MLSA) is a molecular identification technique that uses concatenated sequences from a number of gene targets to clarify the phylogenetic relationships of closely related species.[1] This is regarded as a more effective method of identification, as single-gene targets may be susceptible to recombination, gene transfer, and stochastic variation.[77] MLSA has been useful for the identification of known *Nocardia* spp. and demonstrated the clustering of previously uncharacterized clinical isolates.[4,77–79] Although whole-genome analysis of clinical isolates would be the gold standard in terms of *Nocardia* identification and allow the detection of resistance genes, current limitations to routine laboratory usage include cost, access to next-generation sequencing, and the need to manipulate and analyze large datasets.[80]

MALDI-TOF MS compares the spectra produced by bacterial proteins with a library generated from well-characterized organisms, allowing rapid identification. In a European study, performed after optimization of the spectral library, MALDI-TOF MS identified 91% of 171 isolates

to the species level and 6% to the genus level; species were confirmed by molecular testing.[81] In a multicenter trial the use of three combined libraries resulted in identification at species level in 84% and at genus level in 6%.[3] Reextraction of specimens with a low MALDI-TOF MS identification score (<2.0) and modification of extraction methods have also improved identification.[3,82] In two studies, where in-house libraries were developed, identification to species level was made in 95% and 90.6% of isolates and to genus level in an additional 5% and 9.4%, respectively.[4,82] A strategy for improved *Nocardia* identification would be to use MALDI-TOF MS technology for rapid identification of the majority of isolates and, when identification is uncertain, perform nucleic acid–based molecular identification.[82]

MANAGEMENT

Antimicrobial Selection

Successful management of *Nocardia* infection requires the use of antimicrobial drugs, often in combination, and, where appropriate, surgical drainage or débridement. As there are no randomized trials to determine optimal regimens, recommendations are based on retrospective and observational data, animal studies, in vitro susceptibility profiles, and expert opinion.

Initial selection of a therapeutic regimen should be based on the species of *Nocardia*, the site and severity of infection, the host immune status, and potential drug interactions or toxicity. As clinical isolates of *Nocardia* exhibit variable resistance to antimicrobial agents, antimicrobial susceptibility testing is advised. Although there is a lack of data directly correlating in vitro susceptibility with clinical outcome, with the exception of CNS disease,[83] therapy based on in vitro susceptibility is often effective.

In Vitro Susceptibility Testing

The CLSI has approved broth microdilution methods for antimicrobial susceptibility testing of aerobic actinomycetes and has set interpretive breakpoints for commonly used antimicrobials.[84] Other available methods include the E-test (AB Biodisk; Solna, Sweden) and BACTEC radiometric methods. Both correlate well with broth microdilution results and are easier to use in the routine clinical laboratory.[85]

Susceptibility profiles for commonly isolated *Nocardia* spp. are summarized in Table 253.3. Although resistance patterns can be predicted for some *Nocardia* spp., geographic variability has been reported, and new species for which susceptibility data is lacking continue to be identified.[86]

Discrepancies in susceptibility testing between laboratories have also been well-documented, particularly with testing of TMP-SMX.[86–90] These are largely due to technical issues inherent in broth microdilution methodology and include inoculum preparation, end-point determination, and lack of standardized interlaboratory proficiency testing programs.[87,91] For these reasons, referral of isolates to a specialized reference laboratory is recommended in the following circumstances: if local susceptibility testing is performed and yields data contrary to that expected from published literature, for patients with deep-seated or disseminated infection, for patients intolerant of treatment with TMP-SMX, and for those who fail therapy or relapse after therapy. Isolates of newly described species and of *Nocardia* spp. known to be more inherently resistant should also be considered for susceptibility testing in a reference laboratory.[86,91]

Antimicrobial Regimens

Sulfonamides, most recently in the form of TMP-SMX, have been the mainstay of therapy for *Nocardia* infection since their introduction in the 1940s and have substantially improved outcomes. In cases of disseminated (including CNS) disease and in immunosuppressed patients, mortality rates with sulfonamide monotherapy are greater than 50%,[92–94] and combination antimicrobial therapy is recommended. This should be commenced empirically pending susceptibility results. Amikacin combined with imipenem or meropenem, or three-drug regimens consisting of TMP-SMX, amikacin, and a carbapenem or third-generation cephalosporin, have been used for high-risk patients.[14,15] Increasing experience with linezolid suggests it is effective in combination with the above agents and may have a useful role in initial empirical management of disseminated or CNS *Nocardia* infection pending susceptibility results.[92–94] TMP-SMX, linezolid, carbapenems, and ceftriaxone may be preferred to amikacin-containing regimens in solid-organ transplant populations because of the high incidence of renal impairment in this group.[15] Other agents that have been used in combination regimens include broad-spectrum quinolones, minocycline, and tigecycline.

Trimethoprim-Sulfamethoxazole

TMP-SMX, available in the fixed ratio of 1:5, is the sulfonamide preparation preferred for management of *Nocardia* infection. Synergistic activity between the two drug components has been demonstrated against the majority of *Nocardia* spp. in vitro,[95,96] giving this formulation an advantage over older sulfonamide agents, such as sulfadiazine and sulfisoxazole. Although it is not known whether synergy occurs in vivo, optimal ratios of TMP to SMX for demonstration of synergy in vitro vary from less than 1:5 to 1:10.[96,100] Drug levels in serum and CSF are estimated to reach 1:20[95] and 1:7 or less in tissues and pus, including cerebral abscesses.[96,97]

The recommended dose of TMP-SMX in adults with normal renal function and localized disease is 5 to 10 mg/kg/day TMP and 25 to 50 mg/kg/day SMX given in two to four divided doses, depending on extent of disease.[96] Although use of 5 mg/kg/day (TMP component), together with surgical débridement, is considered sufficient for effective

TABLE 253.3 Antimicrobial Susceptibility of Selected *Nocardia* Species

	N. cyriacigeorgica	*N. farcinica*	*N. nova complex*	*N. transvalensis complex*	*N. brasiliensis*
Trimethoprim-sulfamethoxazole (TMP-SMX)	S	S[a]	S	S	S
Amoxicillin clavulanate	R	S	R	V (0%–53% R)	S
Ceftriaxone	S	R	V (25%–53% R)	V (15%–37% R)	V (13%–66% R)
Imipenem	V (3%–57% R)	V (4%–67% R)	S	R	R
Amikacin	S	S	S	R	S
Linezolid	S	S	S	S	S
Moxifloxacin	R	S,?V[b]	R	S	S
Clarithromycin	R	R	S	R	R
Minocycline	V (15%–95% R)	R	V (44%–88% R)	R	V (23%–76% R)
Tigecycline	V	R	V	ND	S

[a]Recent studies suggest resistance rates of 0.5%–6% to TMP-SMX in *N. farcinica;* however, rates of 45% have been described in Spain.
[b]Generally active with variable resistance in some reports.
ND, No data; *R,* generally inactive; *S,* generally active (some isolates may be resistant); *V,* variable resistance in vitro (published ranges in parentheses).

management of primary cutaneous infection,[96] doses of 15 mg/kg/day TMP and 75 mg/kg/day SMX are used in severe or extensive infection, disseminated infection, cerebral abscess, or AIDS.[60,95] Lower doses of TMP-SMX have been used successfully to treat infection in some immunocompromised patients; for example, 5 mg/kg/day of the TMP component given daily in two doses has successfully treated pulmonary infection in renal transplant recipients. In these cases, however, TMP-SMX was usually prescribed as only one component of a combination therapy regimen.[83,99] Lower-dose regimens using 10 mg/kg/day[100,101] or less[102] of the TMP component have also successfully cured cases of cerebral abscess. Dose reduction of TMP-SMX is recommended in renal impairment.

Therapeutic drug monitoring of serum sulfonamide levels may have a role where absorption from the gastrointestinal tract is uncertain, in patients who require high doses of TMP-SMX and are at risk of dose-related toxicity (renal failure and bone marrow impairment), and in cases of poor therapeutic response. The recommended therapeutic level of sulfonamide, measured 2 hours after an oral dose at steady state, is 100 to 150 mg/L[103]; however, there are minimal data equating sulfonamide levels to toxicity or efficacy.[98]

The decision to use sulfonamides in therapy will in part depend on the causative species of *Nocardia*. Although sulfonamide-resistant *Nocardia* have been reported (see Table 253.3), resistance of *Nocardia* spp. overall to TMP-SMX appears to be between 2% to 3%.[78,86,87] Alternative antimicrobial agents should be considered in infections caused by *Nocardia* demonstrated to be sulfonamide-resistant, in patients who are clinically failing sulfonamide therapy, and in those intolerant of sulfonamide-containing regimens due to hypersensitivity or toxicity. Sulfonamide intolerance has been reported in 3.4% to 8% of exposed non–HIV-infected patients[104,105] and in up to 55% of AIDS patients.[106] Desensitization to TMP-SMX may be considered for those with hypersensitivity, to enable ongoing treatment with sulfonamides. Patients receiving other myelosuppressive agents, such as azathioprine,[107] or nephrotoxic agents, such as calcineurin inhibitors, are at increased risk of sulfonamide-induced myelotoxicity and nephrotoxicity, respectively.

Other Regimens

The choice of alternative therapeutic agents is based on in vitro susceptibility data; efficacy in animal models, primarily short-term murine models of pulmonary and cerebral nocardiosis[108,109]; and published case reports and case series. Assessment of the efficacy of these regimens is complicated by the relative rarity of infection, the diversity of agents that have been used either in combination or sequentially, the variability in host populations studied, and the variable chronic course of *Nocardia* infection.

Amikacin and Carbapenems

Most clinical experience to date has been with amikacin and imipenem. Amikacin exhibits excellent activity in vitro against most species of *Nocardia*, with the exception of *N. amikacinitolerans*, *N. pseudobrasiliensis*, and *N. transvalensis complex,* with resistance to amikacin demonstrated in 57%, 31%, and 72% of isolates, respectively, in one study.[86] Imipenem has good in vitro activity against *N. nova* and many other *Nocardia* spp.; however, resistance has been reported in up to 100% of strains of *N. pseudobrasiliensis* and *N. brasiliensis* and in moderate-to-high numbers of isolates within the *N. transvalensis* complex, *N. otididiscaviarum*, *N. farcinica*, *N. cyricageorgica,* and *N. abscessus*.[86,110] Synergy between amikacin and TMP-SMX has been demonstrated in vitro; with imipenem, the effectiveness is primarily additive.[111]

Amikacin and imipenem have been successfully used, together or in combination with sulfonamides or other agents, in both immunocompromised patients and in patients with *Nocardia* infection involving different body sites.[15,112,113] In one study cure was achieved in seven of eight patients who received amikacin in combination with agents that demonstrated synergy in vitro.[113] Amikacin and imipenem in combination have been recommended as initial parenteral therapy in pulmonary *Nocardia* infection[114] and in severe infection,[14] particularly where there may be concerns regarding TMP-SMX susceptibility or toxicity; however, there are no clinical trials to support this approach. Once-daily dosing regimens of amikacin make it attractive for in-home IV therapy programs; however, the potential for amikacin to cause ototoxicity and nephrotoxicity makes its use problematic in many risk groups that have underlying poor renal function.

Limited data are available on the use of alternative carbapenems (meropenem, ertapenem) in *Nocardia* infection. Meropenem is clinically appealing as it is associated with a lower incidence of seizures compared with imipenem, achieves good CSF penetration, and is active in vitro activity against several *Nocardia* spp.[110,115] Of note, susceptibility of *Nocardia* isolates to meropenem cannot be inferred from susceptibility to imipenem. Imipenem appears to be the most active carbapenem in vitro against *N. farcinica* and *N. otidiscaviarum*,[110,115] whereas meropenem has demonstrated more activity than imipenem in vitro against *N. abscessus* and the *N. transvalensis* complex.[110] Ertapenem demonstrates poor activity against *Nocardia* spp. generally, although some have observed that *N. nova* isolates may be susceptible to all carbapenems, including ertapenem in vitro.[110] A single study of 51 isolates of *Nocardia* spp. concluded that overall meropenem is 4 times less active and ertapenem 16 times less active than imipenem against the species tested.[116] Published reports of the use and efficacy of meropenem in nocardiosis have been in the setting of combination therapy.[15,117–119]

Third-Generation Cephalosporins

The third-generation cephalosporins ceftriaxone, cefotaxime, and cefuroxime exhibit in vitro activity against a variety of *Nocardia* spp., but *N. farcinica* isolates are typically resistant, and variable levels of resistance have been demonstrated in isolates of the *N. transvalensis* complex, *N. pseudobrasiliensis,* and *N. otidiscaviarum*. Greater than 10% of isolates of *N. brasiliensis* and the *N. nova* complex are resistant to ceftriaxone in vitro (see Table 253.3). Synergy between cefotaxime and imipenem has been demonstrated against susceptible strains of *Nocardia* in a murine model of cerebral *Nocardia* infection, where the combination of cefotaxime and imipenem was more effective at reducing colony counts at 72 hours than either agent given alone.[120] Synergistic activity has also been described in vitro between cefuroxime and amikacin.[113]

Oxazolidinones: Linezolid and Tedizolid

The oxazolidinone linezolid exhibits excellent in vitro activity against all known species of *Nocardia*.[86,121,122] and has excellent oral bioavailability and good CNS penetration.[123] Increasing clinical experience suggests that it is efficacious when used in combination with another anti-*Nocardia* agent[92–94,124]; however, its toxicity profile precludes long-term usage. When given for more than 14 days, linezolid is associated with an increased risk of hematologic toxicity,[125] lactic acidosis, retrobulbar optic neuritis, peripheral neuropathy, and the serotonin syndrome. There is some evidence that therapeutic drug monitoring of plasma linezolid levels may reduce the incidence of toxicity; however, results are conflicting.[126–128] In 18 cases of solid-organ transplant recipients treated for *Nocardia* infection, in whom 17 of 18 received TMP-SMX and 15 of 18 received linezolid, the median duration of therapy with linezolid was 21 days.[94] Ten of the 15 (67%) ceased linezolid due to adverse events; thrombocytopenia was noted in 14 of 15 (93%) and anemia in 9 of 15 (60%). However, these rates were similar to those in patients who did not receive linezolid.

Given its potential for toxicity, linezolid may not be appropriate for long-term therapy of *Nocardia* infections. However, it may be useful in initial and empirical management of infection or in combination with other agents, particularly when amikacin may not be an option due to nephrotoxicity, while results of susceptibility tests are pending.

Limited available data suggest that tedizolid, a second-generation oxazolidinone, has greater efficacy than linezolid in vitro with minimal inhibitory concentrations twofold to threefold lower than linezolid against many *Nocardia* spp.[129] Although phase III studies comparing tedizolid with linezolid demonstrated a lower incidence of thrombocytopenia with tedizolid (3.2% vs. 5.6%),[130] there is insufficient clinical experience to recommend its use.[131]

Minocycline and Amoxicillin-Clavulanate

The most frequently used oral alternatives to sulfonamides include minocycline and amoxicillin-clavulanate. Minocycline has the best in

vitro activity of the tetracyclines and has shown efficacy when used alone, in combination with other antimicrobials, as sequential therapy, and in patients intolerant of sulfonamides.[132–134] Reports of failure when used as monotherapy in immunocompromised patients, however, have also been reported.[135]

Amoxicillin-clavulanate has been effective in individual cases when used in combination with other agents or as sequential therapy.[136,137] It may be particularly useful in the treatment of cutaneous infection due to *N. brasiliensis*, a consistent β-lactamase producer, and is the preferred oral agent for this species in patients who cannot tolerate sulfonamides.[138] A case of acquired resistance to β-lactam and β-lactamase inhibitor antibiotics has been described, however, resulting in relapse during therapy of *N. brasiliensis* with amoxicillin-clavulanate.[139] Other species with susceptibility to amoxicillin-clavulanic acid include *N. abscessus* and *N. farcinica*.[2] The use of amoxicillin-clavulanate should be guided by in vitro susceptibility results; demonstration of β-lactamase production is not necessarily predictive of resistance to β-lactam drugs, and isolates of the *N. nova* complex can test ampicillin susceptible/intermediate but may be resistant to amoxicillin-clavulanic acid.[2]

Fluoroquinolones, Macrolides, and Tigecycline

In vitro susceptibility results should also be used to guide the choice of alternative agents for which few clinical data are available, such as the macrolides, fluoroquinolones, and tigecycline. Moxifloxacin demonstrates activity against several *Nocardia* spp., including *N. farcinica*, the *N. transvalensis* complex, *N. pseudobrasiliensis,* and *N. brasiliensis*, and has greater activity in vitro than ciprofloxacin.[86,140] Published clinical experience in patients treated with moxifloxacin has mainly been as salvage therapy in infections due to *N. farcinica*, or in combination with other agents or surgical débridement. Results have been mixed, with both successful and poor outcomes reported.[141,142]

Clarithromycin is the macrolide most commonly used for treatment of *Nocardia* infections and exhibits good activity in vitro against *N. nova*.[143] This agent has been used successfully to treat *N. nova* infections as part of combination therapy, as sequential therapy, and in cases of sulfonamide intolerance.[144,145] Limited in vitro data on use of the IV drug tigecycline suggest that it has activity against a variety of *Nocardia* spp., including imipenem-resistant and TMP-SMX–resistant isolates; however, no clinical efficacy data are available.[116,146]

Superficial Infection and Mycetoma

Localized or isolated cutaneous disease in the immunocompetent host may be treated with monotherapy. Oral TMP-SMX is preferred; however, other agents, including minocycline, amoxicillin-clavulanate, fluoroquinolones, and macrolides, have been used depending on isolate susceptibility.

Nocardia Intravascular Catheter-Related Bloodstream Infection

Nocardia central line–associated bloodstream infections are rare and occur primarily in immunocompromised patients. Early line removal, together with combination antimicrobial therapy, is recommended.[17]

Severe Infection

Empirical Therapy

Although TMP-SMX as monotherapy may be successfully used in mild pulmonary infection with no evidence of dissemination, combination antimicrobial therapy with at least two agents is recommended for immunocompromised hosts, those with more than one site of infection not involving the CNS, and any patient with severe pulmonary involvement or isolated CNS disease. Recommended regimens include amikacin and imipenem or meropenem, or amikacin and TMP-SMX. Although two-drug therapy may be suitable in cases of isolated cerebral disease, when additional sites are involved, or infection is life threatening, three-drug regimens that cover all likely pathogenic *Nocardia* spp. are recommended, for instance, TMP-SMX plus imipenem or meropenem, plus amikacin or ceftriaxone (or linezolid in patients with renal failure). Empirical therapy should be modified after *Nocardia* speciation and susceptibility results.

Surgical Management

The need for surgical management of *Nocardia* infection depends on the site and extent of disease.

Surgery in Extraneural Nocardiosis

In extraneural infection, indications for aspiration, drainage, or excision of abscesses are similar to those for other chronic bacterial infections. Thick-walled, multiloculated abscesses are unlikely to be managed successfully with therapeutic aspiration alone.[147]

Surgery in Cerebral Nocardiosis

Surgical management is advised for brain abscesses that are accessible and relatively large, if the patient's condition deteriorates or lesions progress within 2 weeks of therapy, or when there is no reduction in abscess size within a month.[148] Stereotactic aspiration is useful for decompression of cerebral abscesses, but cure is often achieved only after craniotomy and complete excision of the abscess.[147] Small cerebral abscesses may be cured by prolonged antimicrobial therapy. As cerebral abscesses can progress despite appropriate therapy, all patients should be monitored with regular cerebral CT scans or MRI. Surgical intervention may be required for successful management of empyemas and mediastinal collections. Pericarditis complicating pulmonary *Nocardia* infection is often fatal unless pericardial drainage is performed.[149]

Keratitis and Other Eye Infections

Keratitis

In localized *Nocardia* keratitis, such as infection after LASIK (laser-assisted in situ keratomileusis) surgery, topical amikacin (1.5%–2.5% solution) has most commonly been used[62] due to its activity in vitro against *Nocardia* spp., its good corneal penetration with high local concentrations in the eye, and its safety profile.[55] In a series of 111 cases of culture-proven *Nocardia* keratitis in India, 89.7% of isolates were reported as amikacin susceptible.[150] Treatment consisted of topical amikacin 2.5% eye drops administered hourly with the addition of oral TMP-SMX in cases where response was slow or symptoms worsened; 82% resolved with medical treatment alone. The average duration of treatment for keratitis was 38 days.

Other antimicrobials that have been used topically in *Nocardia* keratitis include TMP-SMX preparations, tobramycin, ciprofloxacin (0.3%), and moxifloxacin (0.5%).[151] Pretreatment of *Nocardia* keratitis with topical quinolone preparations has been associated with increased resistance to moxifloxacin in *Nocardia* spp. in vitro.[152] Topical corticosteroids should be used with caution in *Nocardia* keratitis. In a randomized, placebo-controlled trial comparing topical corticosteroid use with placebo in bacterial keratitis, corticosteroids were associated with worse clinical outcomes at 3 months and with larger scar size at 12 months in patients with *Nocardia* keratitis compared with those who did not receive topical prednisolone.[153]

The use of systemic (oral or IV) antimicrobial therapy depends on the clinical context.

Endophthalmitis

Nocardia is a rare cause of endophthalmitis, either exogenous from surgery or trauma, or, even less commonly, hematogenous. Relatively poor outcomes have been noted after use of intravitreal amikacin in patients with *Nocardia* endophthalmitis despite susceptibility of the causative species to amikacin in vitro (100% and 90%, respectively).[62] Thus systemic TMP-SMX is usually given. Antimicrobial choice depends on species and results of susceptibility testing (see Table 253.3). Intravitreal amikacin carries with it a small risk of macular infarction.[154]

Duration of Therapy and Prognosis

Clinical Responses to Therapy

Clinical improvement is generally evident within 3 to 5 days[108] or, at most, 7 to 10 days after the initiation of effective therapy.[101] Parenteral therapy can usually be safely changed to an oral regimen after 3 to 6 weeks, depending on clinical response. Initial high doses of TMP-SMX may also be reduced at this time. Patients with extensive infection, necrotic foci not amenable to surgery, or those who respond slowly may benefit from prolongation of parenteral and subsequently oral therapy.[14]

Causes of Therapeutic Failure

Lack of response to initial therapy may be due to primary drug resistance; inadequate penetration of drug into sites of infection (dependent on dose, bioavailability of oral drugs, abscess location and pathology, and patient compliance); the presence of a sequestered abscess requiring surgical drainage; and, in an immunocompromised host, overwhelming nocardial infection or a coexisting or secondary opportunistic infection.

Management of Immunosuppressive Drug Therapy in Patients With Nocardiosis

Reduction or cessation of immunosuppressive drugs may be required if *Nocardia* infection is uncontrolled or progressive despite therapeutic serum levels of antimicrobial agents.

Duration of Therapy in Immunocompetent Hosts

Recommendations for the duration of therapy are empirical and based primarily on reports of relapse after sulfonamide therapy of different durations.[a] Isolated cutaneous infection, including sporotrichoid nocardiosis and superficial ulcers, can be cured with 1- to 3-month courses of therapy.[96] Prolonged therapy is required in patients with mycetoma.[147] Immunocompetent patients with pulmonary or systemic *Nocardia* infection and without CNS involvement should be treated for a minimum of 6 months. Those with CNS infection should be treated for 12 months.[14]

Duration of Therapy in Immunosuppressed Hosts

HIV-negative, immunosuppressed patients with isolated pulmonary disease should be treated for at least 6 months and those with disseminated disease for 6 to 12 months, depending on the degree of immunosuppression and response to therapy. Therapy should be continued for 12 months or longer if there are intercurrent increases in immunosuppression (e.g., due to episodes of graft rejection). For patients who must be maintained on steroid or cytotoxic therapy after successful treatment of *Nocardia* infection, prolonged low-dose, maintenance antimicrobial therapy or secondary prophylaxis may be required (see section "Prophylaxis").

In patients with AIDS, early institution of a prolonged primary course of antinocardial therapy is essential, as treatment of patients with late presentations or of those with relapsed nocardial infection has usually been unsuccessful.[59] Although secondary prophylaxis has traditionally been recommended in patients with AIDS at the completion of *Nocardia* therapy, restoration of the immune system with antiretroviral therapy has been associated in one report with clinical cure of *Nocardia* infection in the absence of appropriate therapy, suggesting immune restoration may abrogate the need for secondary prophylaxis.[157]

Short-Course Therapy

Cure of extrapulmonary abscesses has been described in a few cases treated with a short course of amikacin (7–8 weeks) with amikacin and surgical drainage[43,158] or, in a case of cerebral nocardiosis, amikacin plus ceftriaxone.[159]

Prophylaxis

Primary Prophylaxis

Primary prophylaxis against *Nocardia* infection is not usually recommended for immunosuppressed patients posttransplantation as the incidence of infection is low. Of note, prophylaxis against *P. jirovecii* infection is often prescribed in this patient group using TMP-SMX two or three times weekly. This regimen does not prevent infection with *Nocardia,* and substantial numbers of patients develop nocardiosis after solid-organ or stem cell transplantation while on such prophylaxis.[15,48,146,160,161]

Secondary Prophylaxis

The efficacy of secondary prophylaxis to prevent relapse or recurrence of *Nocardia* infection has not been determined. It may be considered for patients with persisting immunosuppression, once therapy for *Nocardia* infection is completed. TMP-SMX at a dose of one double-strength tablet daily (800 mg SMX component) has been used; however, there are no efficacy or outcome data to support this approach.[102,116]

[a]References 59, 95, 96, 100, 155, 156.

Clinical Outcomes

The clinical outcome of *Nocardia* infection depends on underlying host factors, site and extent of disease, the infecting *Nocardia* spp., and duration of therapy.

Worse outcomes have been reported in immunosuppressed patients compared with nonimmunosuppressed patients. A mortality of 70% was described in one study of 27 HIV patients with advanced immunosuppression; however, all but one patient had received monotherapy for their *Nocardia* infection.[59] Mortality rates of 55% have been reported in immunocompromised patients with CNS disease compared with 20% in nonimmunocompromised patients.[148] *Nocardia* infection of the CNS has been associated with worse outcomes in general when compared with other sites of infection. Mortality rates of 47.8% have been reported in CNS infection compared with 7.6% with pulmonary infection alone.[156] Cure rates of up to 80% were described in disseminated disease compared with 60% in CNS disease in another study.[95] Isolated cutaneous disease generally has a 100% cure rate. Mortality rates are higher in immunocompromised patients with *Nocardia* infection than in matched controls without *Nocardia* infection. A case-control study of 35 solid-organ transplant recipients demonstrated a 6-month mortality rate of 14% compared with 4% in non-*Nocardia* control subjects. Cure rates of 89% were described in the study regardless of site of infection, although those with disseminated infection received prolonged therapy (median, 7.5 months) compared with those with nondisseminated infection (median, 6 months).[15] A recent case-control study of 117 solid-organ transplant recipients showed a mortality rate of 16.2% at 1 year compared with 1.3% in non-*Nocardia* control subjects.[119] A multivariate analysis of this population revealed that a history of tumor, invasive fungal infection in the preceding 6 months, and donor age were independent risk factors for mortality from *Nocardia* infection at 1 year (rather than site, dissemination, or antimicrobial regimen). Of interest, a prior episode of acute rejection was associated with improved survival from *Nocardia* infection. Exposure to high-dose steroids, cytomegalovirus infection in the preceding 6 months, and high median calcineurin levels within 30 days have previously been identified as independent risk factors for the development of *Nocardia* infection in organ transplant recipients.[15]

Although immunosuppressive therapy increases the risk of pulmonary and disseminated nocardiosis in recipients of organ transplants, it is not clear to what extent continuation of immunosuppressive therapy during treatment of nocardiosis has an impact on outcome. Most patients can be cured with appropriate antimicrobial therapy even if immunosuppressive drugs are continued, provided that the diagnosis is made early and appropriate full-dose antinocardial therapy is continued for an adequate period of time.[136,160] On the other hand, delay in diagnosis and early cessation of therapy have been associated with increased rates of relapse and worse outcomes.[59,96,156]

Effect of *Nocardia* Species on Outcome

Some *Nocardia* spp. may be more virulent and associated with worse clinical outcomes. Isolates of *N. farcinica* were more virulent than other species in a mouse model,[44] and in a series of 20 microbiologically confirmed cases of CNS nocardiosis, 6 of 7 deaths reported at 1 year were attributed to *N. farcinica*.[162] Multidrug-resistant isolates may also be predicted to have worse outcomes, depending on the availability of effective antimicrobial choices.

Summary of Management

The choice and dose of antimicrobial drugs and the duration of therapy depend on the sites and extent of infection, underlying host factors, the species of *Nocardia*, and the clinical response to initial management. TMP-SMX remains the mainstay of therapy. Initial combination therapy is indicated in patients who are immunosuppressed or who present with brain involvement or disease involving multiple sites. Oral maintenance therapy can be initiated after 4 to 8 weeks, depending on the severity of infection and the clinical response. Newer, orally active drugs may be of value as short-term adjunctive or salvage therapy (linezolid), or as salvage or maintenance therapy when supported by susceptibility testing (late-generation quinolones or macrolides).

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The complete reference list is available online at Expert Consult.

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254 Agents of Actinomycosis

Thomas A. Russo

SHORT VIEW SUMMARY

Definition of Actinomycosis
- Actinomycosis is an indolent infection caused by *Actinomyces* and closely related species.
- Characteristics include chronicity, crossing of tissue boundaries, and masslike features.
- Bulky disease mimics malignancy.
- Sinus tract(s) may develop, resolve, and recur.
- Refractory or relapsing infection may occur after a short course of therapy.
- Not all infections due to *Actinomyces* spp. manifest with the clinical syndrome of actinomycosis.

Microbiology
- *Actinomyces* is a genus of gram-positive, filamentous bacteria.
- Most species are anaerobes; a few are microaerophilic.
- "Companion organisms" are usually present.

Epidemiology and Pathogenesis
- Actinomyces is a human commensal organism of the oral, gastrointestinal, and pelvic mucosa.
- Disruption of the mucosal surface is the initiating factor for infection.
- Individuals of all ages and normal hosts may be infected.
- Actinomycosis is associated with intrauterine devices and bisphosphonates.

Clinical Manifestations
- All organs and sites can be involved.
- Oral-cervicofacial manifestations are the most common.
- A classic presentation is a painless mass at the angle of the jaw.
- Alternative presentations are myriad.

Diagnosis
- The diagnosis of actinomycosis is challenging. The condition is often missed or mistaken for cancer.
- Sulfur granules (grains) are distinctive clusters of organisms is tissue.
- The laboratory should be informed about suspected actinomycosis.
- Prior antibiotics can inhibit growth on culture.
- There is an increasing role for polymerase chain reaction assays and perhaps matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry.
- The diagnosis is often made from the appearance of grains at pathologic evaluation after surgery that may have been unnecessary.

Therapy
- Therapy is based on clinical experience and is individualized.
- Treatment involves a high-dose and prolonged course of antibiotics.
- A standard regimen involves administration for 2 to 6 weeks intravenously, often penicillin G 3 to 4 million units intravenous every 4 hours, followed by 6 to 12 months orally.
- Imaging is helpful in defining duration.
- The most extensive experience has been with penicillin, tetracyclines, and erythromycin (see Table 254.1).
- A short course of treatment directed against companion organisms may be warranted.
- Medical therapy usually is curative, even with extensive disease.
- Interventional radiology is valuable for drainage of accessible abscesses.
- Surgery is reserved for critical sites (e.g., central nervous system) and refractory disease.

Actinomycosis is an indolent, slowly progressive infection caused by anaerobic or microaerophilic bacteria, primarily from the genus *Actinomyces,* that normally colonize the mouth, colon, and vagina. Disruption of mucosa may lead to infection of virtually any site. When the organisms invade tissue, they form tiny, sometimes visible clumps, called grains or "sulfur granules," named for their yellow color. Lesions of actinomycosis are purulent foci surrounded by dense fibrosis. Classic presentations that should prompt consideration of this unique infection are (1) the combination of chronicity, progression across tissue boundaries, and masslike features, which mimics malignancy (with which it is often confused); (2) the development of a sinus tract, which may spontaneously resolve and recur, from which sulfur granules (grains) may be seen in the discharge or at histopathologic/cytologic assessment; and (3) a refractory or relapsing infection after a short course of therapy, because cure of established actinomycosis often requires prolonged treatment.

Although actinomycosis was common in the preantibiotic era, today its incidence is diminished.[1,2] Even when actinomycosis was more common, it was stated to be "the most misdiagnosed disease" and that "no disease is so often missed by experienced clinicians."[3] Actinomycosis remains a diagnostic challenge because it is uncommon, physician experience with its clinical manifestations is limited, and laboratory cultivation and identification are challenging.[4,5] However, this infection is usually curable with medical therapy alone. Therefore an awareness of myriad presentations can expedite diagnosis and treatment and can minimize unnecessary surgical interventions, morbidity, and mortality that all too often occur with actinomycosis.

ETIOLOGIC AGENTS

Actinomycosis is most commonly caused by the gram-positive higher bacterium *Actinomyces israelii*.[6] Additional species that are established but are less common causes of actinomycosis include *Actinomyces naeslundii,*[7] *Actinomyces viscosus,*[8] *Actinomyces odontolyticus,*[9] *Actinomyces gerencseriae,*[10] *Actinomyces graevenitzii,*[11] and *Actinomyces meyeri*, which has been increasingly described in some studies.[12,13] *Pseudopropionibacterium propionicum* (formerly *Propionibacterium propionicum* and *Arachnia propionica*) has been described as a cause of actinomycosis,[6,14,15] but most reports primarily describe this pathogen as causing lacrimal canaliculitis[16] and endodontic infections.[10]

Until recently, classification of *Actinomyces* spp. was based on differences in the results of phenotypic testing (see "Diagnosis" later). However, advances in microbiologic taxonomy, using matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry and genotypic methods such as comparative 16S ribosomal RNA (rRNA)[16,17] or sequencing of alternative genes,[18] have led to the identification of many new *Actinomyces* species from both human and animal specimens.[10] Many *A. naeslundii* isolates are now reclassified as *Actinomyces oris.* These methods have also led to the reclassification of certain *Actinomyces* species as *Trueperella (Arcanobacterium), Actinotignum (Actinobaculum),*[19] or *Cellulomonas.*[10,16,20,21] Presently, 47 species and 2 subspecies have been recognized.[22] Twenty-five species have caused infections in humans,[10] although the "classic" syndrome of actinomycosis has been variably described.[23,24] *Actinomyces europaeus,*[16,20,25,26,27] *Actinomyces neuii,*[26,28–31] *Actinomyces radingae,*[16,20,26,32,33]

Actinomyces turicensis,[16,20,24,26,32] *Actinomyces georgiae,*[34] *Actinomyces urogenitalis,*[35] *Actinomyces funkei,*[26,36,37] *Actinomyces hongkongensis,*[38] *Actinomyces houstonensis,*[26] *Actinomyces massiliensis,*[39] *Actinomyces timonensis,*[40] and *Actinomyces cardiffensis*[23,41] are capable of causing a variety of human infections. *A. neuii* most commonly has been reported to cause endovascular infection and abscesses.[42] *Trueperella (Arcanobacterium) pyogenes*[43] and *Trueperella (Arcanobacterium) bernardiae*[44,45] are additional causes of human infection.

When an adequate bacteriologic evaluation is performed, most if not all actinomycotic infections are polymicrobial in nature.[1,6] *Aggregatibacter (Actinobacillus) actinomycetemcomitans, Eikenella corrodens, Fusobacterium, Bacteroides, Capnocytophaga, Staphylococcus, Streptococcus,* and Enterobacteriaceae have been isolated in various combinations, depending on the site of the infection. The contribution of these additional isolates to the pathogenesis of actinomycosis is difficult to assess; however, it seems reasonable to consider them as being potential copathogens when one is designing therapeutic regimens.

EPIDEMIOLOGY

The agents of actinomycosis have been clearly established as members of the endogenous flora of mucous membranes. The frequency of oral cavity colonization with *Actinomyces* is nearly 100% by 2 years of age.[46] It is also often cultured from the gastrointestinal tract, bronchi, and female genital tract. It has never been cultured from nature, and there are no documented cases of person-to-person transmission.[47] Although the normal habitats for the more recently identified *Actinomyces* spp. have not been optimally defined, data available to date suggest that these species are also members of the endogenous oral, gastrointestinal, and genital flora.[26] Possible transmission via a lamb bite has been described in a single report.[48]

Actinomycosis has no geographic boundaries. Infection may occur in individuals of all ages. The peak incidence of actinomycosis is reported to be from 30 to 60 years, with cases in individuals younger than 10 and older than 60 years being less frequent.[6,49] Nearly all series have reported males to be infected more frequently than females, at a ratio of approximately 3:1.[1,6,49,50] Plausible but unproven explanations for this discordance include poorer dental hygiene and increased oral trauma in males.[49]

Studies on the occurrence of actinomycosis estimated a yearly incidence of 1:100,000 in the Netherlands and Germany in the 1960s and 1:300,000 in the Cleveland area during the 1970s, making this disease uncommon but not rare.[49] Its frequency has undoubtedly diminished since the preantibiotic era, when this disease was not only common but more malignant in nature. Improved dental hygiene and early antimicrobial treatment of infections before the development of a characteristic classic actinomycotic syndrome are likely contributing factors. However, individuals or populations that do not have access to dental or medical care, or both; prolonged use of an intrauterine contraceptive device (IUCD) (see "Pelvic Disease" later); and bisphosphonate use (see "Oral-Cervicofacial Disease" later) are associated with higher risk. Furthermore, many unrecognized cases probably occur, especially oral-cervicofacial disease, owing to early successful empirical therapy.

PATHOGENESIS AND PATHOLOGY

A pivotal step in the pathogenesis of actinomycosis is disruption of mucosal or epithelial barriers enabling entry of colonizing *Actinomyces* or related genera. Oral and cervicofacial disease is frequently associated with dental procedures, trauma, oral surgery, head and neck radiotherapy, or oncologic surgical procedures.[51] Pulmonary infections often arise in the setting of aspiration, and abdominal infection is usually preceded by conditions that result in loss of mucosal integrity, such as surgery, diverticulitis, appendicitis, or foreign bodies (e.g., fish bones).[1,49] Recognition of factors that enable bacterial entry into deep tissues, however, may be absent.[50] The lack of such a history should not prevent consideration of this disease when the clinical circumstance is appropriate.

Other bacterial species concomitantly present have been designated as "companion organisms." They may serve as copathogens by aiding in the inhibition of host defenses or by reducing oxygen tension. The difficulty in establishing an animal model of infection with *Actinomyces* alone and enhancement of infection by coinoculation of *E. corrodens* support the concept that additional organisms are important for the initiation of infection.[52] Furthermore, coaggregation of *Actinomyces* and *Streptococcus* spp. results in increased resistance to phagocytosis and killing.[53]

An acute inflammatory phase manifesting with a painful cellulitic reaction is occasionally observed with oral-cervicofacial disease or with soft tissue infection elsewhere in the body. The chronic phase of this disease is more often seen.[50] "Classic" disease is characterized by a densely fibrotic lesion that undergoes slow, contiguous spread that ignores tissue planes. However, the factor(s) responsible for the unique pathogenesis of this disease remain undefined. Lesions usually appear as either single or multiple indurated swellings. Over time, central fluctuance and suppuration develop. The fibrous walls of the mass have been characteristically described as "wooden" and, in the absence of suppuration, have been frequently confused with neoplasms. This extensive fibrosis, which is one of the hallmarks of this disease, may be minimal, especially in pulmonary and central nervous system (CNS) lesions. Given time, sinus tracts will often extend from the abscess to either the skin or adjacent organs or bone, depending on the location of the lesion. Sinus tracts can spontaneously close and then reform. Overlying skin may assume a red to bluish hue. Lymphatic spread and associated lymphadenopathy are uncommon. Hematogenous dissemination can occur from local sites, which occasionally results in fulminant infection, although in the antibiotic era this clinical syndrome has become rare.

Microscopically, lesions have an outer zone of granulation, consisting of collagen fibers and fibroblasts. There is a central purulent loculation that contains neutrophils that surround the sulfur granules present. Granules are conglomerations of organisms and are virtually diagnostic of this disease. Bacterial biofilms may contribute to granule formation.[54] One to six may be present per loculation, and they range from microscopic to macroscopic in size (see "Diagnosis" later). As many as 50 loculations may be present per lesion, and these loculations are separated by granulation tissue or foamy macrophages and may undergo coalescence. Lymphocytes and plasma cells are usually present, and eosinophils are seen in 15% of abscesses. Multinucleated giant cells are occasionally seen, primarily in pulmonary lesions, but they have also been described in disease elsewhere.[50] Suppuration is a constant feature of active disease but may not be present in all areas of the lesion. Grains are usually surrounded by neutrophils and may be sporadic in biopsy tissue; additional sections may be required for them to be seen.

Foreign bodies appear to facilitate infection. This association has been most commonly observed with IUCDs and pelvic actinomycosis.[55] Associations with actinomycosis and foreign material elsewhere are less strong. Aspirated, ingested, or implanted foreign bodies may contribute to pathogenesis via facilitating the growth and survival, and biofilm formation.

Cases of actinomycosis have been described in the settings of steroid use,[56] anti–TNF-α agents,[57,58] bisphosphonate treatment,[59] radionecrosis,[59,60] acute leukemia during chemotherapy,[61] organ transplantation,[62] common variable immunodeficiency,[48] chronic granulomatous disease,[63] and human immunodeficiency virus (HIV) infection.[64] Ulcerative mucosal lesions (herpes simplex virus, cytomegalovirus, chemotherapy) and abnormalities in host defenses likely facilitated the development of actinomycosis in some HIV-associated cases; however, it remains unclear which arm(s) of the host defense are critical in preventing or controlling this infection and the degree to which the incidence of infection is increased in these settings.

CLINICAL MANIFESTATIONS

Oral-Cervicofacial Disease

Actinomycosis most commonly occurs and is best recognized in the oral-cervicofacial location, with a mean of 55% of cases.[49]

Oral-cervicofacial disease can manifest as a soft tissue swelling, an abscess, a mass lesion,[49,65] or, occasionally, an ulcerative lesion.[66] The diagnosis of actinomycosis not only should be considered in the classic setting of a painless mass at the angle of the jaw (Fig. 254.1) but should be included in the differential diagnosis of any lesion in the head and neck region. When lesions appear solid, neoplasm is the usual diagnostic consideration. Pain, fever, and leukocytosis are variably present.[49] Soft

FIG. 254.1 Submandibular actinomycotic abscess.

tissue infections of the head and neck may also manifest as chronic, recurring abscesses, particularly if the treatment course is short.

Periapical and endodontic infection caused by *Actinomyces* probably occurs far more frequently than is recognized.[67] Appropriate dental intervention and antibiotic therapy usually result in cure before more extensive disease develops.

The most common location for diagnosed actinomycosis is the perimandibular region, but the cheek, submental space, retromandibular space, and temporomandibular joint also may be affected.[68,69] As noted, a hallmark of this disease is the potential for contiguous extension. Spread to the skin may result in sinus tract(s) formation, and these can spontaneously close and open elsewhere. The overlying skin often develops a bluish or purplish red hue. Involvement of the muscles of mastication frequently occurs, resulting in trismus.[1] Associated mandibular periostitis or osteomyelitis may also be present but is surprisingly infrequent.[70] A lytic lesion, rarefaction with sclerosis, or sclerosis alone may be seen, and this latter pattern may be confused with tumor.[71] Maxillary disease, including osteomyelitis, occurs less frequently.[72] Maxillary and ethmoid sinusitis may occur as isolated disease or can be concomitant with infection of the maxilla.[73,74] The hard palate may also be involved, with presentation as a mass lesion.[1,75]

Two clinical settings more recently have been recognized for contributing to an increased incidence of actinomycotic infection of the mandible and maxilla.[59] The first is infected osteoradionecrosis, a complication of radiation therapy used in the treatment of head and neck cancer. The second has been termed *bisphosphate-associated osteonecrosis* (Fig. 254.2). Bisphosphonates are increasingly used to reduce bone disease, particularly due to multiple myeloma and for the prevention of osteoporosis. Although our understanding of the pathogenesis of these syndromes remains incomplete, it appears that the first insult is radiation therapy or bisphosphonates, or both, altering the local host defenses, followed by disruption of the mucosa, usually from dental procedures, thereby enabling *Actinomyces* to access and infect the gingiva and bone.[76,77]

Isolated masses or ulcerative lesions can also occur in the tongue,[78] vallecula,[79] nasal cavity,[80] nasopharynx,[81] soft tissues of the head and neck,[49,82] salivary glands,[83] patent thyroglossal duct,[84] thyroid,[85] branchial fistula or cleft cyst,[86] and hypopharynx, larynx, or both.[87,88] Although grains are frequently seen in tonsillar clefts at histopathologic assessment of excised tonsils, they appear not to be the cause of recurrent tonsillitis or obstructive tonsillar hypertrophy. The absence of a pathologic tissue reaction around the grain makes a causal role for both of these entities unlikely.[89–92]

Actinomycosis is also an uncommon but important cause of otitis media; untreated cases may result in fatal extension into the mastoid and then the CNS. It is characterized by numerous episodes of otitis media that transiently respond to conventional short-course therapy and resistance to myringotomy. Diagnosis can be made through pathologic and microbiologic examination of infected material from the affected middle ear that may appear to be a cholesteatoma.[93] Infection of the external ear and temporal bone may occur from the spread of middle ear disease.

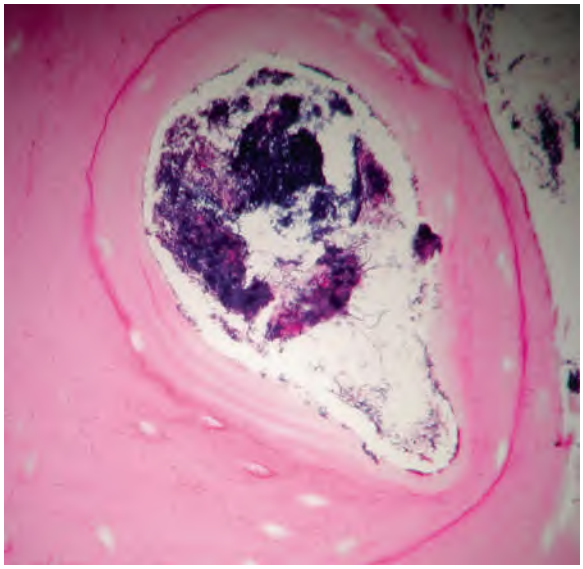

FIG. 254.2 Maxillary osteomyelitis due to *Actinomyces viscosus* in a patient with multiple myeloma who was treated with bisphosphonates and underwent several dental procedures. Pictured is a sulfur granule within necrotic maxilla.

Actinomyces and *P. propionicum* can cause lacrimal canaliculitis.[94,95] *Actinomyces* also has caused postoperative endophthalmitis after intraocular lens implant[96] or intravitreal injection,[97] and keratitis after laser-assisted in situ keratomileusis.[98]

The scenario of temporary improvement with a short course of empirical antibiotic therapy, followed by relapse, should always arouse suspicion for actinomycosis, regardless of the location. As the disease spreads to adjacent structures, there is little regard for normal tissue planes. Computed tomography (CT) scans or magnetic resonance images usually reveal an infiltrative, well- or ill-defined mass with inflammatory changes; associated lymphadenopathy is uncommon.[99,100] Extension to any contiguous structure may occur, including the carotid artery, orbital cavity, cranium, cervical spine, trachea, or thorax.[101,102,103,104]

Thoracic Disease

Thoracic involvement comprises approximately 15% of cases of actinomycosis.[105] Aspiration of organisms from the oropharynx is the usual source of infection, which may be facilitated by foreign material or foreign bodies. Direct extension can occur from disease in either the head and neck or the abdominal cavity; however, such secondary spread has become increasingly uncommon since the advent of efficacious antimicrobial therapy.

The most common clinical presentation is an indolent, slowly progressive process that involves some combination of the pulmonary parenchyma and pleural space. Chest pain, fever, weight loss, and, less commonly, hemoptysis are prominent symptoms, and a cough, when present, is variably productive.[105,106] A relapsing pneumonia after a short treatment course should make actinomycosis a consideration. There are no specific radiographic manifestations, and any lobe may be involved. Cavitary disease may develop and is more readily detected with CT scans because multiple small cavities are more common than large ones.[107] Hilar or mediastinal adenopathy may be present. The usual appearance is either a mass lesion or pneumonia with or without pleural involvement (Fig. 254.3).[100,108] Pleural thickening, effusion, or empyema is present in more than 50% of cases of thoracic actinomycosis (see Fig. 254.3B). Rarely, actinomycosis may manifest as an isolated effusion. The extension of an empyema into or through the chest wall (empyema necessitatis) should raise suspicion for this disease (see Fig. 254.3A).[109] Pulmonary disease that extends across fissures or pleura (see Figs. 254.3C and 68.2A), involves the mediastinum, or has contiguous bony disease should suggest actinomycosis.[108] In the absence of these classic scenarios, however, thoracic actinomycosis is almost never suspected. It is mistaken

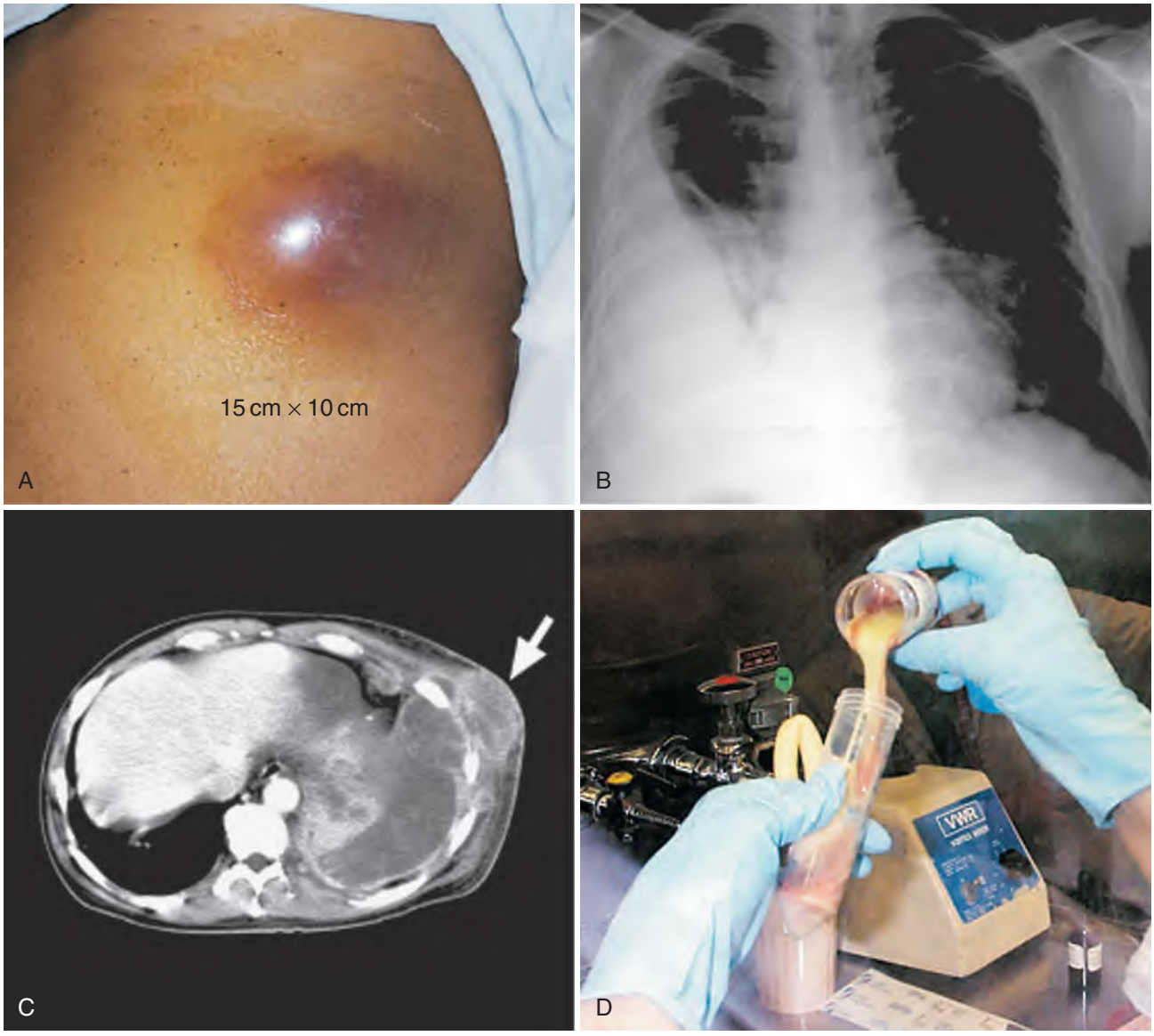

FIG. 254.3 Thoracic actinomycosis. (A) Chest wall mass. (B and C) Chest radiograph and computed tomography demonstrating the pulmonary infiltrate, pleural effusion, and pleural and chest wall extension *(arrow).* (D) Purulent pleural fluid obtained by means of aspiration. *(Courtesy Dr. C.-B. Hsiao.)*

either for malignant disease, with the diagnosis made by the pathologist after resection, or for an empyema or pneumonia secondary to more usual causes. Tuberculosis, nocardiosis, histoplasmosis, blastomycosis, cryptococcosis, mixed anaerobic infection, bronchogenic carcinoma, lymphoma, mesothelioma, and pulmonary infarction are among the entities confused with pulmonary actinomycosis.[106]

Less common manifestations of thoracic actinomycosis include multiple pulmonary nodules, miliary disease, infection of surgical bronchial stumps, and endobronchial lesions, which may be associated with aspirated foreign bodies.[110,111,112] Primary breast disease either manifests as a persistent or recurring abscess(es) or mimics malignancy.[113] Breast abscess is usually unilateral and nonlactional. The *Actinomyces* species are often not those typical of classic actinomycosis. Infection of a mammary prosthesis has also been described.[114]

Endocarditis, Pericarditis, and Mediastinal Disease

Mediastinal actinomycosis is an uncommon event. The structures within the superior, anterior, middle (heart), or posterior mediastinum can be involved alone or in combination, resulting in a diverse array of clinical presentations. Infection usually results from contiguous spread from the thorax but can arise from perforation of the esophagus, chest trauma, or extension of head and neck or abdominal disease.[115] Involvement of cardiac structures represents the majority of mediastinal infections reported. Pericarditis is most common and may be initially asymptomatic or hemodynamically insignificant; but if it is allowed to progress, cardiac tamponade and constrictive or adhesive pericarditis will develop.[4] Less frequently, myocardial, endocardial, or valvular infection occurs, either via extension from the pericardium[116] or by hematogenous seeding.[117] Involvement of the left common carotid, left subclavian, and aortic arch can occur with superior mediastinal disease.[118] Anterior mediastinal involvement may manifest as an isolated mass or, rarely, superior vena cava syndrome.[119] Concomitant anterior chest wall infection is common, but associated sternal disease is rare. Posterior mediastinal involvement results variably in paraspinous muscle and soft tissue disease, esophageal fistula or encasement, or vertebral body infection. Because of the slow progression of the disease, both vertebral body destruction and new bone formation occur, resulting in a mottled, saw-toothed, or honeycombed appearance of bone on radiograph. The transverse processes, and with disease progression the pedicles and spinous processes, are similarly involved as the bodies, in contrast to their usual sparing with tuberculosis. The corresponding posterior ends of ribs are usually involved, and a typical wavy periostitis may be present, but, unlike in tuberculosis, vertebral body collapse and disk space narrowing are not

usually seen. Extension to the epidural space with spinal cord compression may occur.[120] Primary esophageal disease with and without HIV infection has also been described.[64]

Abdominal Disease

The proportion of reported cases involving the abdomen averages 20%.[49] Any disease, traumatic event, or surgical intervention that allows the agents of actinomycosis to breach the gastrointestinal mucosa has the potential to be complicated by this infection. Appendicitis, especially with perforation, is the most common predisposing event and is associated with 65% of the cases of actinomycosis originating in the abdomen. As a result, the right iliac fossa is the most frequent primary site of abdominal disease, and right-sided abdominal infection is more common than left. It is also one of the potential inciting events for tubo-ovarian infection. Diverticulitis or foreign body perforation of the transverse or sigmoid colon tends to be associated with left-sided disease and accounts for 7.3% of cases, a surprisingly low percentage considering the incidence of diverticulitis. The loss of gastric mucosal integrity from peptic ulcer disease, gastrectomy, or gastric bypass is associated with 4.4% of cases.[121] Additional associations include antecedent bowel surgery, spillage of bile or gallstones during laparoscopic cholecystectomy,[122] typhoid fever, amebic dysentery, chicken or fish bones, trauma, and hemorrhagic pancreatitis. Interesting to note, actinomycosis rarely develops as a consequence of Crohn disease or ulcerative colitis.[123] In a number of cases, the inciting condition is not always apparent. It is important to keep in mind that ascension of IUCD-associated pelvic actinomycosis has become an increasingly recognized source of abdominal disease.[124] Hematogenous dissemination and extension from the thorax are other portals of entry.

As a consequence of the flow of peritoneal fluid, direct extension of primary disease, or both, virtually any abdominal organ, region, or space can be involved, either alone or in combination, regardless of the initial site of infection. Abdominal actinomycosis is perhaps the greatest diagnostic challenge. This infection is rarely considered before the clinical laboratory or pathologist establishes the diagnosis. Months to years usually pass from the time of the inciting event to clinical recognition of this indolent disease.[50] Associated symptoms are generally nonspecific, with fever, weight loss, change in bowel habits, abdominal pain, or a sensation of a mass being most common. Abdominal actinomycosis usually manifests either as an abscess or as a firm-to-hard mass lesion that is often fixed to the underlying tissue and mistaken for tumor.[125] Sinus tracts or extension to either the abdominal wall or perianal region or between the bowel and other organs may develop and mimic inflammatory bowel disease (Fig. 254.4). CT findings usually demonstrate a mass lesion with focal areas of decreased attenuation or a thick-walled cystic mass; enhancement is most often heterogeneous, and adjacent bowel is thickened. Lesions often appear invasive, suggesting a tumor, but associated lymphadenopathy is uncommon.[100,126,127] With colonic involvement, mucosal nodules with associated inflammation may be observed.[128]

Perirectal or perianal disease may result from extension of pelvic infection or, less commonly, abdominal disease. Primary disease occurs with either local mucosal damage or infection of anal crypts. The most common presentation is single or multiple perianal abscesses, sinus or fistula tract formation, or both. Infiltrating masses may develop in the buttock, posterior thigh, scrotum, or inguinal region.[129] Recurrent disease over months to years or wounds that fail to heal after drainage or fistulotomy are clues that should suggest actinomycosis, particularly in the absence of documented inflammatory bowel disease. Strictures of the rectum can also occur and cause an alteration of bowel habits, mimicking primary bowel or metastatic prostatic or pelvic tumors.[130] This presentation is most often due to extension of pelvic disease.

Hepatic infection was present in 5% of all cases of actinomycosis.[50] Spread to the liver occurs via extension from a contiguous abdominal focus or hematogenously from more distant but established abdominal or extraabdominal foci. Most commonly, abdominal surgery occurred several months before the recognition of hepatic actinomycosis.[131] A case associated with a pancreatic stent has also been described.[132] Hepatic involvement is common in disseminated actinomycosis. The entity of primary or isolated disease is presumably hematogenous seeding from cryptic foci. Single or multiple abscesses or lesions suggesting neoplasia are the usual presentation (Fig. 254.5).[133] In general, a more indolent course is observed compared with the more usual causes of pyogenic hepatic abscesses, but companion organisms may contribute to a more

FIG. 254.4 Multiple draining sinuses of the right flank secondary to intraabdominal actinomycosis associated with appendicitis.

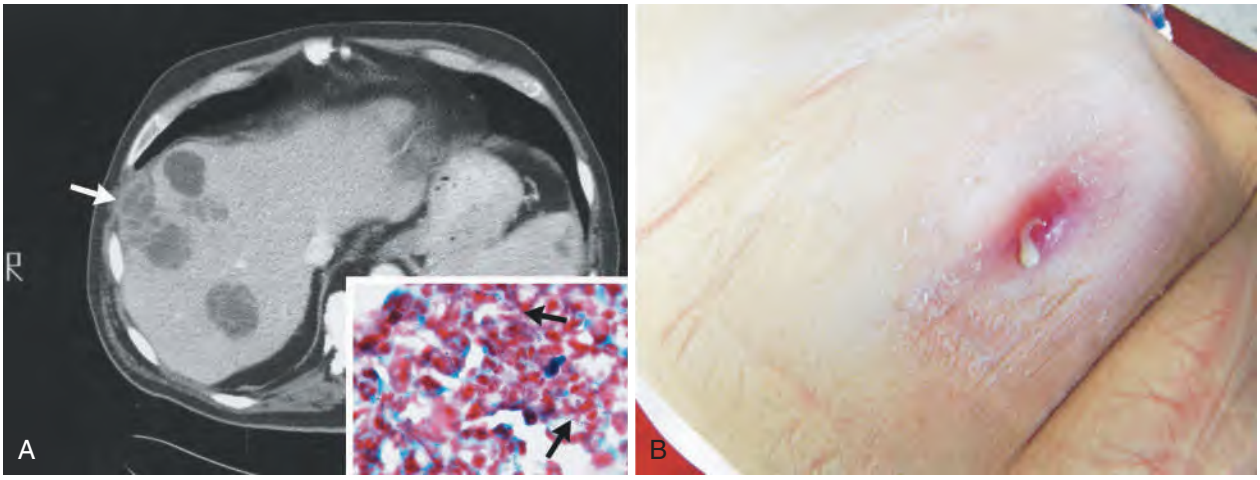

FIG. 254.5 Hepatic-splenic actinomycosis. (A) Computed tomogram showing multiple hepatic abscesses and a small splenic lesion due to *Actinomyces israelii* (*inset:* Gram stain of abscess fluid demonstrating beaded filamentous gram-positive rods). Arrow demonstrates extension outside of the liver. (B) Subsequent formation of a sinus tract. *(From Saad M: Actinomyces hepatic abscess with cutaneous fistula.* N Engl J Med. *2005;353:e16.)*

acute presentation.[134] Symptoms and laboratory findings often point to the right upper quadrant, but liver functions test results may be normal. The presently available imaging modalities and percutaneous diagnostic techniques have allowed for an increasing number of cases to be diagnosed without surgery. The intrahepatic mass is usually mistaken on imaging for a malignancy.[131,135] Percutaneous biopsies may fail to be diagnostic because sulfur granules are in scattered foci.[135] Uncommon presentations or sequelae of hepatic actinomycosis include cholangitis, portal vein occlusion or thrombosis, cholestasis, and extension into the thorax.[136,137] Splenic infection is less common.[138]

Actinomycosis of the gallbladder manifesting as cholecystitis or suspected neoplasm can occur but is exceedingly rare,[4] as is pancreatic involvement.[139] "Primary" actinomycosis of the omentum, abdominal wall, and retroperitoneum has been reported, but the majority of these cases are likely due to secondary spread from a cryptic or obscured abdominal source.[140] Isolated peritonitis associated with peritoneal dialysis has also been reported.

All levels of the urogenital tract can be infected by the agents of actinomycosis. Renal involvement can occur as either a result of hematogenous dissemination from a cryptic or defined focus or via direct extension within the pelvis, peritoneum, or thorax. The disease usually manifests as pyelonephritis, renal carbuncle, or perinephric abscess, and is usually mistaken for tuberculosis, neoplasm, or infection from the usual bacterial agents.[141,142] Hematuria and pyuria are often present, and *Actinomyces* can be successfully detected in the urine with appropriate stains and anaerobic cultures. Renal arteriography usually demonstrates a normal or diminished pattern of vascularization. Extension from pelvic disease or rectal disease may result in (1) ureteric obstruction, (2) infiltration, compression, or encasement of the bladder that can lead to hydronephrosis and renal failure, (3) a pubic mass, or (4) vesicocolic, ileovesical, vesicouterine, or vesicocutaneous fistulas.[143,144] Prostatic, testicular, primary vesical, penile, penile prosthesis, pilonidal sinus, and urachal involvement have been described.[42,145–148] Secondary membranous glomerulopathy that resolved with treatment of pelvic actinomycosis has also been described.[149]

Pelvic Disease

Actinomycotic involvement of the pelvis may occur as a consequence of an intraabdominal inciting event, such as appendicitis or rectal disease. However, the most common portal of entry is ascension from the uterus in association with the presence of any type of IUCD, a widely recognized risk factor for pelvic infection.[150,151] Pelvic infection also has been described with oocyte retrieval,[35] with endometrial curettage, and with other pelvic foreign bodies, including pessaries, an endocervical contraceptive device, retained cervical cerclage, a retained hairpin used for an abortion, surgical mesh, and a retained intrauterine fetal bone.[152–154] Although disease rarely develops within the first year after IUCD placement, the risk of infection likely increases with time.[150,151] On average, an IUCD is in place for 8 years in pelvic actinomycosis-associated cases. Pelvic actinomycosis also has manifested after IUCD removal, thereby warranting diagnostic consideration in this setting.[155] Although the precise risk of IUCD-associated actinomycosis has not been quantitated, it appears to be small.

Presentation is typically indolent, with fever, weight loss, abdominal pain, and abnormal vaginal bleeding or discharge being common symptoms. The earliest form of pelvic actinomycosis associated with an IUCD may be endometritis. A pelvic mass or unilateral or bilateral tubo-ovarian abscess represents the next stage of disease progression (Fig. 254.6), which if untreated evolves into a "frozen pelvis" mimicking malignancy. Disease frequently involves the ureters, bladder, or both, resulting in hydroureter and hydronephrosis. Rectal involvement is also common, and entrapment or impingement of small or large bowel may cause fistula or bowel obstruction.[156] Extension to the abdominal wall may lead to sinus tract development. In contrast to malignancy and tuberculosis, ascites and lymphadenopathy are uncommonly observed with pelvic actinomycosis.[157] CA-125 levels may be elevated, especially with more extensive disease, further contributing to deception.[24,156,157] However, CT and magnetic resonance imaging (MRI) may suggest actinomycosis[158] and, if considered, a minimally invasive diagnostic procedure can be performed, thereby ensuring that surgical intervention is appropriately curtailed.[159] Rarely, the presentation of acute peritonitis, disseminated peritoneal lesions, pelvic bone involvement, extension to the thorax, or hematogenous dissemination may occur.[150,160,161]

FIG. 254.6 Intrauterine contraceptive device (IUCD)–associated pelvic actinomycosis. An IUCD encased by endometrial fibrosis *(solid arrow)*, paraendometrial fibrosis *(open arrow),* and an area of suppuration *(open arrowhead)* can be appreciated.

Actinomyces-like organisms (ALOs) are observed on average in 7% of Papanicolaou-stained cervical specimens of women who use an IUCD.[162] This finding alone has a low positive predictive value for diagnosing pelvic infection. The detection of ALOs in the absence of symptoms warrants patient education and close follow-up but not removal of the IUCD, unless an equally suitable means of contraception can be agreed on.[162,163,164,165] Considering the overall woman-years of IUCD use and the limited number of reported cases of pelvic actinomycosis, the risk appears to be small, but the consequences of infection are significant. Therefore, in the absence of more data, it would appear prudent to remove IUCDs if symptoms of pain, abnormal bleeding, or discharge cannot be attributed to other pathogens, regardless of whether *Actinomyces* or ALOs are detected. A 14-day course of a penicillin or tetracycline should be given for treatment of possible actinomycotic endometritis.

Central Nervous System Disease

Actinomycosis of the CNS is rare. The source may be hematogenous, or it may develop through extension of oral-cervicofacial disease. Individuals with hereditary hemorrhagic telangiectasia are at increased risk for brain abscess, with *Actinomyces* organisms being potential etiologic agents.[166] In one report, the mean duration of symptoms before diagnosis was 2.1 months, longer than with most causes of CNS infections.[167] Headache and focal neurologic findings are the most common clinical features. Fever is variably present.

Single or multiple brain abscesses are the usual disease manifestation, most commonly appearing on CT or MRI scans as a ring-enhancing lesion(s) with a thick wall that may be irregular or nodular.[168] Multiloculation, edema, and contiguous areas of low attenuation may be present. These findings are also consistent with brain abscess and tumor.[100,102] Less commonly, solid nodular or mass lesions termed *actinomycetomas* or *actinomycotic granuloma* occur. Magnetic resonance perfusion and spectroscopy findings have also been described.[169]

A chronic meningitis may develop as a consequence of a parameningeal focus, primarily the middle ear or paranasal sinuses. Presentation may be acute, particularly with rupture of an abscess into the subarachnoid space, or chronic, with the cerebrospinal fluid having a normal or low glucose level, elevated protein, lymphocytic pleocytosis, and negative culture. Primary meningitis has also been described.[170] Diagnosis can be made by means of microscopic examination or, rarely, culture of cerebrospinal fluid.

Extension of disease from foci of cranial osteomyelitis, paranasal sinus, or middle ear disease can result in cranial epidural or subdural infection or both.[171] Spinal epidural disease may occur from direct extension of abdominal, thoracic, or cervical disease; is usually associated with a contiguous osteomyelitis; and may result in spinal cord compression.[172] Cavernous sinus syndrome, spinal intrathecal, and ventriculoperitoneal shunt infection have also been reported.[30,173–175]

Musculoskeletal Disease

Actinomycotic infection of the bone is usually a result of an adjacent soft tissue infection but may also be incited by trauma (e.g., fracture of the mandible) or hematogenous spread. Presently, the mandible and maxilla, in association with and without osteoradionecrosis and bisphosphonate therapy, are the most frequent sites of involvement[59,76] (see "Oral-Cervicofacial Disease" earlier). In the preantibiotic era, the unchecked spread of thoracic and abdominal disease resulted in vertebral infection being the most common site for osseous actinomycosis (see "Thoracic Disease" earlier). Actinomycosis of the skull, ribs, clavicle, sternum, scapula, or pelvis may also occur from extension of oral-facial, thoracic, or abdominal disease. The clinical and radiographic features of infection in these locations were discussed earlier.

Infection of the extremities, although uncommon, often poses diagnostic difficulties. Blunt or penetrating trauma, injections, surgery, and hematogenous dissemination from apparent or cryptic foci are initiating events.[12,176,177,178,179] Skin, subcutaneous tissue, muscle, and bone may be involved alone or in various combinations. Cutaneous sinus tracts or abscesses are present in the majority of cases, as is bony involvement in the form of periostitis or acute or chronic osteomyelitis. Presentation is usually indolent. A mycetoma (Madura foot) is an indolent soft tissue infection, usually of the foot, that progresses over months to years. Bacteria or fungi are introduced from soil or vegetation into the soft tissue by minor trauma. When bacterial agents are the cause, the term "actinomycetoma" may be used, whereas the term "eumycetoma" may be used when fungi are the offending agents. Despite the name being suggestive of *Actinomyces* as a causative agent, actinomycetoma is usually caused by *Nocardia* or *Actinomadura* sp.[180] (see Chapter 261).

Actinomycotic infections of hip and knee prostheses have been described in several reports.[181,182] Early presentations suggest that *Actinomyces* may be introduced perioperatively, whereas late presentations suggest hematogenous seeding from a cryptic distant site. Actinomycotic septic arthritis of the knee has developed in association with trauma or injection of hyaluronate,[183] or as a consequence of hematogenous seeding. Popliteal cyst infection has also been described.[184] Actinomycosis is rarely a result of a closed-fist injury.

Disseminated Disease

Although uncommon, all of the agents of actinomycosis are capable of hematogenous dissemination resulting in multiorgan involvement. *A. meyeri* appears to have the greatest capability of causing this syndrome. Disease in any location may serve as the source for spread. The lungs and liver are the most commonly affected organs, and the presentation of multiple nodules mimics disseminated malignancy. The kidneys, brain, spleen, skin, soft tissues of the extremities, and, less commonly, the heart valves may also be infected in various combinations. The clinical presentation may be surprisingly indolent when the extent of disease is appreciated.[12,177,185]

DIAGNOSIS

The diagnosis of actinomycosis, particularly when it mimics malignancy, is rarely considered. All too often the first mention of actinomycosis is from the pathologist after extensive surgery has been performed. However, an increasing body of evidence supports that medical therapy alone is usually sufficient for cure, including extensive invasive disease.[159,167,186,187] Therefore the challenge for the clinician is to consider the possibility of actinomycosis so that this unique infection can be diagnosed in the least invasive fashion and unnecessary surgery can be avoided.[188] Clinical or radiographic presentations that suggest actinomycosis have been discussed previously.[100] Of note, actinomycotic disease has demonstrated hypermetabolism on ^{18}F-fluorodeoxyglucose–positron emission tomography (FDG-PET).[189] Aspirations and biopsies (with or without CT or ultrasound guidance) are being successfully used to obtain clinical material for diagnosis, although surgery may be required.[167,190–192,193] However, transbronchial biopsies have been less successful in providing diagnostic material for thoracic actinomycosis.[112]

The single most helpful diagnostic maneuver for actinomycosis is the demonstration of sulfur granules—a microscopic or macroscopic in vivo matrix of bacteria, calcium phosphate, and host material—in pus (Fig. 254.7A), via cytopathologic evaluation,[194] or in a histologic section of a tissue specimen (Fig. 254.7B–C). Microscopically, granules are round, oval, or horseshoe shaped. Although bacilli within the granule are rarely visible with hematoxylin-eosin stain, the use of tissue Gram stains, Gomori methenamine silver, and Giemsa stains will demonstrate gram-positive, filamentous, branching bacteria at its periphery (Fig. 254.7). On hematoxylin-eosin stain the granules may be eosinophilic or variably surrounded by a radiating fringe of eosinophilic clubs. This eosinophilic, proteinaceous coating around organisms in tissue has been called the *Splendore-Hoeppli phenomenon.* It represents an ill-defined host response but may be accounted for, in part, by eosinophil granule major basic protein. In tissue sections, granules are most commonly found within microabscesses. Although they may be abundant, they are usually scanty. Only a single granule was identified from 26% of specimens in one series.[50] The examination of additional histopathologic sections and the use of positively charged slides to optimize adhesion increases diagnostic sensitivity.[195] Macroscopic granules are usually yellow (hence their name, sulfur granule) but may be white, pinkish gray, gray, or brown. Granules also may be identified grossly from draining sinus tracts, other purulent material, or sputum, but they may easily escape notice unless sought. When pus is poured down the side of a glass tube, granules will adhere and are identified more readily. A magnifying glass may aid in their identification.

A combination of the clinical scenario and stains of the granule can be used to distinguish actinomycotic sulfur granules from others. The Splendore-Hoeppli phenomenon is not specific for actinomycosis and can also be seen in other chronic infections, such as schistosomiasis, orbital pythiosis, cutaneous larval migrans, sporotrichosis, basidiobolomycosis, aspergillosis, blastomycosis, *Malassezia* folliculitis, mycetoma, botryomycosis, nocardiosis, and some noninfectious entities.[196] Therefore a special stain (e.g., Gram, silver) is needed to show that the granule is composed of branching bacteria and not fungi (eumycetoma), cocci, or bacilli (botryomycosis). Botryomycosis is a chronic bacterial soft tissue and rarely visceral infection that produces loose clumps of bacteria that resemble granules. Etiologic agents include *Staphylococcus, Streptococcus, Escherichia, Pseudomonas,* and *Proteus,* which are easily distinguished from the agents of actinomycosis by the presence of cocci or nonbranching bacilli.[197] If branching bacteria are seen on staining of the granule and the infection did not originate in subcutaneous tissue (a characteristic of actinomycetoma) or tonsillar tissue (see "Oral-Cervicofacial Disease" earlier), then the diagnosis of actinomycosis is established. Clinically, nocardiosis may closely resemble actinomycosis but does not form granules in visceral lesions.[198] However, when *Nocardia* is the causative agent of actinomycetoma, granules are formed. On Gram stain, the branching gram-positive bacilli are indistinguishable from *Actinomyces,* but they may be stained by a modified Fite acid-fast stain, whereas *Actinomyces* is not.[194] The granules formed by the fungal agents of eumycetoma show branching hyphae on periodic acid–Schiff or Gomori methenamine silver stain (see Chapter 261). Specimens obtained from mucus-producing locations, such as the endocervix, the bronchus, or ventricular colloid cysts, may possess pseudoactinomycotic radiate granules. If hematoxylin-eosin stain alone is used, they may mimic actinomycotic granules, as a central region is bordered by the Splendore-Hoeppli phenomenon. However, special stains will reveal the absence of microorganisms.[199]

The bacteriologic identification of one of the agents of actinomycosis from a sterile site will confirm the diagnosis. However, the microbiologic identification occurs in only a minority of cases.[50] This is due, in part, to the fact that the agents of actinomycosis are exceedingly sensitive to a wide variety of agents, and even a single dose can interfere with their isolation. Therefore the most important step for optimal microbiologic yield is the avoidance of any antimicrobial therapy before obtaining the specimen. Because these organisms are normal inhabitants of the oral

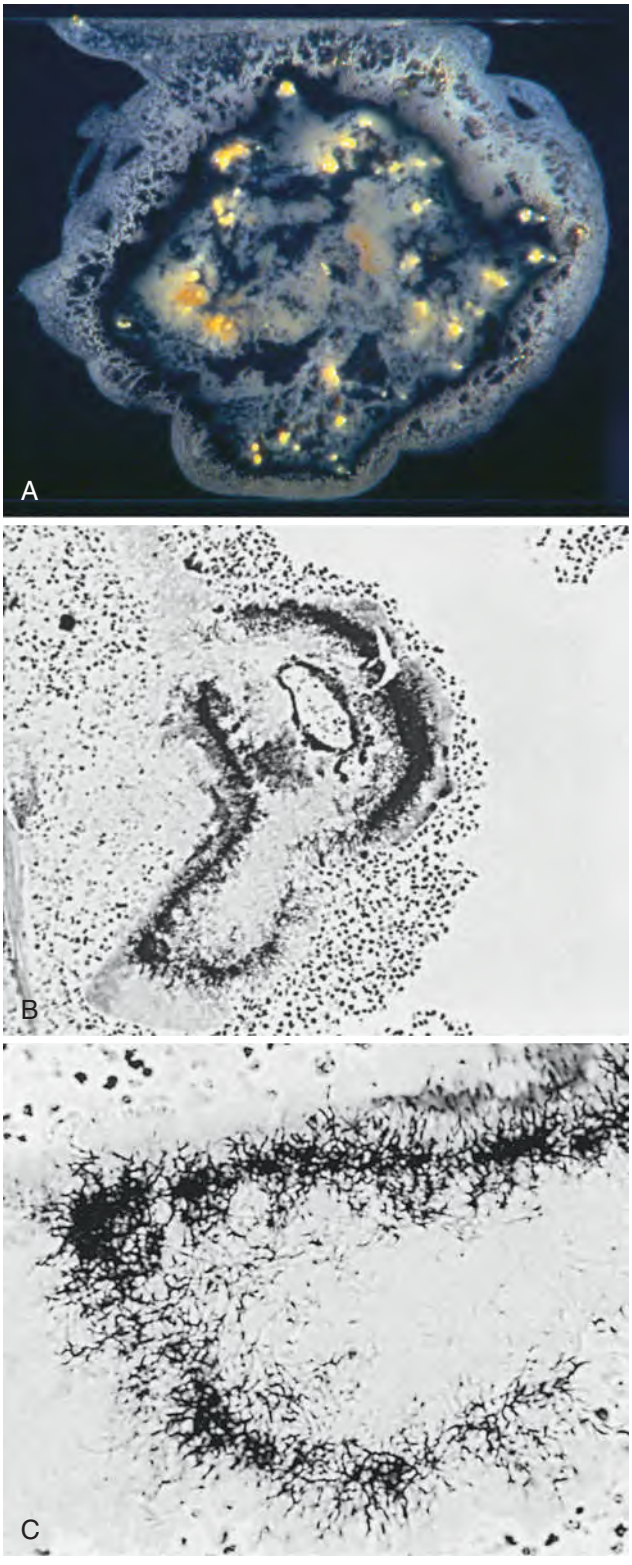

FIG. 254.7 (A), Macroscopic actinomycotic sulfur granules demonstrated by placing pus between two slides. (B) Microscopic actinomycotic sulfur granule surrounded by inflammatory cells. (Hematoxylin-eosin stain, ×250.) (C) Actinomycotic granule. Brown and Brenn stain (×1000) demonstrates the delicate, branched filaments of *Actinomyces.*

cavity and female genital tract, the identification of organisms alone, in the absence of sulfur granules or an appropriate clinical syndrome, from sputum, bronchial washings, and cervicovaginal secretions is of little significance. Isolation of *Actinomyces* from blood cultures in the absence of defined infectious focus may represent contamination or transient bacteremia from a mucosal site of colonization, in which case treatment may not be necessary.[200]

Although most strains of *Actinomyces* are microaerophilic (except *A. meyeri* and *A. neuii,* which can grow aerobically), strict anaerobic processing and anaerobic growth should be used for primary isolation. The laboratory should receive specimens expeditiously or in anaerobic transport media. Tissue, pus, or sulfur granules are ideal, and swabs should be avoided. The microbiology laboratory should be alerted before receiving any specimen that could harbor the agents of actinomycosis. A Gram stain of the specimen is usually more sensitive than culture, especially if the patient has received prior antibiotics. If granules are identified, they should be washed and crushed between two slides for examination (see Fig. 254.7A). The agents of actinomycosis are non–spore-forming, branching, filamentous rods, except for *A. meyeri* and *A. neuii,* which are small and nonbranching. Growth usually appears within 5 to 7 days, but primary isolation may take up to 2 to 4 weeks. Although specialized media are not required, the use of semiselective media may increase isolation rates of *Actinomyces,* particularly when more rapidly growing organisms are also present.[201] *A. israelii* characteristically forms a "molar tooth" colony on agar and grows as clumps within broth. *A. odontolyticus* colonies usually appear rust-brown or red colored. *Actinomyces* are indole negative. Traditional identification is based on these features in combination with tests for urease, catalase, gelatin hydrolysis, and fermentation of cellobiose, trehalose, and arabinose. However, classification of *Actinomyces* based on phenotypic tests may result in misidentification.[16] Likewise, identification with the Vitek 2 ANC card is not yet optimal.[202] Sequencing or restriction analysis of amplified 16S ribosomal DNA can assist in resolving ambiguities in identification of the non–spore-forming, gram-positive rods.[16,203,204]

Actinomycosis should not be excluded if not cultured or the characteristic pathologic findings are not present, especially when only small quantities of tissue are available. Sulfur granules are easily missed and only fibrosis with or without inflammation may be identified. As noted, multiple sections may increase diagnostic sensitivity. The use of 16S rRNA gene amplification and sequencing by clinical microbiology laboratories is increasing, thereby enhancing diagnostic sensitivity and specificity.[205,206] MALDI-TOF mass spectrometry holds similar promise, but databases are still in the process of being optimized.[10,206] A combination of appropriate microbiologic, molecular, and pathologic studies will maximize the chances of success.

THERAPY

The discovery and use of penicillin in the treatment of classic actinomycosis has dramatically altered the course of this disease. Two principles of therapy, based on the clinical experience of the past 70 years, have evolved. It is necessary to treat this disease both with high doses and for a prolonged period of time. The need for intensive treatment is presumably due to the drugs' poor penetration of the thick-walled masses common in this infection and/or the sulfur granules themselves, which may represent a biofilm. Although therapy needs to be individualized, daily treatment with 18 to 24 million units of penicillin given intravenously for 2 to 6 weeks, followed by oral therapy with penicillin or amoxicillin for 6 to 12 months, is a reasonable guideline for serious infections and bulky disease. Interesting to note, a study on the treatment of thoracic actinomycosis had a 22% (5/23) failure rate with medical therapy, but these patients received only 0 to 2 days of initial parenteral therapy.[207] If the duration of therapy is extended beyond the resolution of measurable disease, then relapses, one of the clinical hallmarks of this infection, will be minimized. CT and MRI studies are generally the most objective modalities to accomplish this goal. MRI scans are often more sensitive than CT scans for detecting residual infection and should be employed if possible, particularly in areas where the consequences of relapse are particularly significant (e.g., the CNS).[208] In one case, PET appeared to be more sensitive than CT for monitoring disease resolution.[111]

Cases with less extensive involvement, particularly in the oral-cervicofacial region, may be cured with a shortened duration of therapy.[209,210] Furthermore, in some cases of low bulk, oral-cervicofacial disease therapy can be initiated with an oral agent. The treatment course for nonclassic actinomycotic infections—that is, the absence of tissue

TABLE 254.1 Appropriate and Inappropriate Antibiotic Therapy for Actinomycosis

Group 1: Extensive Successful Clinical Experience[b]
Penicillin (3–4 million units IV q4h or amoxicillin 500 mg PO q6h)[c]
Erythromycin (500–1000 mg IV q6h or 500 mg PO q6h)
Tetracycline (500 mg PO q6h)
Doxycycline (100 mg IV q12h or 100 mg PO q12h)
Minocycline (100 mg IV q12h or 100 mg PO q12h)
Clindamycin (900 mg IV q8h or 300–450 mg PO q6h)[d]
Group 2: Anecdotal Successful Clinical Experience
Ceftriaxone[c]
Ceftizoxime
Imipenem-cilastatin
Piperacillin-tazobactam
Group 3: Agents Predicted to Be Efficacious Based on in Vitro Activity
Vancomycin
Linezolid
Quinupristin-dalfopristin
Ertapenem[c]
Azithromycin[c]
Tigecycline
Group 4: Agents That Should Be Avoided
Metronidazole
Aminoglycosides
Oxacillin
Dicloxacillin
Cephalexin
Fluoroquinolones

[a]Additional coverage for concomitant "companion organisms" may be required.
[b]Controlled evaluations have not been performed. Dose and duration require individualization, depending on the host site and extent of infection. As a general rule, a maximum antimicrobial dose for 2 to 6 weeks of parenteral therapy followed by oral therapy for a total duration of 6 to 12 months is required for classical actinomycosis (e.g., tissue invasive, bulky disease), whereas a shorter duration may suffice for less extensive diseases, particularly in the oral-cervicofacial region. Monitoring therapeutic effect with computed tomography or magnetic resonance images is advisable when appropriate.
[c]Agents to consider for home parenteral therapy (see text for details).
[d]Recent in vitro data demonstrated a >20% resistance rate in the majority of species tested.

changes—especially for the more recently described *Actinomyces* spp. is unclear. In the absence of data, a syndrome-based treatment plan is most appropriate.

Extensive successful clinical experience also has been reported for amoxicillin, erythromycin, tetracycline, doxycycline, minocycline, and clindamycin, although it should be noted that in vitro data have demonstrated >20% resistance to clindamycin in most species.[13,211] Anecdotal successes with imipenem-cilastatin,[212,213] ceftriaxone,[214] ceftizoxime,[215] and piperacillin-tazobactam[216] have been reported (Table 254.1). In vitro data demonstrate that vancomycin, quinupristin-dalfopristin, linezolid, rifampin, ertapenem, tigecycline, and azithromycin are active against *Actinomyces* spp.,[13,211,217,218–221,222] although some variation in in vitro susceptibility exists among species. In vitro data also suggest that fluoroquinolones, oxacillin, dicloxacillin, cephalexin, metronidazole, and aminoglycosides should be avoided.[217,223]

For home parenteral therapy, the ease of once-a-day dosing makes ceftriaxone appealing in certain circumstances; however, a greater body of literature supporting its efficacy would be desirable. The availability of portable infusion pumps for home therapy allows for both the appropriate dosing and practical administration of intravenous penicillin. For infections in critical sites (e.g., the CNS), this approach remains the safest until more information regarding other agents is available. The pharmacokinetic properties, availability of oral and parenteral formulations, and potential efficacy of azithromycin and ertapenem also make these agents appealing. Unfortunately, few in vitro and no clinical data exist on their use to treat actinomycosis.

It is unclear whether other bacteria frequently coisolated with the etiologic agents of actinomycosis require treatment, but many of them are pathogens in their own right. Designing a therapeutic regimen that includes coverage for these organisms during the initial treatment course is reasonable. If microbiology is not available, it is important to consider the site of infection when designing empirical coverage. For example, *A. actinomycetemcomitans, E. corrodens, Fusobacterium,* and *Capnocytophaga* are more likely to be coisolates in head and neck infection, whereas the Enterobacteriaceae and *Bacteroides* are more commonly coisolated in abdominal infection.

In the preantibiotic era, surgical removal of infected tissue was the only beneficial treatment. Despite the advent of efficacious antimicrobial therapy, combined medical and surgical therapy is still advocated in some reports. However, the literature supports the approach of initially attempting a cure with medical therapy alone.[159,167,186,187] Successes with antibiotics alone have been reported in cases of extensive disease that initially appeared to be incurable. CT and MRI should be used to monitor the response to therapy.[127,224] In most cases surgery can be avoided altogether or a less extensive procedure will be required. This approach is particularly important when the possibility of sparing critical organs is involved, such as the bladder or reproductive organs in women of childbearing age. In a patient with disease in a critical location (e.g., epidural space, selected CNS disease), with significant hemoptysis,[225] or in whom suitable medical therapy fails, surgical intervention may be appropriate. In the setting of actinomycosis manifesting as a well-defined abscess, percutaneous drainage in combination with medical therapy is a reasonable approach.[133,226]

Actinomycosis has been described in association with HIV infection, steroid use, and lymphoproliferative tumors. Whether these infections were due to disease-associated disruptions of mucosa (e.g., cytomegalovirus infection with HIV infection), host defense abnormalities, immunosuppressive therapy, or some combination of these is unclear. From a treatment perspective, it is reasonable to initially use the same approach as that for noncompromised hosts. Aggressive treatments directed against HIV and minimizing immunosuppressive therapy are also desirable if possible. Although prospective controlled data are not available, when *Actinomyces* organisms are identified in the setting of bisphosphonate-related osteonecrosis of the jaw (BRONJ), a prolonged course of antimicrobial therapy is reasonable and appears to be efficacious. The role of surgical débridement for BRONJ is less clear, but resection of at least necrotic bone seems prudent.[76,227–229]

Usually actinomycosis responds well to medical therapy. However, refractory or perceived refractory disease has been described in HIV-infected individuals and overtly normal hosts. In this setting, basic principles of infectious disease apply. First, exclude infection elsewhere (e.g., intravenous catheter–acquired bacteremia, *Clostridioides difficile* (formerly *Clostridium difficile*) colitis), noninfectious causes, or both (e.g., drug fever, unrelated disease) as being responsible. Next, confirm that high-dose parenteral therapy is being used for initial treatment. Identify and drain significant purulent collections associated with the actinomycotic infection. Consider the possibility that untreated coisolates (companion organisms) may be responsible. Although penicillin-resistant strains or evolution of resistance during therapy has not yet been clearly documented in vivo, this possibility should be considered when more likely scenarios are excluded. Finally, surgery should be considered when infection is refractory to medical therapy, although as stated previously, this can usually be avoided, at least initially.

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The complete reference list is available online at Expert Consult.

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