STATE-OF-THE-ART CLINICAL ARTICLE

Nocardiosis

Phillip I. Lerner

From the Mt. Sinai Medical Center, School of Medicine, Case Western Reserve University, Cleveland, Ohio

Nocardiosis is a localized or disseminated infection caused by a soil-borne aerobic actinomycete, most commonly introduced through the respiratory tract. The pulmonary event in humans may be self-limited and transient or subclinical, or it may progress to an acute, subacute, or chronic process mimicking tuberculous or mycotic infection or a malignancy. Hematogenous dissemination spreads particularly to the nervous system and skeletal soft-tissue structures.

Aerobic actinomycetes are bacteria belonging to the order Actinomycetales, with a complex and evolving taxonomy [1]. *Nocardia* is a genus in the family Nocardiaceae, of that order. Nocardiaceae were misclassified as fungi for many years because they branch into filaments, erroneously thought to be and still sometimes incorrectly referred to as hyphae. Hyphae are extensions of fungal germ tubes, a uniquely fungal characteristic. On the basis of their cell wall components, particularly their cell envelope lipid and peptidoglycan compositions, the prokaryotic actinomycetes are indisputably aerobic bacteria.

Over the past 20 years, more reliable methods for classifying bacteria have refined the taxonomy of the actinomycetes by means of studies of cell wall amino acids and sugars, whole-cell sugars, fatty acids (including mycolic acids), menaquinones, phospholipids, and DNA relatedness. Consequently, many taxa formerly included in the genus *Nocardia* have been reclassified [1].

The taxonomy of nocardioforms, i.e., bacteria that resemble *Nocardia* species organisms, is also complex and evolving. The taxon *Nocardia asteroides,* as currently designated by traditional hydrolysis patterns in the routine microbiological laboratory, is heterogeneous in terms of traits pertaining to biochemistry, morphology, and antibiotic resistance, and it comprises at least three and perhaps six major subgroups [1]. These include *N. asteroides* sensu stricto, *Nocardia farcinica, Nocardia nova,* and ultimately probably several other distinct serotypes and/or biotypes. The other pathogenic *Nocardia* species, *N. brasiliensis, N. otitidiscaviarum,* and *N. transvalensis,* are taxonomically more homogeneous.

Received 5 January 1996; revised 12 February 1996.

Reprints or correspondence: Dr. Phillip I. Lerner, Division of Infectious Diseases, Mt. Sinai Medical Center, One Mt. Sinai Drive, Cleveland, Ohio 44106-4198.

Clinical Infectious Diseases 1996; 22:891–905

1058–4838/96/2206–0001$02.00

McNeil and Brown recently examined the epidemiology and microbiology of the medically important aerobic actinomycetes, framing the *Nocardia* species in proper perspective to related aerobic actinomycetes, which include *Actinomadura* species, *Dermatophilus congolensis, Gordona* and *Rhodococcus* species, and other rare opportunistic pathogenic and thermophilic actinomycetes [1]. A detailed discussion of the current chemotaxonomic criteria for the genus *Nocardia* is beyond the scope of this clinical discussion, and the reader is referred to this timely review, which details the laboratory aspects of recovery, recognition, and identification of the various *Nocardia* species [1].

Classification and Ecology of the Pathogenic Nocardiae

The ubiquitous aerobic and saprophytic actinomycetes are found worldwide in soil and decaying organic plant matter. Pathogenic species of the genus *Nocardia* can be found in house dust, beach sand, garden soil, and swimming pools [1]. Despite the occurrence of nocardiosis in many animals (e.g., cats, dogs, guinea pigs, and cattle), there is no evidence of respiratory spread from infected animals to humans [1, 2]. There is also no evidence of person-to-person transmission, although rare case clusters suggest the possibility of the latter [1]. Nosocomial cases, some in clustered outbreaks, have been described [3]. Investigators of one outbreak, in a renal transplantation unit, located the epidemic strain (type III antigen) within the dust and air of the unit, thus raising concerns that respiratory isolation (e.g., masks, barrier isolation) might be appropriate for some immunocompromised patients [2–4].

N. asteroides is the predominant human pathogen; the other main pathogenic human species, *N. brasiliensis* and *N. otitidiscaviarum,* can usually be differentiated by routine tests employed in the clinical microbiology laboratory. These include analysis of microscopic and colonial morphology and simple biochemical and hydrolysis testing: casein hydrolysis, gelatin liquefaction, and decomposition of tyrosine, xanthine, and hypoxanthine [1].

These standard hydolysis tests, however, fail to delineate the true heterogeneity of the *N. asteroides* taxon. By a combination of methods (i.e., chemotaxonomy, antibiogram analysis, numerical taxonomy, DNA homology, and serological studies), two specific subgroups of the *N. asteroides* complex have now been accepted as distinct species, *N. farcinica* and *N. nova* [1]. Resistance to tobramycin and third-generation cephalosporins helps define *N. farcinica,* whereas *N. nova* is differentiated

from *N. asteroides* and *N. farcinica* by still other phenotypic tests and its unique antibiotic susceptibility pattern [5–7].

N. farcinica infections occur more frequently than previously recognized. Schiff et al. reviewed cases reported from Asia, Europe, and North America, with varying clinical presentations: cerebral abscess and pulmonary and cutaneous infections [8]. Underlying immunosuppressive conditions (such as therapies or leukemia, lymphoma, or HIV infection) were noted in 36% of these cases.

In Germany the changing spectrum of nocardiosis in recent years features *N. farcinica* as the predominant nocardial pathogen (by a 2:1 ratio over all other nocardial pathogens), and it has emerged as an important nosocomial agent in postoperative wound infections [9]. The sex ratio of patients with nocardiosis has shifted from 3:1 to 2:1 (male:female), and the mean age of these patients is now 8 years younger. A high degree of antibiotic resistance (to cefotaxime, cefamandole, and tobramycin) makes treatment of *N. farcinica* infections more problematic. Results of mouse pathogenicity studies suggest that this species may be more virulent than other members of the *N. asteroides* complex; >50% of patients present with disseminated infection [9].

N. nova, first isolated and characterized by Tsukamura in 1982, currently encompasses ~20% of isolates previously identified as *N. asteroides,* according to Schiff et al. [10]. These isolates have a distinct antimicrobial susceptibility pattern (they are the only *Nocardia* species organisms that are susceptible or moderately susceptible to both ampicillin and erythromycin), have a unique mycolic acid pattern, and are uniquely positive for arylsulfatase activity after 2 weeks [7]. Clinical disease associated with these isolates is very similar to that caused by *N. farcinica* and other *N. asteroides* complex isolates [10].

Initially identified as a cause of mycetoma in Africa, *N. transvalensis* is now recognized to cause life-threatening, invasive, and disseminated infections in severely immunocompromised patients [11]. No environmental source has been identified, but soil is the likely reservoir. Therapy for *N. transvalensis* infections is currently problematic, because clinical isolates of this unusual species often demonstrate an unusually high level of resistance to many antimicrobial agents and therapy with trimethoprim-sulfamethoxazole (TMP-SMZ) may not always be effective [1, 10].

N. brasiliensis, which is responsible for mycetoma in Mexico and South America and is the second most frequently isolated aerobic actinomycete in the clinical laboratory, is usually associated with localized cutaneous infections and has not been considered taxonomically heterogeneous [1]. However, 22% of isolates from the United States and 12% from Queensland, Australia, were associated with extracutaneous and/or disseminated diseases [12]. Sixty percent of these "invasive" isolates were susceptible to ciprofloxacin and/or were susceptible to clarithromycin and resistant to minocycline; thus, they appear to represent a new taxon, according to Wallace and collaborators [12].

These "invasive" isolates differ from other *N. brasiliensis* isolates with regard to their hydrolysis of adenine (92% vs. 4%) and β-lactamase patterns on isoelectric focusing, and they display characteristic early mycolic-acid ester peaks in HPLC [12]. Most cases of *N. brasiliensis* infection in the United States originate in the Southeast and Southwest, especially Texas, North Carolina, Oklahoma, and Florida [1, 12].

Pulmonary and systemic infection with *N. otitidiscaviarum* has been documented in both normal and compromised hosts [2]. The remaining isolates now classified as *N. asteroides* sensu stricto demonstrate sufficient phenotypic heterogeneity to suggest that additional subgroups (also differing in epidemiology, virulence, and pathogenesis) will subsequently be uncovered with modern molecular techniques [1, 5, 7].

McNeil and Brown review in detail these complex testing schemata [1]. Rapid and specific identification of *Nocardia* species is also now being pursued by utilization of DNA probes [9]. A PCR identification and typing schema has been initiated in the laboratory of Dr. Richard J. Wallace, Jr. (personal communication; see addendum).

Laboratory Diagnosis of Nocardiosis

The genus *Nocardia* consists of distinctive gram-positive, variably acid-fast, strictly aerobic bacteria that form branched aerial and substrate (vegetative) filaments which, as they age, fragment into pleomorphic rod-shaped or coccoid elements [1]. Colonial morphology, filamentation (lateral, substrate, and aerial branching), and fragmentation are extremely variable among clinical isolates and relate to the composition of the medium employed, the temperature of incubation, and other conditions of culture.

Colonies with abundant aerial filamentous growth have a chalky white or cotton-ball appearance on blood agar and may resemble *Streptomyces* species or, superficially, even some fungi. Aerial filaments distinguish the genus *Nocardia* from related nocardioform gram-positive bacteria (*Rhodococcus, Gordona, Tsukamurella, Actinomadura,* and *Corynebacterium* species) and mycobacteria [1].

The catalase-positive nocardiae grow in the presence of lysozyme in a nutrient broth, whereas most *Rhodococcus, Actinomadura,* and *Streptomyces* species organisms do not. They grow readily over a wide temperature range on most of the simple media used for bacterial, fungal, and mycobacterial growth (e.g., Sabouraud's glucose agar, blood agar, brain-heart infusion agar, and Lowenstein-Jensen agar) [1]. Added CO_2 (10%) promotes more rapid growth. Colonies on solid media may be smooth and moist or may be wrinkly with a velvety surface, because of aerial filamentation (figure 1).

The laboratory must be alerted when nocardial infection is suspected. Nocardiae are slow-growing organisms and may be difficult to recover and identify in the routine of a busy microbiology laboratory. Colonies in pure culture can grow after only 48 hours' incubation, but in mixed cultures of clinical

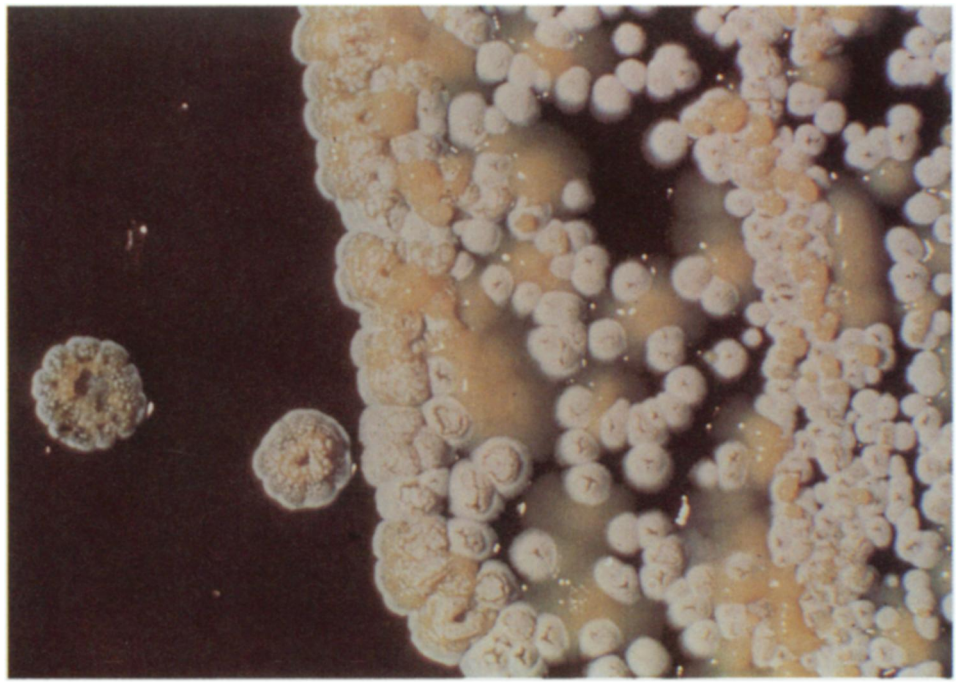

Figure 1. Rugose (wrinkly) colonies of *Nocardia asteroides* on a blood agar plate (original magnification, ×6; reproduced with permission from [2]).

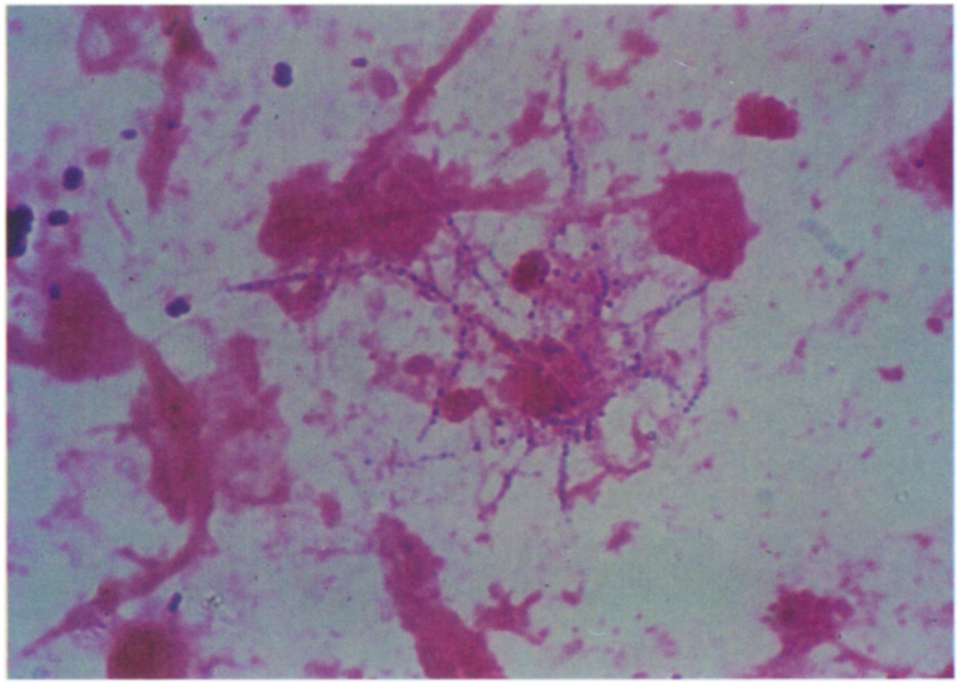

Figure 2. Gram stain of a *Nocardia* species, demonstrating delicate, beaded, branching filaments (original magnification, ×900).

material (e.g., respiratory secretions), other rapidly growing bacteria easily obscure small nocardial colonies; furthermore, colonial characteristics sufficient to arouse suspicion can take several weeks to develop [1].

Delayed growth, unfortunately, may lead to the premature disposal of cultures. Ideally, patients whose specimens are submitted for culture should not be current or recent recipients of antibiotics [2]. Modified Thayer-Martin medium (an antibiotic-containing selective medium for isolating *Neisseria* species) and buffered charcoal–yeast extract agar (for growth of *Legionella* species) also may enhance recovery of *Nocardia* species [1]. Paraffin baiting capitalizes on the ability of aerobic actino-

mycetes (*N. asteroides,* in particular) to utilize paraffin as a sole source of carbon for energy and growth [1].

The importance of microscopic examination of gram-stained clinical specimens cannot be overemphasized, as it is a simple study that can yield a rapid and specific diagnosis [2]. The observation of thin, delicate, weakly to strongly gram-positive, irregularly stained or beaded branching filaments is extremely important in the recognition of *Nocardia* species organisms (figure 2).

Multiple clinical specimens should be submitted for culture since smears and cultures are simultaneously positive in only one-third of cases [2]. The organism can be highly elusive unless pus from a discharging fistula or an abscess is studied. Smears and cultures of specimens from skin lesions are often negative unless the specimens are obtained by biopsy.

Routine blood cultures are not usually positive, but nocardiae can be isolated from blood if biphasic blood culture systems are inoculated and incubated aerobically for up to 30 days and if frequent and terminal subculturing is performed [1, 2]. Blood specimens processed by lysis-centrifugation; exudate, joint, and CSF specimens; and homogenized tissue specimens should be inoculated directly into media such as thioglycollate broth, trypticase soy broth, or chopped-meat glucose broth. All specimens from sterile sites should also be inoculated directly onto solid media, and plates should be sealed to prevent drying during the prolonged period of incubation and observation.

Many pathogenic *Nocardia* species organisms from clinical material are variably acid-fast on primary isolation, a property quickly lost in subcultured colonies [2]. Compared to *Mycobacterium* species, they retain fuchsin less tenaciously, so the modified Kinyoun stain that decolorizes with a weak acid (1%–2% sulfuric acid instead of acid alcohol) is best for demonstrating the variable and transient acid-fast property of *Nocardia* species [1].

A single nocardial colony isolated from the CSF or another normally sterile area (such as a soft-tissue abscess, pleural space, or joint fluid) of a patient with an appropriate clinical picture can never be ignored, as these organisms are seldom laboratory contaminants and not part of the body's normal flora.

The significance of random respiratory tract isolates continues to be debated, since *Nocardia* species are so widely distributed in nature [1, 2]. Single false-positive cultures have been reported from mycobacterial and fungal reference laboratories [2]. Sputum digestion procedures (with *N*-acetyl-L-cysteine, sodium hydroxide, benzalkonium chloride, etc.) used to enhance yields of mycobacterial cultures render some *Nocardia*-positive sputum specimens falsely negative.

Nocardia species are occasionally skin contaminants and probably even respiratory tract saprophytes, but respiratory cultures yielding *Nocardia* species organisms may also signify relatively mild clinical infections, such as pharyngitis, bronchitis, or otitis media [2]. Young et al. described seven patients with fever or upper respiratory tract symptoms, whose sputum specimens all yielded *Nocardia* organisms "of uncertain significance" [13]. Four patients had underlying disease, and three did not; none were receiving steroids. In some cases there were multiple positive cultures while symptoms continued, but therapy was withheld and all patients recovered [13].

Respiratory tract colonization (single isolates) has been documented in patients with malignancy, tuberculosis, cystic fibrosis, asthma, bronchitis, and allergic aspergillosis [14]. Bronchial obstruction or decreased bronchociliary clearance predisposes to colonization, but unless corticosteroid therapy is also part of the picture, infection seldom occurs. Although *Nocardia* species can be occasional respiratory saprophytes in humans, it would be imprudent to withhold therapy when cultures are repeatedly positive, particularly for compromised individuals.

Currently, no serodiagnostic test is available to help identify patients with active nocardiosis more quickly. Serological methods previously studied (including hemagglutination, precipitin, and complement-fixing antibody testing) met with limited success and lacked specificity because of a high degree of shared antigens and serological cross-reactivity among the heterogeneous pathogenic *Nocardia* species and other actinomycetes, especially *Rhodococcus, Streptomyces,* and *Corynebacterium* species [1, 9]. Lack of sensitivity or specificity (cross-reactions of nocardial antigens with sera from patients with tuberculosis or leprosy) hindered earlier serological studies [9].

A recently recognized 55/54-kD glycoprotein antigen (secreted into the culture medium during nocardial growth) displays more species-specificity and is a strong candidate for a more specific antibody marker of active infection by *Nocardia* species [15]. A similar protein antigen is also found in *N. brasiliensis* and *N. otitidiscaviarum* cultures. McNeil and Brown offer further details of this current diagnostic frontier [1]. There are no skin tests for demonstrating delayed cutaneous hypersensitivity.

Host Status

Nocardiosis is chiefly an opportunistic infection, particularly in patients with lymphoreticular neoplasms (leukemia and lymphoma); patients with solid tumors are not exempt [2]. Impaired local pulmonary defenses predispose to pulmonary nocardiosis, particularly in cases of chronic obstructive pulmonary disease such as emphysema, bronchitis, asthma, and bronchiectasis, as well as bronchopulmonary sequestration, anthracosilicosis, tuberculosis, alveolar proteinosis, and almost any condition requiring long-term corticosteroid therapy [2, 16]. Therapy with cytotoxic agents, alone or in combination with steroids, is also an important risk factor.

Systemic immunosuppression, particularly cell-mediated immunity (CMI) dysfunction, predisposes to the evolution of invasive pulmonary nocardiosis, seen frequently in renal, cardiac, and liver transplant recipients [1, 2, 16]. Sarcoidosis, collagen vascular diseases (especially systemic lupus erythematosus),

dysgammaglobulinemia, chronic granulomatous disease, acute and chronic alcoholism, diabetes mellitus, trauma or surgery, and (as noted more recently) HIV infection all enhance susceptibility to nocardiosis [1, 2, 16]. Intravenous drug abusers also are at risk.

Other reported underlying conditions are pemphigus vulgaris, glomerulonephritis, Whipple's disease, Goodpasture's syndrome, vasculitis, Cushing's disease, cirrhosis, hemochromatosis, ulcerative colitis, rheumatoid arthritis, and Paget's disease of bone [2]. Immunoglobulin and leukocyte defects may also be preconditions.

Nocardial pneumonia also occurs without concurrent diseases or therapies. The reported prevalence in reviews usually ranges from 10% to 25%, although in Curry's analysis of 455 cases, 39% of the patients did not have a preexisting illness, trauma, or immunosuppressive therapy [17]. It is interesting that a similar figure (40%) was cited in a recent review of nocardial infections in Germany [9].

Invasive nocardial infections account for ~4% of infections in patients following renal transplantation [1, 16]. Risk factors include multiple early rejection episodes, intensive immunosuppressive therapy, age of <10 years or >40 years, grafting from an unrelated donor, granulocytopenia, and uremia resulting from impaired allograft function [1, 2, 16]. All major organ transplant recipients are also at increased risk [2, 16]. Cardiac transplantation patients with a history of high-dose prednisone therapy, uremia, prolonged respiratory support, and frequent rejection episodes have an increased risk [1]. The use of cyclosporine has notably decreased the incidence of nocardial infections in both renal and cardiac transplantation patients [1].

Nocardiosis in Patients with AIDS

Early reports expressed surprise that so few cases of nocardiosis were occurring, but nocardiosis is no longer an uncommon complication of AIDS, either in the United States or abroad; many cases have not been described in the literature [1]. Geographic variations may relate to the incidence of nocardiosis in patients with AIDS, which is perhaps greater in the southern and rural regions of the United States than in the metropolitan areas of the East and West, such as New York City and San Francisco [1, 16]. Uttamchandani et al. diagnosed 30 cases of pulmonary and extrapulmonary nocardiosis in patients with AIDS in the Miami area during the period of January 1985 through June 1989 [18].

Percutaneous transthoracic needle biopsy of 13 patients with AIDS and undiagnosed focal pulmonary lesions yielded *N. asteroides* in two cases (15%) [19]. During the period 1985–1989, cervical lymph node biopsies were performed for 20 HIV-positive patients, of whom 10 had AIDS [20]. Ten of the 20 HIV-positive patients had tender and enlarging cervical lymph nodes; a *Mycobacterium* species was recognized in 8 patients, whereas a *Nocardia* species was found in the nodes from 2 patients (20%) [20].

Pathogenesis and Host Defenses

Virulent strains of *N. asteroides* are facultative intracellular pathogens that successfully evade the bactericidal defenses of the host's native and acquired immune response. A multifaceted response begins in the reticuloendothelial system with early mobilization of neutrophils, which inhibit but do not kill *Nocardia* species organisms [2, 16]. They limit the spread of infection until the appearance of CMI, triggered by "activated macrophages" and induction of a T cell population capable of direct lymphocyte-mediated toxicity to *N. asteroides;* both of these cells kill nocardiae in vitro [16].

The interactions of phagocytic cells with nocardiae vary with the virulence of the strain and with the growth phase of the nocardial cells. A major virulence factor for *N. asteroides* is resistance to phagocytosis by filamentous log-phase cells, which are 1,000 times more virulent and toxic to mouse macrophages and more virulent in mice than are the easily phagocytized stationary-phase coccoid organisms [16]. Virulent nocardiae inhibit phagosome-lysosome fusion and decrease lysosomal enzyme activity in macrophages, neutralize phagosomal acidification, and even resist the oxidative killing mechanisms of phagocytes. This resistance may be due to production of a unique surface-associated superoxide dismutase and to increased levels of catalase found in virulent strains [1, 2, 16].

Complex cell wall glycolipids also contribute to virulence [16]. In chronic granulomatous disease, neutrophils and macrophages fail to generate a burst of oxidative metabolism during phagocytosis, thus impairing the intracellular killing of catalase-positive bacteria such as *Nocardia* species. However, nocardiae may even be relatively resistant to the consequences of a normal oxidative burst [16].

Host resistance to nocardial infection is a complex interaction pitting the bactericidal mechanisms of the host's cellular immune response against the ability of *N. asteroides* to evade or neutralize that bactericidal response [16]. The host must ultimately mount a lymphocyte response and subsequently release antibody and/or lymphocyte signals enabling the phagocytic cells to kill *N. asteroides,* after early neutrophil mobilization has delayed or retarded nocardial cell growth [16].

Immune T cells effectively clear *Nocardia* species organisms from the lung and prevent extrapulmonary dissemination. Neutrophils predominate in the early lesions of nocardiosis, but infection progresses unless antimicrobial agents are given or CMI takes over [2]. In the event of an inadequate CMI response, neutrophils may account for the characteristic indolence of human nocardiosis.

In experimental animals, on the other hand, virulent strains not only are not killed within 3 hours of an iv injection but clear rapidly from the blood to localize preferentially in the lungs, spleen, liver, kidneys, and brain, where (depending on

the strain) they then grow rapidly. This growth either triggers a lethal infection or provokes, after several days, an effective host immune response that involves functional T lymphocytes and the development of CMI [16]. Macrophages from immunized mice more readily kill *N. asteroides* than do macrophages from normal mice; macrophages from different anatomic sites also display different nocardicidal capacities [2].

Serum antibody has been shown to act in concert with activated macrophages to resist the log-phase filamentous forms of virulent nocardiae, but the role of humoral immunity in human infection is unclear [16].

L-forms (microbial variants lacking an intact cell wall) can be induced and persist within the host for extended periods of time. Their role in human disease is unknown, but they have been isolated from patients, including some with CNS infections [16]. In mice, L-forms play a role in pulmonary and systemic disease and can persist within tissues, especially within the brain, for the life of the animal [16].

Beaman and Beaman recently assessed the current state of our knowledge concerning host-parasite relationships in nocardial infections, focusing on the immunobiologic interactions of nocardiae with phagocytes in both humans and experimental animal models [16]. They reviewed in detail those in vitro phenomena and characteristics that determine virulence for these organisms. The host-parasite relationship was examined with regard to infections in both immunocompetent and immunocompromised hosts, including patients with AIDS. The reader is thus referred to this seminal review for a more comprehensive discussion, which is beyond the scope of this clinical article [16].

Pulmonary Nocardiosis

Nocardial cells, widespread geographically in soil, in water, and on vegetable matter, may be inhaled or become airborne on dust particles, resulting in pulmonary infection [1]. Pathogenic *Nocardia* species, therefore, most commonly infect humans through the respiratory tree [2]. Occasionally the alimentary canal is penetrated, especially the appendix. Rarely, pulmonary infection follows a dental or periodontal infection, ingestion of contaminated food, or aspiration of contaminated raw vegetable material.

Pulmonary nocardiosis is an acute, subacute, or chronic suppurative infection with a pronounced tendency to remissions and exacerbations. Acute pneumonic forms of a few weeks' duration are not rare, particularly in the compromised host. Infection occurs in persons of all ages, even neonates. Men are affected three times as commonly as women [2].

Patients can exhibit the full spectrum of either acute or chronic pulmonary infection, including pneumonia, abscess formation, or both. The most common initial diagnoses entertained, other than pneumonia, are tuberculosis, mycosis, carcinoma, and lung abscess. In high-risk patients, the diagnosis can be suspected when soft-tissue swellings or abscesses and/or CNS manifestations, particularly signs of a brain tumor or abscess, develop in conjunction with a current or recent chronic or subacute pulmonary infection [2].

Nothing in the clinical or radiographic presentation of pulmonary nocardiosis is sufficiently distinctive to be diagnostic. Clinical manifestations are variable and in no way specific: anorexia, weight loss, productive cough, pleural pain, dyspnea, and occasionally hemoptysis, particularly from large cavities [2]. Confluent bronchopneumonia may progress to total consolidation (lobar or even multilobar), with or without abscess formation and/or pleural involvement, both of which are common features. Empyema has been recorded in up to 25% of cases [2].

Radiographs may demonstrate fluffy infiltrates, irregular densities, subpleural plaques, single or scattered regular or irregular nodules or masses (often cavitated), single or multiple abscesses, and even simple alveolar or interstitial reticular or reticulonodular infiltrates. Wegener's granulomatosis has been erroneously diagnosed when cavitating pulmonary lesions and "vasculitic" skin lesions present concurrently [21]. Thick-walled cavities and endobronchial lesions lend further confusion to a picture of malignancy. Miliary lesions have been recorded, and presentation as adult respiratory distress syndrome has been described. Rarely, *Nocardia* species organisms invade preexisting lung cavities, producing a "fungus ball" appearance [2].

Tissues usually exhibit a mixed cellular response with polymorphonuclear leukocytes, macrophages, and lymphocytes but usually not the hallmark epithelioid cell seen in tuberculosis. However, on occasion, tissue sections reveal a granulomatous response; these tissues may undergo central necrosis, occasionally mimicking tuberculosis or histoplasmosis, even (rarely) with some calcifications. Necrotizing lesions may be circumscribed but usually are not encapsulated. Indolent, progressive fibrosis occurs in inadequately treated patients, with a chronic course much like tuberculosis except that lower lobe involvement is more common.

Other clinical respiratory and thoracic manifestations and presentations include tracheitis, bronchitis, pleuropulmonary fistula, mediastinitis with superior vena cava syndrome, and sinusitis [2]. *Nocardia* species have been implicated in paratracheal and anterior neck infections (such as cellulitis over the cricothyroid membrane) complicating transtracheal aspiration, and peritonsillar abscess following needle aspiration of a tonsillar abscess has been reported [2].

Cutaneous, Subcutaneous, and Lymphocutaneous Nocardiosis

Primary cutaneous and/or subcutaneous nocardiosis can follow any puncture or other traumatic introduction of the ubiquitous soil organisms, such as by a thorn, splinter, insect (mosquito or tick) bite, animal scratch or bite, or bullet injury [1, 2, 16]. Cutaneous inoculation by any of the pathogenic nocardiae

probably is (1) a more common clinical event than is recognized, (2) often self-limited, and (3) underdiagnosed because gram stains and prolonged culture incubation are not routinely ordered for most superficial skin infections.

In addition to the classic mycetoma (see below), cutaneous and subcutaneous infections also provoke cellulitis, pustules, pyoderma, paronychia, or localized abscesses mimicking infections due to other pyogenic bacteria, except that nocardial infections tend to be more indolent [1, 2, 16]. The infection may spread to regional lymph nodes and produce a lymphocutaneous or lymphonodular picture that is indistinguishable from sporotrichosis, hence the designation *sporotrichoid nocardiosis* [1, 16].

Posttraumatic keratitis and endophthalmitis have been described, as have wound infections (e.g., compound-fracture infection or poststernotomy mediastinitis) [1, 2, 9]. Postoperative nosocomial *N. farcinica* wound infections were recently seen in 14 patients at two German university hospitals, 3–6 weeks following cardiac, blood vessel, or transplantation surgery [9].

While any pathogenic *Nocardia* species may cause cutaneous or subcutaneous lesions, *N. brasiliensis* infection most frequently evolves as a locally progressive or invasive infection, which may even disseminate [1, 2, 16]. As previously noted, organisms of a separate (new) taxon may be responsible for these disseminated infections [12]. Most reported cases of lymphocutaneous nocardiosis are due to *N. brasiliensis,* but some are mimicked by *N. asteroides* and *N. otitidiscaviarum;* both normal and compromised hosts may be involved.

Rarely, *Nocardia* species organisms can be inoculated directly into the bloodstream during iv drug abuse [2] or accidentally into a vein, producing local septic thrombophlebitis (K. V. Gopalakrishna, personal observation).

Mycetoma (Madura foot, or maduromycosis) is a chronic, deep, penetrating, progressively destructive infection of skin, subcutaneous tissues, fascia, bone, and muscle following localized trauma, usually but not invariably on a foot, leg, arm, or hand [1, 16, 22]. The injury introduces either true fungi (cases of eumycetoma) or aerobic actinomycetes (actinomycetoma cases) and produces an area of localized swelling containing suppurative granulomas and multiple sinus tracts extruding macroscopic colored granules (colonies of the causal organism). Mycetoma is the only clinical form of nocardiosis regularly associated with the presence of such granules [22].

The genus *Actinomadura* now includes nocardioform organisms of the *madurae* species, defined by a distinctive cell wall composition [1, 16, 22]. Aerobic actinomycetes involved include various *Actinomadura* strains (*A. madurae, A. dassonvillei,* and *A. pelletierii*), *Streptomyces somaliensis,* and various *Nocardia* species [1].

At least half of the mycetomas cited in the world literature are caused by aerobic actinomycetes, mostly *Nocardia* species, whereas members of the genus *Actinomadura* are frequently recorded only in certain geographic locations [1]. *N. brasiliensis* is the most frequently recognized cause of *Nocardia*-induced mycetomas, but *N. asteroides, N. otitidiscaviarum,* and *N. transvalensis* can also be etiologic. Further discussion of this chronic form of nocardial infection is beyond the scope of this paper, but the topic is covered in McNeil and Brown's review [1] and by Mahgoub [22].

Systemic and Extrapulmonary Nocardiosis

Primary nocardial infection, either from the lungs or from posttraumatic skin and soft-tissue inoculation, may erode into blood vessels and spread hematogenously. The presence of lesions in two or more organs of the body defines systemic or disseminated disease. The most common sites for dissemination include the CNS (brain), skin and subcutaneous tissues, eyes (especially the retina), kidneys, joints, bones, and the heart [1, 2]. The tendency for the initial pulmonary focus of nocardiosis to clear spontaneously may obscure the source of subsequent metastatic infection and thus make it appear that primary nocardial infection is taking place in these organs or tissues.

In systemic infection, nocardiae behave as pyogenic bacteria during the early stages of infection, with neutrophils dominating the host cell response [16]. Subsequently, a picture involving mixed lymphocytes and macrophages supervenes, as the infection advances into a more chronic phase. Abscesses enlarge because of progressive tissue invasion of the nocardial filaments. Unlike the primary pulmonary infection, lesions of disseminated or systemic nocardiosis progress unless treated; self-limited or subclinical disease is not recognized frequently, although some CNS infections may evolve slowly over a period of many months or even years [9, 23].

A granulomatous picture, as seen with *Mycobacterium tuberculosis* infections, can be found in infection with some nocardial strains, but this type of host response is distinctly uncommon.

Reported types of systemic involvement include peritonitis, epididymo-orchitis, iliopsoas, ischiorectal and perirectal abscess, hematogenous endophthalmitis and retinitis, pericarditis, endocarditis (of natural and prosthetic valves), aortitis, septic arthritis and bursitis, peritonitis in chronic peritoneal dialysis, osteomyelitis, and a disseminated miliary picture with diffuse organ abscesses [1, 2, 16]. Nocardial infection in childhood may present as a cervicofacial syndrome and even cause cervical adenitis [2]. Recovery of *Nocardia* species organisms in blood cultures, while not common, does occur, especially when the specimens are from patients receiving immunosuppressive therapy.

Eye involvement featuring retinal infection or endophthalmitis is consequent to bloodstream dissemination, whereas corneal and other ocular surface lesions (e.g., keratoconjunctivitis) presumably result from traumatic surface inoculation [1].

Beaman and Beaman reviewed 71 published cases of nocardiosis in patients with AIDS from the period 1984–1992; most of these cases were reported since 1990 [16]. The sites of disease were the lung (51.7%), brain (11.7%), and a variety of

other organs: heart, lymph nodes, kidneys, esophagus, paraspinal abscess, peritoneal abscess, bone marrow, skin, pharyngeal abscess, and inner ear. Given the propensity for retinal invasion by *Nocardia* species during bloodstream dissemination (clinically and experimentally), it is surprising that no instances of retinitis were reported among the 60 site-specified cases. Nonetheless, it is worth keeping in mind that some cases of presumed cytomegalovirus retinitis might be due to unrecognized nocardial infection. Low-dose prophylaxis with TMP-SMZ for *Pneumocystis carinii* infection probably offers a further impediment to the laboratory recovery of this already elusive organism.

CNS Infection

Nocardiae have a well-recognized predilection for invasion of the CNS, even when the primary site of infection may no longer be apparent or actively affected [1, 2, 16]. The propensity for virulent nocardial strains to invade and reproduce in the human brain is mirrored in the brains of mice, which have been investigated extensively with regard to this property [9]. In the murine model, nocardiae in the blood bind to capillary endothelial cells within specific regions of the brain, at specific binding sites for each region [9, 23]. Certain strains have a cell surface receptor that recognizes these binding sites. Progressive infection of neurons or clearance without progression varies with the inoculum of organisms employed, the specific strain injected, and the relative dose of nocardiae adherent within the brain [16, 23]. Diminished host resistance may also trigger progressive infection.

The CNS is infected in about one-third of all cases; such infection may dominate the clinical picture, although it often accompanies a widespread disseminated infection [2, 16]. Approximately 45% of patients with systemic nocardiosis have CNS infections; the lungs represent the most common primary source of infection. *Nocardia* species can invade the brain silently and persist for months or even years until clinical events evolve and prompt appropriate studies [23].

The signs and symptoms of nocardial brain infection are highly variable. Infectious foci may be silent and discovered only at autopsy, or they may mimic tumors or present as classic brain abscesses [9] or (rarely) meningitis [24]; the latter condition usually, but not always, is accompanied by a brain abscess. While the presentation may be an acute, rapidly evolving infection, quite often the onset and course are gradual and insidious, occurring as a variable constellation of neurological deficits over a period of months or even years and unaccompanied by any of the expected systemic components of a bacterial infection (such as fever or leukocytosis) [16, 23, 24].

Subtle but objective neurological impairment often heralds this infection, but bizarre (even psychotic) personality and behavioral presentations dominate certain chronic cases. Depression, schizophrenia, dyslexia, amnesia, and palilalia have all been recorded [9, 16, 23]. Neurological presentations include hemiparesis, body tremors, Parkinsonian features, seizure, coma, ataxia, and meningoencephalitis [16].

While an abscess is the most common pathological finding, sometimes areas of diffuse cerebral inflammation are scattered throughout the brain substance; at times granulomas with giant cells are seen. Abscesses, most often multiloculated lesions with satellite extensions, occur in any part of the brain; parietal, frontal, or occipital cortex, basal ganglia, mid-brain, and brain stem (pons) [16]. All patients with pulmonary or disseminated nocardiosis should undergo MRI of the head to rule out occult CNS nocardial infection.

Nocardial meningitis occurs less frequently than abscess and usually, but not invariably, presents with involvement (abscess) of other portions of the brain. Rarely, the spinal cord alone is involved. Epidural spinal cord compression from vertebral osteomyelitis has been reported, and ventriculoperitoneal shunt infections have been noted [16, 23, 24].

Needle aspiration or biopsy of a cerebral mass may not always be necessary to confirm the diagnosis for most patients with pulmonary nocardiosis. In patients with AIDS, the potential for multiple-organism infection (or infection plus tumor, especially lymphoma) challenges that diagnostic dictum. Beaman and Beaman noted that CNS infections tended to be more rapidly progressive in compromised hosts than in persons with normal host defenses, whose infections are insidious and slowly progressive [16].

"Neurodegeneration" in a Murine Model of CNS Nocardiosis

In mice injected with a sufficiently large iv inoculum of cells from certain *Nocardia* strains or in mice immunosuppressed with corticosteroids, brain abscess formation can be readily induced [9, 16, 23].

In the murine model, certain strains of *N. asteroides* injected iv in small, sublethal inocula target specific regions of the brain via specific capillary and arteriole endothelial cell binding sites, without provoking an inflammatory response or damaging the integrity of the blood-brain barrier, despite passing through the basal lamina and growing briefly (for 24–72 hours) within neurons, axons, and glial cells [9, 23]. Growth within the brain parenchyma then subsides and the organisms disappear.

In 10–14 days, although the brain appears sterile, the mice may display a variable picture of movement and behavior disorders involving both pyramidal and extrapyramidal damage, including hemiparesis, gait disturbances (ataxia), rhythmic rest tremors, tremulous movements, rigidity of extremities, head shakes, hypoactivity or hyperactivity, and episodic seizures [23].

In 10% of mice with this subclinical infection (due to *N. asteroides* GUH-2), progressive clinical neurodegeneration occurs that results in an L-dopa-responsive rhythmic, vertical head-shake-movement disorder displaying many features (tremulous movement, hypoactivity, and stooped posture) of

Parkinson's disease. This disorder is accompanied by pathological substantia nigra findings: decreased tyrosine hydroxylase immunostaining and decreased numbers of neurons [23]. Other types of neurodegenerative responses are recognized in other mice; not all pathogenic *Nocardia* strains can induce such neurodegenerative changes. Furthermore, after 1–2 years, clinical nocardiosis reactivated in some of these mice.

The implications of these intriguing observations for humans are unknown but warrant further study, with regard to chronic or recurrent CNS nocardiosis and/or Parkinson's disease.

Antimicrobial Susceptibility Testing and Therapy

It is a challenge to review, extract, and organize the pertinent literature on this topic, since the antimicrobial susceptibility testing of *Nocardia* species remains problematic [1, 2, 9, 25]. Many methods have been tried with variable success, but none has been standardized, validated, or accepted as a reference method following a multiple-site cooperative study. In vitro susceptibility data and clinical outcomes have not been correlated systematically with regard to human infection, since no single medical center treats enough patients to test individual or combination therapies properly. The heterogeneity of the *N. asteroides* complex has been recognized only in the past decade, and studies prior to this revelation are open to reevaluation [1, 2, 5–8, 10, 11, 25].

The National Committee for Clinical Laboratory Standards is pursuing standardized antimicrobial susceptibility testing methods for the aerobic actinomycetes [1]. Testing methods include modified disk-diffusion, agar dilution, broth microdilution, and radiometric growth index. Media composition and inoculum size influence in vitro results, and only inhibitory, not bactericidal, endpoints have usually been tested [1].

Each technique requires a uniform, homogeneous suspension of microorganisms, from which a standard inoculum can be obtained. This may not be achievable with all strains, since nocardiae grow as long, branching filaments that fragment and clump. As many as one-third of nocardial isolates previously tested failed to grow well on Mueller-Hinton agar, but these were often stock laboratory strains, stored for years under oil in an inactive metabolic state [1]. Fresh clinical isolates currently grow 90% of the time; growth of the other 10% can usually be achieved on Mueller-Hinton agar that is chocolatized or supplemented with 5% sheep's blood.

The agar dilution method has advantages over broth microdilution but has not been widely applied because labor-intensive preparation and proper storage of freshly prepared dilution plates strain the resources of the average busy clinical microbiology laboratory, where personnel have limited experience with strains of the *N. asteroides* complex, now known to include several distinct species (e.g., *N. farcinica* and *N. nova*). All clinically significant *Nocardia* species isolates should routinely and promptly be directed to a specialized research or reference laboratory for precise identification and optimal antimicrobial susceptibility testing (see addendum). Commercial laboratories should be avoided.

Patients will benefit from optimal drug selection, particularly when primary drug resistance is noted and an alternative drug therapy is needed. The frequent need for prolonged treatment (6–12 months or longer), chronic suppressive therapy for HIV-infected patients, and/or alternative therapy (or therapies) because of treatment failure, relapse, or breakthrough (of a new abscess) demands that precise and comprehensive in vitro susceptibility data be obtained initially for each isolate. These should be obtained in anticipation of such future concerns, which occur in a high percentage of cases.

No less important is the gathering of multiple isolates by these reference laboratories, with corresponding clinical data from widely scattered geographic areas, which will aggregate much-needed data concerning the proportion of different isolates recovered in different parts of the country. Such collections provide investigators with the opportunity to correlate isolates with clinical presentations and, ultimately, outcomes.

A full discussion of the problems and pitfalls of antimicrobial susceptibility testing of *Nocardia* species is beyond the scope of this clinical article, but this topic is addressed in the timely review by McNeil and Brown [1] and in their laboratory's latest effort in this area [25].

Sulfonamides, particularly sulfadiazine and sulfisoxazole, have been the antimicrobial agents of choice since first introduced 50 years ago, even though the in vitro activity of sulfonamides is often less impressive when compared with that of other agents and is best demonstrated with smaller inocula [2]. This recommendation is based upon accumulated clinical experience, including that in several large series of patients who were successfully treated [2]. Sulfadiazine can induce oliguria, azotemia, and crystalluria in patients who fail to maintain a high fluid intake. This complication can be prevented by alkalinizing the urine with oral sodium bicarbonate.

Sulfisoxazole is equally effective and much less likely to cause oliguria. Trisulfapyrimidine combinations should be as effective and less toxic. In adults with normal renal function, the recommended dosing schedule (6–12 g/d in 4–6 divided oral doses, after a loading dose of 4 g) should lead to a serum level of 100–150 μg/mL 2 hours after administration of a dose. Levels are measured colorimetrically for the specific sulfonamide employed.

TMP-SMZ is now most frequently used to treat this infection, despite the absence of conclusive data supporting the need for this combination (1 part TMP to 5 parts SMZ) rather than sulfonamide therapy alone [1, 2, 25]. Does the addition of TMP add to the efficacy of the sulfonamide? The clinical studies needed to answer this question have not been performed, and sulfonamide alone still produces good results, even in severely immunocompromised patients. Synergy (in vitro) has not been observed by all investigators, and antagonism has been observed by some [2]. Toxic effects, especially myelosuppression, are greater with use of the combination.

If TMP-SMZ is used, dosages for adults with normal renal function are 2.5–10.0 mg/kg (TMP) and 12.5–50 mg/kg (SMZ) twice a day, according to the severity of the infection. Another dosing schedule is 15 mg (TMP) + 75 mg (SMZ)/(kg · d), either iv or po, or ~2 double-strength tablets every 8 hours. The efficacy of sulfonamides and their combination with TMP are maximal against *N. brasiliensis,* most (>90%) *N. asteroides* complex isolates, and *N. transvalensis* [1, 11, 12, 25]. They are not effective, in vitro or in vivo, against *N. otitidiscaviarum* isolates. The only parenteral form of sulfonamide currently available in the United States is TMP-SMZ, thus precluding the use of iv sulfonamide alone.

When susceptible strains of the *N. asteroides* complex are treated with sulfonamides or TMP-SMZ, 90%–95% of pleuropulmonary infections respond favorably. However, in patients with disseminated disease, especially of the CNS, and/or patients with depressed CMI, certain factors may complicate the picture. Most important is the frequent occurrence of side effects in HIV-infected persons or organ transplant recipients: 44%–80% experience fever, skin rash, and/or neutropenia [1].

Therapeutic decisions for patients with nocardiosis have always been largely empirical, but now one must pay even more attention to individual antibiotic susceptibility patterns, as well as to the site and extent of infection involved. Managing nocardial infections is often complicated by drug intolerance (e.g., manifested as cutaneous eruption following use of sulfonamides), recovery of primary drug–resistant strains, or development of resistance during therapy (sulfonamide resistance acquired in vivo has been documented in one case by this author).

There may also be progression of previously seeded abscesses, which evolve despite effective antimicrobial therapy, even when the organism retains in vitro susceptibility to the drug being given. If a patient remains ill or febrile in the face of seemingly adequate therapy, the treatment failure may be due to a sequestered abscess requiring drainage or to a coexistent or secondary opportunistic infection, as multiple opportunistic pathogens often attack these compromised hosts concurrently or sequentially.

There has long been controversy about whether data regarding the in vitro antimicrobial susceptibility of nocardiae have any predictive value for in vivo therapeutic benefit, as well as whether combinations—usually including a sulfonamide or minocycline—are more effective than a single agent for therapy. Reliable data correlating in vitro observations with in vivo clinical outcomes are not available for obvious reasons: too few cases can be studied in any single medical center; multicenter trials carry severe limitations; and the variable and chronic course of nocardiosis (abscesses, other opportunistic infections, and evolution of previously seeded metastatic infection despite adequate therapy) often precludes determination of precise therapeutic endpoints. Surgical intervention can also influence the ultimate outcome, particularly for patients requiring drainage or excision of abscesses or an empyema.

An experimental murine model of nocardiosis (infected intravenously, intraperitoneally, or via the upper respiratory tract) provides an indirect method for evaluating in vivo the therapeutic benefits of various antimicrobial agents and combinations [1, 2]. Colony counts of the organism, per gram of homogenized tissue harvested at intervals (over a period of time) from various target organs (brain, lungs, liver, spleen, and/or kidneys) of both treated and untreated mice, provide quantitative endpoints for examining the in vivo activity of both single and combination antimicrobial therapy. These counts also provide the opportunity to assess the bactericidal potential of newer antimicrobial agents, singly and in combination. Severely ill patients, particularly those who are immunocompromised, might benefit from therapy that is more rapidly bactericidal than is possible with sulfonamides.

While findings with animal models do not necessarily reflect what occurs clinically in humans, inferences can be drawn regarding the extent and rapidity of bactericidal activity in reducing colony counts. For example, this animal model confirms that imipenem and amikacin are statistically superior in reducing bacterial colony counts over time in various target organs, when compared with the activity of other antimicrobial agents, including TMP-SMZ [2]. The failure of TMP-SMZ to be as effective in this experimental model, however, may be explained by its lack of bactericidal activity in the model and the short duration of the study (72–96 hours). Cefotaxime and ceftriaxone also reduce colony counts more significantly than sulfadiazine or TMP-SMZ [2].

HIV-infected patients require long-term maintenance suppressive therapy and are particularly intolerant of the TMP-SMZ combination, manifesting severe hypersensitivity reactions, hepatotoxicity, and/or prolonged myelosuppression [1]. In organ transplantation patients treated with the antirejection medication cyclosporine, TMP-SMZ may cause reversible cyclosporine-induced nephrotoxicity [1].

Alternatives to sulfonamides have included almost all antimicrobial categories, proposed not necessarily on the basis of meaningful clinical studies but rather on the basis of accumulated anecdotal experiences, directed in large measure over the years by in vitro data of uncertain significance. Erythromycin/ampicillin and sulfonamide/ampicillin combinations were effective in selected patients treated in the United States 2 or 3 decades ago [2].

Minocycline (100–200 mg twice a day), which has excellent in vitro activity against the majority of pathogenic *Nocardia* species, continues to be touted in the literature as a substitute for sulfonamides or for use in combination therapy (where needed) with newer, bactericidal agents [1, 2]. Effective particularly in pulmonary nocardiosis, it also was effective in treating a brain abscess that did not require surgery, even though it failed to eradicate organisms from tissue in an experimental murine model of cerebral nocardiosis [2]. Only *N. transvalensis* isolates are significantly resistant (46%) [1, 11].

Antituberculous drugs and antifungal agents (such as amphotericin B and imidazoles) exhibit no in vitro activity. Rifampin

displays poor in vitro activity, although 50% of *N. nova* strains are susceptible to it [6].

The parenteral drugs currently most active in vitro against the largest percentage of nocardial isolates, in a broad survey of studies, are amikacin and imipenem [1, 2, 25]. Amikacin displays impressive in vitro activity against 90%–95% of all tested strains; *N. transvalensis* may be an exception (18% of such isolates were resistant in one report) [1, 11]. Clinical experiences, particularly with compromised patients, have also been encouraging. Amikacin reduced mortality convincingly in a murine intraperitoneal infection model [2].

Imipenem is also consistently active in vitro, although 18%–36% of *N. farcinica* strains are not susceptible and 70% of *N. brasiliensis* strains are resistant as well [1, 12, 25]. A favorable clinical outcome with combination imipenem/amikacin therapy has been reported in a case of prosthetic aortic valve endocarditis [2].

Varying combinations of amikacin and imipenem with cefotaxime and TMP-SMZ display in vitro synergy (a $\geq$4-fold reduction in MICs of both drugs) against most strains. Imipenem/cefotaxime displays synergy in 92% of tests, amikacin/TMP-SMZ in 83% of tests, and imipenem/TMP-SMZ in 80% of tests, while imipenem/amikacin is a predominantly additive, sometimes synergistic, combination [2]. Imipenem and amikacin were statistically superior in combination (than either alone) in reducing tissue organism counts in the brains of mice with cerebral nocardiosis [1, 2].

Combinations of imipenem/cefotaxime and imipenem/TMP-SMZ were effective in reducing bacterial colony counts in this same model in a later study, but they were not statistically superior to imipenem alone; TMP-SMZ was least effective when used alone [2]. Ceftriaxone, cefuroxime, and cefotaxime also display important in vitro activity against nocardiae, with the exception of *N. farcinica* and *N. transvalensis* [1, 2, 5, 7, 11]. Cefotaxime exhibited significant in vivo activity in a murine model of pulmonary nocardiosis [2]. Other antibiotic combinations acting synergistically against susceptible strains of *Nocardia* are amikacin/cefuroxime and amikacin/amoxicillin/clavulanic acid [1, 2].

Amoxicillin plus clavulanic acid is moderately active against many strains of *N. asteroides, N. farcinica,* and *N. brasiliensis,* but *N. nova, N. otitidiscaviarum,* and *N. transvalensis* are essentially resistant to this combination. In addition, the clinical value of β-lactamase inhibitors in managing nocardiosis is unclear, although one European investigator recommends amoxicillin plus clavulanic acid or imipenem in combination with amikacin for the treatment of human nocardiosis, particularly *N. farcinica* infections [1, 2, 9].

Imipenem, utilized in high doses, is effective against most *N. asteroides,* all *N. nova,* and 71%–82% of *N. farcinica* and *N. transvalensis* strains [1, 2, 6, 11, 25]. However, one recent paper noted 23% resistance to imipenem among isolates of *N. asteroides* sensu stricto [25]. The optimal parenteral drug choice for initial therapy, particularly for the very ill patient (pending susceptibility data) is amikacin (5–7.5 mg/[kg · 12 h]) in combination with imipenem. Treatment regimens for *N. otitidiscaviarum* infections should not include sulfonamides but should combine amikacin with minocycline.

Other alternatives proposed in the past, primarily on the basis of anecdotal successes, might now be resurrected and prove selectively effective with more precise species targeting. These include cycloserine (250 mg three times a day), ampicillin (1 g four times a day), chloramphenicol (1 g four times a day), and a combination of ampicillin (1 g four times a day) and erythromycin (500–750 mg four times a day) [2]. The role of oral cephalosporins, particularly cefixime and cefuroxime, is not clear at this time.

Experimental quinolone agents may hold more promise than does ciprofloxacin, which, except perhaps against *N. farcinica* and selected *N. transvalensis* strains [1, 25], demonstrates no consistent or impressive in vitro activity. However, following encouraging in vitro susceptibility results, two postoperative sternotomy infections due to *N. asteroides* were cured with oral ofloxacin therapy [26]. Careful selection of certain strains (*N. farcinica* in particular, but also possibly *N. transvalensis*) for testing against ciprofloxacin and newer quinolones may yet uncover a role for these agents as effective oral therapy in selected cases, a worthwhile pursuit given the continuing paucity of effective oral agents for long-term use.

The most current in vitro data focusing on the antimicrobial susceptibility patterns of the *N. asteroides* complex (*N. asteroides* sensu stricto, *N. farcinica,* and *N. nova*) were reported recently by McNeil and associates (who used the broth dilution method) and are summarized as follows [25].

The majority of *N. asteroides* sensu stricto isolates were resistant to cefixime (87%) and ampicillin (73%), but somewhat less frequently resistant to ciprofloxacin (62%), erythromycin (40%), and amoxicillin/clavulanic acid (33%). Imipenem resistance was notable, at a rate of 23%. Isolates were usually susceptible to doxycycline (12% resistance), dapsone (8% resistance), minocycline (6% resistance), and cefuroxime, cefotaxime, and ceftriaxone (2%–6% resistance). These isolates were uniformly susceptible to amikacin, SMZ, and TMP-SMZ.

All *N. farcinica* isolates were resistant to ampicillin, cefixime, and tobramycin and mostly resistant to third-generation cephalosporins (64%–86%), but they were usually susceptible to dapsone and doxycycline (14% resistance), SMZ (11% resistance), TMP-SMZ (7% resistance), and minocycline (4% resistance). All were susceptible to amikacin, but 36% were resistant to imipenem (the highest percentage of resistance yet recorded in the recent literature), 32% were resistant to ciprofloxacin, and 29% were resistant to amoxicillin/clavulanic acid.

All isolates of *N. nova* were resistant to cefixime and ciprofloxacin, and 94% were resistant to amoxicillin/clavulanic acid. Intermediate resistance characterized tobramycin (67%), ampicillin (56%), and TMP (39%), but susceptibility was noted for third-generation cephalosporins (6%–17% resistance), SMZ and TMP-SMZ (11% resistance), and doxycycline and

dapsone (6% resistance). All isolates of *N. nova* were susceptible to amikacin, erythromycin, cefuroxime, imipenem, and minocycline.

Alternative oral drug therapy for nocardial infections theoretically might include dapsone because its mechanism of action (folate antagonism) is identical to that of the sulfonamides, but it has never been tested in vitro to any significant extent, nor discussed in reports on treatment trials. Other promising folate pathway antagonists have recently been tested in vitro; one in particular (WR 99210), a triazine inhibitor of dehydrofolate reductase, as well as its biguanide precursor (PS 15), exhibited excellent in vitro activity against all strains of *N. asteroides* sensu stricto, *N. farcinica,* and *N. nova* and warrants further investigation [25].

A recent informal poll of the membership of the Infectious Diseases Society of America inquired about nocardiosis patients who were successfully treated with nonsulfonamide drug regimens, either because primary sulfonamide therapy failed or was discontinued because of intolerance or because a more rapidly bactericidal agent or combination of agents was desired for severe, progressive infection (in HIV-positive and other immunosuppressed patients) [9].

Two categories of therapy emerged: one very ill group of patients required parenteral therapy and received imipenem, amikacin, or cefotaxime (or other broad-spectrum cephalosporins) alone or in various combinations; a less-ill group was treated with oral antimicrobial agents (in particular, minocycline) [9]. While the reported clinical response in most patients treated with nonsulfonamide regimens was generally favorable, these are only anecdotal data and are not comparable to those from a prospective study.

Optimal duration of therapy is uncertain, but long-term therapy is the rule because nocardial infections tend to relapse; most recommendations are empirical. In one study of the efficacy of TMP-SMZ, relapse occurred rarely when patients received therapy for >3 months [27]. Nonimmunosuppressed patients with pulmonary or systemic nocardiosis (excluding CNS involvement) should be treated for a minimum of 6–12 months; those with CNS infection should be treated for 12 months. All immunosuppressed patients, whatever their syndrome, should receive a minimum of 12 months' therapy. Immunosuppressive therapy should be continued as needed, but at reduced doses if possible, at least during the early stages of treatment. Primary cutaneous nocardiosis may be curable with a shorter course of therapy (2–4 months) after possible bone involvement is excluded [1].

Parenteral therapy need not be continued beyond a period of 3–6 weeks, as determined by response in individual patients. With improving clinical status and, ideally, data in hand regarding the species of the pathogen and its antimicrobial susceptibility, most patients can be safely switched to therapy with an oral preparation of TMP-SMZ, minocycline, or, selectively, even a quinolone or ampicillin/clavulanic acid, as indicated. If nocardial disease is extensive (e.g., multiple, disseminated abscesses; extensive soft-tissue involvement; or necrotic foci not amenable to surgery), or if the response to therapy is slow, a longer duration of parenteral therapy and then of total therapy is not unreasonable. Continuous suppressive therapy is probably prudent for HIV-positive individuals.

Addendum: Reference Laboratories for Identification and Antimicrobial Susceptibility Testing of *Nocardia* Species

Department of Microbiology, The University of Texas Health Center at Tyler (Dr. Richard J. Wallace, Jr., chairman), P.O. Box 2003, Tyler, Texas 75710; telephone, (903) 877-7680; facsimile, (903) 877-7652.

Epidemiology Section, Emerging Bacterial and Mycotic Diseases Branch (Dr. Michael M. McNeil), Mailstop C-09, Centers for Disease Control and Prevention, Atlanta, Georgia 30333; telephone, (404) 639-3158; facsimile, (404) 639-3970.

References

1. McNeil MM, Brown JM. The medically important aerobic Actinomycetes: epidemiology and microbiology. Clin Microbiol Rev **1994**;7:357–417.
2. Lerner PI. Nocardia species. In: Mandell GL, Bennett JE, Dolin R. Mandell, Douglas and Bennett's principles and practice of infectious diseases. 4th ed. Vol. 2. New York: Churchill Livingstone, **1995**:2273–80.
3. Sahathevan M, Harvey FAH, Forbes G, et al. Epidemiology, bacteriology and control of an outbreak of *Nocardia asteroides* infection on a liver unit. J Hosp Infect **1991**;18(suppl A):473–80.
4. Stevens DA, Pier AC, Beaman BL, et al. Laboratory evaluation of an outbreak of nocardiosis in immunocompromised hosts. Am J Med **1981**; 71:928–34.
5. Wallace RJ Jr, Tsukamura M, Brown BA, et al. Cefotaxime-resistant *Nocardia asteroides* strains are isolates of the controversial species *Nocardia farcinica.* J Clin Microbiol **1990**;28:2726–32.
6. Wallace RJ Jr, Brown BA, Tsukamura M, Brown JM, Onyi GO. Clinical and laboratory features of *Nocardia nova.* J Clin Microbiol **1991**;29: 2407–11.
7. Wallace RJ Jr, Brown BA, Brown JM, McNeil M. Taxonomy of *Nocardia* species. Clinical Infect Dis **1994**;18:476–7.
8. Schiff TA, McNeil MM, Brown JM. Cutaneous *Nocardia farcinica* infection in a nonimmunocompromised patient: case report and review. Clin Infect Dis **1993**;16:756–60.
9. Beaman BL, Boiron P, Beaman L, Brownell GH, Schaal K, Gombert ME. Nocardia and nocardiosis. J Med Vet Mycol **1992**;30(suppl 1):317–31.
10. Schiff TA, Sanchez M, Moy J, Klirsfeld D, McNeil MM, Brown JM. Cutaneous nocardiosis caused by *Nocardia nova* occurring in an HIV-infected individual: a case report and review of the literature. J Acquir Immun Defic Syndr Hum Retrovirol **1993**;6:849–51.
11. McNeil MM, Brown JM, Georghiou PR, Allworth AM, Blacklock ZM. Infections due to *Nocardia transvalensis:* clinical spectrum and antimicrobial therapy. Clin Infect Dis **1992**;15:453–63.
12. Wallace RJ Jr, Brown BA, Blacklock Z, et al. New *Nocardia* taxon among isolates of *Nocardia brasiliensis* associated with invasive disease. J Clin Microbiol **1995**;33:1528–33.
13. Young LS, Armstrong D, Blevins A, Lieberman P. *Nocardia asteroides* infection complicating neoplastic disease. Am J Med **1971**;50:356–67.
14. Rosett W, Hodges GR. Recent experiences with nocardial infections. Am J Med Sci **1978**;276:279–85.
15. Kjelstrom JA, Beaman BL. Development of a serologic panel for the recognition of nocardial infections in a murine model. Diagn Microbiol Infect Dis **1993**;16:291–301.

16. Beaman BL, Beaman L. Nocardia species: host-parasite relationships. Clin Microbiol Rev **1994**;7:213–64.
17. Curry WA. Human nocardiosis. A clinical review with selected case reports. Arch Intern Med **1980**;140:818–26.
18. Uttamchandani RB, Daikos GL, Reyes RR, et al. Nocardiosis in 30 patients with advanced human immunodeficiency virus infection: clinical features and outcome. Clin Infect Dis **1994**;18:348–53.
19. Scott WW, Kuhlman JE. Focal pulmonary lesions in patients with AIDS: percutaneous transthoracic needle biopsy. Radiology **1991**;180:419–21.
20. Burton F, Patete ML, Goodwill WJ Jr. Indications for open cervical node biopsy in HIV-positive patients. Otolaryngol Head Neck Surg **1992**; 107:367–9.
21. Gibb W, Williams A. Nocardiosis mimicking Wegener's granulomatosis. Scand J Infect Dis **1986**;18:583–5.
22. Mahgoub ES. Agents of mycetoma. In: Mandell GL, Bennett JE, Dolin R. Mandell, Douglas and Bennett's principles and practice of infectious diseases. 4th ed. Vol. 2. New York: Churchill Livingstone, **1995**:2327–30.
23. Beaman BL, Beaman L, Kjelstrom JA, Ogata SA. Bacteria and neurodegeneration. In: Calne D, ed. Neurodegenerative diseases. Orlando, Florida: WB Saunders, **1994**:319–38.
24. Bross JE, Gordon G. Nocardial meningitis: case reports and review. Rev Infect Dis **1991**;13:160–5.
25. McNeil MM, Brown JM, Hutwagner LC, Schiff TA. Evaluation of therapy for *Nocardia asteroides* complex infections. Inf Dis Clin Practice **1995**; 4:287–92.
26. Yew WW, Wong PC, Kwan SYL, Chan CY, Li MSK. Two cases of *Nocardia asteroides* sternotomy infection treated with ofloxacin and a review of other active antimicrobial agents. J Infect **1991**;23:297–302.
27. Wallace RJ Jr, Septimus EJ, Williams TW Jr, et al. Use of trimethoprim-sulfamethoxazole for treatment of infections due to *Nocardia.* Rev Infect Dis **1982**;4:315–25.