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☐ Original Article ☐

Nocardia Osteomyelitis in a Pachymeningitis Patient: an Example of a Difficult Case to Treat with Antimicrobial Agents

Kyoo-Ho Shin[1], Woo-Suk Lee[1], Young-Ki Son[1]
Kyungwon Lee[2], and Yunsop Chong[2]

Antimicrobial agents played a miraculous role in the treatment of bacterial infections until resistant bacteria became widespread. Besides antimicrobial-resistant bacteria, many factors can influence the cure of infection. Nocardia *infection may be a good example which is difficult to cure with antimicrobial agents alone. A 66-year-old man developed soft tissue infection of the right buttock and thigh. He was given prednisolone and azathioprine for pachymeningitis 3 months prior to admission. Despite surgical and antimicrobial treatment (sulfamethoxazole-trimethoprim), the infection spread to the femur and osteomyelitis developed. The case showed that treatment of bacterial infection is not always as successful as was once thought because recent isolates of bacteria are more often resistant to various antimicrobial agents, intracellular parasites are difficult to eliminate even with the active drug in vitro, and infections in some sites such as bone are refractory to treatment especially when the patient is in a compromised state. In conclusion, for the treatment of infections, clinicians need to rely on laboratory tests more than before and have to consider the influence of various host factors.*

Key Words: Femur, *Nocardia,* osteomyelitis, pachymeningitis, sulfamethoxazole-trimethoprim

It is a well recognized fact that antimicrobial agents played a miraculous role in the treatment of bacterial infections until resistant bacteria became widespread, improving human health and extending lifespan (Travis, 1994). However, we began to learn that besides antimicrobial-resistant bacteria, many factors can influence the cure of infection. These include bacterial factors such as intracellular parasitism and survival, and host factors such as the site of infection and compromised status of the defence system (Johnson, 1996).

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Departments of [1]Orthopaedic Surgery and [2]Clinical Pathology and Research Institute of Bacterial Resistance, Yonsei University College of Medicine, Seoul, Korea
Address reprint request to Dr. K.H. Shin, Department of Orthopaedic Surgery, Yonsei University College of Medicine, C.P.O. Box 8044, Seoul, Korea. Tel: 82-2-361-5640, Fax: 82-2-363-1139, E-mail: qshin@yumc.yonsei.ac.kr

Nocardia is an opportunistic pathogen and the infection is not very prevalent (McNeil and Brown, 1994). However, *Nocardia* infection may be a good example from which we could learn that some infection is not easily cured with antimicrobial agents alone (Lerner, 1996).

The aim of this report is to present our difficult experience with a *N. asteroides* infection: the etiologic diagnosis of the soft tissue infection was delayed, the antimicrobial susceptibility was difficult to determine, the patient was in a compromised state and did not comply with the prescription, and the infection progressed to osteomyelitis despite adequate surgical and antimicrobial treatment.

CASE REPORT

A 66-year-old man (unit No. 363630) was admitted in March, 1998 with the chief complaints of pain on the right hip and a palpable mass on the

anterior aspect of the right thigh for one-month duration. The patient had a history of hypertrophic pachymeningitis which was treated with 75 mg of azathioprine and 10 mg of prednisolone for 3 months prior to admission. He also had diabetes mellitus and vocal cord palsy. Two months before admission, his lower back pain was treated with acupuncture in a traditional medical clinic.

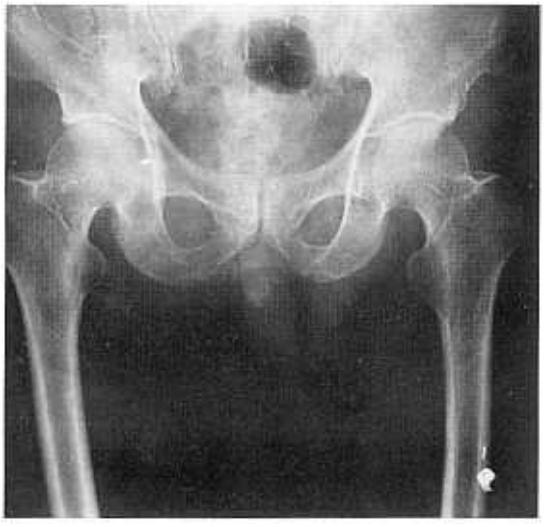

Fig. 1. Plain radiograph at 1st admission demonstrates an ill-defined osteopenic lesion at the proximal portion of the bilateral femur.

The physical examination on admission revealed a mass of 15×15 cm on the right buttock and another one of 10×5 cm on the anterolateral aspect of the right thigh. The patient's right buttock and thigh were tender and the overlying skin was erythematous, but the range of motion of the hips was normal. Laboratory tests revealed the following: white blood cell (WBC) count, 21,600/μL; hemoglobin level, 8.7 g/dL; platelet count, 396,000/μL; erythrocyte sedimentation rate (ESR), 70 mm/h; and C reactive protein (CRP) concentration, 21.5 mg/dL. Radiographs of the hip showed an osteopenic area at the proximal portion of the bilateral femur (Fig. 1). A bone scan showed an increased uptake in the proximal metaphysis of the bilateral femur (Fig. 2).

The masses on his right buttock and thigh were incised and drained. The drained pus was about 100 mL of moderately thick, reddish brown, orderless exudate. Culture of the specimen yielded a large number of yellowish colonies in pure cultures only

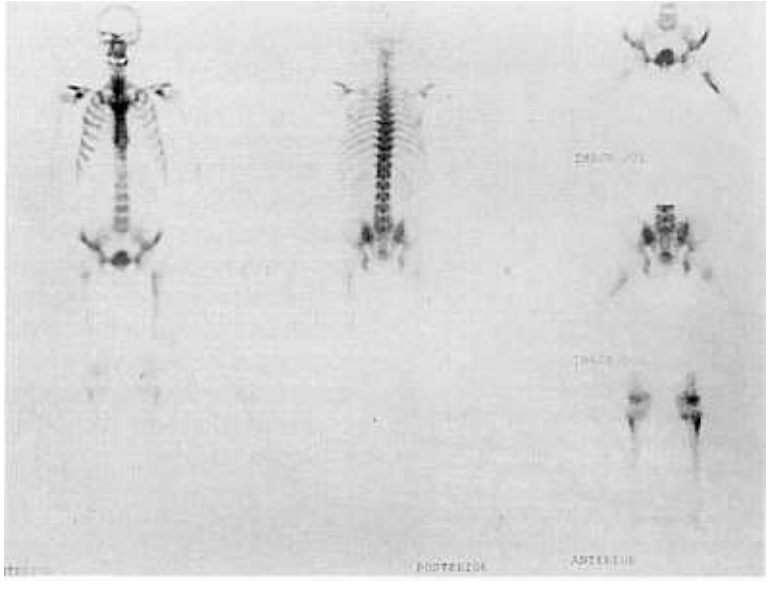

Fig. 2. Radioisotope scanning with ^{99m}Tc-MDP at 1st admission shows an increased uptake in the proximal metaphysis of the bilateral femur.

after 48-hour incubation. It took several days to identify the isolate as *N. asteroides* species and to determine antimicrobial susceptibility. The organism was not isolated from other specimens including blood.

After hospitalization, administration of azathioprine and prednisolone was discontinued. The patient was given intravenous cefodizime 0.5 g every 6 hours and intravenous amikacin 250 mg every 12 hours until the isolate was identified as *N. asteroides.* Cefodizime was replaced by sulfomethoxazole-trimethoprim (2,400 mg of oral sulfamethoxazole, 480 mg of oral trimethoprim) every 12 hours, and 200 mg of intravenous ciprofloxacin every 12 hours, as the in vitro test showed the isolate was susceptible to these antimicrobial agents. After treatment for 33 days, laboratory tests showed the following: ESR, 65 mm/h and CRP, 2.83 mg/dL. The pus discharge and pain had resolved. There was no erythema or swelling on the overlying skin of his right buttock and thigh.

The patient was discharged following the disappearance of clinical signs of active infection and was able to ambulate without support. Oral sulfamethoxazole-trimethoprim every 12 hours was prescribed for 2 weeks. Eight days after discharge, the patient was retreated with azathioprine 75 mg and prednisolone 40 mg per day due to severe headache.

Six weeks after discharge, the patient was read-

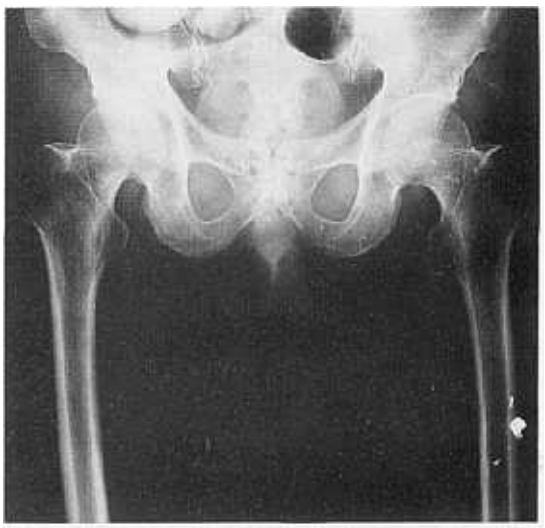

Fig. 3. Plain radiograph on 2nd admission demonstrates a more progressive lytic lesion at the proximal portion of the left femur.

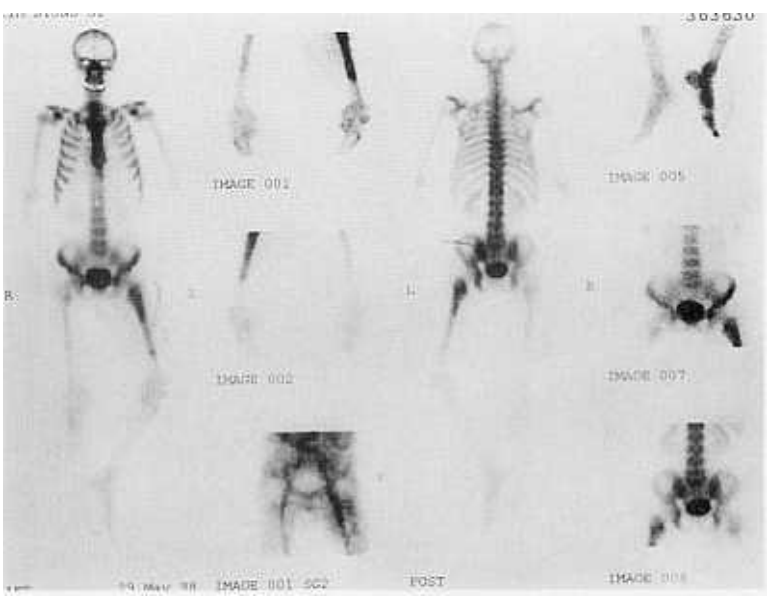

Fig. 4. Radioisotope scanning with ^{99m}Tc-MDP on 2nd admission shows increased uptake at the left femur with increased perfusion.

mitted with pain in his left thigh. Physical examination revealed a tenderness and swelling over the proximal- and mid-thigh, but the overlying skin was normal with no erythema. At the time of readmission, laboratory tests showed the following: WBC count, 11,000/ μL; hemoglobin level, 10.5 g/dL; platelet count, 429,000/ μL; ESR, 63 mm/h; and CRP, 19.0 mg/dL. Radiograph of the left proximal femur showed a lytic lesion (Fig. 3). A bone scan showed increased uptake on the left femur with increased perfusion (Fig. 4).

His left proximal- and mid-thigh was incised and drained. The culture of the material yielded *N. asteroides* again, but blood cultures were negative. The patient was placed on oral sulfamethoxazole-trimethoprim every 12 hours, and intravenous amikacin 250 mg every 12 hours. The patient was given oral azathioprine 75 mg every 8 hours, but prednisolone was discontinued. After 49 days of antimicrobial therapy, follow-up laboratory tests showed the following: ESR, 62 mm/h and CRP, 1.8 mg/dL. The clinical appearance of osteomyelitis had been resolving, but a lytic lesion of his left proximal femur was progressive. We recommended to the patient not to bear any weight on his left leg, but a pathologic fracture occurred on the subtrochanteric portion of the left femur.

The patient died suddenly 2 months after readmission. Postmortem examination was not possible because permission for an autopsy was not granted. Although it was not possible to determine the cause of death it was suspected that vocal cord palsy caused endotracheal aspiration of food resulting in asphyxiation.

DISCUSSION

The first strain of *Nocardia* was isolated from lesions of cattle in 1888, but the human infection was considered to be rare. It was estimated that in 1972−1974 between 500 and 1,000 new cases of *Nocardia* infection occurred in the US annually (Beaman *et al.* 1976). Although it was not a prevalent disease, the number was considered to be underestimated, even at that time. *Nocardia* infection has become a much more prevalent disease lately because of a significant increase of compromised patients in association with a variety of diseases, including malignancy, pulmonary disease, diabetes, alcoholism, and more recently with immunosuppressive drug therapy for autoimmune disease or organ transplant (Lerner, 1996). As agents capable of impairing the host's immune system became more widely used, the infection was expected to increase (Murray, 1961). Most of the reported nocardiosis patients have had predisposing factors in Korea, as well (Ahn *et al.* 1979; Han and Chun, 1987; Park *et al.* 1987; Kim *et al.* 1989; Ra *et al.* 1990; Lee *et al.* 1995). The patient described in this report had diabetes and a history of azathioprine and prednisolone treatment for pachymeningitis.

It was not possible to determine the portal of entry of the *N. asteroides* in our patient. *Nocardia* has been reported to enter most frequently through the lungs, unless it is introduced directly through an open traumatic wound (Almekinders and Lachiewicz, 1989; Lerner, 1996). The organism disseminates to almost any organ system. Secondary infection sites include the brain, meninges, spinal cord, skin and subcutaneous tissue, pleura or chest wall, and kidneys (Lerner, 1995). In our patient, repeated X-rays did not show any chest infiltration.

Lee *et al.* reported a case of *Nocardia* wound infection after a traffic accident in an elderly man with no known underlying disease (Lee *et al.* 1986). Our patient did not have any obvious skin wound prior to infection. It could have been possible that the organism entered through a small skin wound as a result of acupuncture two months before admission. As *Nocardia* is an ubiquitous soil organism (McNeil and Brown, 1994), even a small skin wound can be easily contaminated with this organism. As the patient's immune system was suppressed, the contamination may have progressed to infection as was described by Lerner (1996). A severe infection of the calf due to *Pasteurella multocida*, which is also a rare opportunistic pathogen to man, was reported in a woman who was treated with prednisolone, moxa cauterization and acupuncture (Chong *et al.* 1982).

Nocardia infection can involve every organ system, but the lungs, central nervous system, and skin are most commonly involved (Krick, 1975). A review by Palmer *et al.* showed that among 243 cases

of *N. asteroides* infection, there was no osteomyelitis case (Palmer *et al.* 1974). *Nocardia* osteomyelitis of a distant bone due to hematogenous spread has been reported rarely (Almekinders and Lachiewicz, 1989; Lerner, 1996). Four of these cases involved the vertebral bodies, three cases involved the femur and tibia, and one case involved the ilium, fibula, metatarsus and mandible. When bone is involved, it is most commonly secondary to local spread from adjacent soft tissue infection of the extremities or hematogenous dissemination from pulmonary infiltrations. In our case, it was considered that the bone infection had spread from soft tissue of the femur rather than the chest, as repeated chest X-rays were normal and as blood cultures were negative.

Osteomyelitis is an example of infection which is difficult to cure, as is infective endocarditis or bacterial meningitis even in patients with a normal host defence, requiring a bactericidal drug for treatment (Johnson, 1996). Concentrations of antibiotics in osseous tissue must usually equal or exceed the MIC for a favorable outcome. Measurable trough bactericidal titers are considered desirable. The concentrations of antimicrobial agents in bone are much lower than those in serum.

Identification of the species of *Nocardia* is difficult. Among the *Nocardia* species, *N. asteroides* is the predominant human pathogen, which has now been divided into *N. asteroides* sensu stricto and *N. farcinia*. The other human pathogenic species include *N. brasiliensis* and *N. otitidiscaviarum* and others (Lerner, 1996). Our present isolate was identified as *N. asteroides*.

Because *Nocardia* spp. can produce significant disease, especially in immunocompromised individuals, and because infections with these organisms require an extended treatment course, clinicians are particularly interested in the results of in vitro susceptibility testing (Ambaye *et al.* 1997). Only limited data are available on the susceptibility of *Nocardia* species. McNeil and Brown reported that all of the *N. asteroides, N. farcinia, N. brasiliensis* and *N. nova* strains were susceptible to sulfamethoxazole and amikacin (McNeil and Brown, 1994). Species-dependent resistance was reported to other drugs requiring correct species identification and accurate susceptibility testing. At the moment there is no standard method for *Nocardia* susceptibility testing. The susceptibility of *Nocardia* is difficult to test as the organism grows slowly. Etest was reported to rank second by the percent agreement of the interpretive results, while it is the easiest method to perform in the laboratory (Ambaye *et al.* 1997). Our isolate was susceptible to sulfamethoxazole-trimethoprim, amikacin and ciprofloxacin by Etest. Table 1 compares the susceptibility of our recent isolates and those reported by McNeil and Brown (1994).

Many of the organisms, including *Chlamydia, Legionella, Salmonella, Brucella, Mycobacterium* and *Enterococcus* exist inside phagosomes. Others, such as *Listeria* and *Rickettsia*, escape the phagosomal environment and multiply in the cytoplasm. Staphylococci may also survive inside host cells (Rakita, 1998). Infections due to intracellular parasites are difficult to cure partly because not all antimicrobials attain high levels in host cells. In our patient, surgical and antimicrobial treatment did not prevent the spread of infection to the bone, suggesting the importance of the host factor. Virulent strains of *N. asteroides* are facultative intracellular pathogens which successfully evade the bactericidal mechanisms of the host's native and acquired immune response to infection (Beaman and Smathers, 1976). Although cell-mediated immunity is triggered by "activated macrophages" and the induction of a T-cell population capable of direct lymphocyte-mediated toxicity to *N. asteroides*, a virulent pathogen can avoid or neutralize bactericidal mecha-

Table 1. Antimicrobial susceptibility of *Nocardia* isolates

Antimicrobial agent	MIC range (μg/mL)	
	Gutman *et al.* (1983)*	The authors†
Amikacin	≤0.12−0.5	0.12−0.5
Gentamicin	0.5−16	24 −48
Ampicillin	2 −≥512	48
Cephalothin	8 −>256	>256
Cefotaxime	≤0.5−64	>32
Clarithromycin	NT	0.016−48
Cotrimoxazole	NT	0.047−0.12
Ciprofloxacin	NT	1 −>32

*: *N. asteroides* 12 isolates.
†: *Nocardia* species 3 isolates.

nisms of an immunocompromized host (Beaman and Beaman, 1994). The virulence of nocardiae appears to be related to its ability to inhibit phagosome-lysosome fusion, decrease lysosomal enzyme activity in macrophages, neutralize phagosomal acidification, and even resist the oxidative killing mechanisms of phagocytes. Complex cell wall glycolipids also contribute to virulence (Beaman and Beaman, 1994).

Different classes of antibiotics and sometimes individual agents within classes have markedly differing abilities to penetrate host cells. β-lactams and aminoglycosides penetrate host cells poorly. Intracellular activity of rifampin, macrolides and quinolones are good, while those of tetracyclines, chloramphenicol and sulfamethoxazole-trimethoprim are fair (Rakita, 1998). Concentrations of sulfonamide, tetracycline and ciprofloxacin in host cells are higher than those of extracellular concentrations (Gerding *et al.* 1996). The recommended nocardiosis treatment regimen has been sulfonamides, particularly sulfadiazine and sulfisoxazole in divided doses totalling 4−10 g per day (Cook and Farrer, 1978). The sulfamethoxazole-trimethoprim combination has received considerable attention (Smego *et al.* 1983). If sulfamethoxazole-trimethoprim is used, the dosages for adults with normal renal function are 2.5−10.0 mg/kg of trimethoprim and 12.5−50 mg/kg of sulfamethoxazole twice a day. However, treatment failure and late relapses have been recorded (Smego *et al.* 1983). Minocycline, 100−200 mg twice a day, has been shown to be effective in patients allergic to sulfa drugs or in whom resistance to sulfa has been demonstrated (Wallace *et al.* 1982). Among the newer antimicrobial agents, the aminoglycosides, tobramycin, and particularly amikacin, have demonstrated considerable activity in vitro (Wallace *et al.* 1982). Some of the new β-lactam antibiotics i.e., cefotaxime, were reported to be very active in vitro (Gombert, 1982), but recent data have shown that all of the *N. farcinia* isolates were resistant to cefotaxime (McNeil and Brown, 1994). *N. asteroides* showed high rates of ciprofloxacin resistance, while none of the *N. farcinia* showed resistance. This species-dependant resistance indicates accurate differentiation may be helpful for the selection of antimicrobial agents. Our patient was treated with sulfamethoxazole-trimethoprim. A clinical response was seen after 6 weeks of drug therapy at the first admission, but he relapsed 4 weeks after cessation of medication. The second isolate was *N. asteroides* with the same drug susceptibility, suggesting the relapse was due to a too-short period of therapy.

In conclusion, treatment of bacterial infection is not as simple as it was thought. Our experience with a *Nocardia* infection depicts a difficult problem. Sometimes, determination of an etiologic agent and its susceptibility are difficult. Microorganisms are often resistant to various antimicrobial agents. The in vitro susceptibility cannot predict the clinical outcome especially when the organism is an intracellular parasite, when the site of infection is where the antimicrobial agents do not attain a high enough concentration, when the patient does not comply with the prescription, and when the patient is in a compromised state.

REFERENCES

Ahn YM, Chong Y, Lee SY, Kim BS, Rhee HS: Two cases of *Nocardia asteroides* abscess. *Korean J Pathol 13: 129-133, 1979*

Almekinders LC, Lachiewicz PF: *Nocardia* osteomyelitis. *Orthopedics 12: 1583-1585, 1989*

Ambaye A, Kohner PC, Wollan PC, Roberts KL, Roberts GD, Cockerill FR III: Comparison of agar dilution, broth microdilution, disk diffusion, E-test, and BACTEC radiometric methods for antimicrobial susceptibility testing of clinical isolates of the *Nocardia asteroides* complex. *J Clin Microbiol 35: 847-852, 1997*

Beaman BL, Beaman L: *Nocardia* species: Host-parasite relationship. *Clin Microbiol Rev 7: 213-264, 1994*

Beaman BL, Burnside J, Edwards B, Causey W: Nocardial infections in the United States, 1972-1974. *J Infect Dis 134: 286-289, 1976*

Beaman BL, Smathers M: Interaction of *Nocardia asteroides* with cultured rabbit alveolar macrophages. *Infect Immun 13: 1126-1131, 1976*

Chong Y, Lee HJ, Lee SY, Jahng JS, Yang KH: *Pasteurella multocida* infection of the calf in a patients who had moxa cautery treatment for degenerative arthritis. *Yonsei Med J 23: 65-70, 1982*

Cook FV, Farrer WE Jr.: Treatment of *Nocardia asteroides* infection with trimethoprim-sulfamethoxazole. *South Med J 71: 512-515, 1978*

Gerding DN, Hughes CE, Bamberger DM, Foxworth J, Larson TA: *Extravascular antimicrobial distribution*

and the respective blood concentrations in humans. in Lorian V (ed): *Antibiotics in laboratory medicine.* 4th ed. Baltimore, Williams & Wilkins, *1996, 835-899*

Gombert ME: Susceptibility of *Nocardia asteroides* to various antibiotics including newer β-lactams, trimethoprim-sulfamethoxazole, amikacin, N-formimidoylthienamycin. *Antimicrob Agents Chemother 21: 1011-1012, 1982*

Gutmann L, Goldstein FW, Kitzis MD, Hautefort B, Darmon C, Acar JF: Susceptibilities of *Nocardia asteroides* to 46 antibiotics, including 22 β-lactams. *Antimicrob Agents Chemother 23: 248-251, 1983*

Han KJ, Chun SJ: A case of disseminated *Nocardia asteroides* infection. *Korean J Infect Dis 19: 57-62, 1987*

Johnson CC: *In vitro testing: Correlations of bacterial susceptibility, body fluid levels, and effectiveness of antimicrobial therapy.* In Lorian V, ed. *Antibiotics in laboratory medicine.* 4th ed. Baltimore, Williams & Wilkins, *1996, 813-834*

Kim SM, Kim YS, Pai HJ, Sin HS, Baek KR, Choe KW: Two cases of nocardiosis. *Korean J Infect Dis 21: 217-223, 1989*

Kjelstrom JA, Beaman BL: Development of a serologic panel for the recognition of nocardial infection in a murine model. *Diagn Microbiol Infect Dis 16: 291-301, 1993*

Krick JA: Nocardia infection in heart transplant patients. *Ann Intern Med 82: 18-26, 1975*

Lee KW, Jeong MS, Kim SH, Song SH, Koo SH, Kim SY, Shin YT: Nocardial brain abscess complicated in a patient with systemic lupus erythematosus. *Korean J Intern Med 48: 545-551, 1995*

Lee YS Yoon KJ, Chong Y, Choi CS: *Nocardia asteroides* isolation from traffic accident wound: A case report. *Korean J Clin Pathol 6: 423-427, 1986*

Lerner PI: Nocardia *species. In Principles and Practice of Infectious Diseases.* 4th ed. New York, Churchill Livingstone, *1995, 2273-2280*

Lerner PI: Nocardiosis. *Clin Infect Dis 22: 891-905, 1996*

McNeil MM, Brown JM: The medically important aerobic *Actinomycetes*: epidemiology and microbiology. *Clin Microbiol Rev 7: 357-417, 1994*

Murray J: The changing spectrum of nocardiosis. *Am Rev Respir Dis 83: 315-330, 1961*

Palmer DL, Harvey RL, Wheeler JK: Diagnostic and therapeutic considerations in *Nocardia asteroides* infection. *Medicine 53: 391-401, 1974*

Park K, Chong Y, Lee SY: Pulmonary nocardiosis in a renal transplant patient. *Yonsei Med J 28: 157-161, 1987*

Ra DJ, Choi CH, Woo JH, Park MS, Han DC, Lee SK, Kim SJ, Kim EC: A case of *Nocardia* peritonitis during continuous ambulatory peritoneal dialysis. *Korean J Infect Dis 22: 97-100, 1990*

Rakita RM: Intracellular activity, potential clinical uses of antibiotics. *ASM News 64: 570-575, 1998*

Smego RA, Moeller MB, Gallis HA: Trimethoprim-sulfamethoxazole therapy for nocardia infections. *Arch Intern Med 143: 711-718, 1983*

Travis J: Reviving the antibiotic miracle? *Science 264: 359-362, 1994*

Wallace RJ, Septimus EJ, Williams TW, Conklin RH, Satterwhite TK, Bushby MB, Hollowell DC: Use of trimethoprim-sulfamethoxazole for treatment of infections due to *Nocardia. Rev Infect Dis 4: 315-325, 1982*