

Nocardiosis: An Emerging Infectious Actinomycetic Disease of Humans and Animals

Keywords: Animal; Emerging disease; Human; Nocardiosis; Pathogen; Public health saprobic environment; Soil

Abstract

In recent past, many infectious diseases of diverse etiologies have emerged, which resulted into significant morbidity and mortality in humans as well as in a variety of animals. Among these diseases, nocardiosis is one, which is reported from developing and developed nations; and can occur, in sporadic and epidemic form. Nocardiosis is an emerging actinomycetic zoonosis of public health, and economic importance. Disease is caused by several species of *Nocardia*, which exists as saprobe in the soil. *Nocardia asteroides* is the principal species, which is implicated in various clinical disorders of humans and animals including birds. Soil serves as the source, and reservoir of infection; and the respiratory tract is considered as the chief portal of entry of organism. Rarely, *Nocardia* can enter the body through traumatic injury or wound. There are evidences to believe that humans and animals may acquire the infection from the saprobic environment where the organism exists. The identification and isolation of the pathogen in the clinical specimens both by direct microscopy, and culture still remain the gold standard of diagnosis of nocardiosis. Antimicrobial agents are used as the main stay of treatment. Immediate attention to traumatic injury to the skin, avoiding the visit to dusty environment, early diagnosis and prompt treatment in immunocompromised patients, sanitation in milking parlour, adequate udder hygiene, and proper disposal of excreta will certainly minimise the incidence of nocardiosis both in humans and animals. Further studies on the growing role of *Nocardia* in various clinical disorders of humans and animals will be rewarding. The development of effective, safe, and low cost chemotherapeutic agents for the management of disease is emphasized.

Introduction

Nocardiosis is an acute, chronic, suppurative or granulomatous infectious disease of humans as well as animals [1]. It is primarily an opportunistic infection but can also cause life threatening disease in immunocompetent individuals [2,3]. It is an emerging infectious disease, which has been reported from many countries of the world including India [4-7]. Disease is important from public health as well as economic point of view. The recorded history nocardiosis goes back to year 1888 when Edmond Nocard first described pathogenic aerobic actinomycete in cattle with bovine farcy on the Island of Guadeloupe, West Indies [8]. However, the first human case of disease was reported in a 52-year-old glass blower in 1890 by Eppinger [9]. Pal is credited to elucidate for the first time the etiologic role of *Nocardia asteroides* in corneal ulcer of cattle from India [10].

Nocardia species are widely distributed in the environment, and causes a variety of suppurative infections in humans and many species of animals. Pulmonary and systemic infections occur by inhalation of organisms through respiratory tract. However, the



Journal of Microbiology & Microbial Technology

Mahendra Pal^{1*} and Pratibha Dave²

¹Narayan Consultancy, Veterinary Public Health and Microbiology, Gujarat, India

²Welfare Hospital and Research Center, Bharauch, Gujarat, India

*Address for Correspondence:

Mahendra Pal, Narayan Consultancy, Veterinary Public Health and Microbiology, 4, Aangan, Jagnath Ganesh Road, Anand - 388001, Gujarat, India, E-mail: palmahendra2@gmail.com

Submission: 06 June, 2016

Accepted: 01 July, 2016

Published: 05 July, 2016

Copyright: © 2016 Mahendra P, et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

cutaneous disease is reported following traumatic injury through the soil contaminated objects [11]. Clinical manifestation of disease in humans is variable, which may vary from fever, cough, pleural pain, anorexia, corneal ulcer, pneumonia, mycetoma, to encephalitis. Disseminated nocardiosis may involve any organs, but lesions on the brain or meninges are most common. The majority of nocardial infections in USA are acquired through inhalation [12]. As signs and symptoms are not specific, diagnosis can be challenging. A number of chemotherapeutic agents are available; however, trimethoprim-sulphamethazole is the drug of choice for central nervous system (CNS) nocardiosis due to its good penetration into brain [3]. The early disease may respond to prolonged treatment with antimicrobials, and the duration of therapy is uncertain. However, in refractory case, in vitro susceptibility testing can be performed by agar dilution, and disc agar diffusion techniques. It is important to mention that combination therapy is imperative for the treatment of pulmonary and disseminated nocardiosis [13,14].

Bovine mastitis is a serious concern for dairy farmers, as therapy is not always successful, and diseased animal is sent for slaughter. Early diagnosis and immediate treatment, immediate attention to skin injury, controlling of predisposing factors and hygienic environment is imperative for the better management of disease [1]. The present communication delineates the etiology, epidemiology, diagnosis and management of nocardiosis, which has emerged as an infectious disease of humans and animals worldwide.

Etiology

Nocardia are Gram positive, partial acid-fast, non-capsulated, non-motile, non-sporulated, aerobic actinomycete, which consist of thin, delicate, slender, beaded filamentous hyphae of 1µm or less in diameter. The organism occurs in environment as a saprobe, and has been isolated from the soil, water, air, dust, and decaying vegetation [11,15]. Currently, over 50 species of *Nocardia* have been identified by phenotypic and molecular methods. The most important

pathogenic species for disease in humans and animals was classified as *Nocardia asteroides* complex [14]. *Nocardia asteroides* complex have been recognized as type I, II, III, IV, and V. Type III is called as *N. nova*, and type V as *N. Farcinia* [16]. Recently, *N. cyriaciageorgica* is differentiated from *N. asteroides*, and is now considered as an emerging pathogen in the United States [17]. Hamid and co-workers isolated *Nocardia africana*, a new pathogen, from patients with pulmonary infections [18].

Host

Nocardial infections have been described in humans and in many species of animals including birds [1]. The animals affected include antelope, armadillo, buffalo, camel, cat, cattle, chinchilla, deer, dog, dolphin, fish, fox, goat, guinea-pig, horse, kangaroo, mongoose, monkey, orangutan, oyster, parrot, pig, poultry, rabbit, rat, sheep, wallaby besides marine mammals [1,10,19,20-22]. Cattle and dogs are more affected than other species of animals [1,23].

Transmission

Pulmonary and disseminated infections occur by inhalation of *Nocardia* organisms through the respiratory tract [21,24]. Dry, dusty, and often windy conditions of the region may facilitate the aerosolization, and dispersal of fragmented infectious cells of *Nocardia*, and enhance their acquisition via the respiratory route. Primary cutaneous disease occurs through the soil contaminated wounds or accidental traumatic injury to the skin. The bite or scratch from companion animals can also result into the cutaneous or subcutaneous nocardiosis in humans [25]. Very rarely, organisms can be inoculated directly into the blood during intravenous drug abuse [2]. Occasionally, *Nocardia* may reach the alimentary canal following ingestion. In bovine mastitis, the pathogen enters the mammary gland through teat canal [26]. Transmission of disease in dogs and cats may occur by inoculation of organism through punctured wounds or traumatic injury [15].

Clinical Spectrum

Humans

Disease is characterized by primary pulmonary lesions, which may be subclinical, or pneumonic, transitory or chronic with haematogenous spread to various organs including the brain, and skin [27]. Acute form of disease is particularly observed in compromised host. The clinical signs include fever, cough, sputum, dyspnoea, pleuritic chest pain, malaise, night sweats, nausea, vomiting, weight loss, haemoptysis, pneumonia, empyema, pericarditis, synovitis, peritonitis, encephalitis, severe headache, seizures, ataxia, altered mental status, meningism, polyuria, urinary incontinence, lymphadenitis, lymphangitis, endophthalmitis, and corneal ulcer [1,3,7,28]. About one third of patients with progressive pulmonary disease develop metastatic brain abscesses. Cutaneous infection results in localised development of granulomata and abscesses with soft tissue and bone involvement. Subcutaneous lesion is called actinomycetoma [1]. Empyema has been recorded up to 25 % of the cases [2].

Animals

Mastitis is the most common form of disease in cattle. *Nocardia*

asteroides causes destructive mastitis characterised by acute onset, high temperature, anorexia, dehydration, depression, complete cessation of milk flow, rapid wasting, and marked swelling of udder. Secretion from the affected mammary gland may be viscid or watery, and contain white or yellow flakes or granules. Blood clots are also observed [26]. The induration and fibrosis can occur within 24 to 48 hours after the onset. There is formation of palpable subcutaneous nodules, which may rupture to form draining sinus tracts. Rarely, rupture of affected quarter is noticed. Deaths are not uncommon in acute nocardial mastitis. Slaughter is recommended for such animals as treatment is not successful. Chronic mastitis may occur in animal that survives acute infection. Metastasis to the lungs and supramammary lymph nodes are also noticed [1]. The pathogen can also cause abortion and uterine infections in cows [1]. The etiologic role of *N. asteroides* in corneal ulcer of cattle was first time reported by Pal in 1982 [10].

The disease in canine is manifested with a variety of clinical symptoms such as anorexia, depression, fever, ocular discharge, dyspnoea, cough, nasal discharge, diarrhoea, seizures, weakness, weight loss, emaciation, salivary gland abscess, abdominal swelling, pneumonia, haemoptysis, encephalitis, paralysis, incoordination, convulsion, septic arthritis, osteomyelitis, and lymphadenopathy. Cutaneous or subcutaneous form of disease, which simulates to human mycetoma, shows purulent draining sinuses producing tomato soup like exudates [23]. An unusual case of neurological disorder like rabies has been reported in a dog [23]. The animal had made an unprovoked attack on a child resulting into extensive bite wounds on both legs. The dog succumbed to death in eight days, and on autopsy, the brain was positive for the pathogen and negative for rabies. In addition, *N. asteroides* is implicated as the cause of fatal pneumonia in a buffalo calf, pneumonia in a grey parrot, submandibular abscess in a horse, and pyothorax in a cat has also been described [1,15,21]. Recently, Hattori and co-investigators isolated *N. africana* from a case of mycetoma in a cat [19].

Epidemiology

Nocardiosis is an acute, subacute or chronic infectious disease that occurs in cutaneous, pulmonary, and disseminated form. It has no racial predilection. Disease is more common in males than in females; and all ages are susceptible but maximum cases occur between 21 to 50 years of age. Disease has a high mortality, which ranges from 45 to 85% [12]. The exact data on the incidence of nocardiosis are extremely limited; the number of cases is likely rising as a result of increase in the number of severely immunocompromised patients [12]. In USA, it is estimated that 500 to 1000 cases of nocardiosis are reported each year [11,12]. Approximately, 60% cases of nocardiosis are associated with pre-existing immune compromise [12]. An outbreak of *N. asteroides* infection was reported in a renal unit of a London hospital, England, and epidemiological investigation established the presence of organisms in the dust and air of hospital [29]. Majority of nocardiosis cases in USA are acquired through inhalation of dust containing infectious organisms [12]. Nocardial infections seem to more prevalent in the arid, warm climate of the southwest region of the United States [13]. *Nocardia brasiliensis* is the most frequently recognized agent of mycetoma. Recently, Rodriguez-Nava and others reported *Nocardia mexicana*, a new pathogen from human

mycetoma [6]. A number of risk factors such as organ transplant, HIV/AIDS, lymph reticular malignancy, tuberculosis, alcoholism, diabetes mellitus, cirrhosis, sarcoidosis, renal failure, and long term corticosteroid can predispose the individual to nocardial infections [2,3,30,14]. Though *Nocardia* may act as primary and opportunistic pathogen, the maximum cases are recorded in immunologically compromised patients [3,14]. Systemic nocardiosis occurs more often in immunocompromised persons. The healthy hosts with nocardial infections often have undergone percutaneous trauma, and soft tissue invasion. Certain occupational groups such as farmers, gardeners, brick manufactures, and others engaged in soil related activities are more susceptible to *Nocardia* infections [1]. Nocardial mastitis is usually encountered in dairy herds with poor hygiene in pre and post milking. Epidemiological investigation conducted by Pal revealed *N. asteroides* in the soil of a young buffalo calf died due to pulmonary nocardiosis [21]. In order to establish the source of infection, it is imperative to conduct epidemiological investigation.

Diagnosis

The clinical signs and symptoms of nocardiosis are not pathognomonic, and therefore, laboratory help is imperative to make an unequivocal diagnosis of disease. Computerized tomography (CT) and magnetic resonance imaging (MRI) are useful to reveal the lesions in the organs [3]. *Nocardia* species can be isolated from pus, sputum, broncho-alveolar lavage, pleural fluid, cerebrospinal fluid, blood, peritoneal fluid, synovial fluid, empyema fluid, milk, corneal tissue, lymph nodes, lung, brain on several nutrient media such as brain heart infusion agar, blood agar, Sabouraud dextrose agar, and Lowenstein Jensen agar [3,10,24]. On Sabouraud dextrose agar dry, irregular, whitish to orange coloured colonies are noticed. Circular, dry, white to orange, convex colonies with powdery surface grew on blood agar [31]. *Nocardia asteroides* was successfully grown on Pal sunflower seed agar [1]. The culture should be daily examined for two weeks before discarding as negative. It is important to mention that antibiotic should not be incorporated in the medium as *Nocardia* are sensitive to antibiotics. Direct microscopy of the smear from pus, sputum, tissues etc. by Gram and modified Kinyonn acid fast techniques can detect the presence of organisms, which appear as thin, delicate, branched filaments [31]. Histopathological examination of the biopsied or autopsied tissues by Brown and Brenn method can demonstrate the presence of *Nocardia* and thus helps in diagnosis. Recently, molecular tools such as PCR, RFLP are employed to identify *Nocardia* at species level [3,28]. The pathogenicity test of the organism can be done in laboratory mice, rat, and guinea-pig [1]. The disease should be differentiated from tuberculosis, actinomycosis, blastomycosis, cryptococcosis, histoplasmosis, sporotrichosis, and bacterial brain abscess. Currently, no immunological or molecular techniques are available for routine clinical application [1]. As Gram staining technique is simple, easy, sensitive, and economical, it can be recommended to poor resource nations who cannot afford expensive tests. Further studies are advised to assess the efficacy of Pal sunflower seed medium without antibiotic for the isolation of *Nocardia* from clinical and environmental samples.

Treatment

The treatment of nocardiosis is challenging. Early initiation

of chemotherapy can avoid surgical excision. Trimethoprim-sulfamethazole is the drug of choice for nocardiosis, and can be given by oral or intravenous route [3]. Other treatment regimes include amikacin, ampicillin, ciprofloxacin, imipenem, linezolid, minocycline, tigecycline, levofloxacin, and moxifloxacin [2-4,13]. Linezolid, which binds to a site on the bacterial 23S rRNA of the 50S subunit and prevents the formation of a functional 70S complex, is found effective against all species of *Nocardia* [3]. The management of nocardial mycetoma often requires surgical intervention and antiseptic dressing. Therapy is generally recommended for at least six months [14]. The relapse of disease may occur due to discontinuation of treatment. It is pertinent to mention that there was no fatality among the patients, which were treated with a combination of medical therapy and surgical intervention [3]. Hence, it is suggested to apply combination therapy for getting encouraging results. Mastitis in dairy animals can be managed with udder infusion of nitrofurazone and novobiocin [1].

Prevention and Control

People working out door in the rural setting should avoid trauma to the skin. In case of any skin injury, immediate medical attention is required. Immunocompromised individuals are advised not to work in dusty environment. Persons with wounds, cuts, and bruises should avoid handling of *Nocardia* culture in the laboratory. The use face mask is imperative during sweeping and cleaning of highly contaminated buildings, and old monuments to prevent the entry of infectious organisms through respiratory tract. Proper udder hygiene and adequate sanitation of milking parlour can help to minimise the incidence of nocardial mastitis in dairy animals [1].

Conclusion

Nocardiosis, chiefly caused by *Nocardia asteroides*, is considered as a neglected disease, particularly in patients with some degree of immunosuppression. The source of infection is exogenous, as humans and animals may acquire the infection from saprobic environment. Outbreaks of disease are observed in immunocompromised patients. Nocardial mycetoma occurs predominantly in tropical regions of the world. Among the animals, cattle and dogs are most frequently affected species. Young dogs are more commonly affected with pulmonary infection. In dairy animals, mastitis is the main clinical manifestation of disease. Microbiological, biochemical, and cytological tests are used in the diagnosis of disease. Currently, no immunological test is available commercially for serodiagnosis of nocardiosis. Antimicrobial therapy is the mainstay of medical management of disease. Continuous follow up of the patients is required for monitoring the adverse effects of prolonged antimicrobial therapy. Advance cases of nocardiosis do not usually respond to treatment. Detailed ecological studies of newly recognised *Nocardia* species with different saprobic habitats are suggested. It is emphasized that the etiologic role of newly identified *Nocardia* species in various clinical disorders of humans and animals should be undertaken.

References

1. Pal M (2007) Veterinary and Medical Mycology (1st Edition). Indian Council of Agricultural Research, New Delhi, India.
2. Lerner PI (1996) Nocardiosis. Clin Infect Dis 22: 891-905.
3. Anagnostou T, Arvanitis M, Kourkoumpetis TK, Desalemos A, Carneiro

- HA, et al. (2014) Nocardiosis of the central nervous system: experience from a general hospital and review of 84 cases from the literature. *Medicine (Baltimore)* 93: 19-32.
4. Chedid MB, Chedid MF, Porto NS, Severo CB, Severo LC (2007) Nocardial infections: report of 22 cases. *Rev Inst Med Trop Sao Paulo* 49: 239-246.
 5. Pottumarthy S, Limaye AP, Prentice JL, Houze YB, Swanzy SR, et al. (2003) *Nocardia veterana*, a new emerging pathogen. *J Clin Microbiol* 41: 1705-1709.
 6. Rodrigues-Nava V, Couble A, Molinard C, Sandoval H, Boiron P, et al. (2004) *Nocardia mexicana* sp. nov., a new pathogen isolated from human mycetomas. *J Clin Microbiol* 42: 4530-4535.
 7. Tendolkar UM, Varaiya A, Ahuja AS, Motwane SA, Gogate AS (1998) Corneal ulcer caused by *Nocardia asteroides* in a patient with leprosy. *J Clin Microbiol* 36: 1154-1156.
 8. Nocard EI (1888) Note about the disease of cattle of Guadeloupe, known for farcy. *Ann Inst Pasteur* 2: 293-302.
 9. Eppinger H (1891) About a new pathogenic Cladothrix and induced them pseudotuberculosis (cladothrichica). *Posts Path Anat* 9: 287-328.
 10. Pal M (1982) Etiological significance of *Nocardia asteroides* in corneal ulcer of cattle. *Curr Sci* 51: 533-534.
 11. Pal M (1999) Nocardiosis: a saprozoosis. *Vet* 23: 13-14.
 12. Centers for Disease Control and Prevention (2016) Nocardiosis, Atlanta, USA.
 13. Saubolle MA, Sussland D (2003) Nocardiosis: review of clinical and laboratory experience. *J Clin Microbiol* 41: 4497-4501.
 14. Wilson JW (2012) Nocardiosis: updates and clinical overview. *Mayo Clin Proc* 87: 403-407.
 15. Pal M, Tesfaye S, Boru BG (2011) Nocardial infections of canines and felines. *Indian Pet J* 3: 29-34.
 16. Roth A, Andress S, Kroppenstedt RM, Harmsen D, Mauch H (2003) Phylogeny of the genus *Nocardia* based on reassessed 16S rRNA gene sequences reveals underspeciation and division of strains classified as *Nocardia asteroides* into three established species and two unnamed taxons. *J Clin Microbiol* 41: 851-856.
 17. Schlaberg R, Huard RC, Della-Latta P (2008) *Nocardia cyriacigeorgica* an emerging pathogen in the United States. *J Clin Microbiol* 46: 265-273.
 18. Hamid ME, Maldonado L, Sharaf-Eldin GS, Mohammed MF, Saeed NS, et al. (2001) *Nocardia africana* sp. nov., a new pathogen isolated from patients with pulmonary infections. *J Clin Microbiol* 39: 625-630.
 19. Hattori Y, Kano R, Kunitani Y, Yanai T, Hasegawa A (2003) *Nocardia africana* isolated from a feline mycetoma. *J Clin Microbiol* 41: 908-910.
 20. Pal M (1988) Spontaneous nocardial infection in grey parrot (*Psittacus erithaagus*). *Indian Vet Med J* 12: 252-254.
 21. Pal M (1997) *Nocardia asteroides* as a cause of pneumonia in a buffalo calf. *Rev Sci Tech* 16: 881-884.
 22. Walton AM, Libke KG (1974) Nocardiosis in animals. *Vet Med Small Anim Clin* 69: 1105-1107.
 23. Ackerman N, Grain E, Castleman W (1982) Canine nocardiosis. *J Am Anim Hosp Assoc* 18: 147-153.
 24. McNeil MM, Brown JM (1994) The medically important aerobic actinomycetes: epidemiology and microbiology. *Clin Microbiol Rev* 7: 357-417.
 25. Paredes BE, Hunger RE, Braathen LR, Brand CU (1999) Cutaneous nocardiosis caused by *Nocardia brasiliensis* after an insect bite. *Dermatology* 198: 159-161.
 26. Pal M, Khan ZU (1979) Mastitis in a cow due to *Nocardia asteroides*. *Vet Res Bull* 2: 175-176.
 27. Emmons CW, Binford CH, Utz JP, Kwon-Chung KJ (1977) *Medical mycology* (3rd edn). Lea and Febiger, Philadelphia, USA, pp. 592.
 28. Brown-Elliot BA, Brown JM, Conville PS, Wallace RJ Jr. (2006) Clinical and laboratory features of the *Nocardia* spp. based on current molecular taxonomy. *Clin Microbiol Rev* 19: 259-282.
 29. Lovett IS, Housang ET, Burge S, Turner-Warwick M, Thomson FD, et al. (1981) An outbreak of *Nocardia asteroides* infection in a renal transplant unit. *Q J Med* 50: 123-135.
 30. Filice GA (2005) Nocardiosis in persons with human immunodeficiency virus infection, transplant recipients, and large, geographically defined populations. *J Lab Clin Med* 145: 156-162.
 31. Kiska DL, Hicks K, Pettit DJ (2002) Identification of medically relevant *Nocardia* species with an abbreviated battery of tests. *J Clin Microbiol* 40: 1346-1351.

Acknowledgements

The authors are very grateful to Raj and Anubha for their timely computer help in the preparation of this manuscript.