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Review Article

Nocardia: Updated microbiological review

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Abstract

Nocardiosis caused by *Nocardia* species is a neglected tropical disease with a broad spectrum of clinical manifestations and a diverse geographic distribution. This review focuses on the epidemiology of *Nocardia* species infections, emphasizing a systematic approach to diagnosis and treatment. *Nocardia* can be elusive, often progressing to chronic infections if not promptly identified. Due to its nonspecific presentation, a lack of clinical suspicion frequently leads to missed diagnoses, increasing morbidity and mortality. Understanding the local epidemiology, demographics, clinical course, diagnostic modalities, and antibiotic susceptibility patterns of dominant *Nocardia* species is crucial for controlling its spread. This systematic review provides an updated microbiological overview of *Nocardia* species.

Keywords: Nocardia, Taxonomy, Prevalence, Clinical features, Diagnosis, Treatment

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1. Introduction

Edmond Nocard in 1888 described the genus *Nocardia* as a form of lymphadenitis that affects cattle.[1] Eppinger reported the first human case of nocardiosis in 1890.[2] *Nocardia* is a genus of aerobic actinomycetes which are gram-positive bacteria that appear on microscopy as branching, filamentous cells. *Nocardia* species are ubiquitous in the environment causing wide variety of infections in animals and humans.[3]

With the advancement in diagnostic modalities and the increasing population of immunocompromised hosts there has been a surge in the morbidity and mortality caused by the *Nocardia* spp. Post organ transplant patients, patients having immunocompromised states due diseases like Acquired Immunodeficiency Disease Syndrome (AIDS), malignancies, diabetes, profound neutropenia or those who are undergoing immunosuppressive therapies, chemotherapy, and antirejection regimens, are more commonly affected.[4]

1.1. Epidemiology

The estimated new cases of nocardial infection are about 500-1000 every year with a male preponderance of 3:1. Infection can be acquired by inhalation of aerosols containing bacteria, traumatic inoculation and hospital acquired infection through contaminated medical equipments, surgical site infection.[5] Disseminated nocardiosis usually occurs as a lesion in the lungs (40%), central nervous system (CNS) (20– 40%) and as various kinds of deep seated abscesses involving different parts of the body.[6]

Primary cutaneous nocardiosis can occur in immunocompetent patients through percutaneous route via single or multiple bacterial inoculations.[7] Nocardiosis is diagnosed in 1–5% of patients in whom pulmonary tuberculosis is suspected, and tuberculosis and nocardiosis can occur in the same patient simultaneously.[8] AIDS being an immunocompromised state was previously considered to be among the predominant factors leading to nocardiosis but the recent studies suggest that due to use of active Antiretroviral therapy nocardiosis is less likely to occur in these patients.[9] Incidence of *Nocardia* infection in recipients

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of organ or hematopoietic stem cell transplant (HSCT) is much higher than that of the general population.[10]

Primarily pulmonary infection occurs in the paediatric age group due to underlying immunocompromised state followed by central nervous system (CNS) infection.[11] Approximately 30% of immunocompetent children can also get infected with *Nocardia* and present as lymphocutaneous disease, orbital cellulitis, arthritis, or pneumonia.[12,13,14]

1.2. Taxonomy of nocardia

With the advancement in molecular technology, the taxonomy of Genus *Nocardia* had undergone numerous changes. The etiological agent isolated by Nocard from the infected cattle was named in 1889 by Trevisan as *Nocardia farcinia*.[1] *Cladothrix asteroids* which was isolated from human brain abscess was subsequently renamed as *Nocardia asteroid*.[15]

Six drug pattern types were identified among the members of *N.asteroides* complex.These included *N. abscessus* (drug pattern i), *Nocardiabrevicatena/N. paucivorans*(drug pattern ii), *Nocardia nova* complex (drug pattern iii), *Nocardia transvalensis* complex (drug pattern iv), *N. farcinica*(drug pattern v), and *N. cyriacigeorgica*(drug pattern vi).[4]

Molecular methods like gene sequencing are preferred over biotyping to differentiate among the clinically relevant species. 16S rRNA, *secA1*, *hsp65*, *gyrA*, and *rpoB* gene have been evaluated to adequately discriminate among the various *Nocardia* species.[16]

1.3. Pathogenesis

Nocardia is ubiquitous in nature and can be found in soil and decaying organic matter.[17] In the immunocompetent host, majority of infections occur following traumatic inoculation and due to adequate immune response, it remains localized whereas in immunocompromised host the infection gets established and can spread to various body sites.[18]

Nocardia spp. predominantly infects lung. Pulmonary nocardiosis usually occurs following inhalation of nocardial spore or mycelial fragment from the environment. In the immunocompetent person, the disease may present as mild clinical infection like pharyngitis, bronchitis.[1] Patients having underlying immunocompromised state or suffering from some chronic lung disease or on long term steroid therapy may present with cough, thick purulent sputum, fever, weight loss and malaise resembling Mycobacterial infection.[4] Impaired ciliary clearance in the Cystic fibrosis patients predisposes them to *Nocardia* infection. This infection is characterized by acute inflammation, necrosis, and formation of abscesses, while granulomas are not usually formed.[19]

Most common non-pulmonary site to get infected by *Nocardia* is Central nervous system (CNS).[1] Upto 45% CNS involvement occurs in patients with systemic nocardial infections and 40% of CNS infections has been seen in isolated cases without evidence of infection elsewhere.[20] *Nocardia* shows tropism for the brain cells. It has an adhesion factor for attachment and an invasion factor for penetration. *Nocardia* can adhere with all major regions of the brain. The most common manifestation of CNS involvement is Brain abscess. Meningitis, diffuse cerebral infiltration or spinal cord infections have also been observed.[21] Brain abscesses can be supra-tentorial, often multi-loculated, single or multiple. Isolated Nocardial brain abscess may show insidious onset, with a reported mortality rate of 55% in immunocompromised patients and 20% in immunocompetent patients; these rates increase to 66% with multiple abscesses.[22] European cohort of solid organ transplant recipients with CNS nocardiosis has observed that 43.3% patients had no neurological symptoms and therefore recommends performing brain imaging on all patients with demonstrated or suspected invasive nocardiosis.[7]

N.brasiliensis predominantly causes primary cutaneous nocardiosis. Infection usually occurs in immunocompetent hosts following traumatic inoculation of the micro-organism from contaminated soil.[23] It can be of four clinical types: mycetoma, lymphocutaneous infection, superficial skin infection (abscess or cellulitis), and secondary cutaneous involvement with disseminated disease.[1] Lesions can be in form of expanding nodules, cellulitis or ulcerative in nature. Some of them may develop into mycetoma.[24] Cases having abscess with satellite pustules and lymphadenopathy should be evaluated for cutaneous nocardiosis.[25]

Disseminated nocardiosis has been observed mostly in immunocompromised patients.[26] Corticosteroid therapy affects the functioning of leukocytes by decreasing their entry into the infectious site and thereby reducing the clearance of bacteria by the reticuloendothelial system.[27] Nocardia can hematogenously disseminate to eyes, thyroid gland, heart valves, liver, spleen, and organ tissues.[23]

Nocardia also causes Health care associated infections. Since *Nocardia* is ubiquitous in nature and also found in the soil, hospital environmental dust settling in the wards, medical instruments can result in infectious consequences.[28] *Nocardia* spp. that cause clinical CLABSI also form heavy biofilm on the surfaces of polyurethane and silicone CVC.[29]

1.4. Laboratory diagnosis

Isolation of Nocardia spp. does not necessarily indicates infection. It is ubiquitous in distribution and also found as laboratory contaminant. Diagnosis of *Nocardia* spp. from the respiratory tract and skin should be made by assessing the sign and symptoms of patient and the microbiological diagnosis including direct visualization of the microorganism on a Gram-stained smear, pure or predominant growth in the culture, and repeated isolation from serial clinical samples.[30]

Sample deposited for Nocardial diagnosis from respiratory system can be sputum, bronchioalveolar lavage fluid, bronchial washings. Pus aspirates from abscesses, wound drainages, tissue or skin biopsies, sterile body fluids.[17] Gross inspection of the sample should be done to check for the presence of granules. If present then they should be removed from the sample, washed with saline, crushed between the glass slide and examine microscopically.[28]

Direct microscopic visualization of the sample should always be done by both Gram stain and modified Acid-Fast stain whenever Nocardiosis is suspected. This not only guides for the empiric treatment but also because *Nocardia* shows variable acid-fast property which may be lost in sub cultured samples.[17] Smears should be prepared in duplicate for staining. Gram stain shows positive, beaded, fine right-angled branching filaments which may fragment to form rods and coccoid forms of varying sizes.[30] Modified acid-fast stain (Kinyoun technique using 1% sulphuric acid) shows partially acid-fast nature of *Nocardia*.[32]

Nocardia spp. can grow on wide variety of culture media like sheep blood agar, chocolate agar, brain-heart infusion agar, Lowenstein Jensen media and Sabouraud agar. Thayer-Martin (MTM) media and selective buffered charcoal-yeast extract agar are commonly used for the isolation of *Nocardia* from specimens that may be contaminated with mixed bacteria. *Nocardia* has unique ability to utilize paraffin as sole source of carbon and therefore, paraffin agar or paraffin bait technique is also helpful in its isolation. *Nocardia* is relatively slow growing and therefore inoculated media should be incubated for minimum of 2 weeks (3 weeks for tissue specimen) at 37°C in aerobic conditions enriched with 5% carbon dioxide in a humid atmosphere to avoid drying.[7,18,33] A single *Nocardia* colony isolated from sterile body fluids like CSF and from patient with clinical signs suggestive of *Nocardia* should never be ignored but the same organism should be isolated on repeated culture before making the final diagnosis.[17,21] *Nocardia* colonies are slightly raised dome shaped, aerial hyphae impart chalky appearance to the surface of colonies, carotenoid like pigment production imparts yellow, orange, pink or red color to colonies. Musty basement or freshly turned soil like odour gives the clue to diagnosis.[1,18,21,33]

Biotyping is of limited use in *Nocardia* speciation. Conventional biochemical test are unable to precisely discriminate among the newly found *Nocardia* spp. In addition, the type of biochemical test reported as typical for a new species are not consistent from species to species hence, making the accurate identification impossible.[16] Biochemical test that are helpful in differentiating the more common clinically significant *Nocardia* spp. has been listed in **Table 2**. Serodiagnostic test are not the useful tool for diagnosis of active nocardiosis. Lack of sensitivity and specificity due to cross reactivity among pathogenic *Nocardia* spp. and other actinomycetes, and with sera from patients with tuberculosis and leprosy hinders the serological studies.[17]

Molecular methods have become the most reliable and rapid method for precise speciation of Nocardia spp. Besides this, these methods also help us to understand the heterogenous nature of this group of organisms. A *Nocardia* genus specific PCR targetting 16S rRNA gene is used as a molecular diagnostic tool for the clinical sample. For research purposes multilocus sequence analysis (MLSA) of *Nocardia* housekeeping genes: 16S rRNA gene region, heat shock protein (hsp65) gene, essential secretory protein gene (secA1), DNA gyrase gene (gyrA) (gyrB), and RNA polymerase B gene (rpoB), superoxide dismutase gene (sodA) is done. Combination of (2–3) of these genes helps in accurate identification.[7,19,28,34,35] Recently, MALDI TOF-MS has been found helpful in diagnosing Nocardia spp. With the updated data base common species like *N.brasiliensis*, *N.farcinica* can be easily identified, for others identification has only been shown to extend to the complex level (*N. abscessus* complex, *N.brevicatena-N.paucivorans* complex, *N. nova* complex, and *N. transvalensis* complex). Uncommon species with limited or no representation in the databases are the most difficult to identify.[7,16] Rapid molecular identification of *Nocardia* spp. can also be done by DNA probes, DNA sequencing, Next Generation Sequencing, (NGS), pyrosequencing, ribotyping, and restriction fragment length polymorphism analyses.[28,36]

1.5. Management

Nocardial infections are treated both medically as well as surgically. Basis of treatment depends upon site and severity of infection, drug toxicity, species of *Nocardia* involved. Clinical and Laboratory Standards Institute (CLSI) has approved broth micro dilution method for susceptibility testing. Testing is recommended when patient has deep seated or disseminated infection, failure to respond to initial therapy or relapse after therapy, and those isolates in whom sulphonamides cannot be used.[3]

As recommended by CLSI, the following drugs are tested by micro dilution method: amikacin, amoxicillin-clavulanate, ceftriaxone, ciprofloxacin, clarithromycin, imipenem, linezolid, minocycline, sulfamethoxazole or trimethoprim- sulfamethoxazole and tobramycin.[37] Laboratory where microdilution is not been done regularly, can send their samples to experienced reference laboratory.[31] E-test has shown to correlate well with broth microdilution and is easier to use for checking the susceptibility profile of the isolate in routine clinical laboratory.[39]

Every *Nocardia* species have shown predilection for different infection sites. *N. farcinica* has been predominantly isolated in blood cultures and brain abscesses/cerebrospinal fluid. *N. brasiliensis* has preponderance for skin and soft tissue infections. Accurate species-level identification is therefore necessary for nocardiosis due to discrepancies of

drug patterns among the clinically significant species. The antimicrobial susceptibility profile is highly variable between the *Nocardia* species, but in general, amikacin, linezolid, and TMP-SMX demonstrated good in vitro activity against most species.[1,4,39,40]

Sulphonamides (cotrimoxazole) have been the treatment of choice for Nocardial infections. According to CLSI, (<2/38 mg/L is considered as the susceptible breakpoint for *Nocardia* and >4/76 mg/L as the resistant breakpoint).[37,38] Minocycline is used in patients intolerant or resistant to sulfonamides for less-severe infections such as skin, soft tissue or respiratory infection. Amikacin, imipenem, linezolid and ceftriaxone (normally in combinations) are used for more life-threatening infections [20]. *Nocardia* is a slow growing organism and has tendency to relapse. Prolonged therapy for few to several months is required along with close monitoring to look after the signs of drug toxicity (**Table 3**).[8,28]

A study from Spain showed that *N.cyriacigeorgica* has resistance rates of up to 70% for amoxicillin/clavulanate, erythromycin, minocycline and ciprofloxacin, and <5% for cefotaxime, imipenem, amikacin, tobramycin, trimethoprim/sulfamethoxazole and linezolid. *N.nova* was very resistant to ciprofloxacin and minocycline (□90%) and resistant to amoxicillin/clavulanate and tobramycin (68% and 48%, respectively). *N.farcinia* high resistance rates (□90%) were recorded for tobramycin, clarithromycin and minocycline. For the successful treatment of nocardiosis, the species involved in an infection must be known it would better guide treatment choices.[39] Another study done in China for 12 years, they found all *Nocardia* strains were susceptible to linezolid, followed by amikacin (99.3%) and TMP-SMX (99.1%). For tetracyclines, doxycycline and minocycline-resistant *Nocardia* accounted for 2.0 and 0.9%, respectively.73.9% *Nocardia* strains were found to be resistant to clarithromycin. Beta-lactam antibiotics, including imipenem, cefepime, cefoxitin, amoxicillin-clavulanic acid, and ceftriaxone, showed poor performance against *Nocardia* spp.[40] Another 6 years study from Northern India found that 91.6% of the isolates were sensitive to cotrimoxazole. In renal transplant patients Cotrimoxazole showed 76%.[41]

Surgical management will depend upon the site and severity of infection. Surgical management will be similar to other bacterial disease. Patients with brain abscesses are initially managed medically but if the lesion remains progressive even after 2 weeks of starting the therapy or there is no reduction in abscess size within 1 month then surgical intervention is done. Decompression of lesions, craniotomy and total excision are done.[3,8,42]

Table 1: Case Reports of *Nocardia* spp. in immunocompetent paediatric age group from India

Author, year	**Place**	***Nocardia* spp.**	**Age**	**Site of involvement**	**Treatment**
N P Singh et.al, 2003[43]	Delhi North India	*N. farcinia*	2 months	Disseminated disease	Cotrimoxazole Amikacin
T.sathishkr et.al[44]	Kottayam South India	*Nocardia* spp.	1 year	Cervico facial nocardial infection	Cotrimoxazole Chloramphenicol
SweetyTiple et.al, 2020[45]	Delhi North India	*Nocardia* spp.	15 months	Nocardial endophthalmitis	Cotrimoxazole
Netto Jacob et.al, 2019[46]	Kottayam South India	*Nocardia yamanashiensis*	5 months	Swelling in left arm	Drainage of abscess, Cotrimoxazole
Dias M, 2009[47]	Mangalore South India	*N.asteroides*	8 months	Lungs	Thoracotomy, Cotrimoxazole
Meshram R.M et.al, 2016[48]	Nagpur West India	*Nocardia* spp.	9 year	Abdomen	Cotrimoxazole
Poovazhagi et.al, 2012[49]	Chennai South India	*N.asteroides*	8 year	Lungs	Cotrimoxazole

Table 2: Biochemical test for differentiating the more common clinically significant *Nocardia* spp.

Organism	**Modified Acid-Fast**	**Growth In Lysozyme**	**Decomposition**					**Gelatin Hydrolysis**
			Casein	**Tyrosine**	**Xanthine**	**Hypoxanthine**	**Urease**	
Nocardia asteroides	+	+	-	-	-	-	+	-
Nocardia brasiliensis	+	+	+	+	-	+	+	+
Nocardia otitidiscaviarum	+	+	-	-	+	+	+	-
Nocardia transvalensis	+	+	-	-	-	+	+	-

Nocardia farcinica	+	+	-	-	-	-	+	-
Nocardia nova	+	+	-	-	-	-	V	-
Nocardia pseudobrasiliensis	+	+	+	+	-	+	+	+

Table 3: Treatment Duration for Nocardiosis

Disease	**Duration**
Pulmonary or systemic Intact host defenses Deficient host defenses CNS disease	 6–12 months 12 months[a] 12 months[b]
Cellulitis, lymphocutaneous syndrome	2 months
Osteomyelitis, arthritis, laryngitis, sinusitis	4 months
Actinomycetoma	6 to 12 months after clinical cure
Keratitis	Topical: until apparent cure Systemic: until 2-4 months after apparent cure
[a]In some patients with AIDS and CD4+ T lymphocyte counts of <200/µL or with chronic granulomatous disease, therapy for pulmonary or systemic disease must be continued indefinitely. [b]If all apparent CNS disease has been excised, the duration of therapy may be reduced to 6 months.	

2. Conclusion

Nocardia species can cause infection not only in immunosuppressed patient but also in immunocompetent host. Underlying host immunity, site and extent of involvement, *Nocardia* species causing infection, dose and duration of therapy determines the clinical outcome of the patient. Delay in diagnosis and incomplete treatment leads to poor outcome. Good clinical specimen, microscopy, phenotypic methods of detection and advance diagnostic modalities are helpful in speciation. Isolates should be sent to reference laboratories for detailed identification and antibiotic susceptibility testing.

3. Source of Funding

None.

4. Conflict of Interest

None.

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