

Why Is The Identification of Causative Agent of Nocardiosis Essential at The Species Level?

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Nocardia is a genus of weakly gram-positive, filamentous, aerobic, relatively slow-growing and partially acid-fast bacteria. These bacteria are ubiquitous in environmental resources such as water, soil, dust, decomposing animal feces, and vegetables. This group of bacteria can enter the human body through inhalation and traumatic cutaneous inoculation and cause *Nocardia* infections. There are various types of nocardiosis including pulmonary, brain, cutaneous, cutaneous-lymphatic, and ocular infections. These infections often occur in immunocompromised patients including organ transplant recipients, corticosteroid drugs consumers, human immunodeficiency virus (HIV) patients, cancerous and even healthy individuals [1-3].

Identification of the *Nocardia* species is necessary due to differences in the pattern of drug susceptibility of species and for epidemiological studies as well [4]. These infections are often misdiagnosed with the viral infection, mycoplasma, fungi, cancer, and tuberculosis. Reports from Iran shows an incidence rate of about 1.88% [3]. Phenotypic (conventional) methods and molecular techniques are commonly used to identify the *Nocardia* species. Conventional diagnosis is based on colony morphology, Gram and Kinyoun stains, resistance to lysozyme broth, ability to grow at 45°C, decomposition of casein, xanthine, hypoxanthine, esculin, adenine and gelatin, and utilization of citrate, acetamide, and carbohydrates as a sole source of carbon and nitrogen. This approach is often costly and time-consuming and requires trained technicians, yet leads to the wrong diagnosis in 37% of cases [4]. The current molecular methods such as PCR amplification of 16S rRNA and Heat Shock Protein gene followed by restriction fragment length polymorphism (PCR-RFLP), and sequencing of the conserved regions of 16S rRNA, *hsp65*, *gyrB* and *sodA* genes have proven to be faster and more accurate tools than the conventional methods [4-5].

Initially, *Nocardia asteroides* was assumed to be the only causative agent of nocardiosis. However, studying 78 clinical samples from *Nocardia* patients revealed six different antimicrobial susceptibility patterns for 12 antimicrobial agents (ampicillin, amoxicillin-clavulanic acid, ceftriaxone, linezolid, amikacin, imipenem, ciprofloxacin, clarithromycin, gentamicin, kanamycin, erythromycin, sulfamethoxazole). Later, advances in molecular sciences showed that *Nocardia asteroides* were a

group of bacteria with high genetic similarities and were designated as *Nocardia asteroides* complex [6, 1]. Wallace and colleagues described six drug susceptibility pattern types among 78 clinical isolates previously identified as “*Nocardia asteroides*.” Their work was the most significant study of antimicrobial susceptibilities of *Nocardia asteroides* that revealed the variability of drug susceptibility patterns among the isolates and the first to show a grouping of specific susceptibility patterns. Later in the 1990s, with the development of molecular techniques, molecular taxonomy studies revealed that *Nocardia abscessus* belonged to the first drug susceptibility pattern. Similarly, *Nocardia brevicatena-paucivorans* complex was categorized in the second drug susceptibility pattern, *Nocardia nova* complex (*Nocardia nova*, *Nocardia veterana*, *Nocardia africana*, and *Nocardia kruczakiae*) in the third drug susceptibility pattern, *Nocardia transvalensis* complex (*N. transvalensis sensu stricto*, *Nocardia wallacei*, and *Nocardia blacklockiae*) in the fourth drug susceptibility pattern, and *Nocardia farcinica* and *Nocardia cyriacigeorgica* in the fifth and sixth patterns of drug susceptibility, respectively [1]. According to the difference in the susceptibility pattern of each member of the *Nocardia asteroides* complex, it can be concluded that prescription of effective antibiotics should be after the accurate identification of the causative *Nocardia* species. Also, clinical studies showed that some *Nocardia* species such as *Nocardia otitidiscaviarum* and *Nocardia beijingensis* could cause systematic infections, while other species like *Nocardia brasiliensis* cause limited local infections [1, 6-7]. Trimethoprim-sulfamethoxazole, amikacin, and imipenem are usually the first drug choices for nocardiosis [7]. However, the rate of fatality among patients with pulmonary and brain abscess who consumed trimethoprim-sulfamethoxazole ranged from 20 to 50% [8].

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Also, some patients are allergic to sulfonamide drugs, which necessitates the performance of drug susceptibility test for the *Nocardia* species isolated from the clinical specimens. According to CLSI, the standard method for determining the drug sensitivity for this group of bacteria is microdilution broth [8-9]. All pathogenic *Nocardia* species showed to be susceptible to linezolid and amikacin, except members of *N. transvalensis* complex [8]. Also, another similar study demonstrated susceptibility of clinical isolates of *Nocardia* to linezolid and their minimal resistance to trimethoprim-sulfamethoxazole. While *Nocardia pseudo-brasiliensis* and *N. transvalensis* complex, as the most common species, were resistant to trimethoprim-sulfamethoxazole [10].

In summary, due to differences in the pattern of drug susceptibility among clinical isolates of the *Nocardia* species, especially members of complex species, e.g., *Nocardia asteroides*, accurate identification of *Nocardia* species using reliable molecular tools such as sequencing of 16S rRNA fragment or *hsp*-RFLP is necessary for appropriate and successful treatment of nocardiosis.

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CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest associated with this manuscript.

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