

# Nocardiosis in a Tertiary Care Hospital in Saudi Arabia

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## ABSTRACT

**Background:** Nocardiosis is an uncommon bacterial infection that is caused by aerobic actinomycetes of the genus *Nocardia*. This pathogen has emerged as an important cause of mortality and morbidity among both immunocompetent and (more commonly) immunocompromised hosts. The prevalence of nocardiosis is unknown in Saudi Arabia. Only sporadic cases of cutaneous nocardiosis have been reported. In this study, we performed a 10-year retrospective review of all cases of nocardiosis identified at the King Fahad National Guard Hospital in Riyadh. Clinical presentation, risk factors, site of disease involvement, radiological features, and outcomes of 30 patients with pulmonary and disseminated nocardiosis are presented. **Materials and Methods:** A retrospective chart review of all cases of nocardiosis over the last ten years. **Results:** Thirty cases of nocardiosis were identified. The disease was more common in males. Fever and cough was the most common presentation. Most of the patients had an underlying pulmonary disease. Consolidation was the most prevalent radiological feature. Pleural effusion was common. Unfortunately, none of the isolates were sub-speciated. Cure was possible in 40% of the cases. Ten percent of patients died, while follow-up on the rest of the patients was lost. **Conclusion:** Nocardiosis is not uncommon in Saudi Arabia. Cases are not restricted to the classical immunocompromised host. A database is urgently needed to better evaluate the prevalence of the illness among the Saudi population.

**Key words:** Aerobic actinomycetes, *Nocardia*, Nocardiosis

## INTRODUCTION

**N**ocardiaceae is a family of aerobic, Gram-positive, filamentous higher bacteria that belong to the order Actinomycetales. The organism was first isolated by Edmond Nocard in 1888.<sup>[1]</sup>

The organisms are found in the soil and cause a wide spectrum of clinical illnesses in both immunocompetent and immunocompromised hosts. Manifestations of nocardiosis can be either localized or disseminated.<sup>[2]</sup> Disseminated nocardiosis is seen primarily in immunocompromised hosts. Risk factors for *Nocardia* infection include long-term corticosteroid exposure, malignancy, HIV infection, and a history of solid organ transplantation.<sup>[3-11]</sup>

The *Nocardia* genus contains more than 50 species that have been characterized using phenotypic and molecular methods. Approximately one-half of the species have been recognized as pathogens in humans and/or animals.<sup>[12]</sup> *Nocardia asteroides* and *Nocardia brasiliensis* are the most commonly encountered human illnesses. The aerosol route is the main portal of entry into the body, and the lungs are the most common sites of infection. Other modes of entry include ingestion of contaminated food and direct inoculation of the organism because of trauma. Human-to-human transmission has not been documented.<sup>[4,13]</sup>

The prevalence of *Nocardia* infection in Saudi Arabia is not known. Sporadic cases of nocardia infection causing mycetoma have been reported from the northwest region. Recently, the Kingdom of Saudi Arabia has become a leading center for solid organ and bone marrow transplantations in the Middle East. Infection with this opportunistic pathogen is expected to become more prevalent. The aim of this study has been to highlight

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the clinical experience of a major transplant tertiary care hospital in diagnosing and treating *Nocardia* infections. The prevalence, spectrum of illness, *Nocardia* species involved, and their sensitivity are reported.

## MATERIALS AND METHODS

The microbiology and histopathology laboratory records of King Fahad National Guard Hospital were screened from January 1, 1998 through December 31, 2006 for all cultures and histopathological samples confirmed as *Nocardia* species (spp.). A case report form was developed to retrospectively abstract and collect information from the medical records of possible cases. Positive cases were identified if the *Nocardia* spp. was isolated from a patient and the clinical course or presentation was consistent with an infection. The medical records of these patients were then reviewed retrospectively for demographic and epidemiologic characteristics, co-morbid medical conditions, presenting complaints, clinical findings, chest X-rays, CT scan findings, site of disease involvement, method of *Nocardia* spp. isolation, type of species isolated, laboratory abnormalities, medical and surgical therapy, and clinical outcome. Chest X-ray and computed tomography scan reports were reviewed and documented. If not available, films were obtained and shown to a radiologist for reporting. Clinical nocardiosis was defined according to following definitions:

1. Pulmonary nocardiosis: a positive culture from a respiratory or pleural sample in addition to respiratory symptoms and/or radiographic infiltrates.
2. Disseminated nocardiosis: isolation of *Nocardia* spp. from the blood or at least one more non-contiguous organ. Isolation of *Nocardia* from the brain, joints, multiple cutaneous lesions, or gastrointestinal lesions was considered as disseminated disease.
3. Localized nocardiosis: if the organism was isolated from sites other than the lung and brain. This would include solitary cutaneous lesions and mycetomas (local, chronic, slowly progressive destructive infections of the skin, subcutaneous tissues, fascia, bone and muscle containing suppurative granulomas and multiple sinus tracts that extrude grains).

Descriptive statistics were performed using statistical software Statistical package for the social sciences (SPSS).<sup>[17]</sup> This research project was approved by the Institutional Review Board of King Abdul Aziz Medical City in 2006.

## RESULTS

Thirty cases of nocardiosis were identified over the period

of the study. All patients' characteristics, including age, gender, nationality and site of infection, are summarized in Table 1. It is interesting to note that most of our patients had chronic respiratory problems. Chronic obstructive pulmonary disease (COPD) was the most frequent underlying pulmonary disease followed by bronchiectasis. About 30% (9) of the cases had a prior history of tuberculosis. Diabetes was the second most frequent risk factor after chronic respiratory disease, occurring in 20% of cases. Only two patients were post-transplant and three were on immunosuppressive drugs or high dose corticosteroids. There were four patients with chronic liver disease, four patients with malignancy and three patients with chronic renal failure. There were no patients with HIV. All the identified risk factors for nocardiosis are summarized in Table 2.

Dyspnea, fever, and cough were the most common presenting complaints occurring in 53.3, 56.7, and 66.7%, respectively. Hemoptysis occurred in 26% of the patients. Weight loss and night sweats occurred in about 10% for each symptom. Other symptoms are summarized in Table 3. Mild to moderate leukocytosis ( $15.1 \times 10^6 \pm 8.9$ ) was common, with a mean sedimentation rate of  $64 \pm 44.3$ .

Pulmonary nocardiosis was the most frequent involvement site in 25 cases (83.33%) while disseminated disease

**Table 1: Patients' characteristics**

Characteristic	No. (30)	%
Age	57.7±18.3	
Gender		
Male	22	73.3
Female	8	26.7
Nationality		
Saudi	27	90.
Non-Saudi	3	10
Site of involvement		
Pulmonary	25	83.3
CNS	5	16.7

**Table 2: Nocardia risk factors**

	*No.	%
COPD	13	43.3
Old TB alterations	9	30.0
Bronchiectasis	8	26.7
DM	6	20.0
Immunosuppressive drugs/ organ transplant	5	16.7
CRF	3	10.0
Neoplasm	4	13.3
Chronic liver disease	4	13.3
Others	6	20.0

\*Patients may have more than one risk factor; COPD = Chronic obstructive pulmonary disease; DM = diabetes mellitus; and CRF = Chronic renal failure

occurred in only 6(20%) of cases including five cases with Central nervous system (CNS) involvement. There were no cases of mycetoma or other localized disease.

Unfortunately, none of the isolates were sub-speciated beyond *Nocardia* spp. There were no sensitivity data reported on any of the species isolated. Sputum was the most frequent site for the isolation of *Nocardia* spp. (18 patients). Organisms were isolated either by sputum culture after bronchoscopy with a bronchoalveolar lavage (BAL), or less frequently by pleural fluid or cerebrospinal fluid cultures. Bronchoscopy was performed in five cases and the culture was positive in only two cases. The diagnosis was established by deep tissue biopsy or aspirate in nine cases. Culture findings are summarized in Table 4.

Chest X-ray findings were also variable [Table 5]. The X-ray was abnormal in more than 86% of patients. Films were missing for an additional two cases. The most frequent abnormality in the chest X-ray was consolidation followed by reticulonodular changes. Cavity lesions occurred in two cases. Pleural abnormalities in the plain films were present in 13 patients. The radiological interpretation of these abnormalities was effusion in eight cases, pleural thickness in two cases and effusion and thickness in an additional three cases. Nineteen patients had a CT chest scan performed. Cavitory lesions seen by standard X-ray were not reported in the CT scan. Consolidation was reported in eleven cases. Nodular changes were seen in two cases and interstitial changes were seen in eight cases. A mixed pattern was seen in six cases. Pleural effusion was seen in eight cases, while thickening was observed in three cases and both conditions were found in an additional three cases.

Fifteen patients were lost to follow-up; twelve patients were cured and three patients died. There were no relapses or recurrence in patients surviving the initial infection. Trimethoprim-sulfamethoxazole was used for the treatment of more than 50% of the cases once the diagnosis was established, duration of therapy ranged from 12 days to 95 days.

## DISCUSSION

This is the largest series to date of nocardiosis reported from Saudi Arabia. However, this study represents the experience of a single center, and national data remains unavailable. This series shows that pulmonary nocardiosis is an important cause of pneumonia and is not restricted to patients classically identified as having depressed cellular immunity such as patients who have undergone transplantation, patients with leukemia, patients with acquired immune

**Table 3: Major clinical symptoms**

	No. (30)	%
Dyspnea	16	53.3
Fever	17	56.7
Cough	20	66.7
Night sweats	3	10.0
Chest pain	4	13.3
Hemoptysis	8	26.7
Arthritis/arthralgia	1	3.3
CNS symptoms	2	6.7
Weight loss	3	10.0
Other	14	46.7

**Table 4: Culture sites**

	No (30)	%
Sputum	18	60.
BAL	2	6.7
Pleural fluid	1	3.3
Tissue biopsy / abscess puncture	9	30
CSF	1	3.3
Others	6	20.

\*Patients may have more than one procedure, CSF = cerebrospinal fluid

**Table 5: Chest X-ray findings**

Normal	2	6.7
Not available	2	6.7
Abnormal	26	86.7
Mediastinal LN	0	0.0
Hilar LN	1	3.8
Parenchymal		
Normal	2	7.7
Abnormal	24	92.3
Reticulonodular	10	16.7
Consolidation	14	58.3
Cavity	2	8.3
Mass	1	4.2
Pleural	13	54.2
Effusion	8	61.5
Thickening	2	15.4
Both	3	23.1

deficiency virus infection or patients who have received prolonged high-dose treatments with glucocorticoid or cytotoxic therapies. COPD and bronchiectasis patients do generally receive courses of steroid therapy, but these are usually short and do not alert treating physicians of a significant dysfunction in cellular immunity. Martinez and associates recently published their experience with pulmonary nocardiosis over a 13-year period and noticed a prevalence of nocardiosis in this patient population.<sup>[4]</sup> Similarly, Munoz and his group in their series of 27 cases identified 70% of their patients as having COPD.<sup>[14]</sup>

Diabetes was also common among our patient population and consisted of 20% of cases. Whether this relatively

high prevalence is a true risk factor for nocardiosis or is due to the high prevalence of diabetes mellitus (DM) in Saudi Arabia in general is unknown. However, DM has not previously been reported as a major risk factor for *Nocardia* infection.

The epidemiologic characteristics of our patient population with nocardiosis were similar to what has been reported in the literature.<sup>[4,13]</sup> The male predominance in both pulmonary and disseminated disease was previously reported.<sup>[10,12,15]</sup> Hemoptysis and weight loss were relatively common in our series (10%). This could be due to the prevalence of bronchiectasis and previous tuberculosis in our patient population rather than a sole manifestation of pulmonary nocardiosis. Fever and cough are the most frequent presentation complaints of pulmonary nocardiosis in most reported cases. Some investigators reported chronic obstructive pulmonary disease (COPD) exacerbation to be a common presenting complaint.<sup>[16]</sup>

The presence of *Nocardia* spp. in a respiratory sample does not always indicate a disease process. In our series, the total number of isolates was 52, of which 30 were associated with a disease process. Rosett isolated *Nocardia* spp. from respiratory secretions in 36 patients, 19 of whom were free of disease.<sup>[17]</sup> Several studies have shown that COPD is the disease most often treated with corticosteroid therapy and is therefore probably prone to nocardiosis infection more than other respiratory conditions.<sup>[17-19]</sup> The clinical features of *Nocardia* were similar to those in previous studies. The clinical findings of *Nocardia* were nonspecific, with a chronic course found in 70% before diagnosis. Leukocytes were moderately elevated with a predominance of neutrophils. Chest radiographic manifestations were pleomorphic as described above. Similar to what was reported in other studies, consolidation was the most frequent radiological finding (58.30%); masses appeared in 20%, and a predilection for the upper lobes was also observed (70%) of *Nocardia* in patient with COPD. Feigin, in a review of 21 cases, described similar patterns and emphasized the presence of cavitations due to the necrotizing tendency of the abscesses and the association with obstructive pulmonary disease.<sup>[19]</sup> In another study of 21 patients with HIV infections, Kramer and associates observed the following radiographic findings: consolidation (52%), bilateral interstitial pattern (33%) and solitary mass (24%). Cavitations were present in 62% of the patients, and pleural effusion in 33%.<sup>[20]</sup> The differential diagnosis of a solitary mass in an immunocompromised host must include pulmonary nocardiosis. In patients with acquired immune deficiency syndrome (AIDS) with superior bilateral infiltrates,

pulmonary nocardiosis should be taken into account because, in AIDS patients, pulmonary tuberculosis does not normally show cavitations or upper lobe lesions. Pulmonary disease is the most common presentation in immunosuppressed patients and approximately one-third has a disseminated disease. Most of the cases in our study involved the lungs (83.33%) while one case involved lungs and CNS and 5 cases involved the CNS. The diagnosis can be challenging, as signs and symptoms are not specific and a high index of clinical of suspicion is necessary.

In our series, sputum cultures yielded a positive result in only 60% of cases (18 of 30). BAL was obtained in five cases with two (6.9%) cases yielding positive results. This low yield could not be explained since other studies have reported 100% yield with this procedure.<sup>[21]</sup>

Chronic respiratory disease was the most prevalent risk factor for nocardiosis in our study population. One caveat in our study was that we could not consistently evaluate the doses and duration of steroids given to these patients. Martinez *et al.* reported nocardiosis in 31 patients, four of whom had COPD, and three patients were on steroids for autoimmune disease.<sup>[4]</sup> One patient had inhaled beclomethasone as the only form of steroid used but for an unknown duration. With other patients, steroids were used for a minimum of two weeks. The mean dose of steroid used was 30mg prednisolone per day.<sup>[4]</sup>

One deficit in our retrospective study is the high number of patients lost to follow-up (half of the total number of patients). This high number could be explained by the antibiotics given to the patients upon discharge from hospital and as a result, failure of the patient to return for follow-up or be given follow-up at another hospital. This is an issue since our hospital is a referral nexus for patients from other areas in the Kingdom. Twelve patients were cured and three patients died. There were no infectious relapses or recurrence in patients surviving the initial infection.

## CONCLUSIONS

Pulmonary nocardiosis is common in the Saudi population, particularly among patients with chronic respiratory illnesses. This entity should be kept as a differential diagnosis from pneumonia for all patients with COPD especially if there is a history of steroid use for more than 10-14 days. Clinical and radiologic presentations can vary greatly. Physicians should always keep a high degree of suspicion for this rare form of infection since its treatment is simple and is usually associated with good prognosis.

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