

Clinical Characteristics and Treatment Outcome of Central Nervous System Nocardiosis: A Systematic Review of Reported Cases

Durga Shankar Meena Deepak Kumar Gopal Krishana Bohra Naresh Midha Mahendra Kumar Garg

Department of Internal Medicine, All India Institute of Medical Sciences, Jodhpur, India

Highlights of the Study

- *Nocardia farcinica* is the commonest species, and corticosteroid use is the most common risk factor associated with nocardiosis of the central nervous system. However, 34% of patients are found to be immunocompetent.
- The overall case-fatality rate is 22.8%, and brain abscess is the most common neuroimaging finding.
- A combined approach of antimicrobials with surgery is associated with better survival compared to patients who are treated with antimicrobials alone.

Keywords

Nocardia · Central nervous system infections · Meningitis · Brain abscess · Trimethoprim-sulfamethoxazole · Antimicrobial susceptibility

Abstract

Background: The clinical spectrum of systemic nocardiosis encompasses pulmonary and disseminated disease. Central nervous system (CNS) involvement is an important feature of disseminated disease with significant mortality and high relapse rate, especially in those with suppressed cell-mediated immunity. This systematic review aimed to evaluate the epidemiology, clinical features, diagnosis, therapeutic interventions, and outcome in patients with CNS nocardiosis. **Methods:** A literature search was performed in major databases (PubMed, Google Scholar, and Scopus) by using distinct keywords: “CNS disease,” “*Nocardia*,” “meningitis,” “brain abscess,” “disseminated disease,” and “Cotrimoxazole.” We included all patients ≥ 18 years with CNS nocardio-

sis reported between January 2000 and December 2020. **Results:** A total of 129 papers were included in the final analysis. The mean age of patients was 55 ± 16 years, and the majority were male (70.8%). *Nocardia farcinica* was the commonest species (39.6%), followed by *Nocardia nova* (5.9%). Thirty-four percent of the patients were found to be immunocompetent. Corticosteroid use was the most common predisposing factor (55.8%). Among neuroimaging findings, brain abscess was most common (86.9%), followed by leptomeningeal enhancement (12.1%). The overall case-fatality rate in CNS disease was 22.8%. On multivariate analysis, patients who underwent surgery (OR 2.4, 95% CI 0.99–4.11, p value 0.046) had better survival than those treated with antimicrobial therapy alone. Immunodeficient state (OR 0.32, 95% CI 0.15–0.90, p value 0.019) was independently associated with poor outcome. **Conclusion:** CNS nocardiosis carries significant mortality, especially in immunodeficient patients. We advocate the use of surgery combined with antimicrobials to improve clinical outcome.

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Published by S. Karger AG, Basel

Introduction

Nocardia is a Gram-positive bacillus with the ability to cause localized or systematic suppurative disease. It is generally considered to be an opportunistic pathogen; however, up to one-third of the cases occur in immunocompetent [1, 2]. The central nervous system (CNS) is the second most common site of infection, usually through dissemination from primary pulmonary focus. CNS involvement can be seen in 3–26% of patients with nocardiosis (depending on patient population) [3–6]. The clinical presentation of CNS nocardiosis is diverse and sometimes subtle, especially in immunodeficient patients, which makes it difficult to diagnose. Data regarding CNS disease in *Nocardia* infection are sparse due to its rare presentation, and management depends mainly on expert opinion and case studies [5–8]. A comprehensive review of CNS nocardiosis described the common risk factors and various clinical presentations of CNS disease in 84 cases [6]. The clinical characteristics of CNS nocardiosis are constantly evolving; furthermore, the advent of modern diagnostic tools and the increasing use of immunosuppressants also warrant an updated review. To better understand the various clinical predictors of outcome that were not reported in previous studies, we performed a systematic review of CNS nocardiosis and analyzed cases from the past 20 years.

Methods

Search Strategies and Study Selection

We performed an initial search of the literature to identify all the cases with reported CNS manifestations due to *Nocardia*. This review was performed in accordance with the preferred reporting items for systemic review and meta-analyses (PRISMA) guidelines [9]. A literature search was performed by using different electronic databases of the English literature (PubMed, Google Scholar, and Scopus). Our literature search was focused on reports published between January 2000 and December 2020. Similar review was published earlier which includes cases from 2000 to 2014; however, we also analyzed different predictors of mortality in CNS nocardiosis, which was missing in previous review [6]. The keywords “CNS disease,” “*Nocardia*,” “meningitis,” “brain abscess,” “disseminated disease,” and “Co-trimoxazole” were searched in various combinations (online suppl. file 1; for all online suppl. material, see www.karger.com/doi/10.1159/000525509). To prevent the bias, two independent reviewers assessed all the full articles based on eligibility, and the possible discrepancies were resolved by the consensus of both reviewers.

Qualitative Assessment

All the eligible reports entered were evaluated for risk of bias utilizing the Critical Appraisal Skills Programme checklist. The

risk of bias in selected cases was ranked as low, moderate, and high. Reports with high risk of bias were excluded.

Case Definition and Inclusion Criteria

We included 206 cases with CNS *Nocardia* infection in this systematic review. Our final analysis included patients who met the following criteria: (a) presence of *Nocardia* species in the clinical samples (cerebrospinal fluid [CSF], respiratory samples like bronchoalveolar lavage, abscess/tissue culture) along with the clinical and radiological findings compatible with CNS nocardiosis [10–12], (b) cases of CNS nocardiosis published between 2000 and 2020, (c) cases in which culture was inconclusive, but identification of *Nocardia* species by molecular methods (PCR) and radiological and clinical findings compatible for CNS nocardiosis. We included all patients with age ≥ 18 years, detailed documentation of clinical history, diagnostic methods, treatment modalities, outcome, and follow-up in the analysis. The effect of antimicrobial therapy in nocardiosis is gradual, particularly in CNS disease. Thus, only cases with a follow-up of at least 6 months after the commencement of antibiotic therapy were included in the responder group. Review articles, editorials, conference papers/posters were excluded.

We extracted the following data from the literature search: demographic details, predisposing factors, and comorbidities related to invasive nocardiosis, laboratory diagnosis methods (PCR, histopathology, culture), type and duration of antibiotic therapy, and case fatality rate. For the screening of risk factors, patients who took corticosteroids (≥ 10 mg/day for at least 6 weeks), received solid organ/stem cell transplant, and took long-term immunosuppressants were considered as immunocompromised.

Statistical Analysis

Data analysis was conducted by using SPSS software, version 20.0 (IBM Corp, Armonk, NY, USA). All descriptive data were summarized and tabulated with continuous variables in the form of mean \pm standard deviation and categorical data in the form of number (percentages). We also compared the various clinical predictors of survival (age, gender, clinical presentation, type of *Nocardia* species, immunocompromised state, disease dissemination, and treatment). Univariate analysis was performed to determine the various clinical predictors of survival (age, gender, clinical presentation, type of *Nocardia* species, immunocompromised state, treatment modalities). Statistically significant variables on univariate analysis ($p < 0.05$) were selected for multivariate analysis. Multivariate results were presented as odds ratio and their 95% confidence intervals.

Results

We found 896 case records in the initial electronic database search, which were analyzed for final inclusion. A total of 599 reports were assessed for further inclusion after the removal of duplicate reports, and 129 articles (206 patients) were included in the final analysis (Fig. 1). Out of 129 records, 114 were from individual data and 15 were case series. The majority of the patients were Cau-

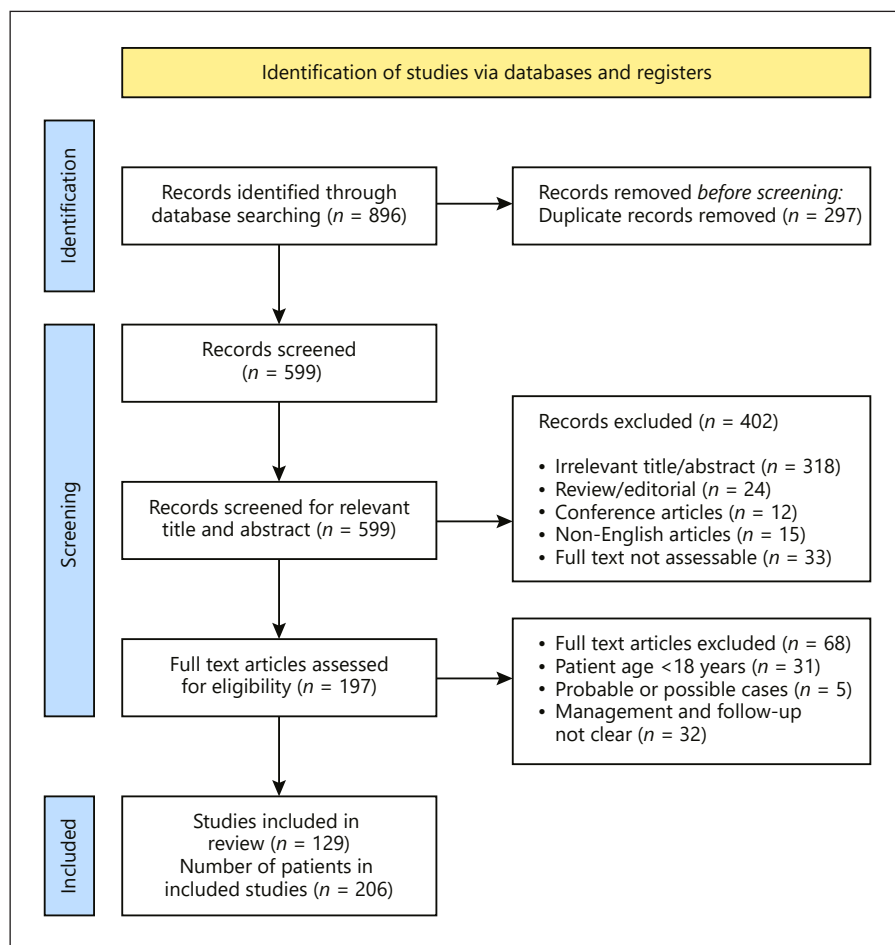


Fig. 1. Flow chart of articles selection according to the PRISMA guideline.

casian, followed by Asian (47.8% and 33.5%, respectively, Table 1). All reported cases with CNS nocardiosis are provided in the online supplementary material (online suppl. file 2).

Patients Characteristics

The mean age of the 206 patients was 55 ± 16.4 years (Table 1). The majority of the patients were male (70.8%). Disseminated *Nocardia* infection was found in nearly 64% of the patients ($n = 131$, Table 1). The other common sites involved were lung (85%), skin and soft tissue (23.5%), adrenal gland (5.3%), and bone (4.3%). Isolated CNS disease was found in 36% of the patients ($n = 75$). Thirty-four percentage ($n = 70$) of the patients were immunocompetent.

Clinical Features, Risk Factors, and Comorbidities

Among the clinical features, focal neurological deficits were the commonest, followed by headache, fever, and

altered mental state (59.6%, 47.7%, 34%, and 30.2%, respectively). Among focal deficits, seizure (19.4%), motor weakness (17.3%), and cranial nerves involvement (13%) were the common presentations. The median duration of illness in cases with CNS nocardiosis (time from the onset of disease to the first presentation in hospital) was 7 days (interquartile range 3–14). We also reviewed the literature for various predisposing factors/comorbidities, which are important factors for invasive nocardiosis. Corticosteroid use was the most common risk factor found in nearly 56% of the patients. 26.2% of the patients received a solid organ transplant, and a majority of them were renal transplant recipients (Table 2). Hematological malignancies were seen in 11% of the patients. Nearly 44% of the patients were on chemotherapy or calcineurin inhibitors. Interestingly, HIV infection was found in only 3.8% of the patients with CNS nocardiosis ($n = 8$).

We also compared the clinical presentation of disseminated CNS nocardiosis with isolated CNS disease. The

Table 1. Clinical and demographic characteristics of patients with CNS nocardiosis

Characteristics	N (%)
Age, years	
Mean age±SD	55±16.4
Median age (range)	57 (18–93)
Gender (N = 206)	
Male	146 (70.8)
Female	60 (29.2)
Ethnicity (N = 161)	
Caucasian	77 (47.8)
Asian	54 (33.5)
Hispanic	25 (15.5)
African	5 (3.2)
Case fatality	47/206 (22.8)
Type of <i>Nocardia</i> species identified (N = 185 cases)	
<i>Nocardia farcinica</i>	73 (39.6)
<i>Nocardia</i> spp. [†]	43 (23.2)
<i>Nocardia Nova</i>	11 (5.9)
<i>Nocardia cyriacigeorgica</i>	11 (5.9)
<i>Nocardia abscessus</i>	9 (4.8)
<i>Nocardia otitidiscaviarum</i>	8 (4.3)
<i>Nocardia paucivorans</i>	7 (3.7)
<i>Nocardia brasiliensis</i>	5 (2.7)
<i>Nocardia transvalensis</i>	4 (2.1)
<i>Nocardia beijingensis</i>	3 (1.6)
Others*	15 (8.1)
Disseminated nocardiosis	131/206 (63.6)
Immunocompromised	136 (66)

[†] Isolates that in the past had been identified as *N. asteroides* complex have now been renamed to other or new species. Because of this, we use the term “*Nocardia* spp.” for the species identified as “*Nocardia asteroides*” in the past. * *N. araoensis* (2 patients), *N. wallacei*, *N. puris*, *N. lillensis*, *N. exalbida*, *N. concava*, *N. cerradoensis*, *N. brevicatena*, *N. arthritidis*, *N. asiatica*, *N. beijingensis* (1 patient each).

proportion of immunocompromised and transplant recipients was higher in disseminated disease compared to isolated CNS nocardiosis (66% and 32% vs. 34% and 19%, respectively). Fever was more common in disseminated cases (50%), as compared to isolated CNS disease (30%). In neuroimaging, ring-enhancing lesions were more common in disseminated nocardiosis as compared to isolated disease (92% vs. 70%).

Laboratory and Radiological Characteristics

A majority of the patients were diagnosed by obtaining tissue biopsy, abscess drainage with aspiration, and culture of the organism (68.9%). For the confirmation of CNS nocardiosis and species identification, molecular methods like gene sequencing (e.g., 16S rRNA gene se-

Table 2. Underlying predisposing factors and comorbidities in 206 patients with CNS nocardiosis

Variables ^a	N (%)
Corticosteroids use	115/206 (55.8)
Hematological malignancies	23/206 (11.1)
Lymphoma ^b	9/23 (39.1)
Multiple myeloma	6/23 (26)
Chronic lymphocytic leukemia	3/23 (13)
Acute lymphocytic leukemia	3/23 (13)
Others ^c	2/23 (8.6)
Solid organ transplant	54/206 (26.2)
Renal	31 (57.4)
Heart	10 (18.5)
Lung	10 (18.5)
Liver	3 (5.5)
Hematological stem cell transplant	4/206 (1.9)
Diabetes mellitus	36/206 (17.5)
Use of cancer chemotherapy/calcineurin inhibitors or other immunosuppressants	90/206 (43.7)
History of head trauma/surgery	7/206 (3.3)
ESRD/MHD*	23/206 (11.2)
HIV	8/206 (3.8)
Others ^d	22/206 (10.6)

^a Some of the patients had more than one risk factor/comorbid condition. ^b Out of 9 patients with lymphoma, 6 were Non-Hodgkin’s and 3 were Hodgkin’s Lymphoma. ^c One patient with chronic myeloid leukemia and myelodysplastic syndrome. ^d Others included hepatitis C with cirrhosis (13 patients), intravenous drug use (7 patients), idiopathic CD4 lymphocytopenia (2 patients). * ESRD, eEnd stage renal disease; MHD, maintenance hemodialysis; HIV, human immunodeficiency virus.

quencing) were used in 90 patients. Out of 206 patients, species identification was made in 185 patients. *Nocardia farcinica* was the most common species identified, followed by *N. nova* (39.6% and 5.9%, respectively). *Nocardia otitidiscaviarum*, *N. cyriacigeorgica*, *N. paucivorans*, and *N. brasiliensis* were the other isolates in the remaining one-third cases in this review (Table 1). Isolates that in the past had been identified as *N. asteroides* complex have now been renamed to other or new species. Because of this, we use the term “*Nocardia* spp.” for the species identified as “*Nocardia asteroides*” in past.

Nocardia was isolated from CSF culture in only 5.8% of the patients, which indicates the rare presentation of nocardiosis as meningitis. CSF analysis showed predominant neutrophilic pleocytosis (89.5%) with a median

Table 3. Radiological and laboratory diagnosis of CNS Nocardiosis

CNS imaging/Diagnostic procedures	N (%)
Brain abscess	179/206 (86.9)
Leptomeningeal enhancement	25 (12.1)
Hydrocephalus/ventriculitis	16 (7.7)
Vasculitis/ICA aneurysm	10 (4.9)
Spinal cord involvement (abscess)*	14 (6.8)
PCR**	90/206 (43.7)
Tissue biopsy/abscess aspiration	142/206 (68.9)
CSF culture	12/206 (5.8)
CSF analysis	
Neutrophilic pleocytosis	17/19 (89.5)
Median total leukocyte counts (IQR)	396 (80–1,416)
Median CSF protein, mg/dL (IQR)	87.5 (75–167)
Median CSF glucose, mg/dL (IQR)	34 (16–56)

* Seven patients with thoracolumbar, 5 patients with cauda equina, and 2 patients with cervical epidural abscess. ** Some patients were diagnosed with a combination of polymerase chain reaction (PCR), cerebrospinal fluid (CSF) culture, and histopathological examination. ICA, internal carotid artery.

protein of 87.5 mg/dL (Table 3). The CSF examination was performed in only those who had meningeal symptoms and signs. The majority of patients with CNS disease had space-occupying lesion without the evidence of meningitis. As this review suggests, *Nocardia* was isolated from CSF culture in 12 patients (12 out of 19 patients who had meningeal signs and symptoms), thus overall sensitivity of CSF culture in patients with nocardial meningitis was 63%. Furthermore, the CSF culture sensitivity was 60% in disseminated cases (6 out of 10 culture-positive), whereas in isolated CNS disease, CSF culture sensitivity was around 66% (6 out of 9 culture-positive). Among the radiological features, brain abscess (single or multiple ring-enhancing lesions) was the most common finding, followed by leptomeningeal enhancement and ventriculitis (Table 3). Spinal cord involvement in *Nocardia* infection was seen in 6.8% of the patients; the thoracolumbar spine was the most common site involved. Five patients presented with cauda equina syndrome secondary to an intramedullary abscess (Table 3).

We have also analyzed the antimicrobial sensitivity reports of these cases, which were available in the literature. We collected information about the four most important antibiotics, which are the fulcrum of invasive nocardiosis management (amikacin, ceftriaxone, trimethoprim-sulfamethoxazole (TMP-SMX), and imipenem). TMP-SMX was found to be the most susceptible drug for *Nocardia* isolates (88.9%). The sensitivity of amikacin and imipe-

nem was 82.8% and 80.6%, respectively. Ceftriaxone was found to be the least effective antibiotic for *Nocardia* isolates (58.7%).

Treatment and Outcome

Effective treatment of CNS nocardiosis includes combinations of various antibiotics for a prolonged period to prevent relapse. Surgical intervention was performed in 47.7% of the patients, including drainage or debridement of the affected tissue. Trimethoprim-cotrimoxazole was the most common drug used for CNS disease. In addition, it was used as a monotherapy in 23 patients (13.4%). A dual combination of TMP-SMX with amikacin, meropenem, or linezolid was used in 74 (43%) patients. A triple antimicrobial regimen was used in 47 patients (27.3%). The rest of the patients received minocycline, ciprofloxacin, moxifloxacin, and TMP-SMX in various combinations. The mean duration of antimicrobial therapy was 10 months in those who survived. The mean duration of antimicrobials was 9 months in isolated CNS nocardiosis, while it was 12 months in cases with disseminated infection.

The overall mortality rate was 22.8% ($n = 47$) in all cases with CNS nocardiosis. For further exploration of the determinants of mortality, we categorized all patients with CNS disease into responders and nonresponders/nonsurvived subgroups (Table 4). The comparison of both groups for different variables is shown in Table 4. Fever, surgical intervention, disseminated disease, and immunocompromised state were found statistically significant determinant factors for the outcome (Table 4). Patients who underwent surgical intervention showed better outcomes (53.3% vs. 25.7% $p = 0.004$). Patients who died were more likely to have disseminated nocardiosis, immunodeficient state, and fever at the presentation (55.3% vs. 39%, 80.9% vs. 59.7%, and 52.3% vs. 29.4%, respectively, Table 4). After multivariate analysis, we found surgical intervention (odds ratio 2.4, $p = 0.046$) as an independent predictor of survival in patients with CNS *Nocardia* infection (Table 4). Furthermore, immunodeficiency was associated with poor survival (odds ratio 0.32, $p = 0.019$). We also tried to estimate the proportion of residual focal neurological deficits among patients who survived ($n = 159$, with a minimum follow-up of 6 months). Out of 159, information about residual focal deficits was available in 96 patients; 21 out of 96 (22%) patients still had persisting residual focal neurological deficits after the end of 6 months.

Table 4. Univariate and multivariate analysis showing various predictors of survival in patients with CNS nocardiosis

Variable	Survivors (n = 159), %	Nonsurvived (n = 47), %	Univariable OR (95% CI)	p value	Multivariable OR (95% CI)	p value
Gender (Male)	71.3	63.8	0.91 (0.41–2.3)	0.802		
Age						
18–30 years	3.7	10.6	1.0 (0.98–1.03)	0.376		
31–50 years	23.3	14.9				
51–70 years	56.6	53.2				
>70 years	16.4	21.3				
Type of <i>Nocardia</i> species						
<i>N. farcinica</i>	35.8	34	1.1 (0.97–1.04)	0.633		
Other spp.	64.2	66				
Fever	29.4	52.3	0.59 (0.30–1.21)	0.014	0.49 (0.26–1.32)	0.183
Focal neurological deficit	67.9	51.6	1.0 (0.44–2.3)	0.343		
Features of meningitis leptomeningeal enhancement	13.1	20	0.97 (0.33–2.9)	0.297		
Surgical Intervention	53.3	25.7	2.7 (1.1–4.8)	0.004	2.4 (0.99–4.11)	0.046
Disseminated disease*	39	55.3	0.39 (0.15–0.81)	0.038	0.57 (0.26–1.38)	0.171
Immunodeficient state	59.7	80.9	0.37 (0.16–0.94)	0.011	0.32 (0.15–0.90)	0.019

* Infection involving >1 noncontiguous site. OR, odds ratio; CI, confidence interval.

Discussion

CNS involvement is a rare manifestation of invasive nocardiosis, which is a significant cause of morbidity and mortality. Most of the treatment decisions depend on anecdotal reports, case series, and expert opinions. Evolving epidemiology, comorbidities, increasing use of immunosuppressants, and the advent of newer drugs are having a significant impact on the clinical spectrum of nocardiosis. *Nocardia farcinica* remains the commonest cause of CNS disease. However, new species are increasingly discovered with the introduction of new molecular methods [13, 14]. *Nocardia beijingensis*, *N. exalbida*, and *N. lillensis* were the recent species isolated from patients with CNS involvement [15–17].

Invasive nocardiosis is traditionally considered a disease affecting immunodeficient; however, nearly 34% of cases in our review were immunocompetent. This emphasizes the need to keep a strong clinical suspicion among cases presenting with focal neurological deficit even in immunocompetent patients. The risk of nocardiosis is highest during the first year after solid organ transplant. Furthermore, the incidence of *Nocardia* infection was described as highest in heart and lung transplant recipients and lowest with liver and renal transplants [18–20]. Conversely, our review showed the highest cases of CNS infection in renal transplant recipients. Despite overt immunodeficiency, nocardiosis is uncommon in HIV patients with a prevalence of 0.2–2% and mostly in-

volves the lungs [21, 22]. This review also showed that only 3.8% of the cases with CNS nocardiosis disease were HIV-positive. Effective implementation of TMP-SMX for the prophylaxis of *Pneumocystis jirovecii* pneumonia could be the reason for the low incidence of invasive nocardiosis among HIV patients. The other factors include misdiagnosis with tuberculosis and other opportunistic infections, which could be seen with low CD4 counts.

Hematogenous spread is the predominant mode of transmission in CNS nocardiosis. Selective tropism for neural tissues is seen in nocardiosis, which is the reason for CNS involvement (seen in nearly 40% of the disseminated cases) [23]. The clinical presentation of CNS nocardiosis usually depends on the site and extent of infection along with the immune status of the patients. Immunocompetent patients typically present with a less virulent form like solitary brain abscess that remains silent for a long time. *Nocardia* meningitis is a rare event that was seen in only 12.1% of the patients. In addition, isolated meningitis without brain abscess is even rarer, seen in only 5.8% of the patients in this review. Fever is an unusual presentation in extrapulmonary nocardiosis, especially in cases with chronic meningitis. In this analysis, fever was associated with increased mortality which might be related to concurrent other opportunistic infections in these patients, particularly those who were immunocompromised.

Diagnosis of invasive nocardiosis required the isolation of the organism from a clinical specimen (CSF, ab-

scuss). Quality of clinical specimen and prolonged incubation (up to 4 weeks) is vital for the isolation of *Nocardia* species [24]. In this review, we found a low CSF culture positivity, which could be due to the low prevalence of meningitis and less quantity of CSF sample sent for culture [25]. One of the highlights of this review is that CSF findings in CNS nocardiosis was the predominant neutrophilic leucocytosis, whereas lymphocytic pleocytosis is usually more common in CNS fungal infections like neuroaspergillosis [26], which can mimic nocardiosis sometimes due to the similar clinical presentation and risk factor profile. Similarly, median number of CSF cells were more in nocardial infections as compared to neuroaspergillosis and other fungal infections like cryptococcosis [26, 27].

Testing for antimicrobial susceptibility is essential, particularly in those with underlying immunodeficiency and high probability of mortality due to relapse or inadequate treatment. Lebeau et al. [28] reported the antibiotic susceptibility in 736 *Nocardia* isolates, which showed linezolid, amikacin, TMP-SMX as the most effective antibiotics against *Nocardia*. However, the majority of these patients (73%) had pulmonary and cutaneous disease, and data regarding CNS infections are scanty [28]. In our analysis of CNS cases, TMP-SMX along with amikacin was found to be the most effective drug. The nonsusceptibility rate of ceftriaxone was high (varies from 44% to 100%) in different reports, which was similar to our findings (42% nonsusceptibility rate for ceftriaxone) [28–31]. The selection of antibiotics in invasive nocardiosis should be based on site of infection, renal functions, comorbidities, and possible interaction with immunosuppressants [24]. Combination of at least two antibiotics (TMP-SMX, amikacin, carbapenems, ceftriaxone/cefotaxime) should be started in suspected CNS disease. TMP-SMX remains a cornerstone of invasive CNS nocardiosis management. In addition, recent evidence showed the promising role of linezolid [32–34]. In cases with TMP-SMX intolerance, linezolid could be an alternate option with good CNS penetration, oral bioavailability, and excellent antimicrobial susceptibility profile [35–37]. However, there are concerns regarding the long-term toxicities of linezolid (myelosuppression and peripheral neuropathy) with prolonged use [37]. The combination of amikacin with linezolid should be discouraged due to the potential antagonism of these two drugs [38, 39]. Antimicrobial therapy should be given for 6–12 months in CNS nocardiosis, though optimal duration is unknown mainly due to the lack of prospective trials with a shortened period [1, 24].

Surgical treatment/aspiration is vital in cases with deep-seated cerebral abscess or patients not responding to antibiotics [40]. This literature review showed that surgical intervention is a determinant of increased survival in CNS disease. According to some reports, stereotactic aspiration should be performed if the abscess fails to shrink after 4 weeks of therapy or remains progressive after 2 weeks of antibiotics [41, 42]. Whether this approach will shorten the hospital stay and antibiotics duration is still a subject of ongoing discussion. The rarity of CNS nocardiosis remains an obstacle for future studies to solve this dilemma.

Managing nocardiosis in high TB burden countries (African and Asia subcontinent) remains challenging. The coexistence of tuberculosis with nocardiosis is an increasingly recognized condition with a reported prevalence of 1.7–6.7% in pulmonary disease [43, 44], especially with HIV. In this systematic review, 2 patients had active tuberculosis (0.97%) and CNS nocardiosis. Owing to the similar presentation, the diagnosis of nocardiosis can be missed or delayed due to underlying tuberculosis. Emphasis should be given to the molecular diagnosis of nocardiosis for better differentiation with tuberculosis. Some of the antimicrobials used for CNS nocardiosis also have antitubercular action (e.g., linezolid, meropenem, and amikacin).

Our review has a few limitations; first, due to heterogeneity in patient population and risk factors, it is difficult to extrapolate the findings to general population. In addition, many cases were excluded due to a lack of information about treatment and follow-up, which were difficult to analyze. Second, in our pooled analysis, the relapse or treatment failure was not studied properly due to the lack of long-term follow-up of the cases. There is also a lack of information about drug susceptibility data in majority of the cases.

Conclusion

Our report shows the promising role of surgical interventions, though disseminated nocardiosis with overt immunodeficiency was associated with unfavorable outcome. Early surgery could be vital in these patients. Emphasis should be given to antimicrobial susceptibility testing and prolonged use of antibiotics to prevent relapse. The diagnostic utility of molecular methods will become important in the near future. There is a need for prospective multicentric studies to confirm these conclusions.

Statement of Ethics

Not required.

Conflict of Interest Statement

The authors declare that they have no competing interests.

Funding Sources

None.

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Author Contributions

Author Durga Shankar Meena and Deepak Kumar conceived the study; Deepak Kumar, Gopal Krishana Bohra, Mahendra Kumar Garg, and Naresh Kumar Midha designed the study protocol; Durga Shankar Meena, Gopal Krishana Bohra, Mahendra Kumar Garg, and Deepak Kumar drafted the manuscript; all authors critically revised the manuscript for critical content. All authors read and approved the final manuscript.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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