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CASE REPORT

Nocardia infections in Italy: from a local to a national view

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SUMMARY

In this paper, we have described cases of nocardiosis that occurred in our hospital and examined the literature on other nocardiosis cases recorded in Italy. We have collected the clinical details of our recent cases and described them in full. Regarding the older cases in our hospital and the Italian cases present in the literature, we noted the clinical data, the *Nocardia* species involved, and the antimicrobial susceptibility reported. The survey was carried out on PubMed. The first of our cases is an elderly woman with compromised health who had a lung and bloodstream infection. A second case is a middle-aged man who developed an infection in the thigh. A third patient is a middle-aged man on immunosuppressive therapy who developed a cerebral abscess. Our review shows that patients are usually immunocompromised, with an average age of 60 years, and more frequently males. The most affected organs are the lungs and the brain, and the most reported species is *Nocardia farcinica*. Antimicrobial susceptibility tests show good efficacy of linezolid, cotrimoxazole and amikacin. We conclude that, if a *Nocardia* infection is suspected, the most likely species to be considered in Italy is *N. farcinica*. In addition, if empirical therapy is needed, we suggest relying on linezolid, cotrimoxazole or amikacin.

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INTRODUCTION

Nocardiosis is a rare infection caused by members of *Nocardia spp.* These are gram-positive, weakly acidic-fast coco-bacilli belonging to the family of the Nocardiaceae (Brown-Elliott *et al.,* 2006). These bacteria have peculiar characteristics. They tend to grow in a filamentous and branched way and incorporate mycolic acids, composed of 46-64 carbon atoms and up to four double bonds, in cellular envelopes (Albuquerque de Barros *et al.,* 2003; M Tille 2016). *Nocardia* is widespread globally and is present as a saprophytic organism in terrestrial and aquatic environments; it can commonly be found in areas with decomposing organic substances (Yamamura *et al.,* 2005; El-Gendy *et al.,* 2008). The main routes of infection are inhalation and penetration into the tissues after trauma; therefore, the most affected organs are the lung, skin, and soft tissues. *Nocardia* can invade the bloodstream and spread to other organs, such as the brain and the liver, forming abscesses. The tendency to form abscesses is due to its ability to resist macrophage phagocytosis. These microorganisms are optional intracellular parasites that can live within the macrophage since they inhibit lysosomal activity and consume acidic lysozyme phosphatase as a carbon source (Beaman and Beaman, 1994; Fatahi-Bafghi, 2018).

Other reported manifestations of nocardiosis are septicaemia, catheter-related infections, osteomyelitis, peritonitis, and endocarditis (Schwartz and Tio 1987; Cargill *et al.,* 2010; Al Akhrass *et al.,* 2011). Rare sites of *Nocardia* infections are the paranasal sinus and the eye, where it can cause keratitis, endophthalmitis, conjunctivitis, and other diseases (Reddy *et al.,* 2010; Welsh *et al.,* 2012; Scott *et al.,* 2013; Castle and Heath 2021). *Nocardia* infection can have severe morbidity and mortality, particularly in patients with impaired immunity or comorbidity. The mortality rate in patients with cerebral abscesses is 20% in immunocompetent subjects, but it can reach 55% in immunocompromised ones (Mamelak *et al.,* 1994; Lynch *et al.,* 2020).

Incidence appears to be growing globally due to the ageing population and increased presence of ideal hosts such as immunocompromised patients (Falagas *et al.,* 2011; Fatahi-Bafghi 2018). Epidemiology can vary constantly from one region to another, and

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there is no clear understanding of the factors influencing the distribution of different species. The most isolated species appear to be *N. cyriacigeorgica, N. abscessus, N. brasiliensis, and N. farcinica* (Brown-Elliott *et al.,* 2006; Rodriguez-Nava *et al.,* 2015; Huang *et al.,* 2019; Ott *et al.,* 2019; Ercibengoa *et al.,* 2020).
Historically, the therapy suggested for Nocardiosis was sulphonamides; cotrimoxazole is currently the most-used drug formulation. Other antibiotics that have demonstrated activity against *Nocardia spp*. are ceftriaxone, imipenem, meropenem, amikacin, minocycline, moxifloxacin, levofloxacin, amoxicillin-clavulanic acid, linezolid, and tigecycline. However, antibiotic susceptibility can vary constantly from one species to another (Cercenado *et al.,* 2007; Ameen *et al.,* 2010).
There are many species of *Nocardia* that have proved difficult to differentiate using standard systems based on metabolism analysis. Better results are achieved using molecular techniques and other newer diagnostic tools like MALDI-TOF (Verroken *et al.,* 2010; Conville *et al.,* 2018).
In this study, we present three clinical cases of *Nocardia* infection that occurred in our hospital in 2021 and 2022, along with a retrospective analysis of cases recorded in our databases from 2017 to 2022. We also have examined similar studies conducted in Italy in recent years to compare these different experiences.

MATERIALS AND METHODS

Collection of data from our hospital cases

In this study, we have analysed the cases of nocardiosis that occurred from 2017 to 2022 in our hospital, 'Azienda Università Ospedale di Padova' Padua, Italy. We have investigated our laboratory archives by selecting the cases in which the presence of *Nocardia spp*. was confirmed. We then retrieved the general clinical information; we noted the gender, age, and basic medical conditions, as well as clinical data of nocardial infections and treatment. Three cases had occurred recently or were still being treated; for these cases, we were able to retrieve the complete clinical data and store the strain of bacteria for further analysis.
Each of the recent-case strains was cultured and isolated from the original sample using the standard culture procedures of the laboratory diagnostic service. Clinical specimens were seeded on non-selective media, like BD Chocolate Agar and BD Columbia Agar with 5% sheep blood (Becton, Dickinson and Company, Franklin Lakes, New Jersey, USA). After 48-72 hours, colonies were stained with Gram stain and observed with a direct light microscope (*Figure 1*). We used VITEK MS (Biomérieux, Marcy-l'Étoile, France) to identify the *Nocardia* species. The analysis was done using the manufacturer's standard preparation for bacterial identification. The database used to define the species is the VITEK MS V3 IVD-CE. This database includes the spectra of fourteen species of *Nocardia*. In recent cases, *Nocardia* spp. was easily identified, while the species had been defined only in some of the past cases due to the lack of advanced identification methods at that time.
The antibiotic sensitivity of the three most recently isolated strains was determined by the broth microdilution technique following the procedure indicated by Clinical & Laboratory Standards Institute (CLSI) guidelines (Woods *et al.,* 2018). We also used the ETEST strips method (Biomérieux, Marcy-l'Étoile, France). Antibiotics verified through the microdilution broth method were imipenem, clarithromycin, amoxicillin-clavulanic acid, cotrimoxazole, cefotaxime, ceftriaxone, amikacin, ciprofloxacin, linezolid, moxifloxacin, doxycycline, and cefepime. On the other hand, with ETEST strips we tested susceptibility to imipenem, clarithromycin, amoxicillin-clavulanic acid, trimethoprim-sulfamethoxazole, cefotaxime, ceftriaxone, amikacin, and ciprofloxacin.
The same procedure for culture, identification, and antibiotic sensitivity testing was also performed on the ATCC strain *Nocardia farcinica Trevisan* (ATCC accession number #3308) to validate the whole procedure, especially the identification step. This ATCC strain does not have a defined antibiogram to compare our

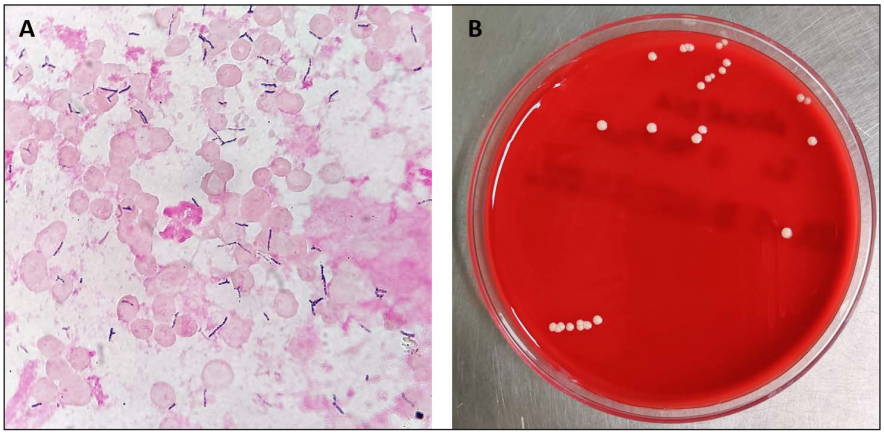

Figure 1 - *Gram stain performed on blood culture, showing N. farcinica cells growing in a filamentous and branching way at 1000X magnification (A); N. farcinica colonies on sheep blood agar (B).*

results with. However, we have also determined its sensitivity, to be used for comparison in future works.

Collection of data from other Italian case reports

The review of other Italian cases of Nocardiosis was carried out using PubMed as a search engine and '*Nocardia* Italia', '*Nocardia* Italian', 'Nocardiosis Italia' and 'Nocardiosis Italian' as research. Only studies published between 2000 and 2022 were selected. Data extracted from each study covered age, sex, immune status of patients, site of infection, susceptibility to antibiotics, and isolated *Nocardia* spp.

RESULTS

Presentation of case 1

The patient, an 87-year-old woman, suffered several episodes of loss of consciousness in the months before hospitalization, resulting in falls. Because of these disorders, she underwent a CT scan of the skull that revealed an expansive lesion in the right temporoparietal region of the brain. She was admitted to the University Hospital of Padua, where the neoformation was surgically removed. At the time of admission, she was alert and able to orient herself, in generally good condition with typical age-related problems. The surgeons performed a craniotomy and extracted the expansive lesion, which was then sent to the pathology service for examination. The brain injury was diagnosed as a meningioma. After surgery, the patient was in stable condition, but after 24 hours she developed a fever and her mental state deteriorated rapidly. She was sleepy and reacted only to painful stimuli. Doctors requested blood cultures, urine cultures, and chest CTs. A broad-spectrum antibiotic therapy was initiated, including meropenem, linezolid, and moxifloxacin. The first set of urine and blood cultures yielded negative results. The radiological examination of the chest revealed a consolidation area with cavitation in the upper left lung. The resulting bronchoscopy found a severe inflammatory state in the upper left lung. The biological samples recovered during bronchoscopy were sent to the microbiology laboratory. However, due to contamination with oral saliva, it was impossible to define a specific pathogen. The patient also tested negative for *M. tuberculosis*. Blood cultures were repeated periodically due to persistent fever, and a week after surgery a set of blood cultures tested positive for Gram-positive bacilli. The bacteria were identified with the MALDI-TOF technique as *N. farcinica*. The antibiotic therapy was then changed, replacing moxifloxacin with cotrimoxazole. After the discovery of *N. farcinica* in the blood, spinal fluid cultures were also performed, but no evidence of infection was found. Subsequently, the meningioma removed from the brain was analysed using molecular means to detect *Nocardia*'s DNA, but the result was negative. In this case, the most likely primary site of nocardial infection was the lung. From there, the bacteria spread due to the state of immunodepression that follows major surgical events and were then isolated from the blood. The patient remained in the hospital for three weeks and was then discharged with a 6-month antibiotic therapy based on ciprofloxacin and cotrimoxazole. She showed radiological and clinical improvements at the subsequent follow-up.

Presentation of case 2

The patient, a 59-year-old man, was suffering from membranous glomerulonephritis in an active phase, so he was on mild immunosuppressive therapy. He reported swelling and painful symptomatology in the adductor region of the left thigh that had developed gradually without any obvious trauma or a recent injury. He underwent an ultrasound and magnetic resonance imaging (MRI) that identified a neoformation in the adductor region of the left thigh. He was admitted to the University Hospital of Padua to have a biopsy of the lesion performed; the material was sent to the Pathology and Microbiology services for further analysis. The patient was discharged with analgesic and antibiotic therapy (amoxicillin-clavulanate). Pathological examination of the biopsy revealed the presence of inflamed necrobiotic tissue. *N. farcinica* was isolated from the culture of the biopsy. Based on the antibiogram, antibiotic therapy was switched to cotrimoxazole to be continued for the following weeks. The following controls showed a good response to the therapy with a reduction of tissue swelling and painful symptomatology.

Presentation of case 3

The patient, a 54-year-old man, was suffering from type 2 diabetes. In the previous months, he had received a heart transplant due to degenerative cardiomyopathy. After the transplant, he had several episodes of organ rejection for which he was hospitalized and received high doses of immunosuppressive drugs. After the resolution of the acute rejection phase, he was discharged and continued immunosuppressive therapy by taking cyclosporine and mofetil mycophenolate. Eight months after the surgery, he had an episode of unconsciousness followed by episodes of seizures. He was then hospitalized, intubated, and started anticonvulsant therapy. The CT scan of the skull showed regions of hypodensity in the frontal and core capsular regions. An embolic origin was suspected. However, angiography ruled out this hypothesis. Therefore, a thoracic CT scan revealed a hyperdense lesion in the basal lobe of the left lung. The patient was extubated and regained consciousness without permanent neurological deficits. He remained on anticonvulsant medication for twenty days until another episode of convulsions occurred. The CT showed an increase in the hypodensity zones,

so an MRI was performed with a contrast agent. The MRI showed signs consistent with a cerebral abscess. Antibiotic therapy was initiated, and a few days later the patient underwent surgery to remove the lesion. The abscess material and spinal fluid samples were sent to our microbiology laboratory to isolate the pathogen. The cerebral spinal fluid was incubated at 37°C in an automated incubation system and seeded on chocolate agar and Columbia sheep blood agar. The material from the abscess was also inoculated in a non-selective liquid medium. After two days, the culture of the liquor on sheep blood agar revealed the presence of tiny white colonies, identified as *N. abscessus*. It can be concluded that the cerebral abscess was caused by *Nocardia*, and the primary site of infection was potentially the left lung where the hyperdense lesion was detected by CT scan. Initial antibiotic therapy was based on cotrimoxazole, meropenem, and linezolid. After identification of the pathogen, therapy was switched to cotrimoxazole, ceftriaxone, and moxifloxacin.

Data from cases of Nocardiosis that occurred in our hospital

The analysis of our database showed that from 2017 to 2022, 11 cases of *Nocardia* infection occurred in our hospital, including the three cases presented above. The data are summarized in *Table 1*. The average age of patients was 70 (the youngest was 60 and the oldest was 87); 60% of patients were males. They all had important health conditions that hinder the immune system. As for the primary location of the infection, more than half of the patients had lung disease. *N. farcinica* was the most frequently isolated species.

Data from cases of Nocardiosis reported in Italy

We examined 17 studies carried out in Italy from 2000 to 2022 (Viganò *et al.,* 2005; Bocchino *et al.,* 2008; Cianfoni *et al.,* 2010; Pea *et al.,* 2012; Monticelli *et al.,* 2015; Mengoli *et al.,* 2017; Mazzaferri *et al.,* 2018; Colaneri *et al.,* 2021a) (Rinaldi *et al.,* 2000; Malincarne *et al.,* 2002; Farina *et al.,* 2007; Cattaneo *et al.,* 2013; De Nardo *et al.,* 2013; Castellana *et al.,* 2016; Colaneri *et al.,* 2021b; Garofalo *et al.,* 2021; Deana *et al.,* 2022). A total of 120 cases were reported. The data are summarised in *Table 2*. It was impossible to recover the same categories of information from all studies, so it was problematic to have a homogeneous pool of cases. Furthermore, not all studies reported the species or the method used to determine it. Considering the well-known difficulties in correctly determining the species of *Nocardia*, we

Table 1 - *Cases of nocardiosis occurred at the University Hospital of Padua.*

Case	*Sex*	*Age*	*Clinical data*	*Site of infection*	*Nocardia spp.*	*Outcome*[1]
1	F	87	Cerebral neoplasia	lungs	*N.farcinica*	Good
2	M	59	Immunosuppressant drugs for glomerulonephritis	skin	*N.farcinica*	Good
3	M	54	Diabetes, immunosuppressant drugs after hearth transplantation	brain	*N. abscessus*	Good
4	M	79	n.d.	n.d.	*Nocardia spp.*	n.d
5	M	70	Mycobacterial infection	lungs	*Nocardia spp.*	n.d
6	M	69	n.d	lungs	*N. abscessus*	n.d
7	M	80	Immunosuppressant drugs for myelofibrosis	brain	*N.farcinica*	Good
8	F	60	Multiple myeloma	lungs	*Nocardia spp.*	Good
9	F	68	Diabetes and general decay	lungs	*Nocardia spp.*	n.d
10	F	80	Pulmonary fibrosis	lungs and skin	*N.farcinica*	Deceased
11	M	50	Cerebral and cutaneous neoplasia	lungs	*Nocardia spp.*	Good

Notes: [1]outcome related to the clinical episode; n.d.: not determined.

Table 2 - *Review of Nocardiosis case reports in Italy.*

Total number of cases reported: 120						
Median age (116 pz[1]): 60 y.o. *Males %* (112 pz[1]): 63 %						
Immunocompromission (119 pz[1]): 71,5%						
Site (116 pz[1])	Lungs	Brain	Multiple	Skin	Eye	Pe
	67 %	11%	12 %	8 %	1%	1%
Nocardia spp. (71 pz[1])	fa	ab	cy	br	as	no
	40%	18 %	14%	11%	6 %	3 %
	as	pa	wa	tr	be	
	3%	1,5%	1,5%	1,5%	1%	

Notes: [1] number of patients for whom this data was available; pe: peritoneum; *fa:farcinica; ab: abscessus; cy: cyriacigeorgica; br: brasiliensis; as: asteroids; no: nova; as: asiatica; pa: paucivorans; wa: wallaci; tr:tranvalensis; be: beijingensis.*

decided to exclude studies carried out before 2000 in order to have only microbiological diagnoses done with modern procedures (Conville *et al.,* 2018).

DISCUSSION

Nocardiosis is a rare disease that can have serious consequences in fragile patients. For this reason, it is important to collect epidemiological and clinical data that will facilitate a prompt diagnosis. Because *Nocardia* has a slower growth rate than other bacteria, it may take a longer time for colonies to grow and even longer to have an antibiogram. Therefore, it is useful to have data regarding the common susceptibility spectrum of the most widespread strains to set up an empirical treatment while waiting for the laboratory response.

Overall, the statistics of our hospital are consistent with previous studies conducted in Italy. These data can help define some common characteristics of this disease in our country, useful to guide clinical decisions. Nocardiosis was found to be slightly more frequent in men, with a male/female ratio of 6/4. More than 70% of patients had an explicit condition that weakened immunity; therefore, a compromised immune state seems to be an important risk factor. Generally, immunosuppression is more related to clinical conditions and immunosuppressive drugs, whereas age does not seem to play an important role since the average age was relatively low (60), and in most cases in the 50-70 range.

As for the location of the infection, the lungs are widely known to be the most affected area, followed by the brain. Our statistics are in line with this, showing a prevalence of 67% of active lung infections and 10% of brain infections. The review shows only a minority of cases of multiple localizations and widespread infections are a minority. The three cases that we have reported provide a representative overview of the variety of presentation and infection sites of a *Nocardia* infection. The site of invasion is mainly the lung, as can be observed from the first and third cases described. From the original infection site, bacteria can cause infections of blood flow (Case 1) or seeds in distant organs and cause abscesses (Case 3). In the second case, the primary site of the infection is not clear. It is impossible to determine if the thigh was infected directly, because the patient did not report significant trauma to let the bacteria in, nor if it is a secondary dissemination site because there was no evidence of infection in any other organ, nor signs of systemic disease. Such observations may lead one to think that *Nocardia* behaves like the closely-related Mycobacteria. It may be able to enter the body and remain in a dormant state until the host's immunity declines. Then bacteria spread, causing an infection long after the first exposure.

As for the *Nocardia* species isolated, our review shows that *N. farcinica* is the most frequently encountered subspecies in Italy, followed by *N. abscessus*. This information can turn out to be useful to define an empirical therapy while waiting for bacteria isolation and characterization, considering that the various *Nocardia spp.* showed different antibiotic sensitivity (Lebeaux *et al.,* 2019).

The susceptibility test results of the three cases described and the ATCC strain showed a relatively uniform sensitivity spectrum. Related data are provided in *Table 3*. Both the microdilution method and ETEST strips were used to determine MIC values. According to the CLSI guidelines, susceptibility of *Nocardia spp.* should be determined with the microdilution test, so we considered the results obtained with this method to be more reliable. All strains of *N. farcinica* showed

Table 3 - *Antimicrobial susceptibility tested with microdilution (MDT) and E-TEST strips.*

	Case 1 (N. farcinica)		*Case 2 (N. farcinica)*		*Case 3 (N. abscessus)*		*ATCC 3308 (N. farcinica Trevisan)*	
	MDT	*E-Test*	*MDT*	*E-Test*	*MDT*	*E-Test*	*MDT*	*E-Test*
IP	16 (R)	0,75 (S)	4 (S)	1 (S)	16 (R)	2 (S)	4 (S)	0,094 (S)
CH	–	24 (R)	–	16 (R)	–	4 (I)	–	24 (R)
XL	> 8 (R)	4 (S)	> 8 (R)	6 (S)	≤ 2 (S)	0,75 (S)	> 8 (R)	2 (S)
TS	1 (S)	0,094 (S)	≤ 0,5 (S)	0,064 (S)	1 (S)	0,094 (S)	≤ 0,12 (S)	2 (S)
CT	> 4 (N)	> 32 (N)	> 4 (N)	> 32 (N)	2 (S)	1,5 (S)	> 4 (N)	2 (S)
TX	> 4 (N)	> 32 (N)	> 4 (N)	> 32 (N)	1 (S)	0,38 (S)	> 4 (N)	2 (S)
AK	≤ 4 (S)	0,5 (S)	≤ 4 (S)	0,5 (S)	≤ 4 (S)	0,25 (S)	≤ 4 (S)	1,5 (S)
CI	1 (S)	0,094 (S)	2 (I)	1 (S)	> 2 (N)	1 (S)	> 2 (N)	2 (I)
LZ	1(S)	–	2 (S)	–	0,5 (S)	–	≤ 2 (S)	–
MX	≤ 0,06 (S)	–	> 1 (N)	–	0,5 (S)	–	1 (S)	–
PM	> 32 (R)	–	> 32 (R)	–	4 (S)	–	> 32 (R)	–
DC	> 2 (N)	–	1 (S)	–	≤ 0,12 (S)	–	> 2 (N)	–

IP: imipenem; CH: clarithromycin; XL: amoxicillin/clavulanate; TF: cotrimoxazole; CT: cefotaxime; TX: ceftriaxone;
AK: amikacin; CI: ciprofloxacin; LZ: linezolid; MX: moxifloxacin; PM: cefepime; DC: doxycycline; S: sensible;
I: intermediate sensibility; R: resistant. N: no interpretation. According to CLSI (Woods *et al.*, 2018).

a general resistance to beta-lactams, reporting high MIC values for ceftriaxone, amoxicillin/clavulanate, and cefepime. The *N. abscessus* strain is more susceptible to these beta-lactams. Variable susceptibility to imipenem was observed: one strain of *N. farcinica* out of three, and the *N. abscessus* strain tested resistant. Ciprofloxacin too seems to be ineffective because all four strains tested from intermediate to resistant. The antibiotics that had low MIC in all strains were linezolid, cotrimoxazole, and amikacin.

Our results are closely in line with those of two Italian studies that have comprehensively reported the antibiogram of the cases of nocardiosis analysed (Mazzaferri *et al.,* 2018; Colaneri *et al.,* 2021a). By combining the data from our study with the data from these two studies we can obtain the sensitivity spectrum of 11 strains of *N. farcinica* and 20 of *N. abscessus*. The results align with the general sensitivity of *N. farcinica* and *N. abscessus* to linezolid and cotrimoxazole, with only one case of each species reported as resistant. The analysis confirmed the efficacy of amikacin, with only one in eleven cases of *N. farcinica* and two in twenty cases of *N. abscessus* reported as resistant. There is a consensus on the low efficacy of beta-lactams in *N. farcinica* (two out of eleven susceptible strains), and on a slightly better efficacy towards *N. abscessus* (sixteen sensitive strains out of twenty). The modest efficacy of imipenem has been confirmed, with about half of the cases tested resistant.

Microdilution is the method recommended by CLSI to determine the susceptibility of *Nocardia* strains. We tested both this method and ETEST strips. Comparing the results obtained with the two techniques, we determined that ETEST, used with *Nocardia* strains, underestimates the MIC values of antibiotics, as reported in other studies (Brown-Elliott *et al.,* 2016). This applies especially to imipenem and amoxicillin/clavulanate, which were found to be incorrectly sensitive to ETEST, while showing high MIC values at the microdilution method. Therefore, the ETEST method should be avoided when testing the susceptibility of *Nocardia* strains.

In conclusion, *Nocardia* infections should always be considered in the differential diagnosis of immunocompromised patients with symptoms related to the brain or lungs. The data we collected showed that *N. farcinica* is the most likely involved species in Italy. Therefore, empirical therapy should be based on cotrimoxazole, linezolid, or amikacin, while beta-lactams should be avoided because of their varying effectiveness against different species of *Nocardia*.

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Conflicts of interest

The authors declare that they have no known competing financial interests or personal relationships that could appear to have influenced the work reported in this paper.

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