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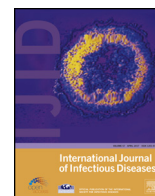
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Nocardiosis in the south of France over a 10-years period, 2004–2014



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SUMMARY

Background: Nocardiosis is a rare disease with polymorphic presentations. The epidemiology and clinical presentation could change with the increasing number of immunocompromised patients.

Methods: The medical records and microbiological data of patients affected by nocardiosis and treated at the university hospitals of Marseille between 2004 and 2014 were analyzed retrospectively.

Results: The cases of 34 patients infected by *Nocardia* spp during this period were analyzed. The main underlying conditions were transplantation ($n=15$), malignancy ($n=9$), cystic fibrosis ($n=4$), and immune disease ($n=3$); no immunodeficiency condition was observed for three patients. No case of AIDS was observed. At diagnosis, 61.8% had received steroids for over 3 months. Four clinical presentations were identified, depending on the underlying condition: the disseminated form (50.0%) and the visceral isolated form (26.5%) in severely immunocompromised patients, the bronchial form (14.7%) in patients with chronic lung disease, and the cutaneous isolated form (8.8%) in immunocompetent patients. *Nocardia farcinica* was the main species identified (26.5%). Trimethoprim–sulfamethoxazole was prescribed in 68.0% of patients, and 38.0% underwent surgery. Mortality was 11.7%, and the patients who died had disseminated or visceral nocardiosis.

Conclusions: The clinical presentation and outcome of nocardiosis depend on the patient's initial immune status and underlying pulmonary condition. Severe forms were all iatrogenic, occurring after treatments altering the immune system.

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Introduction

Nocardia spp are aerobic actinomycetes distributed worldwide, found in soil, decaying vegetation, and water, and may be pathogenic to human beings. Transmission results mainly from the inhalation of spores, or through direct inoculation.¹

Nocardia spp cause localized or invasive infections requiring long-term treatment and surgery, and infections may occasionally be fatal. Nocardiosis is usually reported in immunocompromised patients with AIDS, a malignancy, or who have undergone solid organ transplantation (SOT), and in those on long-term steroid

therapy.^{2–4} It rarely affects patients without any serious underlying condition.^{5,6}

Nocardia spp can be isolated by standard microbiological culture from various samples such as sputum, bronchoalveolar lavage (BAL) fluid, abscess, and blood, and can then be identified by genotypic studies. Up to 80 species of *Nocardia* are currently known. *Nocardia asteroides* was one of the first predominant strains identified and now corresponds to several complexes: *Nocardia abscessus*, *Nocardia brevicatena/paucivorans*, *Nocardia cyriacigeorgica*, *Nocardia farcinica*, *Nocardia nova*, and *Nocardia wallacei*.^{7,8}

Some case series of nocardiosis have been described,^{9–16} but few studies investigating nocardiosis epidemiology have been reported since the recent improvements made in the treatment of HIV infection and immune diseases, and in the field of transplantation. Thus the characteristics of patients with nocardiosis could have changed.

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All cases of nocardiosis diagnosed over a recent 10-year period (2004–2014) in the university hospitals of Marseille were reviewed, to study their demographic, clinical, biological, and bacteriological characteristics, their treatment, and prognosis.

Materials and methods

This was a retrospective study. All cases of nocardiosis identified in the microbiology laboratory of the university hospitals of Marseille between 2004 and 2014 were analyzed. The university hospitals are four hospitals belonging to the Assistance Publique des Hôpitaux de Marseille (AP-HM). This institution treats more than 120 000 patients per year, from a regional population estimated at 3 398 906 persons in 2014. During the study period, 2229 solid organ transplantations were performed, including 1144 kidney, 520 liver, 263 adult lung, 236 heart, and 11 heart–lung transplantations.

Data were collected from the corresponding medical records using a standardized questionnaire. The demographic data and underlying conditions analyzed were as follows: sex, date of birth, age at diagnosis of nocardiosis, history of cancer, transplantation, immune disease, or HIV infection, history of any opportunistic infection (cytomegalovirus disease, aspergillosis, *Pneumocystis jirovecii* infection), and history of acute rejection in transplanted patients. Treatment at diagnosis was also recorded: immunosuppressive drugs, steroids, and trimethoprim–sulfamethoxazole (TMP–SMX) prophylaxis for *Pneumocystis pneumonia*. Clinical, biological, and radiological data at diagnosis, as well as outcomes were also recorded, including fever, cough, dyspnoea, expectoration, pain, confusion, neurological deficit, coma, seizures, C-reactive protein (CRP) level, complete blood count, T lymphocyte count, source of bacteriological diagnosis, *Nocardia spp* strain and antibiotic susceptibility, treatment, cure, functional sequelae, recurrence, and death.

Bacteriological study

Nocardia spp were cultured from clinical specimens and all strains were identified using 16s rRNA PCR. The sequences obtained were compared with those stored in GenBank. Strains had to have >99% sequence similarity with one species only. Sequencing of the 65-kDa heat shock protein gene (*hsp65*) was also performed to separate similar species, as described previously.¹⁷

Antibiotic susceptibility was tested by disk diffusion method. Only TMP–SMX and carbapenem susceptibility were recorded; these are the antibiotics most commonly used when nocardiosis is suspected.⁷

Results

Forty-one cases of nocardiosis occurring during the period January 2004 to January 2014 were identified in the microbiology laboratory database. Thirty-six of the 41 patients had been hospitalized in the AP-HM hospitals, and the medical records were available for 34 of them (Table 1). Data for the seven patients with missing medical records are reported in the **Supplementary Material** (Table S1).

Patient characteristics and underlying conditions

The mean age of the study patients was 55.4 years (range 7–94 years); two patients were children (ages 7 and 9 years). The majority were male (70.6%).

At diagnosis, 61.8% of the patients had been receiving steroids, chemotherapy, calcineurin inhibitors (CNI), and/or antimetabolites

(AM) for over 3 months; 8.8% of the patients had undergone chemotherapy without any other immunosuppressive agent.

A history of allograft was the main underlying condition observed (44.1%): 14 patients had undergone SOT (mean age 56.1 years; eight kidneys, four lungs, one liver, and one heart) and one 9-year-old girl had undergone bone marrow transplantation (BMT) for acute lymphocytic leukaemia. All received an immunosuppressive regimen: 11 had triple therapy including a CNI, AM, and steroids; four had a regimen of CNI and steroids. An episode of acute rejection was reported in 28.0% of the patients before the diagnosis of nocardiosis, and an opportunistic infection was reported in 35.7%. No patient was on TMP–SMX prophylaxis at diagnosis. The mean delay between transplantation and the diagnosis of nocardiosis was 17.5 months (range 2–34 months); 9.4 months after lung transplantation and 16.5 months after renal transplantation. The incidence of nocardiosis was 15.2/1000 lung transplantations (4/263), 7/1000 kidney transplantations (8/1144), 4.2/1000 heart transplantations (1/236), and 2/1000 liver transplantations (1/520). (See Table S2 in the **Supplementary Material** for additional information on the solid organ transplant recipients.)

A history of malignancy was observed in nine patients (mean age 73.7 years): solid cancer in four patients (carcinoma of the ampulla of Vater, anal cancer, metastatic breast cancer, and glioblastoma plus non-small cell lung cancer (two solid cancers in one patient)) and a haemopathy in four patients (Waldenstrom disease, non-Hodgkin lymphoma (NHL), chronic lymphocytic leukaemia (CLL), and dysmyelopoietic syndrome). The remaining patient had a haemopathy and a solid cancer (rectal adenocarcinoma and NHL). At diagnosis, six patients were undergoing chemotherapy, three of them with steroids, and one was receiving only steroids.

An immune disease was observed in three patients (ages 58, 63, and 71 years). They had respectively lymphopenia with an IgG1 and IgG4 deficit, seborrheic pemphigus treated with steroids, and glomerulonephritis with anti-neutrophil cytoplasmic antibodies (ANCA) treated with AM and steroids.

Cystic fibrosis without transplantation was observed in four patients (mean age 16.5 years).

Three patients ages 74, 76, and 94 years were immunocompetent. All of them had high blood pressure and one had diabetes.

No patient was found to have an HIV infection. All patients except one had been tested routinely for HIV and none had an HIV infection. The patient who had not been tested had a cutaneous form of nocardiosis and was treated in a surgery unit.

Clinical and biological characteristics

The main symptoms were fever (61.7%), cough (35.3%), dyspnoea (26.5%), focal neurological deficit (20.6%), pain (17.6%), expectoration (11.7%), headache (8.8%), confusion (5.9%), and coma (5.9%). The main organ localizations of the *Nocardia* infection were the lung (79.7%), brain (26.5%), cutaneous tissue (26.5%), bones and joints (8.8%), thyroid gland (2.9%), kidney (2.9%), pancreas (2.9%), and adrenal glands (2.9%). Bacteraemia was found in 26.5% of patients. At diagnosis, high CRP (> 5.0 mg/l) was observed in 92.3% of patients (mean 121.0 mg/l), hyperleukocytosis in 53.3% of patients, and lymphopenia in 29.2% of patients. Four of the 10 patients with available CD4 counts had a count of <200/mm³.

Microbiological characteristics (Table 2)

Nocardia spp strains were isolated from abscesses in 14 patients, BAL in nine, blood culture in nine, and sputum in eight patients. The main strain isolated was *N. farcinica* (26.5%). Sensitivity to carbapenem was 95.6% and sensitivity to TMP–SMX was 61.2%.

Table 1

Overview of the 34 patients with nocardiosis from 2004 to 2014.

Year of diagnosis	Age/sex	Main underlying condition	Immunosuppressive treatment	Imaging	Clinical form: organs involved, bacteraemia	<i>Nocardia</i> species	Treatment/duration (weeks)/surgery	Outcome
2013	16/M	Cystic fibrosis	No	CXR	Bronchial	<i>transvalensis</i>	CPF, colistimethate sodium (4)	Recurrence
2013	9/F	Bone marrow graft + bronchiolitis obliterans	CNI, steroids/chemotherapy	CXR	Bronchial	<i>nova</i>	Ceftriaxone (2)	Cured
2013	40/F	SOT: lung (2011)	CNI, AM, steroids	T-CT	Bronchial	<i>cyriacigeorgica</i>	TMP-SMX, CBP, amoxicillin	Cured
2013	24/M	Cystic fibrosis	No	No	Bronchial	<i>cyriacigeorgica</i>	TMP-SMX (12)	Recurrence
2013	7/F	Cystic fibrosis	No	CXR	Bronchial	<i>cyriacigeorgica</i>	TMP-SMX, colymicin (4)	Cured
2010	74/M	HBP, diabetes	No	CAP-CT and cervical CT	Cutaneous tissue	<i>farcinica</i>	Ofloxacin, amoxicillin-clavulanic acid (2)/surgery	Cured
2008	94/F	HBP	No	CAPH-CT	Cutaneous tissue	<i>brasiliensis</i>	Doxycycline (12)	Cured
2010	83/M	Carcinoma of ampulla of Vater	No	CXR	Cutaneous tissue	<i>brasiliensis</i>	TMP-SMX, amoxicillin + clavulanic acid/surgery	Cured
2004	73/M	SOT: kidney (2004)	CNI, AM, steroid	CAPH-CT	D: lung, brain, bones cutaneous tissue, bacteraemia	<i>farcinica</i>	CBP, VC, AK (24)	Cured
2007	88/M	Rectal cancer + NHL	Chemotherapy	Abdominal US, h-CT	D: bacteraemia	<i>farcinica</i>	TMP-SMX, ceftriaxone, AK (28)	Cured
2008	57/M	SOT: heart (2006)	CNI, steroids	CAPH-CT	D: brain, lung, arthritis	<i>abscessus</i>	TMP-SMX, CBP (56)/surgery	Cured
2013	76/M	CLL	Chemotherapy	CXR	D: lung, bacteraemia	<i>nova</i>	TMP-SMX, ticarcillin, pristinamycin, cefotaxime (2)	Death, NR
2004	63/M	Seborrheic pemphigus	Steroids	CAPH-CT	D: lung, brain	<i>asiatica</i>	TMP-SMX, CBP, cefotaxime (32)/surgery	Neurological sequelae
2011	58/M	IgG1 and IgG4 deficit	No	CAPH-CT, b-MRI	D: lung, brain	<i>wallacei</i>	TMP-SMX, ceftriaxone, AK, moxifloxacin (52)/surgery	Neurological sequelae
2012	64/M	Glomerulonephritis ANCA	AM, steroids	CAPH-CT	D: lung, brain	<i>cyriacigeorgica</i>	TMP-SMX, CBP/surgery	Neurological sequelae
2007	81/M	Dysmyelopoietic syndrome	Steroids	CAPH-CT	D: lung, brain, bacteraemia	Unknown	Cefotaxime, CPF, MNZ (1)	Death, R
2008	35/M	SOT: kidney (2007)	CNI, AM, steroids	CAPH-CT	D: lung, kidney, pancreas, adrenal glands, bacteraemia	<i>farcinica</i>	TMP-SMX, CBP, AK (56)	Hypoacusia
2007	57/M	SOT: kidney (2007)	CNI/steroids	CAPH-CT	D: lung, liver, kidney	<i>abscessus</i>	TMP-SMX, CBP (36)/surgery	Cured
2009	50/M	SOT: kidney (2008)	CNI, AM, steroids	CAPH-CT	D: lung, cutaneous tissue, bacteraemia	<i>farcinica</i>	CPF, CBP (12)	Cured
2013	69/F	Breast metastatic cancer	Chemotherapy	CAP-CT	D: lung, cutaneous tissue, bacteraemia	<i>farcinica</i>	Ceftriaxone, AK	Death, R
2012	57/M	SOT: kidney (2012)	CNI, AM, steroids	CAPH-CT, h-MRI, PET-CT	D: lung, cutaneous tissue, bacteraemia	<i>farcinica</i>	TMP-SMX, CBP, CPF (28)	Cured
2010	46/F	SOT: kidney (2008)	CNI, AM, steroids	CAPH-CT	D: lung, cutaneous tissue	<i>abscessus</i>	TMP-SMX, CBP (24)/surgery	Cured
2011	60/M	SOT: kidney (2011)	CNI, AM, steroids	CAPH-CT	D: lung, thyroid gland, arthritis, cutaneous tissue	<i>neocaledoniensis</i>	TMP-SMX, CBP/surgery	Recurrent laryngeal paralysis
2007	57/M	Glioblastoma + lung cancer (2)	Steroids/chemotherapy	CAP-CT	D: bacteraemia	<i>farcinica</i>	TMP-SMX, CBP (4)/surgery	Death, NR
2004	54/M	SOT: kidney (2002)	CNI, AM, steroids	CAPH-CT, h-MRI	D: lung and brain	<i>nova</i>	CBP, VC (8)/surgery	Cured
2005	70/F	Waldenstrom disease	Steroids/chemotherapy	CXR, h-CT, h-MRI	Brain	<i>nova</i>	Cefotaxime, CBP, VC, TMP-SMX, MNZ/surgery	Cured
2008	66/M	NHL	Steroids/chemotherapy	CXR, h-CT, h-MRI	Brain	<i>abscessus</i>	TMP-SMX, CBP/surgery	Death, NR
2007	56/M	SOT: lung (2005)	CNI, AM, steroids	CAP-CT	Lung	<i>abscessus</i>	TMP-SMX, CBP, gentamicin (2)	Death, R
2009	51/M	SOT: liver (2009)	CNI, AM, steroids	CAP-CT	Lung	<i>cyriacigeorgica</i>	TMP-SMX, CBP, ofloxacin (3)	Death, R
2009	74/M	Anal cancer	No	CAPH-CT, PET-CT	Lung	<i>abscessus</i>	TMP-SMX, CBP (24)	Cured
2010	19/M	Cystic fibrosis	No	CAP-CT	Lung	<i>farcinica</i>	CBP, minocycline, linezolid (12)	Recurrence
2010	76/F	HBP	No	CAPH-CT	Lung	<i>cyriacigeorgica</i>	TMP-SMX (24)	Cured
2011	55/F	SOT: lung (2011)	CNI, AM, steroids	Th-CT	Lung	<i>cyriacigeorgica</i>	TMP-SMX, amoxicillin (24)	Cured
2013	25/F	SOT: lung (2013)	CNI, AM, steroids	Th-CT	Lung	<i>wallacei</i>	CBP, amoxicillin and clavulanic acid (16)	Cured

AK, amikacin; AM, antimetabolite; ANCA, anti-neutrophil cytoplasmic antibodies; h-MRI; CAP-CT, chest, abdomen and pelvic computed tomography; CAPH-CT, chest, abdomen, pelvic and head computed tomography; CBP, carbapenem; CLL, chronic lymphocytic leukaemia; CPF, ciprofloxacin; CNI, calcineurin inhibitor; CXR, chest X-ray; D, disseminated disease; F, female; HBP, high blood pressure; h-CT, head computed tomography; h-MRI, head magnetic resonance imaging; IS, immunosuppressive treatment; M, male; MNZ, metronidazole; NHL, non-Hodgkin lymphoma; NR, death not related to nocardiosis; PET-CT, positron emission tomography computed tomography; R, death related to nocardiosis; SOT, solid organ transplant; Th-CT, thorax computed tomography; TMP-SMX, trimethoprim-sulfamethoxazole; US, ultrasound; VC, Th-CT, vancomycin.

Table 2
Microbiological characteristics (population N = 34).

	Findings, n (%)
Source of diagnosis	
Sputum	8 (23.5)
BAL	9 (26.5)
Blood culture	9 (26.5)
Abscess	14 (41.2)
Lymph node	1 (20.5)
<i>Nocardia spp</i> strains	
<i>N. farcinica</i>	9 (26.5)
<i>N. cyriacigeorgica</i>	7 (20.6)
<i>N. abscessus</i>	6 (17.6)
<i>N. nova</i>	4 (11.7)
<i>N. wallacei</i>	2 (5.9)
<i>N. brasiliensis</i>	2 (5.9)
<i>N. asiatica</i>	1 (2.9)
<i>N. neocaledoniensis</i>	1 (2.9)
<i>N. transvalensis</i>	1 (2.9)
<i>N. takedensis</i>	0
<i>N. carnea</i>	0
<i>Nocardia spp</i>	1 (2.9)
Antibiotic susceptibility (%)	
TMP–SMX (n = 26) ^a	61.2
Carbapenem (n = 23) ^b	95.6

BAL, bronchoalveolar lavage; TMP–SMX, trimethoprim–sulfamethoxazole.

^a Susceptibility calculated with the 26 available antibiograms for TMP–SMX.

^b Susceptibility calculated with the 23 available antibiograms for carbapenem.

Outcomes

All patients received antibiotics: 44.1% of the patients received dual antibiotic therapy with TMP–SMX and a carbapenem, 23.5% received a regimen of TMP–SMX with other antibiotics, 14.7% received a carbapenem with other antibiotics, and 17.7% did not receive TMP–SMX or carbapenem, and were treated according to the antibiogram results or empirically. The mean duration of treatment was 19 weeks (range 1–56 weeks); the mean duration was 23.3 weeks (range 2–56 weeks) excluding patients who died during the first month after diagnosis.

A surgical procedure was performed in 13 patients (38.2%) for various abscesses or the removal of an implantable chamber.

Cure without sequelae was obtained in 25 patients (67.3%). Four patients (11.7%) died from nocardiosis (two patients with a malignancy and disseminated nocardiosis and two transplant recipients with multi-bacterial and fungal pneumonia). Functional sequelae were observed in five patients (14.7%), including neurological symptoms after brain abscess (cerebellar syndrome, paresis, speech disorder), dysphonia after thyroid removal, and hypoacusia following aminoglycoside treatment.

In three patients, all with cystic fibrosis, the same *Nocardia spp* strain was found again in sputum after treatment of a first episode.

Characteristics according to the clinical presentation (Table 3)

Regarding the clinical presentations and outcomes, four different clinical forms could be identified: a disseminated form defined by two or more organ localizations and/or bacteraemia, an isolated visceral form, a bronchial form with respiratory symptoms and no radiological evidence of lung disease, and an isolated cutaneous form ().

Disseminated form (50.0%)

Disseminated nocardiosis was the main clinical presentation for 17 patients. All presented with an underlying condition: kidney transplantation (n = 8), heart transplantation (n = 1), malignancy (n = 5), autoimmune disease (n = 2), and lymphopenia with

IgG1 and IgG4 defect (n = 1). All were receiving immunosuppressive treatments at diagnosis (10 CNi and/or AM and steroids, two steroids only, one chemotherapy and steroids, and four chemotherapy).

A chest, abdomen, and pelvis computed tomography scan (CAP-CT) was performed in 15 patients (88.2%) and a head CT was performed in 14 (82.3%). With this broad radiological investigation, multiple visceral localizations were found: a lung localization in 15 patients (88.2%), associated with a brain abscess in seven, bacteraemia in seven, multiple extrapulmonary localizations in five, and with a subcutaneous abscess in four. Only two patients with bacteraemia had no visceral localization; however, one of them had not undergone brain CT and the other had not undergone a body scan.

The mean duration of antibiotic therapy was 34 weeks (range 8–56 weeks), excluding the two patients who died quickly. Surgery was performed in nine patients (52.9%).

Cure without sequelae was obtained in 10 patients (58.8%), five had neurological sequelae (29.4%), and two died from sepsis (11.7%).

Isolated visceral form: pulmonary and brain infections (26.5%)

The isolated visceral form was the second most common clinical presentation, occurring in nine patients. Seven of these patients were immunocompromised: three had undergone lung transplantation, two had a haemopathy, one had a solid cancer, and one had undergone liver transplantation. Cystic fibrosis was observed in one patient, and one was a 76-year-old man with high blood pressure only.

A lung localization was observed in seven patients; six of these patients were examined by CAP-CT (associated with a head CT in three patients) and one had a chest and head CT. Localized brain nocardiosis was observed in two patients with haemopathy; these patients were examined only by head CT and head MRI, without blood culture.

The mean duration of antibiotic therapy was 13.6 weeks (range 2–24 weeks). Two patients had surgery for a brain abscess.

Cure without sequelae was obtained in seven patients (77.8%). Two patients (22.2%) died from sepsis (one with a liver transplant and one with a lung transplant from multi-bacterial pneumonia with *Nocardia spp*). A recurrence during the next 24 months was observed in one patient with cystic fibrosis.

Bronchial form (14.7%)

The bronchial form was defined by poor respiratory symptoms and sputum positive for *Nocardia spp*, without radiological evidence of pneumonia. This was observed in five patients. All patients had a chronic lung disease: cystic fibrosis (n = 3), lung transplantation (n = 1), and one BMT complicated with graft-versus-host disease (GVHD) and bronchiolitis obliterans (n = 1).

A chest X-ray was performed in four patients, one of whom also had a chest CT; one patient had no radiological examination.

N. cyriacigeorgica was the main strain isolated (60%). The *Nocardia spp* was always isolated from sputum and was associated with one or more other pathogens for four patients: *Staphylococcus aureus* (n = 3), *Pseudomonas aeruginosa* (n = 2), *Achromobacter xylosoxidans* (n = 1), and *Stenotrophomonas maltophilia* (n = 1).

The mean duration of antibiotic therapy was 5.5 weeks (range 2–12 weeks), shorter than for the disseminated and isolated visceral nocardiosis forms.

All were cured, although there were two cases of recurrence in the next 24 months.

Isolated cutaneous form (8.8%)

An isolated cutaneous localization was observed in three patients. Their mean age was 84.2 years. One patient had a history

Table 3

Characteristics of patients according to the clinical form.

Parameters	General n (%)	Form			
		Disseminated (17 patients)	Visceral (9 patients)	Cutaneous (3 patients)	Bronchial (5 patients)
Mean age, years (range)	55.4	61.5 (60–88)	52.5 (25–76)	84.2 (74–94)	19.2 (7–40)
Underlying condition, n (%)					
SOT	14 (41.2)	9 (53)	4 (44.4)	0	1 (20)
BMT	1 (2.9)	0	0	0	1 (20)
Malignancy: solid cancer/haemopathy	9 (26.5)	5 (29.4)	3 (33.3)	1 (33.3)	0
Cystic fibrosis	4 (11.7)	0	1 (11.1)	0	3 (60)
Immune disease	3 (8.8)	3 (17.6)	0	0	0
HBP	2	0	1 (11.1)	1 (33.3)	0
HBP and diabetes	1 (2.9)	0	0	1 (33.3)	0
Immunosuppressive drugs, n (%)					
Steroids	21 (61.8)	13 (76.5)	7 (77.7)	0	1 (20)
CNI/antimetabolites	16 (47)	10 (59)	4 (44.4)	0	2 (40)
Chemotherapy	7 (20.6)	4 (23.5)	2 (22.2)	0	1 (20)
Symptoms, n (%)					
Fever	21 (61.8)	15 (88.2)	3 (37.5)	2 (66.6)	2 (40)
Dyspnoea	9 (26.5)	6 (35.3)	3 (37.5)	0	0
Cough	12 (35.3)	4 (23.5)	3 (37.5)	0	4 (80)
Neurological deficit/confusion	11 (32.3)	8 (47)	2 (22.2)	0	0
Biology, mean (range)					
CRP (mg/l)	121	152 (53–323)	89 (3–200)	143 (63–223)	20 (8–32)
Leukocytes ($\times 10^9/l$)	12.75	14.9 (2.75–24)	13.4 (7.4–30.8)	12.4 (7.9–19)	7.6 (6.4–9)
Main <i>Nocardia</i> spp strain	<i>N. farcinica</i>	<i>N. farcinica</i>	<i>N. abscessus</i>	<i>N. brasiliensis</i>	<i>N. cyriacigeorgica</i>
Treatment, n (%)					
Hospitalization	30 (88.2)	17 (100)	9 (100)	2 (66.6)	2 (40)
Intensive care unit	9 (26.5)	6 (35)	3 (33.3)	0	0
TMP–SMX with other antibiotics	8 (23.5)	3 (17.6)	2 (22.2)	1 (33.3)	2 (40)
Carbapenem with other antibiotics	5 (14.7)	3 (17.6)	2 (22.2)	0	0
TMP–SMX+carbapenem	15 (44)	9 (53)	5 (55.5)	0	1 (20)
Mean duration of treatment (weeks)	19	34 (8–56) ^a	20 (12–24) ^a	7 (2–12)	7.6 (2–16)
Surgery, n (%)	13 (38.2)	9 (53)	2 (22.2)	2 (66.6)	0
Outcome, n (%)					
Death due to nocardiosis	4 (11.7)	2 (11.7)	2 (22.2)	0	0
Cure without sequelae	27 (79.4)	10 (58.8)	7 (77.7)	3 (100)	5 (100)
Recurrence	3 (8.8)	0	1 (11.1)	0	2 (40)
Sequelae	5 (14.7)	5 (29.4)	0	0	0

BMT, bone marrow transplantation; CNI, calcineurin inhibitor; CRP, C-reactive protein; HBP, high blood pressure; SOT, solid organ transplant; TMP–SMX, trimethoprim-sulfamethoxazole.

^a Excluding patients who died the first month after diagnosis.

of carcinoma of the ampulla of Vater only, treated with surgery, and two had high blood pressure including one with diabetes.

CAP-CT was performed for two patients, associated with cervical CT for one; one patient had only an arm X-ray. *Nocardia brasiliensis* was isolated from an abscess in two cases. The mean duration of antibiotic therapy was 7 weeks (range 2–12 weeks), and two patients underwent surgery. All were cured without sequelae.

Discussion

This study reports one of the largest recent series of nocardiosis from a European country and provides an overview of this infection over the past decade. Table 4 presents a review of the largest series, with more than 30 cases of nocardiosis, published from 1990 to 2014.

Nocardiosis remains a severe disease, with a related mortality of 11.7%. This is lower than the mortality reported previously in Spain (21.6%),¹² Thailand (20%),¹⁰ and China in a cohort of pulmonary nocardiosis (18.7%).¹⁸

Underlying conditions determine the bacteriological dissemination. Steroid therapy is often regarded as a risk factor for nocardiosis.^{19–21} In the present study, 61.8% of patients had received steroid therapy, mainly for cancer or transplantation. The incidence reported in transplant recipients varies between 0.7% and 3.5%.² In the present study, transplantation was the predominant underlying condition – 41.0% of the cohort, close to the 26.1%

observed in Western countries.¹² These patients suffered mainly from the disseminated form. This high rate of invasive nocardiosis in transplant recipients may be explained by a profound immunodeficiency. All patients had received steroids and at least a CNI. Two patients were undergoing their second kidney transplantation, 28.6% of patients had been treated previously for acute rejection, and 35.7% had already had an opportunistic infection. In the literature, high doses of CNI and a history of cytomegalovirus disease have been described as risk factors for nocardiosis in transplantation.²²

Four clinical forms were identified. The disseminated form was the predominant clinical presentation at 50%, higher than reported previously: 13.5% in Spain,¹² 11.4% in Thailand,¹⁰ 6% in Taiwan,²³ and 36% in Israel.¹³ This difference may be related to the systematic radiological strategy used, which allowed more patients with disseminated disease to be identified, or could have been related to the high rate of immunocompromised patients in the study cohort. The disseminated form was always observed in immunocompromised patients and was mainly drug-related: steroid therapy or anti-rejection therapy for organ transplantation, or after chemotherapy for a solid cancer. Most of these patients underwent extensive radiological examinations when compared to patients with the isolated visceral form in this study. With regard to the infection pathway, the lung was the predominant localization, followed by the brain, but many other organs could be infected, such as the liver or thyroid. As recommended, long-term antibiotic therapy was prescribed, and there was no recurrence and a

Table 4

Review of the largest series, with more than 30 cases of nocardiosis, from 1990 to 2014.

Country [Ref.]	Years	No. of patients	Underlying conditions	Patients on steroids at diagnosis (%)	Predominant <i>Nocardia</i> spp strain	TMP-SMX susceptibility (%)	Disseminated nocardiosis (%)	Isolated lung nocardiosis (bronchial/pulmonary disease) (%)	Isolated brain nocardiosis (%)	Isolated cutaneous nocardiosis (%)	Related death (%)
Australia ⁵	5 (1995–2000)	35	15 pulmonary disease, 9 neoplasia, 3 SOT, 3 AI disease, 3 healthy, 1 HIV, 1 TB	60	<i>N. asteroides</i> (60%)	NR	10	NR	NR	NR	31
Thailand ¹⁰	6 (1996–2001)	70	24 HIV, 12 AI disease, 8 neoplasia, 4 DM, 3 nephrotic syndrome, 1 chronic renal failure, 2 pulmonary disease, 1 mitral stenosis, 1 TB	24.3	NR	42.1	11.4	44.3	0	22.8	20
USA ²²	11 (1995–2005)	35	SOT	100	<i>N. nova</i>	94.3	20	77.2	0	2.8	14
Taiwan ²³	18 (1988–2006)	81	11 chronic lung disease, 8 DM, 8 neoplasia, 6 AI disease, 5 SOT, 5 HIV	30	<i>N. brasiliensis</i> (57%)	94	16	29.6	0	54.3	14
Spain ¹²	12 (1995–2006)	37	10 HIV, 7 SOT, 8 AI disease, 8 COPD, 4 neoplasia	62.2	<i>N. cyriacigeorgica</i> (32%)	89.2	16.2	70	2.7	5.4	22
Saudi Arabia ¹⁴	9 (1998–2006)	30	13 COPD, 9 TB, 8 bronchiectasis, 6 DM, 2 SOT, 4 chronic lung disease, 4 neoplasia	6.6	NR	NR	20	80	0	0	10
Spain ¹⁵	12 (1997–2009)	30	30 COPD with 12 HBP, 7 dyslipidemia, 7 neoplasia, 4 chronic kidney failure, 3 DM, 1 chronic liver disease	51.5	<i>N. cyriacigeorgica</i> (56.7%)	NR	3.3	96.6	0	0	33
Taiwan ²³	12 (1998–2010)	100	19 neoplasia, 12 chronic kidney disease, 10 DM, 11 chronic liver disease, 10 chronic lung disease, 8 SOT, 6 AI disease, 6 HIV	17	<i>N. brasiliensis</i> (50%)	NR	6	26	0	55	7
Israel ¹³	6 (1996–2011)	39	Neoplasia, connective tissue disease, chronic lung disease, BMT, HBP, DM, smoker, ischemic heart disease	69.23	NR	75	36	NR	13	NR	32
Japan ¹⁸	13 (1999–2012)	59	13 COPD, 12 lung neoplasia, 9 chronic lung disease, 20 history of mycobacterial pneumonia, 11 pneumoconiosis, 6 aspergillosis, 5 CV disease, 4 DM, 2 AI disease, 1 chronic liver disease, 1 kidney failure	1.2	<i>N. asteroides</i> (68%)	73	1.2	98.8	0	0	NR
China ¹⁹	13 (2000–2013)	40	13 DM, 8 AI disease, 6 chronic lung disease, 5 SOT, 4 chronic kidney disease, 5 history of skin injury, 1 HIV, 5 none	50	NR	NR	30	60	0	10	15
France (present study)	10 (2004–2014)	34	14 SOT, 9 neoplasia, 4 CF, 3 AI disease, 2 HBP, 1 BMT with chronic lung disease, 1 DM	61.7	<i>N. farcinica</i> (26.5%)	59	50	35.3	5.9	8.8	12

AI, autoimmune; BMT, bone marrow transplantation; COPD, chronic obstructive pulmonary disease; CF, cystic fibrosis; CV, cardiovascular disease; DM, diabetes mellitus; HBP, high blood pressure; NR, not reported; SOT, solid organ transplant; TB, tuberculosis; TMP-SMX, trimethoprim-sulfamethoxazole.

relatively low mortality rate; death occurred mainly during the first weeks following diagnosis.

The visceral form was the second most common clinical presentation. Lung nocardiosis was observed mainly in patients with chronic lung disease and/or with an immunosuppressive condition (lung transplantation recipients and one liver

transplantation recipient, or cystic fibrosis), and also occurred in one elderly patient without any serious underlying condition. Most patients with a lung infection were examined by CAP-CT and head CT. In contrast, the two patients with a localized brain infection were not investigated for other visceral localizations; thus a disseminated form could not be excluded. Indeed, the seven other

patients with cerebral localizations had a total body scan and were found to have the disseminated form. Several cases of isolated brain abscess have been reported in the literature, but often with poor information on radiological staging.^{24–26} The strategy for radiological staging was unfortunately heterogeneous and depended on the medical staff. In visceral nocardiosis, especially in immunocompromised patients, a systematic examination including blood cultures, CAP-CT, and head CT should be performed.

The isolated cutaneous form was always observed in elderly patients without serious medical conditions, probably occurring after a skin injury; these infections were locally contained. This clinical form has mainly been reported in Asia, in Thailand,¹⁰ Taiwan,²⁷ and China.¹⁹

The isolated bronchial form, defined by respiratory symptoms without radiological lesions, was observed in patients with chronic lung disease, mainly in those with cystic fibrosis, but also in lung transplantation and bronchiolitis obliterans. Multiple other bacterial species are associated with *Nocardia*, such as *P. aeruginosa* and *S. aureus*. In two cystic fibrosis patients, the same *Nocardia spp* strain was found in successive samples, suggesting colonization; the same happened with the patient with cystic fibrosis who had the visceral lung form.

The pathogenic role of *Nocardia spp* in patients with chronic lung disease remains unclear. *Nocardia spp* have already been reported in the respiratory tract of patients with chronic lung diseases such as cystic fibrosis and bronchiectasis, with evidence of infection in only 62.5% of cases.²⁸ In fact, in patients colonized by *Nocardia spp* without pulmonary lesions, there is no evidence of improved outcomes with antibiotic therapy.²⁹ All patients in the present study received antibiotics active against *Nocardia spp* and other pathogens isolated in the sputum. The duration of treatment has not been established, and has varied from 3 weeks to 3 months, with a good prognosis, as reported by Rodriguez-Nava et al.³⁰ In the bronchial form, in patients with chronic lung disease, chest radiological examinations appear to be sufficient.

No patient in this study had AIDS, probably because of improvements in antiretroviral therapy, as observed in a recent study in Israel.¹³

The *Nocardia* species was identified in most cases, as molecular techniques were applied systematically. *N. farcinica*, *N. abscessus*, *N. cyriacigeorgica*, and *N. nova*, the main species found in the study patients, are known to be responsible for the majority of human *Nocardia* infections. They are all part of the old *Nocardia asteroides* complex.⁸ *N. brasiliensis* was more represented in isolated cutaneous infections, as observed previously by Liu et al. in Taiwan.²³

In recent studies, between 75% and 89% of *Nocardia spp* were found to be sensitive to TMP–SMX.^{11,12,21} In this study, 59.25% of *Nocardia spp* were sensitive to TMP–SMX and 95.6% to carbapenem. Recent studies in the USA have reported only 2% of sulfonamide resistance in *Nocardia spp* when reviewing the susceptibilities of large series of *Nocardia spp* isolates. It has been suggested previously that the increasing in vitro sulfonamide resistance in *Nocardia spp* could actually be due to difficulties in the laboratory interpretation of TMP–SMX susceptibility.^{31,32} The high degree of resistance to TMP–SMX found in the present study could in part be related to the technique, or may be explained by new-found resistance after previous sulfonamide antibiotic therapy, as recommended in the first month after transplantation. In addition, the antibiograms for TMP–SMX were missing for seven of the 34 cases, which could have led to an underestimation of the susceptibility to TMP–SMX. None of the patients were receiving TMP–SMX prophylaxis at diagnosis. TMP–SMX was considered an appropriate prophylactic treatment for nocardiosis, but since

several cases of nocardiosis have been reported despite TMP–SMX prophylaxis in transplantation, this hypothesis does not hold true.^{9,12}

Combination therapy with a carbapenem and TMP–SMX is recommended if invasive nocardiosis is suspected, as in vitro synergism has been demonstrated between carbapenem and TMP–SMX. Amikacin in addition to a carbapenem, and linezolid are also effective and can be used in severe infections.^{31,33,34} The duration of treatment will depend on the severity of the context, clinical form, and immunosuppressive condition. For visceral and disseminated forms, a treatment lasting from 6 to 12 months is largely prescribed.^{13,35,36}

Conclusions

Nocardiosis remains a severe infectious disease, occasionally fatal, with a risk of functional sequelae, especially after brain involvement. The management of nocardiosis often requires medical and surgical treatment and long-term therapy and follow-up. Although this study had several limitations, it revealed the wide range of clinical presentations of nocardiosis in the study area, and the impact of the main underlying conditions. Transplant recipients, patients with a malignancy, and those on long-term steroid therapy or with a chronic lung disease are the most affected. The epidemiology and treatment of nocardiosis are evolving, requiring further studies. A systematic radiological evaluation could improve the description of the clinical forms and the adapted treatment.

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Conflict of interest

The authors declare that they have no competing interests.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.ijid.2017.01.005>.

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