Nocardiosis in Quebec, Canada, 1988–2008

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Abstract

Nocardia is an uncommon pathogen, but immunosuppression, its main risk factor, is becoming more frequent. We aimed to evaluate changes in the annual incidence of nocardiosis and in the susceptibility profile of its aetiological agents. Demographic data were analysed for all isolates of *Nocardia* forwarded to the provincial public health laboratory of Quebec, Canada during the last two decades. Population incidence could be measured from 1997 onwards. Resistance patterns were analysed for those isolates selected for *in vitro* susceptibility testing. Throughout Quebec, 575 incident cases were identified between 1997 and 2008. The annual incidence of *Nocardia* infection/colonization increased from 0.33 (1997–1998) to 0.87 (2007–2008) per 100 000 inhabitants (p 0.001). In a small subset of patients for whom detailed clinical information was available, 59% of isolates corresponded to genuine infections. *Nocardia farcinica* predominated in specimens representing invasive infections (blood, brain, lung or pleural aspirates). Isolates were often non-susceptible to several antimicrobials, with the exception of amikacin and linezolid. Overall, 43% of 157 isolates were non-susceptible to trimethoprim–sulphamethoxazole. In conclusion, *Nocardia* infection/colonization remains rare. However, from 1997–1998, a progressive increase in incidence was noted in the province of Quebec. In regions such as ours, where a substantial proportion of invasive isolates are non-susceptible *in vitro* to trimethoprim–sulphamethoxazole, the latter may no longer be the empirical treatment of choice in immunosuppressed and severely ill patients with nocardiosis.

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Introduction

The Gram-positive aerobic actinomycete *Nocardia* is an uncommon human pathogen infecting the lungs, skin, central nervous system (CNS) or other organs. It can present as localized or disseminated infections [1–3]. Immunosuppression is the main risk factor for nocardiosis and/or for disseminated infection, especially those conditions that impair cell-mediated immunity [1–3]. Chronic diseases associated with nocardiosis include diabetes, alcoholism, cancer and alveolar proteinosis [1–3]. *Nocardia* spp. are ubiquitous and are found worldwide in soil and decaying organic plant matter [3,4]. The organism is acquired by inhalation or direct inoculation into the skin, and nosocomial transmission is rare [1]. Colonization or subclinical infection occurs, especially within the respiratory tract of patients with chronic obstructive pulmonary disease (COPD), malignancy, asthma or bronchiectasis [3].

Data on the incidence of nocardiosis are sparse, as it is generally not a reportable disease. Its incidence may be increasing because of a growing population of immunocompromised patients and the enhanced diagnostic capacity of microbiology laboratories [4–6]. Biochemical tests were inadequate for identification of species, especially the differentiation of *Nocardia asteroides* sensu stricto from the species within the *N. asteroides* complex (*Nocardia abscessus*, *Nocardia brevicatena*/*Nocardia paucivorans* complex, *Nocardia nova* complex, *Nocardia transvalensis* complex, *Nocardia farcinica*, and *Nocardia cyriacigeorgica*) [1]. Reference laboratories now rely on 16S rRNA gene sequencing, which is rapid, accurate and reproducible [1,7–10]. However, molecular approaches complicated the taxonomy: there are now 76 species of *Nocardia*, 25 of which can cause human disease [11,12]. Speciation guides initial empirical treatment, as *in vitro* susceptibility

testing is performed only in reference laboratories. Trimethoprim–sulphamethoxazole has been classically recommended [1–3].

We have noted in recent years a higher number of cases of *Nocardia* infections, often involving trimethoprim–sulphamethoxazole-resistant isolates. To improve our therapeutic strategies, we reviewed all cases of nocardiosis diagnosed in our region since 1991, for which detailed information was available, as well as the provincial public health laboratory database, which contains basic demographic and clinical information on a much larger number of isolates.

Materials and Methods

Patients seen at the Centre hospitalier universitaire de Sherbrooke (CHUS)

The Centre hospitalier universitaire de Sherbrooke (CHUS) is a 686-bed hospital that provides secondary care to the 304 702 inhabitants of the Estrie region in the Province of Quebec, Canada, and tertiary care to adjacent regions as well. Peripheral hospitals of the region usually forward their putative *Nocardia* isolates, and it is likely that all patients requiring treatment will be referred as well. Cases with a positive culture for *Nocardia* between January 1991 and December 2008 were identified from our computerized hospital records. Presumptive identification of *Nocardia* isolates was based on microscopic observation of branching Gram-positive bacilli, acid-fast by the modified Kinyoun stain, from a typical dry-chalky colony with aerial hyphae on Lowenstein–Jensen medium [11]. All isolates were sent to the Laboratoire de santé publique du Québec (LSPQ—provincial public health laboratory) for further confirmation and antimicrobial susceptibility testing. We sought to identify additional cases from the discharge diagnoses database, based on ICM-9 codes for nocardiosis. Permission to review these records was obtained from the CHUS institutional review board.

We collected socio-demographic data, past medical history and clinical, diagnostic, therapeutic and microbiology data concerning the episode of nocardiosis. A patient was considered to be infected with a *Nocardia* species if he or she presented with symptoms or signs compatible with a nocardial infection and no other pathogen was isolated or if the pathogen was isolated from a sterile site. Patients were considered to be colonized if a *Nocardia* species was isolated from a non-sterile site without compatible symptoms, signs or radiological signs, and no treatment was ordered by the medical team.

For determination of incidence rates, numerators included only partients living in the Estrie region. Denominators were obtained from the Institut de la statistique du Québec [13]. Rates were calculated only from 1997 onwards, after the four hospitals of Sherbrooke were merged, so it was very unlikely that cases could have been missed by our search methods. Annual incidences were calculated for 2-year periods to decrease random variations. To allow comparisons with the provincial data, we present data for infection and colonization combined.

Isolates characterized at the LSPQ

Nearly all suspected *Nocardia* isolates are submitted by the Quebec hospital laboratories to the LSPQ for further characterization. Its entire database of *Nocardia* isolates obtained between 1988 and 2008 was reviewed. In 1994, biochemical and chemotaxonomic tests were replaced with HPLC and selected traditional tests [14]. From mid-2006, identification was based solely on sequencing of the 16S rRNA gene, colonial morphology and microscopic examination [1,7–11,15]. When requested by the attending physician or if the specimen came from a sterile site, isolates were forwarded to the CDC for *in vitro* susceptibility testing by broth microdilution [16]. Information provided by the primary laboratory (age, sex, source of clinical specimen and, from 1997, region of residence) is kept in the LSPQ database. To avoid any bias from the repeated testing of colonized patients, we considered only the first isolate per patient for a given species, taking into account changes in taxonomy. A patient infected with two different species of *Nocardia* was tabulated as two events. We analysed secular changes in species and resistance patterns, keeping in mind the changes in taxonomy and identification methods.

For the determination of incidence, a patient with dual infections (two species in one or more specimens obtained within 1 year) and a patient with multiple isolates of the same species over a long period of time would be counted as a single episode occurring at the time of initial isolation. Annual infection/colonization incidence was calculated over 2-year periods, and only from 1997 onwards, when information on the region of residence became available for all isolates. To detect possible biases in the referral of specimens, incidence rates were calculated for the heavily populated Montreal metropolitan area (the island of Montreal and peripheral regions; the population in 2008 was 4 129 824) and the rest of Quebec (population of 3 620 680).

Data analysis

Proportions were compared with the chi-squared test or Fisher's test when appropriate. Continuous variables were compared with rank sum tests. Linear regression lines