English full-text version of „Epidemiologie der nichttuberkulösen mykobakteriellen Erkrankungen in Deutschland und weltweit"
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Epidemiology of nontuberculous mycobacterial disease in Germany and worldwide

Nontuberculous mycobacteria (NTM) are a group of over 120 different species [4] that can cause a wide array of infections in humans and animals [7]. Although the first cases of NTM lymphadenitis, caused by *M. avium*, in Germany dates back to 1958 [15], NTM only gained notoriety during the early HIV era. The emergence of NTM, at a time of decline in tuberculosis prevalence, in the late 1980s and early 1990s was well visualized by Schütt-Gerowitt in the Cologne area [25]. With the advent of highly active antiretroviral treatment, the incidence of HIV-related NTM disease has decreased significantly [11].

NTM disease in humans

In humans, three types of disease are now regularly seen in clinical practice:

- NTM lung disease is most frequent and represents 65–80% of all clinical NTM disease [2, 3]; there is growing evidence that the incidence of NTM lung disease is on the rise, mainly in regions with a low prevalence of tuberculosis [22, 34],
- pediatric cervicofacial lymphadenitis is the second most common disease type that often is not diagnosed by culture of the causing mycobacterium, and
- finally, skin infections are most often caused by *Mycobacterium marinum*, the so-called fish tank or swimming pool granuloma [2, 3].

Other extrapulmonary or disseminated NTM infections are exceedingly rare [2, 3, 7, 30].

Differences between NTM diseases and tuberculosis

NTM covers all members of the genus *Mycobacterium*, other than the *M. tuberculosis* complex and *M. leprae*, the causative agents of human tuberculosis and leprosy [7]. There are two major differences between these two diseases and NTM disease that have implications for epidemiological studies. The first is the mode of spread. NTM are environmental bacteria and the environment is the source of human infections [5]. Onward human-to-human transmission is thought not to occur, or to be highly exceptional. For this reason, public health authorities have little interest in NTM disease, and national or regional surveillance programs do not exist; Queensland in Australia is the only notable exception [27]. This severely impacts epidemiological studies; most studies to date have been local studies from single reference centers, with their inherent biases. Population-based studies remain far and few between, although some have been published in the past 2 years. The second difference is that NTM are opportunistic agents that cause disease mainly in patients with local or systemic impairment of immunity. Exposure to NTM from the environment does not *per se* lead to infection and disease [5]. This explains the differences in outcomes of conventional epidemiological studies measuring skin test reactivity in general populations and clinically oriented epidemiological studies that have mostly assessed positive cultures (isolation frequency) or proven clinical disease (disease frequency).

Despite all mentioned limitations of epidemiological studies in this field, an increase in the incidence of NTM disease has been noted in different parts of the world. In this minireview, these novel epidemiological data on NTM disease, as well as the driving forces behind the epidemiology are reviewed.

New epidemiological data on NTM lung disease

Most of the new epidemiological data on NTM lung disease comes from studies in North America, where there is increasing awareness of the clinical importance of NTM disease. In the state of Oregon, NTM disease prevalence amounted to 8.6/100,000 over the 2005–2006 period [34]; in a combined report of four other regions, the mean annual prevalence was 5.5/100,000, ranging from 1.7/100,000 in Southern Colorado to 6.7/100,000 in Southern California [22]. The latter study observed an annual increase in prevalence of 2.6% over the study period [22]; these data are supported by the fact that skin sensitization to *M. intracellulare* has also increased in the United States [13]. In Ontario, Canada, the NTM isolation prevalence (i.e., number of people with a positive NTM culture) increased from 9.1/100,000 in 1997 to 14.1/100,000 in 2003; one-third of the patients met clinical definitions of NTM disease [18], giving an estimated NTM disease incidence of 3/100,000 in 1997 and 4.7/100,000 in 2003. In Queensland, Australia, where NTM disease is a reportable condition, the incidence of notified cases of clinically significant disease rose from 2.2/100,000 in 1999 to 3.2/100,000 in 2005 [27].

In northwestern Europe, the incidence of NTM lung disease appears to be lower, although very few studies on this subject have been published; in the Netherlands, the incidence of true NTM disease has also increased [30] and was conservatively estimated at 1.7/100,000 [29] in 2008. In Denmark, the rising trend is less obvious and incidence of true NTM disease reaches 1.08/100,000 [1]. Recent incidence or prevalence data from Asia are not available.

The backgrounds of these rising incidences and prevalences differ by region, a fact that has not received its deserved emphasis. Despite differences in causal mechanisms, the rising incidence and prevalence of NTM lung disease are evident in the industrialized world.

Epidemiology of NTM cervicofacial lymphadenitis

Cervicofacial lymphadenitis is a distinct clinical entity that tends to affect children below the age of 12 years. Although this disease entity has received less intense study than pulmonary NTM disease, high quality epidemiological studies have been performed, particularly in Germany [23]. In a nationwide study by the Robert Koch Institute and the German Pediatric Surveillance Unit during the 2003–2005 period, an annual incidence rate of 1.3/100,000 children was calculated; the incidence was highest in children under 4 years of age [23]. In fact, 98% of the children were born in Germany and had never lived abroad; 97% of all patients presented with lymphadenitis, mostly of the cervical glands [23]. These data match not only those found in a previous study in the Netherlands, where the annual incidence rate was calculated to be 0.77 per 100,000 [8], but also those found in studies in Finland (0.30/100,000/year) [12] and Australia (0.87/100,000/year) [9].

Factors underlying the changing epidemiology: changing host?

Since NTM are opportunistic pathogens, they will mainly cause disease in patients with some form of immunodeficiency, be it local (e.g., pre-existent pulmonary disease) or systemic (e.g., HIV infection, hematological malignancy, inheritable disorders of immunity, immunosuppressive drug use) [7]. Both groups seem to have become larger in the past decade. In the first group, those with pre-existent pulmonary diseases, three distinct subgroups are evident: cystic fibrosis patients, chronic obstructive pulmonary disease (COPD), and elderly lean, non-smoking female patients.

- In cystic fibrosis (CF) patients, NTM isolation was rarely reported prior to the 1990s [7]; recently, prevalences of 6.6% (France), 13.0% (USA), and 22.6% (Israel) have been measured [17, 21, 24]; in a single center study in Munich, Germany, an isolation frequency of 11% (10/91 patients) was recorded [16]. Whether the appearance of NTM disease in CF patients reflects increased survival or simply increased clinical awareness and laboratory improvements remains uncertain. Interesting differences in predominant species exist as MAC was most common in Munich and the study in the USA, *M. abscessus* in France, and *M. simiae* in Israel [16, 17, 21, 24]. Risk factors for NTM disease in CF patients remain uncertain [21].
- COPD is an important risk factor mainly for the classic fibrocavitary type of pulmonary NTM disease [30, 32, 35]; in the Netherlands, 70% of all patients in whom NTM are isolated from respiratory samples have a formal diagnosis of COPD [30]. The isolation prevalence of NTM in COPD patients and the exact mechanism by which COPD predisposes to NTM disease remain unknown. In the Netherlands, the rising isolation frequency is predominantly caused by *M. avium*, in elderly male patients with presumably cavitary disease and related to aging and an increasing COPD prevalence [30, 32].
- In Australia, the rising incidence was mainly due to rising *M. intracellulare* and *M. abscessus* isolation, accompanied by a shift from cavitary disease in middle-aged males towards non-cavitary disease, predominantly in elderly women [27]. Risk factors for the nodular-bronchiectatic form of NTM lung disease, which primarily affects elderly women who are lifetime nonsmokers [14], remain largely unknown [7]; gastro-esophageal reflux disease prevalences of 26–44% have been described in patients with mostly nodular bronchiectatic NTM lung disease [28], but it is unclear whether changes in the epidemiology of this disease drive the increase in NTM disease incidence and prevalence.

The second group of patients at risk for NTM disease that has become more relevant in the past decade include patients whose immunity to mycobacteria is impaired by iatrogenic factors, i.e., immunosuppressive treatments (see article by Rupp J, Schaaf B, Infektionen mit nichttuberkulösen Mykobakterien bei Patienten mit Immundefekten, this issue). This pertains to steroids as well as to the so-called “biologicals”; among the latter, the TNF-α antagonists have been most strongly related to nontuberculous mycobacterial disease [31]. NTM disease now seems to be more frequent than tuberculosis as a complication of TNF-α antagonist therapy [34]. Other classes of “biologicals” have also become available, including human IL-1 receptor antagonists (anakinra), CD20 + B-cell antibodies (rituximab), and CD4-cell co-stimulation modulators (abatacept). Thus far, NTM disease has only been described for the CD20 + B-cell antibody (rituximab) [31, 34]. The use of these biologicals has increased, as their list of indications has grown to cover a spectrum of immune-mediated inflammatory diseases of the skin, joints, and intestines [31, 34].

… or changing pathogens?

Yet, there may be more than just host factors that determine the changes in incidence and prevalence of NTM disease in humans. A careful analysis of the literature on causative agents of NTM disease reveals important shifts over time. In a study from the former East Germany in the mid 1980s, a shift away from *M. kansasii* to a predominance of *M. xenopi*, was noted [10]. This increase in notification of *M. xenopi* with a decline in *M. kansasii* isolation was also noted in an international study, which timed the increase in *M. xenopi* isolation in Germany to the early 1990s. This study found that during the 1992–1996 period, the reference laboratory in Borstel reported 10,651 positive cultures of NTM; the most common species identified in this laboratory at that time were the following: *M. avium* (31%), *M. xenopi* (16%), *M. gordonae* (15%), *M. fortuitum* (13%), and *M. kansasii* (6%) [20]. A survey of 966 NTM isolated from pulmonary specimens by the reference laboratory in Borstel in 2008 revealed the following species distribution: *M. avium* complex (26%; *M. avium* 8%, *M. intracellulare*/*M. chimaera* 17%), *M. gordonae* (20%), *M. fortuitum* complex (6%), *M. kansasii* (4%), and *M. xenopi* (2%) (E. Richter, personal communication; **Fig. 1a**). These data suggest a decrease in *M. xenopi* isolation, though this subject warrants separate study. Moreover, regional differences in NTM species distribution may exist.

Data from the Netherlands shows some interesting parallels to the German situation. In the period from 1956–1964, the national reference laboratory received NTM from 237 patients; these were identified as *M. kansasii* (*n*=142; 60%), *M. avium* complex (45; 19%), *M. scrofulaceum* (26; 11%), *M. xenopi* (3; 1%), and rapid growers (5; 2%) [26, 33]. By 2008, the distribution had changed dramatically; of 735 isolates received in 2008, 205 were *M. avium* (28%), 88 were *M. intracellulare*/*M. chimaera* (12%), 51 were *M. kansasii* (7%), 15 were *M. xenopi* (2%), and 129 were rapid growers (18%); just one *M. scrofulaceum* isolate was identified (J. van Ingen, personal communication, **Fig. 1b**). Part of these differences are explained by the ever more precise taxonomy of the genus *Mycobacterium*; whereas less than 20 species were known by 1969 [26], over 120 species have been published by 2011 [4]. Still, the decrease in *M. kansasii* isolation and increase in *M. avium* complex

Abstract · Zusammenfassung

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Abstract

Nontuberculous mycobacterial (NTM) lung disease is by far the most common NTM disease. Clinically important are NTM lymphadenitis in children, immune reconstitution syndrome in HIV patients, and NTM skin disease, mostly as fish tank granuloma due to *M. marinum*. In contrast to *M. tuberculosis*, NTM are not spread from human to human and exposure to NTM from the environment does not *per se* lead to infection and disease, explaining the few epidemiological data and published studies. New data, however, show that NTM lung disease prevalence has been increasing in North America since the mid1990s; in northwestern Europe the limited published data suggest a lower, but also increasing incidence that differs by region. The incidence of NTM cervicofacial lymphadenitis (1/100,000 children) is highest in children under 4 years of age; however, data represent only microbiologically confirmed cases. Factors underlying the changing and differing epidemiology are discussed.

Keywords

Nontuberculous mycobacteria · Epidemiology · Cystic fibrosis · COPD · Lymphadenitis

Epidemiologie der nichttuberkulösen mykobakteriellen Erkrankungen in Deutschland und weltweit

Zusammenfassung

Pulmonale nichttuberkulöse mykobakterielle (NTM) Erkrankungen sind bei weitem die häufigsten duch NTM verursachten Krankheiten. Klinisch bedeutend sind die NTM-Lymphadenitiden bei Kindern und im Rahmen eines Immunrekonstitutionssyndroms bei HIV-Patienten sowie die NTM-Hauterkrankungen, meist als Aquariumgranulom, verursacht durch *M. marinum*. Im Gegensatz zu *M. tuberculosis* werden NTM in der Regel nicht von Mensch zu Mensch übertragen, und die Exposition gegenüber NTM aus der Umwelt führt nicht *per se* zur Infektion und Erkrankung, weswegen nur wenige epidemiologische Daten und veröffentlichte Studien existieren. Neuere Studien zeigen jedoch eine zunehmende Prävalenz der NTM-Lungenerkrankungen in Nordamerika seit Mitte der 90er Jahre des vorherigen Jahrhunderts, während die wenigen Daten aus Nordwest-Europa eine geringere, jedoch ebenfalls ansteigende Inzidenz sowie regionale, bisher unverstandene Unterschiede zeigen. Die Inzidenz der zervikofazialen Lymphadenitis ist am höchsten bei Kindern unter 4 Jahren, die Daten repräsentieren jedoch nur mikrobiologisch bestätigte Fälle. Gründe für die wechselnde und unterschiedliche Epidemiologie werden diskutiert.

Schlüsselwörter

Nichttuberkulöse Mykobakterien · Epidemiologie · Cystische Fibrose · COPD · Lymphadenitis

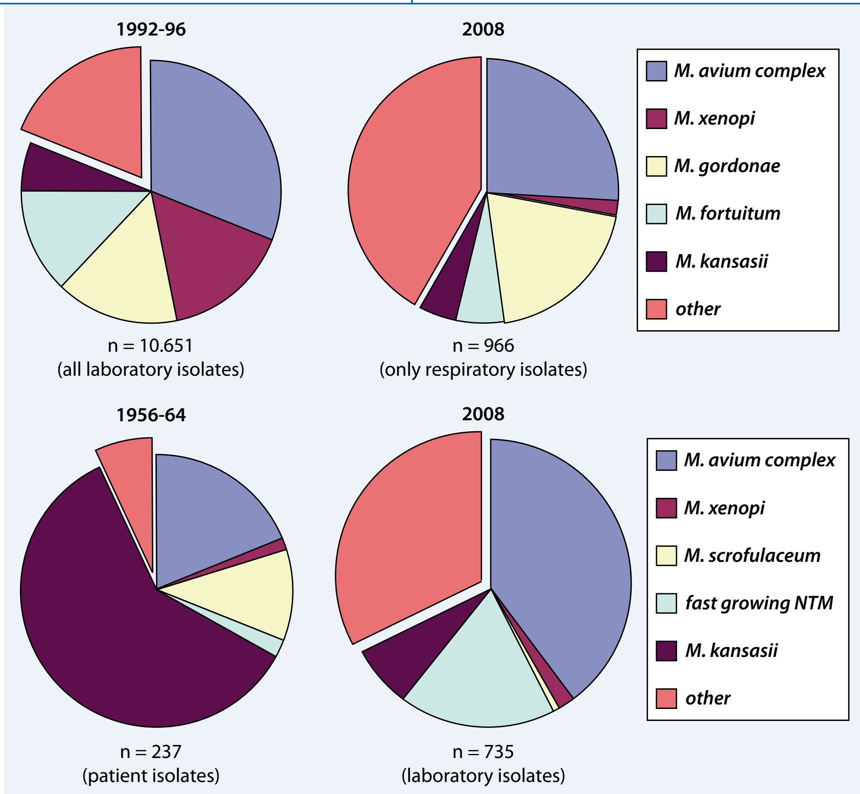

Fig. 1 ▲ Distribution of clinical NTM isolates over time in national reference laboratories in (**a**) Germany and (**b**) the Netherlands

isolation from pulmonary specimens and the replacement of *M. scrofulaceum* by *M. avium* complex bacteria as predominant causative agents of NTM lymphadenitis have been observed in many studies from different parts of the world [7, 19]. The differences in species distribution may be related to the increase in incidence and prevalence of human NTM disease; if people are now exposed to NTM in greater numbers (e.g., due to the increased proportion of elderly people [19]) or of greater virulence, owing to changes in our interactions with the environment (e.g., more frequent exposure to coastal water [19] or shower water [6]) or to changes in the environment itself that may in part explain the increasing incidence of NTM disease. Whether the change in species distribution is also related to the predominance of nodular bronchiectatic NTM disease in the United States and Australia remains to be studied.

Epidemiological research priorities

Many issues in the epidemiology of NTM disease remain unsolved. First, the differences in incidence and prevalence between North America and western Europe warrant additional study. Ethnically, the populations of both parts of the world share common ancestry and gross differences in genetic susceptibility to mycobacteria, therefore, seem unlikely. From recent American and Australian studies, it seems that the nodular-bronchiectatic NTM lung disease manifestation is most frequent [7, 22, 27, 34]; in the Netherlands, this manifestation is very rare and cavitary disease predominates [30]. This may imply that there is a significant underdiagnosis of nodular-bronchiectatic NTM lung disease and, thus, a lower prevalence of NTM disease. Underdiagnosis of this more subtle disease variant may also be relevant in Germany, where NTM, once isolated, are too often dismissed as clinically irrelevant.

Second, the separate NTM disease entities should be studied separately; cavitary NTM lung disease affects a different population of middle-aged men with pre-existent pulmonary disease and may have very different risk factors than the nodular bronchiectatic disease manifestation that mostly affects elderly women. Yet, the two are often studied together. Similarly important is the study of each of the different NTM species by itself. A better understanding of NTM disease and its epidemiology starts by studying each disease manifestation with one species in its own merit. This requires a larger collaborative network like the recently founded NTM-NET, a branch of the TB-NET (http://www.ntm-net.org).

Third, the relationship between NTM skin test reactivity and the chance of NTM disease later in life needs to be investigated. At present, the implications of NTM skin test reactivity in healthy individuals remain elusive. NTM specific skin tests or interferon-γ release assays would aid in this respect.

Conclusion

There is increasing evidence that the incidence and prevalence of NTM disease, particularly NTM lung disease, have increased in countries where the prevalence of tuberculosis is low. Low incidences measured in Europe are—at least partly—due to underdiagnosis, especially in patients with lung disease. Owing to a lack of systematic, population-based studies, the background of this epidemiological transition remains unknown. Both the causative agents as well as the predominant type of NTM lung disease has changed over time in many regions and these two aspects may be interrelated.

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