Nontuberculous Mycobacteria: Clinical Importance and Relevance to Bacille Calmette-Guérin Vaccination

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(See the article by Haverkamp et al. on pages 450–6)

Nontuberculous mycobacteria (NTM) have been recognized to cause human disease since the 1950s, but it was only later, when the AIDS pandemic unfolded, that a more widespread interest in these bacteria started to develop. During the past 20 years, we have seen a search for the best treatment strategies for NTM infection, which has even led some researchers to propose guidelines for lifelong prophylaxis for persons in the advanced stages of AIDS. Novel blood culture systems for the detection of NTM were developed and tested and are now routinely used in many health care centers that provide care for HIV-infected patients.

Most NTM isolated from humans can be found in the environment, where they are widely distributed. Humans are commonly exposed to these bacteria through contact with water (e.g., drinking, swimming, bathing, or exposure to aerosols by, for example, having a shower). One hypothesis holds that cervical lymphadenitis in children is the result of ingestion of contaminated drinking water or contact with dirty toys [1]. Of interest, lymphadenitis is more commonly found in younger children at the time of teething, perhaps as a result of more frequent oral contact with dirty hands.

The ubiquitous distribution of NTM contributes to the difficulties in interpreting positive culture results. NTM may cause disease, usually in immunosuppressed patients. However, the isolation of NTM from respiratory specimens alone may indicate only rather harmless colonization. Furthermore, NTM can potentially contaminate smears and cultures during laboratory processing, which may lead to an incorrect diagnosis of tuberculosis.

Water disinfection is not very effective in destroying NTM, which means that NTM are very common in piped water supplies [2]. As a result of the widespread chlorination of drinking water, a change in the relative incidence of NTM in some areas has been reported. It appears that Mycobacterium scrofulaceum levels in the environment are decreasing and that Mycobacterium avium levels are increasing [3], a finding reflected by the shift seen in human disease. In the 1970s, M. scrofulaceum was the most common cause of cervical lymphadenitis in children [4], but since then, M. avium has been the predominant species isolated in children [1]. In this issue of Clinical Infectious Diseases, Haverkamp et al. [5] report that more than one-half of the culture-proven NTM infections in children with lymphadenitis were caused by M. avium. In the context of AIDS, this species was also reported as a major cause of mortality before the introduction of HAART.

On the whole, the impression seems to be that NTM infections in humans are on the increase. However, most data reporting high rates of infection with NTM come from northern European countries or the United States. In African countries, for example, despite the fact that environmental exposure to NTM is very high, infections with NTM seem to be very rare, even among patients with AIDS [6]. However, low rates of NTM infection in HIV-positive patients are not limited to these areas but are also observed in some southern European countries, such as Portugal [7]. Several factors may explain this situation, and in the case of patients with AIDS, the availability of HAART may be the most important reason for the reduction in the number of these infections in recent years. Nevertheless, several other arguments may be equally important. Some authors question whether the decontamination of biological specimens for mycobacterial cultures might reduce the sensitivity for detection of NTM in some circumstances. However, low rates of isolation of NTM in mycobacterial cultures of blood samples—a type of specimen not subjected to decontamination procedures—obtained from HIV-infected patients were also reported [8].
Yet another important aspect of NTM infection is the role that bacille Calmette-Guérin (BCG) vaccination may have. There is some evidence that prior exposure to NTM may affect the efficacy of BCG vaccine [9]. This finding has important implications as long as there is no replacement for the BCG vaccine on the horizon and as long as tuberculosis continues to kill 2–3 million people per year. This possible interference may be the cause of the reduced efficacy of BCG vaccine demonstrated in the Chingelput BCG trial [10], and it may explain the geographic differences in vaccine efficacy. In fact, repeated exposure to NTM in tropical regions is believed to be the main explanation for the low efficacy of BCG vaccine in these areas. Furthermore, because of cross-reactivity among mycobacterial species, exposure to NTM may provide some protection against tuberculosis, and it can also alter the results of skin tests with PPD. This has important implications for the use of PPD-based skin tests as a diagnostic tool for tuberculosis or for detection of latent Mycobacterium tuberculosis infection. Furthermore, NTM also interfere with the measurement of protective immunity resulting from BCG vaccination. All of these are important reasons to establish the incidence and the geographic distribution of NTM and of human NTM infections, to enable an assessment of the potential interference caused by these mycobacteria. Also interesting is that exposure to NTM in childhood probably plays an important role in modulating the immune system and in determining the pattern of immune response to other infections or to allergens.

Despite these important findings, knowledge about NTM is rather scarce. Most of the data come from studies of skin tests using various NTM antigens. The cross-reactivity among mycobacterial species is well illustrated in the study in this issue by Haverkamp et al. [5], who report that 58% of the studied children had a positive skin test result when PPD was used, despite the fact that tuberculosis and previous BCG vaccination were almost absent in this group, and despite the fact that the prevalence of tuberculosis in The Netherlands is very low. However, it is necessary to interpret these results with some caution, because other studies have suggested that skin reactivity to mycobacterial antigens should not always be interpreted as specific evidence of exposure to particular mycobacteria [9].

On the other hand, and not surprisingly, because Mycobacterium species share many antigens, it appears that infection with M. tuberculosis—but also previous BCG vaccination—may have a protective effect against NTM. This possible interaction may be another argument for persons who oppose the ending of BCG vaccination in some regions. This argument seems to be in line with observations from Sweden, a country with a very low incidence of tuberculosis, where the incidence of cervical lymphadenitis in children caused by NTM increased considerably after BCG vaccination programs ended [11].

Still, a lot remains to be understood with regard to NTM infection and its multifaceted interactions with the immune system, BCG vaccine (and perhaps future replacements for this vaccine), and M. tuberculosis infection, as well as with regard to diagnostic tests for NTM infection. The study by Haverkamp et al. [5] sheds a little light on some of these issues.

Acknowledgment

Conflict of interest. E.V.: No conflict.

References