EDITORIAL

The mycobacterial mystery

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Before the advent of HIV, which led to an increased awareness of *Mycobacterium avium* complex disease, followed by the first prospective comparison studies on treatment regimens [1, 2], the topic of nontuberculous mycobacterial disease was a true example of Aristotelian science. Previously, only a few experts worldwide had compiled empirical data and disseminated knowledge on the subject, which was based upon meticulous observations in small series or case studies from the 1950s onwards [3]. These studies demonstrated the manifold particularities of *M. avium* complex disease and others as compared with tuberculosis, and also showed how even nontuberculous mycobacterial lung diseases alone, quite apart from manifestations in other organs, appear in widely varying forms. To this day, an ever increasing number of reports on uncommon or recently detected and potentially pathogenic species with strange names deepen the impression that we are dealing with an intricate matter.

In 1979, WOLINSKY [4] published his legendary review on nontuberculous mycobacteria (NTM) and associated diseases, which is still worth reading and citing: "The pathogenesis of adult pulmonary disease is obscure. Does it represent primary infection after inhalation of aerosolized infected droplet nuclei that then localize and proliferate in specific areas of damaged lung? Or is it a reactivation of dormant bacilli that had been acquired previously?" [4]. Meanwhile, the history of HIV especially, and the growing number of patients with transplants, have helped in understanding the role, and some mechanisms, of systemic immunosuppression as an important factor in the development of both disseminated and pulmonary disease. Have we, however, deepened our understanding of the pathophysiology of localised lung disease in non-HIV patients, this being a key issue?

Focusing on treatment, in 1985 another pioneer in the field of tuberculosis and nontuberculous mycobacterial diseases, Karl Ludwig Radenbach (1918–1986), wrote: "Clinically, treatment cannot rely on controlled trials, due to the small number of cases. However, retrospective analyses carried out by experienced pneumologists demonstrate that if individualised multiple drug combinations are adjusted to the susceptibility test results of each strain, this helps to avoid secondary bacterial resistance and leads to satisfactory treatment outcome" [5]. The substantial variations in drug susceptibility between species and between different strains within the same species alone prompted RADENBACH [5] to state that no standard

therapy exists. RADENBACH [5] also drew attention to another fact that other authors frequently leave unmentioned: "The basis of chemotherapy is the intensive treatment of resistance-reducing underlying disease." Prospective trials followed and diagnostic and therapeutic recommendations, even guidelines, were elaborated [6, 7]. However, was it wise to broadly reject an individualised therapeutic approach in favour of regimens that are only specific to certain species, and to disregard the vast polymorphism of ubiquitous mycobacteria and the widely varying ways in which they affect the human body?

The prospective nationwide study presented by DAILLOUX *et al.* [8] in the current issue of the *European Respiratory Journal* (*ERJ*) reports on epidemiological data, clinical findings and treatment results in no fewer than 263 patients. Estimating the incidence at 0.73 per 100,000, DAILLOUX *et al.* [8] have documented the persistent presence of a disease group that is responsible for substantial morbidity and a consistently reported mortality. In general, the demographic transformation in Western societies, with rising percentages of older people and a corresponding increase in predisposing diseases, may in turn lead to increasing numbers of patients in the future, although this trend is not yet clearly discernible. With regard to patient characteristics, radiological patterns, the spectrum of underlying diseases and the regional differences in the incidence of species, the study group failed to find any results that improve our understanding of this rare disease complex. The summary of the treatment results confirms the variable and, in some cases, unsatisfactory data published by other working groups.

In the tradition of thorough clinical observation aimed at expanding our knowledge of mycobacterial disease, in the current issue of the *ERJ*, FOWLER *et al.* [9] report on the significant incidence of mycobacterial disease or colonisation (synonymous with infection without evidence of pulmonary disease) in bronchiectasis patients. The central finding seems to be that it was not possible to identify clinical subgroups of patients, or other relevant influencing factors, which might be associated with a higher probability of cultures positive for NTM. With two out of nine patients in the culture-positive group *versus* two out of 75 in the culture-negative group bearing a cystic fibrosis (CF) transmembrane conductance regulator mutation, it is hardly correct to say that due to CF bronchiectasis patients have a higher risk of being affected by NTM. A more important finding is that patients with positive cultures for *Pseudomonas aeruginosa* are not less likely to develop mycobacterial disease. On the contrary, the opposite could be true. The association between positive mycobacterial cultures and the finding of mucous plugging in computed

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tomography may just be an indication of a poor bronchial clearance, which could predispose to either infectious complication.

The astonishingly frequent ancillary finding of more than one species in cultures from the same patient in the study by FOWLER et al. [9] brings us to the almost notorious ongoing battle between clinicians and microbiologists as to how to interpret positive-culture findings as regards the significance of species, the quantity of growth and, most controversially, the results of in vitro tests on drug susceptibility [10]. For decades, M. gordonae was considered to be nonpathogenic and most likely an indicator of laboratory contamination in positive cultures. With at least one reliable case, we can be relatively certain that this skotochromogenous species can in fact be the causative agent of mycobacterial disease [11]. Nevertheless, the rarity of such cases is still a reason to be cautious on this point. Incidentally, M. terrae is another suspect of this kind. For the clinician, it is the appraisal of newly detected species which may be noticeably more pathogenic than close relatives that is most challenging [12].

To avoid misinterpretations, experienced authors and scientific societies have sought for criteria indicating relevant growth in order to be able to distinguish colonisation, or contamination, from disease. The 1997 statement by the American Thoracic Society (ATS) is still considered to be the major milestone [6]. In nonsterile specimens, these criteria are invariably of a quantitative nature; positive smears are more indicative than negative ones, the more positive cultures the better. However, even with a clear resistance-reducing focus, such as bronchiectasis or post-tuberculous cavities, and histological evidence of granulomata, the indication for treatment is finally based upon the patient's overall condition. Thus, the decision is made by the clinician, who may, in view of the sometimes rather uncomfortable effects the drugs can have, be wise enough to keep under observation even some of those patients who fulfil consensus criteria for mycobacterial disease. Optimal conservative treatment of underlying diseases should not be underestimated, either in this or other contexts, despite the fact that drug treatment has improved over the decades, and patients with bronchiectasis and chronic bronchitis, in particular, should profit from such an approach. Is this a mere opinion? The ATS statement is full of opinions, and rightly so!

It is, therefore, hard to understand why the report on the only prospective randomised study on the treatment of non-HIV patients with M. avium-intracellulare, M. malmoense and M. xenopi disease, which was carried out by the British Thoracic Society (BTS), failed to say anything at all about the treatment of the underlying diseases [13]. This study group found a higher death rate in the group treated with rifampin, ethambutol and isoniazid than in the group treated with rifampin and ethambutol only, although the microbiological response rate was higher with the three-drug regimen. The authors seemed well aware of the methodological difficulties involved in interpreting this outcome. Fortunately, their bold conclusion that the two-drug regimen should be recommended for regular treatment was already outdated at the time of publication, as in the meantime clarithromycin had been shown to be highly effective both in vitro and in vivo.

The BTS conclusions as to the ineffectiveness of in vitro susceptibility tests also appeared questionable. In view of the fact that many more difficulties are associated with the treatment of NTM, these results should not simply be interpreted in a similar manner to the comfortable thresholds used for M. tuberculosis. For example, in a series of M. xenopi strains from the current author's institute, eight out of 15 showed a minimal inhibitory concentration of $0.25\ \mu g \cdot mL^{-1}$ for isoniazide [11]. A conventional dose of $3–5\ mg \cdot kg^{-1}$ body weight produces a peak blood concentration of $\sim 5\ \mu g \cdot mL^{-1}$; the drug penetrates well into all body fluids and cavities, producing concentrations similar to those found in serum [14]. A microbiologist would rate the $0.25\ \mu g \cdot mL^{-1}$ concentration as only ''intermediate'' and possibly be wide of the mark. Even more controversially, the majority of M. kansasii strains, but not all, show minimal inhibitory concentrations of $1\ \mu g \cdot mL^{-1}$ for isoniazide, which many microbiologists relentlessly declare ''resistant'', whereas clinicians feel confident using this drug. For M. avium-intracellulare, in vitro testing shows a greater variability of minimal inhibitory concentrations for potential agents, a finding which may be a guide for alternatives to the so-called standard combinations. Since the results of treatment with recommended regimens that are specific for given species remain unsatisfactory, we might ask ourselves whether we are not falling prey to too narrow an interpretation if we only recommend susceptibility tests in the event of expected, or actual, treatment failure, provided that the clinician is aware of the methodological peculiarities. For uncommon or new species, there is no reason at all to abandon the option of susceptibility tests from the start.

However, leaving aside these uncertainties, where has there been real progress within the last 25 yrs? Rapid and precise recognition of species using fluid cultures and the methods of molecular biology has already become routine. New drugs, such as clarithromycin and moxifloxacin, but not so much rifabutin, should improve treatment results in daily practice [3, 15]. In future, we may also expect to obtain faster and more differentiated information on the properties of nontuberculous mycobacterial strains with the aid of microarray techniques [16]. Genetic studies of both the host and visitor could finally reveal why only a minority of patients with locally reduced resistance in the lung are affected by ubiquitous mycobacteria [17, 18].

As far as treatment is concerned, we might do better to abstain from simple solutions. The gap between evidence and experience can probably only be closed if fixed combinations are compared with an individualised approach based upon the concerted, interdisciplinary judgement of undogmatic partners, as clinicians and microbiologists should always be.

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