Pulmonary *Mycobacterium abscessus*: can we identify the road to improved outcomes?

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The findings of this meta-analysis suggest that specific targeted therapy for *Mycobacterium abscessus* subspecies *abscessus* can improve treatment outcomes, and may help to design future antimicrobial drug regimens in this difficult to treat lung infection http://bit.ly/2WOFsRw

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Despite much welcome progress over the past decade in the field of chronic respiratory infections and bronchiectasis [1], treatment of pulmonary disease caused by infections with nontuberculous mycobacteria (NTM-PD) remains an area of significant, and increasing, challenge [2, 3]. Pulmonary disease caused by *Mycobacterium abscessus* (MAB-PD) is of particular interest as, when coupled with underlying lung disease, it is associated with rapidly declining lung function, significant morbidity and mortality, and particularly poor treatment outcomes: cure, as generally defined by persistent culture conversion, is generally reported to be found in less than 50% of cases in published data [4, 5]. The challenge is amplified by the fact that the incidence of MAB-PD may also be increasing [6], possibly as a result of ageing populations with pre-existing lung disease, alongside increasing use of immunosuppressant drugs, and increased environmental exposure.

M. abscessus complex is a rapidly growing nontuberculous mycobacterium, found ubiquitously in soil and water, which can be divided into a number of subspecies (subsp.): *M. abscessus* subsp. a*bscessus*, *M. abscessus* subsp. *massiliense* and *M. abscessus* subsp. *bolletii*. Their intrinsic and easily acquired resistance to commonly used antibiotics (macrolides) make them naturally difficult to treat, as such antibiotics form the cornerstone of most treatment regimens used worldwide. Yet expert guidelines, such as those from the American Thoracic Society/Infectious Diseases Society of America [7], and the British Thoracic Society [8], vary in recommended antibiotic strategies, ultimately muddying the waters when it comes to choosing the most efficacious therapies. A better understanding of the most effective drug combinations in the treatment of MAB-PD is therefore critical if we are to offer patients a less nihilistic treatment pathway. Additionally, if we are to better understand which treatment regimens offer the greatest chance of success, there is a need for consistency in approach to defining the end-points by which we measure treatment success. Looking to the future, this could include development of a tool combining measures of quality of life, and symptomatic and radiographic improvement, alongside sputum culture conversion.

With this in mind, in this issue of the *European Respiratory Journal*, Kwak *et al.* [9] present a timely, and welcome, individual patient data meta-analysis of outcomes in MAB-PD. Defining treatment success as culture conversion for ⩾12 months while on treatment, or sustained culture conversion without relapse,

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they were able to analyse individual data from 303 patients from eight of 14 eligible studies. They demonstrated that overall treatment success for MAB-PD was 45.6% (95% CI 26.7–64.4). Importantly, they were able to show that the use of imipenem was associated with treatment success in MAB-PD overall (adjusted odds ratio 2.65, 95% CI 1.36–5.10), and for *M. abscessus* subsp. a*bscessus* (where treatment success was found in only 33% of cases), the use of azithromycin (but not clarithromycin), and parenteral amikacin was also related to treatment success; cefoxitin was not associated with treatment success. Interestingly, for *M. abscessus* subsp. *massiliense*, where treatment success was higher, in 56.7% of cases, there was not this apparent association of treatment success with antibiotic choice, possibly because the better outcomes masked observable treatment effect.

The authors should be commended for focusing on this challenging infection, and for their work to obtain individual patient data from a wide geographic area (the studies offer a good representation of global NTM practice, with data from seven institutions from six countries spanning the globe). Despite their efforts, they acknowledge several limitations from this work, particularly their inability to derive data from six eligible studies, and the wider difficulties inherent in meta-analyses involving relatively low patient numbers. The effect of parenteral tigecycline, a drug increasingly used in the treatment of MAB-PD in the intravenous induction phase, could not be assessed as it was not used frequently in the patient level data analysed.

Residual bias, and the dangers of multiple testing in small cohorts, mean that one must still interpret these findings with a degree of caution. Having said that, this important paper makes two key contributions to this field of research. Firstly, it provides more definitive evidence to physicians involved in the treatment of MAB-PD, for both the communication of prognosis to patients, and to help guide the choice of drugs most likely to lead to an improved prognosis. But perhaps more importantly, it shows that if nihilism is no longer the right answer, then we must also be better at framing new questions in the search for a roadmap to better therapies for our patients with MAB-PD (and indeed NTM-PD more broadly). The recent demonstration that bacteriophage therapy may offer an alternative treatment approach is one such direction [10], but others may include a better-defined role for improved mucociliary clearance, to help augment antibiotic therapy in MAB-PD, for example.

Finally, as the authors illustrate, this is the first individual patient data meta-analysis in the NTM-PD field, but was ultimately only able to include 303 patients. Continued global collaboration to better study these increasingly common pulmonary infections are now a necessity if we are to build on the promising findings of this study.

Conflict of interest: None declared.

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