The new "Hesitation Blues": initiating *Mycobacterium avium* complex lung disease therapy

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Clinical assessment is the key element for deciding which patient with *Mycobacterium avium* complex needs therapy http://ow.ly/90mo3091Bkh

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I got the hesitation stockings,
The hesitation shoes,
Oh my Lord, I got the hesitation blues.
Tell me how long do I have to wait?
[Should I treat you] now, or must I hesitate?

The "Hesitation Blues" is a traditional blues/folk tune that was first recorded a century ago. Since that time, more than 40 artists with diverse musical pedigrees have recorded the song, ranging from Lead Belly to Doc and Merle Watson to Hot Tuna. An interesting aspect of the various recordings is that while the narrative of the song consistently expresses carnal frustration, the actual lyrics just as consistently vary from one version to the next. It is, therefore, a fitting and appropriate platform to propose further lyric modification that shifts the emphasis to the frustrating hesitation experienced by physicians who must decide about the initiation of *Mycobacterium avium* complex (MAC) lung disease therapy.

The critical element in that decision is a careful risk/benefit determination weighing the potential for disease progression and possible benefits of therapeutic intervention *versus* consideration of potential medication side effects and toxicities. For patients with cavitary MAC lung disease, this risk/benefit assessment overwhelmingly favours initiating MAC therapy at the time of diagnosis because of predictable morbidity and mortality associated with progressive cavitary MAC disease [1]. The risk/benefit balance for patients with nodular/bronchiectatic (NB) MAC lung disease is frequently not as clear, requiring a more deliberate approach. It is widely recognised that MAC isolation from a respiratory specimen in the latter setting does not reflexively or automatically require initiation of therapy [2]. MAC is not a public health threat, but equally as important is the observation that not all patients with MAC isolated from their respiratory specimens subsequently or inevitably have progressive MAC lung disease.

A common scenario is the patient with persistently positive sputum acid-fast bacilli (AFB) cultures for MAC who has minimal and stable NB radiographic abnormalities and symptoms. There is a general consensus in the NTM (non-tuberculous mycobacteria) community that this type of patient would not likely benefit significantly from MAC therapy. Fortunately, NB MAC lung disease is sufficiently indolent that careful longitudinal appraisal without therapy is safe and presents little risk for rapid progression of MAC lung disease or later hindrance to favourable therapeutic response.

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For mild NB MAC lung disease, the physician must balance the risks of treatment with uncertain benefit, thereby exposing patients unnecessarily to medication toxicity and side-effects, with under-treatment of advancing disease, which exposes patients to progressive disease morbidity. This risk/benefit balance is frequently tipped by treating physicians in favour of a conservative approach, as reflected in this frequently encountered patient declaration: 'My doctor told me that the medicines for treating *Mycobacterium avium* complex (MAC) disease are worse than having the disease'. This exaggerated and unjustified apprehension results in over-zealous avoidance of MAC medications, sometimes when they are otherwise appropriate.

There is a strong caveat for managing patients whose risk/benefit assessment for initiating MAC therapy favours a conservative or expectant approach. These patients must be followed indefinitely. There is not yet a recognised statute of limitations for developing progressive MAC lung disease after isolation of MAC from a respiratory specimen.

There are also possible unintended benefits from a cautious initial approach to NB MAC lung disease therapy. Physicians in the USA and around the world do not treat MAC lung disease according to recommended treatment guidelines [3, 4]. If uncertainty about the appropriateness of initiating therapy results in referral of the patient to a centre with interest in MAC lung disease, that in itself could result in better adherence with published treatment guidelines. Even MAC therapeutic nihilists would admit that there are some advantages of adherence to treatment guidelines such as the low risk for inducing acquired macrolide resistance [5, 6].

Additionally, while the impact of MAC on the patient's status is being considered, patients would benefit from attention to comorbid respiratory conditions, especially bronchiectasis. Patients may experience significant symptomatic improvement with bronchiectasis-directed therapy, which can be a major, even transformative, benefit. Bronchiectasis-related symptoms also overlap considerably with MAC lung disease symptoms and obfuscate the effect of MAC infection on patient symptoms. Improving bronchiectasis-related symptoms can significantly impact the decision about MAC lung disease therapy initiation.

Our approach to initiating MAC lung disease therapy has rested on three factors: patient symptoms, microbiological results and radiographic findings. The trump card is frequently radiographic findings, such as the development of cavitation, which would precipitate initiation of therapy regardless of symptomatic or microbiologic stability. This approach requires patience and persistence on the part of both the physician and the patient. Patients must especially trust that the process will not push them into unnecessary therapy, nor abandon them to untreated disease progression. In this context, it is perhaps fortunate that many patients have heard negative things about MAC therapy so that they are content for any excuse to delay or postpone the initiation of such therapy. In our experience a major advantage of this approach is that by the time it is clear to the physician that treatment initiation is necessary, it is also usually clear to the patient as well.

Unfortunately, there are currently few objective markers for predicting which patients with NB MAC lung disease will progress and would benefit from early initiation of therapy and which patients will have persistently and indefinitely indolent disease that does not require therapy. We cannot reliably predict who, among the patients with indolent disease, will eventually have disease progression and when it will happen. In the absence of clear markers for NB MAC lung disease progression, we are stuck with longitudinal clinical evaluation for determining who requires MAC lung disease therapy.

In this issue of the *European Respiratory Journal*, Hwang *et al.* [7] compared the clinical characteristics of 305 MAC lung disease patients who had a progressive course resulting in treatment initiation within 3 years of diagnosis with 115 patients who exhibited a stable course for at least 3 years. Compared to patients with stable MAC lung disease, patients with progressive MAC lung disease had lower body mass index (BMI) and more systemic symptoms, positive sputum AFB smears, and fibrocavitary (FC) radiographic findings. FC radiographic changes were also found to be a negative prognostic factor for survival.

This manuscript re-emphasises important differences between FC MAC lung disease and NB MAC lung disease, the former being a more serious process with higher mortality than the latter [7]. Patients with FC MAC lung disease cannot be managed expectantly. These patients should be excluded from any discussion about conservative management, which pertains only to NB MAC lung disease.

This manuscript also supports and justifies the *de facto* approach for determining appropriate candidates for initiating MAC therapy as outlined above. In that regard it is a confirmation of the current clinically based practices and not a departure from those practices. We are still in need of better objective measures for determining the best candidates for therapy. The findings in this manuscript do not relieve any of the pressure for indefinite longitudinal follow-up of patients who are not started on therapy. It remains to be seen how well the findings from this study will hold up after another 5- or 10-year follow-up. We think it is prudent to maintain some scepticism about whether the negative predictive value of any combination of

their identified disease progression parameters (higher BMI, fewer systemic symptoms, AFB smear-negative sputum, less extensive radiographic changes) will be sufficiently robust to permit cessation of surveillance for active mycobacterial disease at any arbitrary point.

Of particular interest, 51.6% of stable MAC lung disease patients in the current study had spontaneous sputum conversion. A negative sputum AFB smear at diagnosis was one factor associated with this occurrence. As early as the mid-1970s it was recognised that some patients with non-cavitary MAC lung disease – what is now referred to as NB MAC lung disease – could have AFB culture-positive sputum for MAC without radiographic evidence of progressive disease and occasionally with reversion of sputum to AFB culture-negative associated with initiation of airway clearance measures [8]. In this study, there was no routine instruction in airway clearance, so it is difficult to know what impact that might have had. The patients with spontaneous sputum conversion comprise a very interesting cohort that deserves long-term follow-up with serial sputum AFB cultures and genotyping of all MAC isolates.

The lack of clear, reliable, non-clinical objective markers that predict MAC lung disease progression also exposes the profound deficit in our understanding of NB MAC lung disease pathophysiology. Animal models have been pivotal in understanding tuberculosis (TB) pathophysiology. An important recent example is work in a primate TB model demonstrating that latent TB and active TB comprise not a simple two-state process, but rather, are part of a spectrum of states [9]. While there are candidate murine and primate models of MAC and *M. abscessus* lung disease, there is not yet an animal model that is unambiguously analogous to human NB MAC or *M. abscessus* lung disease [10–12]. This lack of an established animal model for NB MAC lung disease is a clear impediment to expanding knowledge about NB MAC lung disease pathophysiology. Understanding the fundamentals of NB MAC lung disease pathophysiology would be enormously helpful in the search for identifiable disease progression markers. Even though the understanding of TB pathophysiology is well ahead of NB MAC lung disease, the search for markers of TB disease progression continues [9].

I ain't no doctor but the doctor's son
Can't [start your treatment] till the doctor's done
Tell me how long do I have to wait?
[Should I treat you] now, or must I hesitate?

Therefore, with the appropriate careful patient assessment and follow-up, a little hesitation for starting NB MAC lung disease is not such a bad thing. As long as the patient knows that their doctor will continue to watch and reassess indefinitely, there is no need for anyone to have the blues.

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