Susceptibility testing of non-tuberculous mycobacteria

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There is little consensus about treatment for the diseases caused by the common non-tuberculous mycobacteria (NTM). Guidelines are based largely on retrospective, non-controlled studies. Where susceptibility testing data is available, *in vitro* testing often correlates poorly or not at all with the clinical response to treatment. Performing non validated susceptibility testing is likely to confuse treatment rather than aid it.

In the clinical situation, the only valid indication for performance of susceptibility testing is if the test will produce a result that will help predict treatment outcome. A 'susceptible' result should predict treatment success with that drug. Conversely, the detection of resistance in a susceptibility test should predict treatment failure.

Mycobacterium avium complex (MAC) is the most commonly isolated opportunistic mycobacterium from HIV/AIDS patients (Figure 1). MAC bacteraemia in these patients is the only NTM disease where controlled clinical trial data demonstrate a predictive correlation between susceptibility test results and clinical outcome. The predictive value of susceptibility testing is validated only for clarithromycin, in a three drug regime of rifabutin, ethambutol and clarithyromycin.

The susceptibility data for rifabutin and ethambutol are often misleading as there was no correlation between pre-treatment ethambutol and rifampicin MICs and treatment outcomes for the patients. The study's authors concluded that susceptibility testing is not indicated, because of expense and lack of predictive value, unless patients had previously failed macrolide therapy or prophylaxis [1].

M. kansasii, after MAC, is the second most common cause of NTM pulmonary disease. Uniquely in the NTM, *M. kansassii* can cause chronic pulmonary disease in patients without underlying lung disease.

A retrospective analysis of *M. kansasii* disease treated with a three drug regime of rifampicin, isoniazid and ethambutol demonstrated that only the susceptibility testing results for rifampicin was predictive of therapeutic success or failure. Susceptibility testing to other drugs should only be performed if an isolate was demonstrated as rifampicin resistant. This "approach would save time and money and prevent some clinical confusion" [2].

There has been a single controlled treatment trial of respiratory disease in HIV negative patients caused by less common slow growing non-fastidious mycobacteria species; *M. malmoense, M. avium* and *M. xenopi.* No correlation was found between susceptibility testing results and the patients' response to chemotherapy. The study's authors reviewed the literature describing treatment of pulmonary infection caused by NTM and noted "a seemingly paradoxical lack of correlation between the clinical response and the results of conventional in vitro susceptibility testing of single antimycobacterial drugs" [3].

The difficulty of interpreting the clinical relevance of a single drug mycobacterium interaction *in vitro* is confounded by treatments that often use multiple antimicrobial agents, as any combination of [drug/drug/mycobacterium/host] interactions are occurring *in vivo.* Animal

Figure 1. *Mycobacterium avium* showing typical colonial variation. The most frequently isolated NTM. Clinical disease caused by MAC includes cervical lymphadenitis in children, respiratory infections in the elderly and disseminated disease in AIDS patients. Routine susceptibility testing is not indicated.

models provide better quality data, particularly for drug combinations, where in vitro synergy studies have not proved useful[4].

In contrast, standardised single drug susceptibility testing is universally accepted as having an important role in the clinical management of tuberculosis. This is because of extensive clinical trial data that demonstrate correlation between susceptibility testing results and treatment decisions[5,6].

NTM are environmental organisms generally causing opportunistic infections. Person to person transmission has not been observed. Because NTM disease is not contagious, cases generally occur sporadically in time and place. Many patients infected by NTM are immunosuppressed or have major concomitant disease. These factors make it very difficult to conduct clinical treatment trials; therefore clinical data to support susceptibility testing are likely to remain scant.

On the other hand, the relative increase in numbers of NTM isolates from clinical specimens has seen an accompanying increase in susceptibility testing requests to mycobacteriology laboratories[7]. In 1997, as a response to the increasing awareness of the NTM as agents of disease, the American Thoracic Society (ATS) updated its official statement on the diagnosis and treatment of disease caused by NTM[8]. Key features are diagnostic criteria to determine the clinical significance of respiratory isolates and defining where routine susceptibility testing is appropriate.

In 2003 the American National Committee for Clinical Laboratory Standards (NCCLS) published an approved standard for the susceptibility testing of mycobacteria[9]. It supplements the 1997 ATS guidelines with recommendations regarding the performance of test methods, selection of agents, interpretive criteria and quality assurance (Table 1).

Table 1. NCCLS approved standard M24-A recommendations.

1. Susceptibility testing only on clinically significant isolates.
2. Rapidly growing mycobacteria (RGM). Because of the variability of susceptibility patterns within this group, susceptibility testing is recommended for all clinically significant isolates.
3. The slow growing NTM. General recommendations are that pre-treatment isolates are stored so if there is treatment failure the development of resistance can be monitored. This will require susceptibility testing – refer to standard for details.
   - 3.1. Pre-treatment susceptibility testing is recommended only for *M. kansasii*, and only for the drug rifampicin. Methods and break points as for *M. tuberculosis.*
   - 3.2. Routine susceptibility testing of MAC is not recommended. First line testing only clarithromycin where isolates are obtained from persons who have failed previous macrolide therapy or prophylaxis.
   - 3.3. *M. marinum:* Routine susceptibility testing not recommended as the susceptibilities of this organism are generally predictable.
   - 3.4. For other all other slowly growing NTM it is noted there is little information on the correlation of *in vitro* susceptibility testing results and clinical outcome – refer to standard for details.

Conclusions

There are very limited clinical data to help interpret susceptibility testing of the non tuberculous mycobacteria. Initial treatment choices should therefore generally be guided by the medical literature, such that it is, and experts should be consulted. Laboratories performing susceptibility testing where there are no validated interpretive guidelines should only report the method and MIC value.

The availability of commercially standardised susceptibility testing kits and external quality assurance programmes are needed to ensure inter-laboratory reproducibility. This may in turn facilitate the clinical treatment trials that are necessary to validate any extension of the current recommendations for the susceptibility testing of NTM.

References

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