Therapeutic drug monitoring in Tuberculosis treatment
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DOI:
10.33612/diss.116866861

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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2020

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

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Chapter 3d

Membrane Filtration is Suitable for Reliable Elimination of Mycobacterium tuberculosis from Saliva for Therapeutic Drug Monitoring

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*Journal of Clinical Microbiology.*
2017 Nov;55(11):3292-3293
Tuberculosis (TB) remains an infectious disease of worldwide concern. Therapeutic drug monitoring (TDM) of blood could be helpful in optimising TB treatment, as anti-TB drug exposure shows interpatient variability [1]. TDM in saliva instead of blood is currently being studied as more practical alternative, since saliva sampling is noninvasive and more acceptable to patients [2,3]. Along with the growing interest in the pharmacokinetics of anti-TB drugs, TDM is increasingly used in daily routine practice. However, saliva of infectious TB patients contains Mycobacterium tuberculosis and TDM sample analysis usually does not take place in a biosafety level 3 laboratory. A quantitative study found a mean bacterial load of $7 \times 10^4$ (range, $1 \times 10^2$ to $6 \times 10^5$) CFU/mL in saliva of infectious TB patients [4]. Laboratory-acquired TB infections should be prevented by applying biosafety measures when working with M. tuberculosis-containing saliva samples [5]. Therefore, saliva samples from TB patients require sterilisation prior to laboratory processing (e.g. centrifugation). Unfortunately, decontamination by heat sterilisation is not possible because of thermal instability of drugs. The objective of this experiment was to test whether membrane filtration is able to reliably decontaminate a solution containing M. tuberculosis.

Five M. tuberculosis strains (Table 1) were incubated in Mycobacteria Growth Indicator Tubes (MGITs; Becton, Dickinson and Company, United States) after the addition of 0.8 mL of oleic acid, albumin, dextrose, and catalase as a growth supplement. For each strain, 2.0 mL of the culture fluid containing at least $10^5$ to $10^6$ CFU/mL was filtered in duplicate using a polyvinylidene fluoride membrane filter with pore size of 0.22 µm and diameter of 33 mm (Millex-GV; Merck Milipore, Ireland). The filtrate was inoculated into a new MGIT tube with culture fluid. For each strain, 0.5 ml of the culture fluid containing at least $10^5$ to $10^6$ CFU/mL was also inoculated in a new MGIT tube as a positive control. All tubes were incubated at 36.5°C for 55 days in the BACTEC MGIT 960 system (Becton, Dickinson and Company, United States). No mycobacterial growth was observed in the MGITs inoculated with filtrate, while all of the control tubes were positive within two weeks (Table 1).

**Table 1.** Growth of five strains of *M. tuberculosis* in positive-control samples and filtrates (in duplicate; A and B).

<table>
<thead>
<tr>
<th>Strain</th>
<th>Species</th>
<th>Drug resistance</th>
<th>No. of growth units</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Positive control</td>
</tr>
<tr>
<td>1</td>
<td><em>M. tuberculosis</em> complex</td>
<td>Sensitive</td>
<td>7037</td>
</tr>
<tr>
<td>2</td>
<td><em>M. tuberculosis</em></td>
<td>Isoniazid, rifampicin</td>
<td>18216</td>
</tr>
<tr>
<td>3</td>
<td><em>M. tuberculosis</em></td>
<td>Rifampicin</td>
<td>20413</td>
</tr>
<tr>
<td>4</td>
<td><em>M. tuberculosis</em></td>
<td>Sensitive</td>
<td>26757</td>
</tr>
<tr>
<td>H37Rv</td>
<td><em>M. tuberculosis</em></td>
<td>Sensitive</td>
<td>22776</td>
</tr>
</tbody>
</table>
This is the first description of membrane filtration of *M. tuberculosis*-containing fluids for sterilisation purposes in the process of TDM. No mycobacterial growth was measured in any of the filtrates. The membrane filter therefore successfully filtered all bacteria of multiple *M. tuberculosis* strains from culture fluids. We found no difference among the five strains in the number of growth units in the filtrates. It is not possible to test all *M. tuberculosis* isolates received at a mycobacteria laboratory, but according to this experiment, variation in the feasibility of membrane filtration between different strains is not likely. Membrane filtration of solutions with a larger bacterial load than tested here requires further investigation, as sterilisation cannot be assured by only this experiment. However, the bacterial load of saliva of TB patients is usually not as large as tested in this experiment [4]. Because of the satisfying results obtained with culture fluids with large bacterial loads, we conclude that membrane filtration is suitable for the decontamination of salivary TDM samples from infectious TB patients.

**REFERENCES**
