OPEN ACCESS

University of BRISTOL

Peer reviewed version

Link to published version (if available):
10.1093/jac/dkv407

Link to publication record in Explore Bristol Research
PDF-document

University of Bristol - Explore Bristol Research

General rights

Time-To-Detection in liquid culture of sputum in pulmonary MDR-TB does not predict culture-conversion for early discharge

Romelie Rieu[1], Chris Chang[1], Simon M Collin[2*], Janka Fazekas[1], Sirima Dassanaike[1], Aula Abbara[1], Robert N Davidson[1]

1. Northwick Park Hospital, Department of Infectious Diseases & Tropical Medicine, Watford Road, Harrow, Middlesex, HA1 3UJ, UK

2. School of Social & Clinical Medicine, University of Bristol, Oakfield House, Oakfield Grove, Bristol, BS8 2BN, UK

*Corresponding author: Dr Simon M Collin

Address: School of Social & Clinical Medicine, University of Bristol, Oakfield House, Oakfield Grove, Bristol, BS8 2BN, UK

Email: simon.collin@bristol.ac.uk

Tel: +44 (0)117 3313307

Running title: Culture-conversion in pulmonary MDR-TB

Abstract

Objectives: UK guidelines advise that patients with pulmonary MDR-TB are isolated in hospital until sputum cultures are negative (culture-conversion), typically after 42 days of incubation with no growth. MDR-TB patients may be isolated at least 42 days longer than is necessary for public safety, which has major implications for patients and hospitals. Our objective was to determine whether analysis of Time-To-Detection (TTD) in liquid culture could predict the earliest safe discharge date of MDR-TB patients.

Patients and methods: 15 pulmonary MDR-TB patients were identified retrospectively from the London TB Register and hospital records. We performed linear regression of TTD against days elapsed between admission and sample date. If the regression line crossed the observed culture-conversion date at TTD=42 days, the data were deemed to give 'precise prediction' of the earliest safe discharge date.

Results: Median length-of-stay was 91 days (IQR 79-131 days). Culture-conversion occurred at a median of 59 days (IQR 46-86 days). Twelve patients were hospitalised beyond culture-conversion, with a median overstay of 52 days (IQR 35-68 days). TTD tended to lengthen until culture-conversion and, for half of the patients (7/15, 47%), linear regression of TTD against time from admission gave a good fit to the data ($r^2 \geq 0.6$) and supported precise prediction. However, data from the remaining patients showed considerable variation, and linear regression did not support prediction of safe discharge.

Conclusion: TTD data from these pulmonary MDR-TB patients did not support a simple clinical prediction tool, but our analysis was limited by the small size of our sample.

Introduction

In the UK, 1.4% of new and 5.7% of previously treated TB cases are estimated to be multi-drug resistant, i.e. resistant to rifampicin and isoniazid, representing approximately 80 MDR-TB patients per year.[1,2] In the absence of direct measures of infectivity, sputum smear and culture status are used as surrogate markers of infectivity. UK guidelines advise that patients with pulmonary MDR-TB are isolated in hospital until all sputum cultures taken within one month are negative (culture-conversion).[3,4] A sample is typically considered culture-negative after 42 days of incubation with no growth. It therefore follows that pulmonary MDR-TB patients are isolated at least 42 days longer than is necessary for public safety, which has major implications for patients and hospitals.

Though "vital" staining methods and molecular indicators of viable bacillary burden are under development, e.g. fluorescein diacetate vital staining,[5] RT-PCR of selected mRNA,[6] 16S rRNA,[7] and pre-rRNA responses to stimulation,[8] none have yet superseded microbiological culture methods in guiding decisions on infectivity and isolation.[9] Time-To-Detection (TTD) in liquid medium is used as an endpoint in MDR-TB drug efficacy studies,[10,11] and may be a stronger predictor of infectivity than smear positivity.[12] We sought to determine whether we could predict, from the analysis of TTD in liquid culture, the earliest possible safe discharge date of pulmonary MDR-TB patients from our unit.

Methods

We identified retrospectively patients from the London TB Register with culture-positive pulmonary TB confirmed as phenotypically resistant to rifampicin and isoniazid, treated at Northwick Park Hospital (NPH) 2003 - 2014. Sputum samples were collected weekly throughout admission, and processed in NPH's microbiology laboratory. Standard Operating Procedures included sodium hydroxide decontamination and incubation in the BacT/Alert 3D Microbial Detection System (bioMérieux, France). Data on patient demographics, phenotypic drug susceptibilities, dates of admission and discharge, and sputum culture TTD throughout treatment were extracted from electronic medical records. We excluded extrapulmonary TB, and those who were culture-positive at less than 3 time points. Treatment regimens were individualized and adjusted during treatment.

The earliest possible date of safe discharge coincides with the 'culture-conversion date', i.e. the date of the first sample which is culture negative after 42 days, and for which no sample dated within 30 days of the first sample becomes culture positive (after 42 days). Positive cultures with contaminants, positive cultures without clear TTD, and reloaded samples were excluded. We calculated Length of Stay as date of discharge minus date of admission, and "Overstay" as date of discharge minus date of culture-conversion. For each patients, we performed linear regression of TTD (days) against days elapsed between admission (or date of first sample, if this taken before admission) and date of sample. Adjusted r^2 values were inspected as a measure of goodness-of-fit of the data. If the regression line crossed the observed culture-conversion date at TTD=42 days, the data were deemed to support 'precise prediction' of the earliest safe discharge date. Data were analysed using Stata (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP).

Results

We identified 52 MDR-TB patients, of whom 32 were pulmonary cases and 15 met all criteria [Supplementary Figure 1]. All 15 were smear positive before treatment, with smear grade from "scanty" to "large numbers". Nine were male (7 HIV negative, 1 HIV positive, 1 HIV status unknown), six female (all HIV negative). The age range was 13-59 years, median 34 years old. Among these 15 patients, Length of Stay was 74-178 days (median 91 days, IQR 79-131 days); culture-conversion occurred at 28-112 days (median 59 days, IQR 46-86 days). Twelve remained in-patients beyond culture-conversion, and Overstay ranged from 16-122 days (median 52 days, IQR 35-68 days). [Supplementary Table 1].

Resistance to other first-line and second-line agents varied [Supplementary Figure 2; Supplementary Table 1]. Initial specimen TTDs ranged from 7 to 29 days. Initial TTD did not predict time to culture-conversion, and TTD tended to lengthen until culture-conversion. For the majority of patients, linear regression of TTD against time from admission gave a good fit. Each plot of TTD vs treatment had different intercept, gradient (0.06-1.29 days-to-detection/day of admission), and goodness-of-fit (r^2 = 0.05-0.90). [Figure 1]. Closer fit (higher r^2) appeared to be more common with shorter initial TTD, particularly if TTD was <12days.

Half of the TTD regression lines (7/15, 47%) crossed observed culture-conversion dates, i.e. "precise prediction" [Figure 1: patients B, D, L, O, R, U, V]. Precise prediction of culture-conversion did not appear to be associated with sputum smear grade or patient age, sex or HIV status. The seven plots with precise prediction were amongst those with better fit of linear regression ($r^2 \geq 0.6$), and represented mycobacterial isolates without additional

resistance to 2nd line injectables, quinolones, or prothionamide. Only 1/7 was resistant to pyrazinamide, compared with 5/8 of those without precise prediction.

Discussion

Our MDR-TB patients had a median Length of Stay of 91 days, of which one third was probably unnecessary, because culture-conversion occurred at a median of 59 days. Although TTD tended to lengthen on treatment, and linear regression allowed "precise prediction" in 7 of 15 patients, the goodness of fit of linearity and the rate of change of TTD varied markedly between patients. This variation may be due to host factors (immune response, nutritional status, pharmacokinetics, and anatomy, including the behaviour of cavities), bacterial factors (drug susceptibilities at baseline and during treatment) and treatment factors (individualized regimens, specific drugs, changes to regimens and treatment interruptions). Precise prediction did not appear to be associated with baseline characteristics (age, sex, sputum smear grade, HIV status), but additional drug resistances were more common amongst patients whose TTD plots did not accurately predict culture-conversion. Further research is needed to identify the characteristics of MDR-TB patients for whom TTD has prognostic utility, e.g. by fitting a single predictive model to combined data from a larger sample of patients, including baseline and treatment factors.

We conclude that conventional bacteriological methods could not have been used to predict date of culture-conversion to facilitate earlier discharge for all of our pulmonary MDR-TB patients. However, our study was limited by the small sample size and, for the subgroup of patients for whom the method accurately predicted culture-conversion, TTD could serve as a useful prognostic tool and aid to discharge planning. This would be a relatively accessible methodology for countries where molecular methods are not readily available.

Figure legends:

Figure 1: Plots of Time-to-Detection (TTD) against time elapsed between admission and date of sample.

Supplementary data:

Supplementary Figure 1: Patient inclusion/exclusion flowchart.

Supplementary Figure 2: Summary chart of phenotypic susceptibilities and resistances to tested agents.

Supplementary Table 1: Patient age, sex, HIV status and drug susceptibilities.

References

1. Public Health England. *Tuberculosis in the UK: 2014 report.* Public Health England: London, 2014.

https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/360335/TB_Annual_report__4_0_300914.pdf.

2. WHO. *Tuberculosis Country Profile. United Kingdom of Great Britain and Northern Ireland.* WHO, Geneva, 2015.

http://extranet.who.int/sree/Reports?op=Replet&name=/WHO_HQ_Reports/G2/PROD/EXT/TBCountryProfile&ISO2=GB&outtype=html.

3. Interdepartmental Working Group on Tuberculosis. *The Prevention and Control of Tuberculosis in the United Kingdom: UK Guidance on the Prevention and Control of Transmission of 1. HIV-related Tuberculosis 2. Drug-resistant, Including Multiple Drug-resistant, Tuberculosis.* Department of Health, London, 1998.

http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_4115299.pdf

4. National Institute for Health and Care Excellence (NICE). *Tuberculosis: Clinical diagnosis and management of tuberculosis, and measures for its prevention and control (NICE clinical guideline 117).* NICE, London, 2011.

http://www.nice.org.uk/guidance/cg117/evidence/cg117-tuberculosis-full-guideline3

5. Datta S, Sherman JM, Bravard MA *et al.* Clinical evaluation of tuberculosis viability microscopy for assessing treatment response. *Clin Infect Dis.* 2015; **60**:1186-95.

6. Li L, Mahan CS, Palaci M *et al.* Sputum *Mycobacterium tuberculosis* mRNA as a marker of bacteriologic clearance in response to antituberculosis therapy. *J Clin Microbiol.* 2010; **48**:46-51.

7. Weigel KM, Jones KL, Do JS *et al.* Molecular viability testing of bacterial pathogens from a complex human sample matrix. *PLoS One.* 2013; **8**:e54886.

8. Honeyborne I, McHugh TD, Phillips PP *et al.* Molecular bacterial load assay, a culture-free biomarker for rapid and accurate quantification of sputum *Mycobacterium tuberculosis* bacillary load during treatment. *J Clin Microbiol.* 2011; **49**:3905-11.

9. Lawn SD, Nicol MP. Editorial commentary: dead or alive: can viability staining predict response to tuberculosis treatment? *Clin Infect Dis.* 2015; **60**:1196-8.

10. Diacon AH, Pym A, Grobusch MP, *et al*. Multidrug-resistant tuberculosis and culture conversion with bedaquiline. *N Engl J Med.* 2014; **371**:723-32.

11. Gler MT, Skripconoka V, Sanchez-Garavito E *et al.* Delamanid for multidrug-resistant pulmonary tuberculosis. *N Engl J Med.* 2012; **366**:2151-60.

12. O'Shea MK, Koh GC, Munang M *et al.* Time-to-detection in culture predicts risk of *Mycobacterium tuberculosis* transmission: a cohort study. *Clin Infect Dis.* 2014; **59**:177-85.