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

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Objectives: UK guidelines advise that patients with pulmonary MDR-TB are isolated in hospital until the results of sputum cultures are negative (culture conversion), typically after 42 days of incubation with no growth. MDR-TB patients may be isolated ≥ 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: Fifteen 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: The 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 hospitalized beyond culture conversion, with a median overstay of 52 days (IQR 35–68 days). TTD tended to lengthen until culture conversion and, for nearly 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.

Conclusions: 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 MDR, i.e. resistant to rifampicin and isoniazid, representing ~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 the results of all sputum cultures taken within 1 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, e.g. fluorescein diacetate vital staining5 and RT–PCR of selected messenger RNA,6 16S ribosomal RNA,7 and ribosomal RNA precursor responses to stimulation,8 are under development, none has 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 it 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, who were treated at Northwick Park Hospital (NPH) within the years 2003–14. Sputum samples were collected weekly throughout the hospital stay and processed in NPH’s microbiology laboratory. Standard operating procedures included sodium hydroxide decontamination and incubation in the BacT/Alert 3D Microbial Detection System.
Figure 1. Plots of TTD against time elapsed between admission and date of sample.
Results

We identified 52 MDR-TB patients, of whom 32 were pulmonary cases and 15 met all criteria (Figure S1, available as Supplementary data at JAC Online). 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, the 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 inpatients beyond culture conversion, and overstay ranged from 16 to 122 days (median 52 days, IQR 35–68 days) (Table S1).

Resistance to other first-line and second-line agents varied (Figure S2 and Table S1). 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 versus treatment had different intercept, gradient (0.06–1.29 days to detection/days since 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 $<12$ days.

Approximately 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 and 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 among those with better fit of linear regression ($r^2 \geq 0.6$), and they represented mycobacterial isolates without additional resistance to second-line injectables, quinolones or protonamide. Only one of the seven patients with precise prediction was resistant to pyrazinamide, compared with five of eight patients 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) or 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 among patients whose TTD plots did not accurately predict culture conversion. Further research is needed to identify the characteristics, including baseline and treatment factors, 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.

We conclude that conventional bacteriological methods could not have been used to predict the 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 methodology would be a relatively accessible one for countries where molecular methods are not readily available.

Funding

This study was carried out as part of our routine work.

Transparency declarations

None to declare.

Supplementary data

Figure S1, Figure S2 and Table S1 are available as Supplementary data at JAC Online (http://jac.oxfordjournals.org/).

References

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