Mycobacterium tuberculosis bacteraemia: experience from a non-endemic urban centre

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Abstract

The isolation of *Mycobacterium tuberculosis* from blood culture specimens has been associated with human immunodeficiency virus (HIV) co-infection with variable impact on tuberculosis (TB) mortality reported. The overwhelming majority of *M. tuberculosis* bacteraemia cases were described in developing countries. We present a nested case–control analysis of clinical, sociodemographic and behavioural risk factors in patients with positive *M. tuberculosis* blood cultures compared with patients with negative blood cultures from a 9-year population-based active TB surveillance study conducted in Houston, Texas. There were 42 patients with *M. tuberculosis* bacteraemia, 47 blood culture negative patients and 3573 patients for whom no mycobacterial blood culture was requested. HIV infection was more common in patients for whom a mycobacterial blood culture was requested (79.8% versus 15.1% p <0.001). Of the patients with *M. tuberculosis* bacteraemia, six were HIV negative or had no documentation of HIV status, including five with immunosuppressive conditions other than HIV. Patients with *M. tuberculosis* bacteraemia were more likely than patients with negative blood cultures to be deceased at diagnosis or to die while on TB therapy (50.0% versus 17.0%, p <0.01), to report men-who-have-sex-with-men behaviour (31.7% versus 13.0%, p 0.03), to have renal failure (28.6% versus 6.4%, p 0.01), and to have HIV RNA levels higher than 500 000 copies/mL (61.9% versus 17.2%, p ≤0.01). Requests for mycobacterial culture of blood specimens were more common in HIV-infected individuals, and the presence of *M. tuberculosis* bacteraemia was associated with a significant increase in mortality.

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The isolation of *Mycobacterium tuberculosis* from blood samples of tuberculosis (TB) patients has been documented since the early twentieth century [1]. However, *M. tuberculosis* blood cultures were rarely used as a modality of diagnosing TB until the human immunodeficiency virus (HIV) epidemic occurred, when mycobacterial blood cultures became widely used to diagnose disseminated *Mycobacterium avium-intracellulare* complex disease. It was then noted that *M. tuberculosis* was increasingly identified from blood culture samples. Initially, the phenomenon was thought to be strictly associated with co-infection with HIV, but various reports pointed to *M. tuberculosis* isolation from blood cultures in HIV-negative patients as well, albeit at much lower frequency [2,3]. The usefulness of blood cultures as a diagnostic tool depends on the pre-test probability of TB in the study population: Gopinath *et al.* [3] found that 19 out of 79 (24%) patients suspected of TB had *M. tuberculosis* isolated from blood in a tertiary-care centre in India; while McDonald *et al.* [4] found that only 10% of all febrile patients admitted to a hospital in Malawi or Thailand had mycobacteraemia in 1997. In a more recent study by Crump *et al.* [5], 5.7% of febrile patients admitted to a hospital in Tanzania had *M. tuberculosis* bacteraemia. Mycobacterial blood culture can be a useful diagnostic adjunct, as documented in a study in HIV-infected individuals in

Spain where blood was the only source of a positive culture in 15% of 33 patients who were documented as having TB [6].

Predictors of *M. tuberculosis* bacteraemia include advanced immunosuppression (as documented by a low CD4 count), HIV infection, prolonged cough, prolonged fever, weight loss, lymphadenopathy, left shift in the white blood cell count and anaemia [2,5–8]. The overall mortality associated with *M. tuberculosis* bacteraemia is generally high: 25–55%, probably a reflection of the advanced immunosuppression observed in these patients [2,5–7]. However, in one prospective study in Malawi, the presence of *M. tuberculosis* bacteraemia in HIV/TB co-infected individuals was not associated with a statistically significant increase in the 1-month mortality: 21% in *M. tuberculosis* bacteraemic versus 32% in not *M. tuberculosis*-bacterae-mic patients [9]. In addition, co-infection with HIV does not seem to predict an additional mortality risk. In a retrospective medical record review study from Spain, all-cause mortality in patients with *M. tuberculosis* bacteraemia was comparable between the HIV-negative and HIV-positive individuals (25% and 29%, respectively) [2].

With a few exceptions, the evaluations of the clinical characteristics of and mortality associated with *M. tuberculosis* bacteraemia have been described and performed in developing countries. We present data on the clinical characteristics and outcomes of patients with *M. tuberculosis* bacteraemia, identified from a 9-year population-based active surveillance study conducted in Houston, Texas.

Methods

Study population

We conducted a prospective, population-based, active surveil-lance study of all TB cases reported in Harris County, Texas (hereafter referred to as Houston) between 1 October 1995 and 30 September 2004. Written informed consent was obtained from all participants. Patients who consented to the study were interviewed to collect pertinent sociodemographic and behavi-oural variables. The patients' next of kin, guardians or proxies were interviewed when patients were deceased or unable to be interviewed. Clinical variables were obtained using public health and medical record review. All enrolled TB patients were used as the underlying study population and those who had a mycobac-terial blood culture requested by the clinician were included in the nested case–control analysis. The study was approved by the Institutional Review Boards of the participating institutions.

Mycobacterium tuberculosis isolates

Mycobacterium tuberculosis isolates were collected and molec-ularly characterized using three genotyping methods: principal genetic group designation, spoligotyping and restriction frag-ment length polymorphism (RFLP) of the IS*6110* insertion element [9,10]. Based on the genotypic findings, isolates were grouped into 'clusters': strains with at least five IS*6110* copies were considered to be part of the same cluster if they had matching IS*6110* RFLP patterns; strains with fewer than five IS*6110* copies were considered clustered if they had matching IS*6110* RFLP patterns, spoligotypes and principal genetic group designations [9,10].

Statistical analysis

Data from study instruments were entered into a MICROSOFT ACCESS database (Redmond, WA, USA) for storage and analysis. Characteristics of *M. tuberculosis* blood-cul-ture-positive subjects (*M. tuberculosis* bacteraemic) were com-pared with those of *M. tuberculosis* blood culture negative subjects (not *M. tuberculosis* bacteraemic) by chi-squared analysis (or Fisher's exact testing when at least one cell size was ≤5); and odds ratios (OR) presented are estimates for the relative risk associated with *M. tuberculosis* bacteraemic patients. Similarly, characteristics of patients with blood specimens evaluated by culture were compared with patients without blood specimens evaluated (but statistical measures are not shown in the tables). Mortality and days to treatment completion were visualized using Kaplan–Meier methods with significance assessed by Cox Proportional Hazard analysis. Values of $p < 0.05$ were considered statistically significant. Statistical analyses were conducted with STATA version 10 SE (StataCorp, College Station, TX, USA) and SAS 9.3 (SAS Institute Inc., Cary, NC, USA).

Results

During the 9 years of the study, there were 4312 patients with confirmed TB reported in Houston of whom 3662 (84.9%) were enrolled and 85.6% of the 3063 culture-positive cases were enrolled. We identified 42 patients with TB for whom at least one *M. tuberculosis* isolate was recovered from a blood culture sample and 47 patients with TB for whom a mycobacterial blood culture sample was requested and was *M. tuberculosis* culture negative. Characteristics of patients with TB with no blood specimen evaluated (*n* = 3573), *M. tuberculosis* bacteraemic patients and the blood culture negative group are presented in Table 1. Overall, there were no significant differences in the age, race/ethnicity or gender distribution between the *M. tuberculosis* bacteraemic and blood culture negative patients. Patients with *M. tuberculosis* bacter-aemia were more likely than blood culture negative patients to be deceased at diagnosis or to die while on TB therapy (50%