Multi-Drug Resistant Tuberculosis: Experiences of Two Tertiary Referral Centres

B Kennedy 1, B O'Connor 1, B Korn 1, N Gibbons 1, T O'Connor 1, J Keane 2
1 Mercy University Hospital, Grenville Place, Cork, 2 St James's Hospital, St James's St, Dublin 8

Abstract

Multi-drug resistant tuberculosis (MDR-TB) is associated with increased morbidity and mortality compared to drug-sensitive disease. Although MDR-TB is infrequent in Ireland, cases continue to be diagnosed in both Irish and foreign-born patients. We conducted a clinical audit of 13 MDR-TB patients treated in two tertiary referral hospitals, the Mercy Hospital, Cork and St James's Hospital, Dublin between 2004 and 2009. The median age was 37 years. Eight patients (61.5%) were foreign-born, five (38.5%) were Irish-born. Seven patients (54%) have now stopped treatment; six (86%) were treated successfully and one (14%) defaulted. Mycobacterium tuberculosis isolates were resistant to a median of seven drugs. Eight patients (61.5%) developed ototoxicity from long-term aminoglycoside use. Our patients' treatment outcomes compare favourably with international reports despite a high degree of drug resistance. However, the high incidence of toxicity is concerning.

Introduction

 Guidelines for the management of drug-sensitive tuberculosis (TB) recommend that isoniazid and rifampicin form the backbone of chemotherapy, combining the early bactericidal activity of isoniazid with the sterilizing activity of rifampicin produces highly effective clinical outcomes. However in multi-drug resistant TB (MDR-TB), these anti-TB drugs are rendered ineffective by mutations in the genome of the M. tuberculosis bacillus. Thus treatment of MDR-TB necessitates the use of second-line agents which are less effective and more toxic. The inadequacy of these second-line agents is manifest in MDR-TB mortality rates of 11-37%. Furthermore in settings of high HIV prevalence one year mortality is as high as 71%.

Given its significant mortality, the emergence of MDR-TB in Ireland and the potential for its transmission are a serious threat to public health. A previous report described 8 cases of MDR-TB which were treated in Ireland between 1991 and 2001 and however the population of this cohort was treated. Recent changes to EU legislation and an economic boom led to an influx of immigrants from countries with a high burden of MDR-TB. Furthermore Ireland has seen a dramatic rise in the number of annual diagnoses of HIV since 2000 and population is at increased risk of developing MDR-TB. Thus the clinical profile of potential hosts for TB disease in Ireland has changed over the last ten years. Treatment guidelines have also been revised over this period. An updated discussion of Irish experience of MDR-TB is now warranted. We describe 13 cases of MDR-TB that have been treated in Ireland since 2004. We discuss the demographic profile of these 13 patients, treatment outcomes and degree of drug resistance.

Methods

We conducted a retrospective chart review of all patients treated for MDR-TB in St. James's Hospital, Dublin or the Mercy University Hospital, Cork between 1st January 2004 and 30th September 2009. These are two of the largest tertiary referral hospitals for TB in Ireland. MDR-TB cases were identified from the TB laboratory database in each hospital. A case of MDR-TB was defined as a patient whose sputum or bronchial washings cultured an isolate of M. tuberculosis that demonstrated in vitro resistance to rifampicin and isoniazid. Treatment regimes were formulated according to WHO (World Health Organisation) guidelines. Firstly ethambutol and/or pyrazinamide were included if drug susceptibility tests (DSTs) showed efficacy. Injectable agents were then added (i.e. amikacin, kanamycin or capreomycin); these drugs were continued for six months. Fluoroquinolones were considered next. Finally second line agents (PAS, cycloserine, prothionamide) were added until the drug cocktail consisted of four to six drugs. The duration of treatment was at least eighteen months and all patients received directly observed therapy.

We used definitions as established by an international consensus group in order to compare outcomes with international reports. We define a case as cure or treatment completion. A cure is defined as a patient who has finished eighteen months of treatment and has had 5 culture negative sputums collected over the last twelve months of treatment. Treatment completion occurs when a patient has finished eighteen months of treatment, has demonstrated a clinical and radiologic response, but lacks sufficient sputum samples to meet criteria for cure. Unsuccessful outcomes were defined as default, treatment failure or death. Default occurs when a patient stops treatment for any reason for two months or more. Failure is defined as 2 or more culture positive sputums in the last year of treatment or a lack of clinical response to a treatment regimen. Death is defined as death from any cause in a patient receiving treatment for MDR-TB. During the eighteen months of treatment, the time to sputum culture conversion was used as an interim marker of treatment efficacy; it is defined as the interval between the date of MDR-TB treatment initiation and the date of the first of two consecutive culture negative sputums.

Results

Our cohort consisted of 13 patients with MDR-TB; 10 (77%) were treated in St. James's Hospital; 3 (23%) were treated in the Mercy Hospital. Over the study period, there was a total of 291 culture positive cases of TB diagnosed in St. James's and 149 cases diagnosed in the Mercy. Thus MDR-TB accounted for 3.4% and 1.5% of all culture positive TB cases in St. James's and the Mercy respectively. The median age was 37 years (range 24-82). Seven patients (54%) were male. Eight patients (61.5%) were foreign-born; 4 (30%) were born in Lithuania, 1 (6%) in Georgia, 1 in Azerbaijan, 1 in Zambia and 1 in South Africa. There were 11 (85%) Caucasians and 2 (15%) Africans. At the time of TB diagnosis, 46% (6) patients were living in rural areas of Ireland while 54% (7) were living in urban areas. Eight patients (61.5%) had a previous treatment for drug-sensitive TB; 3 (23%) were previously treated for MDR-TB. All patients had pulmonary TB; one also had pleural TB. One patient (14%) was co-infected with HIV.

Of the 13 patients who started treatment for MDR-TB, 7 (54%) had stopped treatment by the end of the study period; six (86%) finished a full treatment course and one (14%) defaulted. Of the six who finished a full treatment course all had a successful outcome; 3 (50%) patients met criteria for cure and 3 (50%) were treatment completers. These 6 patients were treated for a median of 19 months (14-28). Each patient received a median of 5 anti-TB drugs (4-7); no patient took less than the study period. Isolates were resistant to a median of 7 drugs (2-10). Clinical characteristics, time to sputum culture conversion, resistance profiles, drug regimens and outcomes are presented in Table 1.

Adverse events were documented in 12 (92%) patients. Ten (77%) reported gastrointestinal disturbance. Eight (61.5%) had documented hearing loss. Ten (77%) reported a five-fold increase in hepatic transaminases. All three of these patients were Irish. None were seropositive for hepatitis B or C virus. One had a history of alcoholism and transaminases returned to normal with cessation of alcohol. In the second case the elevation in transaminases

Multi-Drug Resistant Tuberculosis: Experiences of Two Tertiary Referral Centres
patients sputum was sterilised while receiving first-line treatment for drug-sensitive TB; they were still prescribed a full course of treatment for MDR-TB.

Discussion

In 2007 the incidence of TB in Ireland was 13 cases per 100,000 population; this was considerably less than the global incidence of 1.39 per 100,000. In 2006, the Health Protection Surveillance Centre (HPSC) reported that MDR-TB accounted for 0.9% of all TB cases in Ireland. The same year MDR-TB accounted for 4.8% of all TB cases worldwide. Therefore it appears Ireland has a low burden of TB and MDR-TB when compared to the rest of the world. Nevertheless, MDR-TB continues to be diagnosed in Ireland; the HPSC was notified of 25 cases between 1998 and 2008.

Min et al reported that 3 of 8 (37.5%) patients treated for MDR-TB in Ireland between 1991 and 2001 were foreign-born; these patients were born in Pakistan, Angola and the Ivory Coast. In our cohort, 8 of 13 patients (61.5%) were foreign-born; 6 of these were born in Eastern Europe. Comparing our data with that of Min et al, no patients treated for MDR-TB in Ireland prior to 2001 were born in Eastern Europe but since 2004 nationals of these countries have accounted for almost 50% of cases. This indicates that immigration from these countries since 2004 has contributed significantly to the recent burden of MDR-TB in Ireland. Five of our patients were Irish-born. The median age of this subgroup was 63 years (40-82). None were HIV positive. Four had previously received treatment for drug-sensitive TB. In all four of these cases, compliance with treatment had been an issue during the initial drug regimen. These patients may have acquired MDR-TB through non-compliance with medication leading to incomplete eradication of M. tuberculosis with selection of resistant bacilli. It is unclear how MDR-TB arose in the other Irish-born patient.

Seven patients in our cohort had discontinued treatment by the end of the study period. Six of these patients finished a full treatment course; all were either cured or were treatment completers. Johnston et al published a meta-analysis of 4,959 patients where a treatment success rate of 62% was reported. Although our numbers are small, our success rate of 86% compares favourably with this report. There was one defaulter amongst the 7 patients who have discontinued treatment; this default rate is comparable with the 13% default rate reported by Johnston et al. Treatment failures occurred in our cohort. One patient in our cohort had both HIV infection and MDR-TB. The co-existence of HIV infection and MDR-TB presents multiple difficulties. Mortality is substantially increased while drug interactions increase the risk of hepatotoxicity, peripheral neuropathy and skin rashes. In our patients case, these difficulties were compounded by the patients decision to stop treatment for both MDR-TB and HIV after only 12 months of the planned regimen. This patient has now been off treatment for two years and remains an in-patient in respiratory isolation in a negative pressure room. To our knowledge there was no transmission of MDR-TB amongst the patients of our cohort. All patients were managed in respiratory isolation in negative pressure rooms until stability was demonstrated. In two instances, High Court orders had to be imposed upon patients to ensure compliance with infection control measures.

Latvia is a country with a high burden of MDR-TB. A study of 204 MDR-TB patients treated in Latvia reported that MDR-TB isolates were resistant to a median of four drugs. By comparison our cohort demonstrated resistance to a median of seven drugs. Although this may reflect differences in drug-susceptibility testing between different laboratories, it also suggests that Ireland is confronting a degree of drug resistance that is comparable to that seen in countries with a high burden of MDR-TB. All but one of our patients experienced an adverse event. The most common of these was GI disturbance; this was usually controlled with medication. The use of long-term aminoglycosides predisposes to hearing loss; this occurred in 62% of our cohort and exceeds the rate of 18-42% reported in the literature. The reasons for this excess ototoxicity remain unclear. Peltoquin et al reported that ototoxicity increases with age and with larger cumulative doses of aminoglycosides; however the age of our cohort is comparable to other reports and our use of aminoglycosides does not exceed WHO recommendations.

In summary we report a further 13 cases of MDR-TB that have been treated in Ireland since 2004. A substantial proportion of these patients came from Eastern Europe; this represents an emerging demographic change from the previously reported cohort. Seven patients have discontinued treatment; 6 have been treated successfully. Our cohort demonstrated a relatively high degree of drug resistance even compared with countries of high MDR-TB burden. There is also a high rate of ototoxicity which has important psycho-social implications for this cohort of patients who are often newly immigrated and anxious to begin employment. Although the incidence of MDR-TB is relatively low in Ireland, it remains a transmissible disease with a high mortality rate. Nevertheless, outbreaks of this infection can be averted through clinical vigilance, rigorous reporting and robust surveillance systems.

Correspondence: B Kennedy
Mercy University Hospital, Grenville Place, Cork
Email: barrykennedy2009@gmail.com

Multi-Drug Resistant Tuberculosis: Experiences of Two Tertiary Referral Centres

2
References


