Individualised treatment for multidrug-resistant tuberculosis in New South Wales, Australia

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Abstract

Objective: Multidrug-resistant tuberculosis (MDR-TB) presents a major global health challenge. In high-income countries, treatment is individualised to optimise efficacy and reduce toxicity. We aimed to evaluate the outcomes of patients with MDR-TB receiving individualised antibiotic therapy in Australia.

Methods: This retrospective cohort study was performed in the city of Sydney in Australia and included patients diagnosed with bacteriologically confirmed MDR-TB diagnosed between 2000 and 2016. The clinical characteristics of patients and treatment details were extracted from medical records. The incidence of adverse events and end-of-treatment outcomes were also evaluated.

Results: Fifty-five patients with MDR-TB were identified at TB clinics in seven hospitals. The median age was 32 years (interquartile range [IQR]: 27–36 years). The median duration of the intensive phase treatment was six months (IQR 6–7 months). All patients' treatment administration was directly observed. The commonest reported adverse event was ototoxicity (44%; 23/52) and successful treatment outcomes were achieved by 95% (52/55) of patients.

Conclusion: This study demonstrated the high treatment success rate that can be achieved using individualised treatment for MDR-TB in a well-resourced setting.

Implications for public health: The expansion of individualised therapy promises to contribute to MDR-TB control and advance the ambitious goal of TB elimination by 2035.

Key words: drug-resistant tuberculosis, tuberculosis, management of MDR-TB

In 2018, an estimated 10 million people fell ill with tuberculosis (TB) worldwide.[1,2] Among these, almost half a million people developed multidrug-resistant tuberculosis (MDR-TB), defined as disease caused by *M. tuberculosis* that is resistant to both rifampicin and isoniazid.[1-4] A diagnosis of MDR-TB presents a major challenge for patients due to prolonged treatment, a high incidence of adverse events, high mortality rates and substantial costs of treatment.[5,6] In Australia, the rate of TB notifications has remained relatively stable since 1986.[7] Although rates of TB and transmission within Australia have remained low, migration – often from countries of high TB burden – is an ongoing potential source of new TB cases, including drug-resistant ones.

Treatment outcomes of MDR-TB differ considerably between settings.[8] In some high-income settings, treatment outcomes for MDR-TB approach those of drug-susceptible disease. However, globally, the outcomes are poor. Of the 156,000 persons treated for MDR-TB or rifampicin-resistant TB (RR-TB) in 2018, just 56% achieved a successful outcome.[1,9] Determinants of poor outcomes include the high incidence of adverse events seen with second-line antibiotics, barriers to accessing care[10] and difficulties maintaining adherence during a prolonged course of treatment.[1,9] The programmatic use of individualised therapy may help to improve treatment completion by ensuring that treatment regimens have been optimised for each patient. Individualised regimens can be developed by evaluating the drug-resistance profile of the causative bacteria and patient-specific factors that may determine treatment toxicity. Meta-analyses of published studies have demonstrated that an individualised approach can improve treatment outcomes when compared to programs where empirical regimens were used.[5,6,11-15] For this reason, many high-income countries, including Australia, deliver individualised therapy for drug-resistant TB that is based upon the drug-resistance profile of the causative isolates and patient factors.[5,6,11]

This study aimed to evaluate the programmatic outcomes of patients receiving individualised antibiotic therapy for MDR-TB in the city of Sydney, in New South Wales, Australia. Some cases were reported in a recent study looking at the outcomes of MDR-TB diagnosed in Australia between 1998 and 2012.[16]

Methodology

Study design and setting

This retrospective cohort study included patients treated at the seven chest clinics at tertiary hospitals in Sydney, the most populous city in Australia. The country has a low annual incidence of TB, with the Commonwealth Department of Health reporting a rate of 5.8 cases per 100,000 population in 2018.[17] MDR-TB comprises

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less than 2% of diagnosed cases. Given it is a relatively low-prevalence disease, a prospective study is not feasible.

Treatment for MDR-TB in New South Wales is individualised and based upon molecular drug susceptibility test (DST) results. Empirical treatment is started for the patient being investigated for TB using nucleic acid amplification testing. During the study period, once a patient was found to have resistance to both RIF and INH, a full antibiogram using phenotypic drug susceptibility testing was performed. Following an initial period of empirical therapy for MDR-TB, an individual treatment plan was developed according to the DST profile, in consultation with a statewide expert panel. The panel included experienced respiratory physicians, TB nurses and public health staff.

All investigations and treatment for TB were provided free of cost to patients through government-funded chest clinics.[17] During the study period, government policies mandated the regular observation of patients taking treatment by healthcare workers throughout treatment – also known as Direct Observation of Therapy (DOT).[17,18] The principle of individualised treatment for MDR-TB relies upon the capacity of the healthcare system to delivering individualised treatment regimens including access to quality-assured drug susceptibility testing (DST), regimens including effective antibiotics, medications of good quality and outpatient management of adverse events.[19]

Eligibility and participant identification

Eligible participants were consecutive patients with a laboratory-confirmed diagnosis of MDR-TB in the state of New South Wales (NSW) between 1 January 2000 and 31 December 2016. The study period was selected as the World Health Organization (WHO) released the update of policy recommendations on the treatment of drug-resistant TB in 2016.[20] Patients with confirmed MDR-TB were identified via the state Mycobacterial Reference Lab, which performs drug susceptibility testing for isolates from all patients in New South Wales.

Data collection

Medical and pharmacy records were reviewed at each clinic to obtain clinical information about identified cases. Collected data included patient demographics, comorbidities, risk factors, TB diagnosis (pulmonary or extrapulmonary), prior TB treatment (with first-line drugs or second-line drugs), sputum culture conversion, the details of TB treatment including (intensive and continuation phrase) duration, complications and outcomes. Radiological findings (chest radiography and computed tomography) collected were based on reports by the radiologists. Cases were excluded if no details of the treatment were found. We were unable to exclude an influence of other potential risk factors due to the retrospective observational nature of the study.

Definitions

The 'intensive phase' of treatment was defined as the period of treatment during which a second-line injectable drug was given (either an aminoglycoside, amikacin or kanamycin, or polypeptide, capreomycin). The 'continuation phase' comprised the remainder of treatment. The drug resistance of the bacterium to each antibiotic was documented as sensitive, resistant or not reported. A drug was considered an effective drug if it was given to patients with documented sensitivity to that drug.

Adverse events were evaluated based upon documentation by the treating physicians in patients' medical records. The grade of adverse events was determined from the available clinical information by one researcher (VC), according to standardised criteria.[21] Grade 1 adverse events comprised events with no symptoms or mild symptoms; Grade 2 events comprised adverse events for which local or non-invasive interventions were indicated; Grade 3 events were defined as those requiring hospitalisation or resulting in disability; Grade 4 events comprised events with life-threatening consequences and Grade 5 resulted in death.[21] Adverse events leading to changes to treatment were documented. The treatment outcomes for pulmonary MDR-TB were defined according to the Laserson Criteria.[22] The treatment outcomes for extra-pulmonary MDR-TB were defined as completed, died, failure, relapse and transfer out. The World Health Organization (WHO) defines 'cure' as 'treatment completion' with at least three negative cultures after the intensive phase of therapy in the absence of 'treatment failure'.[23]

Data analysis

Descriptive analyses were performed to characterise the clinical and microbiological characteristics of patients. Quantitative variables were summarised using frequencies or median values, with interquartile ranges (IQR). Adverse events were classified by organ or system. Percentages were calculated for participants without missing values. Statistical analyses were performed using SPSS Statistics (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp).

Ethical considerations

Ethical approval for the study was granted by the Sydney Local Health District Human Research Ethics Committee (HREC, LNR/17/CRGH/129). Site-specific approval to conduct the study was obtained from each hospital prior to the commencement of data collection.

Results

Between 2001 and 2016, 76 patients with confirmed MDR-TB were identified by the state Reference Laboratory. Of these, 55 patients were treated within the seven participating urban chest clinics. Twenty-one cases were excluded from the study as we were unable to identify the complete documentation.

The median age of participants was 32 years (interquartile range [IQR]: 27–36 years). Patients' characteristics are shown in Table 1. Most patients (54/55; 98%) were born outside Australia (East Asia, 16; South Asia, 20; Southeast Asia, 14; North Africa, 3; Oceania, 1). Among 52 patients for whom HIV status was available, one (2%) tested positive and received concurrent anti-retroviral treatment (Table 2). Pulmonary TB was diagnosed in 65.5% (36/55) of patients; of these, smear microscopy was positive in 47.2% (17/36). The median duration of symptoms was eight weeks (IQR 4–12 weeks).

Drug susceptibility test results

Rapid molecular testing for drug resistance was available in New South Wales in 2011 and it was performed for 14/21 patients (66.7%). The median duration between the availability of the rapid drug resistance testing and confirmatory second line (drug susceptibility testing) DST was 16 days (IQR 5–32 days). The median time from diagnosis of TB to the diagnosis of MDR-TB was 40 days (IQR 28–51 days). The proportion of resistance to first-line and second-line drugs is shown in Table 3.

Table 1: Characteristics of patients with MDR-TB .

Characteristic	n (%)
Total	55 (100)
Gender	
Male	32 (58)
Female	23 (41.8)
Age (years)	
less than 18	1 (1.8)
18-24	5 (9.1)
25-34	31 (56.4)
35-44	10 (18.2)
45-54	3 (5.5)
55-64	4 97.3)
65+	1 (1.8)
Employment status	
Working full time	18 (32.7)
Working part-time	11 (20)
Unemployed	4 (7)
Studying	13 (24)
Not stated	9 (16.4)
Smoking status	
Lifelong non-smoker	46 (84)
Current smoker	6 (10.9)
Ex-smoker	3 (5.5)
Alcohol (etoh) usage	
Does not drink etoh	35 (63.6)
Social etoh use	20 (36)
Excessive etoh use	0
Intravenous drug user (IVDU)	
Non-IVDU	54 (98.2)
Current IVDU	0
Ex- IVDU	1 (1.8)
Medical comorbidities	
HIV	
Yes	1 (1.8)
No	51 (92.7)
Not documented	3 (5.5)
Diabetes Mellitus	
Yes	5 (9.1)
No	50 (90.9)
Not documented	0
Chronic hepatitis B	
Yes	3 (5.5)
No	47 (85.5)
Not documented	5 (9.1)
Chronic hepatitis C	
Yes	2 (3.6)
No	48 (87.3)
Not documented	5 (9.1)
Silicosis	
Yes	0
No	6 (10.9)
Not documented	49 (89.1)
Immunosuppression	
Yes	3 (5.5)
No	51 (92.7)
Not documented	1 (21.8)
History of TB	
Yes	11 (20)
No	44 (80)
History of MDR/XDR-TB	
Yes	1 (1.8)
No	54 (98.2)

Table 2: Diagnostic classification of the site of disease for patients with MDR-TB.

Characteristic	Number of patients n (%)
Total	55 (100%)
Site of tuberculosis	
Pulmonary TB only	36 (65.5)
Extrapulmonary TB	12 (21.8)
Lymphadenitis	8 (14.5)
Pleura	2 (3.6)
Abdominal	1 (1.8)
Central Nervous System	1 (1.8)
Pulmonary and extrapulmonary TB	7 (12.7)
Microbiological status at diagnosis	
Sputum smear positive	17 (39.5)
Sputum culture positive	26 (60.5)
Chest radiography findings at diagnosis	
Cavities present	13 (30.2)
Parenchymal present	29 (67.4)
Military disease	4 (9.3)
Normal	11 (25.6)
Radiological changes on Computed Tomography	
Cavities present	17 (39.5)
Parenchymal present	17 (39.5)
Military disease	3 (7.0)
Normal	4 (9.3)
Not performed	2 (4.7)

Table 3: Drug resistance profiles to first and second-line drugs.

Resistance profile for MDR-TB isolates n=55 (%)	Phenotypic resistance to the listed antibiotic(s)	Resistance to antibiotic(s) not documented
1st line		
HR	55 (100)	0 (0)
HRE	12 (21.8)	7 (12.7)
HRZ	16 (29.1)	13 (23.6)
HREZ	4 (7.3)	14 (25.5)
2nd line		
Group A- Fluoroquinolones		
Moxifloxacin	4 (7.3)	33 (60)
Ciprofloxacin	5 (9.1)	6 (10.9)
Levofloxacin	1 (1.8)	48 (87.3)
Ofloxacin	0 (0)	49 (89.1)
Group B- 2nd line injectable agents		
Amikacin	1 (1.8)	9 (16.4)
Capreomycin	1 (1.8)	8 (14.5)
Kanamycin	0 (0)	49 (89.1)
Streptomycin	21 (38.2)	21 (38.2)
Group C- other 2nd line agents		
Ethionamide	20 (36.4)	9 (16.4)
Prothionamide	0 (0)	46 (83.6)
Cycloserine	5 (9.1)	19 (34.5)
Terizidone	1 (1.8)	48 (87.3)
Linezolid	2 (3.6)	32 (58.2)
Clofazimine	8 (14.5)	8 (14.5)
Others add on agents		
PAS	5 (9.1)	43 (78.2)
Imipenum/ Cilastatin	0 (0)	49 (89.1)
Meropenum	1 (0)	50 (89.1)
Augmentin DF	2 (0)	51 (89.1)
Thioacetazone	3 (0)	52 (89.1)
Bedaquline	4 (0)	53 (89.1)

Notes:

H= Isoniazid, R= Rifampicin, E=Ethambutol, Z= Pyrazinamide

Fluroquinolone resistance was present in 10/55 (18.2%) of cases (Table 3).

Hospitalisation and treatment regimens

During the initial treatment period, 32/55 patients (58.2%) were hospitalised. All patients received their treatment under direct observation between three and five days a week. The median durations of inpatient and outpatient treatment were seven days (IQR 0–42 days) and 600 days (IQR 540–713 days), respectively. The median duration of the intensive phase treatment was six months (IQR 6–8 months), and the median duration of continuation phase treatment was 14 months (IQR 12–18 months).

Patients received between four and seven antibiotics. The median number of effective drugs which were given was five (IQR 4–5) for patients with documented sensitivities. The details of the MDR-TB regimens used during the acute and continuation phrase is shown in Table 4. The treatment was consistent with standard WHO guidelines at the time of the study, which included the use of four core second-line drugs with one being the secondary line injectable agents.[18,24] The WHO endorsed the shorter MDR-TB regimen for patients with rifampicin resistant-TB or MDR-TB who were not previously treated with second-line drugs and in whom resistance to fluoroquinolones and second-line injectable agents was excluded or was considered highly unlikely in May 2016, but none of the patients in the study received the shorter regimens.

Treatment outcomes

Table 6 shows treatment outcomes for the cohort. Two patients died before the treatment for MDR-TB treatment was started. One patient transferred out, leaving Australia four months after treatment started. The median duration from treatment commencement to sputum smear conversion was 58 (IQR 38–73) days and culture conversion was 59 (49–130) days. After two months of treatment, 51% (22/43) of patients became smear negative and 49% (21/43) were culture negative. No patient was smear positive at five months. A negative culture was documented for 35% (15/43) of patients who were initially sputum culture positive; however, 63% (27/43) patients were not able to expectorate sputum after they commenced treatment for five months. Only eight patients had sputum collected at seven months and at the end of treatment, of which both were culture negative. (Table 5). A total of 93% of the patients (51/55) achieved treatment completion as defined by the WHO.[23]

Treatment toxicity

Adverse events were commonly reported, as shown in Table 7. The adverse events reported most often were ototoxicity (44%; 23/52 patients). Of the 54 patients taking an injectable antibiotic, more than half of the patients 59% (32/54 patients) had audiometric monitoring once they reported symptoms and only 37% (20/54) patients had audiometry within one month of treatment commencement. Hepatotoxicity (50%; 26/52 patients) and gastrointestinal symptoms (56%; 29/52 patients) were commonly reported. No reported grade four or five adverse events were reported.

Table 4: MDR-TB treatment regimens .

	Intensive phrase	Continuation phrase
Total number of patients n (%)	54 (100)	52 (100)
Group A- Fluoroquinolones		
Moxifloxacin	52 (96.3)	52 (100)
Ciprofloxacin	2 (1.9)	0 (0)
Group B- 2nd line injectable agents		
Amikacin	28 (51.9)	0 (0)
Daily dose	8 (14.8)	0 (0)
5 days per week	20 (37)	0 (0)
Capreomycin	26 (48.1)	0 (0)
Daily dose	12 (22.2)	0 (0)
5 days per week	10 (18.5)	0 (0)
3 days per week	4 (7.4)	0 (0)
Group C- other 2nd line agents		
Ethionamide	2 (1.9)	0 (0)
Prothionamide	20 (37)	18 (34.6)
Cycloserine	14 (25.9)	13 (25)
Linezolid	6 (11.1)	4 (7.7)
Clofazimine	27 (50)	27 (51.9)
Others add on agents		
Pyrazinamide	30 (55.6)	26 (50)
Ethambutol	36 (66.7)	32 (61.5)
High dose Isoniazid	11 (20.4)	10 (19.2)
PAS	4 (7.4)	2 (3.8)
Amoxycillin/clavulanic acid	0 (0)	3 (5.8)
Bedaquline	1 (1.9)	1 (1.9)

Table 5: Results for repeat sputum microscopy and culture for patients on MDR-TB treatment.

Repeat sputum culture n=43 (%)	Sputum smear positive	Sputum smear negative	Sputum culture positive	Sputum culture negative	Not performed
2 months	8 (18.6)	22 (51.2)	9 (20.1)	21 (48.8)	13 (30.2)
5 months	0	16 (37.2)	1 (2.3)	15 (34.9)	27 (63.0)
7 months	0	8 (18.6)	0	8 (18.6)	35 (81.4)
End of treatment	0	8 (18.6)	0	8 (18.6)	35 (81.4)

Discussion

This retrospective cohort study of patients treated for MDR-TB in Sydney, Australia, over a 16-year period demonstrated a high rate of treatment success. Patients' treatment regimens were individualised and based upon molecular drug susceptibility test (DST)

Table 6: Treatment outcomes for MDR-TB patients.

Treatment outcome	n (%)
Patients with pulmonary MDR-TB	
Total	43 (100)
Cure	1 (2.3)
Completed	40 (93.0)
Died	1 (2.3)
Failure	0 (0)
Transfer out	1 (2.3)
Patients with extrapulmonary MDR-TB	
Total	12 (100)
Completed	11 (91.6)
Died	1 (8.3)
Failure	0 (0)
Transfer out	0 (0)

Table 7: Cumulative incidence of adverse events among patients treated for MDR-TB.

Adverse event	Grade of adverse event n (%) n=52 patients*					Treatment decision following adverse event n (%)		
	1	2	3	4	5	Treatment continued	Treatment modified	Treatment stopped
Cardiac arrhythmia	0	0	0	0	0	52 (100)	0	0
Electrolyte abnormality	7 (13.5)	1 (1.9)	2 (3.8)	0	0	50 (96.2)	1 (1.9)	1 (1.9)
Haematological	4 (7.7)	0	3 (5.8)	0	0	49 (94.2)	0	3 (5.8)
Headaches	2 (3.8)	1 (1.9)	1 (1.9)	0	0	50 (96.2)	0	2 (3.8)
Hearing impairment	13 (28.3)	7 (15.2)	3 (6.5)	0	0	38 (73.1)	2 (3.8)	11 (21.2)
Hypo/hyperthyroidism	1 (1.9)	1 (1.9)	0	0	0	52 (100)	0	0
Liver toxicity	15 (28.8)	7 (13.5)	4 (7.7)	0	0	46 (88.5)	1 (1.9)	5 (9.6)
Myalgia _arthralgia	9 (17.3)	0	0	0	0	52 (100)	0	0
Nausea vomiting	25 (48.1)	4 (7.7)	0	0	0	47 (90.1)	3 (5.7)	1 (1.9)
Peripheral neuropathy	5 (9.6)	0	3 (5.8)	0	0	50 (96.2)	2 (3.8)	0
Psychiatry	0	0	0	0	0	52 (100)	0	0
Visual impairment	2 (3.8)	1 (1.9)	0	0	0	52 (100)	0	0

Notes:

**Adverse events for 52 patients were reported; 3 patients did not have adverse event data (1 transferred out and 2 died prior to treatment).*

results. Most included an injectable antibiotic during the intensive phase of treatment. Our cohort showed an excellent treatment completion rate – well above the WHO target of 75%, and similar to that achieved in other high-resource settings.[2,25,26] All patients received treatment under direct observation of healthcare workers. All 52 patients had at least one adverse event. The high treatment completion rates achieved indicated the ability of healthcare workers to continue supervising the MDR-TB treatment despite the frequent occurrence of side effects.

The reporting of drug-related adverse events was inconsistent. The grading of reported adverse events was not documented by clinicians in routine practice. Owing to the presence of multiple concurrent antibiotics, it was difficult to attribute a specific adverse event to a specific antibiotic. According to state policies, serious adverse events of medicine should be reported to the national Therapeutic Goods Administration. However, notification practices vary considerably across sites.[27] While patients were followed up monthly at the clinic by treating physicians, national monitoring guidelines for the monitoring of drug-resistant TB treatment are lacking. Considering the increasing use of the new or repurposed second-line drugs, local guidelines for standardised drug-safely monitoring are warranted. A few patients had repeat sputum collected during the treatment course; developing a standardised monitoring protocol for sputum analysis at regular intervals throughout treatment can improve the reporting of treatment outcomes.

This study had several limitations. As this was a retrospective study, documentation in the medical records was sometimes incomplete – particularly regarding patients' comorbidities. Furthermore, the data available to guide the classification of the severity of adverse events were limited. During the study period, the global treatment guidelines for MDR-TB continued to evolve. Recently, the WHO has endorsed the use of new drugs, such as bedaquiline, and repurposed anti-TB drugs as first-line therapies in the treatment of MDR-TB.[1] However, few patients in our cohort had access to these second-line drugs – bedaquiline only became available in Australia in 2017. Aminoglycosides are not recommended in the treatment of MDR-TB patients on longer regimens.[28] All patients in our study received their individualised MDR-TB treatment with DOT supervised by healthcare workers, which may also have contributed to the high treatment completion rate.

This study has important policy implications. Firstly, individualised therapy can result in excellent treatment outcomes and so should be considered in settings where this is feasible. Secondly, it shows that adverse events are almost universally observed. However, intensive monitoring can ensure that patients safely complete treatment. Lastly, in New South Wales, where just 2% of patients with TB have MDR-TB, further studies should look into the cost-effectiveness of performing rapid molecular testing to detect rifampicin-resistant TB for patients without a prior TB treatment history or other risk factor for drug-resistance.

Conclusion

In conclusion, individualised treatment for patients with MDR-TB in Australia was associated with high rates of treatment success within the public treatment program. The expansion of individualised therapy promises to contribute to MDR-TB control and advance the ambitious goal of TB elimination by 2035.[29] It is important for countries like Australia with high incomes and low TB incidence to continue using individualised treatment for MDR-TB, optimise the use of new agents like bedaquiline and delamanid, and develop strategies to ensure patients' preferences remain at the centre of the clinical decision making.

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