Multidrug-resistant tuberculosis in the Northern Territory: A 10-year retrospective case series

Daniel Judge, Vicki L Krause

Abstract

Background and objective: To describe the clinical characteristics, risk factors, diagnostic modalities, treatments, subsequent outcomes and complications of Multidrug-resistant tuberculosis (MDR-TB) cases residing in the Northern Territory.

Methods: A retrospective case series was conducted of all patients treated for MDR-TB in the Northern Territory between 1 January 2004 and 31 December 2013. This is the first study to analyse data relating to the subset of MDR-TB cases treated in the Northern Territory. Cases were identified by the Northern Territory Centre for Disease Control (NT CDC): the public health unit responsible for the management of tuberculosis in the Northern Territory. Outcome measures included patient demographics, diagnostics, HIV status, treatment methods, outcomes, and complications.

Results and conclusions: Six MDR-TB cases were treated in the Northern Territory; 5 of these were notified by the NT CDC during the study period (1.5% of all Northern Territory TB notifications). The median age of all 6 patients was 31 years (range 21 to 50 years), sex distribution was equal and all were born overseas. Country of birth in a World Health Organization (WHO) high burden MDR-TB country and previous treatment were most highly correlated with a current diagnosis of MDR-TB. Access to rapid drug susceptibility testing reduced the time to effective therapy from 45 to 27 days. Five patients met criteria for the WHO outcome term 'treatment success'. The median length of treatment for the 5 patients treated in Australia was 623 days (537 to 730 days). Side effects to therapy were common and serious. The incidence of MDR-TB in the Northern Territory is similar to other Australian states. Rapid drug susceptibility testing reduces the time to effective therapy. Treatment regimens are complex, toxic and have serious resource implications for health care providers. Successful treatment outcomes are possible with coordinated TB control programs. *Commun Dis Intell* 2016;40(3):E334–E339.

Keywords: tuberculosis, multidrug resistance, Northern Territory

Introduction

Treatment of multidrug-resistant tuberculosis (MDR-TB), defined as resistance to isoniazid and rifampicin, is longer and requires more expensive and more toxic drugs,[1] than fully susceptible disease. Nearly 20 years after the World Health Organization (WHO) declared TB a global health emergency, major progress has been made towards targets for diagnosis and treatment of TB.[1,2] Advancement towards targets for MDR-TB control has been less successful.[1]

A review of the published literature shows the incidence of MDR-TB notifications varies over time and across Australian states. A 10-year review of Victorian data found that MDR-TB accounted for up to 2.2% of all TB notifications between 1998 and 2007.[3] Western Australian MDR-TB notifications over a 15-year period to 2012 accounted for 1.2% of all TB cases.[4] Higher rates of MDR-TB are reported from the Torres Strait Protected Zone (TSPZ), with 26% of isolates from the TSPZ defined as MDR-TB in one Queensland study.[5] Yearly reports from the Australian Mycobacterium Reference Laboratory Network between 1985 and 2013 show that the proportion of isolates from patients with MDR-TB has stayed within a band of 0.5 to 2.4% nationally, excluding those from the TSPZ.[6,7]

The WHO estimates that the cost of treating MDR-TB is 100 times that of susceptible TB and treatment success globally is attained in only 48% of MDR-TB cases.[2] This has wide reaching repercussions for public health planning and may have important implications for hospitals treating even a single case of MDR-TB.[8]

Here we describe the characteristics, risk factors, diagnostics, treatments, subsequent outcomes and complications of MDR-TB cases residing in the Northern Territory, for all or part of their therapy in the 10 years to 2013.

Methods

All patients treated for MDR-TB in the Northern Territory between 1 January 2004 and 31 December 2013 were included in the study. Formal drug

susceptibility testing demonstrating drug resistance was undertaken at the Victorian Infectious Diseases Reference Laboratory.

Data obtained from the Northern Territory Notifiable Disease System (NTNDS) included: patient demographic information; known previous TB infection and anti-tuberculosis therapy; risk factors for MDR-TB including country of birth or residence in a high MDR-TB burden country and contact with an MDR-TB case; diagnostic information including formal drug susceptibility testing (DST) and molecular methods; HIV status; and treatment methods, outcomes, and complications. Descriptive statistical analysis for these data points was undertaken using Microsoft Excel. Treatment outcome was defined as successful in accordance with WHO guidelines adopted from Laserson et al (Table 1).[9]

The study received ethical approval from the Human Research Ethics Committee, part of the Menzies School of Health Research.

Results

Review of the NTNDS revealed 6 patients with laboratory-confirmed MDR-TB who received treatment in the Northern Territory during the study period. Data included 1 individual previously notified in Victoria and subsequently treated in the Northern Territory. The Northern Territory Centre for Disease Control (NT CDC) notified 5 cases of MDR-TB, representing 1.5% (total of 343 TB notifications) of all cases notified over the 10-year period to 2013.

The median age of the 6 patients was 31 years with a range of 21 to 50 years and sex distribution was equal with 3 male and 3 female patients. All patients were born overseas and all countries of origin were defined as WHO high burden TB countries, as well as high MDR-TB burden countries (Table 2).[1,2] Country of origin was therefore the most highly associated risk factor with a diagnosis of MDR-TB. The next most common risk factor was previous diagnosis of TB +/- exposure to treatment and this included 3 patients with a laboratory-confirmed or suspected diagnosis of TB in their past. Of these, 2 had documentation of previous exposure to rifampicin and isoniazid as part of an appropriate treatment regimen (Table 3). Treatment adherence documentation varied. However, 2 of the cases were suspected to have been non-adherent with therapy. Only 1 case had resided in a high MDR-TB country other than country of birth and there were no exposures to known MDR-TB cases. All of the cases identified as MDR-TB were tested for human immunodeficiency virus (HIV) and all were negative.

The period between arrival in Australia and notification of TB was less than 2 years in 4 of the patients. The remaining 2 patients were notified at 10 and 19 years post arrival dates. Two of the patients were permanent residents of Australia. Of the remaining 4, 2 held working visas in Australia, 1 patient was seeking asylum and 1 individual was an unauthorised fisherperson. Three of the cases were identified after self-presentation with symptomatic disease, 2 cases were identified as a part of routine screening in detention, and 1 case was identified as a result of a health care undertaking required for an Australian visa.

Table 1: Treatment outcome definitions for multidrug-resistant tuberculosis patients

Cure	Treatment completed as recommended by the national policy without evidence of failure AND 3 or more consecutive cultures taken at least 30 days apart are negative after the intensive phase.
Treatment completed	Treatment completed as recommended by the national policy without evidence of failure BUT no record that 3 or more consecutive cultures taken at least 30 days apart are negative after the intensive phase.
Treatment failed	Treatment terminated or need for permanent regimen change of at least 2 anti-tuberculosis drugs because of: • lack of conversion by the end of the intensive phase; or • bacteriological reversion in the continuation phase after conversion to negative; or • evidence of additional acquired resistance to fluoroquinolones or second-line injectable drugs; or • adverse drug reactions.
Died	A patient who dies for any reason during the course of treatment.
Lost to follow-up	A patient whose treatment was interrupted for 2 consecutive months or more.
Not evaluated	A patient for whom no treatment outcome is assigned. (This includes cases "transferred out" to another treatment unit and whose treatment outcome is unknown.)
Treatment success	The sum of Cured and Treatment completed.

* World Health Organization guidelines adapted from Laserson 2005[8]

Table 2: Demographics of multidrug-resistant tuberculosis cases undergoing treatment in the Northern Territory, 2004 to 2013

Case	Year of diagnosis	State or territory of notification	Sex	Age	Country of birth	Visa status
1	2004	NT	Female	36	South Africa	Working visa
2	2006	NT	Male	50	Indonesia	Illegal fisherperson
3	2009	NT	Female	33	Vietnam	Permanent resident
4	2010	NT	Male	26	Bulgaria	Permanent resident
5	2010	Victoria	Female	29	Burma	Working visa
6	2012	NT	Male	21	Afghanistan	Illegal arrival

Table 3: Risk factors for multidrug-resistant tuberculosis cases, Northern Territory, 2004 to 2013

Case	Country of birth in a high-burden MDR-TB country	Previous diagnosis of tuberculosis +/- exposure to treatment	Suspected non-adherence or inappropriate tuberculosis therapy	Exposure to a known MDR-TB case	Residence in areas of high MDR-TB prevalence (other than country of birth)	HIV status
1	Yes	No	No	No	No	Negative
2	Yes	Yes	Yes	No	No	Negative
3	Yes	No	No	No	No	Negative
4	Yes	Yes*	Yes	No	No	Negative
5	Yes	Yes	No	No	Yes	Negative
6	Yes	No	No	No	No	Negative

* Empiric treatment in Australia for possible fully susceptible tuberculosis as no culture/susceptibility testing was available.

Adapted from the World Health Organization 2008 guidelines

In addition to formal drug susceptibility testing on all cases, nucleic acid amplification testing (NAAT) was available for 2 of the patients and identified the presence of *Mycobacterium tuberculosis* DNA and rpo*B* gene mutations, a surrogate for rifampicin resistance, in both specimens. Both patients were commenced on second line agents at initiation of intensive phase therapy in the context of suspected rifampicin resistance. The median delay to effective treatment with second line therapies for all patients was 47 days. Those who underwent NAAT testing had a reduced median delay to 29 days. The delay to effective therapy was defined as the time from diagnostic specimen collection to the commencement of a second line treatment regimen. Four patients had pulmonary tuberculosis only, 2 of whom were sputum smear positive. The 2 extra-pulmonary cases included 1 diagnosis of disease limited to the terminal ileum and 1 case of axillary TB lymphadenitis (Table 4). Drug susceptibility testing identified 3 cases of streptomycin resistance (streptomycin was not used at any time in any of these 3 cases) and 1 case of pyrazinamide resistance (the case isolate was not identified as *Mycobacterium bovis*). Resistance to other second line treatment agents was not demonstrated.

Five patients met criteria for the WHO cumulative outcome term 'treatment success' (either cure or treatment completed outcome categories as per Table 1). One case was classified as 'not evaluated' due to a transfer out to a resource limited setting overseas. Data at 1 and 5 years post treatment were limited, but no known cases of reactivation have been identified.

The median length of treatment for the 5 patients who completed therapy in Australia was 623 days with a range of treatment lengths from 537 to 730 days. The entire treatment period was completed in the Northern Territory in only 2 instances. One case was transferred out (deported) at 7 months of therapy having completed only 214 days of treatment. The remainder of the cases had treatment coordinated by multiple Australian jurisdictional tuberculosis control units. Diagnostic, treatment composition, and compliance data were incomplete

Table 4: Site of disease, smear positivity and diagnostic modality for multidrug-resistant tuberculosis cases

Case	Pulmonary disease	Smear result	Site of extra-pulmonary disease	Identification of MDR-TB by diagnostic modality	
				PCR	DST
1	Yes	Negative	NA	Not undertaken	Yes
2	Yes	Positive	NA	Not undertaken	Yes
3	No	NA	Terminal Ileum	Not undertaken	Yes
4	No	NA	Axillary lymph node	Yes	Yes
5	Yes	Positive	NA	Yes	Yes
6	Yes	Negative	NA	Not undertaken	Yes

MDR-TB Multidrug-resistant tuberculosis.
PCR Polymerase chain reaction.
DST Drug susceptibility testing.

as a result of the transfer of patients and it is noted that on at least 1 occasion a significant interruption to therapy complicated this process.

The treatment of MDR-TB in the Northern Territory involves directly observed therapy. Adherence data were excellent (approaching 100%) for all cases during the period of treatment coordinated by the NT CDC. Contact tracing identified 25 at risk individuals for appropriate follow-up.

All 6 cases commenced an injectable therapy (4 intravenous amikacin and 2 intramuscular streptomycin) in the first instance. One case developed a significant adverse outcome acutely (Table 5) and 4 cases on amikacin required permanent vascular access (peripherally inserted central catheter). All cases were treated with a later generation fluoroquinolone (moxifloxacin) and half received a thioamide as part of their regimen (Table 6). Two cases required hospitalisation with a combined total of 248 inpatient days. Adverse reactions to second line treatments were noted in 4 of the 6 cases (Table 5).

Table 5: Side effects by case and drug implicated

Case	Implicated drug	Side effect
1	NA	NA
2	Isoniazid or moxifloxacin	Stevens-Johnson syndrome
3	Amikacin	Ototoxicity
4	Amikacin	Ototoxicity
5	Prothionamide	Nausea
6	NA	NA

Table 6: Multidrug-resistant tuberculosis definitive treatment regimen

Drug	Number of cases employing drug for all or part of treatment regimen
Isoniazid	1/6
Rifampicin	0/6
Rifabutin	1/6
Ethambutol	6/6
Pyrazinamide	5/6
Moxifloxacin	6/6
Prothionamide	3/6
Amikacin*	5/6
Streptomycin	2/6
Para-aminosalicylic acid	1/6

Discussion

MDR-TB accounted for 1.5 % of all TB notifications in the Northern Territory over the decade to 2013. With respect to Australian and global MDR disease burden, this figure was lower than may have been expected in the context of the Northern Territory's position geographically and politically, with 3 immigration detention centres accommodating asylum seekers and alleged illegal fisherpersons (also referred to as unauthorised persons). The nationalities of unauthorised persons reviewed by the NT CDC are represented in the WHO defined 27 countries of high MDR-TB disease burden.[1,2] No significant difference in disease burden is identified between the results of this study and national data.[3,4] The regular transfer of unauthorised persons between detention centres and subsequent notifications interstate may confound results leading to lower than anticipated case numbers.

Distribution of disease between sexes was even. While our numbers are small this finding is contrary to Toungoussova et al 2002,[10] who identified a trend towards women being at higher risk of carrying MDR-TB strains. The median age of diagnosis (31 years) likely reflects the age of expected and unauthorised arrivals to Australia.

Country of birth being a high MDR-TB burden country was the most frequently reported risk factor for a diagnosis of MDR-TB, in keeping with current reports.[1,4] All of the cases treated for MDR-TB in the Northern Territory were born in 1 of the WHO defined 27 high MDR-TB burden countries. One case had resided in a WHO defined high burden TB or MDR-TB country other than their country of birth, prior to diagnosis. Primary transmission of MDR-TB was suspected in half of the cases with the other 3 previously treated for presumed susceptible disease. Previous treatment documentation and adherence varied and initial DST results were unknown. The importance of obtaining an isolate for culture and formal drug susceptibility cannot be overstated in the setting of the emergence of drug resistance. Acquired resistance was considered likely in these 3 cases.

One case considered as possible acquired resistance received an initial supervised and then a subsequent unsupervised treatment in Australia. As there were no links to any other Australian MDR-TB cases this case represents an episode of possible acquired resistance in Australia or a missed primary MDR-TB that was not adequately treated, as an isolate for susceptibility testing was not available.

It is felt that all but possibly 1 of the cases brought latent MDR-TB from their country of birth or residence overseas. It is noted that 4 of the 6 cases were identified within 2 years of arrival. Half of the cases were identified within 2 years of arrival by routine screening of individuals in detention, or health care undertakings. Analysis of enhanced data collected on all national MDR-TB cases will be useful in guiding future policy.

The WHO recommends rapid drug susceptibility testing of isoniazid and rifampicin or of rifampicin alone over conventional testing or no testing at time of diagnosis, subject to available resources.[2] A rapid test is defined as that yielding diagnostic and resistance results within 2 days. Only molecular tests can detect resistance so rapidly, of which 2 technologies: line probe assay and Xpert® MTB/RIF, are currently recommended by WHO.[11] Molecular testing data were available for cases from 2010 onwards. Xpert® was diagnostic on MDR-TB specimens subsequently identified by culture (1 sputum, 1 lymph node tissue sample). Detection of rpo*B* gene mutation, as a surrogate marker for rifampicin resistance, correctly identified both cases of MDR-TB. Diagnosis in the Northern Territory has been based on either diagnostic modality result returning positive in the first instance, with DST taking precedence over NAAT if results are discordant in the same sample.

The positive predictive value of any test will decrease with the decline in the prevalence of the disease in question, an important consideration for the use of molecular testing for resistance in the low prevalence MDR-TB Australian population. Inappropriate treatment with toxic, less effective second-line therapy in patients with susceptible disease is concerning, but specificity on newer generation Xpert® assays are very promising (99.8%).[9]

There are significant disease control implications for the rapid determination of drug resistance, ensuring successful treatment of the patient and preventing further spread of the drug-resistant isolate.[12] One individual diagnosed with smear positive pulmonary disease was diagnosed with MDR-TB on NAAT, allowing appropriate treatment and infection control mechanisms to be employed earlier. This was evidenced in the 18-day reduction in delay to appropriate treatment for patients investigated with NAAT on clinical isolates.

Significant variation in treatment regimens was noted among cases. The attempt to tailor individual treatments is likely to go part of the way to explaining this observation. However, expert consensus with regard to regimen composition, dose, and duration has historically been lacking worldwide and continues to evolve. To work to provide the best standard of care, the Northern Territory has an MDR-TB steering committee that meets to initially assess each case and decide on management and then meets as needed or at least 3 monthly for continued follow-up. Four cases were treated with amikacin necessitating permanent intravascular access. Three of those cases experienced complications specifically related to this drug (Table 6). In effect, only 1 case successfully completed the WHO recommended 8 month intensive phase with a parenteral agent.[8] The increased toxicity of second-line anti-tuberculosis regimens is also evident in the observation that 4 patients experienced significant adverse drug effects including hepatitis, ototoxicity and Stevens-Johnson syndrome. The increased complexity and toxicity of treatment regimens necessitates more frequent reviews and closer clinical and laboratory monitoring for toxicity and drug levels in some instances. There are parallel increases in resource consumption

through inpatient admissions, multidisciplinary specialist input, vascular access and the extended treatment duration associated with this diagnosis.

Contact tracing identified 25 individuals for review and follow-up. These numbers are very manageable, likely as a result of the low number of smear positive individuals, and in those cases seeking asylum or identified as unauthorised fisherpersons, by the early active case finding carried out once in Australia and attendant respiratory isolation. The NT CDC does not advocate routine prophylaxis for infected contacts of MDR-TB patients because of the lack of an agreed-on treatment regimen and paucity of outcome data to support this approach. Rather chest x-ray programs and patient and healthcare provider education are employed for surveillance for those contacts considered to be at increased risk of infection with MDR-TB.

'To fulfil her/his public health responsibility, as well as responsibility to the individual patient, the provider must prescribe an appropriate treatment regimen, monitor adherence to the regimen and, when necessary, address factors leading to interruption or discontinuation of treatment'.[13] Coordination of directly observed treatment programs for patients in this study was complicated by multiple routine transfers of patients in detention, with 1 case experiencing a lengthy interruption in appropriate therapy as a result of transfer between care providers within Australia. A 2nd case was deported and lost to follow-up at 7 months. This preceded completion of the 8 month recommended intensive treatment phase and was 13 months short of the total treatment duration outlined in the most recent WHO MDR-TB guidelines.[8] Successful treatment outcome was defined in all cases as treatment completed rather than cure (Table 1) as definitive sputum smear results were unavailable.

The movement of patients between TB control programs, as well as deportation, represents a potential obstacle to the coordinated treatment and follow-up of MDR-TB patients. The paucity of treatment outcome data in this study is attributed to the regular transfer of patients.

This study is the first to investigate demographic details, diagnostic modalities, treatment regimens, and outcomes associated with MDR-TB in the Northern Territory. Treatment outcomes were known and successful for all but the deported case at the completion of treatment and at 12 months follow-up. It is anticipated that data will be incorporated into a future national study that will offer greater insight into the Australian experience with MDR-TB. Such research is required to address the important gaps in knowledge with regard to: optimising combinations of drug regimens and treatment duration; treatment of paediatric MDR-TB; effective chemoprophylaxis for contacts of MDR-TB cases and strategies to avoid or therapies to relieve adverse reactions to second-line anti-tuberculosis drugs.[8]

Author details

Dr Daniel Judge, Respiratory Physician, Cairns Hospital, Cairns, Queensland
Dr Vicki Krause, Director: Centre for Disease Control Northern Territory, Department of Health, Northern Territory

Corresponding author: Dr Daniel Judge, Cairns Hospital, PO Box 902, CAIRNS QLD 4870. Telephone: +61 7 4226 0000. Email: daniel.judge@health.qld.gov.au

References

1. World Health Organization, Global Tuberculosis Report 2013. Geneva: WHO, 2013.
2. World Health Organization, Multi-Drug Resistant Tuberculosis (MDR-TB) October 2013 Update. Geneva: WHO, 2013.
3. Lavender CJ, Brown LK., Johnson PD. Multidrug-resistant tuberculosis in Victoria: a 10-year review. *Med J Aust* 2009191(6):315–318.
4. Francis JR, Blyth CC, Colby S, Fagan JM, Waring J. Multidrug-resistant tuberculosis in Western Australia, 1998–2012. *Med J Aust* 2014;200(6):328–332.
5. Simpson G, Coulter C, Weston J, Knight T, Carter R, Vincent S, et al. Resistance patterns of multidrug-resistant tuberculosis in Western Province, Papua New Guinea. *Int J Tuberc Lung Dis* 2011;15(4):551–552.
6. Lumb R, Bastian I, Carter R, Jelfs P, Keehner T, Sievers A. Tuberculosis in Australia: Bacteriologically confirmed cases and drug resistance, 2010. *Commun Dis Intell* 2013;37(1):E40–E46.
7. Toms C, Stapledon R, Waring J, Douglas P. Tuberculosis notifications in Australia, 2012 and 2013. *Commun Dis Intell* 2015;39(2):E217–E235.
8. White VL, Moore-Gillon J. Resource implications of patients with multidrug resistant tuberculosis. *Thorax* 2000;55(11):962–963.
9. Laserson KF, Thorpe LE, Leimane V, Weyer K, Mitnick CD, Riekstina V, et al. Speaking the same language: treatment outcome definitions for multidrug-resistant tuberculosis. *Int J Tuberc Lung Dis* 2005;9(6):640–645.
10. Toungoussova OS, Sandven P, Mariandyshev AO, Nizovtseva NI, Bjune G, Caugant DA. Spread of drug-resistant *Mycobacterium tuberculosis* strains of the Beijing genotype in the Archangel Oblast, Russia. *J Clin Microbiol* 2002;40(6):1930–1937.
11. World Health Organization. Guidelines for the Programmatic Management of Drug-resistant Tuberculosis. Geneva: WHO, 2014.
12. Parsons LM, Somosovski A, Urbanczik R, Salfinger M. Laboratory diagnostic aspects of drug resistant tuberculosis. *Front Biosci* 2004;9:2086–2105.
13. Hopewell PC, Pai M, Maher D, Uplekar M, Raviglione MC. International standards for tuberculosis care. *Lancet infect Dis* 2006;6(11):710–725.