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Drug resistance among tuberculosis patients attending diagnostic and treatment centres in Makassar, Indonesia

M. N. Massi,*† S. Wahyuni,*† H. Halik,* Anita,* I. Yusuf,† F. J. Leong,‡ T. Dick,‡ S. Phyu‡

*Novartis Institute for Tropical Diseases–Eijkman Institute–Hasanuddin University Clinical Research Initiative (NEHCRI), Kemerdekaan, South Sulawesi, Makassar, †Medical Faculty, Hasanuddin University, South Sulawesi, Makassar, Indonesia; ‡Novartis Institute for Tropical Diseases, Singapore, Singapore

SUMMARY

SETTING: Government tuberculosis (TB) diagnostic and treatment centres, Makassar, Indonesia.

OBJECTIVE: To determine the proportions and patterns of resistance to commonly used TB drugs (isoniazid [INH], rifampicin, ethambutol and streptomycin) among pulmonary TB patients and assess potential risk factors for drug resistance.

DESIGN: Cross-sectional study.

RESULTS: Of 657 recruited patients, 234 were culture-positive. Drug susceptibility testing (DST) results were available for 216 patients. Among these, 197 were infected with *Mycobacterium tuberculosis* complex (145 new and 52 previously treated). Isolates from 89 new (61.4%) and 31 previously treated (59.6%) patients were susceptible to all four drugs. Resistance to INH was high among both patient groups (28.3% of new vs. 34.6% of previously treated). Multidrug-resistant TB (MDR-TB) cases accounted for respectively 4.1% and 19.2% of these patients. Resistance to >2 drugs was high among previously treated patients (19.2%). MDR-TB cases were more likely to have a history of excess alcohol use (adjusted OR 4.01, 95%CI 1.28–12.53) and previous TB treatment (adjusted OR 6.28, 95%CI 2.01–19.64).

CONCLUSIONS: Regardless of previous treatment history, many culture-positive TB patients were infected with INH-resistant isolates, and a significant proportion of previously treated patients were infected with MDR-TB. Treating culture-positive TB patients, especially previously treated patients, based on DST results should therefore be considered.

KEY WORDS: tuberculosis; drug-resistant TB; MDR-TB; Makassar; Indonesia

INDONESIA ranks third in the world in terms of tuberculosis (TB) morbidity,[1] and TB is third on the list of major causes of mortality.[1] Rates of all notified TB and new smear-positive TB in 2007 were reported to be respectively 119 and 69 cases per 100 000 population, while in 2006 the case detection rate for new smear-positive TB was 73% and the treatment success rate was 91%.[2] The DOTS strategy, adopted in Indonesia in 1993, currently covers all provinces.[2] Under the Indonesian National TB Programme (NTP), new cases are treated with daily isoniazid (H, INH), rifampicin (R, RMP), pyrazinamide (Z, PZA) and ethambutol (E, EMB) during the 2-month intensive phase, followed by INH and RMP 3 days per week during the 4-month continuation phase (2HRZE/4H_3R_3). Previously treated patients are treated with daily HRZE for the first 3 months, supplemented by daily streptomycin (S, SM) injections during the first 2 months; HRE is then given for 3 days per week for a further 5 more months (2HRZE(S)/ 1HRZE/5$H_3R_3E_3$).[3]

Makassar, the capital of the South Sulawesi Province in Indonesia, has a population of ~1.5 million. The DOTS strategy was introduced in Makassar in 2006, and according to the Health Department Office of South Sulawesi Province, 1962 TB patients were treated under DOTS in 2008. Of these, 1396 were smear-positive. The notification rate for smear-positive cases is ~93 cases/100 000. However, the extent and pattern of drug-resistant TB in Makassar is largely unknown.

The aim of the present study was to determine the proportions and patterns of resistance to commonly used anti-tuberculosis drugs among *Mycobacterium tuberculosis* complex isolates from patients attending government urban TB diagnostic and treatment centres in Makassar. Potential risk factors for drug-resistant TB were also assessed.

MNM and SW contributed equally to this study.

Correspondence to: Muh Nasrum Massi, Novartis–Eijkman Institute, Hasanuddin University Clinical Research Initiative (NEHCRI), JL P Kemerdekaan km 11, South Sulawesi, Makassar 90245, Indonesia. Tel: (+62) 411 580687. Fax: (+62) 411 582389. e-mail: nasrum.massi@novartis.com

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STUDY POPULATION AND METHODS

Setting and study population

This cross-sectional study was approved by the Faculty of Medicine Ethics Committee, Hasanuddin University, Makassar. The target population was suspect pulmonary TB patients aged >17 years residing in Makassar for at least 1 year. Clinics included in the study were government-owned TB diagnostic and treatment centres in Makassar: the Balai Besar Kesehatan Paru Masyarakat (BBKPM) Lung Clinic, outpatient clinics of three general hospitals (Wahidin, Labuang Baji and Pelamonia) and six urban community health centres (Batua, Cendrawasih, Kassi Kassi, Jongaya, Jumpandang Baru and Tabaringan). Wahidin Hospital is a referral hospital and BBKPM is a specialist lung clinic. Data and sample collections were obtained from the study population five times a week for 1 month per clinic between February and October 2008.

Epidemiology data and laboratory sample collections

Physicians/nurses at the diagnostic and treatment centres referred suspect pulmonary TB patients to the study coordinators (trained physicians and a trained nurse), who interviewed the patients. The 657 patients who gave written consent were interviewed using structured questionnaires with some open-ended questions. The information collected included socio-economic and demographic characteristics, current and previous history of TB treatment, history of TB contacts, chest X-ray findings and clinical symptoms. TB treatment history was ascertained through history taking and treatment records.

New TB patients were defined as patients who had never been treated for TB or who had taken anti-tuberculosis drugs for <1 month.[2] Previously treated TB patients were defined as patients who had previously received at least 1 month of anti-tuberculosis drugs.[2] Previously treated patients were divided into four categories:[4] relapse (previously declared cured or treatment completed but diagnosed with culture-positive TB again in this study), failure (patients who failed to respond to previous anti-tuberculosis treatment at the 5th month of treatment or later despite taking anti-tuberculosis drugs regularly), default (patients whose previous anti-tuberculosis treatment was interrupted for at least 2 months) and other (patients who did not fit into the above categories and who did not know if they had completed a previous course treatment or who did not know the outcome).

Collected sputum samples were transported to the Novartis Institute for Tropical Diseases–Eijkman Institute–Hasanuddin University Clinical Research Initiative (NEHCRI) Laboratory in Makassar following standard laboratory operation procedures in line with World Health Organization (WHO) guidelines for transporting biological specimens.[5]

Laboratory methods

Two smear-positive sputum samples from each patient were decontaminated using the standard *N*-acetyl-L-cysteine-sodium hydroxide method.[6] The decontaminated sample was smeared on a glass slide and Ziehl-Neelsen staining was performed for the identification of acid-fast bacilli (AFB). Part of the decontaminated sample was inoculated into a Löwenstein-Jensen medium tube and a Mycobacteria Growth Indicator Tube (MGIT, BD, Sparks, MD, USA), as described previously.[7] Sputum smear-positive slides were graded according to the definitions of the WHO/International Union Against Tuberculosis and Lung Disease.[8]

MGIT drug susceptibility testing (DST) and the AccuProbe *M. tuberculosis* complex culture identification test (Gen-Probe Inc, San Diego, CA, USA) were used for all culture-positive isolates. Growth isolates were tested for resistance against INH, RMP, SM and EMB using the standard MGIT DST manual system, as recommended by the manufacturer (BD, USA). The following critical concentrations of anti-tuberculosis drugs were used: INH 0.1 μg/ml, RMP 1 μg/ml, SM 0.8 μg/ml and ETH 3.5 μg/ml. Culture from each positive MGIT tube was inoculated onto a nutrient agar plate to rule out contamination. If isolates were multidrug-resistant (MDR-TB, defined as resistance to at least INH and RMP) or resistant to three or four anti-tuberculosis drugs, MGIT DST was repeated to verify the resistance. There were no discrepant results between the tests.

Confirmed RMP, INH and SM-resistant isolates and the susceptible laboratory strain, H37Rv (American Type Culture Collection 27294), were tested every week using MGIT to assess the performance of DST in the laboratory. The NEHCRI laboratory participates in a quarterly smear microscopy external quality assurance (EQA) programme overseen by the TB laboratory network of the Indonesian NTP. It also participates in the annual EQA programme, which includes verification of the DST panel testing results, and on-site evaluation of laboratory biosafety and staff performance by the supranational laboratory (Institute of Medical and Veterinary Science [IMVS], Adelaide, SA, Australia). The NEHCRI laboratory has passed the DST EQA testing every year.

Statistical analysis

The χ^2 test or Fisher's exact test was used to compare the DST results between new and previously treated patients. The association of potential risk factors with anti-tuberculosis drug resistance was evaluated by χ^2 or Fisher's exact test. Crude odds ratios (ORs) with 95% confidence intervals (95%CIs) were calculated to estimate the magnitude of the association between variables and MDR-TB patients. Variables that showed association with MDR-TB patients (defined as $P < 0.1$ using χ^2 or Fisher's exact test) were included in a logistic regression model, and results were reported in

Table 1 Characteristics of culture-confirmed TB patients

Patient	New patients (n = 145) n (%)	Previously treated patients (n = 52) n (%)
Smear-positive	106 (73)	33 (64)
Age, years, median [range]	40 [19–85]	37 [18–72]
Male	89 (61)	31 (60)
Type of patient		
Relapse	—	31 (60)
Failure	—	2 (4)
Default	—	9 (17)
Other*	—	10 (19)

* Patients who did not fit into the above mentioned three categories and who did not know if they had completed previous treatment or their treatment outcome.

adjusted OR (95%CI). Results were considered statistically significant if $P < 0.05$. All statistical analyses were performed using SPSS version 17.0 (Statistical Package for Social Sciences, Chicago, IL, USA).

RESULTS

TB suspects

Of the 657 TB suspects, samples from 234 (35.6%) were culture-positive, 412 (62.7%) were culture-negative and 11 (1.7%) were contaminated. Of the 234 culture-positive isolates, 18 were not available for DST or the AccuProbe *M. tuberculosis* complex culture identification test (Gen-Probe) due to contamination or insufficient growth. Of the remaining 216 culture-positive isolates, 197 (91.2%) were identified as *M. tuberculosis* complex and 19 (8.8%) were defined as non-tuberculous mycobacteria (NTM).

Patients with culture-confirmed M. tuberculosis *complex*

Among the 197 patients with *M. tuberculosis* complex, 74% were from the BBKPM lung clinic, 15% from hospitals and 11% from community health centres. Table 1 shows the smear microscopy results and demographic data of new and previously treated patients. Only 73% of new patients and 64% of previously treated patients were smear-positive. Male patients were predominant.

Drug resistance patterns of M. tuberculosis *complex isolates*

Table 2 shows the prevalence of drug resistance among TB patients. The proportion of MDR-TB isolates among the new and previously treated cases was respectively 4.1% and 19.2%, ($P < 0.01$). Previously

Table 2 Drug susceptibility patterns of *M. tuberculosis* isolates from tuberculosis patients

Susceptibility pattern	Total patients (N = 197) n (%)	New patients (n = 145) n (%)	Previously treated patients (n = 52) n (%)	P value*
Fully susceptible	120 (60.9)	89 (61.4)	31 (59.6)	0.82
Resistance to any anti-tuberculosis drug	77 (39.1)	56 (38.6)	21 (40.4)	0.82
Any SM	34 (17.3)	22 (15.2)	12 (23.1)	0.28
Any RMP	17 (8.6)	7 (4.8)	10 (19.2)	0.01
Any INH	59 (29.9)	41 (28.3)	18 (34.6)	0.51
Any EMB	37 (18.8)	24 (16.6)	13 (25.0)	0.27
Resistance to one anti-tuberculosis drug	39 (19.8)	33 (22.8)	6 (11.5)	
SM	8 (4.1)	7 (4.8)	1 (1.9)	
INH	23 (11.7)	20 (13.8)	3 (5.8)	
RMP	0	0	0	
EMB	8 (4.1)	6 (4.1)	2 (3.8)	
Resistance to any two anti-tuberculosis drugs	17 (8.6)	12 (8.3)	5 (9.6)	
INH+RMP	2 (1.0)	0	2 (3.8)	
SM+INH	7 (3.6)	5 (3.4)	2 (3.8)	
SM+EMB	1 (0.5)	1 (0.7)	0	
INH+EMB	6 (3.0)	5 (3.4)	1 (1.9)	
RMP+EMB	1 (0.5)	1 (0.7)	0	
Resistance to any three anti-tuberculosis drugs	10 (5.1)	7 (4.8)	3 (5.8)	
SM+INH+EMB	7 (3.6)	5 (3.4)	2 (3.8)	
INH+RMP+EMB	3 (1.5)	2 (1.4)	1 (1.9)	
Resistance to four anti-tuberculosis drugs	11 (5.6)	4 (2.8)	7 (13.5)	0.01
MDR-TB	16 (8.1)	6 (4.1)	10 (19.2)	<0.01
Resistance to >2 anti-tuberculosis drugs	21 (10.7)	11 (7.6)	10 (19.2)	0.04

* New vs. previously treated patients.
SM = streptomycin; RMP = rifampicin; INH = isoniazid; EMB = ethambutol; MDR-TB = multidrug-resistant tuberculosis.

Table 3 Drug susceptibility patterns of *M. tuberculosis* isolates in different groups of previously treated tuberculosis patients

Susceptibility pattern	Total patients (*n* = 52) *n* (%)	Relapse patients (*n* = 31) *n* (%)	Failure (*n* = 2) *n* (%)	Defaulters (*n* = 9) *n* (%)	Other (*n* = 10) *n* (%)
Fully susceptible	31 (59.6)	18 (58.1)	1 (50.0)	7 (77.8)	5 (50.0)
Resistance to any anti-tuberculosis drug	21 (40.4)	13 (41.9)	1 (50.0)	2 (22.2)	5 (50.0)
Any SM	12 (23.1)	10 (32.3)	1 (50.0)	0	1 (10.0)
Any RMP	10 (19.2)	7 (22.6)	0	1 (11.1)	2 (20.0)
Any INH	18 (34.6)	12 (38.7)	1 (50.0)	1 (11.1)	4 (40.0)
Any EMB	13 (25.0)	7 (22.6)	1 (50.0)	2 (22.2)	3 (30.0)
Resistance to one anti-tuberculosis drug	6 (11.5)	3 (9.7)	0	1 (11.1)	2 (20.0)
SM	1 (1.9)	1 (3.2)	0	0	0
INH	3 (5.8)	2 (6.5)	0	0	1 (10.0)
EMB	2 (3.8)	0	0	1 (11.1)	1 (10.0)
Resistance to any two anti-tuberculosis drugs	5 (9.6)	3 (9.7)	0	0	2 (20.0)
INH+RMP	2 (3.8)	1 (3.2)	0	0	1 (10.0)
SM+INH	2 (3.8)	2 (6.4)	0	0	0
INH+EMB	1 (1.9)	0	0	0	1 (10.0)
Resistance to any three anti-tuberculosis drugs	3 (5.8)	1 (3.2)	1 (50.0)	1 (11.1)	0
SM+INH+EMB	2 (3.8)	1 (3.2)	1 (50.0)	0	0
INH+RMP+EMB	1 (1.9)	0	0	1 (11.1)	0
Resistance to four anti-tuberculosis drugs	7 (13.5)	6 (19.3)	0	0	1 (10.0)
MDR-TB	10 (19.2)	7 (22.6)	0	1 (11.1)	2 (20.0)
Resistance to >2 anti-tuberculosis drugs	10 (19.2)	7 (22.6)	1 (50.0)	1 (11.1)	1 (10.0)

SM = streptomycin; RMP = rifampicin; INH = isoniazid; EMB = ethambutol; MDR-TB = multidrug-resistant tuberculosis.

treated patients were more likely than new patients to be resistant to all four drugs (13.5% vs. 2.8%, $P = 0.01$). A similar finding was observed for patients resistant to >2 anti-tuberculosis drugs (7.6% of new vs. 19.2% of previously treated patients, $P = 0.04$).

Table 3 shows the prevalence of drug resistance in the different groups of previously treated TB patients. Twelve of 31 relapsed patients (39%), four of 10 patients who did not know their previous treatment outcome (40%) and one of nine defaulters (11%) were INH-resistant. Among the relapsed patients, 13 (41.9%) were resistant to any one of the anti-tuberculosis drugs and seven (22.6%) had MDR-TB.

Association of different patient variables with susceptible or resistant isolates

Table 4 shows the associations of different variables (socio-demographic, economic, medical and treatment history and clinical symptoms/signs) with different groups of patients with susceptible or resistant *M. tuberculosis*. Excess alcohol use was the only statistically significant socio-demographic variable over-represented among MDR-TB patients ($P = 0.04$), while more than one previous course of TB treatment was over-represented among MDR-TB patients ($P < 0.0005$). Patients presenting with haemoptysis were over-represented among both resistant non-MDR and MDR patient groups ($P = 0.003$).

Table 5 shows the possible predictors of MDR-TB. The χ^2 test showed that the following variables might be associated with MDR-TB: history of excess alcohol use, contact with TB patients or patients with chronic cough, previous TB treatment and haemoptysis. A logistic regression analysis that included these four variables confirmed that excess alcohol abuse and previous TB treatment were statistically associated with MDR-TB (respectively OR 4.01, 95%CI 1.28–12.53, $P = 0.02$ and OR 6.28, 95%CI 2.01–19.64, $P = 0.002$).

DISCUSSION

This is the first survey on anti-tuberculosis drug resistance conducted in government TB diagnostic and treatment centres in Makassar City, Indonesia. Similarly to other studies,[9,10] the proportion of MDR-TB among previously treated TB patients (19.2%) was significantly higher than among new TB patients (4.1%; Table 2). Similar findings were also observed for resistance to all four anti-tuberculosis drugs (13.5% of previously treated vs. 2.8% of new patients) and resistance to >2 anti-tuberculosis drugs (19.2% of previously treated vs. 7.6% new patients). Although other drug resistance was higher in previously treated patients than new patients, a significant difference was found only for RMP resistance (Table 2).

The frequency of MDR-TB among new patients observed in our study is comparable to studies from

Table 4 Association of different variables with susceptible or resistant *M. tuberculosis*

Variable (*N* =197)	Susceptible (*n*= 120) *n* (%)	Non-MDR-TB (*n* = 61) *n* (%)	MDR-TB (*n* = 16) *n* (%)	*P* value
Socio-demographic and -economic				
Age, years				
≤40 (*n* = 112)	68 (60.7)	35 (31.3)	9 (8.0)	1.00
>40 (*n* = 85)	52 (61.2)	26 (30.6)	7 (8.2)	
Sex				
Male (*n* = 120)	72 (60.0)	36 (30.0)	12 (10.0)	0.48
Female (*n* = 77)	48 (62.3)	25 (32.5)	4 (5.2)	
Years of education				
≤9 (*n* = 122)	71 (58.2)	43 (35.2)	8 (6.6)	0.20
>9 (*n* = 75)	49 (65.3)	18 (24.0)	8 (10.7)	
Excess alcohol use				
Yes (*n* = 67)	39 (58.2)	18 (26.9)	10 (14.9)	0.04
No (*n* = 130)	81 (62.3)	43 (33.1)	6 (4.6)	
Smoking				
Yes (*n* = 97)	57 (58.8)	31 (31.9)	9 (9.3)	0.77
No (*n* = 100)	63 (63.0)	30 (30.0)	7 (7.0)	
Unemployed or dependent				
Yes (*n* = 101)	56 (55.4)	39 (38.6)	6 (5.9)	0.05
No (*n* = 96)	64 (66.7)	22 (22.9)	10 (10.4)	
Medical and treatment history				
Diabetes mellitus				
Yes (*n* = 33)	19 (57.6)	11 (33.3)	3 (9.1)	0.85
No (*n* = 164)	101 (61.6)	50 (30.5)	13 (7.9)	
Contact with TB patient or patient with chronic cough				
Yes (*n* = 73)	44 (60.3)	20 (27.4)	9 (12.3)	0.22
No (*n* = 124)	76 (61.3)	41 (33.1)	7 (5.6)	
Previous TB treatment				
>1 course (*n* = 17)	8 (47.1)	3 (17.6)	6 (35.3)	<0.0005
Once (*n* = 48)	28 (58.3)	16 (33.3)	4 (8.3)	
No (*n* = 132)	84 (63.6)	42 (31.8)	6 (4.5)	
Clinical symptom/sign				
Haemoptysis				
Yes (*n* = 86)	44 (51.2)	29 (33.7)	13 (15.1)	0.003
No (*n* = 111)	76 (68.5)	32 (28.8)	3 (2.7)	
Cavitary TB (*n* = 145)	(*n* = 97)	(*n* = 36)	(*n* = 12)	0.88
Yes (*n* = 126)	84 (66.7)	32 (25.4)	10 (7.9)	
No (*n* = 19)	13 (68.4)	4 (21.1)	2 (10.5)	

MDR-TB = multidrug-resistant TB; TB = tuberculosis.

Table 5 Factors associated with MDR-TB*

Variable	Crude OR OR (95%CI)	*P* value	Adjusted OR OR (95%CI)	*P* value
Socio-demographic and -economic				
Age ≤40 years	0.97 (0.35–2.73)	0.96		
Male sex	2.03 (0.63–6.53)	0.23		
Education ≤9 years	0.59 (0.21–1.64)	0.31		
Excess alcohol use	3.63 (1.26–10.46)	0.01	4.01 (1.28–12.53)	0.02
Smoking habit	1.36 (0.48–3.80)	0.56		
Unemployed or dependent	0.54 (0.19–1.56)	0.26		
Medical and anti-tuberculosis treatment history				
Associated with diabetes mellitus	1.16 (0.31–4.33)	0.82		
Contact with TB patient or patient with chronic cough	2.35 (0.84–6.61)	0.09	2.58 (0.84–8.01)	0.10
Previous TB treatment	5.52 (1.89–16.07)	0.001	6.28 (2.01–19.64)	0.002
Clinical symptom/sign				
Haemoptysis	3.02 (1.07–8.52)	0.03	2.96 (0.96–9.21)	0.06

*MDR-TB (*n* = 16) vs. susceptible and resistant non-MDR patients (*n* = 181).
MDR-TB = multidrug-resistant TB; OR = odds ratio; CI = confidence interval; TB = tuberculosis.

large cities in other South-East Asian countries, such as Myanmar (4.5%) and Thailand (4.2%).[9,10] However, the frequency of MDR-TB in Makassar was more than double that reported in Mimika District, Papua Province, Indonesia,[11] and in urban settings in Viet Nam and the Philippines.[12–14] The discrepancies between the studies could be due to diverse study populations. Our study population consisted predominantly of patients attending a specialist lung clinic, whereas study populations in the other reports were attending primary health centres.[10] Specialist lung clinics generally receive patients with severe forms of pulmonary TB, an assumption supported by the significant number of TB patients presenting with haemoptysis (86/197, 44%) and lung cavities (126/145, 87%; Table 4).

Of the 145 new TB patients in our study, 28.3% were INH-resistant (Table 2) compared to only 10.3% (range 6.9–13.7) in other countries in the WHO South-East Asia region.[10] Among previously treated TB patients, 39% of relapses, 11% of defaulters and 40% of patients who did not know their treatment outcome were INH-resistant (Table 3). This indicates that the high prevalence of INH resistance in the study population may have been due to poor treatment adherence and patient management, as reported elsewhere.[12] However, it could also be due to ongoing transmission of INH-resistant TB in Makassar, as described in other high TB burden countries.[15] This assumption is supported by the finding that 60% of previously treated patients were relapses (Table 1), which is usually associated with initial drug resistance.[16] Furthermore, more than 22% of relapses in our study had MDR-TB (Table 3). One could therefore assume that some relapsed patients could have been INH-resistant prior to the previous course of treatment. Further studies are warranted to explore the cause of the high prevalence of INH resistance in Makassar.

Among the previously treated patients in our study, MDR-TB was more frequent in relapse cases than in other patient groups (Table 3). In studies from Viet Nam[17] and Ethiopia,[18] MDR-TB was more common among failures than relapses, while in the recent national anti-tuberculosis drug resistance study in Tanzania, the prevalence of MDR-TB did not differ in relapse vs. failure patients.[19] The diverse proportions of MDR-TB among relapsed vs. failure patients could simply reflect imprecision in categorising the treatment outcome, perhaps due to the use of less sensitive laboratory diagnostic methods[20] for determining treatment outcome. In our study (Table 1) and the study from Ethiopia,[18] the proportion of patients who failed on previous treatment was lower than relapses. Similar to other developing countries, smear microscopy is used for categorising treatment outcome in both countries. Many previously treated TB patients in both studies were assumed to be cured at the end of their previous treatment, although they might still have been harbouring bacilli. When these cured patients were again diagnosed with TB, they were categorised as relapses. It would be interesting to explore whether using culture instead of smear microscopy influenced the categorisation of treatment outcome among TB patients in developing countries.

Some studies have reported that standard TB treatment is not very effective in populations with a high prevalence of INH resistance[21,22] and in patients resistant to more than two anti-tuberculosis drugs.[23] In our study, a significant proportion of both new and previously treated patients were INH-resistant (Table 2). Furthermore, a significant proportion of previously treated patients were resistant to >2 anti-tuberculosis drugs (Table 2). The Indonesian NTP could therefore consider implementing routine DST, especially for culture-positive previously treated patients, and basing the retreatment regimen on the DST results. Standardised DOTS-Plus regimens for managing MDR-TB patients and curbing the prevalence of drug-resistant TB may also be considered. In Peru, treatment outcomes improved dramatically after implementing similar practices for managing chronic TB patients, among whom >80% were MDR-TB patients.[24]

Table 4 shows that patients presenting with excess alcohol use, history of more than one course of TB treatment and haemoptysis were over-represented among MDR-TB patients. As excess alcohol use has been associated with treatment default and poor treatment outcome among TB patients,[25,26] it is not surprising to find that MDR-TB patients were more likely to have a history of excess alcohol use (OR 4.01, 95%CI 1.28–12.53; Table 5). Similar to other studies,[8,9] MDR-TB patients in our study were more likely to have had previous treatment (OR 6.28, 95%CI 2.01–19.64). Although haemoptysis could possibly be associated with MDR-TB (OR 3.02, 95%CI 1.07–8.52, $P = 0.03$), this was not statistically significant after adjusting for possible confounders (OR 2.96, 95%CI 0.96–9.21, $P = 0.06$).

Our study revealed that 8.8% of positive cultures were NTM. This is the first report on the frequency of NTM patients in Indonesia. The proportion of NTM is relatively high compared to Tamil Nadu, India (3.9%), but is lower than reports from Kerala, India (18.5%).[27] In our study, NTM isolates were more likely to be resistant to both INH and RMP (OR 6.6, 95%CI 2.3–19.1) and >2 anti-tuberculosis drugs (OR 4.9, 95%CI 1.7–13.8) than non-NTM isolates (data not shown), as mentioned in the literature.[28]

As our study population consisted mainly of patients attending the government referral lung clinic, we cannot extrapolate the findings to TB patients attending community health centres, private clinics and hospitals in Makassar. Further studies need to be conducted to explore resistance patterns among patients attending those clinics. Using a rapid DST method

will be helpful in managing drug-resistant TB patients and controlling the spread of drug-resistant TB. A polymerase chain reaction-based hybridisation assay, GenoType® MTBDR*plus* (Hain Lifescience, Nehren, Germany) has been established in our laboratory to evaluate whether this could be an alternative to culture DST in this setting. Most importantly, treatment of culture-positive TB patients, and particularly previously treated patients, based on DST results should be considered, as a significant proportion of these patients are MDR, INH-resistant or resistant to >2 antituberculosis drugs.

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RÉSUMÉ

CONTEXTE : Les centres de diagnostic et de traitement de la tuberculose (TB) du gouvernement à Makassar, Indonésie.

OBJECTIF : Déterminer la proportion et les types de résistance aux médicaments habituellement utilisés pour la pharmacothérapie de la TB (isoniazide [INH], rifampicine, éthambutol et streptomycine) chez les patients atteints de TB pulmonaire et évaluer les facteurs de risque potentiels de résistance aux médicaments.

SCHÉMA : Etude transversale.

RÉSULTATS : La culture a été positive chez 234 des 657 patients recrutés. Les résultats de la détermination de la sensibilité aux médicaments (DST) ont été disponibles chez 216 patients. Parmi ceux-ci, 197 étaient infectés par le complexe *Mycobacterium tuberculosis* (145 nouveaux cas et 52 cas traités antérieurement). Les isolats provenant de 89 nouveaux cas (61,4%) et de 31 cas traités antérieurement (59,6%) ont été sensibles à l'ensemble des quatre médicaments. La résistance à l'INH a été élevée dans les deux groupes de patients (28,3% des nouveaux cas vs. 34,6% des cas traités antérieurement). Les cas multirésistants (TB-MDR) ont représenté respectivement 4,1% et 19,2% de ces patients. On a noté une fréquence élevée de résistance à plus de deux médicaments chez les patients traités antérieurement (19,2%). Dans les cas TB-MDR, les antécédents d'alcoolisme et de traitement antituberculeux antérieur ont été plus fréquents (respectivement OR ajusté 4,01 ; IC95% 1,28–12,53 et OR ajusté 6,28 ; IC95% 2,01–19,64).

CONCLUSIONS : Quels que soient les antécédents de traitement antérieur, beaucoup de patients TB à culture positive sont infectés par des isolats résistants à l'INH, et une proportion significative de patients traités antérieurement sont infectés par des germes multirésistants. Dès lors, il faudrait envisager de traiter les patients TB à culture positive en se basant sur les résultats de la DST, particulièrement ceux déjà traités antérieurement.

RESUMEN

MARCO DE REFERENCIA: Los centros gubernamentales de diagnóstico y tratamiento de la tuberculosis (TB) en Makassar, Indonesia.

OBJETIVO: Determinar la proporción y los tipos de resistencia a los medicamentos usados en el tratamiento corriente de la TB (isoniazida [INH], rifampicina, etambutol y estreptomicina) que presentan los pacientes tuberculosos y evaluar los posibles factores de riesgo de aparición de esta resistencia.

MÉTODOS: Fue este un estudio transversal.

RESULTADOS: De los 657 pacientes que participaron en el estudio, 234 presentaron cultivo positivo. Se contó con resultados de pruebas de sensibilidad (DST) a los antituberculosos en 216 pacientes. De estos, 197 estaban infectados por una cepa del complejo *Mycobacterium tuberculosis* (145 casos nuevos y 52 con antecedente de tratamiento). Los aislados clínicos de 89 casos nuevos (61,4%) y de 31 casos previamente tratados (59,6%) fueron sensibles a los cuatro medicamentos. La resistencia a INH fue alta en ambos grupos de pacientes (28,3% en los casos nuevos contra 34,6% en los tratados previamente). Se observó TB multidrogorresistente (TB-MDR) en 4,1% y 19,2% de estos pacientes, respectivamente. La resistencia a más de dos medicamentos fue alta en los pacientes con antecedente de tratamiento antituberculoso (19,2%). En los casos de TB-MDR se observó con mayor frecuencia el antecedente de abuso del alcohol (ORa 4,01; IC95% 1,28 a 12,53) y de tratamiento antituberculoso (ORa 6,28; IC95% 2,01 a 19,64).

CONCLUSIÓN: Independientemente del antecedente de tratamiento antituberculoso, muchos pacientes tuberculosos con cultivo positivo albergaban aislados resistentes a INH y una proporción considerable de los casos previamente tratados estaban infectados por cepas TB-MDR. Por esta razón, es necesario considerar la posibilidad de basar el tratamiento de los pacientes con TB y cultivo positivo en las DST a los medicamentos, sobre todo en quienes hayan recibido previamente tratamiento antituberculoso.

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