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Original Article

# Resistance to first- and second-line antituberculosis drugs in Southern Taiwan: Implications for empirical treatment

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## KEYWORDS

Multidrug resistant tuberculosis;  
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Empirical treatment;  
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**Abstract** *Background:* Multidrug-resistant and extensively drug-resistant tuberculosis infections cause public health concerns worldwide. Local epidemiologic data about the drug resistance of *Mycobacterium tuberculosis* isolate (Mtb) is critical to guide appropriate empirical therapy to cure patients and restrain the spread of tuberculosis.

*Methods:* Antituberculosis susceptibility testing was performed for 287 Mtbs, including 63 MDR-Mtbs collected in southern Taiwan from 2011 to 2015. Tuberculosis patients were classified into newly diagnosed cases and previously treated cases based on patients' medical history.

*Results:* Almost no resistance was found to the tested second-line antituberculosis drugs in non-MDR-Mtbs. Higher resistance rates to ethambutol, ofloxacin, and streptomycin were observed in MDR-Mtbs compared to non-MDR-Mtbs. Among 63 MDR-Mtbs, 61.9% of patients were newly diagnosed and 38.1% were previously treated cases. For MDR-Mtb, the drug-resistance rates in previously treated cases were significantly higher for ethambutol, pyrazinamide, ofloxacin, moxifloxacin, streptomycin, and *p*-aminosalicylic acid. When MDR-Mtbs are identified in previously treated cases, empirical administration of ethambutol, pyrazinamide, ofloxacin, or moxifloxacin may not provide effective treatment. The resistance rates to these drugs were all more than 50%. Furthermore, 25% of MDR-Mtbs from previously treated patients were resistant to *p*-aminosalicylic acid.

*Conclusion:* We observed almost no resistance to the tested second-line antituberculosis drugs among non-MDR-Mtbs. Anti-tuberculosis regimen with pyrazinamide, ethambutol, fluoroquinolone, kanamycin, cycloserine and *p*-aminosalicylic acid can be empirically used for newly

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diagnosed MDR-TB cases. For previously treated MDR-TB patients, empirical ethambutol, pyrazinamide, ofloxacin, or moxifloxacin may not provide effective treatment because the resistance rates to these drugs were all >50%.

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## Introduction

The emergence of drug-resistant *Mycobacterium tuberculosis* (Mtb), particularly multidrug-resistant *M. tuberculosis* (MDR-Mtb) that is resistant to at least isoniazid (INH) and rifampin (RIF), has caused concerns about treating tuberculosis patients and halting the spread of tuberculosis in the community.<sup>1–6</sup> The World Health Organization (WHO) estimated that there are 9.6 million new tuberculosis (TB) cases and 480,000 new cases of multidrug-resistant tuberculosis worldwide in 2015. Most cases occurred in Asia and Africa.<sup>7</sup> There were an estimated 1.4 million TB deaths in 2015.<sup>8</sup> Globally, in 2014, 3.3% of new TB cases and 20% of previously treated cases had MDR-Mtbs infections.<sup>8</sup> In Taiwan, there were 1% of new TB cases and 6% of previously treated TB cases infected with MDR-Mtbs in 2015.<sup>9,10</sup> Unfortunately, only 17% of MDR-TB patients received appropriate antituberculosis treatment because of insufficient drug susceptibility testing, the cost of treatment, and the unavailability of antituberculosis drugs.<sup>11,12</sup> Only 48% of treated MDR-TB patients achieved a successful treatment outcome.<sup>13</sup> Furthermore, in 2006 the WHO defined extensively drug-resistant tuberculosis (XDR-Mtb) as a more dangerous strain of *M. tuberculosis* that is resistant to isoniazid, rifampin, and at least one second-line injectable drug (amikacin, kanamycin, or capreomycin) and one fluoroquinolone.<sup>14,15</sup> XDR-TB has now been reported in 105 countries worldwide, and, on average, 9.7% of patients with MDR-TB also present with XDR-TB.<sup>13</sup> The treatment for XDR-TB is more complicated and requires the availability of second-line antituberculosis drugs and the related antimicrobial susceptibility testing.<sup>16</sup>

In Taiwan, the current disease burden of tuberculosis infections totals 11,326 tuberculosis cases (48.4 cases per 100,000 population), and 591 tuberculosis-related deaths (2.54 cases per 100,000 population) occurred in 2015.<sup>9,17</sup> The tuberculosis incidence rate in Taiwan is decreasing when compared to the rate in 2011.<sup>18</sup> Among newly diagnosed tuberculosis cases, the rates of MDR-Mtbs are 0.9% in 2011 and 1.1% in 2012.<sup>19–21</sup>

Empirical treatment for tuberculosis is commonly practiced before resistance-testing results are available. The advantages of treatment after the results are known include reduced morbidity, mortality, and transmission.<sup>22</sup> Knowing the susceptibility patterns of local tuberculosis isolates to antituberculosis drugs is greatly useful for empirical treatment, especially for cases of MDR-TB and XDR-TB and those tuberculosis patients who are intolerant of or allergic to first-line antituberculosis drugs. In Taiwan, the susceptibility data regarding second-line antituberculosis drugs for isolates that are susceptible to both isoniazid

and rifampin are limited.<sup>23</sup> In this study, we aimed to determine resistance patterns to first- and second-line antituberculosis drugs for treating tuberculosis in southern Taiwan. Analysis of resistance patterns among newly diagnosed tuberculosis patients and previously treated MDR and XDR cases may provide guidance for better empirical therapy in southern Taiwan.

## Materials and methods

### *M. tuberculosis* isolates

The Mtb isolates in this study came from the following two collections. 1. A total of 237 isolates were consecutively collected from Kaohsiung Medical University Hospital, Municipal Hsiao-Kang Hospital, and Kaohsiung Municipal Ta-Tung Hospital in Kaohsiung City, Taiwan from March to October 2015. Only one isolate was collected from each individual. Thirteen samples (5.5%) were defined as MDR-Mtbs. 2. In order to assess a larger number of MDR-Mtbs in this study, we included data regarding 50 MDR-Mtbs collected from five hospitals in Pingtung County, Taiwan, in 2011–2015. These isolates were sent to the contracted tuberculosis laboratories of Taiwan's Centers for Disease Control for drug susceptibility testing. Both Kaohsiung City and Pingtung County are located in southern Taiwan. Overall, 287 isolates were evaluated, including 224 non-MDR-Mtbs and 63 MDR-Mtbs.

### Data collection

This project was approved by the Institutional Review Board of Kaohsiung Medical University (KMUH-IRB-20140243). Tuberculosis patients were classified into newly diagnosed and previously treated groups based on available medical documents and the patients' self-reports. The definitions of new and previously treated cases were based on the WHO guidelines.<sup>6</sup>

### Susceptibility testing

The anti-tuberculosis drug susceptibility testing was performed according to the methods reported from Clinical and Laboratory Standards Institute.<sup>24,25</sup> The agar proportion method is used for mycobacterial susceptibility testing. Mtb suspension was inoculated onto Middlebrook 7H10 agar that contained anti-Tb drugs; agar that did not contain any drug was also used for control. The concentrations of the antituberculosis drugs used for susceptibility testing were: 0.2 µg/mL for isoniazid, 1.0 µg/mL for

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