

Original Article

CLINICAL CHARACTERISTICS AND TIME TO SPUTUM CONVERSION OF
ISONIAZID MONO-RESISTANT PULMONARY TUBERCULOSIS

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Abstract [Purpose] There are no comparative studies of treatment outcome of drug susceptible and isoniazid (INH) mono-resistant tuberculosis in Japan. We retrospectively investigated the clinical characteristics and time to sputum conversion of INH mono-resistant tuberculosis.

[Methods] We reviewed the medical records of all patients with smear-positive tuberculosis admitted and treated in Kanagawa Cardiovascular and Respiratory Center between April 2010 and March 2015. Patients in whom negative culture conversion were confirmed were included. The study compared patient characteristics, imaging findings, laboratory results, and time to sputum culture conversion between 20 patients with INH mono-resistance and 523 patients susceptible for all drugs used.

[Results] INH mono-resistant patients were more likely to have a history of tuberculosis treatment, and tended to have more extended lesion. On the other hand, the sputum culture conversion time was not significantly different between two groups. Similarly, there was no significant difference between

low- and high-level of INH resistance in time to sputum culture and smear conversion.

[Conclusion] INH mono-resistance did not affect early treatment outcomes, and initial treatment of standard regimen had validity even in INH mono-resistant tuberculosis.

Key words: Pulmonary tuberculosis, Drug resistance, Initial treatment, Isoniazid, Negative conversion

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Original Article

EXTERNAL QUALITY ASSESSMENT OF PYRAZINAMIDE SUSCEPTIBILITY TESTING AGAINST *MYCOBACTERIUM TUBERCULOSIS*

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and ¹Akiko TAKAKI

Abstract [Objective] Pyrazinamide (PZA) is one of the major anti-tuberculosis drugs. The drug susceptibility testing (DST) method for PZA is unique and many false-resistant results are reported. To reveal the accuracy of DST for PZA in Japan, the external quality assessment (EQA) was implemented.

[Method] A total of 10 *Mycobacterium tuberculosis* strains of which the resistances are confirmed in the Supra-National Reference Laboratory Network of STOP TB partnership was used in this study. The major target of EQA in this study was PZA, but other six drugs, isoniazid (INH), rifampicin (RFP), streptomycin (SM), ethambutol (EB), kanamycin (KM) and levofloxacin (LVFX) could be included in the EQA. The participating facilities performed DST using their routine methods and the results were compared with the judicial diagnoses. The evaluation factors were sensitivity, specificity, efficiency and kappa coefficient.

[Results] A total of 97 facilities (70 hospitals, 21 private commercial laboratories, and 6 public health laboratories) participated in this study, and the overall results became 105 because 8 laboratories submitted multiple results. The average turn-around time (TAT) was 65.4 ± 20.7 (range: 21–109) days. A total of 60 facilities performed phenotypic PZA susceptibility testing, and resulted the sensitivity of 96.6% (95% CI: 87.4–99.4%) and specificity of 64.3% (95% CI: 50.8–76.0%). Forty-four facilities used Kyokuto PZA liquid medium (Kyokuto PZA; Kyokuto Pharmaceuticals) and 16 used MGIT series PZA (MGIT AST PZA; Becton Dickinson). The specificities of Kyokuto PZA and MGIT AST PZA were

69.5% (95% CI: 53.6–82.0%) and 48.8% (95% CI: 24.5–73.5%), respectively. There was a significant difference in specificity between two kits ($p=0.0043$).

[Discussion] The specificity of current PZA DST kits was quite low. There already exist several reports that are showing the low specificity of MGIT AST PZA, the Kyokuto PZA test also showed less than 70% of specificity. Due to the relatively short TAT of liquid PZA DST, it will be happening that the doctor stops PZA in the standard regimen according to the wrong DST result. PZA also contributes deeply for the treatment of drug resistant tuberculosis, then the accuracy of DST results are surely important. It will be recommended to conduct appropriate training of DST for PZA, to revise the standard operational procedure, and to use alternative DST like line probe assay or pyrazinamidase testing to improve the performance of PZA DST.

Key words: *Mycobacterium tuberculosis*, Pyrazinamide, Drug susceptibility testing, External quality assessment

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USEFULNESS AND LIMITATION OF OUTPATIENT DEPARTMENT MANAGEMENT OF SPUTUM SMEAR NEGATIVE MDR-TB IN JAPAN

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Abstract [Objective] Treatment is basically done on outpatient department (OPD) basis for sputum smear negative tuberculosis cases. We evaluated the treatment result of MDR-TB cases with emphasis on the admission or OPD treatment.

[Method] Retrospective review of medical record of MDR-TB cases that were treated at Fukujuji Hospital from January 1990 to November 2016.

[Result] Among 46 cases, four cases defaulted including two cases that were culture positive at the time of default, twenty five cases completed medical treatment including surgical treatment for four cases, four cases were without treatment, eight cases were transfer out and two of them were culture positive at the time of transfer, no dead case and five cases were without information of treatment results. Multivariate analysis showed the risk factors of default with OPD cases, foreign born cases, cases that were treated in earlier years, cases that were treated with less drugs, and cavitary cases.

[Discussion] OPD management of MDR-TB was safe but the risk of default was higher, especially among foreign born cases with less social contact with Japanese society. Considering the higher proportion of cases with loss to follow up, some sputum smear negative cases will need to be admitted for directly observed treatment.

Key words: Multi drug resistant tuberculosis (MDR-TB), Outpatient clinic management (OPD management), Default, Sputum smear negative

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Short Report

EFFECTIVENESS OF SECOND QFT-3G FOR CONTACTS
6 MONTHS AFTER THE LAST CONTACT WITH INDEX CASES
IN THE HIGH-INFECTION-RATE POPULATIONS

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Abstract [Purpose] In populations with first QFT-3G (QFT)-positive rate of $\geq 50\%$ 2 to 3 months after the last contact with index cases (high-infection-rate populations), we conducted second QFT after 6 months, and analyzed/evaluated the results to improve future contact investigations.

[Methods] Among contacts belonging to the high-infection-rate populations on a contact investigation between 2014 and 2015, the subjects were those for whom second QFT was conducted 6 months after the last contact with index cases with first QFT-negative or QFT-equivocal reactions.

[Results] (1) First QFT (2 to 3 months after the last contact with index cases): The number of groups for contacts was 13. First QFT was performed for 108 contacts after 2 to 3 months. The QFT-positive rate was 59.3% (50.0–66.7%). (2) Second QFT (6 months after the last contact with index cases): After 6 months, second QFT was conducted for 27 contacts with QFT-negative reactions and 2 contacts with QFT-equivocal reactions on the first QFT. In 1 contact for whom evaluation was QFT-equivocal on the first QFT, evaluation was also QFT-equivocal, whereas the others showed QFT-negative reactions.

[Conclusion] There was no QFT-positive patient after 6 months among those with QFT-negative reactions after 2 to 3 months in the high-infection-rate populations. In the present situation that the sensitivity of QFT in the diagnosis of tuberculosis infection and the timing of positive conversion have not been sufficiently clarified, contacts of these groups should undergo not only the reexamination of QFT but also chest X-ray examinations and consult a hospital in the presence of symptoms for the early detection of tuberculosis.

Key words: Tuberculosis, Contact investigation, High-infection-rate populations, Second QFT-3G after 6 months, Tuberculosis epidemic

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————— Case Report —————

A CASE OF ADRENAL CRISIS INDUCED BY THE ADMINISTRATION
OF RIFAMPICIN FOR PULMONARY TUBERCULOSIS

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Abstract A 66-year-old woman was diagnosed as having pulmonary tuberculosis based on chest X-ray and TB positive bronchoalveolar lavage. Treatment with antituberculous drugs, including rifampicin (RFP), was started.

However, one week later these drugs were discontinued, because of anorexia, nausea, general lassitude and liver dysfunction. Restart of antituberculous treatment after recovery of symptoms and liver function, developed a state of shock with hypoglycemia. Computed tomography revealed swelling and calcification of the bilateral adrenal glands. In addition, skin pigmentations, the elevated serum level of ACTH and the decreased level of cortisol were also observed. Therefore, the patient was diagnosed as having adrenal insufficiency associated with adrenal crisis due to adrenal gland tuberculosis. The symptoms improved with cortisol supplementation.

RFP is known to induce CYP3A4 and enhance cortisol metabolism. In the current case, RFP administration might

decrease the serum level of cortisol through the induction of CYP3A4, causing adrenal crisis. When pulmonary tuberculosis is complicated by adrenal gland tuberculosis, RFP can cause adrenal crisis. So the caution should be paid when administering RFP to a patient with these conditions.

Key words: Pulmonary tuberculosis, Adrenal tuberculosis, Adrenal crisis, Rifampicin, CYP3A4

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