

## Original Article

## PULMONARY TUBERCULOSIS TREATMENT OUTCOME AMONG FOREIGN NATIONALS RESIDING IN OSAKA CITY

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**Abstract** [Purpose] In this study, we analyzed pulmonary tuberculosis treatment outcomes among foreign nationals of different backgrounds.

[Methods] The research was conducted between January 2006 and December 2011. One hundred fifty nine foreign nationals residing in Osaka city had pulmonary tuberculosis during this period. Patients were grouped according to treatment outcomes. We conducted three different types of comparisons. First, we compared backgrounds of patients with treatment success or default. Second, backgrounds of patients who continued treatment in Japan or who moved overseas (transfer out) were compared. Third, treatment outcomes of foreign nationals between 20 and 39 years of age were compared with those of age-matched Japanese patients registered between 2010 and 2011.

[Results] (1) The treatment outcomes were as follows: cured, 53 cases (33.3%); treatment completed, 55 cases (34.6%); treatment failure, 0 cases (0.0%); treatment default, 14 cases (8.8%); moved overseas, 17 cases (10.7%); moved to another location inside Japan, 13 cases (8.2%); died, 6 cases (3.8%); and under treatment, 1 case (0.6%). (2) Comparison of treatment success and default among foreign nationals with pulmonary tuberculosis revealed a default rate among smear-negative cases of 14.5%, significantly higher than in smear-positive cases (2.1%;  $P < 0.05$ ). (3) We compared backgrounds between foreign nationals with pulmonary tuberculosis who continued taking treatment in Japan and those who moved abroad (transfer out). The rate of overseas transfer out (44.4%) was higher among patients not covered by health insurance. This was significantly higher than among patients covered by public insurance or assistance (9.0%;  $P < 0.01$ ). (4) Comparison of foreign and Japanese nationals

between 20 and 39 years of age revealed a default rate in foreign nationals with pulmonary tuberculosis of 13.6%. This was significantly higher than that of Japanese patients (4.0%;  $P < 0.01$ ). The rate of transfer out among foreign nationals with pulmonary tuberculosis was 19.1%, also significantly higher than that of Japanese patients (5.3%;  $P < 0.001$ ).

[Discussion] The rates of treatment default and transfer out among patients between 20 to 39 years of age were significantly higher among foreign nationals than in Japanese patients. Lack of knowledge about treatment and language problems may contribute to this finding. This suggests that adequate support and definitive directly observed treatment short-course programs are needed for foreign nationals. Patients who moved abroad (overseas transfer out) may also be ultimately categorized as treatment default. However, it is difficult to determine final treatment outcomes of patients who moved abroad. Further measures are needed to ensure that foreign nationals continue to receive treatment when they transfer overseas.

**Key words:** Tuberculosis, Foreign nationals, Treatment outcomes, Default, Transfer out

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## Original Article

## RISK GROUPS FOR TUBERCULOSIS IN JAPAN: ANALYSIS OF RELATIVE RISK AND POPULATION ATTRIBUTABLE FRACTION

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**Abstract** [Objective] Despite the decreasing trend in tuberculosis (TB) cases reported within the general population, TB incidence remains high in certain high-risk groups in Japan. Many of the previous discussions and studies have concentrated mainly on the elderly and those with clinical risks; however, no comprehensive evaluation has been conducted to date. Our study thus sought to estimate the relative risk (RR) and the population attributable fraction (PAF) of selected risk groups in Japan and discuss their relevance to programming future research needs and policies.

[Method] PAF and RR were calculated for patients with human immunodeficiency virus infection, diabetes, rheumatoid arthritis, those on dialysis, the elderly, health care workers, the homeless, people receiving public assistance, foreigners, prisoners, smokers, and those with alcohol problems, and were grouped into “high PAF” (PAF  $\geq 5\%$ ), “middle PAF” (5%

> PAF  $\geq 1\%$ ), and “low PAF” (PAF  $< 1\%$ ) groups.

[Results] The elderly and patients with diabetes showed the highest PAF and RR and should thus be prioritized for policies.

**Key words:** Risk groups, Relative risk, Population attributable fraction, Health policy

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## DRUG-INDUCED LIVER INJURY AND PYRAZINAMIDE USE

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**Abstract** [Background] In the 1950s, high doses (40–70 mg/kg/day) of pyrazinamide were reported to cause drug-induced liver injury (DILI). It remains unclear whether adding pyrazinamide (Z) at the currently accepted low dose (20–25 mg/kg/day) to a regimen of isoniazid (H), rifampicin (R), and ethambutol (E) increases the risk of DILI.

[Method] We reviewed adult patients admitted for smear-positive tuberculosis who were treated with a daily HRE or HRZE regimen. A Cox model was used to analyze the impact of pyrazinamide on the occurrence of DILI.

[Results] We reviewed 195 patients (123 men [63%], 72 women [37%], average age  $65 \pm 19$  years, 65 HRE patients [33%], 130 HRZE patients [67%]). The incidence of DILI in the first two months was 15% (29/195). The HRZE regimen was not associated with DILI (hazard ratio 0.55,  $P=0.263$ ).

[Conclusion] Addition of low-dose (20–25 mg/kg/day)

pyrazinamide to the HRE regimen does not appear to be associated with increased DILI incidence during the first two months of treatment.

**Key words:** Elderly, Adverse reaction, Retrospective cohort study, Observational study, Guideline

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## Original Article

A STUDY OF SURGICAL TREATMENT FOR PATIENTS  
WITH *MYCOBACTERIUM ABSCESSUS* PULMONARY DISEASE AND  
A COMPARATIVE EXAMINATION OF  
*MYCOBACTERIUM AVIUM* COMPLEX DISEASE

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**Abstract** [Objective] This is a retrospective study on six surgical cases of *Mycobacterium abscessus* pulmonary disease, including a comparison with *M. avium* complex (MAC) disease.

[Subjects and Methods] We performed surgery for six cases of *M. abscessus* pulmonary disease between July 2012 and June 2014. In all the cases, video-assisted thoracic surgery alone was performed. Age, sex, bacillus identification method, disease type, preoperative anti-glycopeptidolipid core immunoglobulin A antibody value, preoperative chemotherapy, preoperative chemotherapy period, adaptation of the operation, surgical method, result of the bacillus culture of an organization that was extracted at operation, postoperative hospitalization period, surgical complications, and postoperative relapse were examined for the six cases of *M. abscessus* pulmonary disease. In addition, the cases were compared with 36 cases of MAC disease for which operation was performed during the same period.

[Result] None of the patients had major surgical complications or in-hospital death. Although three patients survived for more than 1 postoperative year and completed chemotherapy, relapses are not accepted in all cases at present. In the comparison with MAC disease, the mean preoperative chemotherapy period for *M. abscessus* pulmonary disease

was 5.5 months, which was 18.9 months shorter than that for MAC disease, with a statistically significant difference.

[Conclusion and Consideration] Surgery for *M. abscessus* pulmonary disease may be considered a safe and effective therapeutic procedure. Moreover, some physicians believe that surgical treatment is required at an earlier stage of *M. abscessus* pulmonary disease compared with MAC disease.

**Key words** : *Mycobacterium abscessus*, Nontuberculous mycobacteriosis (NTM), *Mycobacterium avium* complex (MAC), Surgical treatment

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## HISTOLOGICAL ANALYSIS OF BONE DESTRUCTION IN SPINAL TUBERCULOSIS

Kazutaka IZAWA

**Abstract** [Purpose] To investigate the mechanism of bone destruction in spinal tuberculosis (TB) by immunohistochemical analysis of the pathway that includes receptor activator of NF- $\kappa$ B (RANK), receptor activator of NF- $\kappa$ B ligand (RANKL), osteoprotegerin (OPG), and osteocalcin (OCN) in affected tissues.

[Materials and methods] TB bone specimens were obtained from 30 surgically treated spinal TB patients (13 males and 17 females; average age, 67 years). Normal bone specimens were also obtained from 30 osteoarthritis patients (12 males and 18 females; average age, 70 years) who had undergone knee arthroplasty, wherein a piece of the non-weight-bearing part of the femur was obtained as a part of the resected bone for surgery. The two groups of specimens were examined for the expression of RANK, RANKL, OPG, and OCN by immunohistochemistry.

[Results] Spinal TB specimens were significantly infiltrated by inflammatory cells, and bone resorption by multinucleated osteoclasts was observed. RANKL was predominantly expressed in lymphocytes and osteoblasts, whereas RANK was expressed in mononucleated osteoclast precursors among the inflammatory cells. In contrast, there was no infiltration of the inflammatory cells, and the expression of RANKL/RANK was poor in the control specimens. OCN, a bone formation marker, was expressed in the osteoblasts and in part of the bone matrix in normal tissues; however, it was poorly expressed in the tissues of the spinal TB patients. OPG, a neutralizer of the RANK-RANKL pathway, was expressed in the osteoblasts and stromal cells, and there was no signifi-

cant difference in the expression between the two groups.

[Discussion] In the tissues from spinal TB patients, the RANK-RANKL pathway was strongly activated, whereas the expression of its neutralizer OPG was not sufficiently induced. In addition, the bone formation marker OCN was poorly expressed, indicating a paucity of reactive bone formation. These findings are consistent with bone-resorption-predominant destruction, which is commonly observed in osteoarticular TB. Activation of the RANK-RANKL pathway has been considered to be caused by cytokines such as tumor necrosis factor- $\alpha$  and interleukin-6, which also play important roles in the immune response against TB. In severe pulmonary TB, an intense and prolonged immune reaction sometimes leads to tissue destruction and the formation of cavity lesions. Therefore, such an immune reaction against spinal TB may also cause activation of the RANK-RANKL pathway, thereby leading to bone destruction.

**Key words:** Osteoarticular tuberculosis, Bone metabolism, RANK/RANKL, Osteoclast

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**Short Report**

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**INCREASE IN THE NUMBER OF INFANTS WITH KOCH PHENOMENON  
AFTER BCG VACCINATION**

Kunihiko ITO

**Abstract** [Purpose] To investigate the trends in the number of infants diagnosed with Koch phenomenon after BCG vaccination following the change in the timing of the vaccination.

[Method] We extracted and analyzed data from infants aged  $\leq 1$  year diagnosed with latent tuberculosis infection (LTBI) or active tuberculosis, registered in the Japanese tuberculosis surveillance system, from May 2012 to the end of the year, and from May 2013 to the end of the year.

[Result] There was no increase in active tuberculosis cases between the two periods (5 patients each). However, the number of infants with LTBI doubled (45 to 90), presumably because Koch phenomenon developed after BCG vaccination.

[Conclusion] After changing the timing of vaccination, the

number of infants experiencing Koch phenomenon appears to have increased. However, more in-depth analysis of this finding is required.

**Key words:** Koch phenomenon, BCG, Tuberculosis, Non-tuberculous Mycobacteria, LTBI

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## Case Report

DISSEMINATED *MYCOBACTERIUM INTRACELLULARE* INFECTION  
IN A PATIENT WITH MYELODYSPLASTIC SYNDROME

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Hidefumi SATO, and Hideki MURAMATSU

**Abstract** A 71-year-old man with myelodysplastic syndrome (MDS) was admitted to our hospital because of recurrent high-grade fever. He was examined for bacterial and fungal infections and treated with antibiotics and antifungal agents. However, he did not achieve a definitive diagnosis and had no apparent improvement for more than a month. Bone marrow aspiration revealed transformation of MDS to acute myeloid leukemia and hemophagocytosis. In addition, *Mycobacterium intracellulare* was isolated from both a bone marrow specimen and a blood sample. Therefore, he was diagnosed with disseminated *Mycobacterium avium* complex (MAC) infection with hemophagocytosis. An antibody test was negative for human immunodeficiency virus (HIV). His general condition improved with anti-mycobacterial drug and steroid treatments. Clinicians should suspect dissemi-

nated nontuberculous mycobacterial infections in unexplained febrile patients with hematological disorders.

**Key words** : *Mycobacterium intracellulare*, Disseminated MAC infection, Myelodysplastic syndrome, Hemophagocytosis

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## Field Activities

RATES OF COMPLETION AND TREATMENT OUTCOMES  
FOR TYPE OF COMMUNITY DOTS

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and <sup>3</sup>Akira SHIMOUCI

**Abstract** [Aim] To investigate the relationship between completion rates for community directly observed treatment short-course (DOTS) and treatment outcomes, according to implementation tactics, to improve the treatment outcomes.

[Methods and Subjects] We evaluated 529 newly registered patients with smear-positive pulmonary tuberculosis who underwent community DOTS (checking medication at least once per week) during 2010 and 2011 in Osaka City. DOTS completion was defined as checking medication 3 times or more per month, with checking medication missed less than 3 consecutive times. DOTS was implemented using the following 4 tactics: healthcare staff visited the patients' home or workplace (visiting type), the patients visited a health and welfare center (HWC type), the patients visited a pharmacy (P type), or the patients visited an outpatient department at a medical center (MC type). Regarding treatment outcomes, resolution of the tuberculosis or treatment completion was defined as "successful treatment", and treatment failure or default was defined as "unsuccessful treatment". We then analyzed the DOTS completion rate for each DOTS implementation tactic.

[Results] DOTS was completed in 417 (78.8%) of the 529 patients. The completion rates were 79.7%, 75.4%, 75.9%, and 81.3% for patients who underwent visiting (n=394), HWC (n=61), P (n=58), and MC (n=16) DOTS, respectively; no significant difference was observed. The mean ages for each group were 62.8 years, 53.6 years, 45.0 years, and 56.6 years for patients who underwent visiting, HWC, P, and MC DOTS, respectively; patients who underwent P DOTS were significantly younger ( $P < 0.001$ ). Among the 4 groups, the visiting DOTS group had the lowest percentage of full-time employees (16.2%) and the highest percentage of unemployed individuals (67.3%). In contrast, the percentage of full-time employees was 63.8% and 50.0%

in the P and MC DOTS groups, respectively. The P DOTS group had the lowest unemployment percentage (19.0%) among the 4 groups. Thus, a significant correlation existed between the DOTS implementation tactics and the presence/absence of the patients' occupations ( $P < 0.001$ ).

Among the 417 patients who completed DOTS, 99.8% achieved successful treatment. Among the 112 patients who did not complete DOTS, 89.3% achieved successful treatment, and this success rate was significantly lower than that for the group who completed DOTS ( $P < 0.001$ ). Among the visiting, HWC, and P DOTS groups, the completion of DOTS resulted in a high treatment success rate.

[Discussion] Patients who completed DOTS achieved better treatment outcomes; therefore, it is important to provide patients with medication support until their tuberculosis is resolved. The P DOTS group contained a higher percentage of full-time employees and had a significantly lower mean age; this was likely because pharmacies are accessible at night and during the weekend. There was no significant difference in the DOTS completion rates according to implementation tactic, which suggests that it is important to assist patients with their medication according to their needs.

**Key words:** Pulmonary tuberculosis, Community DOTS, DOTS completion rates, Visiting type DOTS, Pharmacy DOTS, Treatment outcome

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## Report and Information

## TUBERCULOSIS ANNUAL REPORT 2013

## — (1) Summary of Tuberculosis Notification Statistics and Foreign-born Tuberculosis Patients —

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**Abstract** This is the first in a 4-series report based on the Tuberculosis Annual Report 2013. It summarizes general tuberculosis (TB) statistics and gives an overview of foreign-born TB patients notified and registered in Japan in 2013.

TB notification has continued to decline since 2000, and a total of 20,495 patients with all forms of TB were notified in 2013, with a rate per 100,000 population of 16.1. The age of TB patients has increased, with 57.4% of all TB patients in 2013 more than 70 years old. The number of patients with latent TB infection drastically increased from 4,930 in 2010 to 10,046 in 2011, but has been declining since.

The number of foreign-born TB patients increased from 739 in 1998 to 1,064 in 2013; similarly, the proportion of foreign-born patients among all TB patients increased from 2.1% in 1998 to 5.4% in 2013. Foreign-born TB patients aged 20–29 years accounted for 42.7% of all new TB patients in the same age group in 2013. Among foreign-born TB patients, more than half were from China (27.4%) and the Philippines (24.1%). Younger patients were more likely to have entered Japan within the previous 5 years (61.5% and 61.3% of foreign-born patients in their teens and twenties, respectively). The largest occupational category was “regular

employees” (25%), which excluded service workers, health care workers, and teachers, followed by students (24%) and unemployed people (21%).

With the government relaxing restrictions on entry of foreign workers to cope with labor shortage in the construction industry ahead of the 2020 Tokyo Olympics, both the number and proportion of foreign-born TB patients is also expected to rise. Comprehensive programs are urgently required to ensure early diagnosis and treatment completion among one of the vulnerable populations in Japan.

**Key words:** Tuberculosis, Notification rate, Country of birth, Occupation

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