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**Original Article**

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**AN OUTBREAK OF TUBERCULOSIS IN WHICH ENVIRONMENTAL FACTORS INFLUENCED TUBERCULOSIS INFECTION**

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**Abstract** [Objective] We encountered a contact group investigation in which differences in environmental factors, including the ventilation frequency and the airflow, led to differences in the infection risk.

[Materials and Methods] The index case was diagnosed with tuberculosis after cough and sputum persisted for 9 months. The patient was an instructor working at vocational schools A and B. Sixty-six instructors/staff and 446 students had contact with this patient at the schools. The patient taught 24 regular courses and 21 short-term courses at the 2 schools after symptom onset through to the final day of work.

[Results] In a contact investigation of instructors/staff, one person with latent tuberculosis infection (LTBI) was identified. Subsequently, 30 and 240 students with the closest contacts and those with 8-hour or longer contact with the index case, respectively, were examined. In School A, of the 162 students examined, one student developed tuberculosis, 7 were QFT-positive, one was QFT-doubtful, 147 were QFT-negative or judged as not infected (either QFT-negative, or a tuberculin skin test of erythema less than 20 mm, including past history of LTBI treatment or TB treatment), and 6 were not examined. In School B, of the 108 students examined, no one developed tuberculosis nor was QFT-positive, 4 were QFT-doubtful, 98 were either QFT-negative or judged as not infected, one was QFT-indeterminate, and 5 were not examined. Since the onset of tuberculosis and QFT-positivity occurred in only School A,

the difference in the incidence of infection between the 2 schools, despite the levels of contact being similar, was assumed to be due to environmental factors. Thus, the ventilation frequency, which had been not reported initially, was re-investigated. The frequency of air change was as low as 0.45–1/hour in School A, whereas it was better (3.57–7/hour) in School B. Moreover, the air flew from the instructor side toward students in School A, while it was reversed in School B.

[Discussion] It was clarified that the ventilation frequency and airflow markedly influenced infection. It is important to investigate environmental factors on epidemiological investigations and to educate people regarding the importance of ventilation.

**Key words:** Contact investigation, Infection risk, QFT, Ventilation frequency, Airflow

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## Original Article

EPIDEMIOLOGICAL SIGNIFICANCE OF PATIENTS WITH EXTRA-PULMONARY TB  
—A Study of 10,082 Patients with Tuberculosis—<sup>1</sup>Takeo INOUE, <sup>2</sup>Haruki KOYASU, and <sup>3</sup>Satoru HATTORI

**Abstract** [Objectives] To elucidate the epidemiological significance of patients with extra-pulmonary TB.

[Subjects and Methods] The subjects of this retrospective study were 10,088 TB patients registered in Aichi prefecture between 1989 and 2003. Of these, 8,629 patients had pulmonary TB and 1,459 had extra-pulmonary TB. All registration files were reviewed to identify the epidemiological links of patients. When linked patients with an interval of less than 10 years between registrations were found, the earlier registered case was considered the primary or index case, and the other patients were regarded as secondary cases.

The index case rate (ICR) for a category of patients was defined as follows:  $ICR = NI/NA$ , where  $NA$ : number of TB patients in a category A, and  $NI$ : number of index cases in category A.

[Results] The ICR for the 1,459 extra-pulmonary TB patients was 1.1%, which was significantly different from 7.2% for 3,332 patients with sputum smear-positive pulmonary TB ( $p < 0.001$ ), as well as from 2.1% for 2,139 patients with sputum smear-negative and bacillus-positive pulmonary TB ( $p < 0.05$ ). The ICR differences were not significant between extra-pulmonary TB patients and 3,158 patients with bacteriologically negative pulmonary TB (1.2%). Of the 16 index cases with extra-pulmonary TB, the organs in which tuberculosis was found were the pleura in 13 patients, the bone in two,

and the hilar nodes in one. The relationship between the 16 index cases and 18 secondary patients were husband-wife in 7 pairs, parent-child in 7 pairs, brother or sister in 2 pairs, and grandparent-grandchild in 2 pairs. The interval of the dates of registration for the index and secondary patients was within one year in 14 pairs or 77.8%.

[Discussion] The index cases with extra-pulmonary TB can be considered as a good control in the epidemiological study on the ability of TB transmission in patients with pulmonary tuberculosis, so that they can form clusters by chance, or false positive clusters.

[Conclusion] Our findings suggest that patients with extra-pulmonary TB have no ability of TB transmission, nor do patients with bacteriologically negative pulmonary TB.

**Key words:** TB transmission, Index case rate, Clustered secondary patient rate, Extra-pulmonary TB, Epidemiological study, Pretended cluster

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## Original Article

## RETROSPECTIVE COHORT STUDY OF RISK FACTORS FOR ADVERSE EFFECTS OF ANTITUBERCULOUS THERAPY

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**Abstract** [Purpose] This study was designed to identify clinical risk factors for adverse effects of antituberculous therapy and their frequency.

[Methods] A retrospective study of cohorts was undertaken from April 2004 to March 2007. We analyzed the clinical records of 861 patients with tuberculosis treated at Higashi Nagoya Hospital. The factors that were associated with adverse effects in univariate analysis ( $P < 0.1$ ) were then subjected to multivariate Cox regression analysis for calculation of the hazard ratios (HRs) and their 95% confidence intervals (95% CIs).

[Results] Suspension of antituberculous therapy was necessary because of adverse effects in 247 patients (28.7%). The chief adverse effects leading to discontinuation of treatment were liver dysfunction (12.9%), skin rash (6.7%), and gastrointestinal dysfunction (4.1%), while other effects accounted for less than 5.0% of discontinuations. Risk factors for liver dysfunction according to Cox proportional hazards analysis were HCV infection (HR 2.86 ; 95% CI 1.59 to 5.15 ;  $p < 0.001$ ) ; hepatocellular damage at admission (HR 2.06 ; 95% CI 1.25 to 3.39 ;  $p = 0.005$ ) and high-dose isoniazid (increase per mg/kg: HR 1.36 ; 95% CI 1.18 to 1.56 ;  $p < 0.001$ ). Collagen disease was a risk factor for skin rash (HR 6.06 ; 95% CI 2.81 to 13.05 ;  $p < 0.001$ ). Risk factors for gastrointestinal

dysfunction were a high body mass index (increase per  $\text{kg}/\text{m}^2$ : HR 0.80 ; 95% CI 0.71 to 0.91 ;  $p < 0.001$ ) and advanced age (increase per year: HR 1.03 ; 95% CI 1.01 to 1.06 ;  $p = 0.018$ ).

[Conclusion] Adverse effects may lead to substantial additional medical costs because of the need for more medications and tests, as well as a longer hospital stay. Identification of the risk factors for adverse effects of antituberculous therapy should help to minimize such events in tuberculosis patients.

**Key words:** Tuberculosis, Antituberculosis drugs, Adverse effects, Multivariate analysis, Retrospective cohort study

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## Case Report

A CASE OF PULMONARY TUBERCULOSIS WITH DIMINISHED LUNG FUNCTION  
WHOSE PARADOXICAL REACTION LED TO DEATH

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**Abstract** Paradoxical reaction in tuberculosis treatment is not generally fatal. On rare occasion it can lead a patient with diminished lung function and poor general condition to death.

A 60-year-old man with history of left upper lobe resection from tuberculosis was referred to our hospital due to the recurrence of tuberculosis. Sputum examination showed a positive smear with a Gaffky score of 10, and the chest X-ray and CT revealed pulmonary infiltrate with many cavities (*bII2*) on the whole left lung field. Anti-tuberculosis drugs (isoniazid, rifampicin, ethambutol and pyrazinamide) were administered, but his high fever persisted, and the infiltrate on the chest X-ray deteriorated. While the positive sputum smear persisted, the culture became negative after one month. The tuberculous bacilli were susceptible to all anti-tuberculosis drugs *in vitro*. Though we performed examinations and trial treatments for non-tuberculous conditions such as pneumonia and drug-induced pneumonia, the patient died after 6 months. A necropsy specimen taken from the worsening lesion (the right upper lobe) as shown on the chest X-ray revealed many epithelioid granulomas. The patient had malnutrition, diabetes, alcoholic hepatic disorder, and insanity. It is supposed that although anti-tuberculosis drugs were effective, a large quantity of killed

organisms was continuously excreted from many cavities in the left lung toward the right lung. Lesions in the right lung thus newly produced in this paradoxical reaction seemed to reduce the remaining lung function. In addition, poorly controlled diabetes caused deteriorated heart function. These multiple factors contributed to the poor prognosis of the patient and his ultimate death.

**Key words:** Pulmonary tuberculosis, Paradoxical reaction, Killed bacteria, Cavity, Immune reconstitution syndrome

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————— Review Article —————

PRESENT STATUS OF STUDIES ON EPIDEMIOLOGY  
AND MOLECULAR EPIDEMIOLOGY OF *MYCOBACTERIUM KANSASII*,  
IN SPECIAL REFERENCE TO ITS EPIDEMIOLOGY

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**Abstract** *Mycobacterium kansasii*, a slow-growing photochromogen, causes serious pulmonary diseases in humans. Since the 1980s the isolation rate of *M. kansasii* has been surpassed by that of *Mycobacterium avium* complex (MAC). Pulmonary disease caused by *M. kansasii* is known to be more common in urban areas than in rural areas, and its changing epidemiologic features and geographical distribution have been known for several decades. The disease had been found almost only in and around Tokyo areas until the 1970s, but after the 1990s, the disease spread to the rest of Japan. The incidence rate of the disease due to *M. kansasii* remained at the same level, while non-tuberculous mycobacterioses as a whole are rapidly increasing, especially because of the increase in *Mycobacteriu avium* complex diseases, and because of the improvement of identification techniques in recent years. This change in the epidemiologic picture of *M. kansasii* in Japan

seems to be influenced by the international trends of this disease. The complicated environmental and other factors related to *M. kansasii* infection are discussed in this review.

**Key words:** *Mycobacterium kansasii*, Epidemiology, Geographical distribution, Environmental source, Annual change

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## NONTUBERCULOUS MYCOBACTERIOSIS MORTALITY IN JAPAN

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and <sup>1</sup>Shoji KUDOH

**Abstract** The aim of this research was to clarify epidemiological characteristics of nontuberculous mycobacteriosis deaths in Japan. We analyzed the frequency of deaths due to nontuberculous mycobacteriosis (NTM) and regional differences using the Vital Statistics of Japan, published by the Ministry of Health, Labour and Welfare. The crude death rate was calculated using the Population Census of Japan published every 5 years (Ministry of Internal Affairs and Communications). In addition, changes in the proportions of death cases due to NTM disease among total autopsies were calculated using the Annual of the Pathological Autopsy in Japan (The Japanese Society of Pathology).

Results: NTM disease deaths appeared for the first time in 1970, with a marked increase by 2007, when there were 912 certified deaths. The increase was more marked after the mid-1990s. The number of women's deaths exceeded 300 in 1999 and reached 570 in 2007, while that of men exceeded 300 in 2001 and remained at nearly the same level until 2007. The death rate increased in all eight regions of Japan. The highest

single-year regional death rate was 212 in Kanto in 2005. However, correcting by population size, the crude death rate was higher in the western regions of Japan than in the eastern ones. The proportion of NTM among total autopsies also showed an increase from 0.066% in 1993 to 0.304% in 2007. Included in the report is a comparison of trends of NTM deaths with those of major respiratory diseases including tuberculosis, emphysema, bronchial asthma and airway cancers.

**Key words:** Nontuberculous mycobacterial disease, Mortality, Gender difference, Regional difference, Yearly transition

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**Report and Information**

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**TUBERCULOSIS ANNUAL REPORT 2009**  
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**Abstract** The number of newly reported childhood tuberculosis (TB) cases (0–14 years old) in 2009 was 73, corresponding to a case rate of 0.43 per 100,000. In 2007 and 2008, the case numbers and rates of childhood TB increased slightly from the previous years, but in 2009 the case number and case rate were the lowest in the long history of the Japanese TB surveillance system. Among 73 childhood TB patients, 34 (46.6%) were aged 0–4 years, 3 (4.1%) were foreigners and 27 (37.0%) were extra-pulmonary TB. No TB meningitis case in this age group (0–14 years old) was reported for 3 years (from 2006 to 2008), but one case was reported in 2009. Also, 4 cases of disseminated TB were reported in 2009, the highest figure during those 10 years (from 2000 to 2009).

As for the mode of detection in 2009, 33 patients (45.2%) were detected at medical institutions with some symptoms or signs, 24 patients (32.9%) were detected by family contact examination, and 8 (11.0%) were detected by other contact

examination. In the previous year (2008) these proportions were respectively 36.8%, 45.3% and 8.4%.

Of the 47 prefectures in Japan, 27 had no cases of childhood TB in 2009. Childhood TB cases were concentrated in metropolitan areas, such as Osaka (13 cases), Tokyo (11 cases) and Kanagawa prefecture (7 cases).

**Key words:** Tuberculosis, Childhood TB, Age, Trend, Prefectures, Mode of detection

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