

THE INDEX AND SECONDARY PATIENTS IN TUBERCULOSIS TRANSMISSION — A Retrospective Epidemiological Study of 3,783 Patients Newly Registered in Recent 15 Years in Aichi, Japan —

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Abstract [Objectives] To elucidate the characteristics of the index and secondary patients in clusters containing multiple TB patients who were examined epidemiologically.

[Subjects and Methods] The subjects of this retrospective study were 3,783 TB patients registered in Aichi between 1989 and 2003. All recorded files were reviewed to identify multiple TB patients in the same transmission group. When multiple patients with a registration interval of less than 10 years were found in the same transmission group, the first patient was considered as the index case, and the other patients were regarded as secondary cases.

[Results] A total of 106 index patients and 132 secondary patients were found. The index patients occupied 2.8% of the total 3,783 registered patients, or 0.9 per 100,000 population. Secondary patients occupied 3.5% and 1.2 per 100,000. Of the 106 clusters, 77.4% consisted of two patients, 15.1% three patients, and 7.5% four or more patients. Smear-positive patients were found in 66.0% of the index patients, 27.3% of the secondary patients, and 30.3% of the 3,783 overall patients, and the differences were highly significant between the index and secondary patients, as well as between the index and overall registered patients ($p < 0.001$). The proportion of

the index patients to all registered patients was 6.1% for smear-positive patients, 1.8% for culture-positive patients, and 1.1% for bacilli-negative patients. The differences were highly significant between smear-positive and culture-positive patients, as well as between smear-positive and bacilli-negative patients ($p < 0.001$).

[Conclusion] The findings of this retrospective study suggest that 2.8% of the total registered patients, 6.1% of smear-positive patients, and 0.9 per 100,000 population was the index patients.

Key words: Tuberculosis transmission, Familial infection, Non-familial infection, Epidemic infection, Small-sized group infection, Retrospective study

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Original Article

BACTEC MGIT 960 SYSTEM FOR DRUG SUSCEPTIBILITY TESTING OF
MYCOBACTERIUM TUBERCULOSIS: A STUDY USING
EXTERNAL QUALITY ASSESSMENT STRAINS¹Ikuo KOBAYASHI, ¹Chiyoji ABE, and ²Satoshi MITARAI

Abstract [Objective] To evaluate the performance of the BACTEC MGIT 960 system for drug susceptibility testing (MGIT AST) of *Mycobacterium tuberculosis* to isoniazid, rifampin, streptomycin and ethambutol.

[Design] Fifty external quality assessment strains of *M. tuberculosis* provided by the Coordinating Centers of WHO/IUATLD were tested by BACTEC MGIT 960 system, and the results were compared with the referee results of the WHO/IUATLD Supranational Reference Laboratory Network (SRLN).

[Results and conclusion] Overall concordance rates of the results obtained by MGIT AST and the referee results of the SRLN were 97.3% for four first-line drugs. Agreement rates were particularly high for isoniazid, rifampin, and streptomycin (agreement rate of over 97%), but somewhat lower for ethambutol, which relates to a lower sensitivity of MGIT AST. Turnaround times from inoculation to drug susceptibility results ranged from 6 to 13 days for the MGIT AST system with a median time of 7 days; this contrasted with three weeks for the proportion method using Middlebrook 7H10 agar,

indicating that MGIT AST system has the potential to consistently meet with the turnaround time guidelines suggested by the Centers for Disease Control and Prevention of the United States. These results demonstrate that the fully automated BACTEC MGIT 960 AST system is useful for the rapid diagnosis of drug resistant tuberculosis.

Key words: MGIT AST, Susceptibility test, *Mycobacterium tuberculosis*, WHO/IUATLD

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A CASE OF SILICOTUBERCULOSIS WITH DIFFICULTY IN ITS DIAGNOSIS

Seiyu HIRATA

Abstract A 68 year-old man who had worked as a stone mason for more than 50 years with a heavy smoking history consulted our clinic with symptoms of cough, low grade fever, weightloss, malaise and a single expectoration of hemo-sputum. He had been diagnosed as silicosis by the mass survey 5 years ago based on nodular shadows with egg-shell calcification in hilar lymphnodes on his chest radiography, and has received chest radiographic examination once a year. As the author was not so familiar with the radiographic features of silicotuberculosis, it was difficult to interpret ill-defined contour of silicotic nodules accompanied by patchy opacities formation in right midlung field and silicotic conglomeration accompanied by an ischemic cavity in the left basal segments. A definitive diagnosis could not be established until 10 months later when a second attack of exacerbation of silicotuberculosis occurred showing multiple thin walled fresh tuberculous cavities on the chest radiography with positive smear and culture. Among multiple tuberculous cavities, there was a cirrhotic-walled cavity caused by endogenous reactivation of a quiescent tuberculous lesion on the right apex. This lesion was considered to be the source of

dissemination of this case. Finally, it took about two and a half years before establishing the diagnosis in this case because of a series of doctors delays. He was treated successfully with antituberculous drugs for one and a half years including one year rifampicin medication.

The clinico-pathological findings of silicotic conglomeration in the left basal segments were discussed based on the findings of transbronchial biopsy from occluded B¹⁰ and chest radiographic findings, and it was revealed that silicotic conglomeration might consist of inflammatory granulation combined with granulomatous tubercle, but not a fibrous lesion.

Key words : Silicotuberculosis, Silicotic conglomeration, Early cavity, Ischemic cavity

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TUBERCULOSIS CONTROL IN HEALTH CARE FACILITIES FOR THE ELDERLY, FROM THE VIEWPOINT OF RISK MANAGEMENT

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Kunihiko ITO, Yuko YAMAUCHI, and Shinji SHISHIDO

Abstract [Objectives] To discuss the optimal TB control system in health care facilities for the elderly where the periodic TB screening is currently not obligatory.

[Methods] A study was conducted in three health care facilities for the elderly in Tokyo during the period from 2002 to 2004, and 212 admitted elderly persons were enrolled in this study. Medical charts were analyzed to identify information about mental and physical conditions and TB risk factors. Questionnaire-based interviews were conducted in 58 residents who had no dementia or no serious conditions. TB mass screening was carried out with a mobile vehicle equipped with computed radiography, financially supported by the Tokyo Metropolitan Government. Since this mobile vehicle is equipped with a special wheelchair for chest X-ray examination, most elderly persons were able to receive chest X-ray examination. Medical chart review and interview were conducted at around the time of TB mass screening. The screening results of 183 elderly residents who received X-ray examination were reviewed.

[Results] Of the 212 persons admitted to the facilities, 73.1% were women. The mean ages of men and women were 80.7 and 84.2 years, respectively. Mental disorders were observed in 42.9% and dysfunction of extremities in 54.7%. At the time of admission, chest X-ray records were submitted by the attending doctors in 73.1% of the residents, but this proportion differed among facilities. From these records, old TB was found in 12.3%; however this proportion was 20.8% according to the TB mass screening results. A history of TB was more prevalent in the group interviewed than in the non-inter-

view group (24.1% vs. 6.5%; $p < 0.001$). Two facilities had conducted TB screening for three consecutive years and comparative reading of chest X-ray films could be done in 35.8%. The remaining facility conducted TB screening for the first time, and comparative reading was not possible. The proportion of cases requiring further investigations was higher in the facility where TB screening was conducted for the first time (2.8% vs. 13.0%; $p = 0.008$). No active TB patient was detected in this study.

[Conclusion] From the viewpoint of risk management for tuberculosis, it is important to establish a system of early case finding for the aged persons admitted to health care facilities for the elderly. Therefore, the information on risk factors should be collected properly at the time of admission, and careful attention should be paid to the residents with risk factors, for the possible development to active disease. X-ray records submitted by the attending doctors or by screening would provide useful information for early diagnosis, when abnormal shadows are found on chest X-ray films.

Key words: Tuberculosis, Elderly, Health care facility for the elderly, Risk management, TB mass screening

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EXOGENOUS RE-INFECTION IN TUBERCULOSIS

Chairperson: Toshiaki TSUCHIYA

Abstract Patients infected by tuberculosis (TB) had been thought to never experience exogenous re-infection. However, exogenous re-infection in HIV-positive patients is well known. Thanks to the introduction of histopathological examination, analysis of similarities in drug-resistance patterns and epidemiological surveys of genetic phage typing for TB infection, we have begun to understand that even people with a normal immune system can experience re-infection.

Recent advances in the techniques of restriction fragment length polymorphism (RFLP) and spoligotyping allow determination of similarities in tubercle bacilli, revealing a high ratio of exogenous re-infection.

In this mini-symposium, Dr. Kazunari Tsuyuguchi reported cases of nosocomial multidrug-resistant tuberculosis (MDRTB) infection, as exogenous re-infection, at 3 tuberculosis hospitals in the Osaka area. Although the virulence of MDRTB as a variant strain has generally been regarded as weaker than that of drug-sensitive strains, he reported even non-Beijing strain MDRTB, which displays strong virulence, could possess possible infectivity with a 42% ratio of clustering formation and 2 of 8 patients with MDRTB exhibiting exogenous re-infection, as analyzed by RFLP.

Dr. Hideo Ogata reported the actual condition of exogenous re-infection, having cited a large number of reports at home and abroad. In his report he indicated that even among hosts without serious hypimmunity, re-infection rate is high in high-prevalence countries. Conversely, endogenous TB reactivation is high in low-prevalence countries. As Japan has become a low-prevalence country, endogenous reactivation might be seen in TB wards.

Dr. Katsuhiro Kuwabara reported on his study about exogenous re-infection of *Mycobacterium avium*, which represented resident flora in the environment, using IS1245 RFLP analysis. He demonstrated that re-infection and multiple infections were frequently observed in *M. avium* infection.

Dr. Tomoshige Matsumoto finally added that about 90% of patients with recurrence in the Osaka area exhibit endogenous reactivation, as found using molecular epidemiologic analysis of bacterial strains from initially treated and retreated patients. Compared with reports from other countries, the ratio of exogenous re-infection in Japan is lower than elsewhere. Thanks to the public health service about TB, sources of TB infection are not present, so patients with TB do not experience exogenous re-infection, he concluded. He also discussed the variable number of tandem repeats (VNTR)-typing method that has been taking the place of the IS6110 RFLP.

In this mini-symposium referring to molecular epidemiological analyses and reports from Japan and overseas, we showed that depending on factors involving hosts, parasites and the density of TB re-exposure, the possibility of universal exogenous nosocomial re-infection exists. Each presenter alerted us to the fact that as exogenous re-infection occurs mainly in TB inpatient wards, prevention of TB infection is crucial for inpatients and medical staff in Japan as a low-prevalence country.

1. Exogenous re-infection by multidrug-resistant tuberculosis: Kazunari TSUYUGUCHI, Shiomi YOSHIDA, Katsuhiro SUZUKI, Masaji OKADA, Mitsunori SAKATANI (NHO Kinki-chuo Chest Medical Center)

We describe three recurrent cases of multidrug-resistant (MDR) tuberculosis (TB) nosocomially re-infected with MDRTB strain during treatment for drug-sensitive TB. The first and the second patients, both of whom were middle-aged heavy smoker men, were associated with the outbreak caused by non-Beijing MDRTB strain. The third patient was a immunocompetent young man and the isolated strain was Beijing MDRTB strain. All the patients were HIV-seronegative. We conclude that exogenous re-infection by

MDRTB can occur on various situations. These results underscore the importance of placing MDRTB patients separately from drug-sensitive TB patients.

2. Reviews of the exogenous re-infection in tuberculosis: Hideo OGATA (Fukujiji Hospital, JATA)

In Japan, they have thought that a tubercular relapse is based on endogenous reactivation in almost all cases. However, there are many studies which prove exogenous re-infection using tuberculin test or drug susceptibility test. The technique of developed strain typing contributed exogenous re-infection to clarifying greatly in a real proof and its frequency in recent years.

3. Multiple and repeated polyclonal infections in patients with *Mycobacterium avium* lung diseases: Katsuhiro KUWABARA (NHO Nishi-Niigata Chuo National Hospital)

The routes of transmission and environmental reservoirs of *Mycobacterium avium* infections have been unclear. IS1245 based RFLP analysis showed genetic diversity of *Mycobacterium avium* clinical isolates and the relation between clinical subtype and polyclonal infection. Our study demonstrates that polyclonal infections are common in *Mycobacterium avium* lung diseases, especially nodular bronchiectasis type. In addition, not only simultaneous polyclonal infections but also repeated polyclonal infections were observed in some patients. The knowledge of polyclonal infection will lead to

better understanding of *Mycobacterium avium* pathogenesis and epidemiology.

Special commentaries: Consideration of exogenous re-infection of tuberculosis in Osaka, Japan, by using molecular epidemiologic tools: Tomoshige MATSUMOTO (Osaka Prefectural Medical Center for Respiratory and Allergic Diseases)

By using IS6110 RFLP, we showed that 9.5% of TB recurrence was caused by re-infection in the middle-eastern area of Osaka Prefecture, Japan. The molecular typing tools are now being applicable not only to epidemiological but also to clinical fields by an introduction of PCR-based method, such as Variable Numbers of Tandem Repeats (VNTR) typing. We showed some examples about usefulness of the clinical application of molecular epidemiology, using VNTR.

Key words: Exogenous re-infection, Endogenous reactivation, Multidrug-resistant tuberculosis, Nosocomial infection, *Mycobacterium avium* infection, Molecular epidemiology.

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