

## Original Article

CURRENT EPIDEMIOLOGICAL SITUATION OF TUBERCULOSIS IN THE WORKPLACE:  
CONSIDERING THE RISK OF TUBERCULOSIS AMONG NURSES

Masako OHMORI, Hitoshi HOSHINO, Yuko YAMAUCHI, and Kazuhiro UCHIMURA

**Abstract** [Objective] To observe the trends and methods of tuberculosis (TB) detection in different occupations; to estimate the incidence of TB among nurses, and calculate the relative risk by comparing with the aged-matched general population; and to estimate the incidence of TB and relative risk also for teachers and doctors.

[Materials and Methods] The background of TB patients was analyzed using the annual reports of TB registry for the period between 1987 and 2004. The population obtained from the national census, which was conducted every five years, was used for the calculation of TB incidence by specific occupation. The annual population between the two census years was obtained by interpolation. The TB registry assigns the same occupation code for nurses, public nurses and nursery teachers, and similarly assigns a common code for teachers and medical doctors. Therefore, TB incidence of nurses was calculated by subtracting the estimated number in nursery teachers. The number of nursery teachers contracting TB was obtained assuming that their TB incidence was the same as that for the 20–59 year-old population of the same sex. On the other hand, TB incidence for teachers and doctors was calculated together, because of the difficulties in separating the two occupations.

[Results] Among nurses with TB, the proportion of cases detected by periodic mass screening in the workplace increased gradually from 21.4% in 1987 to 40.4% in 2004. Conversely, the proportion of cases detected by symptomatic visit to medical institutions declined from 69.4% in 1987 to 43.9% in 2004. In general population, the proportion of cases detected by contact tracing is low. Among nurses, however, cases detected by contact tracing had increased since around 1995; the proportion was 1–2% before 1995, increased to 7.0% in 1999 and leveled off at around 6–9%.

TB incidence of female nurses declined slightly from 54.1 per 100,000 population in 1987 to 46.3 in 2004 (14.4%), and

that of male nurses also declined from 127.0 in 1987 to 82.5 in 2004 (35.0%). However, the relative risk of female nurses increased from 2.1 (95%CI: 1.9–2.3) in 1987 to 4.3 (95%CI: 3.9–4.8) in 2004, and that of male nurses also increased from 2.4 (95%CI: 1.6–3.4) in 1987 to 3.8 (95%CI: 2.8–5.2) in 2004. The relative risk had increased gradually from the middle of 1990s in both sexes.

TB incidence of female teachers and doctors decreased from 14.8 per 100,000 population in 1987 to 10.0 in 2004 (32.4%), and that of male teachers and doctors decreased from 39.3 in 1987 to 18.8 in 2004 (52.2%). While the relative risk was below 1 in both sexes, the relative risk in females increased from 0.6 (95%CI: 0.5–0.7) in 1987 to 0.8 (95%CI: 0.7–1.1) in 2004, and that in males also increased from 0.7 (95%CI: 0.7–0.8) in 1987 to 0.9 (95%CI: 0.8–1.0) in 2004.

[Conclusion] Based on the relative risk data, approximately 80% of nurses with TB might have been infected by nosocomial infection and developed the disease. Since about half of them were detected in an early stage by mass screening in the workplace or contact tracing, TB control measures for nurses may be considered effective. However, the relative risk of TB among nurses had continued to increase without any trend of decline. The infection control at the hospitals may be inadequate, and should be reinforced by evaluating the methods or contents of control measures conducted so far.

**Key words:** Tuberculosis, Surveillance, Incidence rate, Workplace, Case finding, Nurse, Relative risk

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## Original Article

## TREATMENT RESULTS OF RIFAMPICIN (RFP) RESISTANT ISONIAZID (INH) SUSCEPTIBLE TUBERCULOSIS, A HOSPITAL BASED STUDY

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**Abstract** [Settings] Fukuji Hospital, Japan.

[Purpose] To evaluate treatment results of Rifampicin (R) resistant Isoniazid (H) susceptible tuberculosis cases.

[Method] Cohort analysis of twenty-three H susceptible R resistant tuberculosis cases started treatment in 1985–2004 at Fukuji Hospital, by the retrospective review.

[Results] Three cases became Multi-drug resistant tuberculosis (MDR TB), seventeen cases were cured, two cases died, and one case transferred out. One started treatment with HR became MDR, one of the two started treatment with HR + Ethambutol (E) became MDR and one of them was cured, eight among ten cases started treatment with HR + Pyrazinamide + (E or Streptomycin (S)) were cured, one among the ten died and one among the ten transferred out, one started treatment with RZE was cured, three among the five cases started treatment with three effective drugs without Z were cured, one among the five died, one among the five became MDR. Three cases started treatment with four effective drugs were cured. Among the nineteen cases continued treatment for more than six months, ten cases treated with four or five effective drugs for at least two months were cured, two cases of nine cases treated with three drugs or less became MDR, seven of the nine cases were cured. Among the same nineteen cases, eleven cases not treated with two or less effective drugs

were cured, one case treated with two or less effective drugs for six months became MDR and one of them treated with one or two effective drug for one to three months became MDR and some were cured. The used drugs were H, E, Pyrazinamide, Streptomycin, Kanamycin, Ethionamide and New Quinolones. The duration of treatment of cured cases were eleven to twelve months in 3 cases, twelve to eighteen months in 3 cases, eighteen to twenty-four months in 8 cases and more than two years in 3 cases.

[Conclusion] If the starting regimen is HRZE, we can cure R resistant H susceptible tuberculosis by the use of four effective drugs for more than two months and at least three effective drugs with the total duration of treatment for twelve to twenty-four months.

**Key words:** Rifampicin, Drug resistance, Tuberculosis

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## Original Article

MOLECULAR EPIDEMIOLOGICAL ANALYSIS OF *MYCOBACTERIUM KANSASII* ISOLATES

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<sup>1</sup>Masaji OKADA, and <sup>2</sup>Mitsunori SAKATANI

**Abstract** [Purpose] To make molecular epidemiological analysis of *Mycobacterium kansasii* (*M. kansasii*) isolates.

[Methods] We examined 174 *M. kansasii* isolates from clinical samples of patients at National Hospital Organization Kinki-chuo Chest Medical Center from June 1, 2002 to August 31, 2005 by polymerase chain reaction (PCR)-restriction analysis (PRA) of the heat shock protein (*hsp*) 65 gene (*hsp65*-PRA), sequencing (ITS, 16S-23S internal transcribed spacer, and *hsp65* for discrepant case between *hsp65*-PRA and ITS sequence), pulsed-field gel electrophoresis (PFGE), and restriction fragment length polymorphism (RFLP) with the major polymorphic tandem repeat (MPTR) probe and the IS1652 probe of genomic DNA.

[Results] Of the 174 *M. kansasii* isolates, 170 strains were classified as *M. kansasii* type I using *hsp65*-PRA, while two isolates belonged to type II and one each isolate to type IIb and VI, respectively. Although the ITS sequence of these isolates also identified the same region of polymorphism by *hsp65*-PRA, only type IIb might be revealed atypical type II, a transitional type from typical type II to intermediate type I by *hsp65* sequence. The polymorphic patterns by RFLPs with MPTR and IS1652 probe were shown specific for each

homogeneous cluster by *hsp65*-PRA. In addition, 159 isolates were recognized the same common pattern A by PFGE analysis. In contrast, the rest 15 isolates revealed significant polymorphism within 11 isolates of type I, and 4 isolates among type II, IIb, and VI.

[Discussion] We verified the *M. kansasii* genotype I was predominant, with the same pattern of major worldwide type regions, and reflected a very tight clonal structure. Type I was furthermore indicated recognition of subtypes by PFGE analysis.

**Key words:** *Mycobacterium kansasii*, *hsp65*-PRA, 16S-23S ITS sequencing, PFGE analysis, RFLP analysis

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## ————— Case Report —————

A CASE OF TUBERCULOUS ANEURYSM OF SUBCLAVIAN ARTERY OCCURRED  
IN THE COURSE OF TREATMENT FOR MILIARY TUBERCULOSIS<sup>1,2</sup>Keitaro SAKAKIBARA, <sup>2</sup>Tetsuya OKANO, <sup>2,3</sup>Shuji KURANE, and <sup>2</sup>Shouji KUDOHO

**Abstract** This case is a 56-year old woman. Steroids were being administered perorally after a thymectomy for myasthenia gravis. A fever of 38–39 degrees Celsius appeared during night, an abnormal shadow showed up on a chest X-ray and the patient was hospitalized. Gaffky No. 2 acid-fast bacilli were detected in the patient's sputum and the chest CT showed diffuse granular-like shadow, the patient was diagnosed as miliary tuberculosis and treatment with combined use of INH, RFP, EB, and PZA was started. Subsequently, fever started to subside and the miliary shadow on chest X-ray improved, however, six weeks after the start of treatment, hoarseness and dysphagia appeared. From the cervical CT and cervical angiography findings, the diagnosis of right subclavian artery impending ruptured aneurysm was made. Because the patient's sputum was acid-fast bacilli positive and because the patient had undergone thymectomy, it was decided that it would be difficult to treat her by a thoracotomy again. Therefore, a right subclavian artery stent insertion, right subclavian artery–right common carotid artery bypass creation operation was carried out with the objective of blocking the flow of blood to the aneurysm. The hoarseness and dysphagia im-

proved post-operatively and the patient's progress is being monitored. Tuberculous aneurysms are a rare affection and they are mostly discovered when the autopsy is done, however, this case was diagnosed due to the manifestation of subjective symptoms. While this case was not diagnosed histopathologically, it is envisaged from the clinical progress that this was a tuberculous subclavian aneurysm complicated during the treatment for miliary tuberculosis.

**Key words:** Miliary tuberculosis, Tuberculous aneurysm, Myasthenia gravis, Steroid

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————— The 81st Annual Meeting Educational Lecture —————

## OUTCOMES AND PROBLEMS OF DOTS STRATEGY IN JAPAN

Tadayuki AHIKO

**Abstract** The DOTS strategy promoted by the World Health Organization (WHO) was applied in 183 countries in 2004. The DOTS coverage, defined as the percentage of the population living in areas where health services have adopted DOTS, was 83% globally in 2004, but it was 71% in Japan.

The global 2005 targets for tuberculosis (TB) control are to detect at least 70% of infectious TB cases and cure 85% of those cases detected. According to the most recent WHO annual report, the DOTS case detection rate in 2004 was 45% in Japan whereas the global average of it was 53%. The treatment success rate, defined as the percentage of patients (in the 2003 cohort) who are cured or who complete treatment, was 82% globally, but it was 76% in Japan. This relatively low achievement is attributed to the fact that public health centers in some districts operated insufficient monitoring system for evaluation of the treatment outcome by cohort analysis. However, the treatment success rate will not be improved easily because more than half of new TB patients in Japan are old people who tend to have various complications.

The Ministry of Health, Labour and Welfare demonstrated the framework of the DOTS Japan version in 2003 to promote the DOTS strategy with collaboration between hospitals, public health centers and welfare organization. The new strategy includes the program for treatment of TB inpatients and the community-based program for outpatients. The latter

program called “community DOTS” is classified into three types according to the risk of treatment interruption with an individual patient.

The Japanese Society for Tuberculosis should urge the government (at central and regional levels) to enhance political commitment to accelerate activities for TB elimination. It is necessary that the central government build a new public funding system to improve the cure rate under the DOTS Japan version. The local government should strengthen the function of public health centers not only to secure the quality of monitoring system for evaluation of the treatment outcome but to develop human resources who are able to collaborate with public health nurses in promoting the community-based DOTS program.

**Key words:** DOTS, Japan version, Outcome, Political commitment, Public health center

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THE NEW CRITERIA FOR DISCHARGE FROM TUBERCULOUS WARD  
— Practical Use and Problem —

Chairpersons: <sup>1</sup>Emiko TOYOTA and <sup>2</sup>Kenji OGAWA

**Abstract** Abstract of “Requirement for Discharge of Tuberculosis Patients” was published by the Japanese Tuberculosis Society in January, 2005. According to the recommendation, new guideline made by National Hospital Organization and practical use started in March, 2005. In this symposium how new criteria were applied in each hospitals were reported and the merits and problems which the change of criteria brought about were discussed.

In National Hospital Organization Tokyo National Hospital, discharge had been based on conversion of cultivation of *Mycobacterium tuberculosis*. By settled this rule, mean period of hospitalization has been 70 days a little shortened than before. It takes so long times to get the result of cultivation.

Adapting the new criteria made by National Hospital Organization which is not based on bacteriological conversion, mean hospitalized period has changed to be on 50 days. The problems are insufficiency of DOT system after discharge and defect of consensus with clinicians and medical care staffs. Patients are occasionally obliged to attend the hospital until conversion to bacteriological negative.

In case of International Medical Center of Japan, by changed criteria from conversion of serial 2 culture to conversion of smear negative or reduction of bacteria, hospitalized periods has been shortened and the rate of successful treatment has been improved due to extension of DOTS for out-patients by public health center. As one other problem, application of new

criteria has been limited by disagreement with health center about discharge of patients with still smear positive after some effective treatment.

Review of hospitalization in western countries was presented by Dr. Ito. Documents about the criteria for discharge of TB patients from the hospital in western countries were reviewed. For the most part, bacteriological conversion are necessary to release isolation in the hospitals. On the other hands, going back to the home is possible if the patients had already received for some duration and there is no compromised person or children less than 4 years old. Continuation of appropriate treatment and support as out patients are more concerned in these countries.

The points and warning of the new guideline of admission and discharge from the Japanese Society for Tuberculosis were commented. Improvement of management of patients with tuberculosis will be necessary and expected. It is attached importance to keep continuation and success of the treatment adding the reduction of infectiousness. We still emphasized the guideline should not be easily used for the purpose to shorten duration of hospitalization and reduce the cost. More support or mandatory treatment should be considered for the patients with risk of treatment failure or incompliance.

The view of administrative side on the criteria of discharge from hospital was reported. We took notice of DOTS during out-patients treatment after discharge. On performance of new criteria, DOT for outpatients should be intended and extended. But administrative system has not been ready with staffs and budget. National support is necessary for systematical change of TB control in Japan. Moreover unification to law concerning prevention of infection and medical care for patients with infection will changed the practice of managements.

1. Application of new discharge criteria for TB patients and issue in large TB hospital : Kazuko MACHIDA (National Hospital Organization Tokyo National Hospital)

New criteria for discharging patients with tuberculosis (TB) from NHO Tokyo Hospital is classified by drug resistance and continuity of standard treatment. To evaluate the criteria, patients were divided into two groups. For group I patients with sensitive TB bacilli who were treated with standard regimen, the following 6 conditions should be satisfied : 1) All drugs except PZA (that is RFP, INH, EB, SM) are sensitive in MGIT medium. 2) Standard chemotherapy is being done without adverse reaction. 3) Symptoms, such as cough and fever, improved. 4) Sputum smear-negativity on two successive and separate days, or one sputum culture-negativity is confirmed. For transfer to other ward except TB, to other hospital or to collective facilities such as residence home for aged persons, sputum smear-negativity or sputum culture-negativity on two successive and separate days is required. 5) Not to live together with new born babies, children without BCG vaccination, or immuno-suppressed persons are guaranteed. 6) Chemotherapy can be continued with certainty.

For group II patients who are not being treated with standard chemotherapy, or for patients with resistant TB bacilli, in addition to the above mentioned 3 conditions (3, 5, 6), the following two items should be satisfied. 1) Effective treatment using more than or equal to 3 sensitive drugs is being done without adverse reaction. 2) Sputum smear-negativity or sputum culture-negativity are confirmed on two successive and separate days. Two hundred thirty five TB patients admitted from March 1 to August 31 in 2005 were evaluated.

[Result] Excluding early death (34) or early discharge (8) without bacterial negative conversion, group (Gr.) I was 122 cases and Gr. II was 71 cases. The reason classified to Gr. II were drug resistance (19), retreatment (17), adverse reaction (22), complication (13). In Gr. II compared with Gr. I, older age, more severe findings on X-ray film or more sputum smear-positive rate were found. Culture negative conversion rate on sputum after 2 and 3 month treatment was delayed in Gr. II (50.9%, 74.5%), compared with Gr. I (76.1%, 92.0%). Discharge rate except death within 60 days and 90 days was less in Gr. II (19.7%, 32.4%), compared with Gr. I (47.5%, 70.5%). This tendency was marked in sputum smear-positive (S+) cases compared with smear-negative (S-) ones. Discharge rate within 60 days and 90 days was 13.2% and 26.4% (Gr. II, S+ : 53 cases), 32.1% and 61.7% (Gr. I, S+ : 81 cases), 38.9% and 50.0% (Gr. II, S- : 18 cases), 76.9% and 87.2% (Gr. I, S- : 39 cases) respectively. While main reason for stay beyond 90 days in Gr. I (35 cases) was delay of smear negative conversion (57.1%), complication (31.4%) and adverse reaction (14.3%), that in Gr. II (47 cases) was delay of smear negative conversion (42.6%), adverse reaction (27.7%), retreatment (23.4%), drug resistance (21.3%) and complication (14.9%).

[Discussion] Our criteria contributed to longer hospital stay especially in smear positive cases. Continued smear positivity, delayed culture negative conversion in MGIT culture compared with OGAWA culture, necessity of susceptibility to all four drugs and adverse reaction are main responsible factors for longer hospital stay. In conclusion cooperation with public health center for patients to continue therapy is very important.

2. An evaluation of discharge criteria for tuberculosis patient by NHO (National Hospital Organization) : Kazunari TSUYUGUCHI, Katsuhiko SUZUKI, Mitsunori SAKATANI (NHO Kinki-chuo Chest Medical Center)

National Hospital Organization (NHO) established discharge criteria for tuberculosis patients (NHO criteria) based on formerly established discharge criteria by the Japanese Society for Tuberculosis (JST criteria). NHO criteria was made to substantiate two major points in JST criteria : 1) disappearance of infectiousness ; and 2) establishment of adherence to treatment.

To evaluate NHO criteria, NHO mailed a questionnaire to all NHO hospitals. Mean duration of hospitalization of tuberculosis patients at most NHO hospitals was shortened

after adoption of NHO criteria. The most important criterion for discharge was how to improve adherence to treatment. NHO criteria was effective in shortening duration of hospitalization, although the problem of nonadherence to treatment remains to be solved.

3. Effects of change of discharge criteria on hospitalization duration and treatment outcomes of patients with tuberculosis: Nobuyuki KOBAYASHI, Eriko MORINO, Emiko TOYOTA, Koichiro KUDO (Division of Respiratory Medicine, International Medical Center of Japan)

The criteria for discharge of TB patients from our hospital have been changed from “negative conversion of culture” to “negative conversion of smear” since January 2003. The median length of hospitalization of 259 patients discharged under renewed discharge criteria (new criteria group) was 69 days, 15 days less than that of 459 patients discharged under previous criteria (old criteria group), although the TB diseases of new criteria group were more severe and more extended. In spite of reduction of hospitalization duration, the rate of treatment completion increased slightly after the change of discharge criteria. This is due to the increased ratio of DOTS in out-patient treatment period (from 6.1% to 45.0%) in cooperation with local health centers, and decreased ratio of drop-out patients in the new criteria group. For the treatment of one TB patient, about 150 thousand yen was saved by changing discharge criteria. Importantly, there was no deterioration in 1 year relapse ratio in new criteria group.

4. Concept about following patients with smear positive tuberculosis in western countries: Kunihiko ITO (Department of Research, Research Institute of Tuberculosis, Japan Anti-Tuberculosis Association)

The criteria for discharge of tuberculosis patients from hospitals in western countries were reviewed. In most countries, the criteria for discharge are not concerned with the infectivity of patients itself, unless the patient is not multi-drug resistant tuberculosis, and there is no person of high-risk for tuberculosis disease, such as HIV-positive person or children less

than 4 year-old, within home the patient come back to. But the criteria in most countries has concerned with the security of treatment, such as support system for regular drug taking or socio-economical support for homeless persons.

5. Opinion from Tuberculosis Society about requirement for discharge of tuberculosis patients: Eriko SHIGETO (National Hospital Organization Higashihiroshima Medical Center)

In the Guidelines for Admission and Discharge of Tuberculosis published on 2005, we emphasized that DOTS have to be prepared on discharge. Further, we suggest that hospital care should be approved and public subsidy for medical treatment should be extended for patients who are at risk of treatment failure and acquiring drug resistance regardless of present infectiousness. Mandatory treatment should be considered for the patients who do not obey treatment instruction.

Various changes have been carried out about medical surroundings of tuberculosis including criteria of discharge from hospital. Throughout the discussion, successes of treatment of each patients with tuberculosis are most important goal in medical care of tuberculosis. Therefore foundation of DOTS should be established with support by the government and then we can secure both human right and health. Curtailment of hospitalization and saving medical cost will be followed as a result.

**Key words** : Tuberculosis, Infectiousness, Criteria to release isolation, Criteria for discharge, DOT for outpatients

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The 81st Annual Meeting Educational Seminar

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## TREATMENT OF NON-INVASIVE PULMONARY ASPERGILLOSIS WITH NEW ANTI-FUNGAL DRUGS

Atsuyuki KURASHIMA

**Abstract** Pulmonary aspergilloma is characterized radiographically by the presence of a fungal ball. However, this disease process begins from a considerably earlier date. X-ray findings can detect the early stages of this disease better than any other inspective methods. From the treatment perspective, it is too late to start anti-fungal drugs after a fungus ball has already appeared. Therefore, image analysis of this disease process is important for early diagnosis.

We examined 48 lesions in 41 cases where images were traceable before the recovery of precedent lung diseases.

We could divide the development of pulmonary aspergillosis into the following 10 steps, through analysis of all films including CT findings.

- Step 0: Basic state
- Step 1: Initial consolidation
- Step 2: Cavity wall thickening
- Step 3: Further thickening
- Step 4: Irregular inner layer
- Step 5: Desquamation
- Step 6: Fungus ball formation
- Step 7: Enlargement downward
- Step 8: Spreading to other lung field
- Step 9: Extra pulmonary extension

The sequential line could be indicated as the development of pulmonary aspergillosis through plotting the points of each steps and elapsed days from step 0. The longest observation days are about 8200 days.

We learned the followings from this analysis.

1. The courses of progression revealed that pulmonary aspergillosis is not worsening linearly, while with ups and downs.

2. General tendencies are divided into two groups as a rapid development group and as a chronic development group.

3. Fungus ball is configured on average one month later

after the irregular inner layer appeared.

4. Initial consolidation appears on average at 783 days after the image of the precedent disease improved it most, and fungus ball is configured afterwards at 1588 days.

5. Pulmonary aspergillosis is not a static disease that has dynamic process.

6. Spontaneous limited remissions were observed in 14%, but the usage of anti-fungal drugs (mainly with ITCZ) shortened the interval period to remission significantly.

7. In the same analysis of another 21 cases with MCFG treatment, the interval period to remission was 66.4 days, and 17 cases with VRCZ treatment, that was 58.5 days.

Consequently, pulmonary aspergilloma originates from minor changes without fungus ball, and terminates with fatal extensive destructive lesions. This disease is configured with each different sequential stage.

The clinical terms of "Pulmonary aspergilloma" or "Semi Invasive Pulmonary Aspergillosis" describes only a limited phase of this chronic and prolonged disease. We consider that the term of "Chronic Necrotizing Pulmonary Aspergillosis" is more suitable expression for this disease entity, if the original definition could be re-defined.

**Key words:** Non invasive pulmonary aspergillosis, Sequela of pulmonary tuberculosis, Cavity, Pulmonary aspergilloma, ITCZ, MCFG, VRCZ, Surgical treatment

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