

Original Article

FREQUENCY OF MDR-TB/XDR-TB STRAINS ISOLATED
FROM CHRONIC PULMONARY TUBERCULOSIS PATIENTS IN JAPAN

¹Yuko KAZUMI, ¹Nobunori ITAGAKI, ¹Masako OHMORI, ¹Masako WADA,
¹Hitoshi HOSHINO, ¹Satoshi MITARAI, ¹Isamu SUGAWARA, ¹Nobukatsu ISHIKAWA,
and ²Toru MORI

Abstract [Purpose] To observe the frequency of MDR-TB/XDR-TB strains isolated from chronic pulmonary tuberculosis patients in Japan.

[Object] Ad hoc National Tuberculosis Survey 2000 on frequency of MDR-TB and XDR-TB strains.

[Materials and method] Four hundred and thirty four clinical isolates were collected by the Ad hoc National Tuberculosis Survey 2000, the drug susceptibility testings (proportion method, MGIT Middlebrook, and BrothMIC NTM) were conducted on these strains. These clinical isolates were obtained from patients registered at Health Centers in Japan by the end of 1999 who were culture-positive in 1999 and were registered before January 1st, 1998. The isolates used in this study were selected from patients who were culture-positive at shortest 2 years after the registration.

[Result] The clinical isolates resistant to both INH and RFP were 321 out of 434 (74.0%). The 180 MDR-resistant clinical isolates were also resistant to levofloxacin and amikacin and/or kanamycin. These phenotypes are XDR-TB. No previously registered cases were 165, and previously registered cases were 143 and unknown cases were 13 out of 321 MDR-TB. In 180 XDR-TB cases, no previously registered cases were 95, previously registered cases were 78 and unknown cases were 7. In no previously registered cases, more than 50%

cases started treatment in 1990s. Approximately 50% of previously registered patients started treatment in 1960s and 1970s.

[Conclusion] We performed drug susceptibility testing for 434 clinical isolates which were culture-positive at shortest 2 years after registration. No. of MDR-TB patients was 321 and that of XDR-TB patients was 180. The treatment outcome of these patients have to be followed up carefully at Health Centers. The frequency of amikacin resistance was relatively high. This may be due to either common use of amikacin or cross-resistance against streptomycin and kanamycin.

Key words : Multi drug-resistant tuberculosis : MDR-TB, Extensively drug-resistant tuberculosis : XDR-TB, National survey, Cross-resistance

¹Research Institute of Tuberculosis, Japan Anti-Tuberculosis Association (JATA), ²National Hansen Disease Research Center

Correspondence to : Yuko Kazumi, Pathology Division, Mycobacterium Reference Center, The Research Institute of Tuberculosis, JATA, 3-1-24, Matsuyama, Kiyose-shi, Tokyo 204-8533 Japan. (E-mail: kazumi@jata.or.jp)

————— Short Report —————

NEW COHORT ANALYSIS SYSTEM IN NEW TUBERCULOSIS SURVEILLANCE SYSTEM IN JAPAN

Hitoshi HOSHINO, Masako OHMORI, Takashi YOSHIYAMA, Masako WADA,
Yuko YAMAUCHI, and Kazuhiro UCHIMURA

Abstract [Purpose] To know factors to influence treatment outcome of new cohort analysis method in revised TB surveillance system and important points for quality improvement of the system using hospital based real data of TB patients.

[Methods] To analyze treatment outcome of new sputum smear positive TB patients hospitalized to Fukujuji Hospital during 2004 year by new cohort analysis method.

[Results] One hundred and ninety-four TB patients were hospitalized. Out of them, 166 were new cases. Cohort analysis showed 104 treatment success cases (62.7%), 27 died cases (16.3%), 2 failure cases (1.2%), 9 defaulter cases (5.4%), 15 transfer-out cases (9.0%), 7 cases with treatment longer than 1 year (4.2%), and 2 other cases (1.2%). Among 27 died cases, 18 cases were due to TB death. Out of other 9 cases, 4 were due to malignancy, 3 due to pneumonia, and 2 other causes. Out of 9 defaulter cases, 6 were self-interruption, 2 were due to medical doctor's decision to resolve side effects. Out of 7 cases with treatment longer than 1 year, half were due to drug resistance and another half were due to side effects. Twenty-eight retreatment cases showed 15 treatment

success, 4 failure cases, 5 transferred-out, 2 cases with longer treatment than 1 year, and 2 other cases.

[Discussion] To evaluate TB treatment outcome, died cases should be categorized into TB death and non-TB death. Defaulter cases and cases with treatment longer than 1 year should be categorized by causes into drug resistant cases and cases with interruption by side effects. At national level, data collection of drug sensitivity test results and development of cohort analysis method for drug resistant cases, especially multi-drug resistant cases, are needed to make new cohort analysis method more relevant to TB treatment outcome.

Key words: Tuberculosis, Cohort analysis, Surveillance

Research Institute of Tuberculosis, Japan Anti-Tuberculosis Association (JATA)

Correspondence to: Hitoshi Hoshino, Research Institute of Tuberculosis, JATA, 3-1-24, Matsuyama, Kiyose-shi, Tokyo 204-8533 Japan. (E-mail: hhoshino@jata.or.jp)

THE PATHOGENESIS AND THE DEVELOPMENT MECHANISM OF *MYCOBACTERIUM AVIUM* COMPLEX INFECTION

Kenji HIBIYA, Futoshi HIGA, Masao TATEYAMA, and Jiro FUJITA

Abstract *Mycobacterium avium* complex (MAC) causes respiratory tract infections and develops granulomatous lesions in the alveolar areas and bronchioles in humans. In contrast with the above, the intestinal tract is the primary infection site of immunocompromised hosts, such as patients with acquired immune deficiency syndrome (AIDS), or animals, such as pigs. Recent studies have revealed that hosts with hereditary dysfunction of mediators in the Th-1 cascade as well as hosts with a high titer of auto-antibodies against interferon- γ are susceptible to MAC, and such hosts facilitate dissemination of MAC. However, their disseminated lesions are formed mainly in the lung or in soft tissues, and the mechanism of development of MAC in such host may be different from that of AIDS-related MAC infection. In this review, we specifically discuss the development mechanism of disseminated MAC disease in recently-identified several

pathological conditions.

Key words: Acquired Immune Deficiency Syndrome, Pigs, *Mycobacterium avium* complex, Dissemination, Pathogenesis, Development mechanism

Department of Medicine and Therapeutics, Control and Prevention of Infectious Diseases, Faculty of Medicine, University of the Ryukyus.

Correspondence to: Kenji Hibiya, Department of Medicine and Therapeutics, Control and Prevention of Infectious Diseases, Faculty of Medicine, University of the Ryukyus, 207 Uehara, Nishihara-cho, Okinawa 903-0215 Japan.
(E-mail: k068736@eve.u-ryukyu.ac.jp)

Case Report

A SURGICALLY TREATED CASE OF ILEUS CAUSED BY SMALL INTESTINAL TUBERCULOSIS DURING TREATMENT FOR PULMONARY TUBERCULOSIS

¹Norihiko IDA, ²Keizo YAMAMOTO, ¹Hideo GONDA, ¹Takashi OISHI,
¹Nobukazu SUGANUMA, ³Ikuo YAMAGUCHI, ³Keiko KINOSHITA, and ¹Ryujiro SUZUKI

Abstract A 44-year-old man consulted medical clinic, complaining of cough and sputum. Then he was admitted to our hospital, because of positive acid-fast bacilli in his sputum and positive PCR (polymerase chain reaction) for *Mycobacterium tuberculosis*. Combined use of isoniazid (INH), rifampicin (RFP), ethambutol (EB) and pyrazinamide (PZA) was started. But 4 days after starting treatment, we had to suspend tuberculosis chemotherapy because of hepatopathy. Since then he started to complain epigastralgia and vomiting. Plain abdominal X-ray and abdominal computed tomography (CT) led to a diagnosis of ileus. In spite of insertion of ileus tube symptoms of ileus did not improve. Small bowel series showed severe stenosis at ileum end, necessitating jejunectomy.

Macroscopic study revealed a ring ulcer and multiple epithelioid cell granuloma with Langhans' giant cells was detected histopathologically. PCR for *M. tuberculosis* of extracts from ileum was positive. Therefore the patient was

diagnosed small intestinal tuberculosis. Treatment was continued by the combination of INH, RFP, EB, and the symptoms markedly improved. There have been no sign of recurrence since the end of the 6-month treatment for tuberculosis.

Key words: Small intestinal tuberculosis, Pulmonary tuberculosis, Ileus, Peritonitis, PCR

Department of ¹Respiratory Medicine, ²Infection Control Center, and ³Clinical Laboratory, Toyohashi Municipal Hospital

Correspondence to: Norihiko Ida, Department of Respiratory Medicine, Toyohashi Municipal Hospital, 50 Hachikennishi, Aotake-cho, Toyohashi-shi, Aichi 441-8570 Japan.
(E-mail: norihiko@mva.biglobe.ne.jp)

THE NEW MEASURES AGAINST TUBERCULOSIS IN JAPAN

Satoru MIYAKE

Abstract The incidence rate of TB is 236 in western pacific region in 2004, and is 23.3 in Japan. Though the rate in Japan is getting lower steadily, it is still higher than that in UK, USA or in Canada. The advent of patients is more popular among elderly and urban population. The localized outbreak of TB in medical institutions or schools is not rare yet.

The Tuberculosis Control Law was altered two years ago, to fit new policy including adoption of DOTS, direct BCG inoculation without tuberculin test, and so.

In this year, that Law was abrogated and integrated to the Law Concerning the Prevention of Infections and Medical Care for Patients of Infections. That Law provides proper management of pathogen, provides tuberculosis with the position of second grade hazardous disease, with enforced isolation for smear positive patients. It is improved to treat

patients promptly and properly, especially in light of human rights. Even new measures are carried out, control of tuberculosis is still difficult problem as before and we must keep tackling with it.

Key words: New measures against tuberculosis, Tuberculosis Control Law, Law Concerning the Prevention of Infections and Medical Care for Patients of Infections

Tuberculosis and Infectious Disease Control Division, Health Service Bureau, Ministry of Health Labour and Welfare, Japan

Correspondence to: Mitsunori Sakatani, NHO Kinki-chuo Chest Medical Center, 1180 Nagasone-cho, Kita-ku, Sakai-shi, Osaka 591-8555 Japan.

————— The 82nd Annual Meeting Educational Lecture —————

MOLECULAR EPIDEMIOLOGY OF TUBERCULOSIS

Tomoshige MATSUMOTO

Abstract Tuberculosis is one of the ancient diseases with a long history of afflicting mankind. The incidence rate of tuberculosis in Japan, which is gradually decreasing, is the highest among the industrial countries. But it may be re-emerging according to the situations around Japanese tuberculosis policies. Especially, the problems of the extensively drug-resistant (XDR) strains of tuberculosis disease have appeared in wealthy countries, also in Japan. We must focus attention on how to decrease the scourge.

One of the tools to trace and prevent the development of tuberculosis, especially, the XDR strains is molecular epidemiology. Research of molecular epidemiology has expanded to study tuberculosis transmission, re-activation and re-infection based on DNA fingerprinting, such as IS6110 RFLP, spoligotyping, and VNTR. The global scale and molecular epidemiology of the XDR strains of tuberculosis require urgent assessment.

The molecular epidemiology can be applied in clinical practice. We showed some examples about usefulness of the clinical application of molecular epidemiology, especially

using VNTR.

Now, we can use a various kinds of DNA fingerprinting. Each method has its own respective merits and demerits. So, it is important to select molecular epidemiology method according to the purpose.

Key words: XDR-TB, MDR-TB, VNTR, IS6110 RFLP, Molecular epidemiology of tuberculosis

Department of Clinical Research and Development, Osaka Prefectural Hospital Organization Osaka Prefectural Medical Center for Respiratory and Allergic Diseases

Correspondence to: Tomoshige Matsumoto, Department of Clinical Research and Development, Osaka Prefectural Hospital Organization Osaka Prefectural Medical Center for Respiratory and Allergic Diseases, 3-7-1, Habikino, Habikino-shi, Osaka 583-8588 Japan.

(E-mail: tom_matsumoto@sutv.zaq.ne.jp)

EFFECTIVE MEASURES FOR PROMOTING THE NEW TUBERCULOSIS CONTROL PROGRAM OF JAPAN

Chairpersons: ¹Tadayuki AHIKO and ²Noriko KOBAYASHI

Abstract Although the incidence of tuberculosis has markedly decreased over the last half-century, Japan is still classified by WHO as an “intermediate burden” country. In April 2007, the Tuberculosis Control Law was integrated into the Infectious Diseases Control Law. The integration of these laws and technical innovations in diagnosis of tuberculosis such as QuantiFERON will be helpful to improvement in the quality of tuberculosis control programs.

Effective measures promoted under the new law are the contact investigation and the treatment of persons with latent tuberculosis infection (LTBI) to prevent the development of active disease. Furthermore, practical measures are needed to improve tuberculosis case detection and cure rates.

In this symposium, we discussed how to implement the above-mentioned measures effectively aiming at the elimination of tuberculosis in Japan.

1. Development and application of a regional cooperation critical pathway for tuberculosis : Chinami MOCHIZUKI, *Tadatoshi SURUDA (Division of Nursing, and *Respiratory Medicine, NHO Wakayama National Hospital)

After introducing the new criteria for discharge of tuberculosis patients, the mean period of hospitalization has been shortened in Wakayama National Hospital. The next problems are insufficiency of DOTS system after discharge and defect of consensus with clinicians and other medical care staffs. One of the solutions may be an application of a regional cooperation critical pathway for tuberculosis, in which a support of executive agency, including public health center, is indispensable. The role of pharmacy is also very important.

In order to develop a liaison critical pathway for tuberculosis in all areas of Wakayama Prefecture, a conference group was established with aid of executive agency, pharmacy, medical

care staffs and others. A concrete critical pathway was applied in some patients and some problems to be solved were discussed.

2. Turning point of treatment of hospitalized patients with tuberculosis — under the Infectious Diseases Control Law — : Emiko TOYOTA (Division of Respiratory Medicine, NHO Tokyo National Hospital)

In the process of innovation, number of beds for management of patients with infectious tuberculosis has decreased every year. The Tuberculosis Control Law integrated into the Infectious Diseases Control Law in April 2007 and more rapid management will be required.

To recognize the actual state of hospitalized patients with tuberculosis, I studied 674 cases who admitted to the TB wards in International Medical Center of Japan and National Hospital Organization Tokyo National Hospital. 558 cases were active tuberculosis and other 102 cases (15%) were suspected but finally diagnosed other disease.

Although patients with multi-drug resistant tuberculosis (MDR-TB) were 0.9% and patients with HIV-TB dual infection were 1.3%, 20% of 558 cases were elder over 80 years old, and 37% had various severe complications. 18% were classified severe tuberculosis with large numerous cavities, extensive lesions more than one lung field or disseminated to other organs. 12% died during hospitalization and 31% predicted non-adherence after discharge. Finally 75% cases had more than one of these considerable factors to adapt fundamental clinical (critical) pathway.

Clinical pathway is supposed to be available for treatment of tuberculosis at least 25% of hospitalized patients with tuberculosis.

3. Investigation of contacts of persons with infectious tuberculosis: Makoto TOYOTA (Kochi City Health Center)

In 2007, a new guideline for the investigation of contacts of persons with infectious tuberculosis was published in Japan. Index patients with positive acid-fast bacillus sputum-smear results have the highest priority for investigation. When exposure is related to households, or cough-inducing medical procedures, contacts are designed as high priority. Contacts aged <5 years and immunocompromised persons are also designed as high priority. QuantiFERON-TB Gold test is recommended for evaluation of LTBI. Treatment for LTBI should be offered to all contacts that have a positive QFT result, after active tuberculosis is excluded.

4. Treatment of Latent Tuberculosis Infection: Yuka SASAKI (NHO Chiba-East National Hospital)

[Purpose] To evaluate the problem of treatment of LTBI.

[Result] 1) In Japan, the treatment of persons with LTBI was not recommended to those over 30 years old. In our hospital, 10 cases of 21 cases having the history of recent infection were over 30 years old. So recent contacts with LTBI should be treated regardless of age.

2) Immunocompromised persons infected tuberculosis previously have high incidence of tuberculosis. Many of diabetes mellitus or HIV infected patients do not visit hospitals for treatment, so many of them cannot receive the treatment for LTBI.

3) In Japan, the investigation of contacts of persons with

MDR-TB is always carried out, but the effective treatment protocol for latent MDR-TB infection has not been established.

5. Framework of tuberculosis control in low incidence situation: Seiya KATO (Research Institute of Tuberculosis, Japan Anti-Tuberculosis Association)

The framework for tuberculosis control in low incidence situation was discussed based on the experience of UK and US. The challenges of tuberculosis control in the low incidence situation are to secure human and financial resources and to maintain technical expertise. Future TB control in Japan needs to consider the following; (1) strengthened commitment of the central government, (2) securing technical expertise by utilization of experts and technical support from central level, (3) restructuring of medical service, (4) establishment of bacteriological surveillance, especially genotyping, (5) network of experts.

Key words: Tuberculosis control, Latent tuberculosis infection, Contact investigation, DOTS, Critical pathway

¹Yamagata Prefectural Institute of Public Health, ²Research Institute of Tuberculosis, Japan Anti-Tuberculosis Association

Correspondence to: Tadayuki Ahiko, Yamagata Prefectural Institute of Public Health, 1-6-6, Tokamachi, Yamagata-shi, Yamagata 990-0031 Japan.

(E-mail: ahikot@pref.yamagata.jp)