

SUGGESTIONS FOR BETTER MANAGEMENT OF THE TUBERCULOSIS ADVISORY COMMITTEE

Kazuhiko KAMEDA

Abstract Since 1951 tuberculosis advisory committee, established according to the tuberculosis control law, has played an important role in improving the quality of tuberculosis control programme in Japan.

The management of tuberculous patients has changed markedly in the past ten years due to advances in chemotherapy and changes in the epidemiological situation of tuberculosis.

In this paper, several suggestions were made on better management of the tuberculosis advisory committee intending to judge cases by unified criteria.

Key words: Tuberculosis advisory committee, Tuberculosis control law, Unified standard

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Original Article

ISOLATION OF MPB63 IN THE CULTURE FLUID OF *MYCOBACTERIUM BOVIS* BCG TOKYO : GENETICAL AND IMMUNOLOGICAL CHARACTERIZATION

Katsuhide KAWAJIRI

Abstract MPT63 is a secretory protein first isolated from a culture fluid of *M. tuberculosis* H₃₇Rv by Nagai et al. In this study, this protein was isolated from an 8-day-culture fluid (Sauton synthetic medium) of *M. bovis* BCG Tokyo 172 according to Nagai's method. It was shown that *M. bovis* BCG Tokyo 172 secreted this protein in the medium. The *mpt63* gene was detected only in the species of *M. tuberculosis* complex by polymerase chain reaction (PCR) among 40 different mycobacterial species. Therefore, it is appropriate to designate this protein as MPB63 or MPB/T63 from *M. bovis* BCG, in similar way as other major secretory proteins of Mycobacteria, such as MPB59 and MPB64. Comparison of the nucleotide sequences of the genes encoding MPB63 protein of *M. bovis* BCG and MPT63 protein of *M. tuberculosis* showed only single nucleotide difference at the position 474 where thymine (T) in the former was replaced by adenine (A) in the latter. Amino acid sequences of both proteins were completely identical. MPB63 didn't show delayed-type hypersensitivity

(DTH) skin reaction in the sensitized guinea pigs with live or heat-killed *M. bovis* BCG or heat-killed *M. tuberculosis*.

However, the measurements of serum IgG antibody titers of active tuberculosis patients by enzyme-linked immunosorbent assay (ELISA) showed 74% sensitivity and 96% specificity compared to healthy subjects. Therefore, MPB63 seems to be a promising candidate as an antigen for serodiagnosis of active tuberculosis.

Key words: MPB63, Secretory protein, Culture fluid, BCG, PCR, ELISA

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CLINICAL EVALUATION ON THE DURATION OF HOSPITALIZATION FOR PATIENTS WITH PULMONARY TUBERCULOSIS

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Terufumi KATO, Minoru SAKURAMOTO, Yuji MAEDA, and Ko MANIWA

Abstract In 1996, six-month short course regimen containing PZA was adopted as the standard method of chemotherapy for tuberculosis. According we reevaluated discharge criteria for patients with pulmonary tuberculosis and tried to shorten the duration of hospitalization. We investigated retrospectively the duration of hospitalization for patients with pulmonary tuberculosis who were admitted to the Tenri Hospital.

PZA was used for 23.3% of patients who were admitted during 1992 to 1996 (group A, N = 200), and 80.1% of patients who were admitted during 1996 to 2000 (group B, N=234). The time needed to bacterial negative conversion was significantly shortened from 2.5 months in group A to 1.8 months in group B. The mean duration of hospitalization for patients with pulmonary tuberculosis was significantly shortened from 133.8 days in group A to 63.7 days in group B. Moreover, the mean duration of hospitalization for patients with smear positive pulmonary tuberculosis was significantly

shortened from 147.5 days in group A to 73.0 days in group B. There was no significant difference between group A and group B as to the rate of adverse reactions, discontinuation of drug taking and recurrence of the disease.

We concluded that the duration of hospitalization for patients with pulmonary tuberculosis could be shortened by applying PZA in the initial phase of tuberculosis chemotherapy.

Key words: Pulmonary tuberculosis, Hospitalization period, Pyrazinamide, PZA

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TRENDS IN DRUG-RESISTANT TUBERCULOSIS IN NATIONAL HIGASHISAITAMA HOSPITAL, 1994–2001

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¹Tetsuya SHIOMI, ¹Tsuneo SUZUKI, and ¹Takeo KAWASHIRO

Abstract To know the prevalence of resistance to four first-line anti-tuberculosis drugs, we reviewed the results of drug-susceptibility tests of patients with tuberculosis who were admitted to our hospital from 1994 to 2001. Among patients with no prior chemotherapy against tuberculosis, the complete resistance rate was 1.9% for INH, 0.81% for RFP, 5.1% for SM, 0.81% for EB, and 0.32% for multiple drug-resistance (MDR). The acquired resistance rate was 9.7% for INH, 11.5% for RFP, 7.3% for SM, 2.4% for EB, and 6.1% for MDR. There was no significant increase in the prevalence of drug resistance between the first half (1994–1997) and the latter half (1998–2001) of the investigation periods. Compared with the previous reports, our results indicated no increase in the prevalence of drug resistance in tuberculosis patients with no prior treatment and the decrease of prevalence in patients with prior treatment of tuberculosis. A multi-drug regimen consisted of INH, RFP, PZA and EB or SM, which is currently

considered as a standard regimen of tuberculosis chemotherapy and used quite widely, does not seem to induce the increase of drug-resistant tuberculosis.

Key words: Drug-resistant tuberculosis, Multiple drug-resistant tuberculosis, Resistance ratio, Primary resistance, Acquired resistance

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Original Article

USEFULNESS OF CRANIAL AND CHEST IMAGING IN THE DIAGNOSIS OF TUBERCULOUS MENINGITIS AMONG INFANTS AND YOUNG CHILDREN

Shinya KONDO and Masaki ITO

Abstract We retrospectively evaluated the clinical and laboratory data of children with tuberculous meningitis (TBM) treated at our hospital from 1990 to 1999 to determine the optimal method of diagnosing TBM. The evaluated diagnostic criteria for TBM were as follows: (1) fever and malaise as symptoms of acute/subacute inflammation, (2) positive cerebrospinal fluid and/or gastric aspirate cultures for *Mycobacterium tuberculosis*, (3) pleocytosis of cerebrospinal fluid, and (4) a good response to anti-tuberculous therapy. The data for eleven patients (6 boys, 5 girls) with TBM (mean age, 10.7 months) were reviewed. Three patients (27%) were previously vaccinated with BCG. A known contact with tuberculosis was established at the time of admission in four patients (36%). Symptoms related to tuberculosis appeared on the average 14.8 days before the diagnosis. Three patients (27%) were diagnosed as clinical stage I, three (27%) as stage II, and five (46%) as stage III; all patients had fever (100%). With regard to the cerebrospinal fluid examinations, pleocytosis with mononuclear predominance was noted in all patients but one (91%), and mycobacterial staining was positive in three patients (27%). Tuberculin skin test was positive in four out of 10 patients (40%). Mycobacterial staining of gastric aspirate was positive in four patients (36%). Chest radiologi-

cal examinations showed a swelling of the mediastinal lymph nodes and/or parenchymal infiltration in all patients (100%). A cranial CT examination demonstrated a basal meningeal enhancement in all patients (100%), hydrocephalus in nine patients (82%), and infarction in eight patients (73%). These results suggest that chest and cranial CT examinations are useful adjunct methods for diagnosis of TBM in infants and young children suffering from meningitis with pleocytosis of the cerebrospinal fluid and mononuclear predominance, in addition to conventional methods such as the tuberculin skin test, plain chest radiography, and staining for mycobacteria in body fluids.

Key words: Tuberculous meningitis, Infant, Cranial Imaging, Basal meningeal enhancement, Chest radiographic study

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TUBERCULOSIS AND SOCIETY

Toru MORI

Abstract Brief review is made of the interconnections between tuberculosis and poverty and other social factors, with special emphasis on the current Japan's tuberculosis situation. In pre-war Japan, the tuberculosis had apparently an aspect of a socioeconomic problem which led to lively discussions. With the progress in medical technology and control measures after the war, such aspect of the disease has become more masked and difficult to see. Often, it is viewed merely as a problem of a small and special fragment of the population such as homelesses, and its wide and diffuse connections with the society and economy are likely to be overlooked. Studies in tuberculosis, both basic and epidemiological, as well as multidisciplinary, should be further encouraged from such a point of view, in order to lay

such interconnections bare, on which the new control strategy should be based.

Key words: Tuberculosis control, Society, Poverty, DOTS, Epidemiology

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————— The 77th Annual Meeting Educational Lecture —————

MANAGEMENT OF RESPIRATORY FAILURE IN PATIENTS
WITH PULMONARY TUBERCULOSIS

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Abstract The prognosis is very poor in patients with acute respiratory failure (ARF) due to active pulmonary tuberculosis, especially in those who necessitate mechanical ventilation. The underlining factors of ARF are low nutrition, old age and severity because of patient's delay and doctor's delay. So, management consists of two parts, one, early patient detection considering of tuberculosis and early treatment, the other, focused control to high risk groups.

Patients with chronic respiratory failure due to pulmonary tuberculosis sequelae have long insidious period and mainly restrictive, sometimes mixed pulmonary dysfunction. Hypercapnea, pulmonary hypertension and respiratory disorder during sleep are seen in high percentage in them. In acute on chronic failure the principles of therapy are treatment of precipitating factors such as respiratory infection or congestive heart failure, controlled (low flow) oxygen therapy, bronchial hygiene and maintaining adequate pulmonary and circulatory condition. In chronic stage patient education is very important. Management of chronic stage is constructed of nutrition control, long-term oxygen therapy, pharmacologi-

cal therapy, pulmonary rehabilitation including controlled breathing technique, physical chest therapy and exercise training. Noninvasive positive pressure ventilation is effective on improvement of prognosis in chronic respiratory failure, and on treatment in acute on chronic failure.

Key words : Active pulmonary tuberculosis, Pulmonary tuberculosis sequelae, Respiratory failure, Acute respiratory failure, Chronic respiratory failure, Mechanical ventilation, Long-term oxygen therapy, Noninvasive positive pressure ventilation

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BREAKTHROUGH FOR TUBERCULOSIS CONTROL PROGRAM IN JAPAN

Chairpersons: ¹Nobukatsu ISHIKAWA and ²Tadayuki AHIKO

Abstract Half a century has past since the frame of the national TB prevention law was legislated in 1951. Many aspects of the law are now unable to meet the changing needs of current TB problems. This symposium aimed to propose a breakthrough to a new national tuberculosis control program in Japan with 5 speakers from various aspects of the program.

1. BCG vaccination: Isamu TAKAMATSU

The effectiveness of primary BCG vaccination is shown by Meta-Analysis to be 70–80% effective against the serious disease, and 50% effective against pulmonary tuberculosis. Under the current epidemiological situation, BCG vaccination should be continued for infants, especially in the urban cities and the surrounding areas. As for the re-vaccination, there is no enough evidence either for positive or negative effect. WHO, however, does not recommend the re-vaccination because of no grounds for the positive effect. Globally many countries take a negative view. We should critically review efficacy and discontinue the on-going re-vaccination program at the earliest, because the demerit of the re-vaccination particularly of skin scars or keloid is larger than its merit if any. The mea-

asures for childhood tuberculosis need to shift from mass approach to individual and high risk focused ones.

2. Case-finding: Hidenori MASUYAMA

The case detection rate of the annual mass chest X-ray examination (MMR) has recently dropped so low to 0.0069% as the whole and 0.016% for general inhabitants. We need to discontinue the annual MMR for indiscriminate population. However among the young aged 15–19 years, 29% of the total patients were detected by MMR. For people under 40 years of age, MMR is recommended at the special occasions such as the entrance to college, new job, or new environment. For those aged 40 years or above, MMR is advised as a part of the routine periodical health examination. Special attention needs upon high-risk groups, for them annual MMR is recommended.

3. Treatment program: Motoyasu OKUNO

Standard regimen with 2HRZE(S) /4HR(E) and DOT particularly for the in-patients should be further promoted unless there are contraindications. The current use of standard regimen is still 55% for the sputum smear positive cases. Most

of the sputum smear patients spend more than 2 months in hospitals in Japan. We have however little study results yet in Japan how or to whom DOT should be applied. For preventing drug resistance, we need to promote studies for effective tuberculosis treatment.

4. Issues for Tuberculosis prevention Law : Tomokazu INAGAKI

Current TB Prevention Law needs revision because of the changing situations in TB epidemiology, medical technology, concept for human rights and decentralized government system. For the revision, following viewpoints are necessary: 1) objective and policy of the law, 2) notification and surveillance system, 3) actions for infectious patients and patient's rights, 4) control measures for group infection in community and institutions, 5) new control measures to changing epidemiological situation, 6) legal issues for protecting executor of the control measures, 7) flexible control measures to meet local needs, 8) does legal system contribute to TB elimination? 9) to include TB control in "Infectious Disease Law" or to develop New TB Law?

5. TB control program and decentralization : Tadayuki AHIKO

NTP in Japan has been carried out by the central government throughout the country in the last five decades, and the TB incidence has considerably declined. However, Japan has yet the highest TB incidence among the industrialized nations. Current national surveillance data show that the decrease of TB is stagnating and the difference in the epidemiological features among prefectures has been expanded. The quality of control activities through public health centers has been also

deteriorating in many prefectures. It is anticipated that a promotion of decentralized health care systems will be a breakthrough to TB elimination in Japan. However, a strategic plan needs to be developed by each local government under the revised national program, and the plan should be periodically revised based on local surveillance and program evaluation data.

6. TB programs in European countries : Akira SHIMOUCI

An international workshop is held every year for TB coordinators from most European countries to exchange the data and to standardize the criteria. Evaluation of treatment result evaluation and RFLP analysis are also made. Hospitalization of patients is only for examination and care of severe patients, but not for isolation. Despite no isolation policy, TB incidence of indigenous population has steadily decreased in Western Europe. The effectiveness of isolation policy should be also critically reviewed in Japan. As TB incidence decreased, TB coordinator's posts are secured at national and provincial levels, and their network is strengthened.

Key words: TB control program, BCG revaccination, Health examination, DOTS, TB prevention law, Decentralization

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EDUCATION AND TRAINING CONCERNING DIAGNOSIS AND TREATMENT OF TUBERCULOSIS

Chairpersons: ¹Ryoichi AMITANI and ²Hirohisa TOGA

Symposium Topics and Presenters:

1. Current status of tuberculosis education in medical schools and future tasks : Shuji KURANE (Fourth Department of Internal Medicine, Nippon Medical School)
2. How to refine the education of tuberculosis in teaching hospitals: suggestion by a physician in a National Chest Hospital: Katsuhiko SUZUKI (Department of Antimicrobial Drug-resistance, Clinical Research Center, National Center Hospital for Chest Diseases)
3. Education of tuberculosis in a general hospital that doesn't have tuberculosis beds: Yasuo NISHIZAKA (Department of Respiratory Medicine, Osaka Red Cross Hospital)
4. Education of tuberculosis for general practitioners, residents in the section of respiratory medicine and co-medical staff: Masakatsu TAKAHASHI et al. (Department of Respiratory Medicine, National Nanao Hospital)
5. A novel system of tuberculosis education for doctors and co-medical staff organised by a public health center, in association with the outbreaks of tuberculosis infections: Makoto TOYOTA (Kochi City Health Center) et al.

Abstract In Japan the incidence of tuberculosis has not declined so much as predicted for a past few decades and is still much higher compared to that in most western industrialized nations. Among several factors probably related to the high incidence of tuberculosis in our country, effects of decrease in concern and knowledge of medical staff, especially doctors, as well as citizens regarding tuberculosis should not be under-

estimated, because they may cause delay in diagnosis and treatment of tuberculosis. In order to resolve the problem, it is urgent to organize an efficient education system in university hospitals and other teaching hospitals concerning the diagnosis and the treatment of tuberculosis. However, there are several disadvantages to the teaching hospitals for tuberculosis education. The number of the teaching hospitals including university hospitals holding tuberculosis beds is gradually decreased, and most tuberculosis patients are hospitalized in some selected hospitals other than university and other teaching hospitals. Consequently, it is easy to surmise that the opportunities and time available for educating medical students and younger doctors concerning tuberculosis has been decreased.

In this symposium, each symposist presented current status of tuberculosis education in university hospitals, national chest hospitals holding tuberculosis beds, teaching hospitals without tuberculosis wards and public health center. They also presented some proposals concerning education and training of tuberculosis management from each different standpoint.

Dr. Kurane from Nippon Medical School outlined the problems of tuberculosis education, and he also referred to the current status of tuberculosis education in medical schools in Japan by analysing the responses to a nationwide questionnaire survey on tuberculosis education sent to 80 medical schools in our country. He emphasized the importance of tuberculosis beds in education and training of younger doctors and co-medical staff regarding tuberculosis management.

Dr. Suzuki from National Center Hospital for Chest Diseases emphasized that university hospitals should possess tuberculosis wards or beds in order to adequately educate medical students and younger doctors regarding the diagnosis and the treatment of tuberculosis, and he also emphasized the importance of establishment of department of infectious diseases in university hospitals to educate specialists of infectious diseases well accustomed to the management of the diseases including tuberculosis.

Dr. Nishizaka from Osaka Red Cross Hospital explained the way of tuberculosis education for doctors and co-medical staff in the teaching general hospital that doesn't have tuberculosis beds. In the hospital tuberculosis education was involved in regular lecture meetings on prevention of nosocomial infections held twice a year. He suggested the importance of tuberculosis education for not only respiratory physicians but doctors of internal medicine, emergency section and otolaryngologists who are likely to be faced with tuberculosis patients.

Dr. Takahashi from National Nanao Hospital holding tuberculosis wards has organized lecture meetings and seminars for educating general practitioners, younger doctors and co-medical staff in hospitals in Ishikawa Prefecture. He collaborated with doctors in a university hospital and in other teaching hospitals to organize the meetings. Each meeting was com-

posed of at least two subjects (combination of tuberculosis and other familiar respiratory diseases) to increase the number of attendants.

Dr. Toyota from Kochi City Health Center presented lecture meetings and seminars on tuberculosis management for educating general practitioners, younger doctors and co-medical staff in hospitals in Kochi Prefecture. The lecture meetings and the seminars are organized by Kochi City Health Center, in association with the outbreaks of tuberculosis infections which were sensationally informed to the public through mass media.

Key words: Tuberculosis education, Tuberculosis wards, University hospital, General hospital without tuberculosis beds, Core curriculum, Public health center

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