

CHARACTERISTICS AND TREATMENT OUTCOMES OF INH-RESISTANT OR RFP-RESISTANT TUBERCULOSIS

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Abstract [Background] As an effective regimen for isoniazid-resistant but rifampicin-susceptible tuberculosis (INHr-TB), the use of a 6-month three or four-drug treatment regimen including rifampicin (or rifampin) and pyrazinamide has been recommended by many experts of the world. On the other hand, treatment regimen for rifampicin-resistant but isoniazide-susceptible tuberculosis (RFPr-TB) has not been well established because of the small number of such patients. In Japan the standard regimen has not been established even for INHr-TB, and the treatment has been done by each physician on the empirical bases.

[Objectives] To determine the adequate therapy of INH-resistant TB or RFP-resistant TB.

[Design] Retrospective cohort study.

[Subjectives] Hundred and eleven INHr-TB patients (4.9%) and 5 RFPr-TB patients (0.2%) out of 2252 new smear-positive tuberculosis patients who were admitted to our hospital from 1994 to 1998.

[Results] Patients with previous tuberculosis history was found in 35 of 111 INHr-TB (31.5%) patients, of which 13 (37.1%) were re-treated within 3 years. On the other hand 146 patients (21.1%) of all new culture-positive tuberculosis

patients (N=690) treated in our hospital from 1997 to 1999 had the previous tuberculosis history of which only 8 patients (5.5%) were retreated within 3 years while 115 patients relapsed more than 10 years after the onset of previous tuberculosis history. The frequency of recurrence within 3 years after the onset of previous tuberculosis history was, significantly higher ($p<0.0001$) in cases of INHr-TB (13/111 [11.7%]) than in cases of newly registered ones (8/690 [1.2%]), and the fact indicates that the incidence of tuberculosis recurrence was higher in INHr-TB patients than in pan-sensitive TB patients when the previous treatment was discontinued or insufficiently implemented.

The resistance pattern of the INHr-strains were as follows. INH alone 40 (36.0%), SM-resistant 47 (42.3%), TH resistant 19 (17.1%), EB-resistant 18 (16.2%), KM-resistant 6 (5.4%), and others 3 (2.7%). Therefore the mean number (\pm SD) of resistant drugs excluding INH was 1.4 ± 0.7 .

Eighteen out of 71 (25.4%) strains with low grade INH-resistance ($0.1 \mu\text{g/ml}$ complete resistance) had also TH-resistance, while only one out of 40 (2.5%) strains with high grade INH-resistance ($1 \mu\text{g/ml}$ resistance) was resistant to TH ($p=0.005$).

Of 111 INHr-TB patients, 9 patients (8.1%) discontinued treatment by themselves, 17 patients (15.3%) admitted to another hospital, and 17 patients (15.3%) died. The patients who died (age [$M \pm SD$] 66.4 ± 14.0 yrs) were older than those who were alive (48.7 ± 17.8 , $p<0.001$), and were too seriously ill to accept sufficient chemotherapy, and therefore their deaths were not considered to be related to INH resistance.

The treatment outcomes of the remaining 68 patients who were followed in our hospital were summarized as follows.

1) Treatment failure occurred in 3 patients, of whom 2 patients could not be treated with full dose rifampicin in the initial phase of treatment because of side effects to liver or accompanying idiopathic thrombocytopenic purpura (ITP). Two out of these 3 patients developed multi-drug resistant tuberculosis (MDR-TB). Success rate of treatment was 65/68 (95.6%).

2) Alterations of regimens after knowing INHr-TB were done in 41 of 65 patients (63.0%) with treatment success in all cases. The susceptible drugs used were 65 (100%) for RFP, 62 (95.4%) for EB, 23 (35.4%) for PZA, 26 (40.0%) for SM, 32 (49.2%) for new quinolone (NQ).

3) The sputum culture conversion rates two months after starting chemotherapy with (N=16) and without (N=52) PZA were 13/16 (81.3%) and 31/52 (59.6%), respectively.

4) After the completion of treatment, relapse occurred in 4 patients during follow-up period (1–39 months). The recurrence occurred in 3 out of 20 patients (15%) treated with INH and two susceptible drugs, none out of 13 with three susceptible drugs (0%), 1 out of 20 with INH and three susceptible drugs (5%), and none out of 11 with more than 4 susceptible drugs (0%), and the fact indicates that there was no significant advantage to add INH of usual dose to the regimens.

5) The durations of treatment were not less than 9 months except one case. When 3 or more susceptible drugs were used, the recurrence rate in the group of treatment duration 9–12 months was 0/12 and that in the group of treatment duration more than 12 months was 1/33. Even in the groups without PZA in the initial 2 months of treatment, the recurrence rate in the group of treatment duration 9–12 month was 0/8, and that in the group of treatment duration more than 12 months was 0/22. The fact indicates that 12 months therapy was sufficient irrespective of the use of PZA.

6) One of 5 RFPr-TB patients discontinued treatment by himself. Remaining 4 patients were treated by 4.5 ± 0.5 susceptible drugs including INH for more than 20 months (21.7 ± 2.8 months) after sputum culture conversion with the successful result of treatment and no relapses during the followup period for 3–60 months.

[Conclusion] For INHr-TB, even when PZA can't be used because of adverse effects or resistance, 3 or 4 susceptible drugs regimens including RFP for 12 months were effective. For RFPr-TB, the treatment with 4 or more susceptible drugs for 20 months after sputum culture conversion might be adequate.

Key words : Tuberculosis, INH-resistance, RFP-resistance, Chemotherapy

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Field Activities

MINOR OUTBREAK OF TUBERCULOSIS INFECTION IN A JUNIOR HIGH SCHOOL — Infection from a Preventable Case —

Hiroko KOBAYASHI, Megumi IRIYAMA, and Taeko AMANO

Abstract A second-year junior high school student (14 years old) was diagnosed as pulmonary tuberculosis. She was a member of the volleyball club in the school. She complained a high fever of 39 degrees at first on September 13, 2001. She visited a local physician and was administered medicine for a cold. On September 18, she was seen again for cough and fever, and informed the physician that her father was under treatment for pulmonary tuberculosis since June 2000. As a result, she was examined by chest X-ray, and was diagnosed as pulmonary tuberculosis with moderately positive smear and she was referred to hospital "N" where she was admitted on the next day. Three days after admission, a smear specimen of her sputum was heavily positive for tuberculosis bacilli. She had not been given any preventive chemotherapy when her father was diagnosed with TB because the results of her tuberculin skin test performed two months after her father's onset did not meet the criteria for preventive chemotherapy. Restriction fragment length polymorphism (RFLP) was carried out with 2 strains of tuberculosis bacillus isolated from her and her father, and the RFLP pattern of both strains was same. Thus, it can be concluded that the patient was infected from her father and developed pulmonary tuberculosis.

A contact survey was subsequently carried out on October 4, 2001 for 107 students and 20 teachers at the school. None of

the subjects examined showed any abnormalities on their chest X-ray. A tuberculin skin test survey of 105 students and one teacher was also carried out on November 12, 2001, about 2 months after the final contact. The diameter of skin reactions revealed a monomodal distribution pattern in subjects. The results of the present tuberculin skin test were verified with respect to the degree of contact and last tuberculin test in routine health examination at the school. Four students who had close contact with the patient evidently and showed a strong positive skin reaction of more than 30 mm in diameter in the present tuberculin skin test, accompanied by enhanced reaction of more than 20 mm compared with the last tuberculin skin test, were administered preventive chemotherapy.

Key words: Preventable case, Contact survey, Tuberculin skin test, Preventive chemotherapy, Pulmonary tuberculosis, Junior high school

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FIRST TIME TUBERCULIN SKIN TEST AMONG CHILDREN IN ASAMINAMI-WARD, HIROSHIMA CITY

Hirofumi OKUNO

Abstract Tuberculin skin test (TST) was performed on 7,398 babies and infants from April 2000 to September 2002 in Asaminami Public Health Center, Hiroshima City.

Positive (diameter of erythema ≥ 10 mm) rate first time TST among children above six months was higher than that of babies below six months.

Second time TST among children above six months hardly became negative.

Six children were indicated chemoprophylaxis by the results of second time TST and detailed examination, however, all 6 children did not meet with clinical criterion of chemoprophylaxis, and further studies are needed whether such weak positive reaction is specific for tuberculosis infec-

tion or not.

Key words: Babies and infants, 1st tuberculin skin test, 2nd tuberculin skin test, Positive ratio, Negative conversion rate, Chemoprophylaxis

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MORTALITY RATE OF PULMONARY TB IN THE LATE 19TH CENTURY

Tadao SHIMAO

Abstract Statistics Annual of Japan was first published in 1882, and it covered all aspects of statistics in Japan including demography. Sex- and age-specific population and the population in each prefecture were available, and the number of death classified by major causes of death was also shown. R Koch reported the discovery of tubercle bacilli in 1882, and from the latter half of 1883, the number of death due to pulmonary tuberculosis (phthisis) were collected and tabulated together with the death due to meningitis and apoplexy, and the collection of data on death due to pulmonary tuberculosis had continued until 1906 except 1885. Industrialization took place in the late 19th century in Japan, and in accordance with the industrialization, the new epidemic of TB started. Mortality statistics on TB was available since 1899 classified as TB of all forms, pulmonary TB, TB meningitis, intestinal TB and other TB, and official statistics on TB was said to be started from 1899. The data on death due to pulmonary tuberculosis

in the late 19th century was found out by the author from the old Statistics Annual of Japan, and the mortality rate due to pulmonary tuberculosis was tabulated and calculated for the first time, and the secular trend of mortality from pulmonary TB in 47 prefectures in Japan from 1883 and that of sex- and age-specific rate from 1884 until 1899 were shown in this paper.

Key words: Mortality rate of pulmonary TB, TB statistics in the late 19th century

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Memorative Lecture by the Imamura Award Winner

MOLECULAR EPIDEMIOLOGY OF *MYCOBACTERIUM TUBERCULOSIS*
USING BY RFLP ANALYSIS BETWEEN GENOMIC DNA
— Its Accomplishment and Practice —

Mitsuyoshi TAKAHASHI

Abstract Recently, epidemiology of *M. tuberculosis* have been performed by molecular techniques as a probe with the insertion sequence (IS) 6110. In the traditional study of tuberculosis epidemiology, information about social contact of persons and patient's illness history used to be an only relevant basis for elucidating transmission of tuberculosis infection. Therefore, it was very difficult to give a clear conclusion of whether isolates from different patients derived from a common source of infection or not. The subspecies typing of *M. tuberculosis* strains by IS6110 has become possible, based on the visualization of multiple loci of an insertion sequence (IS6110) that is a relatively stable gene fragment existing in a specific region of the genome. The variability of the number of copies and locations of this IS6110 in a genome is the basis that enables this technique to be used for the above purpose, which is a unique tool applicable to the analysis of *M. tuberculosis*. Generally, this technique, i.e., restriction fragment length polymorphism (RFLP) analysis, depends on the diversity of pattern of any polymorphic marker found in a genome of a strain. Among various markers so far developed and examined, IS6110 has been proved most appropriate for the purpose of typing strains of *M. tuberculosis* complex, especially in such circumstances as in Japan where isolated strains' RFLP patterns are similar each with others so that finer subtyping is needed.

In this time, I would like to review the following topics based on the world literature of molecular epidemiology and the findings of our own that we have achieved during 1992 through 2001 in our Institute; (1) typing for the tracking of source of infection, (2) diffuse infection, (3) the presence of region-specific influential strains, (4) cross-contamination of strains in the laboratory, (5) the stability of IS6110, (6) phylogeny of tuberculosis (genotypes in Okinawa prefecture), and (7) the distinction between *M. tuberculosis* and *M. bovis* BCG, (8) computer-assisted patients management system. We also investigated the mode of transmission and risk factors of tuberculosis, based on the tuberculosis epidemiological data obtained in many parts of the world as well as the findings we gathered in our country from 1992 to 2001.

Key words: Molecular epidemiology, *M. tuberculosis*, RFLP

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The 78th Annual Meeting Lunch Time Lecture

ROLE OF ORAL FLUOROQUINOLONES IN PATIENTS
WITH RESPIRATORY DISEASES

Tadahi ISHIDA

Abstract The characteristics of recently developed oral fluoroquinolones include their broad spectrum involving gram-positive/gram-negative bacteria and atypical pathogens, potent antimicrobial activity against *Pneumococcus*, rapid tissue/sputum transfer, prolonged half-life, and reduction of their interaction with other agents. However, it has been reported that the common use of oral fluoroquinolones increases the number of fluoroquinolone-resistant bacterial strains. We review the appropriate use of these agents in patients with respiratory infections.

In most cases, upper respiratory inflammation is a viral infection. Generally, antimicrobial agents are not necessary, and should not be administered. In Japan, a large number of antimicrobial agents, especially quinolones, are frequently prescribed to treat upper respiratory infection. This tendency must not be corrected.

With respect to treatment for community-acquired pneumonia, it is controversial whether oral fluoroquinolones should be prescribed under various guidelines. In elderly patients and those with an underlying disease, oral fluoroquinolones may be a first-choice treatment at the outpatient clinic, because it is difficult to differentiate atypical pneumonia from bacterial pneumonia, and because the risk of drug-resistant *Pneumococcus* or gram-negative bacteria is high.

With respect to treatment for hospital-acquired pneumonia,

oral fluoroquinolones are recommended for patients with moderate or mild conditions without risk factors under the Guidelines established by the Japanese Respiratory Society.

Bacteria causing acute infectious exacerbation in patients with chronic pulmonary diseases include gram-positive/gram-negative bacteria and anaerobic bacteria. Therefore, oral fluoroquinolones may be the most appropriate treatment for such patients.

New oral fluoroquinolones show potent antimicrobial activity against tubercle bacillus, and may also be effective for infection with bacteria resistant to standard antitubercular agents. It may be controversial whether these agents should be indicated for atypical acid-fast bacterial infection.

Key words : Fluoroquinolones, Respiratory infections, Drug resistance, Appropriate use

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The 78th Annual Meeting Lunch Time Lecture

MEASURES FOR TUBERCULOSIS IN COMPROMISED HOSTS

— Mainly on Chemoprophylaxis —

Fumio YAMAGISHI

Abstract As for the measures for tuberculosis in Japan, BCG inoculation and chemoprophylaxis have been done with emphasis placed on children and young people. Since, however, about 90% are older than 30 years and more than 50% are older than 60 years among the new TB patients, measures, particularly chemoprophylaxis aiming at the middle-old aged people are needed in the future.

We discuss the method to select cases for chemoprophylaxis as to the cases of diabetes, collagen diseases and lung cancer administered corticosteroid preparations as well as the cases of Crohn's disease and rheumatoid arthritis administered anti-TNF- α among compromised hosts.

In diabetics, chemoprophylaxis is necessary for those who show healing of TB despite there being no history of TB treatment. Where a corticosteroid preparation, more than 10 mg in terms of prednisolone is administered over a long period of time for collagen disease and lung cancer, chemoprophylaxis is necessary for those who show healing of TB despite there being no history of TB treatment and those who are suspected of having TB infection by a tuberculin test. In

the cases of Crohn's disease and rheumatoid arthritis administered anti-TNF- α , chemoprophylaxis is necessary for those who show healing of TB despite those who are suspected of having TB infection by a tuberculin test.

The administration period of INH as chemoprophylaxis should preferably be set at 9 months instead of 6 months hitherto used.

Key words: Compromised host, Pulmonary tuberculosis, Chemoprophylaxis, Diabetes mellitus, Corticosteroid, Anti tumor necrosis factor- α

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