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Review Article

TRANSMISSION OF TUBERCULOSIS (II)

Masakazu AOKI

Abstract In the previous paper (Kekkaku. 2004; 79: 509–518), the author has made a review on (1) development of droplet nuclei infection theory, (2) experimental basis and (3) epidemiological evidence of droplet nuclei infection, and has discussed about the factors influencing on tuberculosis infection. Various mode of transmission of tubercle bacilli from nonpulmonary sources was reviewed in the present paper, such as (1) infection from cutaneous tuberculosis, (2) infection in the bacteriology laboratory, (3) infection by needle stick, (4) transmission by bronchoscopic examination, (5) tuberculosis infection in the autopsy room, (6) infection followed vaccination and/or cortico-steroid injection therapy, (7) congenital tuberculosis, and (8) other rare transmission of tuberculosis. Moreover, three topics concerning tuberculosis infection were discussed, they are (1) tuberculosis infection risk index, (2) highly infectious case, and (3) virulence and infection. Infection risk index is the product of smear positivity (expressed by Gaffky Grading) by duration of cough (expressed by month). This index is being used widely at the occasion of contact survey at present in Japan so that instructions for use were discussed.

Key words: Tuberculosis infection from nonrespiratory sources, Infection risk index, Highly infectious case, Virulence and infection

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VALIDITY OF MEASURING TIME TO DETECT GROWTH OF M.TBC
BY BACTEC MGIT960 SYSTEM FOR
QUANTITATION AND PREDICTION OF MYCOBACTERIAL GROWTH

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Yutaka NISHIGAKI, Yuka FUJITA, Toshiaki FUJIKANE, and Tetsuo SHIMIZU

Abstract  [Study design] Time to detect growth of M.tbc by BACTEC MGIT 960 system was examined in sputum specimens collected from 114 patients with active pulmonary tuberculosis before and during antituberculosis therapy. By measuring TTD under chemotherapy, we tried to quantify mycobacterial growth and determine the sensitivity of MGIT system.

[Results] The mean TTD significantly decreased in response to an increment in the range of the quantitation scale for solid media. Moreover, the TTD negatively correlated with colony counts ($r = -0.636, P < 0.01$). When automated monitoring continued until Day 28 after incubation, MGIT system had been capable of detecting 98% of Ogawa-positive specimens. The receiver operating characteristic (ROC) curve was plotted to determine the sensitivity and specificity in MGIT system, indicating the sensitivity of 98.3% corresponding cutoff level for TTD of Day 28.

[Conclusion] Measuring TTD in MGIT system could allow estimating the mycobacterial growth in similarly quantitative manner. The appropriate endpoint of monitoring could be decided as 4 weeks, accurately reflecting an outcome of cultivation with solid media.

Key words: Mycobacterium tuberculosis, Mycobacteria Growth Indicator Tube (MGIT) system, Ogawa medium, Culture

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Original Article

CLINICAL EVALUATION ON CAUSES OF DEATH IN PATIENTS WITH PULMONARY TUBERCULOSIS

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Abstract  [Purpose] We evaluated the cause of death in patients with active tuberculosis.

[Object and Method] 40 patients (male 32, female 8, mean age 76 years old), died under treatment for tuberculosis during 1999 to 2002 in our hospital, were analyzed. We compared patients’ backgrounds, complications, extent of pulmonary tuberculosis, and outcome of the treatment between 40 died cases and 162 patients who were supposed to be successfully treated by cohort analysis (control group).

[Results] 17 cases died of tuberculosis and 23 cases died of non-tuberculous diseases. Pneumonia occupied the top (9 cases) in the latter group. Died cases were higher in age and showed larger performance status score than the control group. Further, laboratory findings revealed poorer nutritional conditions and higher inflammatory reactions in the died group. The duration of symptoms before admission seemed to be longer in the died group, however, the difference with the control was not significant. All of the died group had complications and the rate of having liver diseases and cerebrovascular diseases was higher than that of the control group. Furthermore, the extent of lung lesions was more extensive in the died group. The frequency of changing drugs due to side effects was higher in the died group, therefore, the proportion of cases completed the standard treatment was lower in the died group.

[Discussion and Conclusion] Impossibility of continuing the standard treatment gave unfavorable impact in the died cases rather than the delay in their admission. Due to the above reasons, negative conversion of their sputum culture was difficult, and they died of tuberculosis directly or indirectly. Some of the patients who died of pneumonia (non-tuberculous death) might be included in cases died of tuberculosis.

Key words: Tuberculous death, Non-tuberculous death, Pneumonia, Standard treatment

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PROCESS OF ACQUIRING DRUG RESISTANCE, RETROSPECTIVE REVIEW OF RECORDS OF MDR TB

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Abstract  [Purpose] To investigate the reasons of acquiring drug resistance among MDR TB cases and to learn lessons for the prevention of acquiring of drug resistance.

[Method] Retrospective review of 159 MDR TB cases who were treated at Fukujuni Hospital from 1990 January to 2003 August.

[Result] We found that among 159 cases, 48 cases were infected with multidrug resistant *M. tuberculosis* bacilli, 35 cases acquired drug resistance, 7 cases were with the history of tuberculosis treatment before 1970 only, and that remaining 69 cases were difficult to evaluate because of the lack of informations on previous drug susceptibility tests. Among 35 cases that acquired drug resistance, the drug susceptibility test patterns before becoming MDR TB were categorized as follows: 12 HR susceptible, 18 H resistant R susceptible, 3 R susceptible (H unknown), and 2 H susceptible R resistant. The factors that may have influenced to acquire MDR were lack of modification of the regimen after knowing drug resistance among H resistant R susceptible cases, and defaulting among cases that were not evaluated (15/69) and H resistant R susceptible cases (3/18).

[Discussion] Control of MDR TB needs to be strengthened. Proper drug susceptibility test, proper choice of drugs at the beginning of treatment and modification of treatment after knowing drug susceptibility test results are important for the prevention of MDR TB. Ensuring patient adherence to treatment is important in the medical institutions where drug susceptibility test is not properly done, in particular, for H resistant R susceptible cases, and guidance to these institutions by the public health centers should be intensified.

Key words: Multidrug-resistant tuberculosis, Acquired drug resistance, Preventable

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vivo analysis of antigen-specific IFN-gamma-secreting CD4
T cells in *Mycobacterium tuberculosis*-infected individuals:
associations with clinical disease state and effect of treatment.
contacts but not patients have higher gamma interferon
responses to ESAT-6 than do community controls in The
17) 森 亨：結核の現状と対策. 日本内科学会雑誌. 2001 ;

ORIGINAL ARTICLE

BASIC CHARACTERISTICS OF A NOVEL DIAGNOSTIC METHOD
(QuantiFERON®-TB-2G) OF LATENT TUBERCULOSIS INFECTION WITH A USE OF
*MYCOBACTERIUM TUBERCULOSIS*-SPECIFIC ANTIGENS, ESAT-6 AND CFP-10

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3Takashi KITO, and 4Toru MORI

Abstract [Purposes] To determine the optimum cut-off level
of a newly developed method for diagnosing tuberculosis
infection based on whole-blood interferon-gamma measure-
ment, and to study the basic characteristics of the method.
[Study Subjects] 1) A total of 220 young, healthy individuals
having no apparent exposure to tuberculosis infection,
most of whom had a vaccination with BCG vaccine. 2) One
hundred eighteen tuberculosis patients who were diag-
nosed by positive *Mycobacterium tuberculosis* on culture. 3) A
group of 75 youngsters exposed to an infectious tuberculo-
sis patient and who showed a strong tuberculin reaction (with
erythema diameter of 30 mm or more).
[Method] Whole-blood specimens of donors were stimu-
lated with antigens, i.e., ESAT-6 and CFP-10, and then cul-
tured. Plasma concentrations of interferon-gamma discharged
were then determined with QuantiFERON®-CM1. Correlation
between interferon-gamma concentrations in response to
ESAT-6 and CFP-10, and their correlation with Mantoux test
results were analyzed for various categories of donors. The
Receiver Operating Characteristics analysis was performed
considering the loss due to misclassification.
[Results and Discussion] The optimum cut-off level was
determined as 0.35 IU/ml for both ESAT-6 and CFP-10. This
gave the test a sensitivity of 89.0% and specificity of 98.1%
in detecting tuberculosis infection. The correlation of interferon-
gamma response with tuberculin tests among BCG-vaccinated
individuals was low, which suggested that the test was not
influenced by previous BCG vaccination. The low correlation
between ESAT-6 and CFP-10 tests suggested that the simulta-
neous use of the two tests was beneficial. As in the case of
clinical tests in general, the cut-off should be set at a lower
level when the test is applied to high prevalence situation and
vice versa.

Key words: Latent tuberculosis infection, Diagnostics, ESAT-
6, CFP-10, IFN-γ, ELISA

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CLINICAL STUDY FOR DEVELOPMENT OF NONTUBERCULOUS MYCOBACTERIAL LUNG DISEASE

Atsuyuki KURASHIMA

Abstract

Development of MAC lung disease

An increase of nodular bronchiectatic type of MAC lung disease becomes a problem among respiratory physician today. The reason is still unknown, but it seems to be globally recognized that this type of MAC disease is developing particularly in middle-aged woman. Some papers mentioned the existence of such type of MAC lung disease already early in the 70s, in Japan. Yamamoto described that 17 cases of middle lobe type lung disease out of 154 non-photochormogen cases, and 76.5% were female, in 1970. Shimoide also pointed such type of 39 cases out of 240 MAC lung disease and 84.6% were female, in 1980. Prince reported MAC lung disease seen in old and middle age female of 21 cases including lethality example of 4 cases without a precedent disease in 1989. After his report, the international consensus of this peculiar type of MAC lung disease seems to be spread.

In 1989, we compared 72 cases of nodular bronchiectatic type of MAC lung disease and 56 cases of diffuse panbronchiolitis (DPB) that was a most typical chronic airway disease at that time in Japan. The average age of disease onset of DPB group was 37.0 ± 16.3 years old and that of MAC group was 54.5 ± 16.3 years old. The percentage of female was 32% in DPB group and 87.5% in MAC group. It was highly possible that two groups belong different parent population. We could grasp that nodular bronchiectatic type of MAC lung disease patients is a unique group. We observed the serial films of 21 cases of nodular bronchiectatic MAC lung disease, and divide the progression of the disease to sequential 7 steps as Fig. 1. Small nodules progress to cavities in mean about 10 years.

However, why is MAC which is opportunistic pathogen with weak virulence, able to form a lesion at unimpaired lung parenchyma? Is there really normal site? Why dose it start from lingula? Why is MAC seen a lot in woman? While it is extremely pathognomonic clinical picture, and, is an extremely interesting problem, most are still unidentified.

Study of MAC lung disease treatment

It was known that Mycobacterium kansasii lung disease is healed with a chemotherapy like analog of anti-tuberculosis chemotherapy, already in those days. However, the results of MAC lung disease chemotherapy were extremely poor. We tried to express a physicians experience quantitatively as follows, in 1987. The results of 8 weeks sputum culture on Ogawa egg medium were converted semi-quantitatively to CFU numbers based on “Japanese standard guideline of Mycobacterium tuberculosis inspection”. We exhibit the ratio of post-treatment consecutive 6 months culture yield to pre-treatment culture yield as response rate, about 110 pulmonary MAC cases. Through this study, we clarify the followings.

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7）相良勇三，林 孝二，倉島篤行：他：肺非定型抗酸菌症の手術成績．結核. 2002 ; 77 : 323.
The results of chemotherapy do not correlate susceptibility test for *Mycobacterium tuberculosis*. Multidrug regimen is more useful. Small extent of lesion is more responsive. Combination with aminoglycoside chemotherapy is more effective. These conclusions were almost same as the ATS guideline of 1990.

New drugs such as, new macrolides and new quinolones appeared for pulmonary MAC treatment through the feedback from systemic MAC complicated AIDS treatments from the latter half of 90’s. We measured the sensitive strain ratio at 2 mcg/ml of OFLX, CPFX, LVFX about 990 clinical isolates and could expect availability for *M. kansasii* or *M. fortuitum*, but these new quinolones are not enough effective for MAC. Also we examined MIC for various antimycobacterial agent by 50 MAC clinical isolates, and we could expect a certain availability of SPFX, GFLX, CPFX, CAM for MAC. The availability of clarithromycin (CAM) has been established through many randomized clinical trials for disseminated MAC complicated AIDS, but for pulmonary MAC, complete cure is still difficult if we use CAM including regimen.

We performed surgical treatment for relatively young patients with localized lesions. We carry out the adaptation reference such as Table, now. The localization of the lesions become a problem at surgical resection. Through the study of our 55 surgical treatment cases, 8 cases (67%) relapsed out of 12 cases which had destructive airway structure in unrected lung field. On the other, only 1 case relapsed (10%) relapsed out of 10 cases without airway destruction in unrected lung. Therefore, even if there is a little dispersal focus without airway destruction in the other pulmonary lobe except purpose focus of resection, it seems that control is possible by post operational chemotherapy.

**Long survival**

As overall consequence, we calculate the survival curves of 201 pulmonary MAC patients visited Tokyo National Hospital from 1953. The survival medium value was 7332 days. The prognosis of nodular bronchiecatic type was better than that of post-tuberculosis type. Extent of disease measured by chest X-ray examination at the time of first visit may be a most affecting factor to the survival rate.

**Key words**: Nontuberculous mycobacteriosis, Nodular bronchiecatic type, Chemotherapy, Surgical treatment

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The 79th Annual Meeting Symposium

NURSING ON TUBERCULOSIS PATIENTS
— Quality Nursing to Support Patient’s Compliance to Treatment —

Chairpersons: ¹Ayako NASU and ²Noriko KOBAYASHI

Abstract  Tuberculosis control program in Japan focuses more on completion of treatment. The activities for patients to complete treatment are being actively done with collaboration between nurses of hospitals and public health nurses of the health centers.

In 2000, Ministry of Health Welfare announced DOTS program version Japan. As a result, health centers of big cities implemented DOTS for homeless tuberculosis patients and hospitals DOT for in-patients. In 2003, the government demonstrated the scheme of DOTS strategy Expansion Program version Japan, which includes community DOTS types to be selected depend upon the risk of default with an individual patient. It is necessary to develop and utilize social and human resources in the community to expand surely supporting system for patient’s compliance. Mutual understanding and collaboration of the relevant organizations become very important.

In this symposium, four panels from hospital, clinic and public health center discuss on the current situation and challenge of supporting system and the assessment of treatment outcome.

1. DOTS implementation with collaboration on nursing activities between hospital and public health center in Kyoto Prefecture: Ikuyo HIROHATA (National Hospital Organization Minami Kyoto National Hospital)

2. From standpoint of clinical practice: Hidenori MASUYAMA (Japan Anti-Tuberculosis Association Shibuya Clinic)

3. The activities for case support based on DOTS Program in Wakayama Prefecture: Kimiko KAWASAKI (Tanabe Public Health Center, Wakayama Prefecture)

4. Assessment of supporting activities for patient’s compliance: Tomoko TAKANO (Uki Public Health Center, Kumanoto Prefecture)

Three speakers gave additional comments and advice on quality supporting and nursing activities for patient’s compliance through good coordination between hospitals and publics health centers.

Key words: DOTS, Hospitals DOTS

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CONTENTS

Review Article

Diagnosis and Treatment of Tuberculous Pleurisy
— With Special Reference to the Significance of Measurement of Pleural Fluid Cytokines — ............................................. 289
Transmission of Tuberculosis (I) ................................................................................................................................. 509
Transmission of Tuberculosis (II) .................................................................................................................................. 693

Original Article

Clinical Analysis of Pulmonary Tuberculosis Detected during Follow-up of Other Underlying Diseases ........................................ 1
The Usefulness of Lymphocyte Stimulation Test (LST) in Side Effects of Antituberculosis Drugs ............................................ 7
The Value of Proper Sputum Collection Instruction in Detection of Acid-Fast Bacillus ......................................................... 33
Relations between Clinical Subtypes of Mycobacterium avium Pulmonary Disease and Polyclonal Infections
Detected by IS1245 Based Restriction Fragment Length Polymorphism Analysis .......................................................... 39
Beijing Family and Other Genotypes of Mycobacterium tuberculosis Isolates in Okayama District ......................................... 47
The Clinical Features of Ultra-Old Tuberculosis Patients in Our Hospital ............................................................... 297
Thoracic Malignancies in Patients with Chronic Tuberculous Empyema ........................................................................... 301
Comparison of Inhibitory Effect of Rifalazil and Rifampicin against Mycobacterium ulcerans Infection Induced in Mice ........ 333
Leukopenia Due to Anti-Tuberculous Chemotherapy Including Rifampicin and Isoniazid .................................................... 341
Tuberculous Lymphadenitis: A Clinical Study of 23 Cases ........................................................................................... 349
A Study on Cases Developed Pulmonary Tuberculosis after Receiving Gastrectomy ....................................................... 355
Pulmonary Nontuberculous Mycobacteriosis in Patients with Lung Cancer .............................................................. 367
Current Status of the Criteria for Discharging Patients with Pulmonary Tuberculosis — Results of Questionnaire
Survey on the Criteria for Discharging Patients from Tuberculosis Wards of the Hospitals in Kanto Area ................................ 375
Tuberculin Skin Test Reaction of Health-Care Workers Exposed to Tuberculosis Infection ................................................. 381
Clinical Evaluation on Isolation of Mycobacterium kansasii in Our Hospital ................................................................. 431
Mycobacterium shinshuense Isolated from Cutaneous Ulcer Lesion of Right Lower Extremity in a 37-Year-Old Woman .......... 437
Evaluation of Quantitative Fit-Testing of N95 Filtering Facepiece Respirators Using Mask-Fitting Tester and
Improvement of Mask Fitting by Instruction .................................................................................................................. 443
Drug Resistance in Recurrent Cases of Tuberculosis .................................................................................................... 461
Molecular Epidemiological Analysis by IS1245 Based Restriction Fragment Length Polymorphism Typing on
Cases with Pulmonary Mycobacterium avium Disease Observed in the Same Family ...................................................... 519
Direct Detection of Rifampicin Resistant Mycobacterium tuberculosis in Sputum by Line Probe Assay (LiPA) .................. 525
Estimation of the Number of Necessary Beds for Tuberculosis Patients, in Japan .............................................................. 553
Miss-managements in Treatment Failure of Pulmonary Tuberculosis .............................................................................. 561
A Study on Inoculum Density and Reproducibility of Drug Susceptibility Testing by BACTEC MGIT960 ......................... 625
Are Tuberculosis Advisory Committees Well-Functioning? ............................................................................................ 631
Usefulness of a Novel Diagnostic Method of Tuberculosis Infection, QuantiFERON® TB-2G, in an Outbreak of
Tuberculosis ................................................................................................................................................................. 637
Validity of Measuring Time to Detect Growth of M.tbc by BACTEC MGIT960 System for Quantitation and
Prediction of Mycobacterial Growth .................................................................................................................................. 705
Clinical Evaluation on Causes of Death in Patients with Pulmonary Tuberculosis ......................................................... 711
Process of Acquiring Drug Resistance, Retrospective Review of Records of MDR TB .................................................... 717
Basic Characteristics of a Novel Diagnostic Method (QuantiFERON® TB-2G) of Latent Tuberculosis Infection
with a Use of Mycobacterium tuberculosis-Specific Antigens, ESAT-6 and CFP-10 ................................................................ 725

Short Report

C-Reactive Protein in Patients with Bacteriological Positive Lung Tuberculosis ................................................................. 309

Case Report

A Case of Pulmonary Tuberculosis Complicated with Tuberculosis of Bilateral Cervical Lymph Nodes and
Exacerbated Pericostal Abscess ........................................................................................................................................ 11
Four Cases of *Mycobacterium xenopi* Pulmonary Disease ................................................................. 313
Pyothorax Associated Lymphoma with Increased Neuron-Specific Enolase Level in Serum and Pleural Effusion:
  A Case Report ................................................................................................................................. 361
Multi-Drug Resistant Lung Tuberculosis Due to Double Infection of MDR Strain ................................ 387
CT Imaging Findings in Congenital Tuberculosis, Part I: Usefulness of Periportal Hypodensity in the Diagnosis
  of Congenital Tuberculosis ............................................................................................................ 391
A Case of Pulmonary *Mycobacterium kansasii* Infection Complicated with Pleural Effusion ........................................ 397
Pseudo-Recurrence of Lung Tuberculosis Based on the Detection of Smear AFB Positive Sputum Due to
  Excretion of Necrotic Material ...................................................................................................... 449
A Case of Cervical and Mediastinal Lymph Nodes Tuberculosis, Tuberculous Pleurisy, Spinal Caries and
  Cold Abscess in the Anterior Chest Wall ..................................................................................... 453
Acute Onset of Somnolence and Amnesia Due to Cerebral Infarction of Bilateral Thalamus Accompanied
  with Tuberculous Meningitis: A Case Report .............................................................................. 469
Pulmonary Tuberculosis Case with Consistant Findings of Endobronchial Spread in Chest Roentgenography
  for about Three Years: A Case Report .......................................................................................... 475
A Case of Pubic Tuberculotic Osteomyelitis and Pericarditis during Anti-Tuberculosis Chemotherapy .......... 531
An Infant with Tuberculosis Who Previously Contacted with an Infant with Congenital Tuberculosis .... 537
A Case of Pulmonary Tuberculosis in Late Stage of Pregnancy ....................................................... 569
Pulmonary *Mycobacterium fortuitum* Infection with Multiple Nodular Shadows in a Healthy man .......... 573

**Field Activities**

Tuberculosis Control in Kawasaki City — Promoting the DOT Program — ............................................. 17
An Outbreak of Tuberculosis in a Long-term Care Unit of a Mental Hospital ........................................... 579

**The 78th Annual Meeting Special Lecture**

Diabetes and Tuberculosis — Bad Companions — ............................................................................. 25

**The 78th Annual Meeting Educational Lecture**

Diagnostic Key-point of the Pulmonary Tuberculosis .......................................................................... 645

**The 78th Annual Meeting Symposium**

Tuberculosis Control Programme for the Elderly with Special Focus on Early Detection ................. 55
The Results of DOTS Strategy ........................................................................................................... 59

**The 79th Annual Meeting Special Lecture**

Reform of Japan’s NTP and Its Technical Perspectives ....................................................................... 587
A Cultural History of Tuberculosis .................................................................................................... 655

**The 79th Annual Meeting President Lecture**

Tuberculous Infection and Biological Response in Man .................................................................... 541

**Memorative Lecture by the Imamura Award Winner**

Molecular Pathogenesis in Tuberculosis Complicated with AIDS .................................................... 659
Clinical Study for Development of Nontuberculous Mycobacterial Lung Disease ............................ 737

**The 79th Annual Meeting Educational Lecture**

Tuberculosis in the Elderly .................................................................................................................. 481

**The 79th Annual Meeting Symposium**

Cutting Edge of Basic Study on Tuberculosis .................................................................................. 487
Present State of Regional Tuberculosis Health Care and Future Accommodations ............................ 605
Strategies against Multidrug-Resistant Tuberculosis ......................................................................... 669
Nursing on Tuberculosis Patients — Quality Nursing to Support Patient’s Compliance to Treatment — 743