Original Article

A STUDY ON INOCULUM DENSITY AND REPRODUCIBILITY OF DRUG SUSCEPTIBILITY TESTING BY BACTEC MGIT 960

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Abstract [Objective] The BACTEC MGIT 960 drug susceptibility system (MGIT AST) has been recently introduced in Japan. The issue of discordant MGIT results compared with the conventionally used Ogawa method has been raised. It has been speculated that discordant results might be due to MGIT inoculum density since there is no standardization step other than dilution of growth for tubes beyond 2 days after MGIT turns out to be positive. In this study, we examined the reproducibility of the MGIT AST system.

[Materials and Methods] Nineteen sputum specimens from drug-resistant and susceptible pulmonary tuberculosis patients were processed with CCE pretreatment reagent (Japan BCG), inoculated into 3 MGIT tubes, and loaded into the MGIT 960. Inocula for MGIT AST were prepared l, 3, and 5 days after MGIT tubes became positive. Cultures on day 3 and 5 were diluted l : 5 with saline. Ten-fold dilutions from each positive culture were plated on Middlebrook 7H11 agar plates for CFU determination. MGIT AST results were compared with those of the conventional proportion method on Ogawa egg and Vite-spectrum (Kyokuto), or Pyrazinamidase (Pzase) assay and Kyokuto PZA test.

[Results and Conclusion] A total of 15 specimens were culture positive in all 3 tubes. Four of 19 cases were removed from the analysis because of negative cultures in one or more tubes. Three of 4 culture negative cases were MDR-TB. Colony counting showed the mean CFU/m*l* of inocula prepared from tubes 1, 3, and 5 days after MGIT tube became positive were 3.6×10^6, 1.6×10^6, 3.1×10^6, respectively. There was no significant difference although the CFU range was wide ($8\times10^4-2\times10^7$). MGIT AST results were consistent among 3 inocula. Moreover, overall concordance rates between MGIT AST and the conventional methods were over 90% for 5 first-line antituberculosis drugs. These results indicate that the BACTEC MGIT 960 system is very useful for rapid diagnosis of drug resistant tuberculosis.

Key words: *Mycobacterium tuberculosis*, BACTEC MGIT 960, MGIT series, Drug susceptibility testing, Reproducibility

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Original Article

ARE TUBERCULOSIS ADVISORY COMMITTEES WELL-FUNCTIONING?

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[1]Masako WADA, and [3]Hideo OGATA

Abstract [Purpose] To evaluate the function status of TB advisory committee to assess treatments of tuberculosis.

[Object and Method] Estimate by questionnaire sheets to public health nurses attending to seminars on tuberculosis at Research Institute of Tuberculosis.

[Result] 137 answers are available for analysis. Of these, 57 (41.6%) TB advisory committees are estimated not to assess treatments of tuberculosis at all and/or to assess treatments without necessary informations on drug sensitivity in more than around half of the cases. In 13 (16.3%) committees of the other 80, many cases are in fact self-assessed. Number of committees that are estimated to functioning well is only 44 (32. 1%).

[Conclusion] Many TB advisory committees are estimated to be malfunctioning from the stand point of assessments of treatment. As TB advisory committee is one of key agency to control drug-resistant tuberculosis, its reform and revitalization are urgently needed.

Key words: Drug resistance, Tuberculosis control law, Tuberculosis advisory committee, Drug sensitivity test

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USEFULNESS OF A NOVEL DIAGNOSTIC METHOD OF TUBERCULOSIS INFECTION, QuantiFERON®TB-2G, IN AN OUTBREAK OF TUBERCULOSIS

Nobuyuki HARADA, Toru MORI, Shinji SHISHIDO, Kazue HIGUCHI, and Yukie SEKIYA

Abstract [Objective] The purpose of this study was to evaluate QuantiFERON®TB-2G (QFT), a novel method of detecting tuberculosis infection among contacts of a tuberculosis patient by determining the whole-blood interferon-gamma response to the specific antigens.

[Subjects and Methods] A teacher of a college who had been coughing for the preceding two months was diagnosed with smear-positive tuberculosis. About 270 students of the college were considered to have been exposed to tuberculosis infection, of whom 73 were in closer contact with the index case because they participated in a one-week group excursion attended by the teacher. Two of the contact students developed active tuberculosis shortly thereafter. Tuberculin tests were conducted to almost all students, and QFT was performed for only those with tuberculin reactions having erythema diameters of 30 mm or larger.

[Results] Tuberculin tests of students, all of whom had been vaccinated with BCG at least once, revealed that the distribution of the close contact group was slightly shifted to right (larger side) than those with less close contacts. The QFT positive rate for close contacts was 45.5%, while that for less close contacts was only 7.1%, which obviously indicates that QFT is hardly affected by the tuberculin allergy due to past BCG vaccination. The distribution of interferon-gamma measurements (log-transformed) of the close contacts showed typical bimodality, one mode representing the infected, another the non-infected. This was not clear for the less close contacts. The correlation of interferon-gamma measurements (log-transformed) with tuberculin reaction erythema size was weak, if not non-significant.

[Conclusion] It was concluded that QFT was a useful method for diagnosing tuberculosis infection and was unaffected by the BCG-caused tuberculin allergy. In the case of the outbreak mentioned above, QFT greatly reduced the indication of chemoprophylaxis, from 28% of all the contacts solely based on tuberculin test to only 7%.

Although there remains some problems to be overcome for QFT to be widely used with high confidence, this technology will provide a high possibility for wider and more accurate indication of chemoprophylaxis and will be one of the essential tools of tuberculosis control of the 21st century in Japan.

Key words: Tuberculosis outbreak, Latent tuberculosis infection, Tuberculin skin test, Whole blood interferon-gamma assay, Chemoprophylaxis

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The 78th Annual Meeting Educational Lecture

DIAGNOSTIC KEY-POINT OF THE PULMONARY TUBERCULOSIS

Toshihiko KURAOKA

Abstract I have been engaged in the diagnosis and treatment of pulmonary tuberculosis for about 25 years. I have presented many interesting tuberculosis cases such as cavity, nodule, infiltration, miliary pattern, and bronchial tuberculosis.

I summarized that the key point of the diagnosis for pulmonary tuberculosis is, 1) X-ray diagnosis shows no specific findings, so it is important to remind pulmonary tuberculosis as not unusual disease. I will make a proposal to insert pulmonary tuberculosis in the guideline for the diagnosis of pneumonia by the Japanese Respiratory Society. 2) Sputum PCR examination is very rapid and useful diagnostic method. The diagnostic evaluation of PCR is equal or over that of AFB culture. 3) CT diagnosis is useful for the detection of minimal pulmonary shadow or cavity lesion. 4) Brocho-fiberscopic examination is useful for the detection of the Mycobacterium in the bronchial brushing smear or washing samples. We should suspect bronchial tuberculosis in the cases with strongly positive sputum smear without cavity shadow. 5) The rate of complication with diabetes mellitus is significantly higher than that of 10 years ago in adult male tuberculosis patients. Recently 1 of 4 patients complicated with diabetes mellitus in adult male patients.

Key words: Pulmonary tuberculosis, Diagnosis, Key-point

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A CULTURAL HISTORY OF TUBERCULOSIS

Mahito FUKUDA

Abstract Tuberculosis (TB) has a long history. Regarding terminology, TB has, roughly speaking, three stages. These are, PHTHISIS, CONSUMPTION and TUBERCULOSIS. Each stage has its own meanings and characteristics. In the second stage consumption, TB was thought to be responsible for the patients' beauty and creativity. This kind of romanticization can be seen both in the West and East, not only in literature but also in paintings.

Key words: Tuberculosis, History, Romanticization of diseases, Early death, Beauty, Genius

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Memorative Lecture by the Imamura Award Winner

MOLECULAR PATHOGENESIS IN TUBERCULOSIS COMPLICATED WITH AIDS

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[3]Naohiko TANAKA, [4]Akira HEBISAWA, and [5]Michael WEIDEN

Abstract HIV-1 infection is a major cause of worldwide epidemic of tuberculosis. There is increasing clinical evidence that coinfection with *M. tuberculosis* accelerates progression of AIDS. We found that, *in vivo*, HIV-1 load and mutation increase in involved lung segments in patients with pulmonary tuberculosis. We also reported that *Mycobacterium tuberculosis* stimulates HIV-1 replication by enhancing transcription on the 5′ LTR in a macrophage cell line, THP-1, *in vitro*. In contrast, HIV-1 replication is suppressed by *M. tuberculosis* infection of monocytes derived macrophages (MDM) or differentiated monocytic THP-1 cells. We observed that HIV-1 5′ LTR function was repressed in PMA differentiated THP-1 cells after co-infection with *M. tuberculosis*. Point mutations in C/EBP β binding domains of the HIV-1 LTR negative regulatory element (NRE) abolished promoter repression. Monocyte-derived macrophages and differentiated THP-l cells increased expression of the 16kDa inhibitory form of C/EBP after *M. tuberculosis* co-infection. Bronchoalveolar lavage cells obtained from normal controls and alveolar macrophages from uninflamed lung of tuberculosis patients also expressed the 16kDa inhibitory form of C/EBP. However, alveolar macrophages from lung segments involved with pulmonary tuberculosis had markedly reduced C/EBP expression. These data suggest that 16kDa isoform of C/EBP plays an important role for the control of HIV-1 replication in macrophages. We propose derepression of HIV-1 LTR mediated transcription as one mechanism for enhanced HIV-1 replication observed in pulmonary tuberculosis. Since the cellular immune response in pulmonary tuberculosis requires lymphocyte/macrophage interaction, a model system was developed in which lymphocytes were added to AM. Contact between lymphocytes and AM reduced inhibitory C/EBP β, activated NF-κB and enhanced HIV-1 replication. If contact between lymphocytes and macrophages was prevented, inhibitory C/EBP β expression was maintained and the HIV-1 long terminal repeat (LTR) was not maximally stimulated although NF-κB was activated. Antibodies which cross-linked macrophage expressed B-7, VCAM and CD-40 were used mimic lymphocyte contact. Cross-linking antibodies abolished inhibitory C/EBP β expression; however, the HIV-1 LTR was not maximally stimulated and NF-κB was not activated. Maximal HIV-1 LTR stimulation required both lymphocyte derived soluble factors and cross-linking of macrophage expressed co-stimulatory molecules. These results demonstrate that neither contact nor soluble factor(s) are sufficient to maximally enhance HIV-1 LTR activity in macrophages. Contact between activated lymphocytes and macrophages is necessary to down-regulate inhibitory C/EBP β, thereby derepressing the HIV-1 LTR. Lymphocyte derived soluble factor(s) activate NF-κB, further enhancing the HIV-1 LTR.

Key words: Human immunodefficiency virus, *Mycobacterium tuberculosis*, Transcription factor, Macrophage

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The 79th Annual Meeting Symposium

STRATEGIES AGAINST MULTIDRUG-RESISTANT TUBERCULOSIS

Chairpersons: [1]Tetsuya TAKASHIMA and [2]Yoshiko KAWABE

Abstract Pulmonary tuberculosis can be cured by 6 months chemotherapy, consisting of isoniazid (INH), rifampicin (RFP), pyrazinamide (PZA), and etahanbutol (EB). However, the patients with pulmonary tuberculosis caused by multidrug-resistant tuberculosis (MDR-TB) bacilli, defined as resistance to at least INH and RFP, poorly respond to this regimen. Therefore, the epidemic of MDR-TB in the community is a major threat to tuberculosis control.

According to the interim report of the survey of drug-resistant tuberculosis carried out by Tuberculosis Research Committee Japan in 2002, the prevalence of MDR-TB among new cases, previously treated cases and combined cases was 0.9%, 9.9% and 2.1%, respectively. Thus, the latest Japanese prevalence of MDR-TB was as high as the median prevalence of 72 geographical settings in the world, reported in the WHO/IUATLD Global Project on Drug Resistance Tuberculosis Surveillance, 1994-1999. In Japan, there is still an estimated 2,000 cases of MDR-TB patients. In the last meeting of the Japanese Society for Tuberculosis, an outbreak of MDR-TB in tuberculosis wards was reported, and a careful infection control of MDR-TB was recognized again.

To work out the strategy for the elimination of MDR-TB, two issues were taken up in this symposium. First, not to make new MDR-TB cases, an intervention in the development and spread of MDR-TB was discussed. Second, the effectiveness of conventional anti-tuberculosis chemotherapy and pulmonary resection in the treatment of patients with MDR-TB was reevaluated, and a new approach for the treatment of chronic cases was also discussed.

Dr. Koji Sato (National Amamiwakouen Sanatorium) surveyed the number of patients with MDR-TB in 72 hospitals with tuberculosis wards, and examined the clinical characteristics of chronic cases who had been expecting MDR-TB bacilli in the sputum for more than 5 years. One hundred and twenty-one of 149 chronic cases (81%) in this study were sputum-smear positive. Thirty-seven of them (25%) were outpatients. Thus, the high risk of MDR-TB transmission and the difficulties of infection control of chronic cases were reported.

Dr. Yuka Sasaki (National Hospital Organization Chiba East National Hospital) conducted the questionnaire survey to the ordinance-designated cities and National Sanatoria Hospitals in Japan. Only a few contacts of patients with MDR-TB received preventive treatment, mainly due to the difficulties of diagnosis of latent MDR-TB infections and no effective treatment regimens. She pointed out the importance of preventive treatment guideline for contacts of patients with MDR-TB.

Dr. Masako Wada (Research Institute of Tuberculosis, Japan Anti-Tuberculosis Association) examined the details of acquired MDR-TB cases. Among 2,375 pulmonary tuberculosis patients newly treated in Fukujuji Hospital form 1991 to 2002, 4 cases had developed drug resistance to INH and RFP during treatment. First case was initially INH mono-resistant, which had treated with INH, RFP and EB. Second case had received a sequential mono-therapy after serious adverse reaction. The remaining two cases were supposed to be re-infected with MDR-TB during treatment. This study indicated the importance of improvement of treatment guideline for patients with adverse drug reactions and infection control of MDR-TB in the sanatoria hospitals, in addition to the avoidance of sequential mono-therapy.

Unlike the treatment of drug susceptible tuberculosis, it is not possible to develop a standard treatment regimen for MDR-TB. To know the treatment outcome by the number of susceptible drugs included in each regimen, Dr. Takayuki Nagai (Osaka Prefectural Medical Center for Respiratory and Allergic Diseases) reviewed the 37 patients with pulmonary MDR-TB, knowing the results of susceptibility testing to all 11 anti-tuberculosis drugs, such as INH, RFP, PZA, EB, streptomycin (SM), kanamycin (KM), Enviomycin (EVM), Ethionamide (TH), Cycloserine (CS), Para-aminosalicylic acid (PAS) and levofloxacin (LVFX). Among 11 patients who had received at least 3 susceptible drugs of PZA, LVFX and aminoglycoside, 10 patients (90.9%) had favorable response, converting their sputum cultures to negative at 2 months after the start of chemotherapy. He said that surgical interventions should be considered for any cases, which will not be effectively treated by the regimens including PZA, LVFX and aminoglycoside.

Dr. Yuzo Sagara (National Hospital Organization Tokyo National Hospital) reviewed the surgical outcome of 28 patients with pulmonary MDR-TB with sufficient follow up data. All 8 patients, whose lung lesions had been completely removed, had achieved sputum-culture conversion after surgery and in combination with adequate chemotherapy. Even among 20 patients who still have some lesions after surgery, 14 patients (70.0%) had negative results of sputum cultures. Thus, it is shown that surgical intervention is a major treatment approach to MDR-TB.

Finally, Dr. Koh Nakata (Niigata University Medical Dental Hospital) reported a clinical trial of activated autologous T lymphocytes transfusion to chronic cases. This immunotherapy was well tolerated by all 3 patients. Two patients had responded to this treatment and their sputum culture had become negative for 3−5 months. The host immune up-

regulation was proved by the tuberculin skin test conversion and the increment of IFN-γ production by peripheral blood in response to EAST-6 antigen. It was shown that activated T lymphocyte transfusion might be an effective treatment measure for some chronic cases, by enhancing the host anti-mycobacterial defense systems.

MDR-TB control strategies should be primarily aimed at preventing the emergence of new cases. The rational approach devised by each panelist in this symposium will be the first step to containing the further spread of MDR-TB.

1. Current status of patients with multidrug resistant tuberculosis (MDR-TB) in the long term in Japan: ˚Koji SATO (National Amamiwakouen Sanatorium), Masashi MORI (National Hospital Organization Tokyo National Hospital)

We surveyed the number of MDR-TB cases in Japan. Four hundreds and eighty-seven cases (4.8%) of 10,208 tuberculosis patients registered in 72 hospitals were MDR-TB. Of them, 149 cases (30.6%) had been expecting MDR-TB bacilli in sputum for a long time more than 5 years. We examined the clinical profiles of these so called chronics. There were 33 females and 116 males. Ninety-eight (65.8%) of them were more than 60 years old. Thirty-seven (24.8%) were out patients. Among 103 cases with the reports of chest X-ray examination, 76 cases (73.8%) had cavity formations. Of them, 24 cases (64.9%) were sputum-smear positive. Difficulties of management and treatment of chronics were recognized again.

2. Chemoprophylaxis for contacts of patients with multidrug-resistant tuberculosis: Yuka SASAKI (Department of Thoracic Disease, National Hospital Organization Chiba East National Hospital)

The chemoprophylaxis to the contacts of patients with multidrug-resistant tuberculosis was considered. The questionnaire survey was conducted to the ordinance-designated cities in Japan. Chemoprophylaxis was performed in 2.4% of contacts of patients with multidrug-resistant tuberculosis, and in the contacts, 20 cases were diagnosed as tuberculosis in the ordinance-designated cities for the past five years. Chemoprophylaxis to the contacts of patients with multidrug-resistant tuberculosis is not carried out positively from many problems in National Sanatoria Hospitals. The present condition is troubled by the correspondence to the contacts of patients with multidrug-resistant tuberculosis.

3. Retrospective examination of treatment failures in newly diagnosed cases, whose strain had acquired multidrug resistance in initial treatment: Masako WADA (Research Institute of Tuberculosis, Japan Anti-Tuberculosis Association)

Not to make a new multidrug resistant tuberculosis case, what should we do for it? First of all, we should treat all new pulmonary tuberculosis cases with 6-month regimen using INH, RFP, EB and PZA, if pyrazinamid is not contraindicated. In this review, two cases of far-advanced multidrug resistant pulmonary tuberculosis patients were presented. One patient received left pneumectomy with chemotherapy of second line anti-tuberculosis drugs, and she had been cured after the completion of 24-month chemotherapy. The other patients died due to massive hemoptysis with chronic respiratory failure at the age of 30 years old. It was supposed the critical different subject to their fates was the timing of reference to a specialist for tuberculosis treatment.

Among 2,608 newly diagnosed pulmonary tuberculosis patients from 1 January 1991 to 31 December 2002, only 4 cases (0.15%) had treatment failures with the emergence of multidrug resistance. First case infected with INH resistant strain was treated with INH, RFP and EB without PZA. Second case complicated with tuberculous pyothorax was also treated with above three drugs regimen. Third case had suffered from a serious skin adverse reaction, and then she had a sequential mono-therapy. The remaining case was suspected to have re-infected with MDR-TB strain.

We should initially treat all pulmonary tuberculosis patients with four drugs regimen. When the treatment failure had occurred due to drug resistant strain, adverse drug reactions or other reasons, it is essential to consult with a specialist for tuberculosis treatment. It should be never done to add anti-tuberculosis drugs one by one to the case of treatment failure.

4. Treatment outcomes of multidrug-resistant tuberculosis: ˚Takayuki NAGAI, Tetsuya TAKASHIMA, Izuo TSUYUGUCHI (Osaka Prefectural Medical Center for Respiratory and Allergic Diseases)

[Objective] To study the results of anti-tuberculosis chemotherapy of the patients with diagnoses of MDR-TB in our hospital and determine the adequate chemotherapy regimen for MDR-TB.

[Methods] Retrospective study of 37 cases of MDR-TB patients in our hospital between 1999 and 2002. In this study, the five cases were excluded, because they had not received TB treatment for at least 6 months.

[Results] The sputum culture conversion rates at 6 months after starting chemotherapy were 68.8% (22/32). Of them, 2 patients had relapsed bacteriologically during 2 years chemotherapy, 1 patient died, and 2 patients never completed a satisfactory course of treatment. Success rate of treatment was 50.0% (16/32). When 4 or more susceptible drugs were used, treatment success rate was significantly higher than 3 or less drugs were used ($p=0.012$). Among 11 patients who had received at least 3 susceptible drugs of PZA, LVFX and aminoglycoside, 10 patients (90.9%) had favorable response, converting their sputum cultures to negative at 2 months after the start of chemotherapy.

[Conclusion] Surgical interventions should be considered for any cases, which will not be effectively treated by the regimens including PZA, LVFX and aminoglycoside.

5. Surgical management of multidrug resistant pulmonary tuberculosis (MDR-TB): Yuzo SAGARA (National Hospital Organization Tokyo National Hospital)

From January 1991 through December 2002, we operated on 36 MDR-TB patients. Eight complete resections, 23 incomplete resections, and 5 thoracoplasties were performed.

Final success rate of complete resection was 100%. On the other hands, that of incomplete resection was 70%. The cases of MDR-TB within four resistant drugs were successfully treated by incomplete resection.

Complete resection of the pulmonary lesion was the best surgical treatment for MDR-TB, if it is possible.

6. A clinical trial of activated autologous T lymphocytes transfusion for multidrug resistant tuberculosis: °Koh NAKATA*, Emi HAMANO (International Medical Center of Japan, *Bioscience Medical Research Center, Niigata Medical Dental Hospital), Yoshiko KAWABE, Kimihiko MASUDA, Hideaki NAGAI, Haruyuki ARIGA, Atsuyuki KURASHIMA (National Hospital Organization Tokyo National Hospital), Tomohiro MORIO, Norio SHIMIZU (Center for Cell Therapy, Tokyo Medical and Dental University, Medical Hospital)

In multidrug resistant tuberculosis (MDR-TB), T cell function is supposed to be attenuated against *M. tuberculosis*. It is rational to consider that chronic infection lead the host immune system to be anergy state against pathogeons. This study was performed to evaluate the efficacy of activated T lymphocyte transfusion on MDR-TB to reactivate host defense system. One thousand million activated autologous T lymphocytes were transfused every two weeks to three patients with MDR-TB who were chronically positive AFB in their sputum. Two cases responded to this treatment and become negative bacilli in the sputum for 3−5 months, however, they reoccurred afterwards. The other one case did not respond at all. In all three cases, no side effect was observed. Interestingly, in two cases with response, tuberculin skin test and peripheral blood interferon gamma production reacting tuberculosis specific antigen, ESAT-6 were both dramatically augmented during negative bacilli in their sputa. Activated T cell transfusion is safe and may improve the anergy state in some patients with MDR-TB.

Key words: MDR-TB, Case management, Chemoprophylaxis, Treatment

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