Original Article

EXTERNAL QUALITY ASSESSMENT OF DRUG SUSCEPTIBILITY TESTING FOR *MYCOBACTERIUM TUBERCULOSIS*

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Abstract [Objective] The Committee for Mycobacterial Examinations has planned and implemented the third external quality assessment of drug susceptibility testing for *Mycobacterium tuberculosis* to the hospital and private laboratories.

[Method] The Committee delivered 20 *M. tuberculosis* strains, exactly pairs of 10 strains, which were evaluated and standardized for the drug resistance pattern in the WHO/IUATLD supra-national laboratory network (SRLN). The agreement of the majority of SRLN laboratories was considered as the gold standard of susceptibility result for each strain tested. Each laboratory performed the drug susceptibility testing (DST) with its own routine method. The sensitivity to detect drug resistance, the specificity for susceptible strain, the efficiency of overall agreement, the reproducibility for each pair, and kappa coefficient were calculated to evaluate their performance. DST was performed for isoniazid (INH), rifampicin (RFP), streptomycin (SM) and ethambutol (EB).

[Results] A total of 48 results has been collected. The overall sensitivity, specificity, efficiency, reproducibility and kappa coefficient for each anti-tuberculosis drug tested were as follows respectively ; 100%, 99.0% (62.5−100), 99.6% (85.0−100), 99.6% (90−100) and 0.991 for INH ; 97.7% (83.3−100), 100%, 98.6% (90−100), 99.0% (90−100) and 0.972 for RFP ; 87.5% (66.7−100), 99.0% (87.5−100), 92.1% (80−100), 97.5% (70−100) and 0.84 for SM ; 99.5% (75.0−100), 97.9% (75.0−100), 98.5% (85.0−100), 97.9% (70−100) and 0.97 for EB. Regarding private laboratories, all indicators showed 100% for INH but 2 hospital laboratories showed less than 90% in sensitivity. As for RFP, one private laboratory (4.3%) and 3 hospital laboratories showed less than 90% in sensitivity. The major difference between private and hospital laboratories was seen in EB. One hospital laboratory (4.0%) showed less than 90% in sensitivity and three (12.0%) showed less than 90% in specificity, compared to none in private laboratories. Additionally, six hospital laboratories (24.0%) showed less than 90% in reproducibility. As for quality improvement, two private laboratories that showed poor performance in 2003 have improved their quality up to 100% in 2004.

[Discussion] The overall efficiency by private and hospital laboratories satisfied WHO criteria. However, it diverged in each category of laboratories and hospital laboratories tended to show poor performance compared to the private ones. The reason for the difference was not clear, but the routine workload, allocated time and cost for the panel testing might contribute to it. The sensitivity of SM was relatively low compared to the other drugs as it was observed in 2003. It was mainly due to two strains to which the participating laboratories showed poor agreement to the gold standard. The difference of critical drug concentration for SM in Löwenstein-Jensen and in 1% Ogawa medium might contribute to the discrepancies. As for quality improvement, two private laboratories with poor performance in 2003 have shown marked improvement after on-site evaluation. The results indicated the usefulness of external quality assessment for the maintenance and improvement of the quality of the test.

Key words: Tuberculosis, Drug susceptibility testing, Private laboratory, Hospital laboratory, External quality assessment

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Original Article

NUMBER OF SPUTUM CULTURES BY MGIT SYSTEM NEEDED TO DIAGNOSE PULMONARY TUBERCULOSIS

[1]Kunihiko ITO, [2]Akio AONO, [3]Takashi YOSHIYAMA, [1]Masako WADA, and [3]Hideo OGATA

Abstract [Purpose] To study the number of sputum cultures by MGIT system (Becton-Dickinson) needed to diagnose pulmonary tuberculosis.

[Object and Method] Prospective study of all patients who visited our hospital, and were strongly suspected of pulmonary tuberculosis during the period from Jan. 2002 to Sept. 2003. In these patients, 3 consecutive sputum cultures were done by both MGIT-system and egg-based Ogawa medium (1 slant).

[Results] Altogether 290 cases of sputum-culture positive pulmonary tuberculosis were available for analysis. In 210 first-sputum-smear positive cases, incremental yield of 3rd sputum culture in 3 consecutive MGIT cultures was equal to or less than 1.0% and 98.1% of culture positive cases were detected by 2 consecutive MGIT cultures. In 80 first-sputum-smear negative cases, incremental yield of 3rd sputum culture in 3 consecutive MGIT cultures was equal to or more than 5.0%, and 90.0% of culture positive cases were detected by 2 consecutive MGIT cultures. This detection rate was almost the same as the calculated detection rate (91.4%) by 3 consecutive Ogawa (2 slant) cultures (previous standard method).

[Conclusion] It was suggested that 2 consecutive sputum cultures by MGIT were sufficient to detect *M. tuberculosis* in first-sputum-smear positive cases, but 3 consecutive sputum cultures by MGIT were relatively useful in first-sputum-smear negative cases.

Key words: Pulmonary tuberculosis, Diagnosis, Culture, Ogawa medium, MGIT (Mycobacterium growth indicator tube)

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A CASE OF ENDOBRONCHIAL LESION DUE TO INFECTION WITH *MYCOBACTERIUM INTRACELLULARE*

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Abstract A 53-year-old man was hospitalized in April 2001 because of left cervical lymphadenopathy and a mass shadow in the left lingular segment. Bronchoscopy revealed an elevated lesion in the left main bronchus, but a biopsy showed no specific findings. A left cervical lymph node biopsy revealed lymphoid hyperplasia only and no malignancy. After the patient was discharged, bronchial irrigation solution from the left lingular segment was found to be positive for *Mycobacterium intracellulare*. In July 2001 the shadow in the left lingular segment had worsened, and bronchoscopy was performed again. This revealed ulceration in the left main bronchus and edematous narrowing of the bronchial lumen at the opening of the lingular segment. A granulated lesion accompained by severe inflammation was seen in a biopsied specimen taken from the same site. Bronchial lesion induced by an acid-fast-stain positive nontuberculosis mycobacteria was noted. Treatment with rifampicin (RFP), clarithromycin (CAM), ethambutol (EB), and streptomycin (SM) was started, but a rash most likely caused by RFP developed, and RFP was replaced by ciprofloxacin (CPFX). The treatment was continued and symptoms improved. Since non-tuberculous mycobacteriosis accompanied with bronchial lesions is rare, a case report was made.

Key words: Non tuberculous mycobacteria, *Mycobacterium intracellulare*, Endobronchial lesion

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A CASE OF PULMONARY *MYCOBACTERIUM FORTUITUM* INFECTION SUCCESSFULLY TREATED WITH KAMPO TREATMENTS

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Abstract A 72-year-old male was referred to our hospital in August 2001 for his pulmonary *M. fortuitum* infection. His symptoms were coughing, pyrexia, hemoptysis, general malaise, and insomnia. He had been suffering from these symptoms since 1982, though the intensive anti-mycobacterial chemotherapy such as three-drug (RFP, SM, & INH), twice two-drug (KM & SM and cycloserine & enviomycin) and four-drug (CAM, EB, RFP, & KM) regimens were administered for 26 months from July 1999. His symptoms tentatively improved after chemotherapy, but soon recurred with smear positive sputum. We decided to withdraw all antibacterial agents to treat him with decoction of Ninjinyoueito according to the diagnostics Kampo medical science in September 2001. After this prescription, his subjective symptoms gradually improved, and ten months later his sputum converted to smear negative. Because of recurrence of his general malaise in August 2002, we replaced the Ninjinyoueito by Seishoekkito, based on the Kampo diagnostics. His physical conditions remained good until 2005. In addition, the sputum smear examination maintain the level below ±.

We evaluate that Kampo (Chinese traditional medicine) treatment resulted in favorable response. Though it is not common to prescribe Kampo-medicine for intractable infectious diseases, we believe that Kampo-medicine is effective in some cases associated with host defense mechanisms.

Key words: Nontuberculous mycobacterial infection, *Mycobacterium fortuitum* pulmonary disease, Ninjinyoueito, Seishoekkito, Kampo treatment

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TRANSIENT WORSENING OF CHEST RADIOGRAPH AND DEVELOPMENT OF LYMPHADENOPATHY DURING CHEMOTHERAPY FOR MILIARY TUBERCULOSIS

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Abstract A-37-year old woman was referred to our hospital because of bilateral pulmonary micronodular shadows on chest X-ray. Prednisolone was reported to be administered for her coughs and dyspnea more than a month, but was discontinued recently. Under the diagnosis as miliary tuberculosis, we started to treat her with the combined use of pyrazinamide, isoniazid, rifampicin, and ethambutol. Then her symptoms subsided gradually. Two months later, however, high fever developed, followed by exacerbation of the radiographic shadows, and marked cervical and mediastinal lymphadenopathy. We considered them so-called paradoxical worsening, and continued the antituberculosis therapy unchanged. Those clinical manifestations began to subside about 4 months after the initiation of the treatment.

Paradoxical worsening has been described as a relatively rare manifestation, and seem to be attributable to prompt recovery of the immunity to mycobacterial antigens after the use of antituberculous therapy. We considered that, in this case, disseminated tuberculosis and firstly administered steroid that might suppress immune function, and discontinuation of steroid therapy followed by the bactericidal antituberculous chemotherapy were associated with the development of the paradoxical reactions, by analogy with immune reconstitution syndrome frequently reported in HIV-related tuberculosis patients.

Key words : Miliary tuberculosis, Paradoxical worsening, Antituberculous chemotherapy, Corticosteroid

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Case Report

A CASE OF PULMONARY *MYCOBACTERIUM SHIMOIDEI* INFECTION

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[1]Minoru OHKOCHI, and [2]Naohiko INASE

Abstract A 68 year-old male who was ex-smoker presented with fever and cough. Chest radiograph showed infiltrative shadows in both upper lung fields. A sputum smear for acid-fast bacilli was positive. But the isolate was not identified by polymerase chain reaction method. Acid-fast bacilli were cultured from sputum, but the identification was not done by DNA-DNA hybridization method. *Mycobacterium shimoidei* was identified by 16S ribosomal RNA sequencing with 98.42 % matching. Rifampicin, ethambutol, clarithromycin, pyrazinamide, and ciprofloxacin were administered, and the symptom and abnormal shadows on chest radiography improved. And three months later from the initiation of treatment, sputum smear for acid-fast bacilli became negative. Chest CT scan four months after treatments showed decrease of infiltrative shadows. We had treated him for six months, and after that no recurrence occurred.

Key words: *Mycobacterium shimoidei*, Nontuberculous mycobacteria, 16S ribosomal RNA sequencing, Ethambutol, Pyrazinamide

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CLINICAL MANIFESTATION OF Q FEVER AND TUBERCULOSIS, SIMILARLY CAUSED BY INTRACELLULAR PARASITES

Akira WATANABE

Abstract Q fever is a generic term for pneumonia, bronchitis, etc. caused by infection with *Coxiella burnetii*, a rickettsia-related species of bacteria, in humans. Q-fever is a transient and acute febrile illness that takes a course similar to influenza, and its clinical picture greatly differs from that of tuberculosis that takes a chronic course. The reason for this is thought to be because the generation time of *C. burnetii* is extremely short (several tens of minutes) compared with *Mycobacterium tuberculosis*, though those are similar intracellular parasites. Q fever is fourth- or fifth-ranked among the community-acquired pneumonias in the United States and Europe but has a good prognosis with 1−2% of mortality even in the cases that follow a natural course without treatment. Meanwhile, there is a chronic type that follows a protracted course or has a poor prognosis. Therefore, cases definitely diagnosed with Q fever or strongly suspected of Q fever should seek aggressive treatment. Q fever is definitely diagnosed by confirming significant increase in serum antibody titer, but the patients should be followed because in many cases it takes a long time before serum antibody titer increases. Beta-lactams are ineffective against *C. burnetii*, an obligate intracellular parasite. Although tetracyclines, macrolides, quinolones, rifampicin, etc. are used effectively in the treatment of Q fever, many cases appear to improve by beta-lactam administration because the illness often takes a natural course.

Key words: Q fever, Zoonosis, *Coxiella burnetii*, Intracellular parasite, Atypical pneumonia

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