

Original Article

IDENTIFICATION OF 23 MYCOBACTERIAL SPECIES BY INVADER ASSAY
WITH TARGETING 16S rRNA GENE AND ITS-1 REGION

— Comparison with DDH Method in Clinical Isolates —

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Abstract [Purpose and Method] The Invader assay was developed to identify 23 mycobacterial species using probes derived from the species-specific region of the 16S rRNA gene and the 16S–23S rRNA internal transcribed spacer 1 (ITS-1) region, with minor modifications of our previous study. In the present study, we compared the identification capability between the Invader assay and DNA-DNA hybridization (DDH) method. DDH is commonly used to identify non-tuberculosis mycobacterium in Japan and 636 clinical mycobacterial strains cultured on Ogawa slants were tested.

[Results] The Invader assay could identify 615 (96.7%) of the 636 strains. The results contained 14 *M. lentiflavum*, 3 *M. parascrofulaceum* and 1 *M. intermedium*, which were undetectable with DDH method. On the other hand, DDH method could identify 580 (91.2%) strains with duplicate assay. Of 628 strains except 8 strains identified as a few species by Invader assay, 551 (87.7%) strains were identified as the same species by two methods. Discordant results were mainly recognized for the identification of *M. gordonae*, *M.*

avium, *M. lentiflavum* and *M. intracellulare*. The results of other methods targeting 16S rRNA indicated correctness of the Invader assay.

[Conclusion] These results indicate that Invader assay could identify more correctly than DDH method and could identify about 97% of clinically important mycobacterium.

Key words: Identification of mycobacteria, Invader assay, 16S rRNA gene, ITS-1 region, DDH method

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肺結核短期強化療法に用いる Pyrazinamide の副作用である高尿酸血症の疫学調査

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要旨：〔目的〕 Pyrazinamide (PZA) は肺結核治療の短期強化療法のなかで初期2カ月間に投与される抗結核薬である。抗結核薬の副作用はさまざまであるが、このうち PZA が原因と考えられる高尿酸血症に注目し、その患者背景と尿酸値との関係、さらに PZA 投与による尿酸値の変動、また高尿酸血症出現時の尿酸コントロール薬使用および痛風・関節痛症状の有無など多施設共同によるレトロスペクティブな疫学調査を実施した。〔方法〕 2006年1月から2006年12月までの期間に肺結核として入院し、短期強化療法に PZA を投与した国立病院機構4施設226例を対象に検討を行った。〔結果と考察〕 男172例、女54例、平均年齢59.5歳。平均 BMI 19.8 kg/m²。PZA 投与前の血清尿酸値は平均4.73 ± 1.78 mg/dl、PZA 投与後の血清尿酸最高値の平均は10.63 ± 2.67 mg/dl となり両者には p < 0.0001 と統計学的有意差が認められた。また PZA 投与による 8 mg/dl 以上の高尿酸血症は84.5%に見られたが関節痛は4.42%の出現であった。さらに投与中断または中止例は51例 (22.57%) に見られたが、その理由は Isoniazid (INH)、Rifampicin (RFP) が原因として起こる可能性が高い肝機能障害と発疹であり、尿酸値上昇による PZA 中断例は見られなかった。また、高尿酸血症に対する尿酸コントロール薬の使用例は21例 (9.29%) であった。〔結論〕 短期強化療法において PZA の投与は重要であり、その副作用として特有な高尿酸血症は出現しても経過観察は可能であり投与中断には至らないことが分かった。
キーワード：ピラジナミド、肺結核、高尿酸血症、短期強化療法、痛風

ESTIMATION OF THE PREVALENCE OF TUBERCULOSIS INFECTION IN THE 1950s IN TOKYO

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Abstract [Purpose] We estimated the prevalence of tuberculosis infection in the 1950s in the urban area of Tokyo using results of the tuberculin skin test (TST) in infants and children.

[Subject and methods] We analyzed prevalence of tuberculosis using the results of the TST in 728 children (5 m.o.–24 m.o.) without BCG vaccination in 1954 in Koto Ward, Tokyo.

[Results] Assuming that the sensitivity and specificity of the TST were 95% and 98%, respectively, the prevalence of TB was estimated to be 2% (95% C.I., 0.4–4.3%) among 448 infants under 12 m.o. (mean age 0.69 y.o.), and 16% (95% C.I., 11.9–21.5%) among 280 children aged 12 m.o.–24 m.o. (mean age 1.44 y.o.).

[Conclusion] Being different from the current situation of tuberculosis, the risk of infection among infants was high in 1950s in Japan, therefore, it was considered that the preva-

lence of tuberculosis infection rose rapidly among infants in their early period after birth. Also, the risk of infection in urban areas was higher comparing with the average national rate at that time.

Key words : Tuberculosis, Children, Prevalence, Annual risk of infection, Bayes formula

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Original Article

CLUSTERED SECONDARY CASE RATE IN 10,088 PATIENTS WITH TUBERCULOSIS

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Abstract [Objectives] To elucidate characteristics in clustered secondary TB patients transmitted from culture positive pulmonary TB patients.

[Subjects and Methods] The subjects of this retrospective study were 10,088 TB patients registered in Aichi Prefecture between 1989 and 2003. Pulmonary TB was found in 8,629 patients, and 1,459 had extra-pulmonary TB. Bacteriological examination revealed sputum smear-positive (SPBP) in 3,332, sputum smear-negative bacillus-culture-positive (SNBP) in 2,139, and smear-negative bacillus-culture-negative (SNBN) in 3,158.

All registration files were reviewed to identify epidemiological links of patients. When linked patients with an interval of the dates of registration of less than 10 years were found, the first case was considered as the index case, and the other patients were regarded as secondary cases.

A clustered secondary case rate (CSR) for a category of patients was defined as follows; $CSR = NCS/NA$, where *NA*: number of TB patients in a category A, and *NCS*: number of secondary cases in category A.

A cluster rate for a category of bacillary pulmonary patients was defined as follows; $Cluster\ rate = (NIC + NCS) / NA$, where *NA*: number of TB patients in a category A, *NIC*: number of index cases in category A, and *NCS*: number of secondary cases in category A.

[Results] A total of 417 patients were considered as clustered secondary cases, and the CSR was 4.1% in total. The CSRs were 3.5% for the SPBP patients, 3.8% for the SNBP patients, 5.4% for the SNBN patients, and 3.4% for the extra-pulmonary patients. The CSR in SNBN patients was significantly higher than the SPBP patients ($p < 0.001$). The significant differences in the CSRs were found between the SNBN patients and the SNBP patients ($p < 0.01$), as well

as between the SNBN patients and the extra-pulmonary patients ($p < 0.01$).

The CSRs were 42.5% in patients aged 0–9, 30.3% in those aged 10–19, 11.2% in those aged 20–29, 7.4% in those aged 30–39, 4.6% in those aged 40–49, 3.2% in those aged 50–59, 2.4% in those aged 60–69, 1.8% in those aged 70–79, 1.3% in those aged 80–89, and 0.6% in those aged 90–99. There were significant differences in the CSRs between those aged 10–19 and those aged 20–29 ($p < 0.001$), between those aged 20–29 and those aged 30–39 ($p < 0.05$), and between those aged 30–39 and those aged 40–49 ($p < 0.05$). The male patients showed significantly lower CSR than female patients (2.9% vs 6.3%, $p < 0.001$). The cluster rate for the 5,471 bacillary patients was 8.8%. The cluster rates were significantly different between those patients aged 10–19 and those aged 20–29 (37.1% vs 21.1%, $p < 0.001$), as well as between those aged 40–49 and those aged 50–59 (16.4% vs 8.5%, $p < 0.001$).

[Conclusion] These findings suggest that the CSR is closely related with patient's age, gender, and bacillary findings, and that the CSR is significantly high in young, female, and SNBN patients.

Key words : Clustered secondary case rate, Cluster rate, Smear-positive pulmonary TB, Culture positive pulmonary TB, Close contact, TB transmission, Aging, Gender difference

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————— Case Report —————

A CASE OF MULTI-DRUG RESISTANT PULMONARY TUBERCULOSIS
AFTER ADMINISTRATION OF STANDARD ANTI-TUBERCULOSIS
TREATMENT FOR TWO TIMES

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Abstract We reported a case in which multi-drug resistant tuberculosis was recognized after two courses of anti-tuberculosis treatment. A 41-year-old woman who had received two courses of anti-tuberculosis treatment for pulmonary tuberculosis was admitted to our hospital due to productive cough, high fever and positive sputum smear showing acid fast bacillus. In the past treatment, drug susceptibility was unknown because of culture-negative TB. Chest radiograph showed atelectasis of the right upper lobe. The pathological examination of surgically resected lung specimen revealed that atelectasis was formed by a granulation tissue with caseous necrosis progressed to the bronchus wall. We examined cultures three times using both solid and liquid media. Liquid culture of the first time specimen was positive for *Mycobacterium tuberculosis* after six weeks and multi-drug resistant tuberculosis was recognized on drug susceptibility test. Thereafter she was treated with KM, LVFX, PZA and PAS,

and maintained sputum smear negative for 7 months after treatment. Physicians must consider possibility of MDR-TB despite findings showing smear-positive and culture-negative TB.

Key words : Tuberculosis recurrence, Multi-drug resistant tuberculosis, Smear-positive and culture-negative TB, TB liquid culture

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A CASE OF MILIARY TUBERCULOSIS WITH INTERSTITIAL NEPHRITIS DUE TO RE-ADMINISTRATION OF RIFAMPICIN TREATED SUCCESSFULLY WITH STEROID

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Abstract A 26-year-old man was admitted to a hospital complaining of continuous high fever and abdominal swelling. As his sputum and ascites culture was positive for acid-fast bacilli and PCR-TB, he was diagnosed as miliary tuberculosis, tuberculous with pleuritis and peritonitis, and transferred to our hospital. After initiation of treatment with isoniazid, rifampicin (RFP), ethambutol, and pyrazinamide, RFP was suspended because of direct-reacting hyperbilirubinemia. As the liver function recovered after discontinuation of RFP, low dose of RFP was re-administered and renal dysfunction was observed. The renal dysfunction continued after discontinuation of suspicious drugs including RFP. As renal biopsy revealed interstitial nephritis, prednisolon 20 mg/day was started and renal function recovered quickly. From the clinical

course and examination, we considered interstitial nephritis was due to re-administration of RFP and steroid therapy was effective.

Key words : Miliary tuberculosis, Rifampicin, Re-administration, Drug-induced interstitial nephritis, Steroid therapy

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THE INTERNATIONAL STANDARDS FOR TUBERCULOSIS CARE (ISTC): WHAT IS THE IMPORTANCE FOR JAPAN?

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Abstract In 2005, the World Health Assembly resolved that all Member States should ensure that all persons with tuberculosis (TB) “have access to the universal standard of care based on proper diagnosis, treatment and reporting consistent with the DOTS strategy...” The purpose of the International Standards for Tuberculosis Care (ISTC) is to define the widely accepted level of care of persons either suspected of, or diagnosed with, TB by all health practitioners, especially those in the private sector, who often lack guidance and systematic evaluation of outcomes provided by government programs. Since their publication in 2006 on World TB Day, the standards have been endorsed by the major international health organizations as well as many country-level professional societies.

The intention is to complement local and national control policies consistent with those of the World Health Organization: they are not intended to replace local guidelines, but are written to accommodate local differences in practice. The ISTC comprise seventeen evidence-based standards on tuberculosis diagnosis and treatment, as well as the responsibility of the public health sector. These are based on the basic principles of TB care: prompt and accurate diagnosis, standardized treatment regimens of proven efficacy, appropriate treatment support and supervision, monitoring of response to treatment and the carrying out of essential public health

responsibilities.

The relevance of the ISTC to the Japanese context is highlighted, in terms of when persons should be suspected of TB; the appropriate diagnostic modalities, including the use of chest radiographs; the advantages of fixed dose combinations; the importance of follow-up laboratory tests to document response to treatment, the importance of record-keeping and reporting to public health authorities, the value of HIV testing of TB patients and the use of anti-retrovirals for those dually infected; and the assessment of drug resistance and the appropriate treatment of multidrug-resistant tuberculosis. Finally, some proposals were made on the way forward for Japan.

Key words: International standards, Tuberculosis care

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