# REVIEW OF "STANDARDS FOR TUBERCULOSIS CARE" —2008

April 2008

### The Treatment Committee of the Japanese Society for Tuberculosis

## I. Introduction

In 2002 and 2003, the Treatment Committee of the Japanese Society for Tuberculosis (hereinafter referred to as The Committee) discussed and announced the standard treatment regimens for previously untreated patients and also announced alternative regimens for when isoniazid (INH) and/or rifampicin (RFP) cannot be used, as well as standard dosage and administration recommendations for individual drugs[1)2)]. In the subsequent five years, the need for intermittent treatment has increased due to the introduction and development of the DOTS (Directly Observed Treatment, Short-Course) strategy, and new fluoroquinolones became commercially available.

The Tuberculosis Control Law was repealed in April 2007. Since then, tuberculosis control actions have been carried out under the revised version of the Infectious Diseases Control Law. It is important that this revised law considers conventional chemotherapeutic prevention as "a treatment of latent tuberculosis infection." In 2006, the International Standards for Tuberculosis Care (ISTC) was published (The Tuberculosis Coalition for Technical Assistance: International Standards for Tuberculosis Care. (http://www.wpro.who.int/internet/files/stb/busan/raw_files/Background_documents/ISTC/ISTC_Ver10_Jan_2006_.pdf http://www.stoptb.org/resource_center/assets/documents/istc_report.pdf_). The Japanese Society for Tuberculosis (hereinafter referred to as The Society) then endorsed the ISTC in June 2007. It was found, however, that the standards of the ISTC and other tuberculosis treatment standards in foreign countries, such as those provided by the American Thoracic Society (ATS)[3)], differed subtly from the standard tuberculosis care in Japan. Therefore, the Japanese standards for tuberculosis care were reviewed.

In light of the recent circumstances described above, the review included consideration of additional statements on intermittent treatment and amendments to the two publications of 2002 and 2003. The updated standards are described here. It is hoped that, under the revised Infectious Diseases Control Law, even higher quality care will be provided for tuberculosis patients.

## II. Viewpoints of this document

When the Tuberculosis Control Law was revised in 2004, the so-called Japanese version of the DOTS strategy was designated to help patients adhere to the prescribed regimen for completing tuberculosis treatment. This DOTS strategy has gradually become routine. At the same time, there has been an increase in the proportion of patients who require support to adhere to the drug regimen with a directly observed treatment (DOT) strategy. In addition, there are demands for restrictions on hospitalizations and shortening hospital stay durations. Accordingly, promotion of patient adherence to the regimen at outpatient clinics will play an increasingly important role in tuberculosis care, which has so far been dependent on inpatient treatment in Japan. At present, a face-to-face DOT for outpatients is given to only a small percentage of patients; however, in the future it will be necessary to increase the number of patients receiving this type of DOT. Under these circumstances, intermittent treatment should be more actively adopted, since it has the advantages of administering drugs at a lower frequency and of imposing a smaller burden on patients[3)~5)].

The present standards include additional descriptions of the dosage and administration of drugs for intermittent treatment, in addition to the proposed standards stated in the previous report. Furthermore, the present standards provide pediatric dosage levels for INH, which is also used for the treatment of latent tuberculosis infection.

In the standard treatment regimens of the ISTC and the US standards[3)], the use of ethambutol (EB) in the continuation phase of tuberculosis treatment is not recommended. In Japan, however, the use of this drug is allowed for 6 months at most with Method A and for 9 months at most with Method B. The Committee reviewed the duration of EB treatment and, as a result, the present standards specify the criteria for discontinuation of EB (or streptomycin [SM]) treatment to avoid unnecessary drug treatment and prevent adverse reactions. The Committee also reviewed the conditions and symptoms leading to the previously accepted prolongation of a continuation phase in the treatment of patients with severe lesions, such as miliary or far-advanced cavitary tuberculosis, or patients with delayed negative conversion of bacilli. As a result, the present standards describe slightly broader conditions for prolongation than accepted previously.

Fluoroquinolones are internationally accepted as essential drugs in the treatment of drug-resistant tuberculosis, especially multidrug-resistant tuberculosis[3)6)]. Because therapeutic outcomes with new drugs such as moxifloxacin (MFLX)[7)] have been reported recently in foreign countries, the present standards add consideration of fluoroquinolones that have become

commercially available as antibacterial agents.

### III. Principles of chemotherapy and antituberculosis drugs

1. Antituberculosis drugs

The principal objective of current tuberculosis care is to maximize the elimination of tubercle bacilli in the body of patients with tuberculosis. To achieve this, a multidrug therapy in the early phase of the treatment is essential: use of at least three drugs to which the bacilli are susceptible that exert different modes of action. This multidrug regimen should be continued for at least 6 months. The principles are to select an effective and safe treatment regimen and to continue that regimen for a necessary period.

The antituberculosis drugs currently available in Japan are divided into three groups, as shown in Table 1, on the basis of antibacterial activity and safety. Although fluoroquinolones, which have not yet been officially approved for Japanese health insurance coverage, are listed at the end, they are highly useful in the treatment of tuberculosis, particularly when other drugs are difficult to use because of the emergence of multidrug resistance or adverse reactions. The Society will continue to request that the regulatory authorities grant official approval for fluoroquinolones as antituberculosis agents.

2. Standard dosage of antituberculosis drugs (Table 2)

Treatment with antituberculosis drugs is associated with adverse reactions due to allergic (allergy-like) mechanisms and also frequently with drug-specific adverse reactions. Allergic reactions are unpredictable. Since drug-specific adverse reactions are primarily related to the dosage of a particular drug[8], prevention of their occurrence requires setting a dosage at which "that drug is effective against tubercle bacilli and causes fewer adverse reactions."

The Committee has set the standard dosages for antituberculosis drugs for adults at a daily standard dose per kg of body weight (mg/kg/day) and a daily maximal dose (mg/day) on the basis of the reported findings on pharmacokinetics of antituberculosis drugs[9], the statement on treatment of tuberculosis published by the ATS[3], and the therapeutic achievements that have long been accumulated in Japan (Table 2). In addition, The Committee has recommended that a once-daily regimen should be used for antituberculosis drugs (except ethionamide [ETH], para-amino-salicylic acid [PAS] and cycloserine [CS]) as a rule for ensuring an effective blood concentration of a drug and for promoting the success of a DOTS[1].

In the elderly, age-related impairment is usually noted in various organs, particularly in the liver and kidneys. Many of the antituberculosis drugs are metabolized by the liver and predominantly excreted by the kidneys (note that RFP is excreted from the liver). When antituberculosis drugs are administered to elderly patients, special attention must be paid to these impaired functions and reduction of the daily maximal dose (mg/day) must be considered.

For patients who already have hepatic or renal dysfunction as a complication, a dosage needs to be determined with reference to the "Opinions on use of antituberculosis drugs in hepatic or renal dysfunction" provided by The Committee[10].

**Table 1** Grouping of antituberculosis drugs and the principles for their use

| | Characteristics | Drug name | Abbreviation |
|---|---|---|---|
| First-line drugs (Category A) | Exert the strongest antibacterial activity and are inevitable for bacterial elimination. RFP and PZA exert a sterilizing effect and INH has a bactericidal effect. | Rifampicin* Isoniazid Pyrazinamide | RFP INH PZA |
| First-line drugs (Category B) | Are expected to be effective when used in combination with the drugs included in Category A first-line drugs. SM exerts a bactericidal effect and EB primarily exhibits a bacteriostatic effect. | Streptomycin Ethambutol | SM EB |
| Second-line drugs | Are inferior to the first-line drugs in antibacterial activity but are expected to be effective when used in a multidrug regimen. | Kanamycin Ethionamide Enviomycin Para-amino-salicylic acid Cycloserine Levofloxacin** | KM TH EVM PAS CS LVFX |

In the table above, the drugs are listed from the top to the bottom in the order of priority. SM, KM and EVM should not be concurrently used. On the basis mainly of antibacterial activity and cross resistance, these drugs can be selected in the order of SM, KM and EVM.
*RFP has interactions with many drugs and therefore requires particular attention. Especially when HIV-infected patients require treatment with antiviral agents, administration of rifabutin instead of RFP should be considered.
**Another fluoroquinolone may be substituted for LVFX. On the basis mainly of antibacterial activity and adverse reactions, the substitute can be selected from moxifloxacin, gatifloxacin, ciprofloxacin and sparfloxacin. In antibacterial activity, these fluoroquinolones are as potent as those included in Category B. However, these drugs are listed at the end, because they had not yet obtained official approval for Japanese health insurance coverage by the time of publication of the 2008 review.

## IV. Standard treatment regimens for previously untreated patients

For previously untreated patients, it is rare that drug susceptibility is known at the initiation of treatment. It is therefore necessary to administer multidrug combination therapy to ensure bacterial elimination, since there may be a possibility of initial drug resistance. Even for previously treated patients, standard treatment regimens that are in accordance with those used for previously untreated patients are recommended if drug resistance did not develop during a previous treatment and the treatment was completed. In either case, drug susceptibility test results must be confirmed. If resistance to any of the drugs used is noted, then a therapeutic strategy needs to be reconsidered in accordance with Section Ⅵ.

1. Drug selection in the initial intensive phase

A four-drug therapy for an initial 2-month period, consisting of three first-line drugs selected from Category A and any first-line drug of Category B, is already widely employed worldwide as the strongest strategy that can achieve the therapeutic goal of "bacterial elimination" with the shortest (6 months [180 days]) course[3)11)].

In light of the above, the standard treatment regimen for previously untreated patients will be Method A described in Table 3, regardless of disease type or bacterial discharge. Method B will be used only when pyrazinamide cannot be administered due to adverse reactions.

For patients with underlying hepatic disorders, such as cirrhosis or chronic type C hepatitis, and elderly patients at the age of 80 years or older, selection of Method B will be

**Table 2** Standard dosages and maximal dosages for adults

| Drug name | Standard dosage (mg/kg/day) | Maximal dosage (mg/body/day) | Remarks |
|---|---|---|---|
| Rifampicin | 10 | 600 | The dosage for intermittent therapy is stated in the text of this report. |
| Isoniazid | 5 | 300 | |
| Pyrazinamide | 25 | 1500 | |
| Streptomycin | 15 | 750 (1000) | Up to 1000 mg is acceptable for twice-weekly administration. During an initial 2-month period, daily administration is acceptable. When administered daily, the maximal dose is 750 mg. |
| Ethambutol | 15 (20) | 750 (1000) | During an initial 2-month period, 20 mg/kg may be administered. However, when the treatment is continued thereafter, the dose should be 15 mg/kg (750 mg/day). |
| Kanamycin | 15 | 750 (1000) | Up to 1000 mg is acceptable for a three-time weekly administration. During an initial 2-month period, daily administration is acceptable. For daily administration, the maximal dose is 750 mg. |
| Ethionamide | 10 | 600 | The dose should be gradually increased from 200 mg/day. |
| Enviomycin | 20* | 1000 | The drug may be administered daily for an initial 2-month period and subsequently, two or three times weekly. |
| Para-amino-salicylic acid | 200 | 12 g | |
| Cycloserine | 10 | 500 | |
| Levofloxacin | 8 | 600 | The drug is contraindicated in pediatric patients and pregnant women. |

1. The drug may, as a rule, be administered once daily. TH, PAS and CS are administered in divided doses.
2. Dose reduction should be considered for elderly patients and those with renal function impairment.
3. When patient's renal function is impaired, the *-marked drugs should be administered at lower doses or at intervals.

**Table 3** Standard treatment regimens for previously untreated patients

Method A is used as a rule. Method B is used only when PZA cannot be administered. When drug susceptibility is unknown and symptom improvement is unclear, SM (or EB) is continued until drug susceptibility is identified and clinical improvement is confirmed.

Method A : Four-drug therapy with RFP＋INH＋PZA＋SM (or EB) for 2 months, followed by RFP＋INH for 4 months

Method B : Three-drug therapy with RFP＋INH＋SM (or EB) for 2 months, followed by RFP＋INH for 7 months

considered from the beginning since drug-induced serious hepatic disorders may likely occur in these patients. Neither SM nor PZA will be used in pregnancy since there is a concern that SM may cause an eighth cranial nerve disturbance in a fetus, and the safety of PZA in fetuses has not yet been established. In the treatment of pregnant women, Method B with EB as the third drug will be administered as a rule.

For patients who begin on Method A, are confirmed to have the microbes susceptible to the drugs and can continuously receive the regimen because no adverse reactions have occurred, intermittent therapy stated in Section V will also be considered.

### 2. Use of EB (or SM) in the continuation phase

With either Method A or B, after confirmation that the microbes are susceptible to RFP and INH, EB (or SM) should be discontinued after the 3rd month. This is because the continued use of EB (or SM) in the continuation phase of treatment has little significance after the 3rd month, and because long-term use of EB (or SM) increases the risk of adverse reactions. It should be noted that INH resistance refers to the resistance at 0.2 $\mu$g/m$l$ as measured according to the Ogawa method[12]. When the MGIT method is used for a drug susceptibility test, the concentration for resistance is 0.1 $\mu$g/m$l$. In patients in whom drug susceptibility cannot be confirmed because of the absence of organisms, but drug resistance is unlikely, and clinical improvements are obvious, EB (or SM) is discontinued as a rule.

### 3. Treatment period

The standard length of the treatment period will be 6 months for Method A and 9 months for Method B.

However, the treatment period can be prolonged by 3 months for patients with severe lesions, such as those with cavitary (far-advanced cavitary type, in particular) or miliary tuberculosis, those who persistently show positive culture results in the 3rd month of treatment and onwards (i.e., after the completion of an initial 2-month therapy), those with diabetes or pneumoconiosis, those who concurrently take systemic adrenocorticoids or immunosuppressants and those who receive retreatment. Accordingly, Method A can be carried out for 9 months and Method B for 12 months.

For patients in whom bacterial discharge persists for more than 4 months, there is a possibility that the mycobacteria acquired resistance to the drugs used and susceptibility testing should be repeated using the most recent strains.

### 4. Promoting adherence

The key in tuberculosis treatment is continuous administration of the prescribed drugs, without fail, for a set period. This requires special considerations to facilitate the completion of treatment as planned. Upon treatment, an appropriate DOTS for each patient will be performed in accordance with the Guidelines provided by the Committee on Health and Nursing of The Society[13] or any other relevant standards.

Patient adherence to the drug regimen should be promoted through cooperation between physicians and public health centers: physicians pay attention to how patients adhere to the drug regimen and the instructions given at clinic visits, remind the patients to visit a clinic if they miss an appointment and communicate with the public health center. The public health center directly observes a patient if needed and ensures patient adherence by visiting his/her home through communication with his/her attending physician. Monitoring of the treatment and outcome by a public health center (cohort analysis) should be performed since this is a mandatory requirement for the Japanese version of a DOTS strategy.

### 5. Situations where the standard treatment cannot be performed

When resistance to either INH or RFP, or both, is noted and when RFP or INH cannot be administered due to adverse reactions, an alternative regimen should be selected in accordance with Section VI. When there has been little experience with tuberculosis care, as a rule, a patient will be referred to a specialist and a therapeutic strategy will be changed after due consultation with the specialist.

However, Japan has no official system for qualifying medical institutions or physicians specializing in tuberculosis care. When a nearby tuberculosis care institution or specialist to be consulted is not known, the local public health center should be asked to introduce an appropriate specialist.

Discontinuation of drugs due to adverse reactions or any other relevant circumstances, without careful consideration, makes it inevitable that treatment will need to be extended and there will be concern that the therapeutic objective may be achieved only incompletely. With hepatic injury, which is a most frequently noted adverse reaction, efforts should be made to continue RFP and INH as long as possible with reference to the Guidelines on how to handle hepatic injury[14] provided by The Committee. When RFP or INH is discontinued due to the occurrence of drug-induced allergy-like adverse reactions (e.g., rash and fever), it is recommended that desensitization therapy be attempted. In desensitization therapy, "the drug is discontinued, and then readministered at an extremely small starting dose and subsequently at gradually increased doses"[15], after resolution of these symptoms and consultation with a specialized medical doctor.

Within about 3 months after the start of treatment, worsening of chest X-ray findings or lymph node swelling may be transiently noted. Even in such a case, if mycobacterial examination gives negative results or indicates reduced quantities of microbes, then the treatment is considered effective and no change in drugs will be made. The therapeutic strategy will be determined only after drug susceptibility test results are obtained.

## V.  Intermittent treatment

Intermittent treatment will ensure continuation of therapy, with less frequent observation for adherence. Intermittent treatment should be used particularly in cases where it has been judged, under the Japanese version of the DOTS strategy, that direct observation is necessary at an outpatient clinic[5) 16)].

### 1.  Patients who will receive intermittent treatment

Intermittent treatment is administered to patients who have begun with the standard treatment Method A (comprising PZA) and are confirmed by culture results to have tubercle bacilli susceptible to both RFP and INH. Intermittent treatment should not be given to patients who have been treated with Method B or for whom RFP, INH or PZA has been discontinued because of the occurrence of adverse reactions, since relapse rates are high in these patients. Intermittent treatment should not be performed on HIV-infected patients.

### 2.  Treatment methods (Table 4)

After completion of an initial 2-month four-drug therapy, both RFP and INH are administered two or three times weekly for the subsequent 4 months. In cases of far-advanced cavitary-type tuberculosis, the drugs should be administered three times weekly. As the fourth drug in the initial phase, EB or SM is preferred. SM, which is more bactericidal than EB, should be selected in severe-type cases.

The treatment period will be, as a rule, 6 months. However, in diabetes-associated, far-advanced cavitary-type, or retreatment cases, the treatment period will be prolonged by 3 months (i.e., 9 months total).

### 3.  Dosage levels of the drugs

(1)  RFP: Throughout the entire period, 10 mg/kg, with a daily maximal dose of 600 mg (the standard treatment, the same as in Table 3).

(2)  INH: For an initial 2-month period, 5 mg/kg daily, with a daily maximal dose of 300 mg. During the intermittent period, 15 mg/kg, with a daily maximal dose of 900 mg.

The dosage levels of PZA, EB and SM are the same as those for the standard treatment (Table 3) for an initial 2-month period.

### 4.  Implementation of DOTS

During the intermittent period, missing even a single dose results in treatment failure; therefore, a DOT must be performed without fail. Namely, as a rule, the patient is directly observed by the supervisor when taking the medication. Confirmation of adherence by telephone calls or FAX or by counting empty drug bags is not allowed. The supervisor will be a physician, a nurse, a public health nurse, a pharmacist, a nurse who visits the patient's home, a care giver who visits the patient's home, or any others who have received DOTS training. It is necessary to establish a system that triggers appropriate actions immediately whenever a patient does not visit a clinic to take the scheduled medication.

## VI.  Alternative regimens when the standard treatment cannot be performed

When the standard treatment cannot be performed, selection of alternative drugs and determination of a treatment period are made in accordance with the principles stated below.

(1)  Early in the treatment course, at least 3 drugs (or 4 to 5 drugs whenever possible), which are applicable and are effective against tubercle bacilli *in vitro*, are administered for 6 months after negative conversion of bacilli; then, the treatment regimen, excluding drugs that are difficult to use for a long-term period, will be continued[17)]. (Regarding a specific length of period for treatment continuation, see the statements below.)

(2)  When bacteriological relapse is noted during therapy and the emergence of drug resistance is strongly suspected, replacement of only the suspected drug with an alternative agent is contraindicated because the post-replacement therapy is highly likely to consist of monotherapy using the new agent, which also probably induces the emergence of resistance. With a drug change, multiple components of the regimen should be simultaneously replaced with effective drugs.

(3)  Drug selection is made according to the order stated in Table 1. However, SM, kanamycin (KM) and enviomycin (EVM) cannot be concurrently used. On the basis mainly of antibacterial activity and cross resistance, SM is first preferred, followed by KM and EVM in this order. Multiple fluoroquinolones should not be concurrently used. On the basis mainly of antibacterial activity and adverse reactions, one drug should be selected from LVFX, MFLX, gatifloxacin, ciprofloxacin and sparfloxacin.

### 1.  Alterative regimens when RFP or INH cannot be used

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**Table 4**  Intermittent treatment for previously untreated patients

Twice-weekly strategy: Daily administration of RFP＋INH＋PZA＋EB (or SM) for 2 months, followed by RFP＋INH twice weekly for 4 months*

Three-time weekly strategy: Daily administration of RFP＋INH＋PZA＋EB (or SM) for 2 months, followed by RFP＋INH three times weekly for 4 months*

The dose of INH during the intermittent phase is 15 mg/kg up to the maximum 900 mg.

RFP and INH are the most potent and most indispensable drugs for modern tuberculosis care. When one of these drugs cannot be used because of the emergence of drug resistance or the occurrence of adverse drug reactions, it becomes more difficult to achieve the therapeutic goal of eliminating viable mycobacteria in the body as soon as possible. Accordingly, early in the treatment course, when the number of viable mycobacteria in the body is presumed to be highest, the most desirable strategy is to use at least four bacteriologically effective antituberculosis drugs, including fluoroquinolones, which have been confirmed to be effective by drug-sensitivity test[6) 7) 18)].

In reference to the examples stated below, effective therapeutic drugs are selected and a multidrug therapy is performed. When some of the drugs listed below cannot be administered, an alternative agent that is effective *in vitro* can be selected in the priority order indicated in Table 1 from the second-line drugs (those listed under KM inclusive in the table) or fluoroquinolones (e.g., LVFX) and used successively.

The length of the treatment period is in accordance with those of the standard treatment regimens, namely, the treatment period may be prolonged by 3−6 months for patients with severe tuberculosis, such as miliary or far-advanced cavitary tuberculosis, those with persistently positive culture results even 3 months after the start of treatment, those associated with diabetes or pneumoconiosis, and those who concurrently take systemic adrenocorticoids or immunosuppressants.

[1] Alternative regimens when RFP cannot be administered (in cases where INH is effective *in vitro* and applicable)

(1) When PZA can be administered

A four- or five-drug therapy with INH＋PZA＋SM (or KM or EVM)＋EB＋(LVFX or one of the second-line drugs effective *in vitro*) is administered for 6 months after negative conversion of bacilli; subsequently, a two- or three-drug therapy with INH＋EB＋(LVFX or one of the second-line drugs effective *in vitro*) is performed. The treatment period will be 18 months, after negative conversion of bacilli. However, SM (or KM or EVM) will be administered for 6 months at most.

(2) When PZA cannot be administered

A four-drug therapy with INH＋SM (or KM or EVM)＋EB＋(LVFX or one of the second-line drugs effective *in vitro*) is continuously performed for 6 months after negative conversion of bacilli; subsequently, a three-drug therapy with INH＋EB＋LVFX or one of the second-line drugs is given. The treatment period will be 18−24 months after negative conversion of bacilli. However, SM (or KM or EVM) will be administered for 6 months at most.

[2] Alternative regimens when INH cannot be administered (in cases where RFP is effective *in vitro* and applicable)

(1) When PZA can be administered

A four- or five-drug therapy with RFP＋PZA＋SM (or KM or EVM)＋EB＋(LVFX or one of the second-line drugs effective *in vitro*) is continuously performed for 6 months after negative conversion of bacilli; then, a two-drug therapy with RFP＋EB is administered. The treatment period will be the longer of the following two: 9 months or 6 months after negative conversion of bacilli. However, SM (or KM or EVM) will be administered for 6 months at most.

(2) When PZA cannot be administered

A four-drug therapy with RFP＋SM (or KM or EVM)＋EB＋(LVFX or one of the second-line drugs effective *in vitro*) is continuously performed for 6 months after negative conversion of bacilli; then, a two-drug therapy with RFP and EB is administered. The treatment period will be the longer of the following: 12 months after the start of treatment or 9 months after negative conversion of bacilli. However, SM (or KM or EVM) will be administered for 6 months at most.

2. Alternative regimens when neither RFP nor INH can be administered

When neither RFP nor INH can be administered because of the emergence of drug resistance or the occurrence of adverse reactions, alternative regimens should be based on the principles stated above. Even in cases of multidrug resistance, INH may be used when INH resistance is noted at 0.2 $\mu$g/m*l* and INH susceptibility at 1 $\mu$g/m*l*, although this drug will not be counted as an effective drug component of the regimen. The treatment period will be 24 months after negative conversion of bacilli. For patients in whom surgical treatment is applicable, that treatment can be selected as a positive therapeutic option at the beginning of tuberculosis treatment. For success of such surgical therapy, use of several effective antituberculosis drugs will be inevitable[17) 19)].

Patients with multidrug-resistant tuberculosis should be treated in a specialized medical institution equipped with infection-preventive facilities and private rooms adequate for long-term hospitalization. Also, DOT and surgical therapy must be available in that institution. Importantly, a tuberculosis care team must pay careful attention to monitor any signs indicating the occurrence of adverse reactions, and repeatedly inform the patient and his/her family members that tuberculosis care will take a long time, and that treatment success rates are not always high. The team must also repeatedly explain the adverse effects likely attributable to the drugs, methods for early detection of these reactions/symptoms, post-treatment changes in bacterial discharge and any other relevant matters. The team will thus help patients to complete the therapy, in cooperation with public health centers.

## VII. Therapeutic interventions, other than antituberculosis drugs, in the treatment of pulmonary tuberculosis and extrapulmonary tuberculosis

1. Adrenocorticoids

Use of adrenocorticoids is considered for patients with tuberculous meningitis, tuberculous pericarditis or severe tuberculosis, especially miliary tuberculosis associated with poor systemic conditions, such as respiratory failure or high

**Table 5** Dosage levels for adults and children in the treatment of latent tuberculosis infection

| | | Dose for adults mg/kg of body weight (once daily) | Dose for children at the age of 12 years or younger mg/kg of body weight (once daily) | Daily maximal dose mg |
|---|---|---|---|---|
| Isoniazid | INH | 5 | 8−15 | 300 |
| Rifampicin | RFP | 10 | 10−20 | 600 |

fever.

2. Disease conditions for which other types of therapeutic intervention, including surgical treatment and other non-chemotherapeutic treatments, should be considered

[1] Pulmonary tuberculosis

When multidrug resistance is noted and, in addition, a lesion is localized and resectable, surgical therapy will be considered in the initial stage of treatment. Whether or not surgical therapy is applicable is to be discussed with a specialist. Resection is indicated when chemotherapy has effectively reduced quantities of bacilli; that is, approximately 3 to 4 months after the start of chemotherapy.

[2] Extrapulmonary tuberculosis

When an abscess of a noticeable size is formed in the lymph node, bone, joint, or iliopsoas muscle, or subcutaneously, chemotherapy alone exerts limited effectiveness, and surgical treatment appropriate for individual lesions, such as dissection or drainage, will be required.

### VIII. Treatment of latent tuberculosis infection (Table 5)

For diagnosis and implementation of therapy, see the report published by The Prevention Committee of The Society[20]. Using diagnostic imaging or any other relevant measures to prevent the emergence of drug resistance, the possibility that active tuberculosis may develop otherwise should be excluded. The drug to be used will, as a rule, be INH. When the infection source is resistant to INH, RFP can be used. INH is administered for 6 or 9 months and RFP for 4 or 6 months. For either drug, the dosage levels will be the same as those for the treatment of active tuberculosis. Patients with latent tuberculosis infection requiring treatment are commonly children, and attention should be paid to the fact that the standard daily dose of INH per body weight is greater for children (8−15 mg/kg of body weight; maximal daily dose 300 mg) than for adults.

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