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= Abstract =

Pediatric tuberculosis and drug resistance

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Drug-resistant tuberculosis in children has important implications for both the patients and tuberculosis control programs. In Korea, among all new patients, the isoniazid resistance rate was 9.9% and multidrug-resistant tuberculosis rate was 2.7% in 2004 (in patients aged 10-19 yr, the multidrug-resistant tuberculosis rate reached 2.1%). Tuberculosis in pediatric patients is difficult to diagnose because many children have nonspecific clinical signs and the detection rates of acid-fast bacilli smears and cultures are low. Therefore, every effort should be made to identify adult sources and obtain information on drug sus-ceptibility because symptomatic adult patients have a higher chance of culture positivity and drug-susceptibility patterns are the same in most adult-child pair patients. Korean children are at significant risk of drug-resistant tuberculosis. As the isoniazid resistance rate is greater than 4% among the new cases in Korea, a four-drug regimen should be considered for initial treatment of children with active tuberculosis, unless drug-susceptibility test results are available. Treatment of drug-resistant tuberculosis in children is challenging and there are only few available data. Tuberculosis control programs should be continuous with specific focus on pediatric populations because they can serve as reservoirs for future active cases. Further studies are needed regarding treatment of drug-resistant tuberculosis in children. **(Korean J Pediatr 2009;52:529-537)**

Key Words : Children, Tuberculosis, Drug resistance, MDR, XDR

Introduction

The global burden of tuberculosis (TB) indicates that this disease is a serious health threat. Infection due to drug-resis-tant tuberculosis (DR-TB) has increased over the recent years and TB control is becoming more difficult in various parts of the world. DR-TB was considered to be less infec-tious and less likely to cause disease than drug-susceptible strains[1]. However, it is now known that these strains cause infection and disease as often as the drug-susceptible count-erparts[2-4]. Currently, there is paucity of data regarding DR-TB in pediatric populations in terms of the epidemiology

and management strategies of either latent or active TB. In this review, the recent available data mainly focusing on the epidemiology and treatment options will be discussed.

Definition and epidemiology of DR-TB

DR-TB is confirmed through laboratory tests. Four diffe-rent categories of drug resistance have been established [5]:

· Monoresistant TB: resistance to one anti-TB drug.
· Polyresistant TB: resistance to more than one anti-TB drug, other than both isoniazid and rifampin.
· Multidrug-resistant (MDR) TB: resistance to at least isoniazid and rifampin.
· Extensive drug resistance (or extensively drug-resis-tant; XDR) TB: resistance to any fluoroquinolone and at least one of three injectable second-line drugs (capreo-mycin, kanamycin, and amikacin) in addition to MDR-TB.

Information on drug susceptibility is crucial because it has

been shown that, in adults, infection with MDR–TB strains causes significantly high (43–93%) mortality[6, 7]. Therefore, the worldwide epidemiologic data on DR–TB is important to guide the treatment strategies.

Globally, the World Health Organization (WHO) currently reports only smear–positive cases by age. The International Union Against Tuberculosis and Lung Diseases (IUATLD) currently recommends stratification of the reported smear–negative cases into two age groups: <15 yr and ≥15 yr. The WHO has estimated the global epidemiology of tuberculosis as 1.3 million annual cases in children less than 15 yr of age and 450,000 deaths in 1989[8]. In 1994, it was estimated that 9% of the total TB cases (650,000 of 7,500,000) occurred in children[9]. Estimation of the prevalence of pediatric TB patients is difficult because childhood TB is diagnosed by variable case definitions (usually a combination of clinical symptoms, tuberculin skin testing [TST], chest radiography, and contact history) rather than by bacteriology[10]. Pediatric DR–TB appears to be an increasing problem in many parts of the world. However, the current data on drug–resistance epidemiology are mainly from adult cases, with limited data from pediatric populations.

The epidemiologic data of drug resistance in Korea and the world are shown in Table 1. In Korea, any first–line drug resistance was observed in 12.8% (95% confidence interval [CI]=11.5–14.1), isoniazid resistance in 9.9% (95% CI=8.8–11.0], rifampin resistance in 3.7% (95% CI=3.0–4.4), and MDR–TB in 2.7% (95% CI=2.1–3.3) of the 2,636 new smear–positive patients from the 2004 survey. The drug–resistance rates were significantly higher in patients with a history of previous treatment[11]: any first–line drug resistance, 27.7%

Table 1. Median Prevalence Values of Resistance to Antituberculosis Agents in Korea

Type of resistance	Korea			World
	1998 (%)	2003 (%)	2004 (%)	2002 (%)
New cases				
Any drug	10.9	12.8	12.8	10.2
Isoniazid	8.6	9.9	9.9	5.9
Rifampin	3.0	3.2	3.7	1.4
Multidrug	2.2	2.4	2.7	1.1
Retreatment cases				
Any drug	22.3	28.9	27.7	18.6
Isoniazid	17.3	24.8	24.1	NA
Rifampin	10.2	15.8	16.9	NA
Multidrug	7.1	13.0	14.0	6.9

Source: Adapted from Bai et al.[11] and Aziz et al.[12]
Abbreviations : NA, not available

(95% CI=22.4–33); isoniazid resistance, 24.1% (95% CI=19.1–29.1); rifampin resistance, 16.9% (95% CI=12.5–21.3); and MDR–TB, 14.3% (95% CI=9.9–18.1]. It is noteworthy that a statistically significant increase in the drug resistance was observed among the new cases in 2004 compared with those in the previous years. Further, the patients with previous treatment had almost a 5.3 times higher MDR–TB rate than the untreated patients. Therefore, during evaluation of a child for known exposure to an adult patient with TB, it is important to investigate the treatment history of the adult source. If the adult was previously treated for TB, the possibility of the child being exposed to MDR–TB strains is about 14% in Korea.

The data from the Global Project on Anti–Tuberculosis Drug Resistance Surveillance, performed in 79 countries or geographical settings from 1999 to 2002, showed that the median of the new cases with any drug resistance was 10.2 % (0–57.1%), and those with drug resistance to streptomycin, isoniazid, rifampin, and ethambutol were 6.3%, 5.9%, 6.3%, and 0.8%, respectively[13]. The median prevalence of MDR–TB was 1.1%, with the highest prevalence seen in Kazakhstan (14.2%), Israel (14.2%, although a substantial decrease was seen in 2001 and 2002), Tomsk Oblast (Russia, 13.7%), Karakalpakstan (Uzbeikistan, 13.2%), Estonia (12.2 %), Liaoning (China, 10.4%), Lithuania (9.4%), Latvia (9.3%), and Henan (China, 7.8%). In the previously treated cases, the median prevalence of any resistance was 18.6% and that of MDR–TB was 6.9%. Overall, MDR–TB represented a serious problem for TB control in countries of the former Soviet Union and some provinces of China. In addition, a trend of significant increases in the prevalence of new MDR–TB cases in certain parts of the world (mostly resource–poor settings) where the TB burden is still high was observed[12]. In another report, the estimated total number of MDR–TB cases in 2004 was 4.3% (95% CI=3.8–6.1%) or 424,203 (95% CI=376,019–620,061) of all the new and previously treated TB cases. Three counties China, India, and the Russian Federation–accounted for 62% or 261,362 (95% CI=180,779–414,749) of the MDR–TB cases in the estimated global burden[13].

Although there are few data on pediatric MDR–TB rates, studies have shown that the rates are comparable between children and adults in the same community and are considered to represent the resistance patterns and transmission among the general population. In South Africa, children with TB aged less than 5 yr had a 5.6% isoniazid resistance rate and 1% MDR–TB rate[14]. A study from central Africa re-

ported that children aged 0–15 yr had overall resistance rates of 15.2% and MDR–TB rates of 0.6% compared with the adult rates of 16.4% and 1.1%, respectively[15].

As in the adult population, drug resistance rates have increased in pediatric patients. In a study of South African children (median age=2.5 yr, 26.3% of those tested were HIV–positive), the prevalence of all isoniazid resistance was shown to have increased from 6.9% to 12.8%, isoniazid monoresistance from 4.6% to 7.4%, and MDR–TB from 2.3% to 5.4% when the rates were compared between the study periods 1994–1998 and 2003–2005. In these periods, the proportion of patients with HIV infection also increased[16].

The age distribution of MDR–TB in Korea is shown in Table 2. The MDR–TB rate of untreated teenagers was 2.1%, higher than that of adult patients in their 40s or elderly patients (older than 60 yr). Therefore, MDR–TB should be suspected when the patients condition does not respond to treatment once adherence to medication is confirmed. Another important finding is that most of the MDR–TB cases were reported among patients in their childbearing ages (20s to 40s). In the United States, the highest percentage of MDR–TB cases (34%) was also observed among patients of childbearing age (25–44 yr)[17]. This is a significant finding because MDR–TB infection of children from adult family members or relatives would be an inevitable consequence. Data on the MDR–TB rates of younger children are very limited and should be addressed in future studies. Drug resistance in pediatric populations has an important implication because children exposed to resistant strains will serve as future reservoirs for active DR–TB cases. Moreover, treating pediatric patients with more toxic and less effective secondary drugs having safety concerns is very challenging for any clinician.

Korea is one of the countries where XDR–TB cases are uncommonly diagnosed in clinical practice. The drug–susceptibility data on XDR–TB strains from various countries are listed in Table 3. In the 2004 survey, 11% of all Korean TB isolates were MDR–TB strains, of which 15% were XDR–TB strains. The threat from XDR–TB in Korea is substantial and surely needs close monitoring in the future. Pediatricians should be aware of any child XDR–TB exposure cases especially around previously treated adult source cases.

Mechanisms and detection of drug resistance

Genetic studies have shown that antimycobacterial resistance is caused by spontaneous mutations in genes encoding either the drug target or enzymes involved in drug activation. Resistance–associated point mutations, deletions, or insertions have been reported for first–line agents (isoniazid, rifampin, pyrazinamide, ethambutol, and streptomycin), and for other second–line and newer agents (ethionamide, fluoroquinolones, macrolides, and nitroimidazopyrans)[18]. Several putative resistance genes are reported in the literature: *katG, inhA, ahpC, kasA* for isoniazid; *rpoB* for rifampin; *pncA* for

Table 2. Prevalence of Multidrug–Resistant Tuberculosis by Age in Korea

Age (yrs)	New cases (%)	Retreatment cases (%)
All ages	2.7	14.0
10–19	2.1	–
20–29	5.0	12.5
30–39	2.8	21.4
40–49	1.5	18.1
50–59	3.3	4.9
60–69	0.8	7.4
70	1.1	8.7

Source: Adapted from Bai et al.[11]

Table 3. Emergence of Multidrug– and Extensive Drug–Resistant Tuberculosis in Korea and the World

	Total number of isolates tested	MDR–TB of all isolates tested (%)	XDR–TB of all MDR–TB isolates tested (%)
South Korea	11,939	11	15
Industrialized nations	2,499	33	6
Central, South America	985	55	6
Eastern Europe, Western Asia	1,153	35	14
Africa and Middle East	665	23	1
Asia (excluding South Korea)	391	70	1

Source: Adapted from Centers for Disease Control and Prevention[36]
The data from the regions except South Korea were collected between 2000 and 2004. Data from South Korea are from the 2004 survey. Abbreviations : MDR–TB, multidrug–resistant tuberculosis; XDR–TB, extensive drug–resistant tuberculosis

pyrazinamide; *embB* for ethambutol; *rpsL* and *rrs* for streptomycin; *rrs* for amikacin and kanamycin; *gyrA* for quinolones; and *inhA* for ethionamide[19].

Resistance is thought to occur within cavitary pulmonary lesions with large numbers (10^8 to -10^9) of mycobacteria. Spontaneous drug-resistance mutations occur at a rate of one in 10^3 to one in 10^8 mycobacteria even without previous drug exposure. The mutation rate is one in 10^6 for isoniazid, streptomycin, and ethambutol, and one in 10^8 for rifampin. The probability of a spontaneous mutation causing MDR-TB is the product of the cumulative rate of mutation for isoniazid and rifampin ($10^6 \times 10^8$ or one in 10^{14}) rather than spontaneous resistance to more than one drug by chance because mutations are not linked[17, 20].

A drug-resistance mutation database is available on the Internet at http://www.tbdreamdb.com[22].

Clinical course and outcome of MDR- and XDR-TB

The poorer clinical outcomes associated with MDR-TB compared with drug-susceptible TB has been well documented for adult patients. The even worse clinical outcomes are associated with XDR-TB.

In a study of 211 non-HIV-infected Korean adults with TB[22], a higher treatment failure rate was observed among the XDR-TB patients than the non-XDR-TB patients (44.2% vs. 27.4%). In addition, the patients with XDR-TB had higher all-cause mortality (49.3% vs. 19.4%) and TB-related disease mortality (41.3% vs. 11.8%) than the patients with MDR-TB. In a multivariate analysis[23], infection with XDR-TB significantly lowered the treatment success (odds ratio=0.23) and increased all-cause mortality (hazards ratio=3.25) as well as TB-related mortality (hazards ratio=4.45).

Studies in Europe have also shown that that the presence of XDR-TB is an independent predictor for treatment failure. A fivefold increase in the risk of death among patients with XDR-TB was observed in a study conducted in Germany and Italy[24].

Diagnosis of DR-TB

TB in pediatric patients is difficult to diagnose because more than half of the active cases do not show any symptoms and have negative cultures[25], whereas adult patients with pulmonary TB are acid-fast bacilli smear-positive 60–80% of the time[26]. Many of the pediatric TB patients are identified by diagnosis of an adult source case in close contact with the child. In children with latent or active TB, any possibility of drug resistance should be always considered and contact tracing is fundamental to collect any information on drug-susceptibility test results from a source case.

In a study of six adult-child pairs with positive culture, the drug-susceptibility pattern and restriction fragment length polymorphism analysis were identical for five of the pairs[27]. Pediatric patients with TB from a known adult source case of MDR-TB should be treated according to the drug-susceptibility patterns of the source case strain unless the susceptibility test results of their own strain are available. Therefore, simultaneous and continuous investigation of the test results of an adult source case should be pursued while the child is evaluated and placed on initial empiric treatment. Drug resistance should be suspected in the following situations: known adult source case with DR-TB; high prevalence of drug resistance in the childs community; adult source case with treatment-adherence problems, treatment failure, or recurrent TB; compliant child not responding or deteriorating while on TB treatment; and child relapsing after incomplete or incorrect TB treatment[17].

In Korea, drug-susceptibility tests are available at certain centers and at the Korean National Tuberculosis Association (KNTA). At the KNTA, tests are performed against 15 antiTB agents: isoniazid, rifampin, streptomycin, ethambutol, kanamycin, capreomycin, prothionamide, cycloserine, para-aminosalicylic acid, ofloxacin, moxifloxacin, amikacin, gatifloxacin, rifabutin, and pyrazinamide.

As traditional drug-susceptibility tests take several weeks before the results are available, rapid polymerase chain reaction (PCR)-based molecular diagnostic tests for isoniazid and rifampin resistance are useful during the early course of treatment while awaiting the final report.

Treatment of DR-TB

Directly observed preventive therapy (DOPT) for the treatment of latent TB infection (LTBI) and directly observed treatment, short-course (DOTS) for the treatment of TB disease are strategies developed by the WHO to increase medication adherence and decrease the emergence of resistance.

1. Latent TB

There are significant decision-making dilemmas for the treatment of children with latent MDR-TB (i.e., diagnosed with LTBI and having a known definite source case of

MDR-TB). At present, there is no consensus on whether to treat such children. The WHO guidelines published in 2008 do not recommend treatment of patients with latent MDR-TB (the WHO still uses the term "chemoprophylaxis") and suggest observation of the patients for 2 yr[5]. However, this has a significant potential risk: eventually, the patient has to receive more drugs with toxicities for a longer duration to control the mycobacterial burden with or without organ damage when the child develops active disease. The decision is more difficult when considering the fact that young children may not have specific symptoms during the earlier course of active TB disease and may present with very serious conditions such as meningitis that can leave significant irreversible sequelae[28].

In a report from South Africa, five children (median age=0.4 yr, range=0.4-13.3 yr, one HIV-positive) exposed to MDR-TB eventually presented with active MDR-TB. Their initial treatment regimens for latent MDR-TB included isoniazid and/or rifampin, according to the 2006 WHO recommendation[29]. Eventually, they all received a combination of six drugs, including high-dose isoniazid (15-20 mg/kg), pyrazinamide, ethambutol, ethionamide, ofloxacin, and amikacin (seven-drug regimen adopted for two children by addition of cycloserine), for a minimum duration of 12-18 months after their first negative culture[30].

In a retrospective study conducted in New York, 51 children with latent MDR-TB infection (including 27 children aged 0-9 yr) were treated with various regimensmostly pyrazinamide, ethambutol, cycloserine, ethionamide, and quinolone (three drugs on average, range of two to seven drugs). Seventy-five percent (38 of 51) of these patients completed treatment after a median duration of 9 months (range=4.8-18.3 months). Their TB registry did not show recurrent disease or progression of latent MDR-TB during the study period and for 2 yr thereafter, although the clinical course of the children who did not complete the treatment was not clearly stated[31].

There is still no satisfying recommendation on whether to treat patients with latent-MDR-TB; if treatment is preferred, additional questions arise regarding the appropriate regimens and duration for each drug-resistance level. The American Thoracic Society recommends 2 months of rifampin and pyrazinamide or 4 months of rifampin (for persons with pyrazinamide intolerance) administration for isoniazid-resistant, rifampin-susceptible TB. For high-risk contacts of patients with MDR-TB, pyrazinamide and ethambutol or pyrazinamide

and a fluoroquinolone for 6-12 months are recommended provided the organism is susceptible to these agents[32].

It is very difficult to discuss with parents whether to initiate treatment and what drugs to be used if a decision is made for treatment. This issue should be discussed with parents openly and in a sincere manner while considering the family dynamics because many MDR-TB-infected parents feel guilty about their childs situation; all current information on pediatric latent MDR-TB infection should be provided and the various aspects of risk and benefit resulting from the medication should be also considered before arriving at any decision. Further studies are needed to guide therapy for latent MDR-TB infections in children who may present with a serious progressive disease later and serve as a reservoir for new TB cases in their community.

2. Active TB

For initial TB treatment, if isoniazid resistance among the new cases is greater than 4% in the community, at least four anti-TB drugs should be administered to children with active disease[33]. Of note, in Korea, isoniazid resistance among the new and retreatment cases was 9.9% and 24.1%, respectively, as of 2004. In children with MDR-TB, a combination regimen usually involving two drugs to which the isolate is susceptible should be started. In children and adults, streptomycin and ethambutol are usually recommended as the fourth agent. In Korea, resistance to streptomycin and ethambutol was similar (2.36% vs. 2.66% for new cases and 9.71% vs. 5.76% for previously treated cases) among the strains isolated in 2004[11]. Despite the potential adverse effects of optic neuritis and decreased visual acuity, ethambutol is usually recommended rather than streptomycin because the latter agent is only available in parenteral form and has potential adverse effects on the vestibular and auditory system.

The hierarchy of the anti-TB medications is listed in Table 5, and the typical regimens for DR-TB cases are shown in Table 6. Additional information on second-line agents for pediatric MDR-TB cases is provided in Tables 7 and 8.

Individualized treatment should be based on drug-susceptibility testing or drugs considered to be sensitive. Drugs are added until five adequate drugs are found. More than five can be used if a drugs sensitivity is unclear or if the regimen contains few bactericidal drugs. The following design is generally recommended for MDR-TB treatment[34, 35]:

· Daily therapy should be used.
· Use any first-line oral agent if sensitive (isoniazid, ri-

Table 5. Hierarchy of Antituberculosis Agents

Class	Type	Drug name	Nature of activity
Group 1	Oral first-line agents	Isoniazid, rifampin, pyrazinamide, ethambutol	Bactericidal, ethambutol is generally bacteriostatic but can be bactericidal at high doses (25 mg/kg)
Group 2	Injectable	Streptomycin, kanamycin, amikacin, capreomycin	Bactericidal
Group 3	Fluoroquinolones	Ciprofloxacin, ofloxacin, levofloxacin, mosifloxacin, gatifloxacin, sparfloxacin	Bactericidal
Group 4	Oral bacteriostatic second-line agents	Ethionamide, cycloserine, para-aminosalicylic acid	Bacteriostatic
Group 5	Other drugs	Clofazamine, amoxicillin/clavulnate, clarithromycin, linezolid, imipenem, thioacetazone	Unclear efficacy, used in certain cases with multidrug resistance (not recommended by WHO for routine use in multidrug-resistant tuberculosis patients)

Source: Adapted from WHO[5] and Mukherjee et al.[34]

Table 6. Treatment Regimen for Children with Drug-Resistant Tuberculosis

Type of infection	Initial regimen	Continuation regimen
Uncomplicated pulmonary TB and extra-pulmonary disease except meningitis	2 HRZ	4 HR
Severe disease or concern regarding drug resistance	2 HRZE	≥4 HRE
Isolated H-resistance	6-9 RZE thrice weekly	A fluoroquinolone may be added for patients with extensive disease
Isolated R resistance	2 HZEF	10-16 HEF
Isolated H+R resistance	≥6 EZFI	≥10 EZF
MDR-TB with additional resistance or XDR-TB	3-5 drugs to which the isolate is susceptible	Optimal duration of therapy not established

Source: Adapted from WHO[5] and Cruz et al.[35]
The regimes are for non-HIV, TB-infected patients.
The numbers indicate the months of treatment with each drug.
In cases of MDR-TB, XDR-TB, or R resistance, therapy should be continued daily.
Abbreviations : E, ethambutol; F, fluoroquinolone; H, isoniazid; I, injectable agent (amikacin, capreomycin, kanamycin, or streptomycin); MDR, multidrug-resistant R, rifampin; XDR, extensive drug resistant; Z, pyrazinamide.

fampin, ethambutol, or pyrazinamide); use at least three agents (with documented susceptibility) to which the patient is naïve.

· Never add a single agent to a failing regimen; do not use drugs with documented resistance.

· Use an injectable drug with documented susceptibility (e.g., an aminoglycoside or capreomycin); injectable agents can be used for more than 6 months after culture conversion.

· Use a quinolone; ciprofloxacin is not recommended any more for TB treatment.

· Add as many bacteriostatic second-line agents as needed to complete a five-drug regimen (ethionamide and cycloserine are generally used first because of their efficacy, side-effect profile, price, *in vivo* and *in vitro* evidence, and historical use in TB); para-aminosalicylic

acid is frequently used in patients with higher-grade resistance.

· For any pediatric patients with cavitary pulmonary lesions, patient containment should be considered until the sputum is negative, particularly with other young children or immunocompromised patients around the source case.

· Resistance to aminoglycosides is often not across the entire class (however, kanamycin and amikacin are almost always cross-resistant); do not use more than one aminoglycoside concomitantly due to the increased risk of ototoxicity and nephrotoxicity.

· If possible, consider once a daily dosing for pyrazinamide, ethambutol, and fluoroquinolones to increase the blood drug level. Other secondary agents such as ethionamide, cylcoserine and para-aminosalicylic acid are

Table 7. Second-line Antituberculosis Agents for Potential Use in Pediatric Patients

Drug name	Activity	Dose	Remarks	Adverse reactions
Rifabutin	C	10 mg/kg daily (up to 300 mg max.)	P-450 induction causes drug interactions Dose reduction required with some antiretrovirals Decrease dose if CrCl <30 mL/min Penetrates inflamed meninges	GI upset, increased LFTs, ageusia pseudojaundice, anterior uveitis, decreased platelets, decreased WBCs, arthralgia, and rash
Ethionamide	Weakly C	15-20 mg/kg/day in 2-3 divided doses (up to 1 g max.) Parenteral not available	Given with vitamin B6 (adults=100 mg/day; children as per body weight) May need thyroid replacement during treatment Good CNS penetration	GI upset, increased LFTs, metallic taste, neurotoxicity (peripheral neuropathy, headaches, giddiness), endocrinal disturbances (reversible hypothyroidism, acne, gynecomastia, menstrual irregularity), rash, and hair loss
Cycloserine	S	10-20 mg/kg/day in 2 divided doses (up to 750 g max.)	Adjust dose if renal insufficiency present Vitamin B6 (50 mg for every 250 mg) decreases the CNS effects Good CNS penetration	Psychosis, personality changes, depression, increased phenytoin levels, convulsions, rash, and Steven-Johnson Syndrome
Para-amino salicylic acid (PAS)	S	200-300 mg/kg/day in 2-4 divided doses (up to 10 g max.)	Slowly increase dose over 7-10 days to avoid with renal failure May need thyroid replacement therapy Penetrates inflamed meninges only (0-50%)	GI upset, hypersensitivity, hepatotoxicity, PAS levels decrease with Benadryl, decreased digoxin levels, increased phenytoin levels, increased sodium load, decreased thyroid hormone and platelets
Streptomycin	C	20-40 mg/kg/day for 5 days/week initially and then 2-3 days/week (up to 1 g/day or 1.5 g 2-3 days/week max.) May be given IV	Use cautiously while adjusting the dose and interval if renal impairment present Penetrates inflamed meninges Significant resistance exists to the drug	Nephrotoxicity, ototoxicity, vestibular toxicity, electrolyte abnormalities, hypersensitivity, perioral numbness, hypokalemia, and hypocalcemia
Amikacin	C	15-30 mg/kg/day for 5 days/week initially and then 2-3 days/week (up to 1 g/day max.) May be given IV	Use cautiously while adjusting the dose and interval if renal impairment present Penetrates inflamed meninges	Nephrotoxicity, ototoxicity, vestibular toxicity, electrolyte abnormalities, hypokalemia, and hypocalcemia
Capreomycin	C	15-30 mg/kg/day for 5 days/week initially and then 2-3 days/week (up to 1 g max.) May be given IV	Use cautiously while adjusting the dose and interval if renal impairment present Does not penetrate the meninges	Nephrotoxicity, ototoxicity, vestibular toxicity, electrolyte abnormalities, hypokalemia, hypocalcemia, hypomagnesemia, and eosinophilia
Linezolid	C	10 mg/kg/dose every 8-12 h May be given IV	Vitamin B6 recommended when CSF levels are about 1/3rd of the serum No adjustment with renal disease needed	Myelosuppression, diarrhea, nausea, optic and peripheral neuropathy (rare) MAO inhibition may cause serotonin syndrome with SRIs
Levofloxacin	C	10 mg/day for older children, 15-20 mg/day for younger children May be given IV	Adjust dose if Ccr <50 mL/min Sucralfate, antacids with Al, Mg, CaSO4, or FeSO4 inhibit absorption, as may enteral supplements Good CNS penetration	GI upset, dizziness, hypersensitivity, photosensitivity, headaches, tendonitis, tendon rupture, insomnia, psychosis, agitation, thrush, and hepatitis
Moxifloxacin	C	May be given IV Doses for children are not established, yet.	No dose adjustment for renal failure needed Sucralfate, antacids with Al, Mg, CaSO4, or FeSO4 inhibit absorption, as may enteral supplements Good CNS penetration	GI upset, dizziness, hypersensitivity, photosensitivity, headaches, tendonitis, tendon rupture, insomnia, psychosis, agitation, thrush, and hepatitis

C : bactericidal, S : bacteriostatic, IV : intravenously
Source: Adapted from Smith et al. (17).
CSF, cerebral spinal fluid; CNS, central nervous system; Ccr, creatinine clearance rate; GI, gastrointestinal; LFT, liver function test; WBCs, white blood cells; MAO, monoamine oxidase; SRI: serotonin reuptake inhibitor.

generally given as divided doses to reduce the adverse reactions.

The effects of many second-line agents have not been studied in children. Further, the risk of MDR-TB infection and/or disease and the treatment needs are increasing among children in many parts of the world. However, there is limited information for pediatricians to consult when treating these patients. Although controversial in the pediatric field due to possible adverse effects and lack of extensive trials, ethambutol and fluoroquinolone are considered the two most important medications for the treatment of pediatric MDR-TB cases. For adults, ethambutol is initiated at a bactericidal dose of 25 mg/kg until culture conversion and then decreased to 15 mg/kg, which is the same dosing recommendation for children[17].

Table 8. WHO Recommendations for Monitoring During Drug-Resistant Tuberculosis Treatment

Monitoring evaluation	Recommended frequency
Evaluation by clinician	At baseline, at least monthly until conversion, and then every 2-3 months
Screening by DOT worker	At every DOT encounter
Sputum smears and cultures	Monitor monthly throughout treatment (Note: programs with limited resources may choose to obtain smears monthly but cultures only every other month)
Weight	At baseline and then monthly
Drug susceptibility	At baseline in programs with individualized drug-susceptibility testing or in programs with standardized treatments that need to confirm multidrug resistance For patients who remain culture-positive, it is not necessary to repeat drug-susceptibility testing within less than 3 months of treatment
Chest radiograph	At baseline and then every 6 months
Serum creatinine	At baseline and then monthly if possible while receiving an injectable drug Every 1-3 weeks in HIV-infected patients, diabetics, and other high-risk patients
Serum potassium	Monthly while receiving an injectable agent Every 1-3 weeks in HIV-infected patients, diabetics, and other high-risk patients
Thyroid stimulating hormone (TSH)	Every 6 months if receiving ethionamide or prothionamide, and/or para-aminosalicylic acid Monitor monthly for signs or symptoms of hypothyroidism TSH is sufficient for hypothyroidism screening; it is not necessary to measure thyroid hormone levels
Liver serum enzymes	Periodic monitoring (every 1-3 months) in patients receiving pyrazinamide for extended periods or those at risk of or with symptoms of hepatitis For HIV-infected patients, monthly monitoring is required
HIV screening	At baseline and repeat if clinically indicated
Pregnancy tests	At baseline for women of childbearing age and repeat if indicated
Hemoglobin and white blood count	If on linezolid, monitor weekly at first and then monthly or as needed based on symptoms; there is little clinical experience with prolonged use.
Lipase	Indicated for workup of abdominal pain to rule out pancreatitis in patients on linezolid, D4T, ddI, or ddc
Lactic acidosis	Indicated for workup of lactic acidosis in patients on linezolid or antiretroviral therapy
Serum glucose	If receiving gatifloxacin, monitor glucose frequently (weekly) and educate patient on signs and symptoms of hypoglycemia and hyperglycemia

WHO,World Health Organization; DOT,Directly Observed Therapy
Source: Modified from WHO[5]

고　　찰

　　DR-TB is an increasing problem in pediatric populations and more children are at risk of infection and active disease due to DR-TB isolates. Diagnosis of DR-TB and the treatment options are challenging. Although studies on DR-TB in Korean adults can provide useful information regarding the management of this disease in children, there are few data on DR-TB in Korean children, warranting further studies.

References

1) Cohn ML, Davis CL. Infectivity and pathogenicity of drug-resistant strains of tubercle bacilli studied by aerogenic infection of guinea pigs. Am Rev Respir Dis 1970;102:97-100.
2) Steiner P, Rao M, Mitchell M, Steiner M. Primary drug-resistant tuberculosis in children. Correlation of drug-susceptibility patterns of matched patient and source case strains of Mycobacterium tuberculosis. Am J Dis Child 1985; 139:780-2.
3) Snider DE, Jr, Kelly GD, Cauthen GM, Thompson NJ, Kilburn JO. Infection and disease among contacts of tuberculosis cases with drug-resistant and drug-susceptible bacilli. Am Rev Respir Dis 1985;132:125-32.
4) Schaaf HS, Vermeulen HA, Gie RP, Beyers N, Donald PR.

Evaluation of young children in household contact with adult multidrug-resistant pulmonary tuberculosis cases. Pediatr Infect Dis J 1999;18:494-500.

5) World Health Organization. Guidelines for the programmatic management of drug-resistant tuberculosis. Geneva: World Health Organization; 2008.

6) Kent JH. The epidemiology of multidrug-resistant tuberculosis in the United States. Med Clin North Am 1993;77: 1391-409.

7) Goble M, Iseman MD, Madsen LA, Waite D, Ackerson L, Horsburgh CR, Jr. Treatment of 171 patients with pulmonary tuberculosis resistant to isoniazid and rifampin. N Engl J Med 1993;328:527-32.

8) World Health Organization. Expanded program on immunization. Geneva: World Health Organization; 1989.

9) Dolin PJ, Raviglione MC, Kochi A. Global tuberculosis incidence and mortality during 1990-2000. Bull World Health Organ 1994;72:213-20.

10) Nelson LJ, Wells CD. Global epidemiology of childhood tuberculosis. Int J Tuberc Lung Dis 2004;8:636-47.

11) Bai GH, Park YK, Choi YW, Bai JI, Kim HJ, Chang CL, et al. Trend of anti-tuberculosis drug resistance in Korea, 1994-2004. Int J Tuberc Lung Dis 2007;11:571-6.

12) Aziz MA, Wright A, Laszlo A, de Muynck A, Portaels F, van Deun A, et al. Epidemiology of antituberculosis drug resistance (The Global Project on Anti-Tuberculosis Drug Resistance Surveillance): an updated analysis. Lancet 2006; 368:2142-54.

13) Zignol M, Hosseini MS, Wright A, Weezenbeek CL, Nunn P, Watt CJ, et al. Global incidence of multidrug-resistant tuberculosis. J Infect Dis 2006;194:479-85.

14) Schaaf HS, Gie RP, Beyers N, Sirgel FA, de Klerk PJ, Donald PR. Primary drug-resistant tuberculosis in children. Int J Tuberc Lung Dis 2000;4:1149-55.

15) Kassa-Kelembho E, Bobossi-Serengbe G, Takeng EC, Nambea-Koisse TB, Yapou F, Talarmin A. Surveillance of drug-resistant childhood tuberculosis in Bangui, Central African Republic. Int J Tuberc Lung Dis 2004;8:574-8.

16) Schaaf HS, Marais BJ, Hesseling AC, Gie RP, Beyers N, Donald PR. Childhood drug-resistant tuberculosis in the Western Cape Province of South Africa. Acta Paediatr 2006; 95:523-8.

17) Smith KC, Seaworth BJ. Drug-resistant tuberculosis: controversies and challenges in pediatrics. Expert Rev Anti Infect Ther 2005;3:995-1010.

18) Somoskovi A, Parsons LM, Salfinger M. The molecular basis of resistance to isoniazid, rifampin, and pyrazinamide in Mycobacterium tuberculosis. Respir Res 2001;2:164-8.

19) Riska PF, Jacobs WR, Jr, Alland D. Molecular determinants of drug resistance in tuberculosis. Int J Tuberc Lung Dis 2000;4:S4-10.

20) Iseman MD. Treatment of multidrug-resistant tuberculosis. N Engl J Med 1993;329:784-91.

21) Sandgren A, Strong M, Muthukrishnan P, Weiner BK, Church GM, Murray MB. Tuberculosis drug resistance mutation database. PLoS Med 2009;6:e2.

22) Kim HR, Hwang SS, Kim HJ, Lee SM, Yoo CG, Kim YW, et al. Impact of extensive drug resistance on treatment outcomes in non-HIV-infected patients with multidrug-resistant tuberculosis. Clin Infect Dis 2007;45:1290-5.

23) Kim DH, Kim HJ, Park SK, Kong SJ, Kim YS, Kim TH, et al. Treatment outcomes and long-term survival in patients with extensively drug-resistant tuberculosis. Am J Respir Crit Care Med 2008;178:1075-82.

24) Migliori GB, Ortmann J, Girardi E, Besozzi G, Lange C, Cirillo DM, et al. Extensively drug-resistant tuberculosis, Italy and Germany. Emerg Infect Dis 2007;13:780-2.

25) Eamranond P, Jaramillo E. Tuberculosis in children: reassessing the need for improved diagnosis in global control strategies. Int J Tuberc Lung Dis 2001;5:594-603.

26) Leonard MK, Osterholt D, Kourbatova EV, Del Rio C, Wang W, Blumberg HM. How many sputum specimens are necessary to diagnose pulmonary tuberculosis? Am J Infect Control 2005;33:58-61.

27) Schaaf HS, van Rie A, Gie RP, Beyers N, Victor TC, van Helden PD, et al. Transmission of multidrug-resistant tuberculosis. Pediatr Infect Dis J 2000;19:695-9.

28) Padayatchi N, Bamber S, Dawood H, Bobat R. Multidrug-resistant tuberculous meningitis in children in Durban, South Africa. Pediatr Infect Dis J 2006;25:147-50.

29) Word Health Organization. Guidelines for the management of drug-resistant tuberculosis. Geneva: World Health Organization; 2006.

30) Sneag DB, Schaaf HS, Cotton MF, Zar HJ. Failure of chemoprophylaxis with standard antituberculosis agents in child contacts of multidrug-resistant tuberculosis cases. Pediatr Infect Dis J 2007;26:1142-6.

31) Feja K, McNelley E, Tran CS, Burzynski J, Saiman L. Management of pediatric multidrug-resistant tuberculosis and latent tuberculosis infections in New York City from 1995 to 2003. Pediatr Infect Dis J 2008;27:907-12.

32) Targeted tuberculin testing and treatment of latent tuberculosis infection. Am J Respir Crit Care Med 2000;161: S221-47.

33) Bass JB, Jr, Farer LS, Hopewell PC, OBrien R, Jacobs RF, Ruben F, et al. Treatment of tuberculosis and tuberculosis infection in adults and children. American Thoracic Society and the Centers for Disease Control and Prevention. Am J Respir Crit Care Med 1994;149:1359-74.

34) Mukherjee JS, Rich ML, Socci AR, Joseph JK, Viru FA, Shin SS, et al. Programmes and principles in treatment of multidrug-resistant tuberculosis. Lancet 2004;363:474-81.

35) Cruz AT, Starke JR. Treatment of tuberculosis in children. Expert Rev Anti Infect Ther 2008;6:939-57.

36) Centers for Disease Control and Prevention. Emergence of Mycobacterium tuberculosis with extensive resistance to second-line drugsworldwide, 2000-2004. MMWR Morb Mortal Wkly Rep 2006;55:301-5.