Africa, and mainly sub-Saharan Africa, have a high incidence of tuberculosis (TB) and the highest prevalence of human immunodeficiency virus (HIV) in the world. In addition, Africa is experiencing an increase in multidrug-resistant TB (MDR-TB) (ie, resistance to at least isoniazid [INH] and rifampicin [RMP]), with 14% of the global burden of new MDR-TB cases occurring in Africa,1,2 and early warnings of extensively drug-resistant TB (XDR-TB; ie, MDR plus resistance to the fluoroquinolones and 1 of 3 second-line injectable agents), especially in South Africa.3 Until recently, many African countries treated TB with a 2-month 4-drug intensive Phase including INH and RMP, and a 7-month continuation Phase of INH and ethambutol, excluding RMP. This regimen, together with the lack of second-line anti-TB drugs, protected many poorly resourced countries from developing high rates of MDR-TB, and especially prevented XDR-TB.2 National TB programs, together with nongovernmental organizations such as the Green Light Committee and other technical and financial partners, are currently rolling out TB treatment to include second-line MDR-TB treatment to many of these countries,4 and it is of utmost importance that this should be done responsibly to avoid the development of additional drug resistance. Special attention needs to be given to identifying drug resistance patterns in communities, treatment regimens with
an optimal number of drugs to which patients’ isolates are susceptible or naive, and supply of and adherence to treatment.

EPIDEMIOLOGY

The World Health Organization (WHO) estimates that 511,000 new cases of MDR-TB occurred in 2007, 4.9% of all TB cases; of these 40,000 (6.6%) are estimated to be XDR-TB. Few national surveys have been reported for Africa from 2002 to 2007, but, with available data, Africa together with the Americas and western and central Europe reported the lowest prevalence of MDR-TB. Few MDR-TB hotspots (ie, MDR-TB >3% of TB cases) have been reported in Africa; these include Mozambique, Cote d’Ivoire, and, more recently, Rwanda and Democratic Republic of Congo. However, taking into account the number of TB cases in sub-Saharan Africa, this region is still responsible for 14% of the total MDR-TB burden, with South Africa in first place with more than 16,000 new cases per year. Nine African countries rate among the 27 high-burden MDR-TB countries: South Africa (4th), Nigeria (9th), Democratic Republic of Congo (13th), Ethiopia (16th), Kenya (20th), Mozambique (21st), Zimbabwe (23rd), Cote d’Ivoire (25th), and Sudan (26th). In South America, Peru and Ecuador are the only MDR-TB hotspots, with Peru 22nd among the 27 MDR-TB high-burden countries, but Brazil, which has almost one-third of the region’s TB cases, is also responsible for a high number of MDR-TB cases. Surveys of anti-TB drug resistance in Africa and South America reported between 2002 and 2007 are summarized in Table 1.

Few surveys of drug resistance are done amongst childhood TB cases, yet they usually reflect the currently circulating strains in the community, as more than 90% of children who develop disease after infection will do so within a year of infection. Children usually have transmitted drug resistance; they rarely develop drug resistance because of the paucibacillary nature of their disease. Table 2 summarizes results of drug resistance surveys in children reported since 2000.

CLINICAL PRESENTATION OF MDR/XDR-TB

Clinical features and chest radiographic changes are not helpful in distinguishing MDR/XDR-TB and drug-susceptible TB, and are not discussed here. However, a previous history of TB treatment, particularly combined with a history of non-adherence to TB treatment or substance abuse problems, exposure to known source cases of MDR- and XDR-TB, failure to culture-convert by month 5 to 6 while on MDR treatment (or month 2 while on first-line therapy for presumed drug-susceptible TB), and relapse soon after treatment completion should prompt suspicion of MDR- or XDR-TB. Molecular epidemiologic methods have shown that transmission of drug-resistant strains is common, and is probably responsible for more than half of MDR/XDR-TB cases. However, in another study of 270 South African XDR-TB patients, almost 90% had a history of previous anti-TB treatment, and molecular genotyping confirmed the predominance of secondary, rather than primary, drug resistance. Even in some areas with low TB incidence, transmission may be responsible for most MDR-TB cases. In children, although not confirmed with molecular epidemiology, more than 90% of drug resistance is likely due to transmission from adult source cases.

HIV coinfected patients are more susceptible to TB, and progression in this group may be rapid. The only available XDR-TB outcome data from Africa to date indicate that, in a setting of probable nosocomially transmitted XDR-TB, almost all patients were infected with HIV and died at a median of 2 weeks after sputum collection for culture and drug susceptibility testing (DST). Hence, a widely held view is that XDR-TB in Africa occurs predominantly in individuals infected with HIV who are more susceptible to infection. By contrast, a recent study based on 270 South African patients with XDR-TB showed that a large proportion (55%) of XDR-TB patients are not infected with HIV.

DIAGNOSIS OF MDR- AND XDR-TB

Drug-resistant TB is a microbiologic diagnosis. Most TB diagnosis in adults in Africa is by sputum smear microscopy for acid-fast bacilli (AFB), and TB in children is diagnosed by a constellation of history of contact with an infected case, chronic symptoms, tuberculin skin test, chest radiography, and, rarely, by smear or culture. Until recently, only a few African countries had laboratory facilities for culture and DST. Currently there is a strong international drive for the upgrade of laboratories in resource-limited countries to include culture and DST facilities. Although no African country will be able to do culture and DST in all suspected TB cases soon, it will be important to identify patients at risk of drug resistance, such as relapse, retreatment, and chronic TB cases, individuals infected with HIV, those not responding to adherent first-line anti-TB treatment, and close contacts.
<table>
<thead>
<tr>
<th>Number of Patients Tested</th>
<th>Any Resistance n (%), SD</th>
<th>Resistance to INH n (%), SD</th>
<th>MDR n (%), SD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>African region, year</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cote d'Ivoire, 2006</td>
<td>N = 320</td>
<td>76 (23.8, 19.2–28.8)</td>
<td>39 (12.2, 8.8–16.3)</td>
</tr>
<tr>
<td></td>
<td>P = ND</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethiopia, 2005</td>
<td>N = 804</td>
<td>216 (26.9, 23.4–30.7)</td>
<td>62 (7.7, 5.9–9.9)</td>
</tr>
<tr>
<td></td>
<td>P = 76</td>
<td>37 (48.7, 37.0–60.4)</td>
<td>19 (25.0, 15.8–36.3)</td>
</tr>
<tr>
<td>Madagascar, 2007</td>
<td>N = 810</td>
<td>51 (6.3, 4.7–8.3)</td>
<td>37 (4.6, 3.2–6.3)</td>
</tr>
<tr>
<td></td>
<td>P = 51</td>
<td>6 (11.8, 4.4–23.9)</td>
<td>5 (9.8, 3.3–21.4)</td>
</tr>
<tr>
<td>Rwanda, 2005</td>
<td>N = 616</td>
<td>64 (10.4, 8.0–13.3)</td>
<td>38 (6.2, 4.4–8.5)</td>
</tr>
<tr>
<td></td>
<td>P = 85</td>
<td>19 (22.4, 14.0–32.7)</td>
<td>9 (10.6, 5.0–19.2)</td>
</tr>
<tr>
<td>Senegal, 2006</td>
<td>N = 237</td>
<td>25 (10.5, 6.9–15.2)</td>
<td>10 (4.2, 2.0–7.6)</td>
</tr>
<tr>
<td></td>
<td>P = 42</td>
<td>13 (31.0, 17.6–47.1)</td>
<td>10 (23.8, 12.1–39.5)</td>
</tr>
<tr>
<td><strong>South American region, year</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Argentina, 2005</td>
<td>N = 683</td>
<td>68 (10.0, 7.7–12.6)</td>
<td>39 (5.7, 4.1–7.8)</td>
</tr>
<tr>
<td></td>
<td>P = 136</td>
<td>34 (25.0, 18.0–33.1)</td>
<td>25 (18.4, 12.3–25.9)</td>
</tr>
<tr>
<td>Paraguay, 2001</td>
<td>N = 235</td>
<td>26 (11.1, 7.4–15.8)</td>
<td>15 (6.4, 3.6–10.3)</td>
</tr>
<tr>
<td></td>
<td>P = 51</td>
<td>10 (19.6, 9.8–33.1)</td>
<td>6 (11.8, 4.4–23.9)</td>
</tr>
<tr>
<td>Peru, 2006</td>
<td>N = 1809</td>
<td>420 (23.2, 21.0–25.5)</td>
<td>209 (11.6, 10.0–13.2)</td>
</tr>
<tr>
<td></td>
<td>P = 360</td>
<td>150 (41.7, 36.5–46.9)</td>
<td>109 (30.3, 25.6–35.3)</td>
</tr>
<tr>
<td>Uruguay, 2005</td>
<td>N = 335</td>
<td>7 (2.1, 0.8–4.3)</td>
<td>4 (1.2, 0.3–3.0)</td>
</tr>
<tr>
<td></td>
<td>P = 33</td>
<td>3 (9.1, 1.9–24.3)</td>
<td>2 (6.1, 0.7–20.2)</td>
</tr>
</tbody>
</table>

Abbreviations: N, new tuberculosis cases; P, previously treated tuberculosis cases; SD, standard deviation.

including children, of drug-resistant source cases. In countries, such as South Africa, where this has been the policy, culture and DST were often neglected, leading to longer duration of infectiousness and transmission of drug-resistant TB. The current strategy of improved hospital-based confirmation of MDR/XDR-TB by DST, and improved infection control measures, is not going to be sufficient to curtail the XDR-TB epidemic in some areas. In countries with high TB incidence and high rates of MDR/XDR-TB and HIV, it has been shown that more aggressive case finding, especially identifying drug-resistant cases at initial TB diagnosis by rapid diagnostic methods and active contact tracing, is necessary to reduce MDR/XDR-TB rates.

High mortality and transmission rates in MDR/XDR-TB patients, especially in those infected with HIV, have made rapid diagnosis of drug resistance essential. Although liquid broth culture methods and DST are considerably faster than using solid media, they are expensive and still take 2 to 6 weeks. Because of the risk of infectiousness and the risk of acquiring further drug resistance with incorrect treatment regimens, development of more rapid diagnostic methods for drug resistance is receiving much attention.

The nucleic acid amplification tests (NAATs), the line-probe assays, are a major advance in rapid diagnostic methods of drug-resistant TB. These genotypic evaluation assays are used either for detection of Mycobacterium tuberculosis directly from clinical samples or for identification of mycobacteria from culture. The major advantages of the nucleic acid–based assays are speed (results available within 48 hours for smear-positive specimens) and ease of interpretation. The tests are still expensive, and laboratory infrastructure is needed, but a large study in a laboratory in Cape Town, South Africa, with a high throughput of specimens has shown this test to be reliable and practicable. The GenoType MTBDRplus (Hain Lifescience, Nehren, Germany; Fig. 1A) for the diagnosis of MDR-TB is probably the best known of these assays. The kit can be used to detect M. tuberculosis directly from clinical samples, or for identification of mycobacteria from culture. The underlying principle involves multiplex amplification of extracted mycobacterial DNA by polymerase chain reaction (PCR), with subsequent hybridization of the biotin-labeled amplicons to oligonucleotide probes bound to a membrane strip (line probe). This test can simultaneously identify most RMP and INH resistance; identification is done by evaluation of the resultant banding pattern. The kits have been shown to have excellent correlation with conventional methods, usually more than 95%. One disadvantage of the test is that it does not identify INH resistance other than inhA promoter region or katG gene mutations, which may lead to over-diagnosis of RMP monoresistance and a proportion of INH-resistant strains may be missed. This disadvantage may potentially lead to a pool of INH-monoresistant cases incorrectly treated as drug-susceptible cases, which may lead to these

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### Table 2

Results of anti-TB drug resistance surveys amongst childhood TB cases reported after 2000

<table>
<thead>
<tr>
<th>Country and Region</th>
<th>Time of Survey</th>
<th>Number of Children</th>
<th>Any Drug Resistance (%)</th>
<th>INH Resistance (%)</th>
<th>Multidrug Resistance (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central African Republic, Bangui&lt;sup&gt;91&lt;/sup&gt;</td>
<td>Apr 1998–Jun 2000</td>
<td>190 (DST done in 165)</td>
<td>25 (15.2)</td>
<td>15 (9.1)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Egypt&lt;sup&gt;92&lt;/sup&gt;</td>
<td></td>
<td>150 (DST done in 73)</td>
<td>18 (24.7)</td>
<td>4 (5.4)</td>
<td>2 (2.7)</td>
</tr>
<tr>
<td>Greece&lt;sup&gt;93&lt;/sup&gt;</td>
<td>1994–2004</td>
<td>77</td>
<td>16 (20.8)</td>
<td>12 (15.6)</td>
<td>3 (3.9)</td>
</tr>
<tr>
<td>India, TB Research Center&lt;sup&gt;94&lt;/sup&gt;</td>
<td>1996</td>
<td>201</td>
<td>NA</td>
<td>NA (10)</td>
<td>NA (3.5)</td>
</tr>
<tr>
<td>Madagascar, Antananarivo&lt;sup&gt;95&lt;/sup&gt;</td>
<td>1997–2000</td>
<td>97</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>0</td>
</tr>
<tr>
<td>South Africa, Western Cape&lt;sup&gt;20&lt;/sup&gt;</td>
<td>March 2003–Feb 2005</td>
<td>320</td>
<td>41 (12.8)</td>
<td>41 (12.8)</td>
<td>19 (5.9)</td>
</tr>
<tr>
<td>South Africa, Western Cape&lt;sup&gt;21&lt;/sup&gt;</td>
<td>March 2005–Feb 2007</td>
<td>291 (DST done in 285)</td>
<td>43 (15.1), only INH and RMP</td>
<td>41 (14.4)</td>
<td>19 (6.7)</td>
</tr>
</tbody>
</table>

Abbreviation: NA, not available.
becoming MDR-TB cases. All RMP-monoresistant TB cases diagnosed by the line-probe method only should be managed as MDR-TB cases. Another line-probe assay is INNO-LiPA Rif.TB (Innogenetics, Zwijndrecht, Belgium), which identifies only RMP resistance; with more than 90% of RMP-resistant strains being MDR, patients identified as RMP-resistant are treated as
MDR-TB cases. Technicians in developing countries have mastered these assays rapidly.27

A recent South African study of XDR-TB cases found only 16% of 270 cases to be smear-positive for AFB, and the median time from sputum acquisition to XDR treatment initiation, when using conventional DST, was 65 days.18 This diagnostic delay may be considerably shortened by using rapid NAATs such as the new GenoType MTBDRsl assay (Hain Lifescience for second-line drugs, Nehren, Germany; see Fig. 1B).28 This test has a turnaround time of 4 to 5 days. However, unlike MDR-TB, for which performance outcomes are excellent,29 the assay requires validation in larger field studies, and its place in diagnostic algorithms requires further study.

Other established, newer, and emerging diagnostic platforms (reviewed by Pai and colleagues)30 include the microscopic observed drug susceptibility (MODS) assay,31,32 Xpert MTB/RIF assay (Cepheid, Sunnyvale, California),33 and loop-mediated isothermal amplification (LAMP),34 which have been, or may in future be, adapted for the diagnosis of drug-resistant TB. These newer technologies and their likely advantages are summarized in Table 3 and Fig. 2. The Foundation for Innovative New Diagnostics (FIND) is undertaking large-scale demonstration projects for diagnosis and DST, using the mycobacterial growth indicator tube (MGIT) 960 liquid culture platform,35 in high-burden settings. However, the newer technologies will not affect diagnostic delay for patients and health workers, which may be considerable.36

Most resource-poor settings, if they have access to laboratory facilities, will still use conventional culture and DST techniques to establish the diagnosis of XDR-TB (reviewed by Whitelaw and Sturm).37 The lack of standardization of second-line DST remains problematic,12,22 because 2 laboratories may provide conflicting results. Clinicians will also be familiar with the presence of multiple strain types and DST patterns within the same individual.38 This may cause diagnostic confusion, and patients with XDR-TB may therefore temporarily improve on MDR or conventional anti-TB treatment. The authors tend to interpret laboratory results within the clinical context and treat for XDR-TB if there is any doubt. Further drug resistance may evolve while awaiting DST results.

PRINCIPLES OF MANAGEMENT OF MDR- AND XDR-TB

The basic principles of MDR/XDR-TB management in adults and children are the same. Adults usually have large numbers of bacilli compared with children who often have paucibacillary disease, and children more often than adults have extrapulmonary disease. Therefore some aspects of management may differ; for example, fewer drugs and shorter duration of treatment may be required in children with early primary disease, and children will more often receive drug-resistant treatment without microbiologic confirmation, because of known contact with an adult drug-resistant TB source case. Extrapulmonary TB, such as tuberculous meningitis and miliary TB, which is common in young children, require drugs that penetrate the blood-brain barrier sufficiently to reach minimal inhibitory concentrations (MICs) in the cerebrospinal fluid (CSF).

The first principle of managing any drug-resistant TB is never to add a single drug to a failing regimen. The WHO regimen II for retreatment cases, which only adds streptomycin in the first 2 months, may do exactly that if patients were previously treated with WHO regimen I, consisting of INH, RMP, pyrazinamide, and ethambutol. Regimen II is therefore no longer recommended, especially where the prevalence of drug resistance is high.39

There are no randomized controlled trials of MDR-TB treatment and, therefore, recommendations are based on case series and expert opinion. A recent meta-analysis of existing MDR-TB treatment literature pointed out the discrepancies and limitations of current studies, and concluded that treatment success was associated with treatment durations of more than 18 months and patient receipt of directly observed therapy throughout the treatment course.40

MDR-TB treatment could be standardized (ie, a regimen with a set number of first- and second-line drugs, preferably reflecting the most common drug resistance pattern in the region), individualized (ie, a regimen built according to the DST result of the patient), or empirical (ie, if MDR-TB has not been confirmed, but the treatment regimen is changed because of a known MDR-TB contact or failure to respond to adherent treatment, taking into account previous drugs used).

Treatment of MDR or XDR-TB should be daily and directly observed. If at all possible, second-line DST should be carried out immediately in any patient with MDR-TB to exclude pre-XDR (MDR plus resistance to the fluoroquinolones or one of the second-line injectable agents) or XDR-TB. WHO guidelines recommend a treatment regimen with 4 or more drugs to which the patient’s isolate is susceptible or naive (ie, no previous treatment with the drug). Drug groups
that can be used are summarized in Table 4. Health workers should take into account possible cross-resistance and adverse effects of drugs when building a treatment regimen.41

Treatment of children who have known contact with infectious adult MDR/XDR-TB cases should be guided by the isolate DST result of the adult source cases (empirical treatment) if no M tuberculosis isolate is obtained from the child. However, every effort should be made to confirm the diagnosis by culture in the child, as, in high incidence areas, approximately 20% of these children may have drug-susceptible TB.21

Adherence to treatment is essential and is one of the cornerstones of treatment. Patients and caregivers need support by regular counseling about adverse effects, treatment duration, and importance of adherence. The need for psychological and socioeconomic support in adults and children
cannot be overemphasized. Failure of adherence urgently needs further studies. Clinical, radiologic, and culture response to treatment should be carefully monitored, with cultures done at least monthly until negative, as treatment duration is based on the first negative culture. Thereafter monthly or bimonthly cultures can be done.
TREATMENT

In children with early primary TB such as uncomplicated hilar lymphadenopathy or primary lung parenchymal (Ghon) focus, 3 bactericidal drugs to which the isolate is susceptible should be sufficient, but in more extensive or complicated pulmonary or disseminated extrapulmonary disease, 4 or more active drugs should be included in the regimen, as with adults. If either the child or the source case had previous treatment with pyrazinamide or ethambutol for more than 1 month, these drugs could be used if DST shows susceptibility, but, because of the difficulty of performing pyrazinamide DST and high resistance rates in MDR-TB cases, and the unreliability of some phenotypic DST methods for ethambutol, they should count only as additional drugs. In a surveillance study among children in the Western Cape, 12 of 24 (50%) children with MDR-TB had phenotypic resistance to ethambutol. In building an MDR- and XDR-TB treatment regimen, 1 drug each from groups 2 (second-line injectables) and 3 (fluoroquinolones), and 1 or more drugs from group 4 (other proven second-line drugs) should be included in the regimen according to DST or nonexposure to these drugs. If these groups are not sufficient to build an acceptable regimen of 4 active drugs, drugs from group 5 could be added. In the South African experience in the public sector, where only DST to RMP, INH, ethambutol, streptomycin, ethionamide, terizidone, amikacin/kanamycin, and ofloxacin are available, XDR-TB patients are usually commenced, notwithstanding DST, on a backbone of capreomycin and paraaminosalicylic acid (PAS), and ethambutol (if susceptible) and cycloserine/terizidone are then added. The value of pyrazinamide, although frequently used, is of uncertain significance (see earlier discussion), and frequently amoxicillin/clavulanate and clarithromycin, and sometimes dapsone, are added. Although the latter drugs are of arguable value, little else is available.

Linezolid and moxifloxacin are not available in the public sector in most developing countries. Recent data indicate that moxifloxacin is a key predictor of favorable outcome and may explain the more favorable outcomes seen in the Peruvian cohort. The mycobactericidal effects of the different fluoroquinolones is likely to be drug specific. The authors believe that moxifloxacin should be made available in resource-poor settings.

INH at high-dose (15–20 mg/kg daily), especially when given in combination with ethionamide where MICs for INH and ethionamide DST are not routinely available, may be beneficial as, depending on which mutation causes INH resistance, the patient may have low-level INH resistance (mainly inhA promoter region mutation), but could then be resistant to ethionamide. Studies have shown low-level INH resistance in 80% of children with INH-resistant TB and, in an adult randomized controlled trial in India, the addition of high-dose INH to a standard MDR-TB treatment regimen, compared with normal dose (5 mg/kg daily) or no INH, found earlier sputum conversion and improvement in chest radiographs in the high-dose INH study group.

TB of the central nervous system needs drugs that penetrate the blood-brain barrier. INH, pyrazinamide, ethionamide, and cycloserine/terizidone penetrate the CSF well. The fluoroquinolones reach reasonable CSF concentrations, whereas the second-line injectables only penetrate the blood-brain barrier during acute inflammation.

Our data indicate substantially improved outcomes in XDR-TB patients coinfected with HIV and on highly active antiretroviral therapy (HAART), which is generally well tolerated with second-line drugs. All XDR-TB patients coinfected with HIV should be commenced on HAART after a run-in period on XDR treatment, irrespective of CD4 count.

Although the optimal duration of treatment of MDR- and XDR-TB is not known, a minimum of

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Fig. 2. Newer technologies for the diagnosis of drug-resistant TB. MODS assay (A, B) relies on recognition of the characteristic cording pattern (B) of M tuberculosis using an inverted microscope; simultaneous susceptibility testing is performed, and results are available within a median time of 7 days. The technology is cheap but labor-intensive. (C) Thin-layer agar (TLA) relies on early detection of microcolonies by conventional microscopy not only for identification of M tuberculosis but also for the simultaneous detection of resistance to rifampicin and INH directly from sputum. FIND is currently working with investigators to develop a standardized version suitable for high-burden countries. MODS and TLA plates remain sealed in plastic wrapping/bags for biosafety purposes. LAMP (D, E) does not require a thermal cycler, is a closed tube system, results are available within an hour, and the fluorescence-based readout does not require a microscope. This technology could in future be adapted for the diagnosis of drug-resistant TB (With the permission of Eiken Chemical Co. Ltd, Japan). TB Xpert MTB/RIF (Cepheid) (F) GeneXpert System module is a real-time PCR user-friendly detection system that uses a cartridge into which the unprocessed sputum sample is placed.
<table>
<thead>
<tr>
<th>Drug Group</th>
<th>Drug Name</th>
<th>Daily Dosage for Children (mg/kg)</th>
<th>&lt;33 kg Dose in mg/kg</th>
<th>33–50 kg</th>
<th>51–70 kg</th>
<th>&gt;70 kg (also Maximum Dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group 1: oral</strong>&lt;br&gt;first-line drugs to which the organism shows in vitro susceptibility by DST&lt;br&gt;a Cannot rely on DST; use as additional drug if DST not done, or if the result is susceptible on solid media culture.</td>
<td>Ethambutol</td>
<td>20–25</td>
<td>25</td>
<td>800–1200</td>
<td>1200–1600</td>
<td>1600–2000</td>
</tr>
<tr>
<td><strong>Group 2: second-line injectable agents</strong>&lt;br&gt;b Choose 1 drug in each of these groups; amikacin is preferred to kanamycin in children.</td>
<td>Amikacin</td>
<td>15–22.5</td>
<td>15–20</td>
<td>500–750</td>
<td>750–1000</td>
<td>1000</td>
</tr>
<tr>
<td></td>
<td>Kanamycin</td>
<td>15–30</td>
<td>15–20</td>
<td>500–750</td>
<td>750–1000</td>
<td>1000</td>
</tr>
<tr>
<td></td>
<td>Capreomycin</td>
<td>15–30</td>
<td>15–20</td>
<td>500–750</td>
<td>750–1000</td>
<td>1000</td>
</tr>
<tr>
<td><strong>Group 3: fluoroquinolones</strong>&lt;br&gt;c Choose 1 or more of these drugs to make up total of 4 new drugs.</td>
<td>Ofloxacin</td>
<td>15–20</td>
<td>15–20</td>
<td>800</td>
<td>800</td>
<td>800–1000</td>
</tr>
<tr>
<td></td>
<td>Levofloxacin</td>
<td>7.5–10</td>
<td>7.5–10</td>
<td>750</td>
<td>750</td>
<td>750–1000</td>
</tr>
<tr>
<td></td>
<td>Moxifloxacin</td>
<td>7.5–10</td>
<td>7.5–10</td>
<td>400</td>
<td>400</td>
<td>400</td>
</tr>
<tr>
<td><strong>Group 4: second-line oral bacteriostatic agents</strong>&lt;br&gt;d Consider using these drugs if there were insufficient drugs to build an acceptable regimen with previous groups.</td>
<td>Ethanionamide (or prothionamide)</td>
<td>15–20</td>
<td>15–20</td>
<td>500</td>
<td>750</td>
<td>750–1000</td>
</tr>
<tr>
<td></td>
<td>Cycloserine (or terizidone)</td>
<td>10–20</td>
<td>15–20</td>
<td>500</td>
<td>750</td>
<td>750–1000</td>
</tr>
<tr>
<td></td>
<td>para-Aminosalicylic acid (PAS)</td>
<td>150</td>
<td>150</td>
<td>8 g</td>
<td>8 g</td>
<td>8–12 g</td>
</tr>
<tr>
<td></td>
<td>Linezolid</td>
<td>10 twice daily</td>
<td>600 mg twice daily, but recent data suggest 300 mg twice daily, or 600 mg or 300 mg once daily (see text – New drugs)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Amoxicillin/ clavulanate</td>
<td>30–40 amoxicillin</td>
<td>Dosage for DR-TB not well defined. Normal adult dose 875/125 mg twice daily or 500/125 mg 3 times daily. Higher dose limited by adverse effects</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Clarithromycin</td>
<td>7.5–15 twice daily</td>
<td>500 mg twice daily</td>
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<td></td>
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</tr>
<tr>
<td></td>
<td>Thioacetazone</td>
<td>3–4</td>
<td>150 mg daily (contraindicated in patients infected with HIV)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Imipenem/cilastatin</td>
<td>Only IV</td>
<td>Usual adult dose 500–1000 mg IV 6-hourly</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
18 months after the first negative culture (or 24 months for XDR-TB) is usually recommended. In general, treatment of MDR/XDR-TB in children should also be 18 months after the first negative culture, but children with early primary (uncomplicated) disease without cavitary lung disease or extrapulmonary dissemination could probably be treated for 12 months only.

MDR/XDR-TB patients are often hospitalized during the intensive Phase of treatment or, in the case of XDR-TB, until they become culture negative. The extent of disease or the clinical condition of the patient may require admission in some patients. The authors usually admit children for the time that they receive second-line injectable drugs, and, if social circumstances and the clinical condition of the child permit, the rest of the treatment is given at primary health care level as daily directly observed therapy. However, with the increasing number of adult patients, this is no longer possible, and while patients are waiting for admission, transmission of infection continues. Community-based diagnosis and early ambulatory treatment of patients has become essential, and studies in Peru on patients not infected with HIV have shown home-based, directly observed treatment to be effective. Community-based treatment programs in patients who are coinfected are needed in high prevalence areas, and some treatment programs in patients who are coinfected but have fewer adverse effects. At 300 mg twice daily, linezolid was still effective, myelosuppression was prevented, but some cases of peripheral neuropathy still occurred. Yew and Leung have also suggested using linezolid only in the intensive Phase of treatment (2-3 months) to reduce adverse effects. A single case study in a young child with XDR-TB treated with 10 mg/kg 12-hourly showed an excellent response with no serious adverse effects.

Although several potentially good drugs are being developed, none are soon to be marketed. The diarylquinoline Tibotec Medical Compound 207 (TMC207), which has a unique mode of action inhibiting mycobacterial ATP synthase, showed delayed bactericidal activity in early bactericidal activity (EBA) studies in new TB patients, with no serious TMC207-related adverse effects. A recent, randomized, controlled, Phase 2 study in MDR-TB patients receiving either TMC207 (400 mg daily for 2 weeks and 200 mg daily for 6 weeks) or placebo in addition to a 5-drug standard second-line MDR-TB regimen, found a significant reduction in time to sputum smear-negative conversion and conversion to sputum culture negative at the end of 2 months treatment. This result was achieved with only mild to moderate adverse effects, with only vomiting more common than in the placebo group. Other promising bactericidal and potentially sterilizing compounds currently evaluated in Phase 1 trials and EBA studies are the 2 nitroimidazoles, PA-824 (nitroimidazo-oxazine) and OPC-67683 (dihydroimidazo-oxazole), sudoterb (pyrrole LL-3858), and an ethambutol derivative (diamine SQ109).

Of the available drugs, the combination of meropenem and clavulanate, which are Food and Drug Administration-approved drugs, could potentially be used to treat patients with currently untreatable TB, as it has shown potent in vitro activity against M tuberculosis. Recently Forgacs and colleagues, after observing clinical improvement on trimethoprim-sulfamethoxazole in a patient, showed that 43 of 44 M tuberculosis isolates tested in vitro were susceptible to trimethoprim-sulfamethoxazole at 1 μg/mL or less of trimethoprim and 19 μg/mL of sulfamethoxazole. Both these drug combinations need further evaluation.

NEW DRUGS

The armamentarium of anti-TB drugs specifically for XDR-TB is limited. According to some investigators, the later-generation fluoroquinolones (eg, moxifloxacin) seem to have activity against some of the ofloxacin-resistant M tuberculosis strains and could be included in XDR-TB regimens, but this is not confirmed by other studies. Linezolid, one of a new class of antibiotics, the oxazolidinones, has shown good activity against MDR and XDR M tuberculosis strains in case series, but serious adverse effects, such as partially irreversible peripheral neuropathy, optic neuritis, and severe myelosuppression, and cost has prevented more frequent use. The initial 600 mg twice daily dose of linezolid has been reduced to a half dose (300 mg twice daily), and to as low as 300 mg daily to find an optimal dose at which it is still effective but has fewer adverse effects. At 300 mg daily, linezolid was still effective, myelosuppression was prevented, but some cases of peripheral neuropathy still occurred. Yew and Leung have also suggested using linezolid only in the intensive Phase of treatment (2-3 months) to reduce adverse effects. A single case study in a young child with XDR-TB treated with 10 mg/kg 12-hourly showed an excellent response with no serious adverse effects.

ROLE OF SURGERY IN THE MANAGEMENT OF MDR- AND XDR-TB

The role of surgery in MDR/XDR-TB remains controversial. In conditions such as lymph node obstruction of airways in young children, draining of pericardial effusion, insertion of ventriculoperitoneal shunt for noncommunicating hydrocephalus and some other procedures, the
The need for surgery is the same as for drug-susceptible cases.

Thoracic resectional surgery (e.g., lobectomy or pneumonectomy) and, in some cases, collapse therapy, has proven to be a useful adjunct to MDR-TB drug treatment in adults infected with strains resistant to most drugs.\textsuperscript{74–76} Given the poor outcomes of XDR-TB, it is reasonable to embark on surgical intervention in patients with localized unilateral or bilateral disease who are fit for surgery. Trivial contralateral disease (e.g., small nodules) are not a contraindication to surgery. These patients should have prior drug treatment to minimize the risk to theater staff, and strict infection control measures should be observed in the operating room. The results of surgical intervention in patients with XDR-TB patients are encouraging.\textsuperscript{77,78} These procedures are not without complications. Stump breakdown with bronchopleural fistulas, empyemas, bleeding, and even death may occur; therefore patients should be carefully selected.

### ADVERSE EFFECTS OF SECOND-LINE ANTI-TB DRUGS

Second-line anti-TB drugs cause more adverse effects than first-line drugs, and these are usually underestimated. Adults and children, although the latter seem to have fewer adverse effects, need to be monitored carefully. Adverse effects such as hypothyroidism can be asymptomatic, but some children present with a goiter. Important adverse effects to monitor, and how to monitor them, are summarized in Table 5. Adverse effects should be treated early, because neglecting to do so could lead to poor adherence or even irreversible problems such as hearing loss and peripheral neuropathy, or death (e.g., acute renal failure in capreomycin). Adverse effects of first-line drugs and antiretroviral drugs in patients infected with HIV often have overlapping adverse effects with second-line anti-TB drugs, such as gastrointestinal disturbance (almost all), hepatitis (INH, pyrazinamide, nevirapine, efavirenz, and all protease inhibitors), peripheral neuropathy (INH, d4T, ddl),

<table>
<thead>
<tr>
<th>Second-Line Drug</th>
<th>Adverse Effect\textsuperscript{a}</th>
<th>Tests to Monitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin</td>
<td>Ototoxicity (cumulative dose important)</td>
<td>Audiology (hearing test). Monthly, if possible</td>
</tr>
<tr>
<td>Kanamycin</td>
<td>Nephrotoxicity</td>
<td>Serum creatinine and potassium levels. Monthly; high-risk patients more often</td>
</tr>
<tr>
<td>Capreomycin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>Gastrointestinal disturbance</td>
<td>Clinical observation</td>
</tr>
<tr>
<td></td>
<td>Insomnia</td>
<td>Serum uric acid if used with pyrazinamide</td>
</tr>
<tr>
<td></td>
<td>Arthralgia</td>
<td></td>
</tr>
<tr>
<td>Ethionamide (or protonamide)</td>
<td>Gastrointestinal disturbance</td>
<td>Clinical observation. Prevent by initially splitting dose or increasing dose (drug ramping)</td>
</tr>
<tr>
<td></td>
<td>Hepatotoxicity</td>
<td>Jaundice. Serum alanine transferase and bilirubin</td>
</tr>
<tr>
<td></td>
<td>Hypothyroidism</td>
<td>Thyroid-stimulating hormone levels (free T4). At least 6-monthly</td>
</tr>
<tr>
<td>Cycloserine (or terizidone)</td>
<td>Psychosis, seizures, parasthesia</td>
<td>Clinical observation. All patients to receive preventive pyridoxine</td>
</tr>
<tr>
<td></td>
<td>depression</td>
<td></td>
</tr>
<tr>
<td>para-Aminosalicylic acid (PAS)</td>
<td>Gastrointestinal disturbance</td>
<td>Clinical observation</td>
</tr>
<tr>
<td></td>
<td>Hypothyroidism</td>
<td>Thyroid stimulating hormone levels (free T4). At least 6-monthly</td>
</tr>
<tr>
<td>Linezolid</td>
<td>Myelosuppression</td>
<td>Full blood count. Weekly at first, then monthly</td>
</tr>
<tr>
<td></td>
<td>Lactic acidosis</td>
<td>Serum lactate level</td>
</tr>
<tr>
<td></td>
<td>Peripheral neuropathy</td>
<td>Clinical observation</td>
</tr>
<tr>
<td></td>
<td>Pancreatitis (abdominal pain)</td>
<td>Clinical and serum amylase as indicated</td>
</tr>
<tr>
<td></td>
<td>Optic neuritis</td>
<td>Vision testing</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Adverse effects of first-line drugs and antiretroviral drugs in patients infected with HIV often have overlapping adverse effects (see discussion of adverse effects in the text).
central nervous system effects (INH, efavirenz), pancreatitis (d4T, ddI), and lactic acidosis (d4T, ddI, AZT, 3TC).41

OUTCOME OF MDR- AND XDR-TB

Long-term outcomes of MDR-TB in adults have improved markedly in recent years, with between 33% and 96% long-term cure or treatment completion with good clinical response.79

Treatment of XDR-TB shows varying results.80–82 Data from Estonia suggest poor outcomes associated with resistance to capreomycin.83 In contrast, limited data from Peru are encouraging in that 60% of XDR-TB patients completed treatment or were cured with intensive multidrug therapy.45 An initial report from South Africa indicated a 98% mortality and a median survival of 16 days among patients coinfected with XDR-TB and HIV.3 In a recent South African XDR-TB study of 270 patients, the overall culture-conversion rate was 17.8% (36/202 who initiated treatment), and, of those, 25/36 (69%) culture-converted within 6 months of treatment initiation.18 Those with a body weight of less than 50 kg were significantly less likely to convert (P = .009). Overall and 12-month mortality rates were 44% (103/234) and 35.9% (84/234), respectively; 25.7% (26/103) of all deaths occurred before treatment initiation. Patients infected with HIV had a higher mortality (12-month mortality of 50% vs 35%; P = .04), but culture-converted at the same rate as uninfected patients. Patients infected with HIV and treated with HAART had lower mortality than untreated patients (12-month mortality of 35% vs 75%; P = .02). In Cox multivariate regression models, HIV status, treatment with a fluoroquinolone or INH, and radiographic unilateral cavitation were independent predictors of survival. Thus, in South Africa, despite intensive, directly observed, multidrug treatment, the prognosis of XDR-TB, regardless of HIV status, remains poor. Survival, however, in patients infected with HIV is better than previously reported, and substantially improved with HAART. These data have implications for improving case-finding strategies, streamlining diagnostic algorithms, and intensifying the urgent development of XDR-TB–related immunotherapeutic interventions for high-HIV-prevalence environments.18,23

Few outcome studies are available for children with MDR/XDR-TB. In Peru, cure or probable cure was obtained in 36 of 38 (95%) MDR-TB cases.52 A South African study of 39 culture-confirmed childhood MDR-TB cases had 4 (10%) deaths and most of the children clinically cured.50 More data are needed to compare cure rates of children with and without HIV infection with MDR-TB and specific types of TB. In general, MDR tuberculous meningitis has a high mortality.84 Only case reports of XDR-TB in children are available.66

MANAGEMENT OF CONTACTS OF MDR OR XDR-TB

All close contacts of infectious TB cases should be evaluated for TB disease. Once TB disease has been excluded, WHO guidelines recommend that all children less than 5 years old and all patients infected with HIV, irrespective of age, should receive preventive therapy (chemoprophylaxis).85 In developed countries with low TB incidence, older age groups and all patients infected with HIV will also be advised to take preventive therapy. However, in the case of drug-resistant contacts, no randomized controlled trials for preventive therapy have been conducted. In the case of MDR-TB, the WHO recommends INH preventive therapy only, not to prevent MDR-TB but because, in high TB incidence areas, the patient may have been infected by a drug-susceptible source case.86 Several failures of INH or INH/RMP combination preventive therapy for MDR-TB child contacts have been documented.87

For MDR-TB contacts there is no universally accepted regimen. The WHO does not recommend the use of second-line drugs for preventive therapy for MDR-TB contacts, and recommends only regular follow-up for a minimum of 2 years.86 However, one study has shown that giving a combination of 2 drugs to which the source case’s isolate is susceptible or naive prevents the development of disease in high-risk child contacts.88 This is also the current recommendation of the American Academy of Pediatrics.89 The authors prefer a combination of a fluoroquinolone, ethambutol (if DST shows susceptibility), or ethionamide plus high-dose INH for 6 months in high-risk cases such as young children (<3 years) or patients infected with HIV.

There is no effective preventive therapy for XDR-TB contacts. Regular follow-up as for MDR-TB contacts is the only option, with early treatment once disease occurs.

INFECTION CONTROL

No discussion of TB is complete without the mention of proper infection control measures. In developing countries, good ventilation (>6 air changes per hour) by opening windows and doors is the most important and easily implemented measure, other than diagnosing and treating infectious cases early and effectively, and separating...
suspected cases, especially from children and patients infected with HIV. A recent modeling study of infection control outcomes estimated that half of anticipated XDR-TB cases could be averted by the application of a combination of available strategies in developing countries. In the case of children presenting with possible TB, the adult accompanying the child may be the source case, and therefore it is important that a history of TB should be obtained from the adult or they should be screened, if they are symptomatic, to prevent possible transmission of disease in the health care setting.

REFERENCES


