proper social support including education, psychosocial counseling, and material sustainment. In an increasing number of countries, personnel to supervise therapy are usually available through TB control programs of local public health departments and from members of the community who are accepted by the patient to undertake that role and who have been properly educated by health workers. Direct supervision with patient support usually increases the proportion of patients completing treatment in all settings and greatly lessens the chances of failure, relapse, and acquired drug resistance. Fixed-drug-combination products (e.g., isoniazid/rifampin, isoniazid/rifampin/pyrazinamide, and isoniazid/rifampin/pyrazinamide/ethambutol) are available and are strongly recommended as a means of minimizing the likelihood of prescription error and of the development of drug resistance as the result of monotherapy. In some formulations of these combination products, the bioavailability of rifampin has been found to be substandard. Stringent regulatory authorities ensure that combination products are of good quality; however, this type of quality assurance is not always operative in low-income countries. Alternative regimens for patients who exhibit drug intolerance or adverse reactions are listed in Table 202-3. However, severe side effects prompting discontinuation of any of the first-line drugs and use of these alternative regimens are uncommon. The fluoroquinolones moxifloxacin and gatifloxacin have been tested as 4-month treatment-shortening regimens for drug-susceptible TB. Recently published results from these clinical trials failed to show that a 4-month regimen substituting gatifloxacin for ethambutol or moxifloxacin for either ethambutol or isoniazid is noninferior to the standard 6-month regimen. Thus, currently there is no 4-month regimen available for TB treatment.

MONITORING TREATMENT RESPONSE AND DRUG TOXICITY

Bacteriologic evaluation through culture and/or smear microscopy is essential in monitoring the response to treatment for TB. In addition, the patient's weight should be monitored regularly and the drug dosage adjusted with any significant weight change. Patients with pulmonary disease should have their sputum examined monthly until cultures become negative to allow early detection of treatment failure. With the recommended regimen, more than 80% of patients will have negative sputum cultures at the end of the second month of treatment. By the end of the third month, the sputum of virtually all patients should be culture negative. In some patients, especially those with extensive cavitary disease and large numbers of organisms, AFB smear conversion may lag behind culture conversion. This phenomenon is presumably due to the expectoration and microscopic visualization of dead bacilli. As noted above, patients with cavitary disease in whom sputum culture conversion does not occur by 2 months require immediate testing for drug resistance. When a patient's sputum cultures remain positive at ≥3 months, treatment failure and drug resistance or poor adherence to the regimen are likely, and testing of drug resistance should guide the choice of the best treatment option (see below). A sputum specimen should be collected by the end of treatment to document cure. If mycobacterial cultures are not practical, then monitoring by AFB smear examination should be undertaken at 2, 5, and 6 months. Smears that are positive after 3 months of treatment when the patient is known to be adherent are indicative of treatment failure and possible drug resistance. Therefore, if not done at the start of treatment, drug susceptibility testing is mandatory at this stage. Bacteriologic monitoring of patients with extrapulmonary TB is more difficult and often is not feasible. In these cases, the response to treatment must be assessed clinically and radiographically.

Monitoring of the response during chemotherapy by nucleic acid amplification technology has not been shown to be suitable. Thus Xpert MTB/RIF should not be used to monitor treatment. Likewise, serial chest radiographs are not recommended because radiographic changes may lag behind bacteriologic response and are not highly sensitive. After the completion of treatment, neither sputum examination nor chest radiography is recommended for routine follow-up purposes. However, a chest radiograph obtained at the end of treatment may be useful for comparative purposes should the patient develop symptoms of recurrent TB months or years later. Patients should be instructed to report promptly for medical assessment if they develop any such symptoms. In addition, an end-of-treatment chest radiograph may reveal earlier the post-TB complications described above.

During treatment, patients should be monitored for drug toxicity. The most common adverse reaction of significance is hepatitis. Patients should be carefully educated about the signs and symptoms of drug-induced hepatitis (e.g., dark urine, loss of appetite) and should be instructed to discontinue treatment promptly and see their health care provider should these symptoms occur. Although biochemical monitoring is not routinely recommended, all adult patients should undergo baseline assessment of liver function (e.g., measurement of serum levels of hepatic aminotransferases and bilirubin). Older patients, those with concomitant diseases, those with a history of hepatic disease (especially hepatitis C), and those using alcohol daily should be monitored especially closely (i.e., monthly), with repeated measurements of aminotransferases, during the initial phase of treatment. Up to 20% of patients have small increases in aspartate aminotransferase (up to three times the upper limit of normal) that are not accompanied by symptoms and are of no consequence. For patients with symptomatic hepatitis and those with marked (five- to sixfold) elevations in serum levels of aspartate aminotransferase, treatment should be stopped and drugs reintroduced one at a time after liver function has returned to normal. Hypersensitivity reactions usually require the discontinuation of all drugs and rechallenge to determine which agent is the culprit. Because of the variety of regimens available, it usually is not necessary—although it is possible—to desensitize patients. Hyperuricemia and arthralgia caused by pyrazinamide can usually be managed by the administration of acetylsalicylic acid; however, pyrazinamide treatment should be stopped if the patient develops gouty arthritis. Individuals who develop autoimmune thrombocytopenia secondary to rifampin therapy should not receive the drug thereafter. Similarly, the occurrence of optic neuritis with ethambutol is an indication for permanent discontinuation of this drug. Other common manifestations of drug intolerance, such as pruritus and gastrointestinal upset, can generally be managed without the interruption of therapy.

TREATMENT FAILURE AND RELAPSE

As stated above, treatment failure should be suspected when a patient's sputum smears and/or cultures remain positive after 3 months of treatment. In the management of such patients, it is imperative that the current isolate be urgently tested for susceptibility to first- and second-line agents. Initial molecular testing for rifampin resistance should be done if the technology is available. When the results of susceptibility testing are based on molecular methods and are expected to become available within a few days, changes in the regimen can be postponed until that time. However, if the patient's clinical condition is deteriorating, an earlier change in regimen may be indicated. A cardinal rule in the latter situation is always to add more than one drug at a time to a failing regimen: at least two and preferably three drugs that have never been used and to which the bacilli are likely to be susceptible should be added. The patient may continue to take isoniazid and rifampin along with these new agents pending the results of susceptibility tests.

Patients who experience a recurrence after apparently successful treatment (relapse) are less likely to harbor drug-resistant strains (see below) than are patients in whom treatment has failed. Acquired resistance is uncommon among strains from patients in whom relapse follows the completion of a standard short-course regimen. However, pending the results of susceptibility testing, it is prudent to begin the treatment of all patients whose infections have relapsed with a standard regimen containing all four first-line drugs plus streptomycin. In less affluent countries and other settings where facilities for culture and drug susceptibility testing are not yet routinely available and where the prevalence of MDR-TB is low, the WHO recommends that a standard regimen with all four