is no diagnostic test for IRIS, and its confirmation relies heavily upon case definitions incorporating clinical and laboratory data; a variety of case definitions have been suggested. The first priority in the management of a possible case of IRIS is to ensure that the clinical syndrome does not represent a failure of TB treatment or the development of another infection. Mild paradoxical reactions can be managed with symptom-based treatment. Glucocorticoids have been used for more severe reactions, and prednisolone given for 4 weeks at a low dosage (1.5 mg/kg per day for 2 weeks and half that dose for the remaining 2 weeks) has reduced the need for hospitalization and therapeutic procedures and hastened alleviation of symptoms, as reflected by Karnofsky performance scores, quality-of-life assessments, radiographic response, and C-reactive protein levels. The effectiveness of glucocorticoids in alleviating the symptoms of IRIS is probably linked to suppression of proinflammatory cytokine concentrations, as these medications reduce serum concentrations of IL-6, IL-10, IL-12p40, TNF-α, IFN-γ, and IFN-γ-inducible protein 10 (IP-10). Recommendations for the prevention and treatment of TB in HIV-infected individuals are provided below.

DIAGNOSIS

The key to the diagnosis of TB remains a high index of suspicion. Diagnosis is not difficult in persons belonging to high-risk populations who present with typical symptoms and a classic chest radiograph showing upper-lobe infiltrates with cavities (Fig. 202-6). On the other hand, the diagnosis can easily be missed in an elderly nursing-home resident or a teenager with a focal infiltrate. Often, the diagnosis is first entertained when the chest radiograph of a patient being evaluated for respiratory symptoms is abnormal. If the patient has no complicating medical conditions that cause immunosuppression, the chest radiograph may show typical upper-lobe infiltrates with cavitation (Fig. 202-6). The longer the delay between the onset of symptoms and the diagnosis, the more likely is the finding of cavitary disease. In contrast, immunosuppressed patients, including those with HIV infection, may have "atypical" findings on chest radiography—e.g., lower-zone infiltrates without cavity formation.

The several approaches to the diagnosis of TB require, above all, a well-organized laboratory network with an appropriate distribution of tasks at different levels of the health care system. At the peripheral and community levels, screening and referral are the principal tasks—besides clinical assessment and radiography—that can be accomplished through AFB microscopy and/or real-time automated nucleic acid amplification technology (the Xpert MTB/RIF assay; see below). At a secondary level (e.g., a traditional district hospital in a high-incidence setting), additional technology can be adopted, including rapid culture and drug susceptibility testing.

AFB MICROSCOPY

A presumptive diagnosis is commonly based on the finding of AFB on microscopic examination of a diagnostic specimen, such as a smear of expectorated sputum or of tissue (e.g., a lymph node biopsy). Although inexpensive, AFB microscopy has relatively low sensitivity (40–60%) in culture-confirmed cases of pulmonary TB. The traditional method—light microscopy of specimens stained with Ziehl-Neelsen basic fuchsin dyes—is nevertheless satisfactory, although time-consuming. Most modern laboratories processing large numbers of diagnostic specimens use auramine–rhodamine staining and fluorescence microscopy; this approach is more sensitive than the Ziehl-Neelsen method. However, it is expensive because it requires high-cost mercury vapor light sources and a dark room. Less expensive light-emitting diode (LED) fluorescence microscopes are now available. They are as sensitive as—or more sensitive than—traditional fluorescence microscopes. As a result, conventional light and fluorescence microscopes are being replaced with this more recent technology, especially in developing countries. For patients with suspected pulmonary TB, it has been recommended that two or three sputum specimens, preferably collected early in the morning, should be submitted to the laboratory for AFB smear and mycobacterial culture. Two specimens collected on the same visit may be as effective as three. If tissue is obtained, it is critical that the portion of the specimen intended for culture not be put in formaldehyde. The use of AFB microscopy in examining urine or gastric lavage fluid is limited by the presence of commensal mycobacteria that can cause false-positive results.

NUCLEIC ACID AMPLIFICATION TECHNOLOGY

Several test systems based on amplification of mycobacterial nucleic acid have become available in the past few years. These tests are most useful for the rapid confirmation of TB in persons with AFB-positive specimens, but some also have utility for the diagnosis of AFB-negative pulmonary and extrapulmonary TB. One system that permits rapid diagnosis of TB with high specificity and sensitivity (approaching that of culture) is the fully automated, real-time nucleic acid amplification technology known as the Xpert MTB/RIF assay. Xpert MTB/RIF can simultaneously detect TB and rifampin resistance in <2 h and has minimal biosafety and training requirements. Therefore, it can be housed in nonconventional laboratory settings. The WHO recommends its use worldwide as the initial diagnostic test in adults and children presumed to have MDR-TB or HIV-associated TB. Taking into account the availability of resources, the test may also be used in any adult or child presumed to have TB or as a follow-up test after microscopy in adults presumed to have TB but not at risk of MDR-TB or HIV-associated TB. Xpert MTB/RIF should be the initial test applied to CSF from patients in whom TB meningitis is suspected as well as a replacement test (over conventional microscopy, culture, and histopathology) for selected nonrespiratory specimens—obtained by gastric lavage, fine-needle aspiration, or pleural or other biopsies—from patients in whom extrapulmonary TB is suspected. This test has a sensitivity of 98% among AFB-positive cases and ~70% among AFB-negative specimens. Other tests, such as those based on manual amplification platforms, have not yet been deemed satisfactory for introduction into clinical practice as replacements for existing tests.

MYCOBACTERIAL CULTURE

Definitive diagnosis depends on the isolation and identification of *M. tuberculosis* from a clinical specimen or the identification of specific DNA sequences in a nucleic acid amplification test. Specimens may be inoculated onto egg- or agar-based medium (e.g., Löwenstein-Jensen or Middlebrook 7H10) and incubated at 37°C (under 5% CO_2 for Middlebrook medium). Because most species of mycobacteria, including *M. tuberculosis*, grow slowly, 4–8 weeks may be required before growth is detected. Although *M. tuberculosis* may be identified presumptively on the basis of growth time and colony pigmentation and morphology, a variety of biochemical tests have traditionally been used to speciate mycobacterial isolates. In modern, well-equipped laboratories, liquid culture for isolation and species identification by molecular methods or high-pressure liquid chromatography of mycolic acids has replaced isolation on solid media and identification by biochemical tests. A widely used technology is the mycobacterial growth indicator tube (BBL™ MGIT™; BD, Franklin Lakes, NJ), which uses a fluorescent compound sensitive to the presence of oxygen dissolved in the liquid medium. The appearance of fluorescence detected by fluorometric technology indicates active growth of mycobacteria. A low-cost, rapid immunochromatographic lateral-flow assay based on detection of MTP64 antigen may also be used for species identification of the *M. tuberculosis* complex in culture isolates. These new methods, which are also being introduced in low-income countries, have decreased the time required for bacteriologic confirmation of TB to 2–3 weeks.

DRUG SUSCEPTIBILITY TESTING

Any initial isolate of *M. tuberculosis* should be tested for susceptibility to isoniazid and rifampin in order to detect drug resistance and/or MDR-TB, particularly if one or more risk factors for drug resistance are identified or if the patient either fails to respond to initial therapy or has a relapse after the completion of treatment (see "Treatment Failure and Relapse," below). In addition, expanded susceptibility testing for second-line anti-TB drugs (especially the fluoroquinolones