GENERAL GUIDELINES FOR THE EVALUATION OF NEW ANTIMYCOBACTERIAL DRUGS FOR THE TREATMENT OF SYSTEMIC MYCOBACTERIAL INFECTIONS

Evaluation of New Anti-Infective Drugs for the Treatment and Prevention of Tuberculosis

Philip Hopewell, Michael Cynamon, Jeffrey Starke, Michael Iseman, and Richard O'Brien

From the Chest Service, San Francisco General Hospital, San Francisco, California; the Division of Infectious Diseases, Syracuse VA Medical Center, Syracuse, New York; the Department of Pediatrics, Baylor College of Medicine, Houston, Texas; National Jewish Hospital, Denver, Colorado; and the Division of TB Control, Atlanta, Georgia

This guideline addresses the evaluation of new antimycobacterial drugs in the treatment and prevention (secondary prophylaxis) of infection by M. tuberculosis. Patients may be enrolled in clinical trials on the basis of clinical and/or microbiological criteria. A therapeutic regimen will likely include a combination of drugs; a randomized, active-control, comparative clinical trial is recommended. If appropriate samples can be obtained for culture during follow-up without placing the patient at unwarranted risk, the assessment of microbiological outcome is paramount. Prophylaxis will probably require a single drug, and a similar study design is preferred.

I. INTRODUCTION AND BACKGROUND
A. Background

II. CLINICAL DEFINITIONS OF THE DISEASE
A. General Definitions
B. Minimal Diagnostic Criteria for Inclusion

III. INFORMATION NEEDED BEFORE CONDUCTING CLINICAL TRIALS
A. In Vitro Studies
B. In Vivo Studies

IV. QUALIFICATIONS OF INVESTIGATORS AND INSTITUTIONS
A. Investigators
B. Institutions

V. DESIGN AND IMPLEMENTATION OF PHASE 1, 2, AND 3 CLINICAL TRIALS

VI. ELEMENTS TO BE CONSIDERED IN DESIGNING PHASE 2 AND 3 CLINICAL TRIALS
A. Demographic Characteristics of the Study Population
B. Inclusion and Exclusion Criteria
C. Selection of the Comparison Drug
D. Study Design and Stratification
E. Administration of the Study Drug
F. Modification During the Study
G. Definitions of Response to Therapy
H. Methods of Assessing Safety

This work was supported by a contract to the Infectious Diseases Society of America from the U.S. Food and Drug Administration (no. HHS 223-88-1301).

Correspondence: Dr. Philip Hopewell, Chest Service, Room 5K1, San Francisco General Hospital, 1001 Potrero Avenue, San Francisco, California 94110.

Clinical Infectious Diseases 1992;15(Suppl 1):S282-95
© 1992 by The University of Chicago. All rights reserved.
I. INTRODUCTION AND BACKGROUND INFORMATION

This is one of a series of disease-specific guidelines that have been prepared to assist sponsors and investigators in the development, conduct, and analysis of studies of new antituberculous drugs. These guidelines deal with the conduct of phase I through phase IV clinical trials and are subsets of the General Guidelines for the Clinical Evaluation of Anti-Infective Drug Products, which should be consulted for the prerequisites to the conduct of studies in humans.

A. Background

Effective chemotherapy for tuberculosis became a reality in 1952 with the introduction of isoniazid [1]. Although streptomycin had been introduced 6 years earlier, it soon became apparent that patients whose condition initially improved with the drug subsequently became more ill again, and isolates of Mycobacterium tuberculosis from these patients were discovered to be resistant. The lack of a suitable companion agent that would inhibit the emergence of such resistant organisms precluded striking therapeutic success with streptomycin [2]. The observation of resistance to this drug defined an important bacteriologic principle upon which successful chemotherapy for tuberculosis depends: populations of M. tuberculosis are not uniformly susceptible to antituberculous agents, and hence it is always necessary to treat tuberculosis with more than one drug.

The second important bacteriologic principle in chemotherapy for tuberculosis—that relatively long courses of therapy are necessary—was established by studies conducted by the British Medical Research Council in the late 1950s [3]. As a consequence of these studies, it became generally accepted that the optimal duration of treatment with combinations of isoniazid, streptomycin, and \( p \)-aminosalicylic acid was 18–24 months.

After the introduction of rifampin in the 1970s, a series of studies by the British Medical Research Council in East Africa demonstrated that 6 months of isoniazid, streptomycin, and rifampin was nearly as effective as 18 months of isoniazid and thiacetazone with streptomycin given in the first 2 months [4–6]. Further trials examined various permutations of the regimens, including a more intensive initial phase and intermittent administration.

Studies of chemotherapy both in the United States and abroad began to focus on the possible benefits of pyrazinamide, which has long been known to be active at an acid pH, such as that existing within macrophages [7]. It was suggested that this feature of pyrazinamide accounted for its beneficial effects, which had been noted in an earlier study of its use in combination with isoniazid and streptomycin [8]. This hypothesis was complemented by the observations of Dickinson and co-workers [9] that streptomycin, rifampin, and isoniazid were quickly bactericidal for actively growing M. tuberculosis under in vitro conditions that could be likened to those under which the large pool of extracellular organisms in tuberculous lesions are living. Moreover, while both rifampin and isoniazid were rapidly bactericidal, Mitchison and Dickinson [10] demonstrated that rifampin was more effective in killing organisms that grow sporadically rather than continuously. Although both isoniazid and rifampin were effective in killing intracellular organisms, pyrazinamide was more effective. Thus, the addition of pyrazinamide was postulated to strengthen the isoniazid/rifampin combination. Two studies substantiated that the addition of pyrazinamide to a regimen of isoniazid and rifampin for 2 months enhanced the effectiveness of a 6-month course of treatment [11, 12].

The value of isoniazid alone for the prevention of tuberculosis was suggested initially by studies in animals [13]. Subsequently, it was found that isoniazid given to children with primary tuberculosis nearly eliminated extrapulmonary spread [14]. On the basis of these observations, the U.S. Public Health Service undertook a series of studies that eventually included some 70,000 participants in a number of different settings. The findings were remarkably similar in all groups studied: isoniazid reduced the incidence of tuberculosis by 80% during the year in which the drug was given and by \( \sim 50\% \) each year thereafter through 10–12 years of observation [15]. Several smaller studies yielded similar results. These trials included a comparison of two durations of isoniazid prophylaxis in patients with fibrotic (presumably old tuberculous) pulmonary lesions [16]. This study demonstrated that 6 months of isoniazid administration was nearly as effective as 12 months in preventing tuberculosis among patients with fibrotic lesions <2 cm in diameter but that the shorter duration was not as effective in the presence of larger lesions.

Recent studies examining the effectiveness of combinations of drugs in preventing tuberculosis in patients with silicosis have suggested that courses as short as 2–3 months may be effective [17]. Data from studies of animals have suggested that combinations of rifampin and pyrazinamide may be especially useful [18].
B. Standards of Care

1. Current Standards

The American Thoracic Society (ATS), the Centers for Disease Control (CDC), and the International Union Against Tuberculosis and Lung Disease [19, 20] currently recommend a 6-month regimen of isoniazid and rifampin, supplemented by pyrazinamide for the first 2 months, for the treatment of tuberculosis. If pyrazinamide is not used, the minimal duration of treatment with isoniazid and rifampin is 9 months. With either a 6-month or a 9-month regimen, ethambutol should be used, at least in the initial phase, if there is a significant likelihood of resistance to isoniazid. If the organisms are resistant to isoniazid or if isoniazid cannot be used for some other reason, the minimal regimen is rifampin and ethambutol for 12-18 months, usually supplemented initially with pyrazinamide. The duration of therapy with isoniazid and ethambutol is similar if rifampin cannot be used.

Essentially all the clinical trials upon which the standards of antituberculosis chemotherapy are based have excluded children, and choices of treatment for children with tuberculosis have been based mainly upon the regimens used in adults. None of the reported trials of short-course antituberculosis chemotherapy in children has included a control regimen [21-23]. Rather, results for the test regimen have been compared with those for historical controls. The lack of controlled studies in children is due largely to the small numbers of cases seen at any single center. Moreover, since most studies have followed patients for only a few years after treatment, the development of tuberculosis in adolescence or adulthood has not been assessed. A special problem is the paucity of data on pharmacokinetics in children. This situation makes establishment of a standard regimen for the treatment of tuberculosis in children difficult.

There is no established regimen for the treatment of patients with tuberculosis caused by organisms resistant to both isoniazid and rifampin. The basic principle of always using at least two agents to which the organism is either known or presumed to be susceptible should be followed.

In the 30-40 years since the basic elements of effective drug therapy were established, a number of important modifications have been made in the management of patients with tuberculosis. Hospitalization, which had been regarded as an essential component of care for all or part of the treatment period, was shown to offer no advantage over treatment at home [24]. Moreover, it was demonstrated that chemotherapy was very effective in reducing or eliminating infectiousness, thereby greatly decreasing the need for isolation [25, 26]. Diet and rest were shown not to be important factors in outcome, and surgical procedures became less widely used [27-29]. At present, these ancillary measures do not have a significant role in the management of tuberculosis.

Currently, the standard regimen for the prophylaxis of tuberculosis is isoniazid: 300 mg daily for adults and 10 mg/kg (up to 300 mg) daily for children [19]. The minimal duration of prophylaxis is 6 months. For persons with radiographic abnormalities suggestive of "old" tuberculosis and for immunosuppressed persons, the recommended duration of prophylaxis is 12 months. There are no established preventive regimens for persons who cannot take isoniazid or who are thought to have been infected with isoniazid-resistant organisms. Rifampin alone or in combination with pyrazinamide may be a suitable alternative.

Table 1 lists the drugs currently used to treat tuberculosis, the standard doses, and adverse reactions.

2. Future Trends

Investigations will continue to focus on shortening of the total duration of both therapy and prophylaxis and on the development of regimens whose greater acceptability to patients enhances compliance. Substantial shortening of the current 6-month minimal duration of chemotherapy will likely require the development of new antimycobacterial drugs. In specific, identifiable groups of patients, shorter courses of currently available drugs may prove effective. Potential innovations that may make regimens more acceptable include the development of drugs with a longer half-life for less frequent administration.

The rate of resistance to isoniazid [30] as well as to other drugs is increasing progressively. Thus new drugs that can replace isoniazid and/or rifampin—in both therapeutic and prophylactic regimens—are needed. Of particular relevance in developing countries is the need for inexpensive drugs. A large proportion of cases of tuberculosis occur in poor, non-industrialized nations where new drugs that are costly will be of limited usefulness [31].

C. Scope of the Guideline

1. Clinical Entities and Microorganisms

This guideline covers studies of the treatment and prevention of pulmonary and nonpulmonary tuberculosis; only infection and disease caused by M. tuberculosis are included. Specifically excluded are infection and disease caused by other members of the tuberculosis complex, such as Mycobacterium bovis, Mycobacterium africanum, and Mycobacterium microti.

2. Microbiological Techniques

(a) Clinical Specimens

(1) General diagnostic procedures. A definitive diagnosis of tuberculosis can be established only by isolation of M.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose forms</th>
<th>Daily dose</th>
<th>Maximum daily dose for children and adults</th>
<th>Twice-weekly dose</th>
<th>Adverse reactions</th>
<th>Recommended regular monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>Tablets: 100 mg, 300 mg; syrup: 50 mg/5 ml;</td>
<td>10-20 mg/kg po or im</td>
<td>5 mg/kg po or im</td>
<td>300 mg</td>
<td>20-40 mg/kg (maximum, 900 mg)</td>
<td>Hepatic enzyme elevation, neuropathy, hepatitis, peripheral neuritis, hypersensitivity</td>
</tr>
<tr>
<td></td>
<td>Capsules: 150 mg, 300 mg; syrup formulated from</td>
<td>10-20 mg/kg po</td>
<td>10 mg/kg po</td>
<td>600 mg</td>
<td>10-20 mg/kg (maximum, 600 mg)</td>
<td>Orange discoloration of secretions and urines, naevus, vomiting, hepatitis, fever, reaction, purpura (rare), skin rash</td>
</tr>
<tr>
<td></td>
<td>capsules, 10 mg/ml</td>
<td></td>
<td></td>
<td></td>
<td>10 mg/kg (maximum, 600 mg)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>mg</td>
<td></td>
</tr>
<tr>
<td>Rifampin</td>
<td>Capsules: 150 mg, 300 mg; syrup formulated from</td>
<td>10-20 mg/kg po</td>
<td>10 mg/kg po</td>
<td>600 mg</td>
<td>10-20 mg/kg (maximum, 600 mg)</td>
<td>Hepatotoxicity, hyperuricaemia</td>
</tr>
<tr>
<td></td>
<td>capsules, 10 mg/ml</td>
<td></td>
<td></td>
<td></td>
<td>10 mg/kg</td>
<td></td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>Tablets: 500 mg</td>
<td>15-30 mg/kg po</td>
<td>15-30 mg/kg po</td>
<td>2.5 g</td>
<td>50-70 mg/kg</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>50-70 mg/kg</td>
<td></td>
</tr>
<tr>
<td>Streptomycin</td>
<td>Vials: 1 g, 4 g</td>
<td>20-40 mg/kg im</td>
<td>15 mg/kg im</td>
<td>1 g</td>
<td>25-30 mg/kg im</td>
<td>Otoxicity (vestibular nerve), nephrotoxicity (rare)</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>Tablets: 100 mg, 400 mg</td>
<td>15-25 mg/kg po</td>
<td>15-25 mg/kg po</td>
<td>2.5 g</td>
<td>50 mg/kg</td>
<td>Optic neuritis (decreased red-green color discrimination), decreased visual acuity, skin rash</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>50 mg/kg</td>
<td></td>
</tr>
<tr>
<td>Capreomycin</td>
<td>Vials: 1 g</td>
<td>15-30 g/kg im</td>
<td>15-30 g/kg im</td>
<td>1 g</td>
<td></td>
<td>Auditory, vestibular, and renal toxicity</td>
</tr>
<tr>
<td>Kanamycin</td>
<td>Vials: 75 mg, 500 mg, 1 g</td>
<td>15-30 g/kg im</td>
<td>15-30 g/kg im</td>
<td>1 g</td>
<td></td>
<td>Auditory and renal toxicity, rare vestibular toxicity</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethionamide</td>
<td>Tablets: 250 mg</td>
<td>15-20 mg/kg po</td>
<td>15-20 mg/kg po</td>
<td>1 g</td>
<td></td>
<td>Hepatotoxicity, hypersensitivity, hepatotoxicity, sodium load</td>
</tr>
<tr>
<td>Paraaminosalicylic acid</td>
<td>Tablets: 500 mg, 1 g, bulk powder</td>
<td>150 mg/kg po</td>
<td>150 mg/kg po</td>
<td>12 g</td>
<td></td>
<td>Gastrointestinal disturbance, hypersensitivity, hepatotoxicity, sodium load</td>
</tr>
<tr>
<td>Cycloserine</td>
<td>Capsules: 250 mg</td>
<td>15-20 mg/kg po</td>
<td>15-20 mg/kg po</td>
<td>1 g</td>
<td></td>
<td>Psychosis, personality changes, convulsions, rash</td>
</tr>
</tbody>
</table>
tuberculosis in culture. When infection of the lung is suspected, sputum is the initial specimen of choice. A sputum specimen should be collected at the initial evaluation: if microscopic examination yields negative findings, additional specimens should be collected. Single early-morning specimens have a higher yield and a lower rate of contamination than do specimens pooled over 24 hours. Cumulative yield does not increase with more than five specimens, and the increase between three and five specimens is slight [32]. Therefore, examination of three sputum samples is optimum.

There are several options for obtaining specimens from patients who are not producing sputum. The first and most useful is the induction of sputum by inhalation of a hypertonic saline mist generated by an ultrasonic nebulizer. Sampling of gastric contents via a nasogastric tube has a lower yield than sputum induction and is more complicated and uncomfortable for the patient [33]. However, gastric contents may be the only specimen that can be readily obtained from children and uncooperative adults. To ensure a maximal yield, gastric lavage should be performed early in the morning (before the patient has gotten out of bed). Once a sample has been obtained, prompt neutralization of gastric acid is necessary.

Specimens have been collected with laryngeal swabs, but the yield is lower than with either sputum induction or gastric aspiration. Specimens may also be obtained by transtracheal aspiration, but the risk of complications generally exceeds the potential benefit.

If the sputum gives a negative result or cannot be obtained, the next diagnostic step is usually bronchoscopy. In general, this procedure should include bronchoalveolar lavage and transbronchial lung biopsy. The yield of bronchoscopy has been high in both miliary tuberculosis and local disease [34, 35]. Needle aspiration biopsy may, on occasion, provide a specimen from which mycobacteria are isolated. This technique is better suited to the evaluation of focal lesions in which malignancy is suspected.

(2) Tuberculous lymphadenopathy. The diagnosis of tuberculous lymphadenopathy is established by lymph node biopsy or aspiration with histologic examination, acid-fast staining, and culture of the material obtained. Smears show acid-fast organisms in ~25%–50% of biopsy specimens, and M. tuberculosis is isolated in roughly 70% of instances in which the diagnosis is considered to be tuberculosis [36]. Caseating granulomas are seen in nearly all biopsy samples from immunocompetent patients. In immunodeficiency states, poorly formed granulomas—or none at all—may be noted [37].

(3) Tuberculous pleuritis. Smears of pleural fluid rarely give a positive result because few organisms are present in the pleural space. M. tuberculosis is isolated by culture from only 20%–40% of samples of pleural fluid from patients with tuberculosis. A single closed-needle biopsy of the pleura, with collection of three or four specimens and histologic examination, acid-fast staining, and culture of the tissue, confirms the diagnosis in ~65%–75% of patients in whom the diagnosis is ultimately established [38]. A second set of biopsy specimens when a patient's initial biopsy results are negative increases the yield to 80%–90%.

(4) Genitourinary tuberculosis. When genitourinary tuberculosis is suspected, at least three first-voided, early-morning urine specimens should be collected for acid-fast staining and culture. In men, Mycobacterium smegmatis, a saprophytic species, may cause a false-positive smear. However, in the presence of leukocytes and proteinuria, a positive smear should be interpreted as a presumptive indicator of tuberculosis until the results of cultures are known. Diagnosis of isolated genital lesions usually requires biopsy because the differential diagnosis often includes neoplasia as well as other infectious processes. M. tuberculosis is isolated from the urine in 80%–95% of cases of genitourinary tuberculosis [39].

(5) Disseminated (miliary) tuberculosis. Acid-fast smears of sputum are positive in 20%–25% of cases of disseminated (miliary) tuberculosis, and M. tuberculosis is isolated from sputum in 30%–65% of cases [40]. Induced sputum may yield a positive result when the patient is not spontaneously producing sputum. For a patient whose chest radiograph is abnormal, suggesting disseminated tuberculosis, and whose sputum yields negative results, bronchoscopy with lavage and biopsy should be performed. Other potential sites for biopsy include liver and bone marrow; biopsy of either of these sites has a 70%–80% likelihood of detecting granulomas but only a 25%–40% chance of providing bacteriologic confirmation [40]. Urine is easy to obtain and may give a positive result in up to 25% of cases of disseminated tuberculosis. Selection of other potential sources of diagnostic material should be guided by specific findings in the individual patient.

(6) Osteoarticular tuberculosis. A diagnosis of osteoarticular tuberculosis may be confirmed by aspiration of joint fluid or of para-articular abscesses or by biopsy of bone or synovium with histologic and microbiological evaluation of the material obtained. Acid-fast stains of joint fluid are positive in 20%–25% of the cases examined, and M. tuberculosis is isolated in ~60%–80% [41]. Biopsies of synovium or bone have a higher yield and permit histologic examination as well. The detection of granulomatous inflammation, even in the absence of bacteriologic proof of the diagnosis, is a sufficient basis on which to begin therapy for tuberculosis unless another etiology is found.

(7) Tuberculous meningitis. Acid-fast organisms are seen on smears of CSF in only 10%–20% of cases of tuberculous meningitis, and the rate of culture positivity varies from 55% to 80% [42]. A substantial number of patients with tuberculous meningitis have M. tuberculosis isolated from other sites.
In conjunction with compatible CSF findings (e.g., lymphocytosis, elevated protein concentration, and hypoglycorrhachia), isolation of *M. tuberculosis* from any site is sufficient to diagnose tuberculous meningitis.

(8) *Peritoneal tuberculosis*. In peritoneal tuberculosis, acid-fast organisms are rarely seen on smears of peritoneal fluid and cultures are positive in only ~50% of cases. In one study, however, 1 liter of fluid was submitted for culture and *M. tuberculosis* was isolated from this fluid in 83% of ultimately proven cases [43]. Because of the generally low yield from cultures of peritoneal fluid, biopsy under laparoscopic guidance is often necessary to confirm the diagnosis.

(9) *Tuberculous pericarditis*. Tubercle bacilli can be identified in pericardial fluid (by smear and culture combined) in ~25%-30% of cases of tuberculous pericarditis. Biopsy of the pericardium, with both histologic and bacteriologic evaluation, is much more likely to provide a diagnosis, although a nonspecific histologic pattern and failure to recover the organism do not exclude a tuberculous etiology [44].

(b) Laboratory Procedures

Most laboratories should be able to detect acid-fast organisms by microscopic examination of clinical specimens. The complexity of the laboratory tests performed and the degree of expertise available to correctly identify this unique group of organisms will vary, depending on the level at which the laboratory service is rated. In addition, the majority of laboratories should be able to process specimens, culture them for mycobacteria, identify mycobacteria to the species level, and undertake studies of drug susceptibility.

(1) Detection and quantification of mycobacteria. Mycobacteria are unique because of the high lipid content in their cell membrane. Two basic staining methods can be employed for the detection of mycobacteria. In the classic staining method, carbol-fuchsin is the staining agent and the Ziehl-Neelsen or Kinyoun procedure is used [33]. Specimens stained by either of these two procedures must be examined under oil immersion with a standard bright-light microscope. Fluorochrome techniques use auramine-o as the staining agent, are equivalent to carbol-fuchsin procedures, and require a fluorescent microscope for examination. However, slides can be read more rapidly than by the classic method because a lower magnification can be used. It is suggested that all positive fluorochrome slides be overstained with carboxyl fuchsin to confirm the presence of acid-fast bacilli.

Several available quantitative-scaling systems can be employed to report the number of acid-fast bacilli observed in stained smears. A semiquantitative scoring method should be used when at least three bacilli are observed per slide. If only one or two bacilli are seen in a slide, the result should be reported as “none seen,” but the slide should be viewed as suspicious and another sample should be analyzed if extra material is available.

Proper microscopic examination for mycobacteria and proper interpretation of results require the close attention of experienced laboratory personnel. In general, the percentage of acid-fast smears interpreted as positive is higher if the specimen is first digested and centrifuged and the sediment stained. Careful consideration should be given to the interpretation of stained slides to differentiate artifacts from bacilli.

For optimal recovery of mycobacteria, several points must be considered before a specimen is cultured. The potentially low numbers of mycobacteria present in a clinical specimen necessitate the use of special procedures that will reduce bacterial contamination and enhance mycobacterial recovery. Specimens normally contaminated with bacteria should be digested, decontaminated, and concentrated before being inoculated into culture media. Several reagents, including N-acetyl cysteine and sodium hydroxide, quaternary ammonium compounds, and trisodium phosphate, can be used to digest and decontaminate clinical specimens. The timing of the decontamination process is critical not only for the adequate killing of contaminating bacteria but also for minimization of the killing of mycobacteria. Specimens that are aseptically collected from normally sterile body sites need not be decontaminated. However, they may need to be digested, minced, or concentrated.

(2) Growth of mycobacteria. It is generally recommended that two types of selective media be inoculated, preferably one that is egg based (such as Lowenstein-Jensen) and one that is agar based (such as Middlebrook-Cohn 7H10 or 7H11). Egg-based media are generally regarded as the reference standard and may yield a greater number of positive cultures, whereas agar-based media may permit earlier detection of mycobacterial growth.

Liquid medium, such as Middlebrook 7H9 or 7H12, may also facilitate the recovery of mycobacteria. Middlebrook 7H12 incorporates 14C-labeled palmitic acid; 14CO2 is liberated when the mycobacteria actively metabolize the palmitic acid. This radiometric detection method can reduce to 7–10 days the time it takes to detect mycobacteria in culture [45].

Optimal environmental conditions for the growth of mycobacteria include 5%-10% carbon dioxide and a temperature of 35°C–37°C. One tube of medium should be placed in a black jacket and kept in the dark for the entire incubation period. Cultures of samples from superficial sources, such as skin lesions, should also be incubated at 25°C–28°C to detect *Mycobacterium marinum* (a possible cause of ulcerative lesions of the skin) and other cool-growing mycobacteria. Cultures should be examined twice weekly for mycobacteria. Once growth has been detected, the tube in the black jacket should be exposed to light and observed for the production of a yellow-orange pigment characteristic of the photochro-
mogenic organisms (e.g., Mycobacterium kansasii). Pigment production without exposure to light is suggestive of the sco-tochromogenic mycobacteria (e.g., Mycobacterium gordonae).

The time it takes for the initial growth of the organism should be recorded. Rapidly growing mycobacteria generally appear within 7 days, while slow-growing mycobacteria may take as long as 6 weeks. Only rarely do colonies first appear after 6 weeks of incubation. Cultures showing no growth at 6 weeks should be reported as negative, although they generally should be held for an additional 2–4 weeks before being discarded.

(3) Identification of mycobacterial species. Many of the mycobacterial species can be placed into the appropriate Runyon group by observation of the rate of growth, pigment production, and colonial morphology on solid media. However, for the correct identification of mycobacteria to the species level, laboratories must be capable of performing the complex biochemical tests pivotal in differentiating nontuberculous bacilli from Mycobacterium tuberculosis [46]. Along with identification of the morphological characteristics mentioned above, findings in niacin, nitrate, and 68°C catalase tests are critical. In addition to biochemical tests, DNA probes are currently available for the identification of Mycobacterium tuberculosis, the Mycobacterium avium complex, and Mycobacterium gordonae.

Preliminary data suggest that the polymerase chain reaction may prove more rapid, sensitive, and specific for identifying Mycobacterium tuberculosis in clinical specimens [47, 48]. Such techniques may become standard diagnostic tests in the future, at least in industrialized countries [49].

(4) Drug susceptibility testing. Drug susceptibility patterns are of considerable clinical importance in the treatment of newly diagnosed tuberculosis as well as recurrent disease [50]. Of the several techniques that can be employed for the evaluation of drug resistance, the indirect proportion agar method is most commonly used in the United States and Canada [51]. This technique involves isolation and subculture of the organism before its inoculation into drug-free media and into medium containing appropriate concentrations of antimycobacterial agents, with use of one or more dilutions of the subculture. The media are then incubated at 37°C in 5%–10% carbon dioxide and read weekly for 3 weeks. The control plate (drug-free medium) should contain 50–200 individual mycobacterial colonies, to which the number of colonies on drug-containing medium should be compared. The population of organisms is considered resistant when the number of colonies on drug-containing medium is >1% of the number on drug-free medium. Isolates of M. tuberculosis should be tested with the primary antimycobacterial drugs: isoniazid, streptomycin, ethambutol, rifampin, and pyrazinamide. Secondary drugs, such as capreomycin, p-aminosalicylic acid, cycloserine, ethionamide, and kanamycin, are usually evaluated at reference laboratories. The concentration of the drug tested will vary with the type of medium used.

The second agar dilution method that can be employed is direct susceptibility testing. This method is used as soon as a clinical specimen is found to be positive by microscopy rather than after the organism has grown and been subcultured. It is not as precise as the indirect method and is subject to potential bacterial contamination, but it can provide susceptibility results 3–6 weeks earlier than the indirect proportion agar method.

Susceptibility testing can also be performed in liquid medium, with MICs calculated for established and experimental drugs. Radioactively labeled liquid medium can be used to evaluate drug susceptibility patterns, with assessment of the ability of mycobacteria to metabolize 14CO2 released from the drug-containing medium. For M. tuberculosis the radiometric and standard methods have correlated >95% of the time in tests with the primary antimycobacterial drugs [52]. However, problems have been encountered with both intra- and interlaboratory reproducibility.

II. CLINICAL DEFINITIONS OF THE DISEASE

A. General Definitions

Infection with M. tuberculosis is defined by a cutaneous reaction to 5 tuberculin units of purified protein derivative. The reaction size that separates positive from negative tests depends in part on the clinical circumstances under which the test is performed [53]. For individuals who have recently been exposed to a person with infectious tuberculosis or for those who may be immunosuppressed, an area of induration >5 mm in diameter indicates infection. In the screening of general (low-risk) populations, induration with a diameter of 15 mm is defined as positive.

Tuberculosis is defined as a clinically detectable infection of tissue with M. tuberculosis and is confirmed by isolation of the organism from appropriate specimens (as described in section I.C.2). However, in some cases, bacteriologic confirmation cannot be obtained and the diagnosis is based on compatible clinical and histologic findings and a favorable response to antimycobacterial therapy.

A culture positive for M. tuberculosis is obtainable in a minority of cases of tuberculous disease in children. In the absence of a positive culture, diagnosis of extrapulmonary tuberculosis can be particularly problematic. For example, cervical adenitis due to either M. tuberculosis or the M. avium complex can be associated with a positive tuberculin skin test, caseating granulomas in a histologic specimen, and indolent, nontender lymph-node enlargement.

B. Minimal Diagnostic Criteria for Inclusion

Ideally, all patients included in clinical trials of chemotherapy for tuberculosis should have cultures positive for M. tu-
berculosis. If bacteriologic confirmation cannot be obtained, the minimal diagnostic criteria for adults are (1) a positive tuberculin skin test (as defined in section II.A); (2) compatible histologic findings (i.e., granulomas on biopsy) or compatible findings on analysis of body fluids (e.g., lymphocytic, exudative pleural fluid); and (3) lack of an alternative diagnosis. For children with presumed pulmonary tuberculosis, the minimal diagnostic criteria for inclusion in clinical trials are (1) a positive tuberculin skin test; (2) identification of a possible source case of contagious tuberculosis (if possible); and (3) lack of an alternative diagnosis. For children with presumed extrapulmonary tuberculosis, a culture positive for *M. tuberculosis* is essential.

For inclusion in trials of prophylaxis for tuberculosis, adults and children must have a positive tuberculin skin test and must not have current (active) tuberculosis.

III. INFORMATION NEEDED BEFORE CONDUCTING CLINICAL TRIALS

A. In Vitro Studies

See General Guidelines, section II.D. For in vitro susceptibility testing of *M. tuberculosis*, several specific studies are recommended: (1) evaluation of the study drug—alone and in combination with currently used drugs—by agar and/or broth dilution susceptibility studies, with testing at pH 5.6 or 5.8 in addition to pH 6.6 (since the pH in the intracellular environment of the normal macrophage is likely to be in this range or lower); (2) evaluation of mycobactericidal activity in cultured *M. tuberculosis*-infected human and/or animal macrophages; and (3) estimation of the frequency of emergence of resistant organisms.

B. In Vivo Studies

See General Guidelines, section II.E. In addition, the following specific studies are recommended: (1) examination for potential interactions between new and previously available antituberculosis drugs, between combinations of new drugs, and between new drugs and other classes of agents; (2) determination of effects of the drug on the microbial flora of various mucosal surfaces (particularly bowel and oral flora); (3) determination of the potential for development of resistance of mycobacteria and of normal flora; (4) comparison of the activity of standard drugs (isoniazid, rifampin, pyrazinamide, ethambutol, and streptomycin) with that of the new agent in an animal model; (5) comparison of the activity of the new agent in combination with one of the standard drugs to the activity of the current best regimen (i.e., isoniazid and rifampin) in an animal model; (6) characterization of antimicrobial effects as bacteriostatic or bactericidal; (7) assessment of possible synergistic combinations; and (8) assessment of long-term effects of treatment, as measured by rates of survival and relapse.

IV. QUALIFICATIONS OF INVESTIGATORS AND INSTITUTIONS

A. Investigators

See General Guidelines, section VII.

B. Institutions

See section I.C.2.b of this guideline. The institution should have a microbiology laboratory that participates in an ongoing program of quality improvement and that can perform the following tests: (1) culture of any clinically appropriate specimen for mycobacteria; (2) speciation of mycobacteria; and (3) determination of mycobacterial susceptibility to isoniazid, rifampin, ethambutol, and streptomycin. Moreover, the institution must have access to a laboratory capable of determining susceptibility to pyrazinamide.

Alternatively, a single laboratory may process samples referred from participating centers. This laboratory should be certified by recognized authorities and should employ personnel skilled in the procedures to be undertaken.

The institution should have all of the facilities required to care for patients with tuberculosis, including (1) diagnostic radiology services; (2) certified biological chemistry and hematology laboratories that participate in an ongoing program of quality improvement; (3) facilities and trained personnel for the care of both inpatients and outpatients; and (4) experience in providing chemotherapy for tuberculosis with established rates of compliance consistent with the requirements of the protocol.

Clinical trials evaluating chemotherapy and prevention of tuberculosis may be conducted outside the United States by either U.S. or foreign investigators. Data from such trials should conform to the standards defined in the General Guidelines, section XV.

V. DESIGN AND IMPLEMENTATION OF PHASE 1, 2, AND 3 CLINICAL TRIALS

See General Guidelines, section III.

VI. ELEMENTS TO BE CONSIDERED IN DESIGNING PHASE 2 AND 3 CLINICAL TRIALS

A. Demographic Characteristics of the Study Population

Groups included in the study of new antituberculosis drugs ultimately should be as broadly representative of the population with tuberculosis and tuberculous infection as possible. However, before fully representative cohorts are de-
veloped, early phase 2 studies limited to adults should be performed.

B. Inclusion and Exclusion Criteria

1. Inclusion Criteria

   Phase 2 studies should include patients who (a) have bacteriologically confirmed tuberculosis; (b) are not identifiable immunocompromised; (c) do not have significant underlying diseases that would interfere with the assessment of outcome; and (d) are judged willing and able to comply with the study protocol.

   Phase 3 studies should include representative cohorts, such as adults, children, and patients with bacteriologically proven tuberculosis, presumptive tuberculosis, pulmonary disease, or extrapulmonary disease.

   Cohorts should be stratified as described in section VI.D of this guideline.

2. Exclusion Criteria

   The criteria for exclusion from phase 2 studies are (a) pregnancy; (b) organ system dysfunction that might place the patient at increased risk for adverse drug reactions; and (c) use of other drugs that might interact with the study or comparison drug to cause toxicity. Patients with tuberculosis caused by drug-resistant organisms may be included or excluded, according to the individual study protocol.

   For Phase 3 studies, exclusions should be minimal and should depend on toxicity demonstrated in preclinical and clinical trials.

   In studies of prophylaxis, a similarly representative cohort composed of persons whose cases meet the definition for tuberculous infection should be established. Prophylaxis should be studied only after preliminary evidence of efficacy has been obtained.

C. Selection of the Comparison Drug

   Ideally, patients in studies of new antituberculosis regimens should be randomized to receive either the study regimen or a comparison (control) regimen. At least in North America, the comparison regimen should generally be one that is recommended by the ATS and the CDC [19]. The choice of this regimen should be reviewed with and approved by the U.S. Food and Drug Administration before the initiation of clinical trials. The current recommendations for a control regimen are standard doses of isoniazid and rifampin for 6 months supplemented by pyrazinamide during the initial 2 months. Depending upon rates of primary resistance to isoniazid, ethambutol may be substituted for isoniazid until the results of susceptibility tests become available. The administration of the drugs should be as closely supervised as possible, preferably with direct observation.

   For certain groups of patients with tuberculosis, numbers will be insufficient for the use of a concurrent control. One such group is children. In these instances historical controls from published studies may be used. Treatment of tuberculosis under study conditions should result in a rate of bacteriologically confirmed eradication of at least 95%. Should the level of efficacy of the new regimen be lower than expected, the sponsor and investigators should consider either abandoning the trial or modifying the regimen.

   For studies of prophylaxis, the comparison regimen should also be recommended by the ATS and the CDC. Currently, the recommended regimen is isoniazid given for 6–12 months (see section I.B.1).

D. Study Design and Stratification

   Placebo-controlled trials of the treatment or prevention of tuberculosis are not ethical. Studies of prophylaxis should always include a standard active-control regimen. Randomized studies preferably should use a double-blind design. If this design cannot be used, a blinded evaluator should assess outcome.

   In clinical trials evaluating new options for treatment, single new agents should always be administered with at least one other antituberculosis drug. The goal of such studies might be to show that the new drug is equivalent to either isoniazid or rifampin as part of a multidrug regimen and/or that the addition of a new drug to a regimen shortens the necessary course, reduces toxicity, or improves compliance in comparison with the standard control. The goals of studies of prophylaxis may be similar.

   For data analysis, study cohorts may be stratified (post hoc) according to age (see General Guidelines, section VI); with additional categories defined if sufficient patients are enrolled; type of tuberculosis (e.g., pulmonary versus extrapulmonary); intrathoracic adenopathy only versus other sites of infection (children); immune status; susceptibility/resistance to isoniazid; or degree of compliance (with compliance defined as >80% of medication taken).

E. Administration of the Study Drug

   In general, any new drug studied should be available in a form that can be administered to outpatients so that hospitalization is not required. One exception may be new regimens designed to treat organisms resistant to multiple drugs; another may be a parenteral drug evaluated for use by severely ill patients.
F. Modification During the Study

The addition or discontinuation of any agent with antituberculosis activity will affect the outcome of treatment and will constitute a modification of the protocol; thus treatment with the initial regimen will be considered to have failed. The patients involved may continue to participate in the study but will be analyzed separately. In general, single drugs should not be added to a regimen that has failed; however, a single new drug may be substituted for a drug to which the patient has reacted adversely.

Experimental protocols should provide contingency plans for alternative forms of therapy in case of clinical or microbiological failure or serious adverse reactions requiring the termination of one or more drugs.

G. Definitions of Response to Therapy

1. General Considerations

Experimental protocols for the treatment of tuberculosis should include microbiological, clinical, and radiographic or other laboratory markers by which the response to therapy can be assessed. Pulmonary tuberculosis, which can readily be monitored by serial sputum cultures, renal tuberculosis, which can be followed by serial urine cultures, are most easily and appropriately assessed by microbiological methods. Thus microbiological outcome is paramount. Other forms of extrapulmonary tuberculosis do not have such readily accessible sites for sampling and microbiological monitoring. In such cases, clinical, radiographic, or other lab may be used to determine response, and clinical outcome is oratory studies paramount unless there is evidence of microbiological failure (i.e., persistence or relapse).

In general, because the great majority of cases of tuberculosis are pulmonary and the response to therapy in such cases can be measured objectively, clinicians have extrapolated the results of treatment for pulmonary tuberculosis to the treatment of extrapulmonary disease, in which numbers of mycobacteria are usually lower. This practice appears to have been acceptable. Certain forms of extrapulmonary disease, such as CNS tuberculosis (wherein the blood-brain barrier may alter drug penetration or availability), vertebral tuberculosis (wherein adjunctive surgical procedures have been performed so frequently that it is difficult to assess the role of drugs alone), and disseminated disease in severely immunodefi cient hosts (wherein defective cellular immunity may allow persistence or recrudescence of infection), should be evaluated by site-specific microbiological and clinical criteria.

2. Pulmonary Tuberculosis

For pulmonary tuberculosis, sputum culture is the principal means of assessing the response to treatment. Sputum samples should be collected at regular intervals defined in the protocol. Sputum smear microscopy is another method of evaluating the response to therapy. Because of delays in the reporting of culture results, it may be clinically useful to monitor trends in semiquantitative microscopy findings. Although such data should be recorded, however, they are not reliable indicators of response to or failure of treatment. Results of sputum cultures are paramount in defining response to therapy and outcome.

During therapy sets of at least three sputum specimens should be collected at monthly intervals or more frequently until at least two consecutive series of cultures are negative. If a culture is positive in the fourth month or later, drug susceptibility should be determined. After termination of therapy, specimens should be collected at least bi-monthly for the first 6 months. Thereafter, specimens should be obtained every 3–6 months until 12–24 months have elapsed.

In ~ 75%–80% of cases of drug-susceptible pulmonary tuberculosis, sputum cultures convert to negative after 3 months of therapy with isoniazid plus rifampin: sputum cultures become negative after 4 months in > 95% of cases [19]. For chemotherapy to be considered microbiologically active, at least two consecutive series of sputum cultures (three samples each) obtained 1 month apart must yield no growth of mycobacteria. With a 6-month regimen, sputum cultures should not be positive beyond the fourth month. If shorter courses of therapy are being evaluated, a shorter interval between specimen collections (e.g., 2 weeks) may be appropriate.

Some adult patients with an apparently successful response to therapy will shed fewer than five colonies of M. tuberculosis in late-therapy or posttherapy specimens. If not associated with clinical or radiographic deterioration and if followed by negative specimens, this finding is not generally regarded as an indication of microbiological failure or relapse.

Failure of treatment is defined as the persistence or recurrence of positive sputum cultures (with or without worsening of symptoms or radiographic deterioration) during chemotherapy. Relapse is defined as substantial mycobacterial growth from one or more sputum specimens or scanty growth from three or more specimens collected at different times (with or without worsening of symptoms or radiographic deterioration) after sputum conversion has taken place.

Clinical evaluation of the response to chemotherapy for tuberculosis is generally secondary to bacteriologic assessment unless no material is obtainable for culture or the risks associated with collection of a sample exceed the potential benefit of microbiological documentation. The wide variety of clinical manifestations of pulmonary tuberculosis include fever, chills, diaphoresis, malaise, cough, phlegm, hemoptysis, dyspnea, weight loss, and chest pain, all of which are
nonspecific. If due to tuberculosis, these symptoms usually resolve with successful therapy. However, because there is such variation among initial clinical presentations and responses to treatment, clinical markers are neither sufficiently objective nor adequately reproducible to be of value in assessing the response to therapy for pulmonary tuberculosis. The results of pretreatment chest radiography should be reported and the extent of disease quantified in terms of estimated percentage of lung involved and presence or absence of cavitation. During the first 2 months of therapy, chest radiographic abnormalities may become more pronounced despite successful chemotherapy. There often is little correlation between the microbiological or clinical response to treatment and the findings on serial chest radiographs. Hence, routine chest radiography is not useful for determination of the early response to treatment in adults with pulmonary tuberculosis.

3. Extrapulmonary Tuberculosis

For extrapulmonary tuberculosis, clinical, radiographic, and fluid analyses—although less precise—may substitute for microbiological evaluations. The types and frequencies of these assessments must be specified in the study protocol and should be specific to the sites of disease included in the study.

4. Tuberculosis in Children

Because children with pulmonary tuberculosis are often asymptomatic, the only reasonable criterion of efficacy is resolution of radiographic findings. An increasingly abnormal chest radiograph in the first 2 months of therapy should not be judged as representing failure unless the patient’s clinical status deteriorates. In general, chest radiographs should be obtained at diagnosis, 1 month after therapy is started, and every 2–3 months thereafter. These films should be evaluated by a radiologist or a clinician experienced in pediatric tuberculosis who is blinded to treatment. With conventional therapy it may take 2–3 years for the chest radiograph to return to normal. Thus a normal chest film is not a necessary criterion for discontinuation of therapy. If the child can produce sputum, respiratory cultures may be monitored, as they are in adults. However, follow-up gastric or pulmonary-aspirate cultures should not be required by the study protocol.

For extrapulmonary tuberculosis in children, monitoring of clinical manifestations, supplemented by appropriate laboratory monitoring, should be used to evaluate the response to therapy. For CNS tuberculosis, follow-up examinations of CSF and serial computed tomography may be useful but should not be protocol requirements.

5. Prophylaxis

The success of prophylaxis for disease due to \textit{M. tuberculosis} may be measured in terms of both incidence and severity. The emergence of drug resistance among patients receiving prophylaxis and developing infection indicates the failure of prophylaxis.

Because of differences in the degree of penetration of drugs into various tissues or body compartments, it is possible that different chemotherapeutic agents or combinations confer different amounts of protection against tuberculosis at different sites. For instance, a preventive intervention might result in a clinically significant reduction of CNS, vertebral, or disseminated tuberculosis but not in an overall lower incidence of tuberculosis in the treated group; this outcome could be defined in the protocol as indicative of efficacy.

6. Follow-Up

Because the incidence of active disease due to \textit{M. tuberculosis} is virtually impossible to predict in any given population, it is imperative that patients be randomly assigned to an active control regimen—generally, isoniazid for 6–12 months. Also, because tuberculous infection may remain latent for many years, it is important that both control and treatment groups be followed for a sufficient period to demonstrate differences in attack rates and to determine whether these differences persist. Populations not infected with the human immunodeficiency virus (HIV) require a longer period of follow-up than populations infected with HIV. For nonimmunosuppressed persons the minimal follow-up period ideally should be 5 years; in the presence of HIV infection, 2–3 years may be sufficient. However, dropout rates often preclude long-term follow-up. The protocol should specify the period of follow-up and time of final evaluation. Study protocols also should specify how patients will be followed, with particular reference to methods of detecting extrapulmonary tuberculosis.

H. Methods of Assessing Safety

See General Guidelines, section XIV. Because participants in protocols for the treatment or prevention of tuberculosis must take two or more medications, adverse reactions or drug interactions must be carefully monitored. Many organ systems may be affected. The adverse reactions warranting special attention are (1) hepatitis (elevation of values in biochemical tests of liver function by at least threefold above the upper limits of normal [alanine and aspartate aminotransferases, alkaline phosphatase, and bilirubin]); symptoms suggestive of or compatible with liver damage, including anorexia, nausea, vomiting, malaise, or right-upper-quadrant tenderness; exclusion of other causes for these phenomena.
including viral infections, gallbladder or pancreatic disease, other infiltrative or infectious diseases of the liver, and use of nonprotocol medications; (2) neurological dysfunction (detected by routine monitoring of peripheral sensory neuropathies associated with diminished touch, vibration, or proprioception in all patients and by monitoring of eighth-cranial-nerve function in all those receiving aminoglycoside, polypeptide, or aminocyclitol injectable antibiotics); (3) rheumatological disease (detected by monitoring for arthralgia [aching or stiff joints] and arthritis [objectively inflamed joints] at each visit; routine monitoring of serum levels of uric acid; and determination of serum titers of rheumatoid factor and antinuclear antibody in patients with rheumatological complaints); (4) renal disease; (5) hematologic disease; (6) ocular disturbances; (7) allergy/hypersensitivity; (8) gastrointestinal disease; and (9) cardiovascular disease.

Patients undergoing chemotherapy for mycobacterial infections should also be monitored for pulmonary superinfection, superficial (mucosal-surface) candidiasis, and drug interactions. The severity of adverse drug reactions should be noted by the investigators (see General Guidelines, section XIV.C).

I. Methods of Presenting and Analyzing Data

See General Guidelines, section XVI and appendix. For most studies of antituberculosis drugs, two analyses should be done. The first analysis should include all study-eligible patients (i.e., an intent-to-treat analysis), with all available data included. The second should include all patients who complete therapy and are followed for the period prescribed by the study protocol.

Important outcome variables are time to bacteriologic conversion of sputum, rate of treatment failure, frequency and severity of adverse drug reactions, and incidence of relapse. In univariate analyses the most important variable is the assigned treatment regimen. While randomization may minimize biases that can affect outcomes, multivariate analyses should be performed and should include other variables that may affect outcome, such as age, sex, race/ethnic background, marital status, associated medical conditions, substance abuse, and extent and severity of tuberculosis disease.

In most trials, the lowest-frequency event of primary concern is bacteriologic relapse during a specified follow-up period, generally a minimum of 2 years after the completion of therapy. The estimated rate of relapse for the control regimen should be based on results of controlled clinical trials reported in peer-reviewed medical journals. The maximum acceptable rate of relapse in the study regimen within 24 months is 5%. Losses during the study (e.g., because of noncompliance, dropping out, adverse drug reactions, or treatment failure) must be considered in the determination of sample size. In recent studies in the United States, these losses have been considerable [12].

In studies of prophylaxis, the event of primary interest is the occurrence of tuberculosis during the follow-up period, and it is appropriate to demonstrate clinical equivalence between the control and study regimens. For control groups receiving isoniazid, it is reasonable to estimate efficacy at 67%.

J. Methods of Assuring Compliance or Ethical Conduct

Compliance may be fostered by a number of methods. The most certain is direct observation of drug administration, which is facilitated by an intermittent (e.g., twice-weekly) program of drug administration. Even with directly administered therapy, patients must come to a clinic or an agreed-upon meeting place. Protocols must describe how compliance will be addressed and provide satisfactory plans for managing poorly compliant patients. For further discussion, see General Guidelines, sections IV and XI.E.

VII. INFORMED CONSENT

See General Guidelines, section IV.D.

VIII. SUMMARY OF THE GUIDELINE

A. Baseline Assessment

Assessment at baseline should include the following: (1) culture of samples from appropriate sites; (2) a history and physical examination; (3) initial laboratory screening for the documentation of disease and the collection of baseline safety data (including complete blood count with differential, platelet count; serum electrolytes, blood urea nitrogen, and/or serum creatinine; liver enzymes; serum uric acid; coagulation parameters [prothrombin time, partial thromboplastin time]; radiographs appropriate to suspected site(s) of infection; and other radiological studies as warranted [computed tomography, magnetic resonance imaging, and contrast studies]); (4) complete neurological examination; and (5) objective determination of visual acuity.

B. Assessment During Therapy

In general, the frequency of follow-up depends on the type of disease being treated, the severity of organ dysfunction (established by baseline laboratory studies), and the suspected rate and degree of toxicity associated with the study drug. Essentially all of the baseline assessment parameters should be reassessed unless otherwise specified in the protocol.
C. Assessment at Completion of Therapy and During Follow-Up

The baseline assessment should be repeated. Patients should be followed for 12–24 months after completion of therapy. In general, microbiological outcome is paramount. The timing of the final assessment of clinical and microbiological outcome must be specified in the protocol.

References


44. Harvey AM, Whitehill MR. Tuberculous pericarditis. Medicine (Baltimore) 1937;16:45-94.


