

procedures [70]. For patients who develop IRIS, prednisone may be given at a dose of 1.25 mg/kg/day (50–80 mg/day) for 2–4 weeks, with tapering over a period of 6–12 weeks or longer.

Tuberculous Pericarditis

Based on small studies that have shown mortality and morbidity benefits [71–73], corticosteroids have previously been universally recommended in combination with a standard 6-month regimen (Table 2) for treating tuberculosis pericarditis; however, a recent placebo-controlled randomized clinical trial with 1400 participants did not find a difference in the combined primary endpoint of the trial, which included mortality, cardiac tamponade, or constrictive pericarditis, between patients treated with adjunctive corticosteroids vs placebo [74]. A subgroup analysis, however, did suggest a benefit in preventing constrictive pericarditis. Similarly, a systematic review conducted to obtain evidence in support of this guideline did not find a statistically significant benefit in terms of mortality or constrictive pericarditis from the use of corticosteroids [71–75]. Therefore, we suggest that adjunctive corticosteroids should not be used routinely in the treatment of patients with pericardial tuberculosis (see PICO Question 7 and Supplementary Appendix B, Evidence Profile 14). However, selective use of corticosteroids in patients who are at the highest risk for inflammatory complications might be appropriate. Such patients might include those with large pericardial effusions, those with high levels of inflammatory cells or markers in pericardial fluid, or those with early signs of constriction [76].

PICO Question 7: Does the use of adjuvant corticosteroids in tuberculous pericarditis provide mortality and morbidity benefits?

Recommendation 7: We suggest initial adjunctive corticosteroid therapy not be routinely used in patients with tuberculous pericarditis (*conditional recommendation; very low certainty in the evidence*).

Tuberculous Meningitis

Chemotherapy for tuberculous meningitis is initiated with INH, RIF, PZA, and EMB in an initial 2-month phase. After 2 months of 4-drug therapy, for meningitis known or presumed to be caused by susceptible strains, PZA and EMB may be discontinued, and INH and RIF continued for an additional 7–10 months, although the optimal duration of chemotherapy is not defined. Based on expert opinion, repeated lumbar punctures should be considered to monitor changes in cerebrospinal fluid cell count, glucose, and protein, especially early in the course of therapy. In children with tuberculous meningitis, the American Academy of Pediatrics (AAP) lists an initial 4-drug regimen composed of INH, RIF, PZA, and ethionamide, if possible, or an aminoglycoside, followed by 7–10 months of INH and RIF as the preferred regimen [77]. There are no data from controlled trials to guide the selection of EMB vs an injectable or ethionamide as the fourth drug for tuberculosis meningitis [78]. Most societies and experts recommend the use of either an injectable or EMB. For adults, based on expert opinion, our guideline

committee prefers using EMB as the fourth drug in the regimen for tuberculous meningitis.

The role of adjunctive corticosteroid therapy in the treatment of tuberculous meningitis has been reported by numerous studies [79–91], and our updated systematic review found a mortality benefit from the use of adjuvant corticosteroids. Therefore, we recommend adjunctive corticosteroid therapy with dexamethasone or prednisolone tapered over 6–8 weeks for patients with tuberculous meningitis (see PICO Question 8 and Supplementary Appendix B, Evidence Profile 15).

PICO Question 8: Does the use of adjuvant corticosteroids in tuberculous meningitis provide mortality and morbidity benefits?

Recommendation 8: We recommend initial adjunctive corticosteroid therapy with dexamethasone or prednisolone tapered over 6–8 weeks for patients with tuberculous meningitis (*strong recommendation; moderate certainty in the evidence*).

Culture-Negative Pulmonary Tuberculosis in Adults

Failure to isolate *M. tuberculosis* from appropriately collected sputum specimens in persons who, because of clinical or radiographic findings, are suspected of having pulmonary tuberculosis does not exclude a diagnosis of active tuberculosis. Some causes of failure to isolate organisms include low bacillary populations, inadequate sputum specimens, temporal variations in the number of expelled bacilli, overgrowth of cultures with other microorganisms, and errors in specimen processing [92]. Alternative diagnoses must be considered and appropriate diagnostic studies undertaken in patients who appear to have culture-negative tuberculosis. At a minimum, patients suspected of having pulmonary tuberculosis have 2 sputum specimens (using sputum induction with hypertonic saline if necessary) for AFB smears and cultures for mycobacteria or for rapid molecular testing for *M. tuberculosis* as part of the diagnostic evaluation. Other diagnostic procedures, such as bronchoscopy with bronchoalveolar lavage and biopsy, are considered before making a presumptive diagnosis of culture-negative tuberculosis.

Patients who, on the basis of careful clinical and radiographic evaluation, are thought to have pulmonary tuberculosis should have treatment initiated with INH, RIF, PZA, and EMB even when the initial sputum smears are negative. If *M. tuberculosis* is isolated in culture or a rapid molecular test is positive, treatment for active disease is continued for a full, standard 6-month course (Table 2), if appropriate based on drug susceptibility test results. Patients who have negative cultures but who still are presumed to have pulmonary tuberculosis should have thorough clinical and radiographic follow-up after 2–3 months of therapy [93]. If there is clinical or radiographic improvement and no other etiology is identified, treatment should be continued.

The optimum treatment regimens and duration for smear-negative, culture-negative tuberculosis have not been convincingly established. We performed a systematic review that evaluated treatment regimens of varying durations in adult patients with