Severe Tuberculosis

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KEYWORDS

• Tuberculosis • TB • Tuberculous meningitis • Miliary TB • Pediatric TB • Severe TB

KEY POINTS

- The global tuberculosis (TB) pandemic continues despite major advances in human medicine. Severe TB kills and disables people around the world everyday.
- Diagnosis remains one of the greatest challenges in childhood TB. Current diagnostics tend to underperform in paucibacillary disease states seen in children.
- Treatment of children with TB uses the same regimens developed for adults since children are usually excluded from clinical trials of antituberculosis treatment.
- The most severe forms of TB are often the most difficult to diagnose so that death often comes before treatment is considered.

INTRODUCTION

Although tuberculosis (TB) may go unnoticed by the average citizen of a wealthy nation such as the United States, TB continues to cause devastation around the world, particularly among the poor and underserved. While maintaining the dubious distinction as the world's most deadly infectious disease, TB continues to evade typical efforts to control global pandemics through vaccination and prevention due to the unique characteristics of *Mycobacterium tuberculosis* (Mtb). As TB is also one of the oldest human infectious diseases, Mtb has evolved with humans over tens of thousands of years so that it has adapted to a near perfect disease state. Mtb can evade the human immune system, lie dormant for years, and cause a subacute disease process that uses the lungs to spread to other humans. Mtb can cause disease in any part of the human body with an infinite range of clinical manifestations.

Typical TB—consumption—is a pulmonary disease with an onset of weeks that leads to cough, fever, and weight loss that can run the course of months to years with lulls and flares. Ideally, it is diagnosed during the first weeks to months and treatment leads to cure in over 95% of people. The range of disease varies especially by

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Abbreviations	
ART	antiretroviral therapy
Mtb	*Mycobacterium tuberculosis*
LAM	lipoarabinomannan assay
TB	tuberculosis
TBM	tuberculous meningitis
TNF	tumor necrosis factor
TPT	TB preventive therapy

age as well as location. Severe disease is most often seen at the extremes of age with young children being most susceptible. Defining severe disease is subjective, as most who are sick with TB: ill, isolated from their family, and unable to work would describe their disease as severe. In this review, we will define severe TB as the disease states with the highest risk for death and permanent disability.

Meningitis

Epidemiology

Tuberculous meningitis (TBM) is the most feared and deadliest presentation of TB. Before human immunodeficiency virus (HIV), the most important determinant for the development of TBM was age. In populations with high TB prevalence, TBM differs from pulmonary, and other extrapulmonary TB in that the peak age is from 0±4 years.[1] In populations such as the United States with less Mtb transmission, most cases of TBM are in adults. The incidence of TBM has been calculated to represent 1% to 5% of the annual risk of infection.[2,3] Coinfection with HIV is the primary risk factor for the development of extrapulmonary TB, and in particular TBM, a risk that increases as the CD4 cell count declines.[4,5] TBM is the second most common cause of meningitis among HIV-infected adults.[6] The extent to which Bacillus Calmette-Guérin (BCG) vaccination accords protection against TBM is still debated. A meta-analysis of the published trials on the efficacy of BCG vaccination suggested a protective effect of 64% against TBM in young children.[7] Overall, these and other studies support the view that BCG vaccination is protective against TBM in children.[8]

Clinical features

The clinical approach to TBM is challenging because once the diagnosis is clear it may be too late to prevent permanent disability or death. The prodrome is usually nonspecific with no one symptom predominating: 28% reported headache, 25% were vomiting, and 13% had fever.[9] Only 2% reported meningitis symptoms. In a review of 205 children, only 38% had fever at presentation with 9% reporting photophobia.[9] A quarter of children had no meningeal symptoms at all. The duration of presenting symptoms varied from 1 day to 9 months, although 55% presented within 2 weeks of onset. More advanced disease may be just as hard to diagnose. The mean delay to TB treatment was 1 week in a report from a French intensive care unit of 48 TBM cases of whom 65% had a fever, 52% had focal neurologic deficit, and 88% had meningism.[10] The neurologic complications that can occur are legion.[11] Their nature and diversity can be predicted from an understanding of the site of disease and the pathogenesis of TBM. Adhesions can result in cranial nerve palsies (particularly II, III, IV, VI, VII, and VIII), constriction of the internal carotid resulting in stroke, and obstruction of CSF leading to raised intracranial pressure, reduced consciousness level, and hydrocephalus. Hydrocephalus and brain lesions occur in up to 40% of cases, causing a

range of disorders from hemiparesis to movement disorders.[12] Prognosis is best gauged by clinical stage of disease at treatment initiation. Stage 1 is patients who are conscious and alert, stage 2 has moderate disease with lethargy and/or cranial nerve palsies, and stage 3 has advanced disease with coma, paresis, paralysis, or seizures. Once disease progresses beyond stage 1, the risk of death and permanent disability increases drastically.[13]

Management

Current WHO and CDC guidelines recommend treatment of drug-susceptible TBM for the first 2 months with rifampicin, isoniazid, pyrazinamide, and ethambutol followed by a continuation phase of INH and rifampin for a total of 9 to 12 months along with adjunctive corticosteroid treatment over the first 6 to 8 weeks of therapy.[14] A randomized, double-blinded trial of 545 TBM adolescents and adults who received prednisone or placebo demonstrated a significantly reduced mortality in the treated group (32% vs 41%).[15] The benefit was greatest in early-stage disease, and no benefit was seen in stage 3 disease. Raised intracranial pressure has long been considered important in the prognosis of TBM.[11] Neurologic deterioration occurring in a patient under treatment for TBM may have various causes and requires urgent radiological assessment. Rising intracranial pressure requires active management. Hydrocephalus is a common complication that may lead to permanent neurologic damage or death if left untreated. Prompt assessment by CT is of value in both diagnosis and management.[16] Repeated lumbar puncture or external ventricular drainage has been advocated in TBM both preventing and predicting the benefit of shunt surgery.[17] Studies suggest that prompt ventriculoatrial or ventriculoperitoneal shunting improves outcomes, particularly in those who present with minimal neurologic deficits.[18] TBM is a complex, devastating, and clinically challenging disease that often requires extensive resources for ideal management.

Miliary Tuberculosis

Miliary TB is the disseminated form of the disease that occurs when overwhelming numbers of TB bacilli enter the circulation and the immune system is unable to adequately control the infection. It is classically defined by the gross pathologic presentation (**Fig. 1**A–H) and most commonly by the miliary pattern on the chest radiograph—a uniform distribution of densities resembling millet seeds which are the round seeds typically found in bird feed.[19] The term miliary TB is often used to describe disseminated TB and for this discussion, we will use the 2 terms interchangeably.

Epidemiology

While miliary TB may be the presenting disease in a small percentage of immunocompetent persons, the greatest risk for miliary TB is impaired cellular immunity along with several other factors (**Box 1**). Another risk factor, especially in low-incidence countries is increasing age. A retrospective study of 104 TB patients in the Netherlands with a median age of 75 years showed that 14% presented with miliary TB, and mortality rates were over 10 times higher than younger patients less than 65 years.[20]

Clinical features

One cannot properly describe a typical presentation of disseminated TB as the range of clinical presentation is infinite and highly influenced by the characteristics and comorbidities of the patient. The classic presentation is one of a febrile wasting disease over weeks to months.[19] Ultimately, the critical component of the presentation

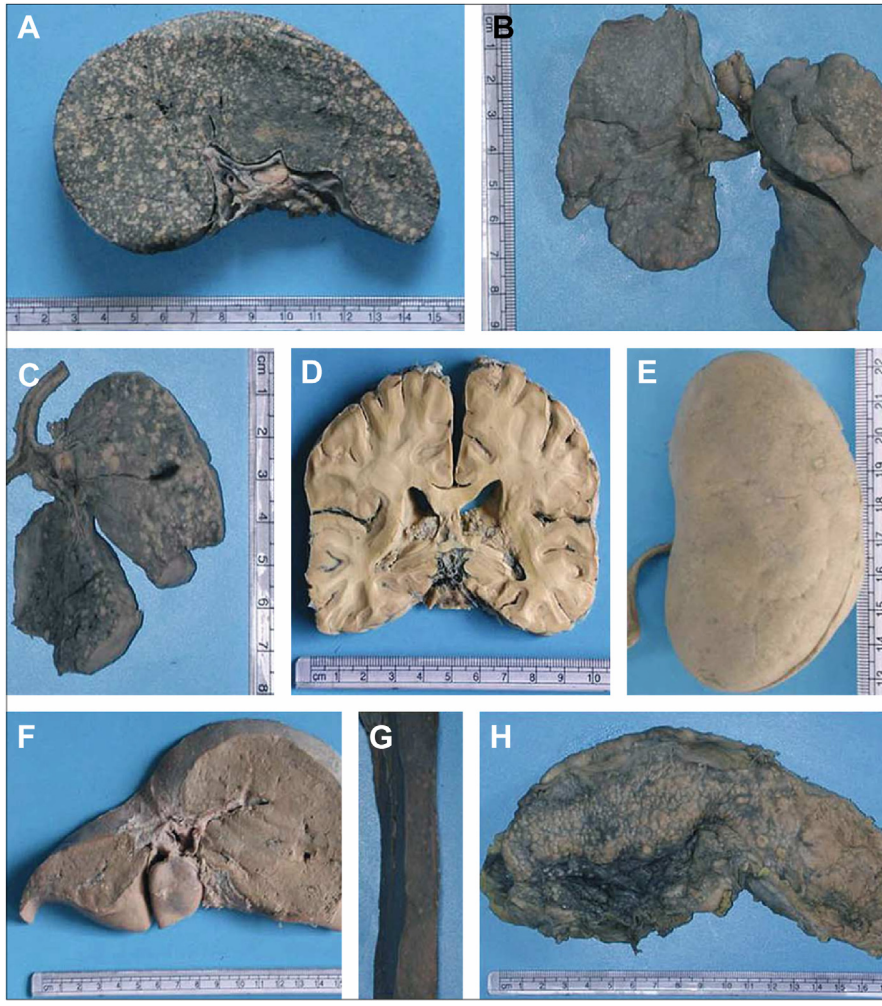

Fig. 1. (*A*) Cut surface of spleen, (*B*) pleural surfaces of both lungs, and (*C*) cut surfaces of right ling showing multiple miliary tubercles; some of the coalesced lesions appear larger. (*D*) Brain section showing basal exudates, enlargement of both lateral ventricles, and granulations in the choroid plexus, (*E*) kidney with tubercles seen over the surface. (*F*) Cut section of liver and (*G*) capsular surface of liver showing miliary tubercles. (*H*) Omentum with multiple gray-white lesions of varying size; larger ones show caseation necrosis. (*Reprinted with permission from* Elsevier, The Lancet Infectious Diseases, Jul 2005;5(7):415-30.)

is the clinician's consideration and diagnosis of TB, especially in low-incidence countries where disease is rarely encountered and atypical presentations are often missed.[21,22] Clinicians should be vigilant for clues that would increase the risk for TB such as country of origin, use of medications such as tumor necrosis factor α (TNF) inhibitors as well as other immunomodulators, and comorbidities such as HIV. A critical component of disseminated TB is meningitis which can occur in 10% to 30% of patients. Likewise, approximately 30% of patients presenting with TBM will have miliary TB.[15]

Box 1
Predisposing factors for the development of miliary tuberculosis

- Childhood infections (eg, measles, whooping cough, and acute tonsillitis)
- Malnutrition
- HIV/AIDS
- Alcoholism
- Diabetes mellitus
- Chronic renal failure, dialysis
- Postsurgery (eg, gastrectomy [predisposes to tuberculosis in general])
- Organ transplantation
- Drugs
  Corticosteroids
  Immunosuppressive and cytotoxic drugs
  Immunomodulator drugs (eg, infliximab, etanercept)
- Connective tissue disorderss
- Pregnancy, postpartum
- Underlying malignancy
- Silicosis
- Iatrogenic causes
  Ureteral catheterization (predisposes to tuberculosis in general)
  Extracorporeal shockwave lithotripsy (patient had undiagnosed genitourinary tuberculosis), "laser lithotripsy (patient had undiagnosed genitourinary tuberculosis)"
  Cardiac valve homograft replacement (contamination of homografts probably occurred at the time of harvest from cadavers)
  Intravesical BCG therapy for urinary bladder carcinoma

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Establishing the diagnosis of miliary TB can be challenging as the Mtb is dispersed and at low levels (paucibacillary). The usual diagnostic approach of expectorated sputum collection has low yield, and the approach should be broad and multimodal. According to Rom and Garay's textbook, *Tuberculosis*: "all accessible secretions and body fluids should be examined microscopically and cultured."[13] A typical workup might include some combination of bronchoalveolar lavage, fundoscopic examination, CSF analysis, bone marrow biopsy, other biopsy of affected tissue with limited immediate yields. If the diagnosis is suspected, treatment should be initiated, and cultures of the obtained specimens may yield Mtb. Isolating the organism, even weeks later, is extremely important to allow for drug susceptibility testing and to exclude other etiologies of disease.

Susceptible populations

Disseminated TB can occur weeks after starting TNF treatment with a high risk for death.[23] Screening for Mtb infection prior to starting TNF therapy as well as multiple other immunomodulatory agents has become the standard of care.[24]

Transplantation is a major risk factor for the development of active TB. Solid organ transplant recipients are particularly vulnerable to reactivation of Mtb or infection from the graft itself. Nearly 50% may develop disseminated TB with mortality rates up to

30%.[25] Immunosuppression is the key risk factor, and most cases occur within the first year after transplant when immunosuppression intensity is highest.[25,26] As with other forms of disseminated TB, diagnosis can be difficult and the most important factor is consideration of TB within the differential. Presentation is often subacute with fever and nonspecific symptoms. Diagnosis usually involves tissue sampling via invasive procedures. Treatment is complicated by drug interactions with immunosuppressant agents. Rifamycins are the cornerstone of TB treatment and have major CYP3A4-mediated interactions with calcineurin inhibitors, mammalian target of rapamycin inhibitors, steroids, and mycophenolate mofetil. Rifampin induces the liver enzyme CYP3A4 leading to increased metabolism and lower drug levels of these medications that are critical to prevent transplant rejection.[27] As rifabutin is a weak CYP3A4 inducer, it is often used in the place of rifampin in transplant patients. TB treatment of the transplant patient requires careful coordination between the TB and transplant teams with careful monitoring of drug levels of immunosuppressant medications to prevent transplant rejection.

Worldwide, HIV is the primary risk factor for disseminated TB in persons with advanced HIV and AIDS. Patients often present with nonspecific symptoms and wasting, but with low CD4 counts patients can also be asymptomatic.[28] Classic symptoms of fever and cough are often not present, and chest imaging also is often nonspecific with typical cavitary disease much less common. Diagnosis is challenging as sputum bacilliary load is often low. Alternative diagnostics such as lipoarabinomannan assay (LAM) are emerging.[28,29] LAM is a Mtb antigen that can be detected in the urine of TB patients, and lateral flow lipoarabinomannan assays have been developed as inexpensive point of care tests.[29,30] Treatment of TB in AIDS patients needs to account for drug–drug interactions with antiretroviral therapy (ART) and for HIV infected persons not yet started on ART, timing of starting HIV treatment after TB treatment depends on the CD4 count: within 2 weeks for CD4 less than 50 cells/μL and within 8 to 12 weeks for those with CD4 greater than 50 cells/μL.[14,31] The major exception is for TBM in which case starting HIV treatment should be delayed for 8 weeks after starting TB treatment as earlier treatment can have worse outcomes.[32]

TUBERCULOSIS IN CHILDREN

TB in young children is the most challenging and devastating form of the disease. Children often progress rapidly to severe disease including miliary TB and TBM.[13] Diagnosis is usually limited by a paucibacillary disease presentation in which current diagnostic assays are inadequate. For example, pulmonary disease in young children is characterized by lymph node involvement not lung cavities, young children cannot provide sputum samples and even if they did the low number of Mtb involved would likely not yield the diagnosis.

Epidemiology

In 2022, children (aged < 15 years) accounted for approximately 12% of global TB cases and 214,000 deaths estimated annually.[33] By contrast, children account for 4% of US TB cases.[34] Young children under age 5 years are especially vulnerable to TB, and they often progress to disease after infection. As young children generally do not transmit TB and they must be infected by an adult, rates of TB in young children serve as a marker of the strength of the public health system.[35] In the United States, per CDC recommendations, all active contagious TB cases are investigated by public health authorities.[36] Contacts with exposure to the index case are screened for active TB and undergo TB testing to identify latent Mtb infection. TB preventive therapy (TPT)

is offered and administered for infected contacts, and children are prioritized in this process. As TB in young children is usually caused by recent infection, in an environment with a strong public health system the contact investigation should discover the infected child before disease onset. In the United States, over 80% of TB cases are due to reactivation and TB transmission is less common.[37] Due to resource limitations in most high burden TB countries, contact tracing is not usually performed and childhood TB disease is not prevented, leading to continued high rates of mortality, especially among young children.[35] Hundreds of thousands of children continue to die each year from this preventable illness, which is just a portion of worldwide under-5 mortality that is mostly due to preventable illness and poverty.[38]

Clinical Features

Edith Lincoln would probably be disappointed by our failure to protect the world's children from TB. She studied childhood TB from 1922 to 1956 at Bellevue Hospital in New York City.[39] Through cohort studies, she demonstrated the terrible burden of disease in children and the association of age, demonstrating that 55% of infants under age 6 months died of their TB disease.[40] The introduction of TB chemotherapy made a major impact on mortality and her work was instrumental in the development of chemoprophylaxis and TPT.[41] As most of the world's children do not have access to timely TPT, TB in young children continues to kill infants and toddlers. TB in young children can present in many forms including pulmonary, TBM, and miliary disease. The symptoms are nonspecific such as fever, poor feeding, and weight loss. In the case of miliary and TBM, the disease can progress rapidly and often by the time the diagnosis becomes clear, it is too late to prevent severe disability or death.[35]

Diagnosis remains one of the greatest challenges in childhood TB. Because current diagnostics focus on the isolation of Mtb in culture or PCR, they tend to underperform in paucibacillary disease states seen in children. Additional challenges include children's inability to produce samples—one cannot ask an infant or toddler to produce a sputum sample. There has been an effort to develop new diagnostics that would work in children, especially alternatives to sputum sampling, such as urine, stool, and blood to detect molecular components or biomarkers of TB.[42] One promising diagnostic candidate is a blood-based nanoparticle immunoassay that detects Mtb virulence factors including LAM that could diagnosis TB in 80% of children who remained unconfirmed by the current diagnostic approach.[43]

Treatment of children with TB uses the same regimens developed for adults. Again, great challenges persist as children are usually excluded from clinical trials of antituberculosis treatment. Historically, children have been a low priority in TB clinical development. This is beginning to shift, and there are several trials that focus on children.[44] In general, treatment is similar to adult regimens. A recent study, the Shine trial, demonstrated that in children with nonsevere TB 4 months of treatment was noninferior to 6 months.[45] Notably treatment was carried out using child-friendly formulations, another important distinction when treating children. Further child-focused research and development will be critical to improving outcomes among children with TB.

Despite great advances in diagnosis and treatment, TB continues to kill people in great numbers throughout the world. Unfortunately, the most severe forms of TB are often the most difficult to diagnose so that death often comes before treatment is considered. Developing new diagnostics with capability in the early stages of TBM and disseminated disease will be critical to improving these outcomes.

Ultimately, the key will be in prevention, improving access to care and strengthening public health worldwide, a difficult task but one toward which we should strive.

CLINICS CARE POINTS

- TB Meningitis must be diagnosed and treated early to prevent irreversible neurological deficits.
- Disseminated TB should be considered in immunocompromised patients presenting with unexplained wasting or nonspecific illness.
- Young children are particularly susceptible to develop severe TB and should be prioritized for TB preventive therapy in the setting of contact investigations.

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