Miliary tuberculosis is a potentially lethal form of tuberculosis resulting from massive lymphohaematogeneous dissemination of *Mycobacterium tuberculosis* bacilli. The emergence of the HIV/AIDS pandemic and widespread use of immunosuppressive drugs has changed the epidemiology of miliary tuberculosis. Impaired cell-mediated immunity underlies the disease's development. Clinical manifestations are non-specific and typical chest radiographic findings may not be seen until late in the course of the disease. Atypical presentations—eg, cryptic miliary tuberculosis and acute respiratory distress syndrome—often delay the diagnosis. Several laboratory abnormalities with prognostic and therapeutic implications have been described, including pulmonary function and gas exchange impairment. Isolation of *M. tuberculosis* from sputum, body fluids, or biopsy specimens, application of molecular methods such as PCR, and histopathological examination of tissue biopsy specimens are useful for the confirmation of diagnosis. Although response to first-line antituberculosis drugs is good, evidence regarding optimum duration of treatment is lacking and the role of adjunctive corticosteroid treatment is unclear.

**Introduction**

Tuberculosis is a leading cause of preventable morbidity and mortality due to an infectious agent worldwide.1–3 Primarily, the disease involves the lungs and, at times, distant blood-borne spread results in the development of extrapulmonary tuberculosis such as tuberculosis meningitis and skeletal tuberculosis. Infrequently, intense systemic dissemination from the rupture of a *Mycobacterium tuberculosis*-laden focus into a vascular channel results in a morphologically characteristic form of disease known as miliary tuberculosis.4–6 In 1700, John Jacob Manget coined the term miliary tuberculosis (derived from the Latin word *miliarius*, meaning related to millet seed) to describe the resemblance of gross pathological findings to that of innumerable millet seeds in size and appearance (figure 1).4–6

Several terms—eg, haematogenous tuberculosis, generalised tuberculosis, disseminated tuberculosis, and pulmonary or hepatic miliary tuberculosis—have been variably used in the literature. Diagnosis of miliary tuberculosis requires the presence of a diffuse miliary infiltrate on chest radiograph or high-resolution computed tomography (CT) scan, or evidence of miliary tubercles in multiple organs at laparoscopy, open surgery, or autopsy. The clinical and morbid anatomic picture must be confirmed by mycobacteriology, histopathology, and/or a dramatic chemotherapeutic response.

**Epidemiology**

Population-based studies on the incidence of miliary tuberculosis are not available. Almost all available data are from hospital-based case series or autopsy studies (table 1).3–11 These studies suffer from heavy selection bias. Autopsy studies contain little information regarding miliary tuberculosis in children and frequently include patients with advanced disease or missed diagnosis. These issues make meaningful comparisons difficult, and must be kept in mind while interpreting these data. Miliary tuberculosis accounts for about 1–2% of all cases of tuberculosis and about 8% of all forms of extrapulmonary tuberculosis in immunocompetent individuals. The disease is more frequently encountered in immunosuppressed individuals.25–18

**Demographic characteristics**

In the pre-antibiotic era, miliary tuberculosis was predominantly a disease of infants and children.4–6

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**Figure 1:** Millet seeds are small grains (average diameter <2 mm) that are consumed without their outer layer being removed. Pearl millet (*Pennisetum typhoides*, bajra) is shown here. These grains (inset, upper right) correspond to the approximate size of miliary lesions on the high-resolution computed tomography scan of the chest (inset, lower left)
Reports from the early 1970s indicated increasing occurrence of miliary tuberculosis in adults. In an autopsy study at a hospital in Belfast, UK (1946–49), 54% of patients with miliary tuberculosis were under 20 years of age; subsequently (1966–69) all miliary tuberculosis patients were over 30 years. During 1984–92 in Edinburgh, UK, the mean age of patients with miliary tuberculosis increased from 59·5 to 73·5 years, compared with 1954–67. The HIV/AIDS pandemic and widespread use of immunosuppressive drugs for varied indications have further influenced the incidence of miliary tuberculosis. The modulating effect of BCG vaccination resulting in substantial reduction in miliary tuberculosis and tuberculosis meningitis among young vaccinees, increasing use of CT scans, and wider application of invasive diagnostic methods could also have contributed to the demographic shift. Presently two additional peaks are evident—one involving adolescents and young adults and another later in life among elderly people. In children as well as adults, men seem to be more frequently affected by miliary tuberculosis (see webtable 1).

Table 1: Epidemiology of miliary tuberculosis

<table>
<thead>
<tr>
<th>Reference</th>
<th>Years</th>
<th>Country</th>
<th>Study population</th>
<th>Number studied</th>
<th>Frequency of miliary tuberculosis Overall n (%)</th>
<th>Among tuberculosis n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults: autopsy studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lewison</td>
<td>1917–28</td>
<td>USA</td>
<td>Autopsies</td>
<td>8800</td>
<td>96 (1·09)</td>
<td>96/804 (11·9)</td>
</tr>
<tr>
<td>Chapman &amp; al.</td>
<td>1937–41</td>
<td>USA</td>
<td>Autopsies</td>
<td>4066</td>
<td>63 (1·55)</td>
<td>63/310 (20)</td>
</tr>
<tr>
<td>Slavin</td>
<td>1937–48</td>
<td>USA</td>
<td>Autopsies</td>
<td>99</td>
<td>1 (1)</td>
<td>ND</td>
</tr>
<tr>
<td>Slavin</td>
<td>1948–59</td>
<td>USA</td>
<td>In-hospital deaths</td>
<td>144</td>
<td>1 (0·7)</td>
<td>ND</td>
</tr>
<tr>
<td>Slavin</td>
<td>1948–59</td>
<td>USA</td>
<td>Autopsies</td>
<td>205</td>
<td>0 (0)</td>
<td>ND</td>
</tr>
<tr>
<td>Jacques &amp; al.</td>
<td>1946–49</td>
<td>Ireland</td>
<td>Autopsies</td>
<td>237</td>
<td>3 (1·7)</td>
<td>ND</td>
</tr>
<tr>
<td>Jacques &amp; al.</td>
<td>1946–59</td>
<td>Ireland</td>
<td>Autopsies</td>
<td>2700</td>
<td>12 (0·47)</td>
<td>ND</td>
</tr>
<tr>
<td>Vasanakari &amp; al.</td>
<td>1973–93</td>
<td>Finland</td>
<td>Tuberculosis</td>
<td>223</td>
<td>ND</td>
<td>456 (20·4)</td>
</tr>
<tr>
<td>Jagirdar &amp; al.</td>
<td>ND</td>
<td>USA</td>
<td>Autopsies</td>
<td>326</td>
<td>17 (5·2)</td>
<td>17/90 (34)</td>
</tr>
<tr>
<td>Ansari &amp; al.</td>
<td>1997–98</td>
<td>Botswana</td>
<td>Autopsies</td>
<td>1281</td>
<td>17 (13·3)</td>
<td>17/42 (40·5)</td>
</tr>
<tr>
<td>Adults: clinical studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Alvarez &amp; al.</td>
<td>1968–77</td>
<td>USA</td>
<td>All extrapulmonary tuberculosis cases</td>
<td>136</td>
<td>ND</td>
<td>27/136 (20)</td>
</tr>
<tr>
<td>Long &amp; al.</td>
<td>1979–93</td>
<td>Canada</td>
<td>All tuberculosis cases</td>
<td>2013</td>
<td>ND</td>
<td>43/213 (2·1)</td>
</tr>
<tr>
<td>Hussey &amp; al.</td>
<td>1981–89</td>
<td>South Africa</td>
<td>Hospital admissions</td>
<td>12 712</td>
<td>164 (1·3)</td>
<td>ND</td>
</tr>
<tr>
<td>Noertjojo &amp; al.</td>
<td>1996</td>
<td>Hong Kong</td>
<td>All tuberculosis cases</td>
<td>5757</td>
<td>ND</td>
<td>37/5757 (0·64)</td>
</tr>
<tr>
<td>Children: Clinical studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Kim &amp; al.</td>
<td>1960–69</td>
<td>Korea</td>
<td>Hospital admissions</td>
<td>499</td>
<td>85 (1·7)</td>
<td>ND</td>
</tr>
<tr>
<td>Hussey &amp; al.</td>
<td>1981–89</td>
<td>South Africa</td>
<td>Hospital admissions</td>
<td>2460</td>
<td>174 (8·3)</td>
<td>ND</td>
</tr>
<tr>
<td>Udani &amp; al.</td>
<td>1968–71</td>
<td>Mumbai, India</td>
<td>Hospital admissions</td>
<td>1524</td>
<td>59 (3·9)</td>
<td>ND</td>
</tr>
<tr>
<td>Somu &amp; al.</td>
<td>1977–92</td>
<td>Chennai, India</td>
<td>In-hospital deaths</td>
<td>11 588</td>
<td>79 (0·7)</td>
<td>ND</td>
</tr>
<tr>
<td>Gorkan &amp; al.</td>
<td>1990–97</td>
<td>Turkey</td>
<td>Hospital admissions</td>
<td>ND</td>
<td>ND</td>
<td>ND (3·2)</td>
</tr>
<tr>
<td>All age groups: epidemiological studies, public health data</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CDC &amp; al.</td>
<td>1975–90</td>
<td>USA</td>
<td>Reported military tuberculosis cases</td>
<td>Nationwide</td>
<td>5599 (350/year)</td>
<td>ND</td>
</tr>
<tr>
<td>CDC &amp; al.</td>
<td>1969–2002</td>
<td>USA</td>
<td>Reported tuberculosis cases</td>
<td>Nationwide</td>
<td>ND</td>
<td>ND (1·3–2·1)</td>
</tr>
<tr>
<td>CDC &amp; al.</td>
<td>1969–2002</td>
<td>USA</td>
<td>Reported extrapulmonary tuberculosis cases</td>
<td>Nationwide</td>
<td>ND</td>
<td>ND (7·4–10·7)</td>
</tr>
<tr>
<td>RNTCP, India &amp; al.</td>
<td>2000–01</td>
<td>India</td>
<td>All new extrapulmonary tuberculosis cases</td>
<td>2843</td>
<td>ND</td>
<td>11 (0·4)</td>
</tr>
</tbody>
</table>

CDC=Centers for Disease Control and Prevention; ND=not described; RNTCP=Revised National Tuberculosis Control Programme. Data from 11 alternate years were included. 114 (64%) of 33 HIV/tuberculosis co-infected patients had miliary tuberculosis, compared with 3 (11%) of 28 HIV-negative tuberculosis patients who had miliary tuberculosis. 1004 (81%) had HIV infection. 14 (44%) of 32 HIV/tuberculosis co-infected patients had miliary tuberculosis, compared with 3 (11%) of 28 HIV-negative tuberculosis patients who had miliary tuberculosis. 1283 patients had extrapulmonary tuberculosis. From July 2000 to June 2001. Data from 16 districts under the RNTCP; source: Central Tuberculosis Division, Directorate General of Health Services, New Delhi, Ministry of Health and Family Welfare, Government of India.

Pathogenesis

The crucial event in the development of miliary tuberculosis is a massive lymphohaematogenous dissemination of M tuberculosis from a pulmonary or extrapulmonary focus and embolisation to the vascular beds of various organs (figure 2).
simultaneous reactivation of multiple foci in various organs can result in miliary tuberculosis. This reactivation can occur either at the time of primary infection or later during reactivation of a dormant focus. When miliary tuberculosis develops during primary disease (early generalisation), the disease has an acute onset and is rapidly progressive. Late generalisation during post-primary tuberculosis can be rapidly progressive (resulting in acute miliary tuberculosis), episodic, or protracted, leading to chronic miliary tuberculosis. Re-infection also has an important role, especially in highly endemic areas with increased transmission of *M* tuberculosis (figure 2). Uncommonly, congenital tuberculosis can develop by

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**Figure 2: The development of miliary tuberculosis**

Small droplet nuclei (1–5 µm) containing *Mycobacterium tuberculosis* get deposited in the alveoli (1) where host–pathogen interactions occur. 70% of individuals exposed do not get infected (2) whereas 30% develop infection (3). Infection is contained in 90% of those infected (latent tuberculosis infection) (4). The remaining 10% will develop progressive primary tuberculosis (5). During this phase, extensive lymphohaematogenous dissemination (6) to various organs can result in miliary tuberculosis. People with latent tuberculosis infection have a 10% lifetime risk of re-activation of the infection, resulting in post-primary tuberculosis (7). 50% of re-activations occur during the first 2 years of primary infection. By contrast, in HIV-infected individuals with latent tuberculosis infection, the risk of re-activation is enormously high (approximately 10%/year). Massive lymphohaematogenous dissemination during re-activation (8) can also result in miliary tuberculosis (progressive post-primary miliary tuberculosis). In areas with high transmission rates, re-infection with a new strain of *M* tuberculosis (9) can occur and the cycle is repeated. *Important in endemic areas.*

†Organ-restricted tuberculosis with adequate host immunity. MTB=miliary tuberculosis, TB=tuberculosis, TNF=tumour necrosis factor.
haematogenous spread from infected placenta through the umbilical vein or by aspiration of amniotic fluid in utero. Miliary tuberculosis is a common manifestation of congenital tuberculosis in neonates.68 Acquisition of infection during the perinatal period through aspiration and ingestion of infected maternal genital tissues and fluid may rarely lead to the development of miliary tuberculosis in neonates.69

Key concepts in the immunopathogenesis of miliary tuberculosis are summarised in figure 3. In most individuals, inhaled bacilli are engulfed by alveolar macrophages and are contained by efficient microbicidal mechanisms inherent to them—eg, the generation of reactive nitrogen and oxygen intermediates. Initial recognition of pathogen-associated molecular patterns through Toll-like receptors (TLRs) on the surface of macrophages may elicit a robust innate immune response leading to bacillary elimination. TLRs also serve as a bridge between innate and adaptive immunity. TLR-mediated signals influence polarised cytokine production and homing of effector T cells to pathological site(s).
Infected macrophages simultaneously process and present antigens to various T-cell subsets including polarised Th1/Th2 cells (CD4+ and MHC class II-restricted), cytolytic (MHC class I-restricted) T cells, γδ T cells, natural killer T cells (CD1-restricted), and CD4+ CD25+ regulatory T (Treg) cells. Processed peptides, together with interleukin 12 secreted by the infected macrophage, trigger Th1 cells to secrete interleukin 2, interferon γ, and tumour necrosis factor α to further activate the macrophages. Th1 cell activation, which is central to protective immunity, is under the control of other T-cell subsets. Polarised Th2 cells downregulate Th1 cells. Finer subsets of natural killer T cells that recognise mycobacterial lipid antigens in the context of non-polymorphic CD1d impose a cytokine bias on effector T cells by rapid release of Th1 cytokines (interferon γ, interleukin 2, tumour necrosis factor α) or Th2 cytokines (interleukin 4, interleukin 5, interleukin 10). CD4+ CD25+ Treg cells favour Th2 skewing of the effector immune response by diverse mechanisms. Treg cells produce Th2-driving cytokines to augment the Th2 response and also inhibit the negative feedback of Th1 cells on polarised Th2 cells. Moreover, Treg cells exert positive influences on Th2 cells by promoting their proliferation via secretion of specific cytokines such as interleukin 4, interleukin 7, and interleukin 9, as their receptors are preferentially expressed by polarised Th2 cells. CD8+ cytolytic T cells also contribute to the protective immunity in tuberculosis. Cytolytic T cells mediate lysis of infected macrophages and direct lysis of the bacilli through the secretion of granulysin. T cells bearing γδ T-cell receptors also influence Th1/Th2 cells.

The dominant Th1 cytokine bias thus generated, particularly in local milieu, further activates macrophages. Tumour necrosis factor α released from Th1 cells and macrophages helps effector T cells to home in to disease site(s) by acquisition of appropriate chemokine receptors (CCR5, CXCR3, etc). These cells therefore bind to their respective chemokine ligands expressed at disease sites. The ensuing granuloma formation contains the infection and prevents dissemination of bacilli. This occurrence coincides with development of delayed-type hypersensitivity to tuberculin. However, this process is not always beneficial to the host. Inflammatory cytokines, particularly tumour necrosis factor α, work as a double-edged sword. Although tumour necrosis factor α, together with interferon γ, facilitates granuloma formation, tissue destruction is also simultaneously triggered, resulting in caseation necrosis.

Meanwhile, immune responses skewed towards Th2 cross-inhibit protective responses such as granuloma formation and fails to limit the infection. Chemokine-directed selective homing of Th2 cells may have a critical role in the development of severe cavitary pulmonary disease and disseminated disease such as miliary tuberculosis. Presumably, severe forms of disease in a susceptible host results from the Th2-biased response as a default pathway. Th2 cells also help antibody production and their class switching thus facilitates opsonisation of bacilli to induce antibody-dependent cellular cytotoxicity. The subsequent balance of the ensuing immune response, either towards Th1 or Th2, dictates development of limited or disseminated disease. Additionally, several host and pathogen-related factors may also influence the type of effector immune response elicited and dictate the disease course, such as response to drugs and cure.

Miliary tuberculosis has also been described to result from several iatrogenic causes (panel 1). As shown in figure 3, tumour necrosis factor α has an important role in the host immune response to tuberculosis. Recent reports indicate development of fatal tuberculosis including miliary tuberculosis in patients with rheumatoid arthritis who were treated with anti-tumour necrosis factor α agents like infliximab and etanercept. Several molecular mechanisms have been described that account for the propensity to develop disseminated tuberculosis. These mechanisms include impaired expansion of γδ T cells, failure to generate adequate cell-mediated immunity, presence of HLA-Bw15, HLA-DRB1*15/16, DRB1*13, and DQBI*0602, absence of HLA-Cw6, HLA-DRB1*10, and DQBI*0501.

<table>
<thead>
<tr>
<th>Panel 1: Predisposing factors for the development of miliary tuberculosis</th>
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<tbody>
<tr>
<td>Childhood infections (eg, measles, whooping cough, and acute tonsillitis)</td>
</tr>
<tr>
<td>Malnutrition</td>
</tr>
<tr>
<td>HIV/AIDS</td>
</tr>
<tr>
<td>Alcoholism</td>
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<tr>
<td>Diabetes mellitus</td>
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<tr>
<td>Chronic renal failure, dialysis</td>
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<tr>
<td>Post-surgery (eg, gastrectomy [predisposes to tuberculosis in general])</td>
</tr>
<tr>
<td>Organ transplantation</td>
</tr>
<tr>
<td>Drugs</td>
</tr>
<tr>
<td>Corticosteroids</td>
</tr>
<tr>
<td>Immunosuppressive and cytotoxic drugs</td>
</tr>
<tr>
<td>Immunomodulator drugs (eg, infliximab, etanercept)</td>
</tr>
<tr>
<td>Connective tissue disorders</td>
</tr>
<tr>
<td>Pregnancy, postpartum</td>
</tr>
<tr>
<td>Underlying malignancy</td>
</tr>
<tr>
<td>Silicosis</td>
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<tr>
<td>Iatrogenic causes</td>
</tr>
<tr>
<td>Ureteral catheterisation (predisposes to tuberculosis in general)</td>
</tr>
<tr>
<td>Extracorporeal shockwave lithotripsy (patient had undiagnosed genitourinary tuberculosis)</td>
</tr>
<tr>
<td>Laser lithotripsy (patient had undiagnosed genitourinary tuberculosis)</td>
</tr>
<tr>
<td>Cardiac valve homograft replacement (contamination of homografts probably occurred at the time of harvest from cadavers)</td>
</tr>
<tr>
<td>Intravesical BCG therapy for urinary bladder carcinoma</td>
</tr>
</tbody>
</table>

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in certain ethnic populations, impaired MHC class II-restricted target cell lysis,77 and over-exuberant lysis of target cell macrophages.78 Relative attenuation of local immune responses in pulmonary tuberculosis compared with other peripheral compartment(s) may be critical for disease causation. Similarly, in miliary tuberculosis, severely compromised local T-cell response probably results in dissemination of the pathology.

Pathology

At autopsy, organs with high blood flow—eg, the spleen, liver, lungs, bone marrow, kidneys, and adrenals—are frequently affected. On gross examination, small, punctate, grey to reddish brown coloured, rounded lesions of more or less uniform size are discernible in the lungs and various other organs (figure 4). The tubercle—or granuloma—is the histopathological hallmark of miliary tuberculosis. When miliary tuberculosis results from acute massive lymphohaematogenous dissemination, all lesions appear alike and are termed soft or exudative;79,80 the caseous focus invading the blood vessel is usually demonstrable and the lesions often reveal acid-fast bacilli. When the dissemination is due to discharge of bacilli into microscopic blood vessels within the caseous lesions, the acute soft lesions are found mixed with hard tubercles. Acid-fast bacilli are seldom demonstrable in the hard tubercles.81 In patients with acute respiratory distress syndrome (ARDS) due to miliary tuberculosis, hyaline membranes are present in addition to the cellular infiltrate. Occasionally, the inflammatory process can involve the blood vessels, especially in patients with meningitis, and focal neurological deficits—eg, hemiplegia—may result from vasculitic lesions in the brain.

The pathological findings in HIV-infected patients with miliary tuberculosis are similar, but have important differences. In advanced HIV infection, the findings include poor granuloma formation with minimal cellular reaction, severe necrosis, and abundant acid-fast bacilli.6,32 In patients with acute respiratory distress syndrome (ARDS) due to miliary tuberculosis, hyaline membranes are present in addition to the cellular infiltrate. Occasionally, the inflammatory process can involve the blood vessels, especially in patients with meningitis, and focal neurological deficits—eg, hemiplegia—may result from vasculitic lesions in the brain.

Clinical features

The clinical manifestations of miliary tuberculosis are protean and non-specific (see webtable 1). Presentation with fever of several weeks’ duration, anorexia, weight loss, lassitude, and cough is frequent. Rarely, especially among older people, afebrile presentation with progressive wasting strongly mimicking a metastatic carcinoma occurs, and is described as cryptic miliary tuberculosis.85–87 Previously, cryptic miliary tuberculosis was often diagnosed only at autopsy. However, with the availability of high-resolution CT scans, these patients can now be diagnosed during life. Several predisposing/associated conditions have been described in patients with miliary tuberculosis (panel 1). Although miliary tuberculosis involves almost all organs, most often the involvement is asymptomatic. Tuberculosis meningitis has been described in 10–30% of adult patients with miliary tuberculosis.9,15,42–55 Conversely, about one-third of patients presenting with tuberculosis meningitis have underlying miliary tuberculosis.88 If present, choroidal tubercles are pathognomonic of miliary tuberculosis and offer a valuable clue to the diagnosis (figure 5). Therefore, systematic ophthalmoscopic examination after mydriatic administration must be done in every suspected patient with miliary tuberculosis. Atypical presentations13–55,56,69–101 can delay the diagnosis and miliary tuberculosis is often a missed diagnosis.

By contrast with adults, fewer published series are available on childhood miliary tuberculosis.15,16,56,57 Clinical presentation of miliary tuberculosis in children is similar to that observed in adults (see webtable 3). In children with miliary tuberculosis, chills, night sweats, haemoptysis, and productive cough have been reported less frequently, while

Figure 4: Gross pathology of miliary tuberculosis

(A) Cut surface of spleen, (B) pleural surfaces of both lungs, and (C) cut surface of right lung 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 grey-white lesions of varying size, larger ones show caseation necrosis.
peripheral lymphadenopathy and hepatosplenomegaly are more common, compared with adults. Likewise, a higher proportion of children with miliary tuberculosis (20–40%) have tuberculosis meningitis16,18,21,56,57 compared with adults.

**Miliary tuberculosis in the immunosuppressed**
No large published series on miliary tuberculosis in patients with HIV/AIDS are available. The clinical presentation of tuberculosis in early HIV infection (CD4+ cell counts >500 cells/μL) is similar to that observed in immunocompetent individuals.83,106,107 With progression of immunosuppression in advanced HIV infection (CD4+ cell counts <200 cells/μL), disseminated and miliary tuberculosis are seen more often.98 Cutaneous involvement is unusual in miliary tuberculosis but is more commonly seen in HIV-infected patients with CD4+ cell counts below 100 cells/μL.109 Typically, the cutaneous lesions are few in number and appear as tiny papules or vesiculopapules,110 described as tuberculosis cutis miliaris disseminata, tuberculosis cutis acuta generalisata, and disseminated tuberculosis of the skin. Rarely, macular, pustular, or purpuric lesions, indurated ulcerating plaques, and subcutaneous abscesses have been reported.118 In HIV/AIDS patients with miliary tuberculosis, intrathoracic lymphadenopathy and tuberculin anergy are more common; sputum smears are seldom positive and blood culture may grow *M tuberculosis*, especially with profound immunosuppression.83,106,107

Immune reconstitution disease (IRD) has been implicated as the cause of paradoxical worsening of lesions in patients with tuberculosis. IRD, occasionally described in HIV-negative individuals with tuberculosis, has been reported to occur in 32–36% of patients with HIV/tuberculosis co-infection within days to weeks of the initiation of highly active antiretroviral therapy (HAART). Manifestations range from isolated instances of fever to increased or initial appearance of lymphadenopathy, new or worsening pulmonary infiltrates, serositis, cutaneous lesions, and new or expanding central nervous system mass lesions.111 IRD can be brief or prolonged with multiple recurrences. Consequently, HIV/miliary tuberculosis co-infected patients may develop acute renal failure112 or ARDS.113

**Laboratory abnormalities**
Several haematological and biochemical abnormalities have been described in patients with miliary tuberculosis. Rarely, pancytopenia, hypoplastic anaemia,93,94 and myelofibrosis may be encountered.119 Disseminated intravascular coagulation occurs in the setting of ARDS and multiple organ dysfunction syndrome (MODS) and causes a high mortality.115 Hyponatraemia may result from tuberculosis meningitis or inappropriate antidiuretic hormone secretion syndrome, and indicates poor prognosis.43,52 Hypercalcaemia has also been described, though rarely in miliary tuberculosis.115

**Tuberculin skin test**
A higher proportion of patients with miliary tuberculosis manifest tuberculin anergy than those with pulmonary tuberculosis or extrapulmonary tuberculosis. Tuberculin conversion may occur following successful treatment. Because of tuberculin anergy, cross reactivity with environmental mycobacteria and tuberculin positivity due to BCG vaccination, the tuberculin skin test is not useful as a diagnostic test in patients with miliary tuberculosis.
Tuberculin positivity implies infection and it does not distinguish between latent tuberculosis infection and active disease. Although a positive tuberculin skin test signifies a possible diagnosis of miliary tuberculosis, a negative test does not exclude it.

**Detection of latent tuberculosis infection**

Newer in-vitro T-cell based interferon γ assays using early secretory antigenic target 6 (ESAT6) and culture filtrate protein 10 (CFP10) that are absent in BCG but are major targets of the T-cell response to *M tuberculosis* have been explored.116 These assays are commercially available in the ELISA and ELISPOT formats. Since the sensitivity of these assays appears to be higher than that of the tuberculin skin test and they seem to be less affected by factors such as malnutrition, HIV infection, and BCG vaccination, they may be potentially useful in detecting latent tuberculosis infection, especially in children with suspected tuberculosis in developing countries. Although a negative test result may be useful in ruling out the diagnosis of miliary tuberculosis, a positive test does not distinguish between latent tuberculosis infection and active disease.

**Pulmonary function and gas exchange abnormalities**

Miliary tuberculosis is associated with abnormalities of pulmonary function typical of interstitial lung disease and these abnormalities are greater than might be anticipated from the chest radiograph.117–119 Impairment of diffusion is the most frequent and severe abnormality encountered.118,120 Additionally, a mild reduction in flow rates suggestive of peripheral airways involvement may be observed.120 Arterial hypoxaemia due to widening of the alveolar–arterial oxygen gradient and hypocapnia due to tachypnoea are also observed during the acute stage. These patients have abnormal cardiopulmonary exercise performance with lower maximum oxygen consumption, maximal work rate, anaerobic threshold, peak minute ventilation, breathing reserve, and low maximal heart rate. Other abnormalities include higher respiratory frequency, peak minute ventilation at submaximal work, and high physiological dead space/tidal volume ratio. Some of these patients manifest a demonstrable fall in oxygen saturation (to 4% or more) with exercise. Following successful treatment, most patients reveal reversal of abnormalities (SKS, unpublished observations). However, some of these abnormalities may persist following treatment.

**Immunological abnormalities and bronchoalveolar lavage**

Bronchoalveolar lavage has become an established method for the diagnosis of opportunistic lung infections. A limited number of reports on the cellular characteristics of bronchoalveolar lavage in patients with miliary tuberculosis have been published, with conflicting results.119–121 The proportion and absolute number of lymphocytes are substantially increased in bronchoalveolar lavage fluid. Although a raised CD4+/CD8+ T-lymphocyte ratio and B lymphocytes were reported in bronchoalveolar lavage fluid in one study,119 a decrease in CD4+/CD8+ T-lymphocyte ratio was reported in another.120 These conflicting results may be explained in part by the small number of patients studied.

Polyclonal hypergammaglobulinaemia with increase in IgG, IgA, and IgM was observed in peripheral blood and bronchoalveolar lavage fluid in one study.119 These findings probably result from increased local synthesis by activated B lymphocytes. Additionally, increased bronchoalveolar lavage fluid fibronectin and serum C3 levels as acute phase response to ongoing inflammation were observed.119,122 Lymphocytic alveolitis and increased IgG and IgA levels persisted following antituberculosis treatment.119

**Imaging**

**Chest radiograph**

A miliary pattern on chest radiograph is considered to be the hallmark of miliary tuberculosis (figure 6A).123 Subtle miliary lesions are best delineated in slightly underpenetrated films, especially when the diamond shaped areas of the lung in between the ribs are carefully scrutinised.124,125 The chest radiographic abnormalities in miliary tuberculosis are described in panel 2. In about 10% of cases, the nodules may be greater than 3 mm in diameter.120 Some patients may have normal chest radiographs initially and the typical changes evolve over the course of disease, emphasising the importance of obtaining periodic chest radiographs in patients presenting with pyrexia of unknown origin.

In the pre-CT scan era, diagnosis of miliary tuberculosis was frequently missed on the chest radiographs and was evident only at autopsy. Evidence from published studies indicates that the classic miliary pattern may not be evident in up to 50% of patients with miliary tuberculosis.5,14,43,44,126 Typical miliary pattern on the chest radiograph represents the summation of densities of tubercles that are perfectly
aligned; whereas curvilinear densities and reticulonodular pattern result from imperfectly aligned tubercles.\textsuperscript{126} The histopathological composition of the tubercles, their number, and their size have been proposed to be the determinants of radiographic visibility of the nodules.\textsuperscript{124,125} Rarely, ground glass appearance can result from intrathoracic lymphatic obstruction.\textsuperscript{127}

**Ultrasonography**

Ultrasonography is useful in the detection of associated lesions such as loculated ascites, focal hepatic and splenic lesions, and cold abscess. Diagnostic thoracic or abdominal paracentesis under ultrasound guidance is useful to procure fluid for diagnostic testing, especially when it is loculated.

**Computed tomography and magnetic resonance imaging**

High-resolution CT scans have considerably improved the antemortem diagnosis of miliary tuberculosis and reveal classic miliary pattern even when the chest radiograph looks apparently normal (figure 6B and C).\textsuperscript{128} Lucent areas conforming to the polygonal shape of the secondary pulmonary lobule are also seen on high-resolution CT scan before and after antituberculosis treatment. These areas are less radiolucent than typical lesions of emphysema and represent areas of air-trapping and are perhaps related to tuberculous bronchiolitis.\textsuperscript{128} The interlobular septal thickening or intralobular fine network that is evident on high-resolution CT scans in miliary tuberculosis seems to be caused by the presence of tubercles in the interlobular septa and alveolar walls. Centrilobular nodules and branching linear structures producing a tree-in-bud appearance—a pattern seen in active post-primary pulmonary tuberculosis—may sometimes be evident in miliary tuberculosis.\textsuperscript{129} Contrast-enhanced CT scans are better for detecting intrathoracic lymphadenopathy, calcification, and pleural lesions. Contrast-enhanced CT scans and magnetic resonance imaging (MRI) are useful in identifying miliary lesions at extrapulmonary sites, an exercise that was possible only at autopsy. Abdominal contrast-enhanced CT scans are useful in identifying lesions in the liver and spleen, intra-abdominal lymphadenopathy, and cold abscess.\textsuperscript{130} Unlike high-resolution CT scans of the chest, where the classic nodular lesions are less than 2 mm, miliary lesions in the liver and spleen may appear as confluent or discrete hypodense lesions, sometimes with peripheral rim enhancement.\textsuperscript{130} Ultrasonography, contrast-enhanced CT scans, and MRI may help in identifying adnexal masses, ascites in women, and epididymitis and seminal vesicle lesions in men with genital tract involvement. Contrast-enhanced CT scans or MRI of the brain and spine are useful in the evaluation of patients with concomitant tuberculosis meningitis or spinal tuberculosis. Interventional radiological procedures such as fine needle aspiration for cytological examination and biopsy under CT scan or MRI guidance are useful for procuring tissue/fluid for confirmation of diagnosis.

**Positron emission tomography**

Positron emission tomographic (PET) scanning has been found to be a useful tool to assess the activity of various infectious lesions including pulmonary tuberculosis.\textsuperscript{131,132} The utility of PET in assessing the activity of lesions that might persist following treatment in miliary tuberculosis needs to be ascertained.

**Diagnosis**

The following criteria have been proposed for the diagnosis of miliary tuberculosis:\textsuperscript{52} clinical presentation consistent with a diagnosis of tuberculosis—eg, pyrexia with evening rise of temperature, night sweats, anorexia, and weight loss of greater than 6 weeks in duration—responding to antituberculosis treatment, with typical miliary pattern on chest radiograph, and/or bilateral, diffuse reticulonodular lung lesions on a background of miliary shadows demonstrable either on chest radiograph or high-resolution CT scan, plus microbiological and/or histopathological evidence of tuberculosis.

A high index of clinical suspicion with efforts towards confirming the diagnosis by demonstrating

\begin{table}[h]
\centering
\caption{Panel 2: Chest radiographic findings in miliary tuberculosis\textsuperscript{4–6,9,15,16,21,32,42–57}}
\begin{tabular}{|c|}
\hline
- Classic miliary pattern (50%)—defined as “a collection of tiny discrete pulmonary opacities that are generally uniform in size and widespread in distribution, each of which measures 2 mm or less in diameter”\textsuperscript{123}
- Non-miliary (10–30%) Asymmetrical nodular pattern Coalescence of nodules Mottled appearance Snowstorm appearance Air-space consolidation (in acute respiratory distress syndrome)
- Other associated findings (<5%) Intrathoracic lymphadenopathy (mediastinal, paratracheal, or hilar) Pleural effusion, empyema Pulmonary parenchymal lesions and cavitation Segmental consolidation Thickening of interlobular septa Pneumothorax Pneumomediastinum Pericardial effusion
\hline
\end{tabular}
\end{table}
M tuberculosis early in the course of disease is imperative. Smear and culture examination of spontaneously expectorated or induced sputum, gastric lavage, pleural, peritoneal or pericardial fluid, cerebrospinal fluid, urine, pus from cold abscess, bronchoscopic secretions, and peripheral blood is helpful in the diagnosis of miliary tuberculosis. Microbiological and histopathological examination of bone marrow, liver and peripheral lymph node, and transbronchial lung biopsy specimens have all been used to confirm the diagnosis of miliary tuberculosis, with varying results. In the published reports, no systematic pattern of diagnostic approach could be identified and invasive diagnostic sampling appeared to be arbitrary and individualised, especially in the paediatric series.4-6,32,21,10,16

Wherever possible, efforts should be directed at procuring tissue/fluid for mycobacterial culture and sensitivity testing. Rapid culture methods such as the BACTEC-460 radiometric method may be useful for rapid drug susceptibility testing.46

**Serodiagnostic and molecular methods**

ELISA for detecting mycobacterial antigens, antibodies, and immune complexes in the blood and body fluids have been used for diagnosis of miliary tuberculosis. The usefulness of serodiagnostic tests and molecular methods such as PCR in the field setting needs to be established. PCR of blood (especially in HIV-infected patients), cerebrospinal fluid, and tissue biopsy specimens may be useful for confirmation of diagnosis. PCR has been found to be most useful when applied to clean specimens such as cerebrospinal fluid, where its sensitivity and specificity have been reported to be 0.5–0.9 and 1.0, respectively.8 When ascitic or pleural fluid is present, adenosine deaminase and interferon γ estimations can be useful adjuncts in the diagnosis, especially in areas where tuberculosis is highly prevalent.8,14-16 Although a positive serodiagnostic or molecular method of diagnosis can support the diagnosis of miliary tuberculosis in the appropriate clinical setting, a negative test cannot rule out miliary tuberculosis and treatment should not be withheld just because of negative test(s).8

**Table 2: Antituberculosis drug regimens used in the treatment of miliary tuberculosis in various clinical series**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year of publication</th>
<th>Age group</th>
<th>Number studied</th>
<th>Drug regimen(s) used</th>
<th>Adjunct corticosteroid (number of patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hussain55</td>
<td>2004</td>
<td>Adults</td>
<td>110§</td>
<td>Ethambutol, isoniazid, rifampicin (n=87); isoniazid, rifampicin, streptomycin (n=14); isoniazid, rifampicin, ethionamide, para-aminosalicylic acid (2 months)/isoniazid (6 months)</td>
<td>ND</td>
</tr>
<tr>
<td>Mert54</td>
<td>2001</td>
<td>Adults</td>
<td>38</td>
<td>Ethambutol, isoniazid, rifampicin (n=1); isoniazid, rifampicin (n=1); ethambutol, rifampicin, cycloserine, kanamycin (n=1); isoniazid, rifampicin, streptomycin (n=1); ethambutol, rifampicin, streptomycin (n=1)</td>
<td>ND</td>
</tr>
<tr>
<td>Sharma56</td>
<td>2000</td>
<td>Adults</td>
<td>100</td>
<td>Ethambutol, isoniazid, rifampicin, pyrazinamide (2 months) or streptomycin, isoniazid, rifampicin, pyrazinamide (2 months)/isoniazid, rifampicin (7 months)</td>
<td>ND</td>
</tr>
<tr>
<td>Hussain57</td>
<td>2004</td>
<td>Adults</td>
<td>110§</td>
<td>Ethambutol, isoniazid, rifampicin, pyrazinamide (n=87); isoniazid, rifampicin (n=14); isoniazid, rifampicin, streptomycin (n=1)</td>
<td>ND</td>
</tr>
</tbody>
</table>

ND—not described. All drugs given daily, if not specified. *Cycloserine was added if meningitis was present. †Total duration of treatment not stated. ‡Two patients did not receive treatment.

**Differential diagnosis**

Even though there are many conditions that can present with a miliary pattern on the chest radiograph,10,16 presence of fever further narrows down the list of differential diagnoses.

**Treatment**

Miliary tuberculosis is uniformly fatal if not treated.4-6,32 Antituberculosis treatment is the cornerstone of management. Critical evaluation of published clinical series on miliary tuberculosis reveals that there is no consensus regarding the optimum duration of treatment (table 2). Additionally, there are no published randomised controlled trials assessing the efficacy of the standard WHO treatment regimens that are widely used in national tuberculosis control programmes worldwide.138,139 There are sparse data regarding the efficacy of standard treatment regimens in the treatment of HIV/miliary tuberculosis co-infection.
In the absence of associated meningeal involvement, the American Thoracic Society (ATS), the Centers for Disease Control and Prevention (CDC), the Infectious Disease Society of America (IDSA), and the British Thoracic Society (BTS) guidelines state that 6 months of treatment (2-month intensive phase with isoniazid, rifampicin, pyrazinamide, and ethambutol or streptomycin, followed by a 4-month continuation phase with isoniazid and rifampicin) is adequate in miliary tuberculosis, whereas the American Academy of Pediatrics (AAP) advocates 9 months of treatment. In the presence of associated tuberculosis meningitis, treatment needs to be given for at least 12 months. In view of the high frequency of associated tuberculosis meningitis in miliary tuberculosis, the BTS guidelines further suggest that all patients with miliary tuberculosis undergo a lumbar puncture so that they receive optimum duration of treatment.

In the absence of associated meningeal involvement, the American Thoracic Society (ATS), the Centers for Disease Control and Prevention (CDC), the Infectious Disease Society of America (IDSA), and the British Thoracic Society (BTS) guidelines state that 6 months of treatment (2-month intensive phase with isoniazid, rifampicin, pyrazinamide, and ethambutol or streptomycin, followed by a 4-month continuation phase with isoniazid and rifampicin) is adequate in miliary tuberculosis, whereas the American Academy of Pediatrics (AAP) advocates 9 months of treatment. In the presence of associated tuberculosis meningitis, treatment needs to be given for at least 12 months.

In view of the high frequency of associated tuberculosis meningitis in miliary tuberculosis, the BTS guidelines further suggest that all patients with miliary tuberculosis undergo a lumbar puncture so that they receive optimum duration of treatment. Under national tuberculosis control programmes, patients with miliary tuberculosis get treated with the directly observed treatment, short-course (DOTS) approach, using short-course intermittent chemotherapy. According to the WHO guidelines, miliary tuberculosis is included under treatment category I and patients receive 6 months of treatment. Although this duration of treatment may be sufficient for many, each patient needs to be assessed individually, and wherever indicated, treatment duration may have to be extended. Large scale randomised controlled trials with a sufficient sample size are required to evaluate the optimum duration of treatment in miliary tuberculosis.

Corticosteroids
Although several randomised controlled trials have been conducted in patients with various forms of extrapulmonary tuberculosis, such as tuberculosis meningitis, pericardial tuberculosis, and pleural tuberculosis, no study has specifically evaluated the role of adjunct corticosteroid treatment in patients with miliary tuberculosis; only limited evidence is available with conflicting results. A beneficial response was observed in some studies, although such benefit could not be documented in others. Presence of...
associated adrenal insufficiency is an absolute indication for their administration. Adjunctive corticosteroid treatment may be beneficial in miliary tuberculosis with tuberculosis meningitis, large pericardial or pleural effusion, dyspnoea and/or disabling chest pain, IRD, ARDS, immune complex nephritis, and histiocytic lymphoma. The benefit of corticosteroid administration in patients with persistent lymphocytic alveolitis, pulmonary function abnormalities, and tuberculosis merits further evaluation in future studies.

Antiretroviral drugs
Co-administration of rifampicin may result in dangerously low levels of antiretroviral agents by inducing the hepatic cytochrome P450 pathway. In general, the WHO recommends that in HIV-infected patients with tuberculosis, antiretroviral treatment is started after the completion of antituberculosis treatment.166,167 However, if the risk of HIV disease progression and death during the period of antituberculosis treatment is high (ie, CD4+ cell counts <200 cells/μL or the presence of disseminated tuberculosis including miliary tuberculosis), the guidelines such as those issued by the WHO146 or the British HIV Association148 (figure 7) can be followed.146

Complications
Complications are often self-limited and improve with antituberculosis treatment alone. However, at times they can be life-threatening, necessitating prompt recognition and treatment.

Air-leak syndromes
Pneumothorax, at times bilateral, may be the presenting feature or may develop while the patient is receiving treatment.129 Typical miliary shadows may not be evident initially and become apparent following lung expansion. Intrapulmonary rupture of alveoli and consequent leaking of air that reaches the mediastinum after spreading along the vascular sheath can result in fatal pneumomediastinum with subcutaneous emphysema.129

Acute respiratory distress syndrome
ARDS is one of the most dreaded complications of miliary tuberculosis and is usually seen at the time of initial presentation. However, ARDS may develop at any time during the course of disease and can occur as a component of MODS.90,96,149

Renal failure
Besides being a part of MODS, renal failure may occur due to direct renal parenchymal involvement,79 and can develop as a manifestation of IRD in HIV-infected patients.112 Rarely, renal failure can occur secondary to obstructive uropathy caused by the disease process.18

Hepatic and gastrointestinal complications
An asymptomatic rise in transaminases can occur in miliary tuberculosis, and treatment should not be withheld on this evidence alone. Liver functions should be periodically monitored during treatment in this situation. Sometimes, miliary tuberculosis may lead to a unique form of hepatitis where widespread liver cell necrosis occurs. Such patients may develop fulminant hepatic failure.110 Remarkably, some of these patients may not have typical lesions in the lungs, which causes a delay in diagnosis.110 This occurrence may represent a situation where an extrapulmonary focus has discharged into the portal circulation, resulting in hepatic miliary tuberculosis. Drug-induced hepatitis may result from antituberculosis treatment; standard guidelines174–176 should be followed in its management. Small intestinal perforations at the site of granulomatous involvement have been described in some patients while on treatment.115

Cardiovascular complications
Life-threatening complications such as myocarditis, congestive heart failure, infective endocarditis, pericarditis, intracardiac mass, mycotic aneurysm, and sudden cardiac death have been described in miliary tuberculosis116–118 and should be carefully examined for.

Prognosis and mortality
The mortality related to miliary tuberculosis is about 15–20% in children16,18,21,26,27 and 25–30% in adults.25,42–45 Delay in the diagnosis or commencement of treatment appears to be an important cause of high mortality. Predictors of poor outcome in miliary tuberculosis are listed in table 3.

Prevention
Evidence from published studies indicates that BCG vaccination is effective in reducing the incidence of miliary tuberculosis, especially in children.112 However, it is not effective in individuals who are already infected and should not be administered to immunosuppressed hosts. Targeted tuberculin testing and treatment of latent tuberculosis infection is often

Table 3: Predictors of poor outcome in patients with miliary tuberculosis

<table>
<thead>
<tr>
<th>Reference</th>
<th>Predictors of poor outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gelb163,164</td>
<td>Stupor, meningealism, increasing age, cirrhosis of liver, leucopenia, leucocytosis</td>
</tr>
<tr>
<td>Greco56</td>
<td>Increasing age, presence of underlying disease, history of cough, night sweats</td>
</tr>
<tr>
<td>Kim129</td>
<td>Female sex, altered mental status</td>
</tr>
<tr>
<td>Maartens162</td>
<td>Age &gt;60 years, lymphopenia, thrombocytopenia, hypoalbuminaemia, raised transaminases, treatment delay</td>
</tr>
<tr>
<td>Sharma121</td>
<td>Dyspnoea, chills, temperature above 39.3°C, icterus, hepatomegaly, hypoalbuminaemia, hypoponatremia, raised urea, alkaline phosphatase levels</td>
</tr>
<tr>
<td>Long15</td>
<td>Presence of one or more risk factors</td>
</tr>
<tr>
<td>Mert54</td>
<td>Male sex, atypical chest radiographic pattern, treatment delay</td>
</tr>
<tr>
<td>Hussain51</td>
<td>Altered mental status, lung crackles, leucocytosis, thrombocytopenia, mechanical ventilation</td>
</tr>
</tbody>
</table>

*No statistical analysis was done. †Listed in panel 1.*
practised in countries with low prevalence of tuberculosis, but drug-induced hepatitis is a potential risk with this intervention. Although BCG vaccination has been helpful in reducing the incidence of miliary tuberculosis, persistent efforts to develop a more effective vaccine must be pursued.

Conclusions and future directions

Miliary tuberculosis is a potentially lethal disease that can perplex even the most experienced clinicians. Modern technological tools should be used to unravel the reasons for the severely compromised local T-cell response resulting in miliary tuberculosis. The potential of new interferon gamma assays in the diagnosis of miliary tuberculosis needs to be explored in the field. Systematic data collection and reporting to study the global epidemiology of miliary tuberculosis should be attempted through national tuberculosis control programmes, ensuring that the proposed diagnostic criteria are strictly adhered to. Miliary tuberculosis is associated with a high mortality despite the availability of effective treatment. The cause of death in patients with miliary tuberculosis merits further study. Appropriately designed randomised controlled trials should be undertaken to define the optimum regimen and duration of treatment in miliary tuberculosis patients, including those with HIV/AIDS. The role of adjunctive corticosteroid therapy needs to be elucidated in future studies.

Conflicts of interest

We have no conflicts of interest to declare.

Acknowledgments

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Search strategy and selection criteria

Articles for this review were identified by searches of PubMed (from January 1950 to November 2004), IndMed, Google, and the extensive personal collections of the authors. Search terms used were “miliary”, “disseminated”, and “childhood” in combination with “tuberculosis”, “extrapolumay”, “tuberculosis”, “HIV”, “AIDS”, “cryptic”, and “latent” in combination with “miliary” or “disseminated tuberculosis”. Cross-references of relevant articles were also hand-searched. English language articles were mainly reviewed; however, articles in other languages covered in PubMed with abstracts in English were also included.

References


64 Cosmi L, Liotta F, Angelii R, et al. Th2 cells are less susceptible than Th1 cells to the suppressive activity of CD25+ regulatory thymocytes because of their responsiveness to different cytokines. Blood 2004; 103: 3117–21.


76 Balamurugan A, HLA-DR restriction of Th1/Th2 cytokine profile in tuberculosis: impact of genetic diversity (PhD thesis). All India Institute of Medical Sciences, New Delhi, India 2002.


83 Sharma SK, Mohan A. Co-infection of human immunodeficiency virus (HIV) and tuberculosis: Indian perspective. Indian J Tuberc 2004; 51: 5–16.


146 WHO Regional Office for Southeast Asia. Fact sheets on antituberculosis drugs; New Delhi: WHO Regional Office for Southeast Asia: 2004; SEA-AIDS-134/SEA-Drugs-154.