INVITED ARTICLE

IMMUNOCOMPROMISED HOSTS

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Tuberculosis of the Central Nervous System in Immunocompromised Patients: HIV Infection and Solid Organ Transplant Recipients

Christina A. Nelson[1,2] and Joseph R. Zunt[1]

[1]Departments of Neurology, Global Health, Medicine, and Epidemiology, University of Washington School of Medicine, Seattle, Washington; and
[2]Vanderbilt Institute for Global Health, Vanderbilt University, Nashville, Tennessee

Central nervous system (CNS) tuberculosis (TB) is a devastating infection with high rates of morbidity and mortality worldwide and may manifest as meningitis, tuberculoma, abscess, or other forms of disease. Immunosuppression, due to either human immunodeficiency virus infection or solid organ transplantation, increases susceptibility for acquiring or reactivating TB and complicates the management of underlying immunosuppression and CNS TB infection. This article reviews how immunosuppression alters the clinical presentation, diagnosis, treatment, and outcome of TB infections of the CNS.

In ~1% of individuals with *Mycobacterium tuberculosis* infection, central nervous system (CNS) involvement develops, including meningitis, tuberculoma, abscess, or other manifestations [1]. Infection of the CNS is the most severe extrapulmonary manifestation of tuberculosis (TB), with a high mortality rate and residual neurologic sequelae, even with adequate treatment [2].

TB is one of the most important opportunistic infections in both patients with human immunodeficiency virus (HIV) infection and transplant recipients. Both patient populations have a high relative risk of disseminated TB (Table 1) and receive medications that complicate treatment. In addition, in both populations immune reconstitution inflammatory syndrome (IRIS) can develop [8, 9].

HIV infection significantly increases the risk for acquisition of TB, the rate of progression from latent to active disease, and TB-associated morbidity and mortality

[5, 10, 11]. Extrapulmonary manifestations appear in ~40% of HIV-infected patients with TB [10]. Compared with HIV-negative individuals, HIV-positive individuals with TB are 5 times more likely to have CNS involvement [5].

Patients with immunosuppression following solid organ transplant (SOT) are also at increased risk for acquiring TB and presenting with extrapulmonary TB. Compared with the general population, SOT recipients are 20–74 times more likely to acquire TB [11, 12]. Most TB infections in transplant recipients are due to reactivation of dormant disease, although nosocomial infection and donor transmission have been reported [13].

This article reviews the clinical manifestations, diagnosis, and treatment of CNS TB in patients with immunodeficiency due to HIV infection or SOT. Bone marrow transplant patients are not included in this review because they have a lower risk of acquiring TB after transplantation and there is little published information on this patient population.

MENINGITIS

TB meningitis accounts for 5% of all extrapulmonary TB and is one of the most devastating manifestations of TB infection [14]. It occurs more frequently in children, particularly those <1 year of age [15, 16]. Of

Table 1. Relative Risk of Tuberculosis (TB) and Central Nervous System TB in Patients With HIV Infection and Solid Organ Transplant Recipients

Patient category	Relative risk	
	TB	CNS TB
HIV-infected patients	20.6–36.7 [3]	2.1 [4], 5.0 [5],[a] 5.3 [6][a]
SOT recipients [7]		
Lung	73.3	…[b]
Liver	29.5	…[b]
Kidney	19.0	…[b]
Heart	13.7	…[b]

Abbreviations: CNS, central nervous system; HIV, human immunodeficiency virus; SOT, solid organ transplant; TB, tuberculosis.

[a] TB meningitis only.

[b] Limited or no data available.

adults with TB meningitis, 40%–66% have extrameningeal TB at the time of diagnosis [2, 17, 18].

The most common symptoms of TB meningitis include fever, headache, vomiting, and altered level of consciousness. Children are more likely to present with seizures, nausea, and vomiting; headache is less frequent [2]. The basilar meninges and cistern are frequently affected and cause cranial nerve dysfunction, especially of the sixth (abducens) and seventh (facial) cranial nerves [16, 19]. TB meningitis may have an insidious onset, so physicians should have a high clinical suspicion in young children with altered level of consciousness in TB-endemic areas.

Hydrocephalus is common during TB meningitis owing to high protein levels causing obstruction of cerebrospinal fluid (CSF) flow [20]. Intracranial vasculopathy is also frequent in TB meningitis, and stroke can occur as a complication of vasospasm, thrombosis, vasculitis, or hemorrhagic infarction [21].

In HIV-infected patients, TB is more likely to produce meningitis [22]. In a study of 2205 patients with TB, 10% of HIV-positive patients had TB meningitis compared with only 2% of patients without HIV infection [5]. The risk of TB meningitis is greater in HIV-infected patients with CD4 counts <100 cells/μL [23–25]. Although the clinical presentation of TB meningitis is generally similar irrespective of HIV status [5, 26–29], some studies have reported more frequent altered level of consciousness, lymph node involvement, and extrameningeal TB in HIV-infected people [5, 17, 26, 30]. One study reported that only 15% of HIV-infected patients with TB meningitis presented with the classic triad of fever, headache, and meningeal signs [23].

After SOT, the median time to development of posttransplant TB is 183 days, and CNS TB infections seem to have a similar temporal pattern [7]. The majority of patients present with disseminated infection, which is more frequent after liver and renal transplantation. Treatment with muromonab-CD3 (OKT3) or anti–T-cell antibodies significantly increases the risk of disseminated TB, whereas cyclosporine, tacrolimus, and azathioprine do not [11].

TUBERCULOMA (TUBERCULOUS GRANULOMA)

The clinical presentation of CNS tuberculoma is usually more subtle than that of TB meningitis and may include headache, seizures, focal neurologic deficits, and papilledema [31]. Tuberculomas accompany TB meningitis in 10% of patients and are multiple in a third of patients [32]. Lesions may occur in the brain, spinal cord, subarachnoid, subdural, or epidural space; they may be solitary but are most often multiple and accompanied by surrounding edema and ring enhancement [33]. In children, lesions tend to be infratentorial, whereas in adults they are typically supratentorial [34].

Clinical presentation of tuberculoma may differ in HIV-infected individuals. A small study in Spain included 4 HIV-infected individuals with tuberculoma who, in contrast to HIV-uninfected patients, all presented with fever and headache and none with seizures [35].

CNS tuberculoma after SOT may present up to 11 years following transplantation [36, 37]. Although immunosuppression and comorbidities probably complicate the presentation of posttransplantation CNS tuberculoma, too few cases have been reported to allow comment on potential differences in clinical presentation.

TUBERCULOUS ABSCESS

Tuberculous abscesses tend to be larger than tuberculomas, often >3 cm in diameter. The clinical presentation of tuberculous abscess is typically more acute than tuberculoma and includes fever, headache, and focal neurologic deficits [31].

In HIV-infected people, TB abscesses may occur more frequently; 1 study found that 20% of HIV-infected persons with CNS TB had tuberculous abscess [39], compared with 4%–7.5% of HIV-negative patients with CNS TB [40]. It is not known whether this increased frequency is a true effect or due to referral bias. HIV-induced suppression of cell-mediated immunity may inhibit the intracerebral response to TB bacilli, thus increasing the likelihood of abscess versus granuloma formation [39]. A review of 12 HIV-positive patients with tuberculous abscess reported that seizures, headache, altered level of consciousness, and hemiparesis were prominent presenting symptoms; all but 1 patient had solitary lesions [40].

In SOT patients, abscess also seems to be a common manifestation of CNS TB. In a review of TB after SOT, Singh et al reported that TB abscess was present in 5 of 18 patients (28%) with CNS TB [11].

Table 2. Cerebrospinal Fluid Abnormalities in Patients With Central Nervous System Tuberculosis

CSF finding	TB meningitis	Tuberculoma[a]	TB and HIV infection[b]	TB-associated IRIS
Cytochemical profile (% with finding)	WBC count, 100–399 cells/μL [48]; lymphocyte predominance (85%) [18]; protein >40 mg/dL (77%) [18]; CSF–serum glucose ratio <0.6 (67%) [18]; opening pressure >200 mm H$_2$O (54%) [18]	WBC counts normal or slightly to moderately elevated [49–51]; elevated protein (88%) [52]; low glucose (83%) [53]	Lower opening pressure [26]; CSF pleocytosis (CSF WBC count, ≥5 cells/μL) absent in 11%–18%; in patients with pleocytosis, WBC counts similar to those in patients without HIV infection [5, 23, 53]; others report lower CSF WBC counts [26, 27]; in patients with CD4 counts <50 cells/μL, pleocytosis is less common (77% vs 85.2%), and median CSF cell counts lower (89 vs 246 cells/μL) [54, 55]; no significant difference in protein or glucose levels [56]; others report lower protein [27, 55]; 64% have classic triad of elevated protein, low glucose, and pleocytosis [23]	In series of 13 patients, CSF pleocytosis was absent in 2 (15%) [57]; in patients with pleocytosis, WBC counts are typically lower (median, 30 cells/μL; range, 14–65) [57]; median protein, 160 mg/mL, and glucose, 37.8 mmol/dL [57]
Acid-fast bacilli stain	20% positive in 1 series [18]; sensitivity, 37% with 1 CSF examination, 87% with 3 examinations [48][c]	Typically negative [58][d]	Similar sensitivity for HIV-infected patients, but higher mortality in those with positive smear sample [59]	Smear sample positive in 1 (9%) of 11 cases of meningitis [57]; negative in all 4 patients with tuberculoma [57]
Acid-fast bacilli culture	11% positive in 1 series [18]; sensitivity, 52% with 1 CSF examination, 83% with 3 examinations [48][c]	Typically negative [58][d]	Similar sensitivity for HIV-infected patients [60]; *Mycobacterium tuberculosis* more likely to be isolated from CSF [26, 56]	Smear sample positive in 1 (9%) of 11 patients with meningitis [57]; negative in all 4 patients with tuberculoma [57]
PCR findings	Sensitivity, 4%–100%, depending on diagnostic criteria used and prior administration of antituberculous therapy [2]; specificity, usually 100% (range, 38%–100%) [2]; diagnosis cannot be excluded based on negative PCR result	PCR may increase diagnostic yield [61, 62], but CSF findings are rarely positive	Similar findings in HIV-infected patients	Insufficient data
IFN-γ levels[e]	CSF IFN-γ, >6.4 IU/mL: sensitivity, 70%, and specificity, 94% [63]; simultaneous use of CSF PCR and IFN-γ increases sensitivity to 80% and specificity to 92.6% [63]	Insufficient data	Insufficient data	Insufficient data
ADA levels	>8 U/L: sensitivity, 59%; specificity, 96%, cannot discriminate between TB and bacterial meningitis [64]	Insufficient data	No difference in mean levels: 12.6 IU/L in HIV-infected patients vs 13.5 IU/L in patients without HIV infection [60]	Insufficient data

Abbreviations: ADA, adenosine deaminase; CNS, central nervous system; CSF, cerebrospinal fluid; HIV, human immunodeficiency virus; IFN, interferon; IRIS, immune reconstitution inflammatory syndrome; PCR, polymerase chain reaction; TB, tuberculosis; WBC, white blood cell.

[a] Of patients with tuberculoma, 50% have concurrent TB meningitis [52].

[b] CSF lactic acid is elevated in HIV-infected patients with TB meningitis and can be useful for distinguishing TB meningitis from chronic HIV meningitis [65].

[c] When possible, a large volume of CSF (10 mL) should be obtained to increase the diagnostic yield of acid-fast bacilli stain and culture [66].

[d] Aspirate fluid may also be tested for presence of acid-fast bacilli. Tuberculoma fluid aspirates do not typically harbor bacilli, whereas abscess fluid is filled with organisms [41, 58].

[e] Note that these results are from a single study.

Table 3. Differences in Central Nervous System Tuberculosis Between Patients With HIV Infection and Immunocompetent Patients

Disease	Clinical presentation	Diagnosis	Outcome
Meningitis	More likely to have altered mental status [30], disseminated or extrameningeal TB [5, 26], and lymph node involvement [17]; only 15% have classic triad of fever, headache, and meningeal signs [23]	PPD less frequently reactive [5, 28]; imaging: basal exudates less frequent and thinner [27], obstructive hydrocephalus less frequent [27, 67], vasculitis and infarcts more common and widespread [27]	Increased mortality at 6-9 months [68]; factors associated with increased 9-month mortality: lower hematocrit [26], lower CD4 count (univariate analysis only) [26], ART before presentation [23], tachycardia [23]
Tuberculoma	More likely to have fever and headache [35], less likely to have seizures [35]	Imaging: lesions more likely to be hypodense [35] and <1 cm [69] and less likely to produce mass effect [69]	No known differences
Abscess	More common in HIV-infected patients, probably because of abnormalities in cell immunity [14, 25, 38, 39]; no apparent differences in presentation; seizures, headache, and altered consciousness are prominent [40, 70]	No known differences; in 1 series, only 14% of HIV-infected patients were PPD positive, and 42% had abnormal chest radiographs [40]	No known differences

Abbreviations: ART, antiretroviral therapy; CNS, central nervous system; HIV, human immunodeficiency virus; PPD, purified protein derivative test; TB, tuberculosis.

Miliary CNS TB, TB radiculomyelitis, and TB encephalitis are not reviewed, because there is little published information regarding these forms of CNS TB in HIV-infected patients or transplant recipients.

DIAGNOSIS

Diagnosis of TB outside the CNS can be useful for making a presumptive diagnosis of CNS TB. Ancillary diagnostic tests include chest radiography, tuberculin skin test, and sputum test. Abnormal chest radiographic findings are present in 41%–60% of patients with TB meningitis [41, 42], 17%–45% have a positive purified protein derivative test (positivity increases to 75% with 100-unit dose) [41, 42], and 50% have a positive sputum result [43]. An elevated level of serum interferon (IFN)–γ has high specificity for diagnosing TB and less interreader variability, and it is not affected by prior BCG vaccination [44]. HIV-infected patients with latent TB have variable results with one type of serum IFN-γ test (Quantiferon), and lower sensitivity is associated with higher degrees of immunodeficiency [45]. Given the similarity of the clinical presentation of CNS TB to other neurologic opportunistic infections, especially cryptococcal meningitis and cerebral toxoplasmosis, a high index of suspicion should be maintained for other opportunistic infections.

Thwaites et al and Török et al have developed and validated diagnostic algorithms for TB meningitis that use basic clinical and laboratory data [46, 47]. CSF culture remains the reference standard for diagnosing CNS TB; ancillary assays such as polymerase chain reaction (PCR), although specific, have widely variable sensitivity and should not be used to exclude the diagnosis of CNS TB (Table 2). Findings of small studies suggest that IFN-γ testing in CSF is both highly sensitive and specific for TB meningitis [63]. Compared with that in immunocompetent patients, the CSF profile in HIV-infected patients with TB meningitis has a wider range of findings [23]. Compared with patients with CD4 counts >50 cells/μL, patients with lower counts are less likely to have CSF pleocytosis or depressed glucose levels [54]. Table 3 summarizes the differences in presentation, diagnosis, neuroimaging findings, and outcome of CNS TB in HIV-infected patients compared with immunocompetent patients.

TREATMENT

Immunocompetent Patients

Given the low sensitivity of existing CSF tests for detecting TB and the slow growth of *M. tuberculosis* in culture, antituberculous treatment is often initiated empirically. Treatment is more complex for multidrug-resistant TB (MDR TB; resistant to isoniazid [INH] and rifampicin) and extensively drug-resistant TB (resistant to INH, rifampin, fluoroquinolones, capreomycin, kanamycin, and amikacin). In a study of 1614 patients with positive CSF cultures, the presence of isoniazid resistance was associated with 2.1 times higher risk of death [71]. Determining the prevalence of drug resistance is extremely important for guiding initial therapy, especially when sensitivities are pending or not feasible [72].

Monitoring TB medication levels in blood or CSF is rarely necessary except in patients with treatment failure, known malabsorptive states, or those who are receiving cycloserine and develop adverse CNS effects. Intrathecal treatment is not the standard of care, but successful use of intrathecal levofloxacin and amikacin for MDR TB has been reported [73].

The use of corticosteroids is widely accepted as adjuvant therapy for CNS TB, particularly for TB meningitis, as well as for CNS TB-associated IRIS (see below) [66]. A meta-analysis of 7 randomized controlled trials concluded that ''corticosteroids should be used routinely in HIV-negative people

Table 4. Drug–Drug Interactions in the Treatment of Central Nervous System Tuberculosis in Patients With HIV Infection and Solid Organ Transplant Recipients

TB drug	Interactions with drugs for HIV infection	Interactions with drugs for transplant recipients
First-line drugs		
Isoniazid	No known interactions with NRTIs, NNRTIs, or PIs	May decrease metabolism of cyclosporine, tacrolimus, and sirolimus through CYP3A4 inhibition; may reduce corticosteroid levels and vice versa [11, 80]; no known interactions with MMF or azathioprine
Rifamycins: rifampicin and rifabutin	Rifampicin decreases concentrations of PIs and NNRTIs [81] and decreases concentrations of the NRTI zidovudine (effect not clinically significant because intracellular concentrations are not substantially changed); rifabutin decreases concentrations of NNRTIs and vice versa but has no known interaction with NRTIs; the NNRTIs efavirez and nevirapine decrease rifabutin concentrations by inducing CYP3A, and most PIs increase rifabutin by inhibiting CYP3A [78, 79]	Increase metabolism of cyclosporine, tacrolimus, sirolimus, MMF, and corticosteroids [7, 11, 82]; significant risk of graft rejection; no known interactions with azathioprine
Pyrazinamide	No clinically significant interaction expected with PIs or NNRTIs; no data on NRTIs [82]	No known interactions with cyclosporine, tacrolimus, sirolimus, MMF, azathioprine, or corticosteroids
Ethambutol	No known interactions with NRTIs, NNRTIs, or PIs	No known interactions with cyclosporine, tacrolimus, sirolimus, MMF, azathioprine, or corticosteroids
Streptomycin	No known interactions with NRTIs, NNRTIs, or PIs	Nephrotoxic effects are additive with cyclosporine; close monitoring is required, and dose should be adjusted if renal function is impaired; no known interactions with tacrolimus, sirolimus, MMF, azathioprine, or corticosteroids
Second-line drugs (most commonly recommended)		
Fluoroquinolones: moxifloxacin and levofloxacin	Moxifloxacin: no clinically significant interaction with NNRTIs or NRTIs; fluoroquinolones and the PIs atazanavir, lopinavir, and saquinavir prolong QTc interval (degree and clinical significance varies), and concomitant use may increase risk of arrhythmia [82]; levofloxacin: no known interaction with NRTIs or NNRTIs	Moxifloxacin: no known interaction with cyclosporine, tacrolimus, sirolimus, or azathioprine [83]; levofloxacin: may increase serum concentration of cyclosporine and tacrolimus [84]; no interaction with sirolimus or azathioprine; fluoroquinolones and tacrolimus both prolong QTc interval (degree and clinical significance varies); concomitant use may increase risk of arrhythmia; fluoroquinolones may decrease serum concentration of MMF, and coadministration of fluoroquinolones and corticosteroids may increase risk of tendon damage
Ethionamide and prothionamide	Ethionamide is metabolized by the CYP450 system, possible interaction with antiretroviral drugs; it is unknown whether doses of ethionamide and/or certain antiretroviral drugs should be modified [78, 85]; prothionamide is structurally very similar to ethionamide, with interactions expected to be the same	No known interactions with cyclosporine, tacrolimus, sirolimus, MMF, azathioprine, or corticosteroids
Amikacin	Coadministration of aminoglycosides and NRTI tenofovir is potentially nephrotoxic; avoid if possible [79, 82]; no clinically significant interaction expected with NNRTIs or PIs	Nephrotoxic effects are additive with cyclosporine; close monitoring is required, and dose should be adjusted if renal function is impaired [86]; no known interactions with tacrolimus, sirolimus, MMF, azathioprine, or corticosteroids
Capreomycin	No clinically significant interaction expected with NRTIs, NNRTIs, or PIs	Nephrotoxic effects are additive with cyclosporine; no known interactions with tacrolimus, sirolimus, MMF, azathioprine, or corticosteroids
Cycloserine	No known interactions with NRTIs, NNRTIs, or PIs; CNS adverse effects of cycloserine may complicate clinical monitoring of underlying CNS disease	No known interactions with cyclosporine, tacrolimus, sirolimus, MMF, azathioprine, or corticosteroids

Drugs for transplant recipients included: cyclosporine, tacrolimus, sirolimus, corticosteroids, mycophenolate mofetil (MMF), and azathioprine.
Abbreviations: CNS, central nervous system; HIV, human immunodeficiency virus; SOT, solid organ transplant; TB, tuberculosis. Drugs for HIV infection included nucleoside analog reverse-transcriptase inhibitors (NRTIs), non-nucleoside reverse-transcriptase inhibitors (NNRTIs), and protease inhibitors (PIs).

Table 5. Treatment of Central Nervous System Tuberculosis in Immunocompetent and Immunocompromised Hosts

Regimen	Drug	Pediatric daily dose	Adult daily dose	CSF penetration (% CSF/Blood with inflammation)	Considerations for patients with HIV coinfection	Considerations for transplant recipients
First-line: 4 drugs for 2 months, then isoniazid plus rifampicin for ≥10 months[a]	Isoniazid	10–20 mg/kg (maximum, 500 mg)	300 mg	Good (90)	Preferred: use identical TB drug regimen in combination with ART containing efavirenz and 2 NRTIs. Some experts recommend increasing efavirenz dose to 800 mg/day in patients >60 kg.[b] If treatment with a PI is necessary, replace rifampin with rifabutin (less effect on levels of PIs). Reduce dose of rifabutin, usually to 150 mg 3 times a week or daily, depending on PI used.[c] Additional combination therapy options are available. Check complete guidelines for treatment and drug-drug interactions.[c] In the continuation phase, patients with CD4 counts <100 cells/μL should receive TB drugs daily or 3 times a week (not twice a week) [81].	Rifabutin has less cytochrome p450 induction and may be used as an alternative to rifampicin [7]. If rifabutin and cyclosporine are coadministered, monitoring cyclosporine levels may assist in dosing [11]. Coadministration of rifampicin and cyclosporine or tacrolimus is typically avoided [11]; if coadministered, increase cyclosporine or tacrolimus dose 3–5-fold and monitor levels closely [8]. If rifamycins are coadministered with corticosteroids, corticosteroid dose may need to be increased 2–3-fold [81]. Isoniazid and rifampicin increase risk of hepatotoxicity [11]; liver enzymes should be monitored during treatment [8]. Consider replacing streptomycin with a fluoroquinolone if there is significant concern for nephrotoxicity [8]. Some experts recommend fluoroquinolones as first-line agents, but their use in CNS TB has not been studied [13].
	Rifampicin	10–20 mg/kg (maximum, 600 mg)	450 mg (<50 kg) or 600 mg (≥50 kg)	Highly variable (7–56)		
	Pyrazinamide	30–35 mg/kg (maximum, 2 g)	1.5 g (<50 kg) or 2.0 g (≥50 kg)	Good, though activity in nonacidic environments is questionable (100)		
	Ethambutol or streptomycin[d]	Ethambutol: 15–20 mg/kg (maximum, 1 g); streptomycin: 20–40 mg/kg (maximum, 1 g)	Ethambutol: 15 mg/kg (maximum, 1 g); streptomycin: 15 mg/kg	Ethambutol: highly variable, poor to good (25–50); streptomycin: fair, with inflammation (0–30)		
MDR TB: initial therapy with at least these 4 drugs[e] (use alternate drugs if index case has proven resistance to any of these); subsequent treatment should be directed by patient resistance profile, national guidelines, and CSF penetration of candidate drugs; 18–24 months total treatment duration	Fluoroquinolone (eg, moxifloxacin or levofloxacin)	Not recommended	Moxifloxacin: 400 mg; levofloxacin: 500–1000 mg	Good, with inflammation (levofloxacin: 30–50; (moxifloxacin: 50)	Typically, treatment duration of ≥24 months; minimum of 18 months after sustained sputum conversion [87]	No published guidelines on management of CNS MDR TB in transplant recipients. Muñoz et al suggest treating initially with 4–5 drugs (isoniazid, pyrazinamide, ethambutol, streptomycin, and/or levofloxacin) and then decreasing the number of agents based on susceptibility tests, but this recommendation is not specific to CNS TB [13]. Fluoroquinolones have been used successfully [86]. No initial dose adjustment is necessary for levofloxacin, but cyclosporine or tacrolimus concentrations should be monitored [84]. Amikacin or streptomycin should be included in the regimen for at least the first 2 months [13]. Prolonged
	Pyrazinamide	30–35 mg/kg (maximum, 2 g)	1.5 g (<50 kg) or 2.0 g (≥50 kg)	Good (100)		
	Ethionamide or prothionamide	15–20 mg/kg (maximum, 1 g)	15–20 mg/kg (maximum, 1 g)	Good (50–100)		
	Injectable agent: (eg, amikacin or capreomycin)	15–30 mg/kg (maximum, 1 g)	15 mg/kg (maximum, 1 g); patients >59 yrs 10 mg/kg (maximum, 750 mg)	Amikacin: fair, with inflammation (0–30); capreomycin: poor		

Adjunctive corticosteroids: recommended for all patients with TB meningitis, regardless of severity; also recommended for tuberculoma and TB radiculomyelitis, but based on limited evidence	Dexamethasone	≤14 years: 0.6 mg/kg (intravenous or PO) for 4 weeks, then reduce course over next 4 weeks	>14 years: stage I TB meningitis: 0.3 mg/kg in week 1, 0.2 mg/kg in week 2, and then 4 weeks of oral therapy; stage II/II: 0.4 mg/kg initially, then reduce course over 6–8 weeks[f]	[89]	Generally recommended for patients with HIV coinfection, but evidence is inconclusive. When IRIS is present or suspected, dexamethasone should be initiated at 4 mg 4 times daily and continued until clinical and radiographic improvement (typically decreased contrast enhancement) is seen; steroids should then be tapered gradually over 3–4 months. If symptoms or enhancement worsen, restart therapy or increase dosage and continue for another 3–4 months before reinitiating taper.	coadministration of levofloxacin and pyrazinamide is associated with gastrointestinal intolerance [88]. No consensus on whether adjunct corticosteroids should be given when not already part of the immunosuppressive drug regimen. Theoretically, the added benefit would be minimal, because patients are already immunosuppressed. Consult with a clinical expert.
	Prednisolone	4 mg/kg (PO or intravenous) for 4 weeks, then reduce course over next 4 weeks				

This table, adapted from British Infection Society guidelines [90] and from Rock et al [2], is for summary and review purposes only. For detailed information and guidelines, refer to the guidelines from the Centers for Disease Control and Prevention (CDC) [91], the American Thoracic Society [81], the British Infection Society [90], the World Health Organization (WHO) [92, 93], and other resources.

Abbreviations: ART, antiretroviral therapy; CNS, central nervous system; CSF, cerebrospinal fluid; HIV, human immunodeficiency virus; IRIS, immune reconstitution inflammatory syndrome; MDR, multidrug resistant; NRTI, nucleoside analog reverse-transcriptase inhibitor; PI, protease inhibitor TB, tuberculosis.

[a] These recommendations are from the British Infection Society guidelines for the diagnosis and treatment of CNS TB in adults and children [90]. In 2003 the CDC recommended an identical regimen, except that the continuation phase of isoniazid and rifampicin may last for 7–10 months [91]. Some experts recommend continuing pyrazinamide for the full duration of therapy owing to concerns about poor penetration of rifabutin once inflammation subsides [94].

[b] Plasma therapeutic drug concentrations may be monitored to determine whether further dose adjustment is necessary.

[c] For more information on drug interactions and dosing, see www.hiv-druginteractions.org and the CDC guidelines for managing drug interactions in the treatment of HIV-related TB [78].

[d] In 2010 the WHO recommended replacing ethambutol with streptomycin in patients with TB meningitis [92].

[e] Cycloserine has good CNS penetration and may also be considered for MDR TB treatment. Intrathecal amikacin and levofloxacin have been successfully used in combination for MDR TB meningitis [73].

[f] Grading system based on modified British Medical Research Council criteria: grade I, Glasgow Coma Scale score of 15 with no focal neurologic signs; grade II, score of 11–14, or 15 with focal neurologic signs; grade III, score of ≤10 [95].

Table 6. Initiation of Antiretroviral Therapy in Patients With HIV and Central Nervous System Tuberculosis, According to CD4 Count

CD4 count, cells/μL	Recommended begin ART (per CDC and WHO guidelines)[a]
>500	Within 8 weeks of starting TB treatment
200–500	Within 2–4 weeks of starting TB treatment or by 8 weeks at latest
<200	Within 2–4 weeks of starting TB treatment

[a] Table adapted from World Health Organization (WHO) and Centers for Disease Control and Prevention (CDC) guidelines [92, 97]. See article by Wells [87] for information on when to initiate ART in patients with multidrug-resistant TB. Abbreviations: ART, antiretroviral therapy; CNS, central nervous system; HIV, human immunodeficiency virus; TB, tuberculosis.

with tuberculous meningitis to reduce death and disabling residual neurologic deficit among survivors" [74]. Potential harms of corticosteroids include decreased penetration of antituberculous medications due to reduced meningeal inflammation, immunosuppression, and gastrointestinal bleeding. Although no randomized controlled trial of steroids has been performed for patients with tuberculoma, most experts recommend coadministration of steroids with antituberculous therapy [75–77].

The most significant drug-drug interactions in HIV-infected patients with TB are due to the rifamycins, which decrease serum concentrations of protease inhibitors and some non-nucleoside reverse-transcriptase inhibitors through induction of the liver enzyme cytochrome P450 and its isoform CYP3A4 [78, 79]. Drug-drug interactions between medications for TB, HIV infection, and SOT are listed in Table 4. Table 5 provides a summary of treatment guidelines for CNS TB in both immunocompetent and immunosuppressed patients.

HIV-Infected Patients

For patients with pulmonary TB and HIV infection who have not recently initiated antiretroviral therapy (ART), emerging evidence supports early initiation of ART to reduce mortality—especially in patients with CD4 cell counts <50 cells/mm³—despite the increased incidence of IRIS (see section below) [96]. The WHO recommends initiation of ART after starting TB treatment irrespective of CD4 cell count (Table 6); however, timing of ART initiation in patients with TB meningitis was not addressed and may differ, as discussed below [90, 98].

A study of TB meningitis in HIV-infected people in Vietnam compared immediate vs. delayed (2 months) initiation of ART for patients with TB meningitis and found no significant difference in mortality; however, patients who initiated ART immediately had higher rates of serious (grade 3 or 4) adverse events. Due to rapidity of death, the authors were unable to determine if these severe reactions were due to IRIS [99].

Two large clinical trials of pulmonary TB in HIV-infected people (SAPIT and the ACTG 5221 STRIDE study) reported ART initiated within 4 weeks of starting TB treatment, in patients with CD4 count <50 cells/mm³, reduced mortality by 68% and 58%, respectively. In both studies, early initiation of ART in people with CD4 cell counts <50 cells/mm³, was associated with higher rates of IRIS (2.2 times and 2.5 times, respectively) and of switching ≥1 antiretroviral medication due to medication toxicity [100, 101]. The Cambodian Early versus Late Introduction of Antiretroviral Drugs (CAMELIA) study enrolled 661 patients with <200 CD4 cells/μL receiving treatment for TB and randomly assigned them to initiate ART either 2 or 8 weeks later. After 50 weeks of follow-up, 59 (17.8%) of 332 participants who started ART 2 weeks after beginning TB treatment had died, while 90 (27.4%) of 329 participants who started ART 8 weeks after beginning TB treatment had died. Of note, none of these studies included people with CNS TB [102].

In some regions of the world, HIV-infected individuals have higher rates of CNS MDR TB, compared with HIV-negative patients, with rates up to 7–12.5% [23, 26, 103] CNS MDR TB in HIV-infected individuals has higher mortality rates and is particularly challenging to treat due to poor CNS penetration of many second-line TB medications [14]. For patients with MDR TB, earlier initiation of ART and prolonged treatment improves survival—see guidelines published elsewhere [78, 87].

HIV Infection and Immune Reconstitution Inflammatory Syndrome

With the widespread availability of ART, IRIS complicates the diagnosis and treatment of CNS TB [104]. Mycobacterial infections comprise ~40% of IRIS cases and cause either unmasking of a subclinical infection or paradoxical recurrence of a previously treated infection. Paradoxical recurrence is driven by antigen-specific immune response to viable bacilli, dead organisms, or remaining antigen; cultures may be negative owing to previous treatment. In a study of 258 patients with pulmonary TB, paradoxical IRIS occurred in 53 (20.5%) and in an additional 8 (3.1%) later during treatment; 6 (10%) of patients with IRIS died [105]. A review of 166 published cases of IRIS associated with mycobacterial infections found that CD4 counts <50 cells/μL, initiation of ART within 2 months of TB treatment, and rapid fall in viral load were risk factors [9]. In the largest series of IRIS affecting the CNS, the median onset of symptoms was 14 days after the beginning of ART [57].

IRIS is particularly worrisome in patients with tuberculoma, in whom new or expanding lesions may cause mass effect, seizures, and clinical deterioration [106, 107]. Compared with tuberculomas in HIV-infected patients not receiving ART, tuberculomas in patients with IRIS have increased perilesional inflammation [107].

Findings in patients with paradoxical TB-associated IRIS (but not CNS TB) and in a series of patients with paradoxical neurologic TB-associated IRIS suggested that steroids improve

morbidity and mortality [57, 107]. In a study of 23 patients with CNS TB-associated IRIS, 21 (91%) received corticosteroids for a median of 58 days (range, 1–49 weeks), and 16 (70%) were still alive at 6 months [57]. Because corticosteroids are recommended for treatment of CNS TB, the same dosing should be useful for preventing IRIS, but prolonged duration and slower incremental tapering is recommended to avoid clinical deterioration.

Transplant Recipients

Treatment of CNS TB in transplant recipients is especially challenging because many TB medications interact with immunosuppressive agents. Rifampicin, in particular, may accelerate the metabolism of cyclosporine, tacrolimus, and corticosteroids and can lead to allograft rejection and higher mortality [7, 11]. Coadministration of rifampicin and cyclosporine is typically avoided, although they may be used together if dosages of both medications are increased [11]. Rifabutin may be used as an alternative to rifampicin because it has less cytochrome p450 induction and theoretically less effect on levels of certain immunosuppressants [7]. Rifampicin, and possibly isoniazid, can increase corticosteroid catabolism and thus affect the level of immunosuppression [109].

Hepatotoxicity is a significant concern in transplant recipients receiving antituberculous therapy, especially after liver transplantation. In one series, hepatotoxicity occurred in 83% of liver transplant recipients after standard TB induction therapy [109]. SOT recipients are at high risk of INH and rifampicin hepatotoxicity, particularly when INH is given as part of a multidrug regimen rather than as a single drug for prophylaxis [11, 13]. MDR TB is rare in transplant recipients (reported incidence, <2%) but will probably increase as transplant programs expand in developing countries [13].

IRIS or paradoxical worsening of pulmonary TB (but not CNS TB) has been described in transplant recipients receiving anti-TB therapy. The time course—within 1–2 months after initiation of anti-TB treatment—and mechanism seem to be similar to HIV-related IRIS. If IRIS is severe, the dose of steroids may be temporarily increased to counteract the exaggerated immune response [110].

OUTCOME

In immunocompetent patients, worse outcome of TB meningitis is correlated with greater neurologic impairment at presentation [2, 41, 48] as well as with the presence of hydrocephalus [30, 111]. Most studies have reported higher mortality rates in HIV-infected patients, with some reporting up to 65% [26, 27, 30, 71]. Factors associated with poor prognosis of TB meningitis in HIV-infected patients include more severe illness at presentation, CD4 cell count <50 cells/µL, and presence of MDR strains [26, 112].

Mortality from tuberculoma is <10% with appropriate antituberculous therapy [31]. Clinical improvement is often delayed and may occur after ≥3 months of treatment [113]. In a small case series of tuberculoma in HIV-infected and HIV-uninfected patients mortality rates were similar in both groups [35]. Because published reports on TB abscess consist mainly of case reports and series, overall mortality rates are not well defined. One review of HIV-infected patients with TB abscess reported that 3 (25%) of 12 HIV patients died within 6 months of follow-up [40].

TB mortality in transplant recipients is high, ranging from 13% to 40% [12]. Disseminated infection, lung transplantation, and receipt of muromonab-CD3 are significantly correlated with higher mortality [7, 11]. Patients who develop TB within the first year after transplantation are more likely to have extrapulmonary manifestations and are at greater risk of death [114].

CONCLUSIONS

CNS TB causes significant morbidity and mortality and is difficult to diagnose and treat. Immunosuppression due to HIV infection or immunosuppressive therapy after transplantation significantly increases the risk of acquiring CNS TB, complicates the clinical presentation, diagnosis, and treatment, and poses a challenge to the clinician attempting to differentiate CNS TB from other potential opportunistic infections.

With some exceptions noted above, HIV infection does not typically alter the radiographic or neurologic presentation of CNS TB; however, CSF pleocytosis is often absent, and patients with CD4 counts <50 cells/µL tend to have abnormal CSF findings less frequently. When a high suspicion for CNS TB is present, further CSF and ancillary testing should be performed and empiric treatment considered, especially if the patient is from an area with endemic TB or has evidence of TB outside of the CNS. ART and IRIS can affect the manifestations and outcome of CNS TB infection.

Physicians treating HIV-infected patients and SOT recipients with CNS TB should be aware of common drug interactions, benefits of adjunctive use of steroids for TB meningitis and IRIS, and lack of consensus regarding timing for initiation of ART. With increased attention to TB diagnosis and treatment from international funding agencies, there is hope that the diagnosis and treatment of CNS TB will become easier and more effective in the near future.

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