Treatment of Tuberculosis in Special Situations

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## TB Epidemiology

<table>
<thead>
<tr>
<th></th>
<th>GLOBAL</th>
<th>USA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infected cases</td>
<td>1.7 billion (33% population)</td>
<td>10 million (4% population)</td>
</tr>
<tr>
<td>Case incidence</td>
<td>8-10 million/year</td>
<td>~ 11,000/year</td>
</tr>
<tr>
<td>Case prevalence</td>
<td>40-50 million</td>
<td>15,000</td>
</tr>
<tr>
<td>Deaths</td>
<td>1.9 million/year</td>
<td>1,000 – 2,000/year</td>
</tr>
<tr>
<td>MDR</td>
<td>Up to 15% (DR and Ecuador)</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>
Treatment of TB in Pregnancy
Pregnancy, Breastfeeding and TB

- Untreated TB is a far greater risk to a pregnant woman and her fetus than is treatment.
- For decades, treatment during pregnancy has been controversial.
- By the 1990’s, the lack of teratogenic effects of first-line agents was evident.

Since TB is increasing worldwide, congenital forms of TB are also increasing.

The mortality rate of congenital TB is as high as 38%.
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Women with Lymph-node Tuberculosis (N=12)</th>
<th>Women with Tuberculosis at Other Extrapulmonary Sites (N=21)</th>
<th>Control Women (N=132)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean duration of gestation — wk</td>
<td>38.9±1.5</td>
<td>38.6±2.1</td>
<td>38.8±1.7</td>
</tr>
<tr>
<td>Infant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean birth weight — g</td>
<td>2894±430</td>
<td>2617±540</td>
<td>2868±498†</td>
</tr>
<tr>
<td>Prematurity — no. (%)</td>
<td>1 (8)</td>
<td>2 (10)</td>
<td>10 (8)</td>
</tr>
<tr>
<td>Low birth weight — no. (%)</td>
<td>1 (8)</td>
<td>7 (33)</td>
<td>14 (11)‡</td>
</tr>
<tr>
<td>Apgar score ≤6 at 1 min</td>
<td>1 (8)</td>
<td>4 (19)</td>
<td>4 (3)‡</td>
</tr>
<tr>
<td>Congenital anomaly</td>
<td>0</td>
<td>0</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Perinatal death — no. (%)</td>
<td>0</td>
<td>2 (10)</td>
<td>2 (2)</td>
</tr>
</tbody>
</table>

*Plus–minus values are means ±SD. P values are for the comparison with the women with tuberculosis at other extrapulmonary sites.

†P=0.04.
‡P=0.01.
<table>
<thead>
<tr>
<th>EVENT</th>
<th>WOMEN WITH LYMPH-NOSE TUBERCULOSIS (N=12)</th>
<th>WOMEN WITH TUBERCULOSIS AT OTHER EXTRAPULMONARY SITES (N=21)</th>
<th>CONTROL WOMEN (N=132)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy-associated</td>
<td>3 (25)</td>
<td>7 (33)</td>
<td>24 (18)</td>
</tr>
<tr>
<td>complications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antenatal hospitalization</td>
<td>1 (8)</td>
<td>5 (24)</td>
<td>3 (2)*</td>
</tr>
<tr>
<td>Preterm labor</td>
<td>1 (8)</td>
<td>2 (10)</td>
<td>14 (11)</td>
</tr>
<tr>
<td>Acute fetal distress†</td>
<td>0</td>
<td>4 (19)</td>
<td>10 (8)</td>
</tr>
<tr>
<td>Mode of delivery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cesarean section</td>
<td>3 (25)</td>
<td>3 (14)</td>
<td>25 (19)</td>
</tr>
<tr>
<td>Forceps delivery</td>
<td>0</td>
<td>2 (14)</td>
<td>8 (6)</td>
</tr>
<tr>
<td>Spontaneous vaginal</td>
<td>9 (75)</td>
<td>15 (71)</td>
<td>99 (75)</td>
</tr>
<tr>
<td>delivery</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*P<0.061 for the comparison with women with tuberculosis at other extrapulmonary sites.

†Acute fetal distress was defined as the presence of any or all of the following: prolonged fetal bradycardia, repeated decelerations, and thick, meconium-stained amniotic fluid in association with cephalic presentation of the infant during labor.
Risks of TB During Pregnancy

- In addition to the risk of congenital TB
  - Increased maternal morbidity
  - Prematurity
  - Small for gestational age births
  - Increased risk of perinatal and early post-natal transmission
  - Up to a six-fold increase in perinatal mortality
Risks of Therapy to the Fetus and Mother

- Mothers who are pregnant or recently post-partum may be at increased risk of liver toxicity.
- With regard to the fetus, INH, RIF, and EMB cross the placenta, but none has been shown to have teratogenic effects.
- SM is the only anti-TB drug shown to be harmful to the human fetus with one study showing 17% of babies with eighth nerve toxicity ranging from mild hearing loss to bilateral deafness.
Breastfeeding

- Most of the TB medications are secreted into breast milk but not in significant concentrations (usually < 1-12% of levels measured in the serum)
- Levels are not likely to lead to toxicity in the infant
- Levels will not be sufficient to protect the infant
- Supplement mom with B6 while breastfeeding
Breastfeeding Should Not be Discouraged for Women Being Treated with First-Line Agents
Risks of Second Line Drugs

- The fluorquinolones have shown toxicity in animal studies and should be avoided if possible.
- The other aminoglycosides and capreomycin probably share the same toxicity as SM but there is no data.
- PAS is likely safe and there are not enough data to comment on cycloserine and ethionamide.
- Recent case series have shown that MDR patients can be successfully treated during pregnancy with no significant observed toxicities in the children.
Treatment Recommendations for Pregnant Women

• Initial regimen should consist of INH, RIF, and EMB
• PZA is not used in the US but there is no data from controlled trial
• When PZA has been used in the US, it has been done so safely
• Minimum treatment duration is nine months
Steroids and TB Treatment
TB Pleural Effusion
Prednisolone and HIV associated TB pleurisy

![Graph showing comparison between Prednisolone and Placebo over different years.](image)
Evidence for Steroids in TB Pleural Disease

- Lee et al, conducted a prospective, double-blind, randomized study of the role of corticosteroids in the treatment of TB pleuritis.
- Forty patients were randomly assigned to take prednisolone 0.75 mg/kg/day orally or placebo for the initial treatment, which was tapered gradually for the next two to three months.
- Twenty-one were treated with steroids and 19 were given a placebo.
- The mean duration from symptoms to relief was 2.4 days in the steroid-treated group, and 9.2 days in the placebo group (p less than 0.05). Complete reabsorption of pleural effusion occurred an average of 54.5 days in the steroid-treated group and 123.2 days in the placebo group (p less than 0.01).
Evidence for Steroids in TB Pleural Disease

- Galarza et al., studied 117 patients in Spain where the study patients received isoniazid 5 mg/kg and rifampicin 10 mg/kg daily for six months.
- They were randomly assigned to a double blind treatment with either prednisone (1 mg/kg/day for 15 days and then tapering off) or placebo during the first month of treatment.
- Fifty seven patients received prednisone and 60 placebo. At the end of the treatment the clinical outcome, the rate of reabsorption of the pleural fluid, the pleural sequelae, as well as lung capacity were similar in both groups.
Evidence for Steroids in TB Pleural Disease

- Elliott and colleagues conducted a collaborative randomized, double-blind, placebo-controlled trial of prednisolone as an adjunct to tuberculosis treatment, in adults with HIV-1-associated pleural TB in Uganda. The primary outcome was death.
- Of 197 participants, 99 were assigned to the prednisolone group and 98 to the placebo group. The mortality rate was 21 deaths/100 person-years (pyr) in the prednisolone group and 25 deaths/100 pyr in the placebo group \( [P = .95] \).
Evidence for Steroids in TB Pleural Disease

- Resolution of tuberculosis was faster in the prednisolone group, but recurrence rates were slightly (though not significantly) higher, and use of prednisolone was associated with a significantly higher incidence of Kaposi sarcoma (4.2 cases/100 pyr, compared with 0 cases/100 pyr \( P = .02 \)).

- In view of the lack of survival benefit and the increased risk of Kaposi sarcoma, the use of prednisolone in HIV-associated tuberculous pleurisy is not recommended.
Lymphatic TB Treatment

- A six-month regimen including HRZE (two months HRZE, four months HR) is recommended
- Although the disease is pauci-bacillary, the development of nodes during therapy or at the end of therapy is common
- Usually there is no evidence of bacteriological relapse
- No role for steroids except perhaps in unusual circumstances of IRIS with HIV co-infection
Bone and Joint TB

- Bone and joint disease due to TB affects all ages but the greatest risk appears to be in those over the age of 65
- Prior to the HIV era, bone and joint disease accounted for about 9% of all extra-pulmonary disease in the US
- Spinal TB or Pott’s is the most common followed by hip and then knee
TB of Bones and Joints

- Diagnosis is ideally made with isolation of the organism from the affected area.
- The diagnosis is supported by:
  - Monoarticular disease
  - Cold abscesses
  - Positive PPD
  - Epidemiological risks
  - Chest x-ray with findings consistent with TB
Treatment of Bone and Joint Disease

- Same therapy as for other forms
- Several studies have shown that six to nine month regimens containing RIF are as effective as 18 month regimens without RIF
- Nine months is favored
- Myelopathy with or without functional impairment responds medically
Tuberculosis of the Spine
Role of Surgery

- The role of surgery comes up most often with the treatment of Pott’s
- A randomized trial of the Medical Research Council comparing surgical debridement with multi-drug regimens found no benefit to surgery
- There are instances where surgery should be considered
Surgical Debridement for Spinal TB

- Despite the results of the MRC study, surgery should be considered for:
  - Failure to respond to therapy despite DOT and evidence of continued infection
  - The relief of cord compression in those with neurological compromise
  - Intractable pain
  - Instability of the spine
TB Meningitis

- Historically, it has been a disease of mostly young children, however, HIV and other forms of immune suppression have led to an increase in older age groups.
- Without therapy, thought to be uniformly fatal.
- Onset is gradual with a prodrome that may last weeks to months marked by headache, malaise, and irritability.
Diagnosis of TB Meningitis

- Can be difficult, need to keep the epidemiologic setting in mind and try to elicit history of recent potential exposure or other risks
- Review the chest x-ray and search for subtle findings of miliary disease
- About 50% of adults will be PPD negative
- The chest x-ray will show evidence of TB in 50% of adults and 90% of kids
### Steroids and Outcome in TB Meningitis in a Pediatric Population

Comparison of Mental, Physical, and Sensory Disability in Steroid and Nonsteroid Treatment Groups at 6 Months' Follow-up

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>&gt;75</th>
<th>&lt;75</th>
<th>Normal</th>
<th>Hemiplegia</th>
<th>Quadriplegia</th>
<th>Normal</th>
<th>Decreased</th>
<th>Blind</th>
<th>Normal</th>
<th>Decreased</th>
<th>Deaf</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steroid, n (%)</td>
<td>34  (52)</td>
<td>31  (48)</td>
<td>42  (64)</td>
<td>16  (24)</td>
<td>8  (12)</td>
<td>54  (85)</td>
<td>6  (10)</td>
<td>3  (5)</td>
<td>57  (95)</td>
<td>3  (5)</td>
<td>0</td>
</tr>
<tr>
<td>Nonsteroid, n (%)</td>
<td>18  (33)</td>
<td>36  (67)</td>
<td>36  (60)</td>
<td>15  (25)</td>
<td>9  (15)</td>
<td>49  (88)</td>
<td>4  (7)</td>
<td>3  (5)</td>
<td>50  (89)</td>
<td>6  (11)</td>
<td>0</td>
</tr>
<tr>
<td>P*</td>
<td>.038</td>
<td>.875</td>
<td>.77</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.31</td>
<td></td>
</tr>
</tbody>
</table>

*P values were calculated by comparing normal with abnormal.*
Evidence for Steroids in CNS TB

- South African Researchers in 1999 conducted a prospective, controlled, randomized study that included continuous lumbar, cerebrospinal fluid pressure monitoring and contrasted CT scanning in 141 consecutive children with TBM at admission.
- All children were then randomly allocated to a nonsteroid group (71 children) or a steroid group (70 children) who received prednisone (first 16 children, 2 mg/kg per day; next 54 children, 4 mg/kg per day) for the first month of treatment.
- ICP monitoring and CT scanning were repeated regularly, and clinical outcome was assessed after 6 months of antituberculosis treatment.

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Evidence for Steroids in CNS TB

- Steroids lowered mortality in stage III TBM significantly.
- Similarly, more surviving children in the steroid group had IQs of greater than 75 than did the those in the nonsteroid group.
- No significant difference was found in the incidence of motor deficit, blindness, or deafness.
- Corticosteroids significantly improved the survival rate and intellectual outcome of children with TBM.
- Enhanced resolution of the basal exudate and tuberculomas by steroids was shown by serial CT scanning. Corticosteroids did not affect ICP.

# CDC Guidelines: TB and Steroids

## TABLE 13. Evidence-based* guidelines for the treatment of extrapulmonary tuberculosis and adjunctive use of corticosteroids†

<table>
<thead>
<tr>
<th>Site</th>
<th>Length of therapy (mo)</th>
<th>Rating (duration)</th>
<th>Corticosteroids‡</th>
<th>Rating (corticosteroids)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymph node</td>
<td>6</td>
<td>AI</td>
<td>Not recommended</td>
<td>DIII</td>
</tr>
<tr>
<td>Bone and joint</td>
<td>6-9</td>
<td>AI</td>
<td>Not recommended</td>
<td>DIII</td>
</tr>
<tr>
<td>Pleural disease</td>
<td>6</td>
<td>All</td>
<td>Not recommended</td>
<td>DI</td>
</tr>
<tr>
<td>Pericarditis</td>
<td>6</td>
<td>All</td>
<td>Strongly recommended</td>
<td>AI</td>
</tr>
<tr>
<td>CNS tuberculosis including meningitis</td>
<td>9–12</td>
<td>BII</td>
<td>Strongly recommended</td>
<td>AI</td>
</tr>
<tr>
<td>Disseminated disease</td>
<td>6</td>
<td>All</td>
<td>Not recommended</td>
<td>DIII</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>6</td>
<td>All</td>
<td>Not recommended</td>
<td>DIII</td>
</tr>
<tr>
<td>Peritoneal</td>
<td>6</td>
<td>All</td>
<td>Not recommended</td>
<td>DIII</td>
</tr>
</tbody>
</table>

*For rating system, see Table 1.
†Duration of therapy for extrapulmonary tuberculosis caused by drug-resistant organisms is not known.
‡Corticosteroid preparations vary among studies. See Section 8.3 for specific recommendations.
Treatment of TB in End Stage Renal Disease (ESRD)
Renal Insufficiency

- Treatment of TB in this setting is not uncommon because of the increased for progressing to active disease of ESRD patients.
- In general, the doses of the anti-TB medications should not be reduced but rather the interval should be increased.
Dosing of TB Medications in Renal Failure

- INH and Rifampin are metabolized by the liver so conventional dosing is used.
- PZA is also metabolized by the liver but active metabolites are excreted by the kidney and requires interval modification.
- EMB is metabolized by the kidney and will need an increase in the dosing interval.
Dosing of TB Medications in Renal Failure

- Strongly consider therapeutic drug monitoring in all patients with renal failure especially diabetic patients, slowly responding patients, and all patients on peritoneal dialysis.
- If the creatinine clearance is 30 ml/minute or less including patients on hemodialysis, dosing for first-line agents:
  - INH 900mg TIW, RIF 600mgTIW, PZA 25-35mg/kg TIW, EMB 15-25mg/kg TIW: all given after dialysis.
Peritoneal Dialysis and TB

- A retrospective study of 10 cases of TB peritonitis complicating continuous ambulatory peritoneal dialysis (CAPD) were identified among 601 dialysis patients between January 1988 and December 1994.

- The patients were treated with isoniazid, rifampicin, and pyrazinamide for 9 to 12 months (mean, 11 months).

- Continuous ambulatory peritoneal dialysis was continued in all patients. Three patients died. Two patients were converted to hemodialysis at 3 months.

- Conclusions: 1) TB peritonitis is a rare but important complication of CAPD, (2) removal of the Tenckhoff catheter is not mandatory in the management of TB peritonitis complicating continuous ambulatory peritoneal dialysis (CAPD), and (3) long-term continuation of CAPD is possible after TBP.
Isoniazid Toxicity in ESRD

- One study observed patients receiving pyridoxine supplements of less than 100 mg/day developed significant CNS toxicity.
- The increased sensitivity of the dialysis population to isoniazid neurotoxicity is predominantly due to abnormal metabolism of pyridoxine resulting in low serum levels of the active metabolite, pyridoxal phosphate.
- In addition, there is rapid clearance of pyridoxal phosphate by hemodialysis, resulting in a severe deficiency of this active metabolite.
- In order to prevent the neurotoxicity associated with isoniazid therapy, the authors of one retrospective study recommended that 100 mg/day of pyridoxine be given as a supplement to hemodialysis patients requiring isoniazid therapy.
TB in ESRD
Clinical Pearls

- Hemodialysis patients and those with creatinine clearance (CrCl) less than 30ml/min should have dose modification of PZA and EMB.

- If dialysis unit assists with DOT, ensure proper documentation. May want DOT staff to come to dialysis unit to do DOT.

- Very little data concerning patients on peritoneal dialysis but likely can be treated with daily regimens but strongly consider therapeutic drug monitoring.

- Be careful with INH associated neurotoxicity
Treatment of Smear and Culture Negative TB
Treatment Algorithm for Culture Negative TB

FIGURE 2. Treatment algorithm for active, culture-negative pulmonary tuberculosis and inactive tuberculosis
Management of TB Drug Allergy
Skin reaction from thiacetazone
Management of Drug Allergy

- Stop all medications if reaction is significant
- After careful history, sequential re-introduction of medications starting with rifampin, then INH
- Try to get patient on an effective regimen
- If reaction severe enough and treatment options limited, strongly consider drug desensitization
Conclusion