TUBERCULOUS MENINGITIS

Summary

- Epidemiology TB, MDR TB
- CNS TB and TBM
- Clinical characteristics
- Pathogenesis
- Diagnosis
  - CSF changes
  - Diagnosis
- Management:
  - TBM
  - Complications
Mycobacterium Tuberculosis

- Characteristic
- Survival
- Molecules, intracellular survival
- Granuloma
- HBHA

\textit{M\text{.}tb.}

- facultative aerobic bacillus 2-4 μm in length and 0.2-0.5 μm in width, acid fast
- Doubling time 13 to 20 hours
- Survives in host by elaborating its own immunological niche
- Delays initiation of adaptive immunity (delays DC response to CCR7 to lymph node
- Adaptive immunity ability to clear organism reduced:
  - Reduced MHC11 ass Ag presentation
  - Reduced activation by IGN gamma
  - Lipoxin 4A generated (anti-inflammatory)
Survival molecules

- Phosphatidylinositol 3-phosphate (PI3P), is continually metabolised by an acid phosphase (SaPM) excreted by infected macrophages (required for phagosome-lysosome fusion)
- Dismutases and reductases counter reactive oxygen species
- ESAT-6
  - Virulence factor binds TLR2 and inhibits cellular immune transcription response via NFκB
  - Important for cell to spread particularly in a granuloma
  - Induced MMP9 by epithelial cells thus attracting more macrophages
- LAM
  - alters TH1 (decreased IL12) to TH2 (increased IL10)
  - Suppresses IFN-γ response
  - Promotes phagocytosis by binding mannose receptors
- Heparin binding hemagglutinin important for dissemination
<table>
<thead>
<tr>
<th>Host defence strategy</th>
<th>Failure mode in tuberculous granuloma</th>
<th>mycobacterial counterstrategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generate granuloma</td>
<td><em>M. tb</em>. Traffic to infect granuloma</td>
<td>Activate specific genes to survive in granuloma within macrophages</td>
</tr>
<tr>
<td>swift and strong adaptive immune response by recruiting effector T cells</td>
<td>Delayed recruitment compared to infections that are cleared</td>
<td>Delay DC migration to node increased T&lt;sub&gt;reg&lt;/sub&gt; and Th2 phenotype</td>
</tr>
<tr>
<td>Rapidly activate adaptive effector T cells</td>
<td>Delayed activation of effector T cells</td>
<td>Render infected cells ‘invisible’ effector CD4 by down-regulation of key mycobacterial antigens and sequestration of mycobacteria within suboptimal antigen-presenting cells</td>
</tr>
</tbody>
</table>

Lahtia Ramakrishnan, Nature 2012
Epidemiology

- PTB:
  - 9.4 million incident cases
  - 14 million prevalent cases
  - 1.3 million deaths in HIV negative patients
  - 0.38 million deaths in HIV positive patients

- 14.8% were EPTB. Of these 5.4% were meningeal
### Burden of Tuberculosis by region

<table>
<thead>
<tr>
<th>Region</th>
<th>New and relapses</th>
<th>Smear Positive</th>
<th>EPTB</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFR (WHO African)</td>
<td>143,404</td>
<td>56</td>
<td>288,834 (20.4)</td>
</tr>
<tr>
<td>AMR (WHO America)</td>
<td>20,012</td>
<td>71</td>
<td>30,934 (15.5)</td>
</tr>
<tr>
<td>EMR (WHO eastern Mediterranean)</td>
<td>46,452</td>
<td>49</td>
<td>87,726 (18.9)</td>
</tr>
<tr>
<td>EUR (WHO Europe)</td>
<td>22,630</td>
<td>38</td>
<td>31,344 (13.6)</td>
</tr>
<tr>
<td>SEAR (WHO South East Asia)</td>
<td>2,124,370</td>
<td>62</td>
<td>329,338 (15.5)</td>
</tr>
<tr>
<td>WPR (WHO Western Pacific)</td>
<td>1,331,353</td>
<td>54</td>
<td>85,849 (6.4)</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>5,780,714</td>
<td>57</td>
<td>854,025 (14.8)</td>
</tr>
</tbody>
</table>

Source: WHO Global report 2010
TBM epidemiology

Majority of clinical episodes had normal CSF
Of abnormal CSF 63% cryptococcal, 28% TBM, bactreial 8%,

Normal: CSF in 5% of TBM 12% cryptococcal
Probably TBM underdiagnosed (large number of sterile abnormal CSF)
Karstead et.al. 21% had acellular CSF

TBM 1%-18%
Canadian database Frequency of TBM 1%
Turkish in-hospital study 18%
Often quoted 5%

Pathophysiology meningitis and complications

• Rich Focus
  – transient bacteraemia results in dissemination throughout, seed occurring mainly in highly oxygenated areas, brain, kidneys. Contained in focus reactivated at some stage

• Immune response contributes to complications
  – Dense granulomatous exudate in the inter-peduncular fossa and suprasellar, peri-pontine areas obstructs CSF flow resulting in hydrocephalus
  – Local vasculitis involving penetrating arteries of the MCS and basilar causing infarcts
  – Tuberculomas:
    • Giant cells from epithelioid cells
  – TB abscess:
    • Central necrosis with AFBs without a granuloma
**Predisposition** (Host genotype/HIV)
- Pulmonary infection M.tb.
- Bacteremia
- Meningeal infection (bacteremia/rupture of "Rich" focus)
- Recruit immune activators
  - $\uparrow$ IL8, TNF-\(\alpha\), IFN-\(\gamma\), IL10
  - $\downarrow$ WCC (neutrophils and lymphocytes)
  - MMP9
  - $\downarrow$ CSF lactate, Protein, $\uparrow$ BBB permeability
- $\downarrow$ Glucose

**Meningitis**
- LOC
- Infarction
- Hydrocephalus
- Cerebral oedema
- $\downarrow$ ICP

**Vasculitis** (infarction)
- Encephalitis (confusion)
- Meningitis (neck stiffness)
- Basal exudate (hydrocephalus)
- $\downarrow$ Glucose

**Pretreatment**
- Survival
  - Glucose $\uparrow$
  - lactate $\downarrow$
  - $\downarrow$ Polymorphs
- Reduced ICP
  - Meningitis Vasculitis
- Timeous treatment
- Delayed treatment
- Coma
  - Hemiplegia
  - Cranial palsies
  - $\uparrow$ ICP
- Death

**Infective (acute bacterial, aseptic (TBM, fungal, Viral, Parasitic, spiro)**
- Non infective (sarcoid, auto-immune disease)
- Neoplastic (primary, secondary, haematological)
- Foreign (SAH, dermoid, epidermoid leaks)
- Drugs (sulfonamides, NSAIDS, INH)

**Inflammatory (infective, non infective)**

**Neoplastic**

**Foreign material** (blood, cystic fluid, drugs)

**Drugs**
Clinical

- TBM presentation is no different to other meningitides
  - Unusually one may have
    - chronic headache for many months
    - mental change, isolated confusion
    - in young children poor feeding, growth and malaise
    - unexplained prolonged (>2 weeks) fever
    - cranial nerve palsies
    - unexplained seizure

- Complications influence clinical features
  - Seizures, CVA, depressed level of consciousness, multiple cranial palsies

- Clinical factors predictive for a chronic meningitis:
  - History >6 days
  - Evidence of TB at another site

**Frequency of Symptoms and Signs in TBM**

<table>
<thead>
<tr>
<th>Symptoms:</th>
<th>Signs:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache (50-80%)</td>
<td>Neck stiffness (40-80%)</td>
</tr>
<tr>
<td>Fever (60-95%)</td>
<td>Confusion (10-30%)</td>
</tr>
<tr>
<td>Vomiting (30-60%)</td>
<td>Coma (30-60%)</td>
</tr>
<tr>
<td>Photophobia (5-10%)</td>
<td>Any cranial nerve palsy (30-50%)</td>
</tr>
<tr>
<td>Anorexia (60-80%)</td>
<td>CN 3 (5-15%)</td>
</tr>
<tr>
<td></td>
<td>CN4 (30-40%)</td>
</tr>
<tr>
<td></td>
<td>CN7 (10-20%)</td>
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<tr>
<td></td>
<td>Hemiparesis (10-20%)</td>
</tr>
<tr>
<td></td>
<td>Monoparesis, quadriparesis</td>
</tr>
<tr>
<td></td>
<td>Aphasia</td>
</tr>
<tr>
<td></td>
<td>Tremor, hemiballismus</td>
</tr>
<tr>
<td></td>
<td>Choreoathetosis</td>
</tr>
</tbody>
</table>
Clinical features

- Prodromal period – fever, myalgia, malaise, headache
  irritability, poor feeding, abdominal pain, drowsiness
- Meningismus
- Altered sensorium, seizures
- Cranial nerve abnormalities
- Focal signs
- Extrameningeal TB
- Metabolic complications
- Tuberculous spinal meningitis
- Tuberculous encephalopathy

Clinical entry criteria
Symptoms and signs of meningitis including one or more of the following: headache, irritability, vomiting, fever, neck stiffness, convulsions, focal neurological deficits, altered consciousness, or lethargy.

<table>
<thead>
<tr>
<th>Clinical criteria</th>
<th>Diagnostic score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptom duration of more than 5 days</td>
<td>4</td>
</tr>
<tr>
<td>Systemic symptoms suggestive of tuberculosis (one or more of the following): weight loss (or poor weight gain in children), night sweats, or persistent cough for more than 2 weeks</td>
<td>2</td>
</tr>
<tr>
<td>History of recent (within past year) close contact with an individual with pulmonary tuberculosis or a positive TST or IGRA (only in children &lt;10 years of age)</td>
<td>2</td>
</tr>
<tr>
<td>Focal neurological deficit (excluding cranial nerve palsies)</td>
<td>1</td>
</tr>
<tr>
<td>Cranial nerve palsy</td>
<td>1</td>
</tr>
<tr>
<td>Altered consciousness</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CSF criteria</th>
<th>Diagnostic score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clear appearance</td>
<td>1</td>
</tr>
<tr>
<td>Cells: 10–500 per µl</td>
<td>1</td>
</tr>
<tr>
<td>Lymphocytic predominance (&gt;50%)</td>
<td>1</td>
</tr>
<tr>
<td>Protein concentration greater than 1 g/L</td>
<td>1</td>
</tr>
<tr>
<td>CSF to plasma glucose ratio of less than 50% or an absolute CSF glucose concentration less than 2·2mmol/L</td>
<td>1</td>
</tr>
</tbody>
</table>
Cerebral imaging criteria

(Maximum category score=6)

- Hydrocephalus 1
- Basal meningeal enhancement 2
- Tuberculoma 2
- Infarct 1
- Pre-contrast basal hyperdensity 2

Evidence of tuberculosis elsewhere

(Maximum category score=4)

- Chest radiograph suggestive of active tuberculosis: signs of tuberculosis=2; miliary tuberculosis=4 2/4
- CT/ MRI/ ultrasound evidence for tuberculosis outside the CNS 2
- AFB identified or Mycobacterium tuberculosis cultured from another source—i.e. sputum, lymph node, gastric washing, urine, blood culture 4
- Positive commercial M tuberculosis NAAT from extra-neural specimen 4

Exclusion of alternative diagnoses

An alternative diagnosis must be confirmed microbiologically (by stain, culture, or NAAT when appropriate), serologically (e.g. syphilis), or histopathologically (e.g. lymphoma). The list of alternative diagnoses that should be considered, dependent upon age, immune status, and geographical region, include: pyogenic bacterial meningitis, cryptococcal meningitis, syphilitic meningitis, viral meningencephalitis, cerebral malaria, parasitic or eosinophilic meningitis (Angiostrongylus cantonensis, Gnathostoma spinigerum, toxocariasis, cysticercosis), cerebral toxoplasmosis and bacterial brain abscess (space-occupying lesion on cerebral imaging) and malignancy (e.g. lymphoma).

HIV and TBM

<table>
<thead>
<tr>
<th>Parameter</th>
<th>HIV uninfected</th>
<th>HIV infected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of symptoms</td>
<td>&gt;6 days</td>
<td>&gt;6 days</td>
</tr>
<tr>
<td>Signs</td>
<td>Similar</td>
<td>Similar. Higher cognitive dysfunction (1 study) Higher frequency of signs outside the CNS</td>
</tr>
<tr>
<td>Cell count</td>
<td>Predominant lymphocytosis</td>
<td>Predominant lymphocytosis (higher frequency of neutrophil predominance Higher chance of normal of low WCC especially with CD4 &lt;50 cells/μl</td>
</tr>
<tr>
<td>Protein</td>
<td>Higher</td>
<td>lower</td>
</tr>
<tr>
<td>Glucose</td>
<td>Low (2.2 mmmol/l)</td>
<td>Low (may be normal)</td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td>present</td>
<td>Less frequent obstructive hydrocephalus</td>
</tr>
</tbody>
</table>
Diagnosis

• Difficult to confirm:
  – High index of suspicion
  – Microscopy yield low (5% to 20% in our environment)
    • 6mls of CSF centrifuged at 3000 g for 15 minutes, layered on to slide 1 cm³ examined immediately has yield of 58%. (perhaps HIV infected patients require a lower volume of CSF (Thwaites, Torok)
  – Culture:
    • Varies from 20% to 80%
    • Takes time (MODS 1 week, Liquid fluorometric cultures 3 weeks, L J medium (4-6 weeks)

• Need rapid diagnosis

CSF Findings

• Typical CSF findings:
  – Lymphocyte pleocytosis
  – Low CSF glucose (2.2 mmol/l)
  – Low CSF: plasma glucose ratio (0.5 or <0.2 in HIV positive)
  – Elevated CSF protein (> 0.5g/L)

• Atypical CSF findings:
  – Early on and in severely immuno-compromised HIV positive neutrophilic (46%) predominance
  – Lower protein level in HIV positive
  – Rarely normal CSF, no cells
Diagnostic methods for TBM (Yields)

- **Microscopy (5%)**
- **Clinical Prediction (50%)**
- **Culture (20%)**
- **PCR (56%), GeneXpert untested (up to 80% if 3 mls CSF, centrifuged used)**
- **Ag-Ab tests (unreliable)**
- **Cytokine assays IFN-γ (90%)**
- **IFN-γ immune responses (90%)**

Rapid diagnosis

- **PCR**
  - GeneXpert untested
  - Standard PCR 98% specific but 56% sensitive
- **Immune based (after excluding cryptococcal and acute bacterial meningitides):**
  - **IGRA (≥46 SFU/million):**
    - 80% sensitive, 92% specific
  - **IFN-γ levels in CSF (≥ 0.244 iu/ml):**
    - 90% sensitive, 95% specific
  - **LAM Ag (≥ 0.18):**
    - 30% sensitive, 100% specific
- **Clinical factors (≥ 6 score)**
  - 31% sensitive, 94% specific
<table>
<thead>
<tr>
<th>Test specifics</th>
<th>Sens (95% CI) [n]</th>
<th>Spec (95% CI) [n]</th>
<th>PPV (95% CI) [n]</th>
<th>NPV (95% CI) [n]</th>
<th>Agreement (95% CI) [n]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smear Microscopy</td>
<td>12 (5;23)*</td>
<td>100 (96;100)</td>
<td>100 (59;100)</td>
<td>61 (21;69)</td>
<td>63 (54;71)</td>
</tr>
<tr>
<td>Centrifuged Xpert® MTB/RIF</td>
<td>82 (62;94)</td>
<td>96 (78;100)</td>
<td>96 (78;100)</td>
<td>82 (62;94)</td>
<td>88 (76;96)</td>
</tr>
<tr>
<td>CPR alone (score ≥8)</td>
<td>30 (14; 50)</td>
<td>100 (85; 100)</td>
<td>100 (83; 100)</td>
<td>55 (39; 70)</td>
<td>62 (47; 75)</td>
</tr>
<tr>
<td>CPR + centrifuged Xpert® MTB/RIF (only done if CPR&lt; 8)</td>
<td>89 (71; 98)</td>
<td>96 (78; 100)</td>
<td>96 (80; 100)</td>
<td>88 (65; 96)</td>
<td>92 (81; 98)</td>
</tr>
<tr>
<td>IFN-γ ≥ 0.244 IU/ml</td>
<td>92% (78;98)</td>
<td>100% (78;100)</td>
<td>100% (90;100)</td>
<td>83% (59;96)</td>
<td>94% (84;99)</td>
</tr>
<tr>
<td>T-SPOT. TB ≥ 46‡</td>
<td>83% (66-92)</td>
<td>100% (78-100)</td>
<td>100% (89-100)</td>
<td>68% (45-86)</td>
<td>67% (75-95)</td>
</tr>
<tr>
<td>Clinical Prediction rule + T-SPOT. TB (≥46)</td>
<td>97% (86-100)</td>
<td>75% (60-86)</td>
<td>75.5% (60-86)</td>
<td>97.3% (86-100)</td>
<td>85% (76-92)</td>
</tr>
<tr>
<td>LM Ag ≥ 0.18</td>
<td>31% (17;48)</td>
<td>95% (74;100)</td>
<td>92% (64;100)</td>
<td>40% (26;56)</td>
<td>52% (38;63)</td>
</tr>
</tbody>
</table>
Rapid diagnosis

- Clinical score (Marais et al.) + clinical suspicion
- Microscopy
  - Ensure adequate volume of CSF, centrifugation (at least 3000 g for 15 minutes)
  - Adequate time (30 minutes) examining slide
- PCR:
  - Xpert after centrifugation using at least 3 mls of CSF
  - Nested PCR
Clinical criteria for TBM

Symptoms and signs of meningitis (headache, vomiting, neck stiffness), fever, seizures, focal neurological deficits (excluding cranial nerve palsies) (1), altered consciousness (1), cranial nerve palsies (2), malaise, history > 5 days (4), night sweats (2), weight loss (2), cough for more than 2 weeks (2), history of close contact with PTB in children <10 years of age (2)

Definite tuberculous meningitis

Clinical criteria with demonstration of M.tubercle in the CSF (by culture, microscopy or PCR)

Probable tuberculous meningitis (requires a score of ≥12 points)

Clinical criteria with

CSF changes:

Clear CSF (1), 10 to 500 cells/μl (1), lymphocyte predominance (>50%) (1), protein level >1g/l (1), CSF: blood glucose ratio <50% (1) or CSF glucose <2.2mmol/l (1)

Imaging changes:

Hydrocephalus (1), basal enhancement (2), parenchymal tuberculomas (2), infarction (1), pre-contrast basal hyperdensity on CT scan (1)

Evidence of tuberculosis elsewhere such as Chest X ray positive for PTB (2), military PTB (4), CT/MRI/ultrasound evidence of TB elsewhere, acid fast bacilli from another site such as sputum, ascitic fluid, urine (by PCR) (4) or microscopy or culture (4)

Possible tuberculous meningitis

Clinical criteria as defined above with diagnostic score of 6 to 9 points without CNS imaging or 6 to 11 points with CNS imaging

Not TBM

Demonstration of an alternate diagnosis

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Clinical meningitis (Headache, neck stiffness, multiple cranial nerve palsy, confusion) in TB endemic HIV prevalent resource poor environment

Focal signs

Yes

CT scan (Hydrocephalus, basal enhancement, infarction) CXR positive for PTB

No

CSF (±1 week history), HIV infected

Hyponatraemia <132 mmol/L

Lymphocytosis ≥ 200 cells/μl

CSF: blood glucose ratio ≥ 0.2

Proteins ≥ 1.0 g/L

CLAT negative, Gram negative

CDS 200 ± cells/μl

Apply clinical score if ≥ 1

Rapid test

Microscopy (m) CSF, 3000 g for 20 minutes, 200ml on slide over 1cm² examine for 30 minutes

PCR (if available)

Positive

IFN-γ level ≥ 0.224 IU/l

CSF ELISPOT ≥ 66 spot forming units

Treat for TBM

Consider alternate diagnosis (Neurosarcoïdosis, Herpes Zostear, CMV, Enterovirus, Neurosarcoidosis)

Negative

If No Contraindication:

Mass lesions (toxoplasmosis, lymphoma, Tuberculoma, Tuberculous or bacterial abscesses)

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Marais et al. LID 2010
TB and ARV

- TB drugs
- Interactions
- MDR and XDR

TBM drug therapy

British Infection Society guidelines for the diagnosis and treatment of tuberculosis of the central nervous system in adults and children

Guy Thwaites a,b,h, Martin Fisher b,l, Cheryl Hemingway c,l, Geoff Scott d,k, Tom Solomon c,l, John Innes f,k,m

J Infect. 2009 (59)
Drug therapy

- **ATS/Thwaites:**
- 7-9 months of antituberculous therapy, four drugs for first 2 months then 2 drugs for rest
- **Our practice**
- **MDR TBM**
  - Little literature
  - Include first line drugs to which the organism is sensitive
  - Add injectable for at least 6 months
  - Quinolone (moxifloxacin)
  - Role of linezolid, prothionamide, newer uncertain

### Drug therapy

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (mg/Kg/d)</th>
<th>Max (mg)/d</th>
<th>Side effects</th>
<th>Duration (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>5-10</td>
<td>400</td>
<td>Hepatotoxicity, neuropathy</td>
<td>Nine</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>10</td>
<td>600</td>
<td>Hepatitis, flu, rash, drug interactions</td>
<td>Nine</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>25-30</td>
<td>1500-2000</td>
<td>Skin photosensitivity, GI upset, anorexia, hepatotoxicity,</td>
<td>Two</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>15-30</td>
<td>1000</td>
<td>Oto/vestibulo toxicity, nephrotoxicity</td>
<td>Two</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>15-20</td>
<td>1600</td>
<td>Optic neuritis, peripheral neuropathy, GI upset arthralgia,</td>
<td>Two</td>
</tr>
<tr>
<td>Drug</td>
<td>Activity</td>
<td>CSF Penetration</td>
<td></td>
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<tr>
<td>------------------</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Isoniazid</td>
<td>Cidal</td>
<td>90%-95%</td>
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<tr>
<td>Rifampicin</td>
<td>Cidal</td>
<td>10%-25%</td>
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<tr>
<td>Pyrazinamide</td>
<td>Static</td>
<td>95%-100%</td>
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<tr>
<td>Ethambutol</td>
<td>Static</td>
<td>10%-50%</td>
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<tr>
<td>Streptomycin</td>
<td>Cidal</td>
<td>20%-25%</td>
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<tr>
<td>Moxifloxacin</td>
<td>Cidal</td>
<td>70%-80%</td>
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<tr>
<td>Ciprofloxacin</td>
<td>Cidal</td>
<td>15%-35%</td>
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<td>Levofloxacin</td>
<td>Cidal</td>
<td>60%-80%</td>
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<tr>
<td>Ethionamide</td>
<td>Cidal</td>
<td>80%-95%</td>
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<tr>
<td>Cycloserine</td>
<td>Static</td>
<td>40%-70%</td>
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</tr>
<tr>
<td>Capreomycin</td>
<td>Static</td>
<td>Unknown</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amikacin</td>
<td>Cidal</td>
<td>10%-25%</td>
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<tr>
<td>Para-amino-salicylic acid</td>
<td>Static</td>
<td>Unknown</td>
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</tr>
<tr>
<td>Thiacetazone</td>
<td>Static</td>
<td>Unknown</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Linezolid</td>
<td>Cidal</td>
<td>80%-100%</td>
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<tr>
<td>Bithaquiline</td>
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<tr>
<td>Delaminid</td>
<td>Cidal</td>
<td>Unknown</td>
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</tbody>
</table>

Timing of ART

Timing of Initiation of Antiretroviral Therapy in Human Immunodeficiency Virus (HIV)--Associated Tuberculous Meningitis

Torok et al.
No difference in outcome between initial and delayed start of ARV
Greater frequency of severe IRIS in early start

Frequency, Severity, and Prediction of Tuberculous Meningitis Immune Reconstitution Inflammatory Syndrome

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14Department of Neurology, National Institute of Neurology Dis...
IRIS

• To consider IRIS:
  • HIV infected persons must respond to ARV (decreased viral load and increase in CD4 count)
  • Close temporal relationship between neurological deterioration and ARV initiation
  • Evidence of an inflammatory reaction
  • Exclusion of alternate diagnosis

• IRIS:
  – Unmasking:
    • ARV therapy reveals a previously undiagnosed infection, thus response to living organism occurs which then can be isolated
  – Paradoxical:
    • Recently successfully treated for an opportunistic infection, deteriorates on a recovering immune response to existing infecting antigens and cause damage. Organism has been cleared.

Frequency and Predictors for IRIS

• Predictors
  • High CSF neutrophil count
  • Positive culture for M.tb.
  • CD4 count <50 cells/µl
  • Viral load ≥2 \( \log_{10} \)
  • High CSF TNF-\( \alpha \), low IFN-\( \gamma \) levels

• Frequency
  • 12-47%
Steroids

Serial MRI to determine the effect of dexamethasone on the cerebral pathology of tuberculous meningitis: an observational study

Guy E. Thwaites, Jenny Macmillan-Hicks, Tan Thanh-Duc, Pham Phuong Mai, Nguyen Thi Dong, Ceranne Fimmen, Nicholas White, Tan Tinh-Hue, and Jeremy Farrar.


Dexamethasone for the Treatment of Tuberculous Meningitis in Adolescents and Adults

Guy E. Thwaites, M.R.C.P., Nguyen Duc Bang, M.D., Nguyen Huy Dung, M.D., Hoang Thi Quy, M.D., Do Tho Huong Oanh, M.D., Nguyen Thi Cam Thoa, M.D., Nguyen Quang Hien, M.D., Nguyen Thi Thuc, M.D., Nguyen Ngoc Hai, M.D., Nguyen Thi Nguyen Lan, Ph.D., Nguyen Ngoc Lan, M.D., Nguyen Hong Duc, M.D., Vu Ngoc Tuan, M.D., Cao Huu Hiep, M.D., Tran Thi Hong Chau, M.D., Pham Phuong Mai, M.D., Nguyen Thi Dong, M.D., Kasia Stepienewska, Ph.D., Nicholas J. White, F.R.C.P., Tian Toh Hien, M.D., and Jeremy J. Farrar, F.R.C.P.


A. All Patients

<table>
<thead>
<tr>
<th></th>
<th>Days</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>100</td>
<td>200</td>
<td>300</td>
<td>9-mo follow-up</td>
</tr>
<tr>
<td>Proportion Surviving</td>
<td>1.0</td>
<td>0.8</td>
<td>0.6</td>
<td>0.4</td>
<td>P=0.01</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

No. at Risk

<p>| | | | | | |</p>
<table>
<thead>
<tr>
<th></th>
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<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexamethasone</td>
<td>271</td>
<td>206</td>
<td>192</td>
<td>165</td>
<td>44</td>
</tr>
<tr>
<td>Placebo</td>
<td>274</td>
<td>179</td>
<td>163</td>
<td>146</td>
<td>37</td>
</tr>
</tbody>
</table>
Steroids and mechanism of benefit

2013/05/02

Tobin et al. Cell 140, 717–730

ART initiation (SA Guidelines)

- CD4 count <350 cells/µl irrespective of WHO clinical stage
- Irrespective of CD4 count
  - All types of TB (in patients with TB/HIV drug resistant or sensitive TB, including extra-pulmonary TB)
  - HIV positive women who are pregnant or breast feeding
- Patients with Cryptococcus meningitis or TB meningitis (defer ART for 4-6 weeks)

- May initiate ART within 7 days of diagnosis if
  - WHO stage 3 or 4 irrespective of CD4 count
  - Patients with TB/HIV co morbidity with CD4 count < 50cells/µl
Drug interactions

<table>
<thead>
<tr>
<th>Antiretroviral Treatment for Adults with Concomitant TB</th>
<th>TB diagnosed before starting ART</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Continue ARV therapy throughout TB treatment.</strong></td>
<td>CD4 count &gt;350/mm³:</td>
</tr>
<tr>
<td><strong>First-line regimen.</strong></td>
<td>Delay ART for two months (until intensive phase of TB therapy is complete).</td>
</tr>
<tr>
<td>Patient can remain on the regimen they are taking.</td>
<td>CD4 count 100 – 350/mm³</td>
</tr>
<tr>
<td><strong>Second-line regimen:</strong></td>
<td>Introduce ART between 2-6 weeks</td>
</tr>
<tr>
<td>The lopinavir/ritonavir dose should be doubled (from 2 tablets 12 hourly to 4 tablets 12 hourly) while the patient is on rifampicin-based TB treatment.</td>
<td>CD4 count of &lt;100/mm³or other serious HIV illness:</td>
</tr>
<tr>
<td><strong>Monitor ALT monthly.</strong></td>
<td>Introduce ART regimen as soon as the patient is stabilized on TB therapy (within 2 weeks after starting TB therapy).</td>
</tr>
<tr>
<td>Reduce lopinavir/ritonavir to standard dose 2 weeks after TB treatment is completed.</td>
<td>First line ART regimen:</td>
</tr>
<tr>
<td>1. Tenofovir 300mg daily</td>
<td></td>
</tr>
<tr>
<td>2. Lamivudine 300mg daily</td>
<td></td>
</tr>
<tr>
<td>3. Efavirenz 600mg at night</td>
<td></td>
</tr>
</tbody>
</table>
## ARV in combination with Rifampicin

<table>
<thead>
<tr>
<th>Drug</th>
<th>Change in dose</th>
<th>Change in Rifampicin</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efavirenz</td>
<td>none</td>
<td>No change</td>
<td>Decreases efavirenz AUC by 22%; no change in rifampin concentration. Efavirenz should not be used during the 1st trimester of pregnancy.</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>none</td>
<td>No change</td>
<td>Nevirapine AUC 37-58% and C min 68% with 200 mg 2x/day dose</td>
</tr>
<tr>
<td>Delavirdine</td>
<td>Not used</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Etavirine</td>
<td>Not used</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

### Single protease inhibitors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Change in dose</th>
<th>Change in Rifampicin</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ritonavir</td>
<td>none</td>
<td>none</td>
<td>Use with caution; decreased AUC by 35%; no change in rifampin concentration. Monitor for antiretroviral activity of ritonavir</td>
</tr>
<tr>
<td>Azatanivir</td>
<td>Not used</td>
<td>N/A</td>
<td>AUC decreased by 95%</td>
</tr>
<tr>
<td>Saquinavir</td>
<td>Not used</td>
<td>N/A</td>
<td>AUC decreased by 82%</td>
</tr>
<tr>
<td>Indinavir</td>
<td>Not used</td>
<td>N/A</td>
<td>AUC decreased by 89%</td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>Not used</td>
<td>N/A</td>
<td>AUC decreased by 84%</td>
</tr>
</tbody>
</table>

### Single protease inhibitors

<table>
<thead>
<tr>
<th>Drug combination</th>
<th>Dose of ARV</th>
<th>Ref Change</th>
<th>effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saquinavir / ritonavir</td>
<td>Not used</td>
<td>No change (600 mg/day)</td>
<td>Use with caution; the combination of saquinavir (1000 mg twice-daily), ritonavir (100 mg twice-daily), and rifampin caused unacceptable rates of hepatitis among healthy volunteers</td>
</tr>
<tr>
<td>Lopinavir/ritonavir (Kaletra)</td>
<td>Increase the dose of lopinavir/ritonavir (Kaletra) to 4 tablets (200 mg of lopinavir with 50 mg of ritonavir) twice-daily</td>
<td>No change (600 mg/day)</td>
<td>Use with caution; this combination resulted in hepatitis in all adult healthy volunteers in an initial study</td>
</tr>
<tr>
<td>Atazanavir / ritonavir</td>
<td>The standard dose of ritonavir-boosted atazanavir (300 mg once daily with 100 mg of ritonavir) should not be used with rifampin</td>
<td>No change</td>
<td>Increased Atazanavir trough concentration by &gt; 90%</td>
</tr>
</tbody>
</table>

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**2013/05/02**
Complications

• SIADH
• Intracranial
  – Hydrocephalus
  – Infarction
  – Encephalitis
• Spinal
  – Myelitis (ischemic, inflammatory, necrotising)
  – Arachnoiditis with polyradiculopathy
  – Extradural abscesses
  – Spinal body disease with compression

Management

• Manage complications:
  – Paraplegia
  – Stroke
  – Arachnoiditis with polyradiculopathy
  – SIADH, avoid dehydration
• Manage
  – TBM:
    • Duration and combination unstudied
    • 7 to 12 months of four drug regimen
    • All qualify for steroids for first 6 weeks
• Drug interactions
• Drug resistant organisms
Suspicion for acute bacterial meningitis

- Immunocompromised, history of CNS disease, new-onset seizure, papilloedema, altered consciousness, or focal neurologic deficit; or delay in performance of diagnostic lumbar puncture

**Yes**

- Blood culture and LP
  - Dexamethasone + empiric antimicrobial therapy
  - CSF findings c/w bacterial meningitis
  - Positive CSF Gram stain
  - Dexamethasone + empiric antimicrobial therapy

**No**

- Blood culture
  - Dexamethasone + empiric antimicrobial therapy
  - Negative CT scan of the head
  - Perform lumbar puncture
  - Dexamethasone + targeted antimicrobial therapy

### Acute Bacterial meningitis

<table>
<thead>
<tr>
<th>Organism</th>
<th>Adults</th>
<th>Children</th>
<th>Infants</th>
<th>Elderly</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptococcus Pneumoniae</td>
<td>30-50%</td>
<td>10-20%</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>Neisseria meningitidis</td>
<td>10-35%</td>
<td>25-40%</td>
<td>Rare</td>
<td></td>
</tr>
<tr>
<td>Hemophilus influenzae</td>
<td>1-3%</td>
<td>40-60%</td>
<td>rare</td>
<td></td>
</tr>
<tr>
<td>Staphylococcus aureus/epiderm</td>
<td>Shunt sepsis in 75%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gram negative</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salmonella typhi</td>
<td>Freq*</td>
<td>20%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shigella</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Listeria monocytogenes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*E Coli, S Agalactae, listeria Monocytogenes*
Therapy when gram stain is helpful

<table>
<thead>
<tr>
<th>Gram stain</th>
<th>Choice of antibiotic</th>
</tr>
</thead>
<tbody>
<tr>
<td>positive cocci</td>
<td>3rd generation cephalosporin + vancomycin</td>
</tr>
<tr>
<td>negative cocci</td>
<td>*Penicillin G</td>
</tr>
<tr>
<td>positive bacilli</td>
<td>Ampicillin + aminoglycoside</td>
</tr>
<tr>
<td>negative Bacilli</td>
<td>3rd generation cephalosporin + aminoglycoside</td>
</tr>
</tbody>
</table>

Culture

<table>
<thead>
<tr>
<th>Culture</th>
<th>Choice of antibiotic</th>
</tr>
</thead>
<tbody>
<tr>
<td>S Pneumoniae</td>
<td>3rd generation cephalosporin + vancomycin</td>
</tr>
<tr>
<td>H Influenzae</td>
<td>Ampicillin or 3rd generation cephalosporin</td>
</tr>
<tr>
<td>N Meningitides</td>
<td>*Penicillin G</td>
</tr>
<tr>
<td>L Monocytogenes</td>
<td>Ampicillin + Gentamicin</td>
</tr>
<tr>
<td>S Agalatiae</td>
<td>Ampicillin + Gentamicin</td>
</tr>
<tr>
<td>Enterobacteriacae</td>
<td>3rd generation cephalosporin + aminoglycoside</td>
</tr>
<tr>
<td>P Aeruginosa</td>
<td>3rd generation cephalosporin + aminoglycoside</td>
</tr>
<tr>
<td>Acinetobacter</td>
<td>3rd generation cephalosporin + aminoglycoside</td>
</tr>
</tbody>
</table>

* Where the prevalence of resistance is <1%

Therapy for Purulent Meningitis

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<tr>
<th>Predisposing factor</th>
<th>Bacterial pathogen</th>
<th>Antimicrobial therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head trauma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basilar skull fracture</td>
<td>S pneumoniae, H influenzae, Gp. A beta haemolytic streptococci</td>
<td>Vancomycin + 3rd generation cephalosporin</td>
</tr>
<tr>
<td>Penetrating trauma</td>
<td>S aureus, coagulase negative staphylococci (S epidermidis), aerobic gm neg bacilli (incl Ps aeruginosa)</td>
<td>Vancomycin + cefepime OR Vancomycin + ceftazidine OR Vancomycin + meropenem</td>
</tr>
<tr>
<td>Post neurosurgery</td>
<td>Aerobic gm neg bacilli, S aureus, coagulase negative staph (esp S epidermidis)</td>
<td>Vancomycin + cefepime OR Vancomycin + ceftazidine OR Vancomycin + meropenem</td>
</tr>
</tbody>
</table>
# CSF picture and diagnosis

<table>
<thead>
<tr>
<th>Polymorphs</th>
<th>Lymphocytes</th>
<th>Protein (g/l)</th>
<th>Glucose (mmol/l)</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>120</td>
<td>1.8</td>
<td>2.1</td>
<td>TBM/Crypto/partially treated bacterial</td>
</tr>
<tr>
<td>1200</td>
<td>100</td>
<td>1.2</td>
<td>0.3</td>
<td>Acute bacterial</td>
</tr>
<tr>
<td>30</td>
<td>30</td>
<td>0.9</td>
<td>2.5</td>
<td>Viral, neurosyphilis</td>
</tr>
<tr>
<td>30</td>
<td>100</td>
<td>1.0</td>
<td>1.8</td>
<td>TBM/viral (herpes, echo, HTLV1)</td>
</tr>
</tbody>
</table>