Pharmacological knowledge gaps in the treatment of TB meningitis

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Viet Nam
TB meningitis: pathogenesis

Bacteremia

↑Inflammation

DEATH (25%)

Arnold Rich
1893-1968

Bull John Hopkins Hosp. 1933;52:5-37
TB meningitis: pathology

- Basal meningitis
- Hydrocephalus
- Infarcts
- Tuberculomas
Treatment: How can we do better?

![Graph showing survival rates for HIV negative and HIV positive groups. The graph includes a Log rank test with P<0.001.]
TBM is a medical emergency

Treatment before the onset of coma is the greatest benefit a physician can give a patient with TBM
What else can we do?

Enhance bacterial killing

Control intra-cerebral inflammation
What’s the optimal anti-tuberculosis drug regimen?

<table>
<thead>
<tr>
<th>Drug</th>
<th>Daily Dose</th>
<th>Route</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Isoniazid</strong></td>
<td>10-15 mg/kg</td>
<td>Oral</td>
<td>12 months</td>
</tr>
<tr>
<td>(max 500mg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Rifampicin</strong></td>
<td>10-20 mg/kg</td>
<td>Oral</td>
<td>12 months</td>
</tr>
<tr>
<td>(max 600mg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Pyrazinamide</strong></td>
<td>30-40 mg/kg</td>
<td>Oral</td>
<td>2 months</td>
</tr>
<tr>
<td>(max 2g)</td>
<td>1.5 g (&lt;50 kg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.0 g (≥50 kg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ethambutol</strong></td>
<td>15-25 mg/kg</td>
<td>Oral</td>
<td>2 months</td>
</tr>
<tr>
<td>(max 1g)</td>
<td>15 mg/kg</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

J Infect. 2009 Sep;59(3):167-87. WHO 2010 guidelines
Intra-cerebral drug penetration

INH
PZA
RIF
ETH
SM

Blood-brain barrier

New agents e.g. FQs

INH
PZA

RIF
ETH
SM
Isoniazid and pyrazinamide

100 children with TBM treated with the 2006 WHO regimen

Isoniazid dose 5mg/kg (range 4-7)

Pyrazinamide dose 27mg/kg (range 21-36)
Rifampicin CSF PK

Dose: 10mg/kg (range 8-14)
Is rifampicin important to TBM outcome?

Rifampicin resistance and bacterial killing in CSF

Rifampicin resistance and survival from TBM

Should we use higher doses for TBM?

**Capetown regimen. South Africa:**
INH 20 mg/kg (maximum 400 mg daily),
RMP 20 mg/kg (maximum 600 mg daily),
PZA 40 mg/kg (maximum 2 g daily)
Ethionamide (ETH) 20 mg/kg (maximum 750 mg daily)
All given in a single daily dose, for **6 months duration**. HIV-infected children are treated for 9 months.

### Complication/Adverse Effect vs. Number (%)

<table>
<thead>
<tr>
<th>Complication/Adverse Effect</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocephalus</td>
<td>75 (40.8)</td>
</tr>
<tr>
<td>No hydrocephalus</td>
<td>72 (39.1)</td>
</tr>
<tr>
<td>Communicating hydrocephalus</td>
<td>37 (20.1)</td>
</tr>
<tr>
<td>Noncommunicating hydrocephalus</td>
<td>34</td>
</tr>
<tr>
<td>VP shunted</td>
<td></td>
</tr>
<tr>
<td>Endoscopic third ventriculostomy</td>
<td>3</td>
</tr>
<tr>
<td>Anti-TB drug-induced hepatotoxicity</td>
<td></td>
</tr>
<tr>
<td>Not tested</td>
<td>41 (22.3)</td>
</tr>
<tr>
<td>Normal ALT &lt; 50 U/L</td>
<td>111 (60.4)</td>
</tr>
<tr>
<td>Grade 1 (mild) ALT 51–125 U/L</td>
<td>18 (9.8)</td>
</tr>
<tr>
<td>Grade 2 (mild) ALT 126–250 U/L</td>
<td>6 (3.2)</td>
</tr>
<tr>
<td>Grade 3 (moderate) ALT 251–500 U/L</td>
<td>6 (3.2)</td>
</tr>
<tr>
<td>Grade 4 (severe) ALT &gt; 500 U/L</td>
<td>2 (1.1)</td>
</tr>
<tr>
<td>Significant nausea and vomiting *</td>
<td>19 (10.3)</td>
</tr>
</tbody>
</table>

*Significant vomiting: vomiting occurring for >2 consecutive days and where separation of drug administration (ETH in the evenings) or additional treatment (antiemetics) was required. Of the 19 patients, 8 with significant vomiting had anti-TB drug-induced hepatotoxicity.

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Higher dose intravenous rifampicin?

- 60 Indonesian adults
- Randomised to:
  - Rif 450mg PO + standard
  - Rif 450mg PO + moxi 400mg
  - Rif 450mg PO + moxi 800mg
  - Rif 600mg IV + standard
  - Rif 600mg IV + moxi 400mg
  - Rif 600mg IV + moxi 800mg

For the first 2 weeks

Rif 600mg IV: CSF AUC 3x the 450mg oral grp

The 4\textsuperscript{th} (or 5\textsuperscript{th}) drug?

- Streptomycin
- Ethambutol
- Ethionamide/Prothionamide
- Fluoroquinolones

Do we know which one is best?

NO
In vivo activity of Fluoroquinolones for TB

Gatifloxacin (WHO TDR) vs Moxifloxacin (TB Alliance)

Outpatient Gatifloxacin Therapy and Dysglycemia in Older Adults

Volume 354:1352-1361

March 30, 2006
Randomized pharmacokinetic and pharmacodynamic comparison of fluoroquinolones for tuberculous meningitis in Vietnamese adults

Fluoroquinolone CSF penetration


*Clin Infect Dis. 2009 Oct 1;49(7):1080-2
Exposure/outcome relationship

**Plasma AUC$_{0-24}$:MIC ratio**

- a. Percent Survival
  - $\leq 112$: 26/30 (86.7%)
  - $> 112, \leq 220$: 15/15 (100.0%)
  - $> 220$: 7/11 (63.6%)
  - $P = 0.031$

- b. Percent with Death/Disability
  - $\leq 149$: 10/34 (29.4%)
  - $> 149, \leq 190$: 8/13 (61.5%)
  - $> 190$: 0/9 (0.0%)
  - $P = 0.008$

**CSF AUC$_{0-24}$:MIC ratio**

- a. Percent Survival
  - $\leq 14.0$: 23/27 (85.2%)
  - $> 14.0, \leq 252$: 20/20 (100.0%)
  - $> 252$: 4/8 (50.0%)
  - $P = 0.004$

- b. Percent with Death/Disability
  - $= 0$: 6/15 (40.0%)
  - $> 0, \leq 246$: 6/32 (18.8%)
  - $> 246$: 6/9 (66.7%)
  - $P = 0.016$
## Comparison of Independent Variables by Total-Drug CSF AUC:MIC Quartile

<table>
<thead>
<tr>
<th>Independent Variable</th>
<th>AUC:MIC Ratio Quartile (Median (Min, Max))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Age</td>
<td>39 (17, 75)</td>
</tr>
<tr>
<td>Glasgow Coma Score</td>
<td>14 (6, 15)</td>
</tr>
<tr>
<td>Lactate</td>
<td>4.4 (2.7, 8.2)</td>
</tr>
<tr>
<td>Creatinine Clearance</td>
<td>84.1 (37.9, 122.4)</td>
</tr>
<tr>
<td>White Cell Count</td>
<td>240 (60, 586)</td>
</tr>
</tbody>
</table>
More data awaited…

High dose rifampicin (15mg/kg) + levofloxacin (1g/24hrs) for 2 months + HZE then 7RH

Versus

Standard drugs at standard doses for 9 months

817 HIV negative/positive adults with TBM randomized

Primary outcome: death and/or disability

Results available March 2015
Controlling intracerebral inflammation improves survival from TBM

2008 Cochrane review

‘Corticosteroids should be routinely used in HIV-negative TBM. There is not enough evidence to support or refute a similar conclusion for those who are HIV positive’

How does dexamethasone save lives?

Thwaites et al. Lancet Neurol. 2007
Green J et al. PLOS One. 2009
Host genes and the selection of adjunctive anti-inflammatory therapy

Polymorphisms in *LTA4H* modulate susceptibility to mycobacteria

LTA4H Genotype is Associated With Mortality & CSF Inflammation in Vietnamese patients with TB meningitis

Survival from TBM

CSF white cells

*LTA4H* Genotype Determines Response to Adjunctive dexamethasone

**NO Dexamethasone**
- C/T (27)
- C/C (27)

**Dexamethasone**
- T/T (13)
- C/T (46)

Survival vs. Days after enrollment

No DEX
- P = 0.042

DEX
- P = 0.005

New data: 650 adults with TBM. All received dexamethasone.

CSF smear positivity

(LTA4H high) AA
(LTA4H low) AG
GG

All patients

HIV negative
Upstream inhibition?

Leukotriene A₄

Lipoxin A₄

LTA₄H

Leukotriene B₄

TNF induction

TNF

inadequate

optimal

excessive

TB drugs + dexamethasone??

TB drugs + dexamethasone?

TB drugs + dexamethasone
Summary: pharmacological knowledge gaps

1. Rifampicin: optimal dose and route of delivery
2. Best 4\textsuperscript{th} drug: fluoroquinolones/ethionamide/ethambutol?
3. Treatment duration: 6 months long enough?
4. Pharmacogenomics: should LTA4H genotype be used to predict anti-inflammatory treatment?
5. Intelligent adjuvants: can we improve upon dexamethasone. Aspirin/thalidomide/anti-TNF.
Thank you

OUCRU TB group