TB; critically ill patients

Reinout van Crevel
This talk

TB in the intensive care
• What brings TB patients tot het ICU?
• Severe immunopathology in TB
• Some thoughts on host-directed therapy in critically ill patients
• Other considerations regarding management

TB meningitis
• Clinical presentation
• Diagnosis
• treatment
Severe hemoptysis: From diagnosis to embolization

Figure 4. Necrotic pneumonia with a pulmonary artery pseudo-aneurysm. a, b: six mm maximum intensity projection, axial (a) and coronal (b) views showing lung consolidation of the ventral segment of the culmen with necrosis (black arrow) and ectasia (white arrow) of a branch of the pulmonary artery representing a pulmonary artery pseudo-aneurysm. This aneurysm requires emergency treatment. The majority of other pulmonary artery aneurysms respond well to appropriate medical therapy.

In infectious disease, the main sign is necrosis which can be identified as a hypodense area within lung parenchymal consolidation which is enhanced by the iodinated contrast media. Late phase CT images or enhanced images can show lung consolidation or ground glass opacity (Fig. 4). This aneurysm requires emergency treatment. The majority of other pulmonary artery aneurysms respond well to appropriate medical therapy.

ARDS

Constrictive pericarditis

Massive lung bleed

large pneumothorax

TB in ICU
Shock 10 days after start of TB treatment

- 55-yr old Indian man, type 2 DM (metformin)
- unilateral pleural fluid, exudative, culture: *M. tuberculosis*
- Started on standard TB drugs
- 10 days later: drowsiness, weak, 3 days of nausea
- Respiratory distress (40 / min), shock (BP 85/40 mm, HR 110/min)
- High lactate, mild liver dysfunction
- Fluids ++, vasopressors ++
- Persistent low blood pressure
- CT: Enlarged adrenal glands
- Hydrocortison: improvement
- Abnormal synacthen (after recovery)
- Adrenal insufficiency triggered by rifamp?
TB patients in intensive care

- ARDS (acute respiratory distress syndrome)
- Respiratory failure (pneumothorax, chronic TB)
- Severe hemoptysis
- Constrictive pericarditis
- Adrenal insufficiency (rifampin..)
- Severe abdominal TB (blow-out)
- ..

- TB ‘sepsis’ and multi-organ failure
- Immunopathology and hyperinflammation
Rapidly progressive disease in an HIV patient

New HIV, CD4 140, cough, mild liver dysfunction
5 weeks later: respiratory failure
Straight to ICU – mechanical ventilation
miliary TB, BAL positive, fully sensitive
Standard TB drugs, ART started 1 week into ICU
Progressive multi-organ failure
Very difficult mechanical ventilation
Severe lung fibrosis (IRIS?)
CMV pneumonitis
Invasive pulmonary Aspergillosis
Cerebral angiitis
...

8 months later..
Inflammation and immunopathology

• Typical for tuberculosis
• Damaging tissue reactions
• Pulmonary cavities
• Lymphnode necrosis
• spondylitis en psoas-abscess
• immunopathology in TB meningitis
• ..
• Both before and during TB treatment
• More frequent with ART in HIV: “IRIS”
Immunopathology in an HIV-neg pt

- Somalian women, 20 years old, HIV-negative
- 2016 pulmonary TB, INH-monoresistence
- 2017 referral: large lung abnormalities
- Stomach pain, admission, abdominal/enteral TB, (sub)ileus, unstable, intensive care
- Prednison on and off, fever ++
- paraparesis, epidural abscess T2-T5,
- Sacral and subcutaneous abscess
- recurrent cervical abscesses
- After start of TB treatment no live, only dead mycobacteria!!
HLH ~ macrophage activation syndrome (MAS)

- Hematologists: hemophagocytic lymphohistiocytosis (HLH)
- Primary (children; mutations affecting cytotoxic T-cells/NK)
- Secondary, triggered by:
  - Infections (EBV, CMV, influenza, HIV...); bacterial; *M. tuberculosis*
  - Malignancies (lymphoma)
  - Auto-immune (juvenile RA, Still’s disease, SLE ... )

- Excessive but ineffective immune activation
  - *fever*
  - *hepatosplenomegaly*
  - *Lymphadenopathy*
  - *hemophagocytosis*
  - *cytopenia*
  - *high CRP*
  - *low fibrinogen, coagulopathy*
  - *high ferritin and triglycerides*
  - *elevated transaminases, LDH*
  - *elevated sIL2R*

Chinese series
8/227 HLH = TB
Mortality: 6 / 8!
hyperinflammation

• 65 yrs, HIV-neg, Indonesian man
• Pulmonary TB en TB pleuritis
• After 1 mth treatment persistent fever and circulatory shock
• No response to low-dose steroids
• No macrophage activation syndrome
• Worsening clinical condition
• Successful trial IL-1 receptor antagonist
Decreased immune host defence

- Afghan woman, 53, type 2 DM, HIV-negative
- Dyspnoe, cough. First amoxi/azitro; then ceftriaxon/cipro
- Respiratory insufficiency, fever, CRP 166, prednisone
- Lung biopsy. Granulomas, AFB++; BAL *M. tuberculosis*
- 80 CD4, 80 CD8

- Trial Interferon-gamma s.c. – gradual improvement
TB patients in intensive care

- ARDS (acute respiratory distress syndrome)
- Respiratory failure (pneumothorax, chronic TB)
- Severe hemoptysis
- Constrictive pericarditis
- TB ‘sepsis’ and shock
- Multi-organ failure
- TB meningitis
- Hyperinflammatory syndromes (including IRIS)
- Severe toxicity
- Tromboembolic complications
- (Nosocomial) superinfections
- Post surgery
- Complications from TB enteritis (‘blow-out’)
- Adrenal insufficiency (rifampicin..)
- ...

...
Management of TB in ICU

• Infection prevention..

• Intensified anti-TB treatment (high-dose or i.v.) & TDM

• Vigilance, diagnostics or empiric Tx for co-infections
• Drainage, surgery, embolization (bleeding), ..

• Supportive care

• Hyperinflammation: consider macrophage activation syndrome
• Corticosteroids?
• Other host-directed therapy?
TB meningitis in ICU (France, n=90)

- 46% immunosuppression (20% HIV)
- Severe findings on brain MRI
- 70% requiring mechanical ventilation
- 2/3 poor outcome
  (death or long-term sequelae)

Cantier M et al, Crit Care 2018
a 27-year old Indonesian MSc student

Progressive headache

Fever +/- sweats

vomiting

Family doctor

ER: LP ‘meningitis’ CFX, amoxi, acyclovir, steroids, Anti-emetics

headache++ vomiting: Side effects?

Desorientation+ Unreactive 39.9 °C ambulance

~1 18 25 27 2 7 12

January February
### Additional examinations

#### Cerebrospinal fluid

<table>
<thead>
<tr>
<th></th>
<th>2 Feb</th>
<th>11 Feb</th>
<th>15 Feb</th>
</tr>
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<tbody>
<tr>
<td>cells</td>
<td>222</td>
<td>107</td>
<td>168</td>
</tr>
<tr>
<td>%PMN</td>
<td>73%</td>
<td>33%</td>
<td>78%</td>
</tr>
<tr>
<td>glucose</td>
<td>2.0 / ?</td>
<td>1.9 / 7.8</td>
<td>2.2 / 5.9</td>
</tr>
<tr>
<td>Protein (g/L)</td>
<td>0.69</td>
<td>1.7</td>
<td>0.85</td>
</tr>
<tr>
<td>Gram</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCR</td>
<td>?</td>
<td>?</td>
<td>+</td>
</tr>
<tr>
<td>Auramine</td>
<td>?</td>
<td>?</td>
<td>+</td>
</tr>
</tbody>
</table>

IGRA: neg (0.07/0.04)
### Aetiology of meningitis in UK adults (n=638)

<table>
<thead>
<tr>
<th>Category</th>
<th>Cause</th>
<th>Count (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Viral</strong></td>
<td><strong>Enteroviruses</strong></td>
<td>127 (20%)</td>
</tr>
<tr>
<td></td>
<td><strong>Herpes simplex virus type 2</strong></td>
<td>52 (8%)</td>
</tr>
<tr>
<td></td>
<td><strong>Varicella zoster virus</strong></td>
<td>43 (7%)</td>
</tr>
<tr>
<td></td>
<td><strong>Herpes simplex virus type 1</strong></td>
<td>3 (1%)</td>
</tr>
<tr>
<td></td>
<td><strong>Epstein-Barr virus</strong></td>
<td>2 (&lt;1%)</td>
</tr>
<tr>
<td></td>
<td><strong>Cytomegalovirus</strong></td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td></td>
<td><strong>Measles</strong></td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td></td>
<td><strong>Mumps</strong></td>
<td>2 (&lt;1%)</td>
</tr>
<tr>
<td><strong>Bacterial</strong></td>
<td><strong>Streptococcus pneumoniae</strong></td>
<td>53 (8%)</td>
</tr>
<tr>
<td></td>
<td><strong>Neisseria meningitidis</strong></td>
<td>29 (5%)</td>
</tr>
<tr>
<td></td>
<td><strong>Haemophilus influenzae</strong></td>
<td>5 (1%)</td>
</tr>
<tr>
<td></td>
<td><strong>Listeria monocytogenes</strong></td>
<td>3 (1%)</td>
</tr>
<tr>
<td></td>
<td><strong>Streptococcus pyogenes</strong></td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td></td>
<td><strong>Streptococcus agalactiae</strong></td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td></td>
<td><strong>Streptococcus oralis</strong></td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td></td>
<td><strong>Mycoplasma pneumoniae</strong></td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td></td>
<td><strong>Fusobacterium spp</strong></td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td></td>
<td><strong>Escherichia coli</strong></td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td></td>
<td><strong>Pseudomonas spp and Klebsiella spp</strong></td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td></td>
<td><strong>Positive 16S PCR with no product identified</strong></td>
<td>2 (&lt;1%)</td>
</tr>
<tr>
<td><strong>Mycobacterial</strong></td>
<td><strong>Mycobacterium tuberculosis</strong></td>
<td>11 (2%)</td>
</tr>
<tr>
<td><strong>Fungal</strong></td>
<td><strong>Cryptococcus neoformans</strong></td>
<td>4 (1%)</td>
</tr>
<tr>
<td><strong>unknown</strong></td>
<td></td>
<td>267 (42%)</td>
</tr>
</tbody>
</table>

‘clinically suspected meningitis’ patients in 42 hospitals in UK
Mc Gill et al, Lancet Inf Dis 2018
Clinical assessment
- Syndromatic approach
- Acute vs chronic
- Non-neurological clues

Epidem. & exposure
- age
- travel
- Exposition
- Vaccination status

Radiology

Microbiological testing

Routine CSF (cerebrospinal fluid)

Immune status
Our student

HIV negative

Admission:
- Slow, drowsy
- Facial nerve palsy
- Deficit left arm

8 weeks admission
- Slight worsening with headache, nausea

Eventual recovery

admission  several weeks later
TB Meningitis..

Hematogenous dissemination
‘Rich foci’ in brainstem or on meninges
Breakthrough to subarachnoid space

‘basal meningitis’

Therefore often:
- cranial nerve palsy
- vasculitis with stroke
- hydrocephalus
Other causes subacute meningitis

**Infectious**
- Syphilis
- Cryptococcal meningitis
- Listeriosis
- Leptospirosis
- Mycoplasma
- Whipple’s disease
- Endemic mycoses
- Brucellosis
- Scrub typhus (*Orienta tsu.*)
- Murine typhus (*Rickettsia typhi.*)
- ...

**Non-infectious inflammatory**
- Neurosarcoïdosis
- Neuro-Behcet
- Malignancies
- Vogt-Koyanagi-Harada
- SLE
- Sjögren
- Aseptic meningitis (NSAIDs, antibiotics, ..)
- Idiopathic hypertropic pachymeningitis
- ..
Bacteriology TB meningitis (Indonesian cohort)

<table>
<thead>
<tr>
<th>Test</th>
<th>reference</th>
<th>culture (n=363)</th>
<th>Clinical Dx (n=690)</th>
</tr>
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<tbody>
<tr>
<td>ZN</td>
<td></td>
<td>20%</td>
<td>12%</td>
</tr>
<tr>
<td>IS6110-PCR</td>
<td></td>
<td>89%</td>
<td>65%</td>
</tr>
<tr>
<td>Xpert MTB/RIF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>liquid culture</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Whatever test:**
- Large volume CSF; preferably > 5 cc
- Centrifugation and sediment
- Strong suspicion: 2nd sample
- No test can exclude TBM!

*Indonesisch cohort (1180 suspects, 15% HIV+). Chaidir L, 2018*
TB meningitis diagnosis

- Epidemiology: exposure & host immune status
- Subacute meningitis
- Cerebrospinal fluid
  - Bacteriological testing lacks sensitivity
  - ‘typical’ CSF (can be atypical)
- CT / MRI
- Extrapulmonary signs (lungs, lymph nodes)
Man from Iraq with intracerebral mass

Non-specific abnormalities chest X-ray, positive TST and IGRA, start TB treatment. No response, referral to Netherlands

CSF: 3 cells, protein 683, glucose 4.1 / ?
Radiological progression
immunophenotyping; Non-Hodgkin lymphoma
Antibiotic treatment for TB meningitis

- Optimal regimen (dose, duration) not defined
- Follows the model for pulmonary TB
- Standard 4-drug regimen
- Cerebrospinal fluid penetration of rifampicin low

Should we increase rifampicin dose?
Should we use/add more potent drugs like FQ?
Bandung: 600 mg i.v. versus standard 450 oral rifampin

All cases (n=60)

Culture-confirmed (n=31)

Ruslami R, Ganiem AR et al, Lancet Inf Dis 2013
Phase 3 Vietnam trial (n=817)

- Standard 9-month regimen containing 10 mg/kg rifampicin
- Intensified regimen containing 15 mg rifampicin and levofloxacin

Heemskerk AD et al. CID 2017
Modelling rifampicin exposure and mortality

Individual patient meta-analysis 3 RCTs
1150 PK measurements from 133 pts

Predicted % survival

Relative change in hazard

Standard dose

Svensson E (Clin Inf Dis. In press)
My next patiënt in ICU..

• Rifampicin 20 mg/kg i.v.
• INH 5 mg/kg i.v. (bolus)
• Moxifloxacin 400 mg i.v.
• Amikacin 15mg/kg i.v.
• Pyrazinamide 30 mg/kg (oral)

(expert opinion..)
Inflammation & immunopathology in TBM

Van Laarhoven, JID 2017

MRIs from Bandung;
Robby Hermawan / Sofiati Dian
Adjuvant corticosteroids

- RCT Vietnam, dexamethason (n=545), *New Engl J 2004*
- Reduced mortality by 30%, especially in mild disease
- No effect on neurological disability
- Waning effect over time
- No proven effect HIV

Torok, *Plos One 2011*
paradoxical reactions (also without HIV)

- Difficulty tapering steroids
- New / bigger tuberculoma’s
- basal exudate
- hydrocephalus
- cerebrale vasculitis / infarcts
- spinal abnormalities
- Abnormal CSF
- extraneural manifestations
- Often steroid-refractory

TB meningitis: paradoxical worsening despite steroids

- Meningitis & stroke
  - Culture: *M. tuberculosis*

2013

- TB drugs & steroids (>6 mths)

2014

- Improving symptoms
  - CSF Culture: neg

Apr

- Decreased consciousness
  - CSF Culture & PCR: neg

Jun

- Adding anti-TNFα

Sep

- Leukocytes
  - 100000

Protein (mg/L)

Leukocytes (cells/μL)
Improving outcome of TB meningitis

Addressing the cascade of care

Targeting immunopathology

high dose antibiotics & good supportive care
TB meningitis

- Rare, life-threatening
- Subacute meningitis, association HIV / immune defect
- Difficult diagnosis
- Low threshold empiric treatment
- High dose rifampicin, consider TB-drugs i.v.
- ‘transaminitis’: don’t stop!
- Adjuvant steroids 6-8 weeks
- Paradoxical reactions also without HIV
- Other host-directed therapy?
TB meningitis in HIV

• More difficult diagnosis
  – Routine CSF less abnormal
  – Broader differential
• Worse outcome
• No gain of early ART
• more IRIS (also “unmasking IRIS” in lung TB)
• Effect steroids on mortality unknown
Radboud TB / NTM

Microbiology

Pulmonology

Wouter Hoefsloot
Martin Boeree
Cecile Maais

Jakko van Ingen
Saskia Kuipers

Pharmacy / Pharmacology

Lindsey te Brake
Rob Aarnoutse
Elin Svensson

Infectious Diseases

Mihai Netea
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Reinout van Crevel

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