Night Fever – TB in the ICU: New faces of the Old Man’s friend

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Conflict of interest: none
Mr N, 55 years old, HIV negative, presented with a productive cough and fever, LFTs (ALT of 120)
CXR showed bilateral infiltrates with pyo-pneumothorax
Case history

- Chest drain was inserted and ventilated (respiratory failure)
- Sputum was positive for AFB (+++). Microscopy - branching filamentous structures (Nocardia)
Case history- what would you do next?

A. TB- start treatment with 1st line agents
B- start treatment with 1st line agents but wait for LFTs to settle
C- Nocardia- start Bactrim
D- TB and Nocardia- treat for both
E- do nothing; this is a false positive AFB (2 to3%)- repeat the test
Case history

- Start anti-TB Rx and Bactrim for Nocardia
- LFTs deteriorated (ALT of 200). TB Rx was stopped. Amikacin, Ofloxacin and ethambutol
- In addition to TB culture, and culture and PCR for Nocardia
  what investigation would you order next?

All the tests are commercially available in SA.
Case history - what would you do next?

A. Gene Xpert MTB/Rif
B. Hain MDRplus and (SL version)
C. Quantiferon Gold IT or T-SPOT TB assay
D. Clearview or Determine LAM TB urine test
E. All of the above tests
F. None of these - this is obviously TB!
Case history

- Correct answer is A or B (Gene Xpert or Hain)
- C (IGRAs) and D (urine LAM) are incorrect. By inference E and F are incorrect.
- Gene Xpert was positive (sensitive to R). Few days later Hain also positive (sensitive to R and I).
- Nocardia culture and PCR also positive from the sputum and pleural fluid
- LFTs deteriorated further; ofloxacin stopped. Then re-challenged with H and R. Successfully extubated.
- Spent a further day in ICU before transfer (AFB+++).
Complexity and problems associated with TB in the ICU

- TB is common, manifestations protean and **mortality significant**
- **Diagnosis**
- ? Absorption (NG vs IV), PKs, drug interactions
- Treatment in special situations (liver, renal, pregnancy)
- **Infection control**
- TB-HIV (**diagnosis**, drug-drug interactions, timing of HAART, IRIS)
- MDR and XDR-TB
Prevalence of TB in the ICU and presentation

- Incidence and prevalence in SA is high so not surprising that it is common in the ICU
  - 500 000 cases per annum (1000 new cases every day!)
  - Half of the cases are HIV infected

1. Setting of HIV- atypical radiographic presentation, EPTB, mixed infection, and CAP picture not uncommon. TB more likely if history of > 2 weeks and nodular infiltrates.

Nyamande K, IJTLID, 2007
Prevalence of TB in the ICU and presentation

2. TB in HIV uninfected often extensive or some other problem precipitating ICU admission (chest infection, PE, renal, liver or other problem)

3. Other respiratory problems, trauma, surgical cases often unmask pre-existing TB cases (1 in 50 prevalent cases, 1 in 10-20 in high burden communities)

4. Miliary or PTB with ARDS (<1%)- mortality 40 to 60%, role of steroids uncertain

Lee K, IJTL, 2011
Sharma SK, IJTL, 2006
Mortality of TB in the ICU

- **Brazilian study** (n=67 over 2 years; 70% HIV-infected); **66% mortality**; half died in the 1st month; 20% had hepatotoxicity; almost 100% had sepsis and 75% had septic shock; 30% had VAP; duration of ventilation was median 7 days; 31% had renal failure
  
  Silva DR, BMC Infect Dis, 2010

- **Taiwanese study** (n= 59 HIV uninfected); mortality= 68%; ~50% had nosocomial pneumonia (associated with high mortality)

- **Korean patients** (n= 32); 59% mortality; 50% had sepsis
  

- **Delayed treatment initiation increases mortality**
  
  Lin S-M, IJTL, 2009
Diagnosis of TB in the ICU - which test and when?
So, what exactly is Xpert MTB/RIF?

- Xpert is an automated real-time PCR platform for the diagnosis of TB and genotypic Rif\(^R\)

- SA DoH plan to replace smear with Xpert for all TB suspects
‘Bazookas’ will help fight TB says Motsoaledi

Kerry Cullinan and Dipuo Sedibe

THE health department has bought 30 multi-million rand machines that can diagnose drug-resistant tuberculosis within two hours rather than the usual four weeks.

Health minister Aaron Motsoaledi unveiled the biggest of these GeneXpert machines, which can process 48 TB tests in a two-hour session, at Prince Mshiyeni Hospital in Durban during a World TB Day function yesterday.

South Africa is the first African

TB was first discovered.

Motsoaledi described the machines as a “revolution”, saying that these were the “bazookas” in the war against TB.

The GeneXpert machines are easy to use and 98 percent accurate. The machines have all been linked to the National Health Laboratory Service’s central computers, which can monitor whether they are being used properly.

One in five South African TB patients has drug-resistant TB, thanks to years of inadequate monitoring and control of TB patients.

Bruce Margot, said many of these patients died in the weeks they spent waiting for their results to come back from laboratories.

“The GeneXpert is a big breakthrough because we can save patients lives by starting them on treatment immediately,” he said.

However, Motsoaledi warned that technology alone could not win the war against TB. For this reason, he also launched a campaign involving house visits to homes of TB patients in areas where there is a high TB rate.

“We need to change the practice of healthworkers are going to visit households in communities with high TB case loads to test people for TB,” he said.

The teams would also screen children for immunisations, offer HIV tests and ensure that pregnant women were attending ante-natal clinics.

“This has already started in Ethekwini which has screened 4 350 people and found 1 390 with TB susceptibility,” said Motsoaledi.

By next TB Day, countrywide teams aim to visit 200 000 homes.

“This is not a once-off camp...
Gandhi and Dheda, Lancet, 2010
Schaaf and Dheda, Clin Chest Med, 2009
Dheda and Warren, Inf Dis Clin N Am, 2010
Xpert MTB/Rif molecular beacon assay

The PCR target is the 81 bp region of the rpoB gene: 5 probes bind to wildtype, but not mutant target.

Each probe is labeled with a different fluorescent dye, permitting simultaneous detection.

Example of Rif-Sensitive Profile – 5 probes & SPC show fluorescence.
Gene Xpert (WHO endorsed)

- **Cost:** R1003 (Path Care) - 19 Jan 2010
- **Indication:** Suspected active TB in HIV-infected and uninfected persons, including those suspected of DR-TB
- **Sample and TT:** Sputum (within 2 hours)
- **Where sited:** Reference or district level laboratory (? clinic)
- **How good is it:** Sensitivity = 97%; Specificity = 99% (smear negative TB = 70%). User-friendly and quick. Closed system.

Low inconclusive rate = 2%.

**Gene Xpert (WHO endorsed)**

- **Interpretation:** +ve test: treat for TB in the clinical context. Negative test does not rule out TB in HIV-infected persons but high NPV in uninfected persons.
  
  Theron and Dheda, AJRCCM, 2011

- **Drawbacks:** Expensive. Need research in HIV-infected persons, in primary clinics, and EPTB. Impact unclear.
Xpert MTB/RIF research gaps
Beyond diagnostic accuracy to patient outcomes

- Early proof of concept studies
- Large scale evaluation studies: What is the diagnostic accuracy?
- Phased demonstration and implementation studies: What is the technical feasibility? What are the short-term patient outcomes?
- Diagnostic RCTs addressing long-term patient outcomes (morbidity, morality etc.)

Secondary questions
RCT of impact of Xpert in the ICU
- 81 patients recruited to date, 52/79 (66%) HIV-infected, 28/76 (37%) died in ICU [HIV rate in those who died was 40% vs 31% in those who survived].

Sensitivity of Xpert 88% (7/8) and of smear 73% (8/11); in addition Xpert detected a further 3 individuals not detected by smear microscopy (11/11 if tests combined vs 8/11 if not combined or 35% relative increase in the rapid diagnostic rate)
DST: Line probe assay

Rifampicin resistance: mutation in the B subunit of rpoB gene; RNA-p

- InnoLiPA assay- Innogenetics, Belgium (CE marked)
- Hain Lifescience GenoType® MTBDRplus (CE marked)
- Davies Diagnostics Pty (Ltd)- Randburg

Barnard M, AJRCCM, 2008
- In WC available if specifically requested (all smear +ve retreatment cases or those failing 1st line regimens)
- Ideally all smear +ve patients should have a Hain MDR+ test

Dowdy DW, Proc Natl Acad Sci U S A. 2008
Hain MDRplus (WHO endorsed)

- **Cost:** R886 (Path Care) - 19 Jan 2010
- **Indication:** Any smear positive patient (state sector - any suspected with DR TB who is smear positive - previous TB, poor response to 1s line therapy, contact of MDR-TB)
- **Sample and TT:** Sputum or culture isolate (same day or 2 to 3 days)
- **Where sited:** reference laboratory
- **How good is it:** Clinical samples (sens, spec): Rif (99; 99%) INH (85; 99%)
Hain MDRplus (WHO endorsed)

- **Interpretation:** +ve test = TB. Treat for INH-resistant or MDR-TB. Negative test rules out DR-TB in a smear-positive patient. Low inconclusive rate.

- **Drawbacks:** Poor performance in smear negative TB (< 50%). Note that 40 to 50% of MDR-TB and 80% of XDR-TB is smear negative. Open system so prone to contamination.

  Barnard M, AJRCCM, 2008
Hain MDR+ sl version- suggested to be used when there is resistance noted. Rapid evaluation of drug-resistance for FQ, AG, capreomycin and ethambutol.

**Only 1 or 2 small studies (total 63 isolates):** FQ (91%), AG/capreo (85%), and ethambutol (69%)

**Cost:** R886 (PC) - 19 Jan 2010
-N= 140 sputum samples

-sensitivity for 2nd line agents is sub-optimal and differs by smear status.

- 42% of XDR-TB samples were indeterminate.

A- all samples

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
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<tbody>
<tr>
<td>Rifampicin&lt;sup&gt;R&lt;/sup&gt; (MTBDRplus)</td>
<td>98.5% (62/64)</td>
<td>100% (4/4)</td>
</tr>
<tr>
<td>Isoniazid&lt;sup&gt;R&lt;/sup&gt; (MTBDRplus)</td>
<td>97% (60/64)</td>
<td>75% (3/4)</td>
</tr>
<tr>
<td>FLQ&lt;sup&gt;R&lt;/sup&gt; (MTBDRsl)</td>
<td>68.9% (37/71)</td>
<td>100% (4/4)</td>
</tr>
<tr>
<td>AG/CP&lt;sup&gt;R&lt;/sup&gt; (MTBDRsl)</td>
<td>77.2% (36/71)</td>
<td>75% (3/4)</td>
</tr>
<tr>
<td>EMB&lt;sup&gt;R&lt;/sup&gt; (MTBDRsl)</td>
<td>92.2% (61/71)</td>
<td>100% (4/4)</td>
</tr>
</tbody>
</table>

Note 1: Specificity was only calculated from 4 drug-sensitive samples. Further samples have been banked and will be run shortly.

Note 2: These results have not been clarified with sequencing and this will likely change the results.

B- smear negative

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
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<tbody>
<tr>
<td>RIF&lt;sup&gt;R&lt;/sup&gt;(MTBDRplus)</td>
<td>98.1% (52/53)</td>
<td>100% (4/4)</td>
</tr>
<tr>
<td>INH&lt;sup&gt;R&lt;/sup&gt;(MTBDRplus)</td>
<td>96.4% (51/53)</td>
<td>100% (4/4)</td>
</tr>
<tr>
<td>FLQ&lt;sup&gt;R&lt;/sup&gt;(MTBDRsl)</td>
<td>83.3% (40/50)</td>
<td>100% (4/4)</td>
</tr>
<tr>
<td>AG/CP&lt;sup&gt;R&lt;/sup&gt;(MTBDRsl)</td>
<td>86.2% (42/50)</td>
<td>100% (4/4)</td>
</tr>
<tr>
<td>EMB&lt;sup&gt;R&lt;/sup&gt;(MTBDRsl)</td>
<td>89.3% (44/50)</td>
<td>100% (4/4)</td>
</tr>
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</table>

B- smear positive

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
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<tbody>
<tr>
<td>RIF&lt;sup&gt;R&lt;/sup&gt;(MTBDRplus)</td>
<td>100% (15/15)</td>
</tr>
<tr>
<td>INH&lt;sup&gt;R&lt;/sup&gt;(MTBDRplus)</td>
<td>100% (15/15)</td>
</tr>
<tr>
<td>FLQ&lt;sup&gt;R&lt;/sup&gt;(MTBDRsl)</td>
<td>54.3% (21/25)</td>
</tr>
<tr>
<td>AG/CP&lt;sup&gt;R&lt;/sup&gt;(MTBDRsl)</td>
<td>64.1% (14/25)</td>
</tr>
<tr>
<td>EMB&lt;sup&gt;R&lt;/sup&gt;(MTBDRsl)</td>
<td>100% (25/25)</td>
</tr>
</tbody>
</table>

Note 1: Specificity for the smear negative samples could not be calculated as there were no known drug sensitive samples that formed part of this group.
Whole blood

- Incubate in the presence of *M. tuberculosis* antigens
- Effector T-cells produce IFN-γ

16-24 hours

- Supernatant removed, and IFN-γ measured by ELISA
- Absorbance measured in ELISA reader
- Results as IFN-γ/ml

Purified PBMCs

Incubate in the presence of *M. tuberculosis* antigens

Effector T-cells produce IFN-\(\gamma\)

IFN-\(\gamma\) binds to antibody on the base of ELISPOT wells

Spots developed and counted (manually or in reader)
Results as Spot Forming Cells (SPC)

T SPOT TB assay, Oxford Immunotec, UK

T cell Extend
positive control

negative control

positive control
500 TB suspects in Cape Town - culture = ref standard

QFT-GIT

<table>
<thead>
<tr>
<th>Test Type</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>PPV (95% CI)</th>
<th>NPV (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CXR (n=311)</td>
<td>99 (95, 100)</td>
<td>28 (22, 34)</td>
<td>40 (34, 46)</td>
<td>98 (91, 100)</td>
</tr>
<tr>
<td>QFT-GIT (n=362)</td>
<td>76 (68, 83)</td>
<td>42 (36, 49)</td>
<td>44 (38, 51)</td>
<td>74 (66, 82)</td>
</tr>
<tr>
<td>QFT-GIT in smear-negatives (n=263)</td>
<td>73 (56, 85)</td>
<td>42 (35, 49)</td>
<td>18 (13, 25)</td>
<td>89 (82, 95)</td>
</tr>
<tr>
<td>TSPOT-TB (n=372)</td>
<td>84 (77, 90)</td>
<td>46 (39, 52)</td>
<td>47 (40, 53)</td>
<td>84 (76, 90)</td>
</tr>
<tr>
<td>TSPOT-TB in smear-negatives (n=274)</td>
<td>74 (57, 87)</td>
<td>46 (39, 52)</td>
<td>18 (12, 25)</td>
<td>92 (85, 96)</td>
</tr>
</tbody>
</table>

TPOT-TB

- Miss 1/3 TB
- Erroneously diagnose active TB in 60% who do not have TB

Ling D and Dheda K, Eur Resp J, 2011
Alere Determine™ TB LAM Ag rapid test and reference card for used for grading and interpretation

Control window (Band indicates valid test)

Patient window (interpret test result using reference card)

Urine Loading platform (60μl)
Urine for the diagnosis of tuberculosis: current approaches, clinical applicability, and new developments
Jonathan Peter, Clare Green, Michael Hoelscher, Peter Mwaba, Alimuddin Zumla and Keertan Dheda

Purpose of review
Urine is increasingly being investigated as a convenient clinical sample for the identification of mycobacterial products for the diagnosis of tuberculosis. The available literature on mycobacterial lipoarabinomannan (LAM) and urine mycobacterial DNA is reviewed.

Recent findings
The available data, despite being extracted from heterogeneous clinical populations and different clinical subgroups, indicate that urine LAM has little diagnostic utility in unselected tuberculosis suspects; however, test characteristics improve in HIV-infected patients, particularly those with advanced immunosuppression (CD4 cell count <200 cells/μl). Methodologies for urine PCR for detection of mycobacterial DNA vary across studies and focus is on standardizing assays with respect to specimen collection, assay design, and processing methodology.

Summary

Clinical Utility of a Commercial LAM-ELISA Assay for TB Diagnosis in HIV-Infected Patients Using Urine and Sputum Samples

Dheda K, PLoS One, 2010
<table>
<thead>
<tr>
<th>Diagnostic test/test combination</th>
<th>HIV uninfected patients</th>
<th>HIV infected patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=30</td>
<td>N=154</td>
</tr>
<tr>
<td></td>
<td>Sensitivity (95% CI)</td>
<td>Specificity (95% CI)</td>
</tr>
<tr>
<td></td>
<td>Sensitivity (95% CI)</td>
<td>Specificity (95% CI)</td>
</tr>
<tr>
<td></td>
<td>N/C</td>
<td></td>
</tr>
<tr>
<td>Sputum smear microscopy</td>
<td>72* (49-88) 13/18</td>
<td>100 (76-100) 12/12</td>
</tr>
<tr>
<td></td>
<td>47* (39-56) 60/127</td>
<td>96 (82-99) 26/27</td>
</tr>
<tr>
<td>LAM ELISA</td>
<td>17* (6-41) 3/17</td>
<td>92 (65-99) 11/12</td>
</tr>
<tr>
<td></td>
<td>59* (50-67) 74/125</td>
<td>98* (94-100) 111/113</td>
</tr>
<tr>
<td>LAM Ag rapid test (cut-point 2)</td>
<td>38* (19-61) 6/16</td>
<td>92 (65-99) 11/12</td>
</tr>
<tr>
<td></td>
<td>52* (43-60) 63/122</td>
<td>98** (93-99) 102/104</td>
</tr>
<tr>
<td>Both (sputum smear and LAM Ag rapid test (cut-point 2))</td>
<td>72 (49-88) 13/18</td>
<td>92 (65-99) 11/12</td>
</tr>
<tr>
<td></td>
<td>69* (61-77) 88/127</td>
<td>93 (77-98) 25/27</td>
</tr>
<tr>
<td>LAM Ag rapid test (cut-point 2) in SN/SS mtb culture +ve pts.</td>
<td>0 (0-49) 0/4</td>
<td>n/a</td>
</tr>
<tr>
<td></td>
<td>45 (33-58) 28/62</td>
<td>n/a</td>
</tr>
</tbody>
</table>

*1 p =0.05; *2p=0.001; *3p=<0.001; &p=0.004; #p=0.02

Specificities are calculated with combined population 1 (cohort) and population 2 (controls) patients
Urine LAM POC test summary in HIV-infected persons

- Urine POC TB test was a useful rule-in test
  (sensitivity of ~50% alone or ~70% when combined with smear microscopy)
- 45% sensitivity in smear negative TB patients
- Rule-in value improved by 5 to 10% with more advanced IS
- Main drawback= useful only in HIV-infected persons with advanced IS
Absorption and PK of 1\textsuperscript{st} line drugs

- Feeding decreases AUC by 20%. What is the NG absorption like? \textbf{No data}.
- Is IV administration better?
  Bioavailability of oral R decreased from 93\% to 68\% after 3 weeks of oral therapy (1\textsuperscript{st} pass effect and auto-induction of enzymes)
- Vd and GFR often increased in the ICU
  R, I, Z are metabolised by the liver with E eliminated by the kidney with a high Vd
- \textbf{Drug-drug interactions} (double steroid dose, increase dose of fluconazole, clarithromycin, warfarin, phenytoin, BZD)
Infection control in the ICU- best practice

- MDR and XDR-TB patients- isolated in negative pressure room, N 95 masks, highest exposure risk during intubation, after extubation and when circuit is broken
- Written SOP (after hours, staffing, expertise in drug regimens)
- GSH policy (isolation, staff from CT ICU will move to ICU with IC facilities)
- Increasing numbers – think about how we will cope with these patients
Infection control

- 0.3u filter masks + fit test
- Infection control measures (patient flow and administrative controls, suitable natural ventilation, air extraction, UV lights etc)
- Ventilated masks (PAPR)
- Health care worker screening
- Administrative infrastructure
### High Incidence of Hospital Admissions With Multidrug-Resistant and Extensively Drug-Resistant Tuberculosis Among South African Health Care Workers

Max R. O’Donnell, MD, MPH; Julie Jarand, BSc, MD; Marian Loveday, BSc, MPhil; Nesri Padayatchi, BSc, MBChB, DCH, DTM+H, DHSM, DPH, MS(Epi); Jennifer Zelnick, MSW, ScD; Lise Werner, MSc; Kasavan Naidoo, MSc, BSc; Iqbal Master, MBChB; Garth Osburn, MBChB; Charlotte Kvasnovsky, MD, MPH; Karen Shean, MSc; Madhukar Pai, MD, PhD; Martie Van der Walt, PhD; Charles R. Horsburgh, MD, MUS; and Keertan Dheda, MBBCh, PhD

(23 XDR-TB and 208 MDR-TB HCWs in KZN)

<table>
<thead>
<tr>
<th></th>
<th>HCWs</th>
<th>General Population</th>
<th>Incidence Rate Ratio (95% C.I.)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annual MDR or XDR-TB Incidence</td>
<td>66.8/100,000</td>
<td>11.7/100,000</td>
<td>5.71 (4.96-6.69)</td>
</tr>
<tr>
<td>Annual MDR-TB Incidence</td>
<td>62.3/100,000</td>
<td>10.7/100,000</td>
<td>5.82 (5.03-6.87)</td>
</tr>
<tr>
<td>Annual XDR-TB Incidence</td>
<td>4.5/100,000</td>
<td>1.04/100,000</td>
<td>4.33 (2.69-8.18)</td>
</tr>
</tbody>
</table>

O’ Donnell, Padayachi, Dheda; Annals Intern Med; 2010
Jarand J & Dheda K, TMIH, 2010
Review of 199 patients with XDR-TB

Dheda K, Lancet, 2010

- Outcomes in high burden settings like South Africa are poorer than in intermediate to low burden settings

Gandhi N and Dheda K, Lancet, 2010
Tuberculosis is common in the ICU and has a high mortality.

Number of new diagnostic tests and intensivists should be familiar with the new diagnostic technologies including Gene Xpert, Hain, and LAM.

IGRAs have no role in the diagnosis of active TB.

TB treatment is characterised by drug-drug interactions and require special regimens in renal failure and liver injury.

Infection control must be taken seriously in the era of MDR and XDR-TB.
Funding Agencies:

- EUFP7
- EDCTP
- NIH Fogerty
- South African National Research Foundation
- South African MRC