Managing Smear Negative Tuberculosis

Douglas Wilson
Department of Medicine
Edendale Hospital
Edendale post mortem diagnosis by TB status \([n = 240]\)

- **Tuberculosis** 68%
- \(*61\%\) of TB cases on Rx diagnosed during final admission
- **14\%** of positive cultures MDRTB

<table>
<thead>
<tr>
<th>Causes of death (Based on the Tenth Revision, International Classification of Disease, 1992)</th>
<th>Rank</th>
<th>Number</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tuberculosis (A15-A19)*</td>
<td>1</td>
<td>77,009</td>
<td>12.7</td>
</tr>
<tr>
<td>Influenza and pneumonia (J10-J18)</td>
<td>2</td>
<td>52,791</td>
<td>8.7</td>
</tr>
<tr>
<td>Intestinal infectious diseases (A00-A09)</td>
<td>3</td>
<td>39,239</td>
<td>6.5</td>
</tr>
<tr>
<td>Other forms of heart disease (I30-I52)</td>
<td>4</td>
<td>26,628</td>
<td>4.4</td>
</tr>
<tr>
<td>Cerebrovascular diseases (I60-I69)</td>
<td>5</td>
<td>25,246</td>
<td>4.2</td>
</tr>
<tr>
<td>Diabetes mellitus (E10-E14)</td>
<td>6</td>
<td>19,549</td>
<td>3.2</td>
</tr>
<tr>
<td>Chronic lower respiratory diseases (J40-J47)</td>
<td>7</td>
<td>15,823</td>
<td>2.6</td>
</tr>
<tr>
<td>Certain disorders involving the immune mechanism (D80-D89)</td>
<td>8</td>
<td>15,736</td>
<td>2.6</td>
</tr>
<tr>
<td>Human immunodeficiency virus [HIV] disease (B20-B24)</td>
<td>9</td>
<td>14,783</td>
<td>2.4</td>
</tr>
<tr>
<td>Ischaemic heart diseases (I20-I25)</td>
<td>10</td>
<td>13,025</td>
<td>2.1</td>
</tr>
<tr>
<td>Other natural causes</td>
<td></td>
<td>254,741</td>
<td>42.0</td>
</tr>
<tr>
<td>Non-natural causes</td>
<td></td>
<td>52,614</td>
<td>8.7</td>
</tr>
<tr>
<td><strong>All causes</strong></td>
<td></td>
<td><strong>607,184</strong></td>
<td><strong>100.0</strong></td>
</tr>
</tbody>
</table>

*Including 604 deaths due to MDR-TB and three (3) deaths due to XDR-TB.*
Sputum smear for acid-fast bacilli is usually negative in patients with HIV and culture-positive TB
The Zone of Uncertainty

- Seriously ill + Ambiguous disease process compatible with TB
- Unable to obtain specimen OR Smear/Xpert test negative
- Intense time pressure + No access to specialist advice

TB or not TB? 

Doctor 

Patient 

Laboratory
Recent developments

1. Implementing the inpatient WHO SNTB algorithm for saves lives and gets patients home sooner
2. The outpatient WHO SNTB algorithm misses 20% of patients with culture-positive PTB
3. Compared to smear - the Xpert MTB-RIF assay rapidly diagnoses more (but not all) patients with culture-positive TB (at $20 / test)
4. A normal CRP is useful to rule out TB in ambulant patients
5. TAC and Section 27 are increasingly interested in TB
Use of a WHO-recommended algorithm to reduce mortality in seriously ill patients with HIV infection and smear-negative pulmonary tuberculosis in South Africa: an observational cohort study

Timothy H Holtz, Gaëtan Kabera, Thuli Mthiyane, Tainos Zingoni, Sidhambaram Nadesan, Douglas Ross, Jennifer Allen, Sekai Chideya, Henry Sunpath, Roxana Rustomjee

<table>
<thead>
<tr>
<th></th>
<th>Standard practice N = 338</th>
<th>WHO algorithm N= 187</th>
</tr>
</thead>
<tbody>
<tr>
<td>On TB Rx</td>
<td>46%</td>
<td>100%</td>
</tr>
<tr>
<td>In hospital after 7 days</td>
<td>38%</td>
<td>27%</td>
</tr>
<tr>
<td>Alive after 8 weeks</td>
<td>68%</td>
<td>83%</td>
</tr>
</tbody>
</table>
Algorithm for the diagnosis of tuberculosis in seriously ill HIV-positive patient

Seriously ill patient with cough 2–3 weeks and danger signs

Referral to higher level facility

Parenteral antibiotic treatment for bacterial infection
Sputum AFB and culture
HIV test
CXR

Immediate referral not possible

Parenteral antibiotics for bacterial infection
Consider treatment for PCP
Sputum AFB and culture
HIV test

HIV+ or unknown

AFB-positive
AFB-negative

Improvement after 3–5 days
No improvement after 3–5 days

Reassess for other HIV-related disease
TB unlikely

Start TB treatment
Complete antibiotics
Refer for HIV and tuberculosis care

The danger signs include any one of: respiratory rate >30/min, fever >39 °C, pulse rate >120/min and unable to walk unaided.
Rapid Molecular Detection of Tuberculosis and Rifampin Resistance

Catharina C. Boehme, M.D., Pamela Nabeta, M.D., Doris Hillemann, Ph.D., Mark P. Nicol, Ph.D., Shubhada Shenai, Ph.D., Fiorella Krapp, M.D., Jenny Allen, B.Tech., Rasim Tahirli, M.D., Robert Blakemore, B.S., Roxana Rustomjee, M.D., Ph.D., Ana Milovic, M.S., Martin Jones, Ph.D., Sean M. O’Brien, Ph.D., David H. Persing, M.D., Ph.D., Sabine Ruesch-Gerdes, M.D., Eduardo Gotuzzo, M.D., Camilla Rodrigues, M.D., David Alland, M.D., and Mark D. Perkins, M.D.
Diagnosis

RESULTS

Among culture-positive patients, a single, direct MTB/RIF test identified 551 of 561 patients with smear-positive tuberculosis (98.2%) and 124 of 171 with smear-negative tuberculosis (72.5%). The test was specific in 604 of 609 patients without tuberculosis (99.2%). Among patients with smear-negative, culture-positive tuberculosis, the addition of a second MTB/RIF test increased sensitivity by 12.6 percentage points and a third by 5.1 percentage points, to a total of 90.2%. As compared with phenotypic drug-susceptibility testing, MTB/RIF testing correctly identified 200 of 205 patients (97.6%) with rifampin-resistant bacteria and 504 of 514 (98.1%) with rifampin-sensitive bacteria. Sequencing resolved all but two cases in favor of the MTB/RIF assay.

Positive in 72% of patients with smear-negative PTB
Feasibility, diagnostic accuracy, and effectiveness of decentralised use of the Xpert MTB/RIF test for diagnosis of tuberculosis and multidrug resistance: a multicentre implementation study

Catharina C Boehme, Mark P Nicol, Pamela Nabeta, Joy S Michael, Eduardo Gotuzzo, Rasim Tahirli, Ma Tarcela Gler, Robert Blakemore, William Worodria, Christen Gray, Laurence Huang, Tatiana Caceres, Rafail Mehdiyev, Lawrence Raymond, Andrew Whitelaw, Kalaiselvan Sagadevan, Heather Alexander, Heidi Albert, Frank Cobelens, Helen Cox, David Alland, Mark D Perkins

Lancet 2011; 377: 1495-1505
Published Online
April 19, 2011
DOI:10.1016/S0140-6736(11)60438-8
Diagnosis

Findings: We enrolled 6648 participants between Aug 11, 2009, and June 26, 2010. One-off MTB/RIF testing detected 933 (90.3%) of 1033 culture-confirmed cases of tuberculosis, compared with 699 (67.1%) of 1041 for microscopy. MTB/RIF test sensitivity was 76.9% in smear-negative, culture-positive patients (296 of 385 samples), and 99.0% specific (2846 of 2876 non-tuberculosis samples). MTB/RIF test sensitivity for rifampicin resistance was 94.4% (236 of 250) and specificity was 98.3% (796 of 810). Unlike microscopy, MTB/RIF test sensitivity was not significantly lower in patients with HIV co-infection. Median time to detection of tuberculosis for the MTB/RIF test was 0 days [IQR 0–1], compared with 1 day (0–1) for microscopy, 30 days (23–43) for solid culture, and 16 days (13–21) for liquid culture. Median time to detection of resistance was 20 days (10–26) for line-probe assay and 106 days (30–124) for conventional drug-susceptibility testing. Use of the MTB/RIF test reduced median time to treatment for smear-negative tuberculosis from 56 days (39–81) to 5 days (2–8). The indeterminate rate of MTB/RIF testing was 2.4% (126 of 5321 samples) compared with 4.6% (441 of 9690) for cultures.
Am J Respir Crit Care Med. 2011 Apr 14. [Epub ahead of print]

Evaluation of the Xpert(R) MTB/RIF Assay for the Diagnosis of Pulmonary Tuberculosis in a High HIV Prevalence Setting.

RESULTS:
Overall, Xpert®MTB/RIF detected 95% (95% CI: 88-98%; 89/94) of smear-positive culture-positive cases and 47% (33-61%; 22/47) of smear-negative culture-positive cases, with an overall specificity of 94% (91-96%; 320/339).

The sensitivity in smear-negative cases was 55% when analysis was restricted to 1ml of unprocessed sputum and culture time-to-positivity of ≤28 days.
Proposed algorithm incorporating the GeneXpert assay into routine clinical care
[Wendy Stephens, NHLS]

1st Xpert assay will miss 23% of confirmed TB cases
2nd Xpert assay will miss 15% of confirmed TB cases

### Table 4. Performance of CRP as a screening test: Confirmed tuberculosis vs. those with possible tuberculosis or without tuberculosis (n = 364).

<table>
<thead>
<tr>
<th>CRP quotient</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>Positive likelihood ratio (95% CI)</th>
<th>Negative likelihood ratio (95% CI)</th>
<th>Diagnostic odds ratio (95% CI)</th>
<th>Positive predictive value (95% CI)</th>
<th>Negative predictive value (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;1 x ULN</td>
<td>0.97 (0.92; 0.99)</td>
<td>0.4 (0.34; 0.47)</td>
<td>1.62 (1.45; 1.81)</td>
<td>0.07 (0.03; 0.20)</td>
<td>22.0 (7.8; 61.6)</td>
<td>0.49 (0.42; 0.55)</td>
<td>0.96 (0.90; 0.99)</td>
</tr>
<tr>
<td>≥2.5 x ULN</td>
<td>0.95 (0.90; 0.98)</td>
<td>0.56 (0.50; 0.63)</td>
<td>2.17 (1.86; 2.53)</td>
<td>0.09 (0.04; 0.19)</td>
<td>23.6 (10.5; 52.7)</td>
<td>0.56 (0.49; 0.63)</td>
<td>0.95 (0.90; 0.98)</td>
</tr>
<tr>
<td>≥5 x ULN</td>
<td>0.88 (0.81; 0.93)</td>
<td>0.67 (0.60; 0.73)</td>
<td>2.66 (2.19; 3.22)</td>
<td>0.18 (0.11; 0.28)</td>
<td>14.9 (8.3; 27.0)</td>
<td>0.61 (0.54; 0.68)</td>
<td>0.90 (0.85; 0.94)</td>
</tr>
<tr>
<td>≥10 x ULN</td>
<td>0.69 (0.60; 0.77)</td>
<td>0.80 (0.74; 0.85)</td>
<td>3.43 (2.59; 4.55)</td>
<td>0.39 (0.30; 0.50)</td>
<td>8.8 (5.4; 14.3)</td>
<td>0.67 (0.58; 0.75)</td>
<td>0.81 (0.76; 0.86)</td>
</tr>
</tbody>
</table>

doi:10.1371/journal.pone.0015248.t004
Diagnosis

2010 the South African National Health Laboratory Service processed more than 3 million smears and 900,000 cultures.

South Africa is / will be funding Xpert TB/RIF in the public sector.

Effective implementation is dependent on much more than just installing the test in the laboratory.
“Trudeau well said, ‘there is a rich man’s tuberculosis and a poor man’s tuberculosis. The rich man recovers and the poor man dies.’ This succinctly expresses the close embrace of economics and pathology.”

(Norman Bethune, CMAJ, 1932)
Logistics and Leadership

Diagnosis and Treatment
Transparency of the national tuberculosis programme’s budget would ensure accountability

“We’ve got no money, so we’ve got to think”

Rutherford
Logistics and Leadership

• A large national survey to determine risk factors associated with default in TB treatment, noted that unfavourable perception of healthcare workers’ attitude by patients carried a 12-fold higher risk of default

• ‘Manpower is the ultimate manifestation of national commitment’
  – British historian Michael Howard during the Cold War
Logistics and Leadership

• Private sector:
  – US$ 8 billion
  – 70% of doctors
  – 55% of nurses
  – 15% of the population

• Public sector
  – US$ 7.2 billion
  – 85% of the population
  – TB is a disease of poverty
Scylla and Charybdis

Presumption

Despair
Logistics and Leadership

• Systems, like politics, are local
  – Managers need to be aware of the issues faced by on-the-ground healthcare workers and ensure their continued ‘buy-in’ to systems changes.

• Ideas are easy
  – Sustained implementation in highly stressed resource-constrained health programmes is remarkably difficult.

• The impact of a new system on current workload should be kept to a minimum
  – Should make the lives of healthcare workers easier rather than more difficult.
Logistics and Leadership

• There are health care workers motivated by more than self-interest
  – Willing to work as a part of a well functioning tuberculosis service
  – If the environment were conducive and a rational and carefully designed programme existed.

• Media campaigns using sophisticated and audience-appropriate advertising with celebrity endorsement.

• Healthcare workers involved in all levels of the programme should pass an accreditation examination every three to five years.
Logistics and Leadership

• Personnel involved in the TB programme should be easily recognizable by specific badges

• Frontline healthcare workers who are routinely exposed to tuberculosis
  – OSD to compensate for specialized knowledge and infection risks
  – Supported by a sound infection control procedures, regular testing for HIV infection and isoniazid prophylaxis

• Line management structures need to be transparent, accountable and empowered to support effective local solutions
What do healthcare workers want?

Regular salary
Recognition / Autonomy
Professional growth

Exercising professional skill
Satisfactory clinical outcomes

Safe
Well equipped
Interactive
Efficient
Predictable

Environment

Personal

Job satisfaction

Good patient care
Retention of skilled doctors
Items needed in clinics to collect specimens for TB testing

Sputum collection:

- Specimen container with screw lid

Nebulization:

- Electrical power point
- Ultrasonic nebulizer
- Compatible tubing – disposable
- Masks – disposable
- 3% (hypertonic) saline
- Salbutamol multi-dose inhaler
- Sterilizing solution
- Resuscitation trolley with oxygen and tubing, paediatric and adult masks that connect to an Ambu-bag, oral airways (various sizes), suction catheters and suction machine, intravenous cannulae, fluids and giving sets, adrenaline and atropine ampoules
- Core biopsy needles - disposable
- 0.9% saline solution – sterile
- Formalin solution

Gastric lavage:

- Paediatric and adult nasogastric tubes
- Lubricant
- 50 mL syringes with compatible nozzle
- Litmus paper
- Sterile saline
- Sodium carbonate buffer solution

Extrapulmonary specimen collection:

- Hypodermic needles (various sizes)
- Syringes (various sizes)
- Skin disinfectant (e.g. chlorhexidine-alcohol)
- Soap and running water
- Sterile plastic test tubes with screw cap
- Middlebrook 7H9 solution (or equivalent) for direct inoculation of aspirated specimens
- Glass microscope slides with frosted edge
- Cytology fixative spray
- Lead pencils
- Sterile packs with towels, drapes and swabs
- Sterile gloves – various sizes
- Spinal needles – various sizes
- Lignocaine solution - sterile
- Scalpel blades – disposable
- Core biopsy needles - disposable
- 0.9% saline solution – sterile
- Laboratory forms
- Sealable plastic bags for transportation of individual specimens
- Adhesive labels
- Non-sterile gloves
- N95 masks for healthcare workers, surgical masks for coughing patients
- Clinic rooms with widely open windows and well-ventilated waiting areas
- Electric fan and electric heater
Logistic steps – getting the result to the patient

1. Entry of patient’s name and contact details into the tuberculosis suspect register.
2. Collection of clinically relevant specimens, including at least two sputum specimens coughed on the same day (‘spot-spot’)
3. Labelling the specimen container (preferably before it is used by the patient) and tightening lid to prevent leakage
4. Completion of the laboratory form
5. Uniting specimen and form either in a plastic bag or with an elastic band
6. Storage of specimens at a single point for collection and transport to the district laboratory
7. Transport of the bio-hazardous specimens to the laboratory in a safe and timely manner
8. Return of smear and culture results to the clinic
9. Results filed, given to the patient and acted upon

Only 32% of KZN patients with proven MDRTB start treatment
Diagnosis

Shrewd use of robust information technology, such as that used widely in the private sector, including financial institutions and retailers, could be helpful in managing large numbers of specimens

Unique patient identifier
Ensuring rapid and accurate diagnosis

and

Effective and uninterrupted treatment
Idealism is fostered by hope

Realism is fostered by experience

Scepticism is fostered by uncertainty

Cynicism is fostered by disappointment
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