Clinical approach to respiratory OIs

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Department of Medicine
Pulmonary OIs in inpatients

- Pulmonary presentations commonest reason for hospitalisation
- Missing the diagnosis is often fatal
- Novel diagnostics (Xpert & uLAM) have improved TB diagnosis, but 40-60% unable to produce sputum
- In Southern African hospitals empiric diagnoses are made in most inpatients
Case 1

28 year old man, newly diagnosed HIV+
5 days: Cough mucopurulent sputum
Fever & rigors
R pleuritic chest pain
Temp 38.2°C
Respiratory rate 23/min
BP 108/78
Oriented
Crackles and bronchial breathing R base
Hb 13.5 WCC 17.1 Pl 255
Bacterial pneumonia in HIV

100-fold increased incidence
Increased risk with lower CD4 count
As in HIV-, diagnosis is clinical: illness <2 weeks & consolidation on CXR

Aetiology:  
- *Streptococcus pneumoniae*  \(\text{COMMON}\)
- *Haemophilus influenzae*
- *Staphylococcus aureus*
- *Klebsiella pneumoniae*
- “Atypical” bacteria  \(\text{UNCOMMON}\)
Case 2

36 year old man interrupted ART for 8 months
CD4 count 122
3 weeks: Progressive dyspnoea
  Dry cough
Temp 37.9°C
Respiratory rate 38/min; O₂ saturation 90%
BP 124/84
Oriented
No focal chest signs
Hb 12.3 WCC 7.2 Pl 248
Pneumocystis pneumonia

Definitive diagnosis is by bronchoalveolar lavage, fungi identified by stain or by fluorescent Ab stain. Induced sputum not as sensitive but is specific. PCR is unable to distinguish between infection & colonisation. Quantitative PCR shows promise.

Silver stain showing cysts of *Pneumocystis jirovecii*
Clinical features of pneumocystis pneumonia

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adjusted odds ratio (95% CI)</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Respiratory rate model</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chest X-ray possible/likely PJP</td>
<td>6.994 (3.769 to 12.979)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Haemoglobin $\geq 9$ g/dL</td>
<td>2.518 (1.236 to 5.131)</td>
<td>0.011</td>
</tr>
<tr>
<td>Respiratory rate (per 10 increase)</td>
<td>2.199 (1.524 to 3.172)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td><strong>Oxygen saturation model</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chest X-ray possible/likely PJP</td>
<td>6.459 (3.455 to 12.074)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Haemoglobin $\geq 9$ g/dL</td>
<td>2.071 (1.008 to 4.255)</td>
<td>0.048</td>
</tr>
<tr>
<td>Saturation $&lt; 94%$</td>
<td>4.967 (2.643 to 9.334)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>
Case 3

31 year old man
Newly diagnosed HIV
9 weeks: Night sweats
Weight loss
Cough
Temp 37.6°C
Respiratory rate 28/min
BP 98/70
Mild confusion
Crackles and dullness LUZ
Hb 7.9 WCC 5.3 Pl 589
WHO TB symptom screen in inpatients

Study of urine LAM in GF Jooste hospital, Cape Town
All HIV+ patients included (except those on TB Rx/known TB)

<table>
<thead>
<tr>
<th>TB status</th>
<th>WHO screen positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>No TB</td>
<td>88.9%</td>
</tr>
<tr>
<td>TB</td>
<td>97.1%</td>
</tr>
</tbody>
</table>

P=0.005
Not clinically significant

Lawn BMC Medicine 2017;15:67
CXR to diagnose TB in inpatients

<table>
<thead>
<tr>
<th>Feature</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffuse micronodular (miliary)</td>
<td>6.45 (2.20-18.87)</td>
</tr>
<tr>
<td>Hilar/mediastinal nodes</td>
<td>2.34 (1.58-3.47)</td>
</tr>
<tr>
<td>Nodularity &gt;3 mm</td>
<td>2.21 (1.49-3.28)</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>1.24 (0.84-1.82)</td>
</tr>
<tr>
<td>Cavitation</td>
<td>1.01 (0.68-1.49)</td>
</tr>
<tr>
<td>Interstitial</td>
<td>0.92 (0.62-1.37)</td>
</tr>
<tr>
<td>Consolidation</td>
<td>0.86 (0.57-1.29)</td>
</tr>
<tr>
<td>TB “possible” (vs “unlikely”)</td>
<td>2.13 (1.00-4.54)</td>
</tr>
<tr>
<td>TB “likely” (vs “unlikely”)</td>
<td>11.01 (4.92-24.66)</td>
</tr>
</tbody>
</table>

48.8% prior TB

Overall impression

Not helpful

Griesel CID 2018
TB clinical prediction rule (TB symptoms not useful)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Category</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temp &gt;39°C</td>
<td>yes</td>
<td>1</td>
</tr>
<tr>
<td>Unable to walk</td>
<td>yes</td>
<td>1</td>
</tr>
<tr>
<td>Tuberculosis on chest radiograph</td>
<td>possible</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>likely</td>
<td>5</td>
</tr>
<tr>
<td>Cough ≥14 days</td>
<td>yes</td>
<td>1</td>
</tr>
<tr>
<td>Haemoglobin (g/dL)</td>
<td>3.3 - 8.3</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>8.4 - 10.6</td>
<td>2</td>
</tr>
<tr>
<td>WCC (x10^9/L)</td>
<td>1 - 6.5</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>11.2 - 40.4</td>
<td>-2</td>
</tr>
</tbody>
</table>
Clinical prediction rule performance

<table>
<thead>
<tr>
<th>Total score</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤1</td>
<td>100.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>2</td>
<td>95.2%</td>
<td>28.8%</td>
</tr>
<tr>
<td>3</td>
<td>92.2%</td>
<td>45.4%</td>
</tr>
<tr>
<td>4</td>
<td>87.2%</td>
<td>59.3%</td>
</tr>
<tr>
<td>5</td>
<td>78.6%</td>
<td>67.7%</td>
</tr>
<tr>
<td>6</td>
<td>66.0%</td>
<td>80.3%</td>
</tr>
<tr>
<td>7</td>
<td>50.8%</td>
<td>90.5%</td>
</tr>
<tr>
<td>8</td>
<td>39.1%</td>
<td>93%</td>
</tr>
<tr>
<td>9</td>
<td>31.2%</td>
<td>96.4%</td>
</tr>
<tr>
<td>10</td>
<td>19.5%</td>
<td>97.9%</td>
</tr>
<tr>
<td>11</td>
<td>5.9%</td>
<td>99.6%</td>
</tr>
<tr>
<td>12</td>
<td>0.2%</td>
<td>100.0%</td>
</tr>
</tbody>
</table>
Sputum induction (5% saline ultrasonic nebuliser)

Successful in >80% of patients who can’t produce sputum

Increases yield of Xpert, smear & TB culture

Useful to diagnose pneumocystis pneumonia

Risk of TB transmission
Ultrasound for diagnosing TB

• **MOST** patients with low CD4 counts have disseminated TB

• Abdominal nodes ≥10 mm, splenic hypodensities, & effusions (pleural, pericardial, or ascites) independently associated with TB

• Systematic review – pooled sensitivity 63%, specificity 68%

• Point of care ultrasound can suggest TB rapidly

Griesel OFID 2019
Van Hoving Cochrane Database Syst Rev 2019
Van Hoving JAIDS in press
Ultrasound vs CXR for TB diagnosis

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>CXR</td>
<td>55%</td>
<td>84%</td>
</tr>
<tr>
<td>US</td>
<td>76%</td>
<td>69%</td>
</tr>
</tbody>
</table>
Could CRP & procalcitonin help differentiate?

- CRP & PCT valuable for deciding on antibiotic use in lower respiratory tract infections in HIV-

- Both available as point-of-care tests

- CRP is a useful rule out test for HIV-TB

- Conflicting results of CRP to differentiate HIV+ CAP, TB, & PJP

  - No data on PCT in this setting

Arch Intern Med. 2011;171(15):1322
Int J Tuberc Dis. 2017;21(9):1013
CRP in HIV+ patients with pulmonary OIs

BMC ID 2018;18:399
Procalcitonin in HIV+ patients with pulmonary OIs
Only CAP vs PJP significant when using cut-off >0.5 for bacterial cause LRTI
CRP & procalcitonin – poor discrimination
(AUC of 1 is a perfect test, AUC of 0.5 is a useless test)
Co-infections (CAP diagnosed clinically):
Cape Town study of inpatients n=284

Clin Infect Dis DOI: 10.1093/cid/ciz332
Bacterial infections by diagnosis using quantitative PCR (>10^5 copies/mL)

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Number</th>
<th>Number (%) with bacterial infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>TB</td>
<td>148</td>
<td>61 (41%)</td>
</tr>
<tr>
<td>CAP</td>
<td>100</td>
<td>52 (52%)</td>
</tr>
<tr>
<td>Pneumocystis</td>
<td>26</td>
<td>9 (35%)</td>
</tr>
</tbody>
</table>

Clin Infect Dis DOI: 10.1093/cid/ciz332
TB (53%), bacterial pneumonia (50.6%), and pneumocystis pneumonia (10.5%) accounted for 91.5% of admissions with cough & WHO danger signs in recent Cape Town study.
Algorithm for managing people living with HIV and suspected of having TB (seriously ill)

- HIV-positive or unknown* and
- Seriously ill, suspected of having TB* and danger signs*

Immediate referral not possible
- Xpert MTB/RIF®
  - Parenteral antibiotics for treatment of bacterial infections*
  - Consider treatment for Pneumocystis pneumonia
  - Chest X-ray if available

Immediate referral to a higher level facility

If CXR compatible or tachypnoea/O₂ sat <94%

At district hospital

Or uLAM

Xpert MTB/RIF-positive
- Treat for TB*
- ART
- Co-trimoxazole preventive therapy

TB cultures

Xpert MTB/RIF-negative* or no test available
- Clinical worsening or no improvement after 3–5 days
- Improvement after 3–5 days

Immediate referral to a higher level facility

TB Unlikely
- Reassess for other HIV-related diseases
- ART assessment*
- Isoniazid preventive therapy
- Co-trimoxazole preventive therapy
- Complete the course of parenteral antibiotics
If you start TB Rx empirically essential to monitor response
Less common respiratory opportunistic infections

Fungi: Disseminated endemic mycoses (e.g. histoplasmosis, emeromycosis), cryptococcosis – biopsy muocutaneous papules or ulcers

Nocardia

Viruses poorly characterised: influenza more severe in HIV+, CMV often found on bronchoscopy with pneumocystis – seldom a pathogen

Toxoplasmosis
Non-infectious causes of pulmonary infiltrates

Kaposi Sarcoma

Lymphocytic interstitial pneumonitis