Subclinical and Incipient TB
Lessons from history

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Binary conceptualization of TB...

Driven by the diagnostic and treatment paradigm...
“The distinction between latent and clinical tuberculosis, which is not infrequently made, has no other basis than the limitations of diagnostic methods and the tendency of tuberculosis to proceed to recovery.”

- Opie and Andersen 1920
Human autopsy studies in those dying from non-TB causes

Post-mortem CXR

Guinea Pig inoculation to determine viable bacilli

Localization of Primary complexes

Localization of minimal TB disease lesions

Opie, J.Exp Med - 1917
Opie and Aronson, Archives of Pathology - 1927

Medlar, Am. Rev Tuberc - 1948
Subclinical TB

Latent

Subclinical TB

Clinical TB

Pathology

Time (months)

Symptoms

CXR

Culture

Adapted Esmail et al Phil Trans R Soc B 2014
FDG-PET/CT for detection of Subclinical TB *in vivo*?
FDG-PET/CT in HIV-1 infected classified as having LTBI

35 symptom -ve, QuantiFERON +ve, CXR no active TB, culture –ve, HIV-1 infected, ART naïve, CD4 > 350/mm³, living in Khayelitsha township, no history of previous TB

No evidence subclinical pathology

Evidence of subclinical pathology

FDG-PET/CT in HIV-1 infected classified as having LTBI

35 symptom -ve, HIV-1 infected, ART naïve, CD4 > 350/mm³, QuantiFERON +ve, CXR no active TB, culture –ve, living in Khayelitsha township, no history of previous TB

Evidence of subclinical pathology
Subset of active TB transcripts identify subclinical disease

Esmail et al – PNAS 2018
Incipient TB – Transcript signatures predict TB progression

- 6363 SA HIV-uninfected adolescents followed for 2 years with 6 months blood
- 53% QuantiFERON +ve, 1.3% developed disease over 2 years
- Transcripts of 46 progressors compared to 107 controls

ROC curve showing predictive potential of 16 transcript signature
Kinetics of Subclinical TB

- 277 TST-ve Nursing students USA 1935-9
- All became TST positive (tested 4mthly)
- CXR (4mthly) – over > 3 years
- 29 (10.4%) developed pulmonary lesions

- Rapid progression 5/29 (17%)
- Slow progression 10/29 (34%)
- Rapid Regression 6/29 (21%)
- Slow Regression 3/29 (10%)
- Undetermined 5/29 (17%)

Israel et al JAMA 1941
Kinetics of Subclinical TB: Impact on diagnostic performance

- Meta-analysis of performance of validated TB transcriptional signatures to predict TB
- 17 validated diagnostic signatures; 4 datasets - 127 cases of incipient TB
- 8 signatures had similar performance

**Time before disease presentation (months)**

<table>
<thead>
<tr>
<th>Time</th>
<th>PPV</th>
<th>Sens</th>
<th>Spec</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-3mths</td>
<td>6.8-9.4 %</td>
<td>25-40 %</td>
<td>92-95 %</td>
</tr>
<tr>
<td>0-6mths</td>
<td>8.3-10.3 %</td>
<td>33-52 %</td>
<td>92-95 %</td>
</tr>
<tr>
<td>0-12mths</td>
<td>9.5-11.7 %</td>
<td>43-57 %</td>
<td>91-95 %</td>
</tr>
<tr>
<td>0-24mths</td>
<td>11.1-14.3 %</td>
<td>47-81 %</td>
<td>91-95 %</td>
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Gupta et al – Lancet Resp Med *in press*
What is the optimal Tx for different parts of disease spectrum?

Number of imperfect tests that loosely relate to pathological spectrum of disease...

- CXR suggestive of active TB and 5x culture –ve
- 68% had symptoms (60% cough)
- 173 not treated – intensive f/u

**Hong Kong 1984**
Active follow-up of 655 CXR+ with 5x Cult-ve

- 2 mths (2SHRZ)
- 3 mths (3SHRZ)
- 12 mths (3SHP/9S2H2)

- 41% in 2 mths
- 6.2% in 3 mths
- 3.1% in 12 mths
- 0.6% Nil
What is the optimal Tx for different parts of disease spectrum?

Number of imperfect tests that loosely relate to pathological spectrum of disease...

TST/IGRA
Sub/Incip
CXR
Sympt
Cult
Smear

- 191 CXR suggestive of active TB and culture –ve
- No symptoms or other signs of disease
- Randomized to 6H_{200}PAS_{10} or observation
- 24 month f/u

- 17.8% bact/radiographic deterioration (control)
- 8.5% bact/radiographic deterioration (6HPAS)

TB Scotland, Tubercle 1958
Conclusions

❖ Binary approach to TB reflects the diagnostic and treatment paradigm

❖ Disease pathology may precede disease presentation by months - years

❖ Likely that novel tests for incipient TB detect those with early disease

❖ Most early disease will be identified by active case finding

❖ Optimal treatment is unclear
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