Transmission and Pathogenesis of Tuberculosis

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Slides adapted from James Watts, Phil Hopewell

Transmission and Pathogenesis of Tuberculosis

• Introduction to the pathogen
• Transmission
  – source case factors
  – environmental factors
  – contact factors
• Pathogenesis--5 stage model

Mycobacteria

• Actinomycetales⇒Mycobacteriae⇒Mycobacteria
  – mycolic acids and high lipid content in cell wall
  – acid fast staining
  – fastidious with respect to culture conditions
• Many species, most non-pathogenic
• Pathogens
  – M. avium complex
  – M. abscessus
  – M. chelonae
  – M. kansasii
  – M. tuberculosis complex
Mycobacterium tuberculosis Complex

M. tuberculosis
M. africanum
M. canetti
M. bovis (cattle)
M. microti (voles)
M. caprae (goats, cattle)
M. pinnipedii (seals)

Characteristics of MTB complex

- Slightly curved, rod shaped bacilli
- 0.2 - 0.5 microns in diameter; 2 - 4 microns in length
- Acid fast - resists decolorization with acid/alcohol
- Multiplies slowly (every 18 - 24 hrs)
- Thick lipid cell wall
- Can remain dormant for decades
- Aerobic
- Non-motile

Pathogen Factors

- Slow growth
- Resistant to:
  - dehydration
  - oxidative stress
  - low pH
- No classical virulence factors
Questions about the Pathogen?

Transmission

“In approaching the consumptive, one breathes pernicious air. One takes the disease because there is in this air something disease-producing”

Aristotle

Fate of Respiratory Droplets

- Large droplets settle to ground quickly
- If inhaled, large droplets impact upper respiratory epithelium
- Smaller droplets dessicate to form “droplet nuclei” of 1-5 µm diameter
  - Droplet nuclei remain airborne indefinitely
  - Small particle size can reach alveoli
  - *M. tuberculosis* stable in droplet nuclei
TB Transmission via Droplet Nuclei

- Millions of tubercle bacilli in lungs
- Coughing projects droplet nuclei containing MTB into the air
- One cough can release 3,000 droplet nuclei
- One sneeze can release tens of thousands of droplet nuclei

Likelihood of TB Transmission

CASE CONTACT
- Site of TB
- Cough
- Bacillary load
  - smear
  - cavity
- Treatment

Environment
- Filtration
- U.V. light
- Procedures
- Ventilation
- Closeness and duration of contact
- Previous infection

Indices of Source Case Infectiousness--Household Contacts

<table>
<thead>
<tr>
<th>Source-Case Variables</th>
<th>Tuberculin Reactors (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiographic extent of disease</td>
<td></td>
</tr>
<tr>
<td>Minimal</td>
<td>16.1</td>
</tr>
<tr>
<td>Moderately advanced</td>
<td>28.3</td>
</tr>
<tr>
<td>Far advanced</td>
<td>61.5</td>
</tr>
<tr>
<td>Bacteriologic status</td>
<td></td>
</tr>
<tr>
<td>Smear –, culture –</td>
<td>14.3</td>
</tr>
<tr>
<td>Smear –, culture +</td>
<td>21.4</td>
</tr>
<tr>
<td>Smear +, culture +</td>
<td>44.3</td>
</tr>
<tr>
<td>Mean 8-hour overnight cough count</td>
<td></td>
</tr>
<tr>
<td>&lt;12</td>
<td>27.5</td>
</tr>
<tr>
<td>12-48</td>
<td>31.8</td>
</tr>
<tr>
<td>&gt;48</td>
<td>43.9</td>
</tr>
</tbody>
</table>

Loudon RG. ARRD 1969;99:109
Transmission of Tuberculosis—Importance of Treatment

- The average tuberculosis (TB) patient generates 75,000 droplets per day before therapy
- This drops to 25 infectious droplets per day within 2 weeks of effective therapy

Likelihood of TB Transmission

- Site of TB
- Cough
- Bacillary load
  - Smear
  - Cavity
- Treatment

Environmental Factors--Procedures

- Sputum induction
- Bronchoscopy
- Wound irrigation
- Autopsy
### Environmental Factors--Ventilation

<table>
<thead>
<tr>
<th>Room Type</th>
<th>Air Changes/Hr. (mean)</th>
<th>Risk of Infection in 24 hr. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;Old-fashioned&quot; natural ventilation</td>
<td>40</td>
<td>11</td>
</tr>
<tr>
<td>--high ceiling wards</td>
<td></td>
<td></td>
</tr>
<tr>
<td>--windows on 2 sides</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&quot;Modern&quot; natural ventilation</td>
<td>17</td>
<td>33</td>
</tr>
<tr>
<td>--smaller rooms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>--windows on one side</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&quot;Modern&quot; mechanical ventilation</td>
<td>12</td>
<td>39</td>
</tr>
</tbody>
</table>

Escombe AR. PLOS Med 2007;4:e68

### Likelihood of TB Transmission

- Site of TB
- Cough
- Bacillary load
  - smear
  - cavity
- Treatment
- Closeness and duration of contact
- HIV
- Previous infection

### Exogenous Reinfection

- 12 of 16 HIV (–) recurrences in study from South Africa (Van Rie, A, et al. 1999)
- 8 of 23 HIV (+) and (–) patients in the Canary Islands with cultures separated by at least 12 months (Caminero JA, et al. 2001)
TB Transmission - Summary

CASE
- Site of TB
- Cough
- Bacillary load
  - smear
  - cavity
- Treatment

Environment

CONTACT
- Filtration
- U.V. light
- Procedures
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- Closeness and duration of contact
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Questions about Transmission?

Pathogenesis--What Happens Next?

No infection

Exposure

Adequate
  - Innate immune response
  - Early progression (5%)

Inadequate
  - Late progression (5%)

Infection

Adequate
  - Immunologic defenses
  - Adequate containment (95%)

Inadequate
  - Immunologic defenses
  - Continued containment (90%)
Pathogenesis of Tuberculosis

**Stage I**
- Alveolar Macrophage
- Ingested Tubercle Bacillus
- Alveolar Lumen
- Alveolar Wall
- Capillary

**Stage II**
- Infiltrating Macrophage

**Stage III**
- Ghon's complex
- Week 0 - 1
- Week 2 - 3
- Week 4 - 5
- Tuberculin reactive
- Hematogenous dissemination
Genetic Susceptibility to Tuberculosis

- Animal models – variation in susceptibility/resistance to TB
- Twin studies – Concordance for TB is higher among mono vs. dizygotic twins
- Allelic variations in the NRAMP1 gene is associated with susceptibility to TB
- Association of HLA-DR2 with vulnerability to TB
- Familial clusters of disseminated mycobacterial infections – IFNγ receptor gene
Questions about Pathogenesis?

A Word about *M. bovis*

- Primarily transmitted to humans in unpasteurized dairy products
- Cause of TB in cattle
- A significant cause of human TB in California
- More likely to cause extrapulmonary and multisite disease
- Resistant to PZA

Questions?