Tuberculosis Transmission and Pathogenesis

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Disclosures

• I'm quite a good skier
• I have no financial or other conflicts of interest that are relevant to this talk

Tuberculosis Transmission and Pathogenesis Goals

Upon completion of this session, participants will be able to:

1) Use the TB transmission risk from an index case to prioritize isolation requirements and subsequent evaluation

2) Understand key elements of TB pathogenesis that have clinical relevance
Tuberculosis Transmission

- What causes tuberculosis?
- How is tuberculosis transmitted?
- What factors or circumstances increase the risk of tuberculosis transmission?

What Causes Tuberculosis?

Mycobacterium tuberculosis

- Slow-growing, weakly Gram positive, acid-fast bacillus (AFB)
- Intracellular pathogen
- Requires special stains & culture medium
- Resistant to most common antibiotics
Tuberculosis Transmission -- Modern Concepts

- Droplet Nuclei Theory
- Experimental Airborne Transmission
- Person-to-Person Spread
- Outbreak Epidemiology
- Insights from Clinical Experiences

Tuberculosis Transmission
Droplet Nuclei Theory

- Industrial Hygiene Movement
- “most droplets atomized into air evaporate almost instantly, leaving disease germs drifting like cigarette smoke in the droplet nuclei”
  - Wells 1948

Droplet Nuclei Formation

- Droplets <100 µm fall less than 2 feet before evaporating to 1-10 µm size
- Droplet “nuclei” settle very slowly (~0.2 mm/second)
- Droplet nuclei particles are respirable; ~50% of inhaled droplet nuclei are deposited in distal airspaces
Generation of “Droplet Nuclei” and Fate of Expelled Droplets

Very small droplets may contain no TB

Intermediate droplets fall slowly and evaporate into respirable “droplet nuclei”

Larger droplets fall to ground before evaporating

Experimental Airborne Transmission
The Baltimore VA Pilot Ward

- TB Ward with varied TB cases
- Effluent air passed through guinea pig cages
- Guinea pigs monitored by TST, and sacrificed (and replaced) if TST+

Experimental Airborne Transmission
Findings from the Pilot Ward

- Effluent air from TB patients’ rooms caused experimental TB infection
- Time to infect one guinea pig was ~10d, and infected animals usually had only a single lung “tubercle”
- One infectious dose or “quantum” was contained in ~11,000-12,500 cubic feet of air; based on exposure time and volume of air inspired (8 cf per animal per day)

-Riley, Wells, et al. 1957
Additional Experimental TB Transmission Findings

- Marked heterogeneity of “infectiousness” among different ward patients
  - Highest was laryngeal TB case (200 cf)
  - 8 of 130 patients accounted for 46% of infectious quanta (most were non-infectious)
- Infectivity diminished 10- to 50-fold soon after starting treatment
- No infections occurred if effluent air was first exposed to UV irradiation
  - Riley, Mills, O’Grady, et al. 1962

Tuberculosis Transmission

- Droplet nuclei theory accepted
- Experimental airborne transmission confirmed from humans to guinea pigs
- But what about human-to-human transmission?

Tuberculosis Outbreak Epidemiology on the U.S.S. Richard E. Byrd

- 437 ft, 4,500 ton guided missile destroyer
- Laid at Todd Shipyard in 1961, commissioned at Puget Sound Naval Shipyard in 1964
- 24 officers and 330 enlisted men
- Varied missions
Tuberculosis Outbreak on the *U.S.S. Richard E. Byrd*

- Index case: coughing cavitory smear-positive TB
- Extensive characterization of all sailors: work and sleep locations, ventilation patterns, etc.
- Overall, 139 of 308 (45%) enlisted crew converted TST; and 7 had active disease at the initial screening
- TST conversion rates showed a dose response: 80% in shared compartment (6 of 7 TB cases), 53% in adjacent compartment with partially shared ventilation, far lower elsewhere on ship
  - Houk et al. 1968

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**Human to Human Transmission Confirmed**

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**Source Case Infectiousness**

(among Household Contacts)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Severity</th>
<th>TST+ (%)</th>
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</thead>
<tbody>
<tr>
<td>Radiographic extent</td>
<td>Minimal</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>Moderately</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>Far advanced</td>
<td>62</td>
</tr>
<tr>
<td>Bacteriologic status</td>
<td>Smear –, culture –</td>
<td>74</td>
</tr>
<tr>
<td></td>
<td>Smear –, culture +</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>Smear +, culture +</td>
<td>44</td>
</tr>
<tr>
<td>Overnight cough cnt</td>
<td>&lt; 12</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>12-48</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td>&gt; 48</td>
<td>44</td>
</tr>
</tbody>
</table>

Not All “Smear Positive” TB Patients are Equally Infectious

- Riley et al. 1960, 1962
  - 4% of patients produced 77% of infections
  - 13% of patients produced all the infections
- van Geuns et al. 1975
  - Only 28% of smear + patients infectious
- Brooks et al. 1973
  - 38% of patients had no TST+ contacts
  - 38% of patients had 1 TST+ contact
  - One patient had 11/13 TST+ contacts

What Are We Missing?
Cough-Generated Aerosols of *M. tuberculosis*

- Cough aerosol sampling system directly measured concentration and size of aerosols in TB patients
- Cough-generated aerosols were positive in 4/16 (25%) of subjects with smear + TB
- Most particles were in the respirable range

Fennelly KP. AJRCCM 2004; 169:604-609

Variability in Infectious Cough Aerosols

Fennelly KP et al. AJRCCM 2012; 186:450-7
Tuberculosis Transmission: Source Case Risk Factors

- Disease (TB) in the lungs or airways
- Spontaneous cough or cough-inducing procedures
- Smear-positive sputum
- Cavitation on chest x-ray
- No therapy, recently started therapy, or inadequate therapy
  (Tendency to produce droplet nuclei)
Probability of TB Transmission

• Concentration of droplet nuclei
  – Rate of production (source case factors)
  – Proximity to source
  – Volume of shared air
  – Rate of clearance (Ventilation)
• Duration of exposure
• Organism infectivity / transmissibility
• Host resistance

Tuberculosis Transmission
-- Other Means

• Cough-inducing procedures (use caution)
• Non-pulmonary aerosol generation
  – Abscess dressing changes
  – Wound irrigation with water jet
  – Autopsy with bone saw
• Direct inoculation
  – Skin—"Prosector's warts"
  – Lung—Contaminated bronchoscopy equipment

Nosocomial Transmission of TB From a Patient with a Hip Abscess

Patient Room

Hospital Ward Floor Plan

Numbers = Proportion of Positive TSTs (with n's)

Hutton MD, et al. JID. 1990;161:286
Transmission of TB: The Concentric Circle Concept

Decreasing risk of transmission

Tuberculosis Transmission -- Summary

- TB is spread person-to-person
  - Only by persons with active TB disease
  - Especially cavitary, smear positive cases that generate infectious aerosols
- Via inhalation of airborne “droplet nuclei”
- Close contacts are at greater risk than those in outer concentric circles
- Transmission is aided by crowding indoors, absence of UV light, and poor ventilation

Tuberculosis Infectivity, Virulence, and Transmission

- Infectivity -- propensity of a strain to establish infection in exposed individuals (Transmissibility)
- Virulence -- capacity of a strain to produce clinically active disease in those infected
- Virulence and Infectivity may be linked but are not identical attributes of a strain
  - Mike Iseman
Tuberculosis Life Cycle:
Exposure, Infection, and Disease

- TB Exposure
- Adequacy of Innate Defenses
- No TB Infection (Evident)
- Infection Contained (Latent TB Infection)
- Infection Not Contained (Primary TB Disease)
- Primary TB Infection (Silent Dissemination)
- Defenses Maintained = TB Remains Latent/Dormant
- Defenses Not Maintained (Reactivation TB Disease)
- Maintenance of Acquired Defenses
- Lack of Acquired Defenses

Tuberculosis Pathogenesis
Experimental Model

- Phase I – bacilli engulfed by naïve alveolar macrophages
- Phase II – proliferation and dissemination
- Phase III – evolution of cell-mediated immunity and delayed-type hypersensitivity
- Phase IV – liquefaction and accelerated bacillary proliferation (and re-transmission)

- Lurie and Dannenberg
**Tuberculosis Pathogenesis**

**Stage I: Invasion and Ingestion**
- TB (within droplet nuclei) inhaled into alveolar spaces
- TB ingested by naïve alveolar macrophages

**Stage II: Proliferation & Dissemination**
- TB replicate within naïve alveolar macrophages
- Macrophages burst and TB released
- TB and infected macrophages transported to draining lymph nodes
- Bacillemia and systemic dissemination

**Stage III: Immune Response & Containment**
**Tuberculosis Pathogenesis**

**Stage IV: Liquefaction & Proliferation**

"Reactivation"
- Immunity wanes
- TB replication resumes
- Granuloma liquifies and bursts
- TB released into airways and tissues
- Potential for new Transmission

**TB Pathogenesis at the Molecular Level**

**"Innate" Immunity**
- NK cells
- IL-12
- IL-18
- TGF-β

**"Acquired" Immunity**
- TH1 T cells
- TH0 T cells
- TH2 T cells
- CD8 T cells
- CD4 T cells
- IL-2
- IL-10
- IL-13

**Mycobacterium tuberculosis**

**Specific Immune Defects Increase Risk of Tuberculosis**
- HIV-related impairment of CD4 lymphocyte functions (especially IFNγ)
- Anti-TNFα therapies prescribed for rheumatologic, inflammatory bowel disease, and other conditions
- Inherited defects in IFNγ and IL-12 receptor genes -- familial clusters of disseminated mycobacterial infections
Genetic Susceptibility to Tuberculosis

- Animal models - variability in TB susceptibility
- Twin studies - concordance for TB is higher among mono vs. dizygotic twins
- HLA-DR2 associated with vulnerability to TB
- Allelic variations in the NRAMP1 gene are associated with susceptibility to TB

Spectrum of Mycobacterial Burden

- No TB Infection
- Latent TB Infection
- Active Tuberculosis Disease
  - "Culture-negative" TB
  - Smear-negative TB
  - Smear-positive TB

TB Risk Factor?
Questions?