Tuberculosis Transmission and Pathogenesis

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DISCLOSURE

NO relevant financial relationships

NO conflicts of interest
OBJECTIVES

Define particular source and contact risk factors for the transmission of M. tuberculosis

Understand the importance of cell-mediated immunity and innate immunity in the pathogenesis of M. tuberculosis

Understand recent developments in the study of innate immunity and its role in the pathogenesis of TB
TB Transmission and Progression

CASE

Droplets

CONTACT

Droplet Nuclei

Cough
Sneezing, talking, singing
Sneezing produces ~ 40K droplets
Coughing produces ~3K droplets = Talking x 5 mins

Journal of Infection Control. 1998
Droplets

1-5 µm droplets
Stay suspended for hours
Risk Factors for Transmission -- SOURCE

Location of Tuberculosis
- Pulmonary/Laryngeal >> Extrapulmonary TB

Bacillary Load
- Cavitary disease
- Smear positive

Treatment
- Decreases bacillary burden

Cough

Duration of Cough
Sputum Bacillary Loads
Non-cavitary vs. Cavitary Disease

Log₁₀ CFU/mL of sputum

BACTEC Culture Mean Time to Positivity (in days)

(n=144) (n=100)

(n=136) (n=93)

Figure 1. Colony-forming unit counts of *M. tuberculosis* in sputum during treatment in Group 1 (isoniazid [H] only), Group 2 (rifampin [R] only), Group 3 (isoniazid and rifampin [HR]), or Group 4 (other drugs). The SDs within patients, suitable for assessing linearity, are 0.492 for Group 1, 0.467 for Group 2, 0.558 for Group 3, and 0.423 for Group 4, each with 117–183 df.

Published in: Amina Jindani; Caroline J. Doré; Denis A. Mitchison; *Am J Respir Crit Care Med* 2003, 167, 1348-1354
Risk Factors for Transmission -- CONTACTS

• Previous exposure (i.e. hx of LTBI) likely confers protection against infection on reexposure and progression to active disease.

• Duration: Longer is worse

• Proximity: Family members, cohabitants

• Immune Status

• Other Host Factors
Proximity and Risk to Contacts

In the US, ~ 30% of household contacts of smear-positive cases can become infected. This rate can be higher in skilled nursing facilities, prisons, and other “closed” areas.

NOTE: ~ 17% of new active TB cases arose from smear-negative, culture positive cases in one US study.
Figure 2. Percentage of persons infected with Mycobacterium tuberculosis, by bacteriologic status of and proximity to the source case—British Columbia and Saskatchewan, 1966–1971.

Specific Risk Factors - CONTACTS

Substance Abuse
- Drug use
- Smoking
- Alcohol

Nutritional Status
- Underweight
- Vitamin D Deficiency, Iron Overload

Systemic Diseases
- Silicosis, Malignancy
- Diabetes Mellitus
- Renal Disease
- Cirrhosis, celiac disease, others
Specific Risk Factors - CONTACTS

Immunocompromised status

- HIV Infection: Risk of TB disease (after PPD conversion) is ~ 10%/year

- TNF-alpha inhibitors: Infliximab >> Etanercept

- Corticosteroids

- Solid Organ and Stem Cell Transplant Recipients

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative Risk (95% CI)</th>
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<tbody>
<tr>
<td>Horsburgh et al.</td>
<td>9.9 (8.7-11.3)†</td>
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<tr>
<td>Palmer et al.</td>
<td>4.1 (1.1-1.9)†</td>
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<tr>
<td>Edwards et al.</td>
<td>1.6 (1.1-2.2)</td>
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<tr>
<td>Corbett et al.</td>
<td>1.3 (1.1-1.7)†</td>
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<tr>
<td>Kleinschmidt and Churchyard</td>
<td>1.7 (1.3-2.1)†</td>
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<tr>
<td>Keane et al.</td>
<td>2.0 (0.7-5.5)†</td>
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<tr>
<td>Pablos-Mendez et al.</td>
<td>2.4 (2.1-2.8)†</td>
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<tr>
<td>Moss</td>
<td>5.2 (3.4-8.0)</td>
</tr>
</tbody>
</table>

Table 3. Relative Risk of Reactivation Tuberculosis among Persons with Medical Conditions That Impair Immune Control of M. tuberculosis.
A Few Things About Environment

Risk greater in “closed” rooms/environs
Non-ventilated areas
Increases proximity and likely duration of exposure
Remember that exposure to UV light decreases infectivity

Andrews, et al.
• Measured carbon dioxide levels on 3 different modes of transportation (taxis, minibuses, trains) in Cape Town, South Africa
• Model-based analysis
• Projected annual risk of TB infection attributable to public transit among daily commuters was ~ 3.5 to 5 %
PATHOGENESIS
Chronological events after inhalation of M. tuberculosis

70%

- Immediate killing of MTB (PPD−)

30%

- Primary complex (PPD+)

--- Small infiltrate with draining LN
--- Small calcification
--- PPD +

- Stabilization (latency)

- Localized disease (primary TB)

- Dissemination of MTB

--- Stabilization (latency)

--- Acute disease (meningitis, miliary TB)

--- Reactivation (post-primary TB)

Reference:
The Immune Response

Characteristics

Innate
- Fast acting
- No memory
- Not “fine-tuned” to specific pathogen

Adaptive
- Slow acting (takes days)
- Long-term memory
- Pathogen specific

The Importance of Cell-Mediated Immunity

Histopathology of a Granuloma

- Alveolar lumena
- Giant multinucleated cell (immature - Muller type)
- Central caseous necrosis
- Collar of lymphocytes
- Aggregation of epithelioid cells
- Giant multinucleated cell (mature - Langhans type)
The Spectrum of Granulomata

a Caseous granuloma

b Non-necrotizing granuloma

c Fibrotic granuloma

B cell  Neutrophil  M. tuberculosis
CD8+ T cell  Caseum  Macrophage
CD4+ T cell  Fibroblast

Nature Reviews | Microbiology
Pathogenesis of M. Tb

Phagosome does NOT fuse with lysosome
Macrophage Immunoevasion and Immunosuppression
Events in Early Infection

IM, et al. Nature Immunology. 2015
Regulatory Activities Determine the Outcome of Infection

Orme, IM, et al. Nature Immunology. 2015
Key Cytokines Involved in TB Pathogenesis

TNF-Alpha Inhibition
Mycobacteria Avoid Host Defenses in the Lower Airway

Ordinarily, microbicidal macrophages are recruited by Toll-like receptor (TLR)-mediated signaling that is activated by PAMPs (pathogen-activated molecular patterns). Mycobacteria express a surface lipid called ‘PDIM’ that hides these PAMPs so they cannot be “seen” by the host innate immune system PGL (phenolic glycolipid), a related surface lipid, helps to recruit and infect other “permissive” macrophages
Mycobacteria Recruit Macrophages in a New Granuloma

Mycobacteria induce MMP9 expression in epithelial cells surrounding young granuloma.

MMP9 stimulates recruitment of new macrophages to the granuloma.

New macrophages phagocytose the mycobacteria in dying, infected macrophages → leads to spread of infection.
A New Paradigm?

**Active Disease**
- Clinical disease
- Bacterial replication maintained at a subclinical level by the immune system
- Infection controlled with some bacteria persisting in non-replicating form
- Infection eliminated in association with T cell priming
- Infection eliminated without priming antigen-specific T cells

**Latent Disease**
- Active infection
- Quiescent infection
- Acquired immune response
- Innate immune response

Nature Reviews | Microbiology

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Questions/Comments??

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