Tuberculosis Pathogenesis

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May 12, 2015

TB for Community Providers
May 12, 2015
Phoenix, Arizona

Renuka Khurana, MD, MPH has the following disclosures to make:

- No conflict of interests
- No relevant financial relationships with any commercial companies pertaining to this educational activity
OVERVIEW

• TB Exposure
• TB Infection
  – Immune Response
  – Source Risk Factors
  – Host Risk Factors
  – Environmental Factors
• LTBI
• Active TB

TB EXPOSURE

• TB Exposure
  – You have been sharing the air you breathe with someone who has active TB
• Outcome of TB Exposure
  – No infection (70%)
  – Infection (30%)
INFECTIOUS PARTICLES

• Droplet Nuclei
  – Particles with < 5 μM in diameter
  – Aerodynamic
  – Contain 1-3 tubercle bacilli
  – Particles > 5 μM captured by mucociliary defenses
• Approximately 5 to 200 droplet nuclei are thought to be needed to result in an infection

FACTORS DETERMINING TRANSMISSION OF MYCOBACTERIUM TUBERCULOSIS?

• TB Organism Factors
• TB Source Patient Factors
• TB Exposed Patient Factors
• Characteristics of the Exposure
TB ORGANISM FACTORS

• Virulence of the TB Organism

TB SOURCE PATIENT FACTORS

• Concentration of organisms in sputum
• Presence of Cavitary disease on CXR
• Frequency and strength of cough

AJCCRM. 2005: 170;1169-1227.
TB EXPOSED PATIENT FACTORS

- Previous M. Tb infection
- Innate Resistance to M. Tb infection
- Genetic susceptibility to M. Tb infection

CHARACTERISTICS OF THE EXPOSURE

- Frequency and duration of Exposure
- Dilution effect (volume of air)
- Ventilation
- Exposure to ultraviolet light
RISK OF TB INFECTION

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. Source: Reference 57.

AJCCRM. 2005: 170;1169-1227.

TB INFECTION
TB INFECTION

• The TB organism is in your body!

• Outcome of TB Infection
  – Latent TB Infection (LTBI) (90%)
    • No Active TB Disease
  – Active TB Disease (10%)
    • 50% Primary Progression in first 2 years
    • 50% Reactivation later in life

IMMUNE RESPONSE 101

• Innate Immunity
  – First line of Defense:
    • Rapid acting
    • Non-specific
    • No Memory
  – Components:
    • Complement
    • Macrophages
    • Natural Killer Cells
IMMUNE RESPONSE 101

• Adaptive Immunity
  – Second Line of Defense
    • Slower Acting
    • Very Specific
    • Generates Immune Memory
  – Components:
    • Humoral:
      – B cells
      – Plasma Cells
      – Immune globulins
    • Cell-Mediated
      – T cells
      – Activated Macrophages
      – Activated Natural Killer cells

INITIAL IMMUNE RESPONSE TO TB INFECTION

• Innate Immunity
  – Alveolar macrophages
    • Activated Macrophages
      – Ingest the TB bacilli
      – Can destroy TB bacilli
    • Non Activated Macrophages
      – Ingest TB bacilli
      – Don’t kill TB bacilli
INITIAL IMMUNE RESPONSE TO TB INFECTION

• Innate immunity
  – Non Activated macrophages
  – Can’t kill the TB bacilli
  – Allow TB to multiply inside the macrophage
  – The macrophage will ultimately burst, allowing the bacilli to infect other macrophages

What activates the Macrophages?
  – Natural killer cells
    • Lymphocytes that can lyse infected macrophages without prior exposure to the pathogen
    • Produce IFN gamma
      – Activates the macrophages
      – Stimulates Th1 immune response
LATER IMMUNE RESPONSE TO TB INFECTION

• Adaptive Immunity
  - All Cell-Mediated Response
    - T cells
      » Th1 cells
      » Interleukin 12
      » Interferon gamma
    - Activated Macrophages
    - Activated Natural Killer cells

• No Humoral Response
  - No B cells
  - No Plasma cells
  - No Immunoglobulins

INITIAL IMMUNE RESPONSE TO TB INFECTION
GRANULOMA FORMATION

- Delayed Type Hypersensitivity
  - Destroy bacilli laden macrophage
  - Caseous Necrosis
  - Very Tissue Damaging
- Some Bacilli may be dormant or minimally metabolically active within macrophages
GRANULOMA FORMATION

Good Cell Mediated Immunity (CMI)
Active Macrophages
surround caseous center
and contain disease
GRANULOMA FORMATION

Poor Cell Mediated Immunity (CMI)
Non Activated Macrophages
allow disease to progress
CAVITIES AND DISSEMINATION

Cavity Formation
Dissemination
  Hematogenously spread
  Bronchial Spread
Replication
  In tissues
  Not just in Macrophages

FROM GRANULOMA TO CAVITY
TB INFECTION

• The TB organism is in your body!
• Outcome of TB Infection
  – Latent TB Infection (LTBI) (90%)
    • No Active TB Disease
  – Active TB Disease (10%)
    • 50% Primary Progression in first 2 years
    • 50% Reactivation later in life

LATENT TB INFECTION

• The TB organism is in your body!
• Asymptomatic
• Outcome of TB Infection
  – About 90% chance of no Active TB Disease
LATENT TB INFECTION

- No symptoms or signs of infection
- NOT infectious
- Positive tuberculin skin test
- T-cells respond to mycobacterial antigens
- Chest x-ray may be normal, or show granulomata, pleural or parenchymal scarring
Pathogenesis of Pulmonary Acquired Tuberculosis

**Latent Tuberculosis Infection**

- Inhalation of Droplet Nuclei
- Localization to mid and lower areas of lung
- Multiplication
- Immune Response
  - Organisms killed
  - Organisms Dormant/walled off

**LATENT TB INFECTION**

1) **Bacteria are dormant (metabolically inactive).** They later start to divide for reasons that are not clear.

2) **Bacteria are metabolically active and dividing, but infection is controlled by the immune system.**
   - Disease develops when immunity wanes.
   - Recent data in animals favor this hypothesis.
LTBI → ACTIVE TB DISEASE

- Recent infection
- HIV infection
- Chest x-ray abnormality
- Underweight by >10%
- Intravenous drug use
- Immunosuppression

ATS-CDC. Am J Respir Crit Care Med 2000;161:S221

LTBI → ACTIVE TB DISEASE

- Immunosuppression
  - Pregnancy
  - Hematologic cancers
  - Medical Comorbidities
  - Medications
    - TNFα inhibitors
    - Prednisone >15 mg, > 4 weeks
    - Chemotherapy
    - Other immunosuppressive drugs
LTBI → ACTIVE TB DISEASE

Disease | Relative risk
--- | ---
Silicosis | 30
Jejunoileal bypass | 27-63
Renal transplant | 37
Head or neck cancer | 16
Renal failure | 10-25.3
Diabetes | 2.0-4.1
Gastrectomy | 2-5

ATS-CDC. Am J Respir Crit Care Med 2000;161:S221-S247

LTBI → ACTIVE TB DISEASE

• Smoking
  – Never Smoked OR 1
  – Current Smoker OR 2.73
  – Ever Smoked OR 2.69

Am J Respir Crit Care Med 2009;180:475-480.
LTBI → ACTIVE TB DISEASE

• Passive Smoking
  • RR 1.64
ACTIVE TB

• 10% Lifetime Risk
• Symptomatic
  – Primary TB
  – Reactivation TB

Pathogenesis of Pulmonary Acquired Tuberculosis

Primary Disease

Inhalation of Droplet Nuclei

↓

Localization to mid and lower areas of lung

↓

Pneumonia  Multiplication  Pleurisy

With poor CMI  ↓

Dissemination

↓

Acute hematogenous disease  Meningitis
PRIMARY TUBERCULOSIS

MILIARY TUBERCULOSIS
Pathogenesis of Pulmonary Acquired Tuberculosis
Post-Primary or Re-Activation Disease

Inhalation of Droplet Nuclei
↓
Localization to mid and lower areas of lung
↓
Multiplication
↓
Immune Response
  Good CMI
↓
Organisms killed
Organisms walled off
↓
Immune Function Decreases
↓
Active disease

REACTIVATION TB

[Image of chest X-ray showing tuberculosis]

EXCELLENCE • EXPERTISE • INNOVATION
SUMMARY

• TB Exposure can result in:
  – No infection
  – Infection without active disease (LTBI)
  – Primary TB
  – Reactivation (post-primary) TB

• Factors that increase likelihood of infection
  – Duration of exposure
  – AFB+/Cavitary source patients
  – Poor Ventilation/Prolonged Contact

SUMMARY

• Immune Response
  – Innate immunity: First Line of Defense
    – Alveolar Macrophages
    – Natural killer cells augment macrophage killing of TB bacilli
  – Adaptive immunity: Second Line of Defense
    – T-cells, Th1 responses
    – IL-12
    – IFN-gamma

• LTBI:
  – Bacteria divide actively during clinical latency but are contained by the immune system
SUMMARY

• Risk Factors for Progression to Active TB
  – Recent TB Infection
  – Low Body Weight
  – IV Drug Abuse
  – Immunosuppression/HIV/Transplant/Meds
  – Abnormal CXR/Silicosis
  – Comorbidities/DM/Renal Disease
  – Active or Passive Smoking

QUESTIONS?
Special thanks to:

Lynn L. Horvath, MD, FACP, FIDSA
Associate Professor of Medicine
University of Texas Health Science Center - Tyler
at the Texas Center for Infectious Disease