Leading causes of global mortality

WHO, World Health Report, 2004

Global deaths due to acute respiratory infections

Source: WHO Global Disease Burden Report

Respiratory tract defense mechanisms

- Upper airway
  - Mechanical barriers
  - Nasal turbinates
  - Glands
  - Reflexes
  - Cough, sneeze
  - Maintenance of oropharyngeal flora
  - Saliva
  - Bacterial competition
  - Naturally occurring bacterial binding site analogues
  - Local immunoglobulins

- Lower Airway
  - Branching airways
  - Mucociliary escalator
  - Alveolar space defenses
    - Alveolar lining fluid
      - Free fatty acids
      - Lysozyme
      - Iron-binding proteins
      - IgG
      - Surfactant
    - Cellular components
      - Macrophages
      - Polymorphonuclear cells
      - Lymphocytes

Mechanical lung host defenses

- The nose and mucociliary transport systems comprise the main mechanical defense system of the lungs
- Particles greater than 10 microns settle in the upper airways and rarely enter the lower airways
- Particles between 5-10 microns deposit in the trachea and main bronchi and can be removed by mucociliary transport
Ciliary structure and function

- 9 + 2 microtubule structure
- Major proteins: tubulin and dynein
- Ciliary beat frequency 12-15 Hz

The cilia are partially covered by a mucous sheet.

Stimulators and inhibitors of ciliary function

- Increase ciliary beat frequency
  - beta-adrenergic agonists (via adenylate cyclase, cAMP, and protein kinase A pathways)
  - Anticholinergic agents (via protein kinase C pathways)
  - Increase in intracellular Na+/Cl- ratio
- Decrease ciliary beat frequency
  - Neuropeptide Y, major basic protein
  - Bacterial products (pyocyanin, 1-hydroxyphenazine, and others)
Diseases associated with abnormal ciliary function

- Primary ciliary dyskinesia; immotile cilia syndrome; Kartagener’s syndrome; autosomal recessive
- Young’s syndrome: sinusitis, bronchiectasis, obstructive azospermia; location of defect
- Cystic fibrosis; autosomal recessive
- Chronic bronchitis

Tobacco smoke and ciliary structure and function

- Smokers and ex-smokers have a higher level of ciliary structural abnormalities (17% of cilia) than never smokers (0.7%)
- Ciliary beat frequency is not diminished by age, but is decreased similarly in smokers and those exposed to environmental tobacco smoke

Humoral immune functions of the lung

- Lymphocytes in the lung are found in submucosal collections known as bronchial associated lymphoid tissue (BALT); Ig may also diffuse into the lung
- IgG, IgA, and IgE are all present in measurable amounts in the lung
- IgA, IgG3, and IgG4 are present in greater concentration in the lung than in serum
- IgG and IgA contribute significantly to defense against infection in the lung

Absolute and relative concentrations of immunoglobulin species in serum and BAL fluid

<table>
<thead>
<tr>
<th>Albumin</th>
<th>IgG</th>
<th>IgG2</th>
<th>IgG3</th>
<th>IgG4</th>
<th>IgA</th>
<th>IgE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum*</td>
<td>49</td>
<td>4.5</td>
<td>2.1</td>
<td>0.03</td>
<td>0.09</td>
<td>1.98</td>
</tr>
<tr>
<td>BAL**</td>
<td>655</td>
<td>50</td>
<td>22</td>
<td>1.4</td>
<td>4.0</td>
<td>183</td>
</tr>
<tr>
<td>ratio</td>
<td>0.88</td>
<td>0.95</td>
<td>4.2</td>
<td>5</td>
<td>7.9</td>
<td>3.8</td>
</tr>
</tbody>
</table>

*mg/mL
**μg/mL

Humoral immunodeficiency syndromes and the lung

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Abnormality</th>
<th>Age of onset</th>
<th>Organisms Causing infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bruton’s X-linked Agammaglobulinemia</td>
<td>IgG &lt; 200mg/dl</td>
<td>infancy</td>
<td>S. pneumoniae, H. influenzae, S. aureus</td>
</tr>
<tr>
<td>Common Variable Immune Deficiency</td>
<td>IgG&lt;300mg/dl</td>
<td>adulthood</td>
<td>same as above</td>
</tr>
<tr>
<td></td>
<td>IgA, IgM low; antibody responses to vaccines impaired</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Humoral immunodeficiency syndromes and the lung

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Abnormality</th>
<th>Age of onset</th>
<th>Organisms Causing infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgA deficiency</td>
<td>IgA &lt; 5 mg/dl</td>
<td>adulthood</td>
<td>similar to CVID, but much less severe</td>
</tr>
<tr>
<td>IgG subclass deficiency</td>
<td>most severe</td>
<td>adulthood</td>
<td>similar to CVID</td>
</tr>
</tbody>
</table>

Role of surfactant in lung immune defense

![Image](image_url)
Cellular immune defenses of the lung

- Alveolar macrophages: 95% of cells recovered by BAL
- Dendritic cells: 0.5% of cells recovered by BAL
- Lymphocytes: 1-2% of cells recovered by BAL
  - CD4+ T cells
  - CD8+ T cells
- Neutrophils: not present in healthy lungs; recruited to the lung by a variety of stimuli

Alveolar macrophages

- The resident immune cell of the alveolar space
- Derived from bone marrow precursors, by way of the blood monocyte
- Proliferation may occur in the interstitium and alveolar space
- Key roles: phagocytosis and immune interactions

Cytokines and other bioactive substances released from alveolar macrophages

- Arachidonate metabolites
  - Thromboxane A2
  - PGE2, D2, F2
  - LTB4
  - 5-HETE
- Cytokines/chemistries
  - IL-1, IL-1RA
  - IL-6
  - TNF-α
  - IFN-α/β
- Reactive oxygen species
  - O2-
  - H2O2
  - Hydroxyl radical
- Nitric oxide
  - Constitutive
  - Inducible?
- Enzymes
  - Metalloproteinases
  - Elastase
  - Procoagulant activity

Receptors expressed and ligands recognized by alveolar macrophages

- Immunoglobulins (Fc receptors)
  - IgG1, IgG3, IgE, IgA
- Protein, cytokine, and matrix receptors
  - Fibronectin, fibrin, lactoferrin, transferrin, GM-CSF, IFN-γ, IL-2, IL-4, IL-1, IL-1RA
- Adhesion molecules and other receptors
  - MHC-II, CD4, CD1, CD18 (β2-integrin), CD29 (α4-integrin), ICAM-1, CD14 (LPS)
- Complement receptors
  - C3b, C4b, C3d, C5a
- Lectin receptors
  - α-linked galactose receptors, N-acetylglucosamine residues, α-linked fructose residues, mannos residues

Sunlight, vitamin D, and host defense against infection

Vitamin D-mediated human antimicrobial activity against Mycobacterium tuberculosis is dependent on the induction of cathelicidin1

![Diagram](image)

Liu et al. J Immunol 2007; 2060-2063
Vitamin D-mediated human antimicrobial activity against *Mycobacterium tuberculosis* is dependent on the induction of cathelicidin1

Cathelicidin = antimicrobial peptide found in neutrophils and macrophages

Liu et al. J Immunol 2007; 2060-2063

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Reported TB Cases by Race/Ethnicity*

United States, 2007

- **White** (26%)
- **Asian** (26%)
- **American Indian or Alaska Native** (1%)
- **Hispanic or Latino** (29%)
- **Black or African-American** (29%)
- **Native Hawaiian or Other Pacific Islander** (<1%)

*All races are non-Hispanic. Persons reporting two or more races accounted for less than 1% of all cases.

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Syndromes associated with impaired cellular immune function in the lung

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Defect</th>
<th>Infections</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic granulomatous disease</td>
<td>Loss of respiratory burst of macrophages</td>
<td>encapsulated organisms, GNRT</td>
</tr>
<tr>
<td>AIDS corticosteroid use</td>
<td>Decreased T-cell number and function</td>
<td>parasites, mycobacteria, fungi</td>
</tr>
</tbody>
</table>

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Infectious pulmonary complications of HIV infection

- **CD4+ T-cell count >250/mm³**
  - Bacterial pneumonia
  - Reactivation tuberculosis

- **CD4+ T-cell count <250/mm³**
  - *Pneumocystis carinii* pneumonia
  - Primary tuberculosis
  - Fungal infections:
    - Cryptococcus
    - Geographic fungus
    - Aspergillus spp.
    - CMV pneumonitis

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Understanding the human host response to tuberculosis

- Development of adjunctive immunotherapy for tuberculosis:
  - Treatment of drug resistant organisms
  - Shorten duration of treatment for drug susceptible disease
- Identify correlates of immunity to *M. tuberculosis* infection and disease
  - Predict success of candidate vaccines
- Identify new diagnostic approaches
Th1-type response

IFN-γ
IL-2

Th2-type response

IL-4
IL-5
IL-10

Protective immunity

Impaired immunity

Tuberculin skin testing

- Non-specific cross-reacts with BCG and NTM
- Requires trained personnel for administration and interpretation
- Requires second patient visit

Species specificity of ESAT-6 and CFP-10 mycobacterial antigens

<table>
<thead>
<tr>
<th>Tuberculosis complex</th>
<th>Antigen</th>
<th>CFP</th>
<th>Environmental strains</th>
<th>Antigen</th>
</tr>
</thead>
<tbody>
<tr>
<td>M. tuberculosis</td>
<td>+</td>
<td>+</td>
<td>M. abscessus</td>
<td>-</td>
</tr>
<tr>
<td>M. africanum</td>
<td>-</td>
<td>-</td>
<td>M. avium</td>
<td>-</td>
</tr>
<tr>
<td>M. bovis</td>
<td>+</td>
<td>-</td>
<td>M. gordonii</td>
<td>-</td>
</tr>
<tr>
<td>BCG strain</td>
<td>+</td>
<td>+</td>
<td>M. intracellulare</td>
<td>-</td>
</tr>
<tr>
<td>Mycobacterium</td>
<td>+</td>
<td>+</td>
<td>M. kansasi</td>
<td>-</td>
</tr>
<tr>
<td>N. brasiiliensis</td>
<td>+</td>
<td>+</td>
<td>M. marinum</td>
<td>+</td>
</tr>
<tr>
<td>N. caninum</td>
<td>-</td>
<td>-</td>
<td>M. microti</td>
<td>-</td>
</tr>
<tr>
<td>N. americanum</td>
<td>-</td>
<td>-</td>
<td>M. Duboisii</td>
<td>-</td>
</tr>
<tr>
<td>N. sudetense</td>
<td>-</td>
<td>-</td>
<td>M. paratuberculosis</td>
<td>-</td>
</tr>
<tr>
<td>N. tenuissimum</td>
<td>-</td>
<td>-</td>
<td>M. xenopi</td>
<td>-</td>
</tr>
</tbody>
</table>

Evaluation of T.SPOT in TB contacts in NYC

- Study of T.SPOT ELISPOT (Oxford Immunotec, Oxford, UK) in TB contacts identified by NYC DOH TB Control Program
- All patients received TST with 5TU of PPD and had blood samples taken for testing by IGRA
- Results correlated with contact status (close, not close) determined by NYCDOH TB Control Program
Evaluation of T.SPOT in TB contacts in NYC

• Characteristics of patient population
  – N=96
  – Female=37%
  – Mean age=33 years
  – Ethnicity
    • Hispanic 60%
  – Evidence of BCG vaccine=68%
  – Close contacts of an active case=58%

Evaluation of T.SPOT in TB contacts in NYC

<table>
<thead>
<tr>
<th>Variables</th>
<th>Adjusted OR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>T-SPOT.TB</td>
<td>2.4</td>
<td>0.9-5.9</td>
<td>0.051</td>
</tr>
<tr>
<td>TST</td>
<td>0.5</td>
<td>0.2-1.2</td>
<td>0.12</td>
</tr>
<tr>
<td>BCG vaccinated</td>
<td>0.1</td>
<td>0.01-0.5</td>
<td>0.01</td>
</tr>
<tr>
<td>BCG unvaccinated</td>
<td>0.1</td>
<td>1.2-67</td>
<td>0.03</td>
</tr>
</tbody>
</table>