**Leading causes of global mortality**

![WHO, World Health Report, 2004](image)

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**Global deaths due to acute respiratory infections**

![Graph showing distribution of deaths](image)

Source: WHO Global Disease Burden Report

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**Respiratory tract defense mechanisms**

- **Upper airway**
  - Mechanical barriers
    - Nasal turbinates
    - Glottis
    - 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

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**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

Stimulators and inhibitors of ciliary function

- Increase ciliary beat frequency
  - beta-adrenergic agonists (via adenylyl 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>IgG1</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 BAL/serum</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  **mg/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 IgA, IgM, IgE, IgD absent</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 IgA, IgM low; antibody responses to vaccines impaired</td>
<td>adulthood</td>
<td>same as above</td>
</tr>
</tbody>
</table>

Humoral immunodeficiency syndromes and the lung

<table>
<thead>
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<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 clinically with IgG1, IgG3</td>
<td>adulthood</td>
<td>similar to CVID</td>
</tr>
</tbody>
</table>
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
  - PGE$_2$, D$_2$, F$_2$
  - LTB$_4$
  - S-HETE
- Cytokines/chemokines
  - IL-1, IL-1RA
  - IL-6
  - TNF-a
  - IFN-a/b
- Reactive oxygen species
  - O$_2^-$
  - H$_2$O$_2$
  - Hydroxyl radical
- Nitric oxide
  - Constitutive
  - Inducible?
- Enzymes
  - Metalloproteinases
  - Elastase
  - Procoagulant activity
- Complement receptors
  - C3b, C4b, C3d, C5a
- Lectin receptors
  - alpha-linked galactose receptors, N-acetylglactosamine residues, alpha fructose residues, mannose residues

Receptors expressed and ligands recognized by alveolar macrophages

- Immunoglobulins (Fc receptors)
  - IgG$_1$, IgG$_2$, IgE, IgA
- Protein, cytokine, and matrix receptors
  - Fibronectin, fibrin, lactoferrin, transferrin, GM-CSF, IFN-g, IL-2, IL-4, IL-1, IL-1RA
  - Adhesion molecules and other receptors
    - MHC-II, CD4, CD18 (b-integrin), CD29 b-integrin, ICAM-1, CD14 (LPS)
### 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, GNR</td>
</tr>
<tr>
<td>AIDS corticosteroid use</td>
<td>Decreased T-cell number and function</td>
<td>Parasites, mycobacteria, fungi</td>
</tr>
<tr>
<td>transplant-related immunosuppression</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### 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

### 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

### Protective immunity vs. Impaired immunity

- **Th1-type response**
  - IFN-γ
  - IL-2
- **Th2-type response**
  - IL-4
  - IL-5
  - IL-10

### Tuberculin skin testing

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

### Measurement of induration and erythema
Species specificity of ESAT-6 and CFP-10 mycobacterial antigens

<table>
<thead>
<tr>
<th>Tuberculosis complex</th>
<th>ESAT-6</th>
<th>CFP</th>
<th>ESAT-6</th>
<th>CFP</th>
</tr>
</thead>
<tbody>
<tr>
<td>M. tuberculosis</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>M. africanum</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>M. leprae</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>BCG strain</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>geilenbergi</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>moccoe</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>treu</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>tokyo</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>caviae</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>glutae</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>monbaul</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>perre</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>

Risk of infection, by TST and IGRA (QFT-Gold), in an intermediate risk, BCG-vaccinated population

<table>
<thead>
<tr>
<th></th>
<th>Group 1 Low risk N=99</th>
<th>Group 1 Casual contacts N=72</th>
<th>Group 1 Close contacts N=48</th>
<th>Group 4 TB patients N=54</th>
</tr>
</thead>
<tbody>
<tr>
<td>TST + 10 mm</td>
<td>51%</td>
<td>60%</td>
<td>71%</td>
<td>78%</td>
</tr>
<tr>
<td>TST + 15 mm</td>
<td>27%</td>
<td>43%</td>
<td>48%</td>
<td>70%</td>
</tr>
<tr>
<td>QFT-G positive</td>
<td>4%</td>
<td>10%</td>
<td>44%</td>
<td>81%</td>
</tr>
</tbody>
</table>

Discrepancy Between the Tuberculin Skin Test and the Whole-Blood Interferon γ Assay for the Diagnosis of Latent Tuberculosis Infection in an Intermediate Tuberculosis-Burden Country

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group 1 Low Risk (n=99)</th>
<th>Group 2 Casual Contacts (n=72)</th>
<th>Group 3 Close Contacts (n=48)</th>
<th>Group 4 TB Patients (n=54)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range)</td>
<td>36 (21-50)</td>
<td>35 (25-46)</td>
<td>41 (36-70)</td>
<td>43 (17-58)</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>Female</td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td></td>
<td>56 (62)</td>
<td>44 (67)</td>
<td>9 (19)</td>
<td>30 (58)</td>
</tr>
<tr>
<td>Female</td>
<td>41 (41)</td>
<td>21 (30)</td>
<td>30 (61)</td>
<td>22 (41)</td>
</tr>
<tr>
<td>BCG scar</td>
<td>40 (40)</td>
<td>65 (85)</td>
<td>32 (77)</td>
<td>30 (56)</td>
</tr>
</tbody>
</table>

Lung-specific host responses in pulmonary tuberculosis

Hypothesis: clinical manifestations of tuberculosis are affected by the local immune response elicited by M. tuberculosis

Study design:
- BAL performed on patients with active, untreated, pulmonary tuberculosis
- cells and BALF obtained from one radiographically involved and one uninvolved lung segment
- cell count and differential performed on samples
- aliquot of cells (10^6/ml) cultured for 24 hr in serum-free RPMI and supernatants assayed for TNF-a, IL1-b, IFN-g, TGF-b

Local cellular immune responses in patients with pulmonary tuberculosis

<table>
<thead>
<tr>
<th>BAL cells</th>
<th>no. of pts.</th>
<th>HIV+</th>
<th>smear+</th>
<th>cavitory CXR</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;80% macrophages</td>
<td>10</td>
<td>6</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>&gt;20% lymphocytes</td>
<td>8</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>&gt;20% PMN</td>
<td>13</td>
<td>2</td>
<td>12</td>
<td>7</td>
</tr>
</tbody>
</table>

Local IFN-g production in lymphocyte predominant pulmonary tuberculosis

![Graph showing IFN-g production](AJRCCM_1998;_157_729-735)
Interferon-γ as adjunctive immunotherapy for MDR-TB

- **Hypothesis:** interferon-γ may aid outcome in MDR-TB by improving host defenses against *M. tuberculosis*

- **Study design:**
  - Patients: smear positive MDR-TB despite documented compliance with best possible medical regimen
  - Administration of IFN-γ: drug given as 500 mg dose via aerosol nebulizer t.i.w. for 4 weeks
  - Data collection: weekly vital signs, symptoms, sputum smears and cultures; HRCT and BAL at beginning and end of treatment

Lancet 1997; 349: 1513-1515

<table>
<thead>
<tr>
<th>Patient</th>
<th>Drug rx</th>
<th>Duration of drug rx</th>
<th>AFB Smear results Pre-rx</th>
<th>AFB Smear results Post-rx</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>cipro, capreo, clofazamine, rifabutin</td>
<td>24 months</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>INH, oflox, cyclo, ethionamide</td>
<td>12 months</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>capreo, cipro, PZA, cyclo, ethionamide</td>
<td>13 months</td>
<td>++++</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>ethambutol, PAS, oflox, ethionamide, capreo</td>
<td>10 months</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>PAS, cyclo, amikacin, ethionamide, clofazamine</td>
<td>5 months</td>
<td>+++</td>
<td>-</td>
</tr>
</tbody>
</table>

Lancet 1997; 349: 1513-1515