Host Factors in Antimicrobial Treatment

I. NON-SPECIFIC HOST DEFENCE MECHANISMS

A. NATURAL BARRIERS TO ENTRY OF MICROORGANISMS

1. Skin
2. Mucous membranes - IgA production, lysozyme
3. Lungs - cilia, bronchial secretions - lysozyme
4. GI tract - stomach acid, intestinal microflora
5. Bladder - flushing, Tamm-Horsfall protein
6. Vagina - normal flora, pH, IgA
7. Eye - tears, lysozyme

II. NON-SPECIFIC IMMUNITY

A. ALTERNATIVE COMPLEMENT PATHWAY

1. Activation of C3bBb C3 convertase by bacterial membrane polysaccharide.
2. Opsonization - Production of C3b that binds to bacterial surface
3. Phagocytosis by PMNs, monocytes, & macrophages.
5. Release of histamine, chemotactic factors, etc.
III. ACQUIRED OR ADAPTIVE IMMUNITY (Antibody-mediated)

The antibody response to invasion of bacteria is the normal protective mechanism against infection.

A. ANTIGEN RECOGNITION AND ANTIBODY PRODUCTION

1. Recognition of antigen
2. Production of B-memory cells and T-memory cells
3. Upon second exposure. Production of large number of antibody-producing B cells.

B. ANTIBODIES AND THEIR ROLE IN MICROBIAL DEFENSE

Table 7. The Antibodies and their Function

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>IgG</th>
<th>IgM</th>
<th>IgA</th>
<th>IgD</th>
<th>IgE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Ig (%)</td>
<td>85</td>
<td>5-10</td>
<td>5-15</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Site of action</td>
<td>Plasma</td>
<td>Plasma (on B cells)</td>
<td>Secretions</td>
<td>Receptor for B cells</td>
<td>Mast Cells</td>
</tr>
<tr>
<td>Complement activation</td>
<td>+</td>
<td>+++</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Opsonic activity</td>
<td>++++</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Antibacterial lysis</td>
<td>+</td>
<td>+++</td>
<td>+</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Antiviral lysis</td>
<td>+</td>
<td>+</td>
<td>+++</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>

C. CLASSICAL COMPLEMENT PATHWAY

1. Antigen-antibody complex activates complement cascade
2. Cleavage of C3 by C4b2b C3 convertase to produce C3b
3. Chemotaxis & increased vascular permeability via triggering of mast cells
4. Phagocytosis by PMNs & macrophages
IV. HOST-IMMUNE RESPONSES

The ability to ward off infection is highly dependent upon the host immune response. The rate of infection and the response to antimicrobial therapy is highly dependent upon the immune response. In patients with little or no immune function it is imperative to use bactericidal therapy.

A. Groups with primary genetic immune deficiencies

1. X-linked agammaglobulinemia e.g. Bruton's disease - males
   a. males only
   b. cannot differentiate pre-B cells into mature B cells - Ig (all classes)
   c. infants get recurrent sinopulmonary infections

2. Thymic hypoplasia (DiGeorge's syndrome)
   a. T-cells are absent or deficient in blood, lymph nodes, and spleen
   b. Infants susceptible to viral, fungal, protozoal, and intracellular organisms

3. Severe combined immunodeficiency (Swiss type agammaglobulinemia)
   a. Defects in both B and T cells
   b. Susceptible to all types of infections - usually die in first year.

B. Groups with secondary immunodeficiencies

1. AIDS patients
2. Aplastic anemia (drug induced or idiosyncratic)
3. Leukemia
4. Neutropenia induced by radiation treatment
5. Cancer patients on immunosuppressive drugs
6. Solid organ transplant recipients on immunosuppressive therapy.

C. Other disease state or conditions associated with depressed immune function

1. Diabetes
2. Neonates
3. Elderly
4. Sickle Cell Anemia patients
5. Alcoholics
6. Persons without a spleen

The importance of these factors will vary depending upon the site and type of infection. For example, risk factors for severe community-acquired pneumonia are listed in Table 8:
Table 8. Risk factors for a Complicated Course or Death in Persons with Pneumonia

<table>
<thead>
<tr>
<th>Risk Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Age of &gt; 65 yrs. old</td>
</tr>
<tr>
<td>2. Comorbid illnesses (renal failure, ischemic heart disease, CHF, COPD)</td>
</tr>
<tr>
<td>3. Concurrent malignancy</td>
</tr>
<tr>
<td>4. Post-splenectomy state</td>
</tr>
<tr>
<td>5. Altered mental status</td>
</tr>
<tr>
<td>6. Alcoholism</td>
</tr>
<tr>
<td>7. Immunosuppressive therapy</td>
</tr>
<tr>
<td>8. Respiratory rate of &gt;30 breaths per min.</td>
</tr>
<tr>
<td>9. Diastolic blood pressure of &lt;60 mm Hg, systolic &lt;90 mm Hg</td>
</tr>
<tr>
<td>10. Hypothermia</td>
</tr>
<tr>
<td>11. Creatinine level of &gt;150 mm/L or BUN &gt;7 mM/L</td>
</tr>
<tr>
<td>12. Leukopenia (&lt;3000 leukocytes/ul) or Leukocytosis (&gt;30,000/ul)</td>
</tr>
<tr>
<td>13. O₂ level of &lt;60 mm Hg or PCO₂ of &gt;48 mm Hg</td>
</tr>
<tr>
<td>14. Albumin level of &lt;30 g/L</td>
</tr>
<tr>
<td>15. Hemoglobin &gt;9 g/L</td>
</tr>
<tr>
<td>16. <em>Pseudomonas aeruginosa</em> or <em>Staph. aureus</em> as etiologic agent</td>
</tr>
<tr>
<td>17. Bacteremic pneumonia</td>
</tr>
<tr>
<td>18. Multi-lobar involvement</td>
</tr>
<tr>
<td>19. Radiographically evident rapid progression of pneumonia (&gt;50% increase in size within 36 hours)</td>
</tr>
</tbody>
</table>


V. OTHER HOST FACTORS ASSOCIATED WITH TREATMENT

The goal is to achieve concentrations at the site of infection that are at least 2-4 times higher than the MIC₉₀ or the MBC (if bactericidal action is needed). To do this several aspects associated with the patient and the individual antimicrobial agent are important.

A. Pharmacokinetics - tissue penetration, volume of distribution

B. Protein Binding in plasma - only free drug is available to kill organism

C. CNS Penetration of Antibiotics for meningitis and other brain infections

1. Uptake is increased during inflammation of the meninges
2. Lipophilic drugs have better penetration e.g. chloramphenicol
3. P-glycoprotein may pump drugs out of the CNS
D. Metabolism - are metabolites active?
   1. Liver failure - may need to adjust dose if metabolized
   2. Biliary excretion - disturbs gut flora - *Clostridium difficile*
   3. Low glucuronidation capacity in newborns - chloramphenicol
   4. Inhibition of P450 & drug interactions – Erythromycin, clarithromycin – CYP3A4
   4. Induction of drug metabolism – Rifamycins

E. Renal function - declines with age. After age 50 - 6% loss in GFR every decade.
   1. Often need dose adjustment - cephalosporins, aminoglycosides, vancomycin
   2. Nephrotoxicity of antibiotics – aminoglycosides

F. GI System - achlorhydria at age > 60 & in AIDS patients
   1. Poor absorption e.g. Ketoconazole & Itraconazole
   2. Neonates - can absorb oral aminoglycosides – toxicity

G. Peripheral blood flow - IM injections

H. Pregnancy - teratogenicity e.g. tetracyclines, quinolones, clarithromycin?