HIV, Aging and B cells: Thanks for the Memory

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Immunity

- L. immunitas - exemption
- Security against a particular disease, including the invasive, toxic and pathogenic effects
HIV and Invasive Mucosal Infections

- S. pneumoniae
- Salmonella
- Bacteremia
- 1-5%/year

Incidence of Invasive Bacterial Infections with HIV-1
Entebbe, Uganda 1995-98

Cases / 1,000 pt-yrs

- >500
- 2-500
- <200

Enrollment CD4+ T cells / µL
Comm.-Acq. Pneumonia - Older Adults
Group Health 1998-2001; Washington State

915,900 cases CAP in US seniors/year  
1,413 CAP/46,237 seniors over 3 years

CAP by: ICD-9-CM  
64% CXR; antibiotics

Role of B Cells in HIV/Aging

- Increased rate of pneumonia
- Increased rate of bacteremia
  (S. pneumoniae, S. aureus, GNR)
- Increased autoimmune disease
- Increased rate of B cell lymphomas
  (inc. EBV-related)
- Decreased responsiveness to immunization
  (Pneumococcal)
- Increased memory B cell population
  decreased naïve B cell repertoire

Jackson M. CID 2004; 39:1642
**B cell Maturation**

- **Resting; Naïve**
  - IgM
  - IgD

- **Activated; Proliferating**
  - IgG, IgA, [IgM]

- **Memory Cells**
  - IgG, IgA, [IgM]

- **Plasma Cells**
  - Ig-producing

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**HIV and Naïve Human B cells**

- **Surface Ig expression is similar in HIV+/controls**
  - IgM$^+$ (75%)    IgD$^+$ (70%)
  - IgG$^+$ (10%)    IgA$^+$ (13%)

- **Naïve $V_{H}$ gene repertoire is normal in blood (inc. each gene)**

60%

Similar in elderly, except perhaps fewer naïve B cells
**CD19+ B cell Activation**

CD86 Costimulatory molecule is increased in untreated HIV infection, but not in the elderly.

T-independent B cell activation is relatively well-preserved
With HIV infection, including response to IL-2

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**B cell Maturation**

Resting; Naïve

Activated; Proliferating

Memory Cells

Plasma Cells
IgG, IgA, [IgM]

IgG, IgA, [IgM]

IgM

IgD

Antigen

T cell help

Plasma Cells
Ig-producing
Total Serum Immunoglobulin Levels

Similar but less in elderly. Functional avidity of specific Ab are normal in both groups (?)..


Problem in Adults

23-valent pneumococcal vaccine:

- Effective for bacteremia (45-75%)
  → systemic
- Not effective for pneumonia
  → mucosal

**Efficacy of 23v Pneumococcal Vaccine**

Entebbe, Uganda 1995-8

<table>
<thead>
<tr>
<th>Case</th>
<th>Invasive S. pneumoniae (all)</th>
<th>Invasive S. pneumoniae (vaccine)</th>
<th>All S. pneumoniae</th>
<th>All-cause pneumonia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hazard Ratio (95% CI)</td>
<td>1.5 (0.7-3.3)</td>
<td>2.1 (0.9-5.2)</td>
<td>1.4 (0.7-2.8)</td>
<td>1.9 (1.1-3.2)*</td>
</tr>
</tbody>
</table>

1,320 patients; >1,600 PY f/u

French. Lancet 2000; 355: 2106

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**Pneumococcal Polysaccharide-specific IgA-Secreting Cells after Vaccine**

- Control
- ≥ 300
- < 300

HIV+ [CD4+ T cells/µL]


(49) (63) (52) (%IgA2)
**Pneumococcal Polysaccharide-specific IgM-Secreting Cells after Vaccine**

![Graph showing ASC per 10^6 PBMC for controls and HIV+ [CD4+ T cells/µL] with greater than or equal to 300 and less than 300](image)

**Controls**
- ≥ 300
- < 300

**HIV+ [CD4+ T cells/µL]**

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**IgG Response to 23v Pneumococcal Vaccine in Healthy Advanced Elderly and Younger Adults**

![Graph showing IgG response to 23v Pneumococcal Vaccine in Healthy Advanced Elderly and Younger Adults](image)

**29 Older** - mean 80 yo (75-102)

**20 Younger** - mean 29 yo (25-33)

Normal:
- CD4+ T cells
- Total Ig’s (↑ IgA)
- Serum TGFβ, IL-6, TNF, IL-10
- Lymph. Proliferation (± IL-2)
- Ig production in vitro
- TNFα production
- TT and DT response

# B cell Physiology in HIV and Aging

<table>
<thead>
<tr>
<th>Variable</th>
<th>Older</th>
<th>HIV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naïve B cells</td>
<td>Normal-low</td>
<td>Normal-low</td>
</tr>
<tr>
<td>Memory B cells</td>
<td>±Increased</td>
<td>±Increased</td>
</tr>
<tr>
<td>Resting B activation</td>
<td>Normal</td>
<td>Increased</td>
</tr>
<tr>
<td>Cytokine production</td>
<td>Normal</td>
<td>Increased</td>
</tr>
<tr>
<td>Total IgG / IgA</td>
<td>± High</td>
<td>High</td>
</tr>
<tr>
<td>V\textsubscript{H} gene utilization</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>V\textsubscript{H} mutation freq.</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>Primary responses</td>
<td>??</td>
<td>Low</td>
</tr>
<tr>
<td>Memory responses</td>
<td>Normal</td>
<td>Normal-low</td>
</tr>
</tbody>
</table>

# How to Evaluate HIV and Aging?

Clinical variables

In vitro stimulation

<table>
<thead>
<tr>
<th>Vaccines</th>
<th>Primary</th>
<th>Memory</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>KLH</td>
<td>Tetanus/Diphtheria</td>
</tr>
<tr>
<td></td>
<td>Phage</td>
<td>Varicella</td>
</tr>
<tr>
<td></td>
<td>Influenza</td>
<td>Pneumococcal</td>
</tr>
<tr>
<td></td>
<td>Hepatitis B</td>
<td>(23v/conjugate)</td>
</tr>
<tr>
<td></td>
<td>Hepatitis A</td>
<td>Influenza</td>
</tr>
<tr>
<td></td>
<td>Mucosal</td>
<td>Mucosal</td>
</tr>
<tr>
<td></td>
<td>Influenza</td>
<td>Influenza</td>
</tr>
<tr>
<td></td>
<td>Typhoid</td>
<td>Polio</td>
</tr>
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</table>