

HIV, Aging and B cells: Thanks for the Memory

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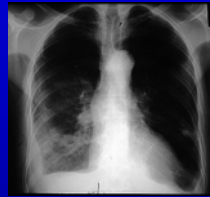


Immunity

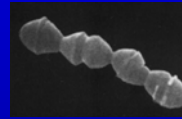


- *L. immunitas* - exemption
 - Security against a particular disease, including the invasive, toxic and pathogenic effects
-

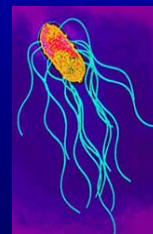
HIV and Invasive Mucosal Infections



S. pneumoniae

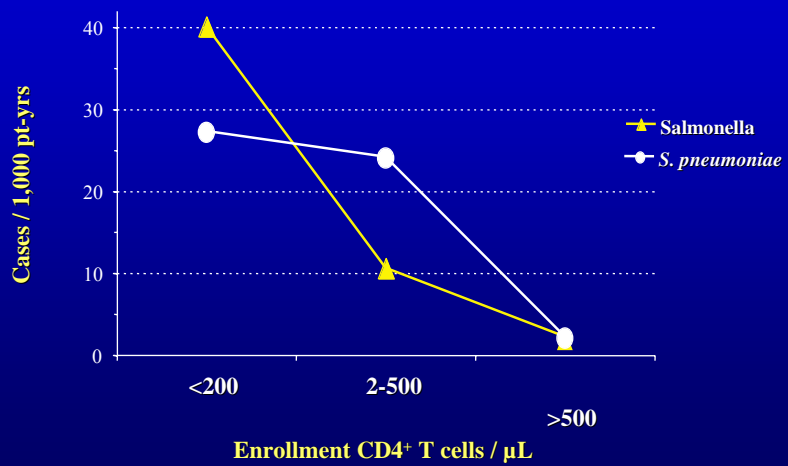


Salmonella



Bacteremia
1-5%/year

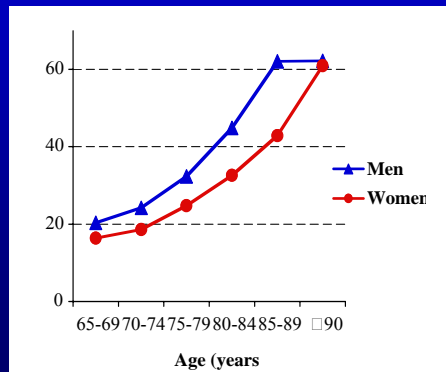
Incidence of Invasive Bacterial Infections with HIV-1 Entebbe, Uganda 1995-98



Comm.-Acq. Pneumonia - Older Adults

Group Health 1998-2001; Washington State

915,900 cases CAP in US seniors/year CAP by: ICD-9-CM
1,413 CAP/46,237 seniors over 3 years 64% CXR; antibiotics

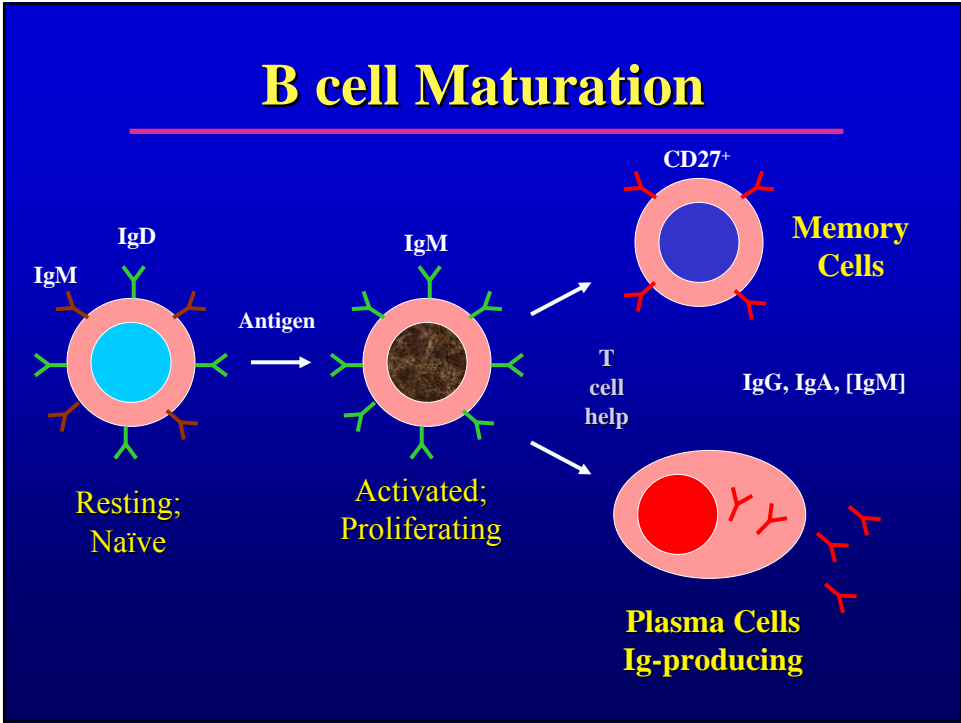


Jackson M. CID 2004; 39:1642

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

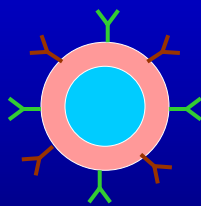
B cell Maturation



HIV and Naïve Human B cells

- Surface Ig expression is similar in HIV+/controls

IgM⁺ (75%) IgD⁺ (70%)
 IgG⁺ (10%) IgA⁺ (13%)



Resting;
Naïve

- Naïve V_H gene repertoire is normal in blood (inc. each gene)

60%



○ Control Subjects (n=17)
 HIV-1-infected Patients
 □ CD4 < 200 (n=15)
 △ CD4 2-500 (n=6)
 ◇ CD4 > 500 (n=3)

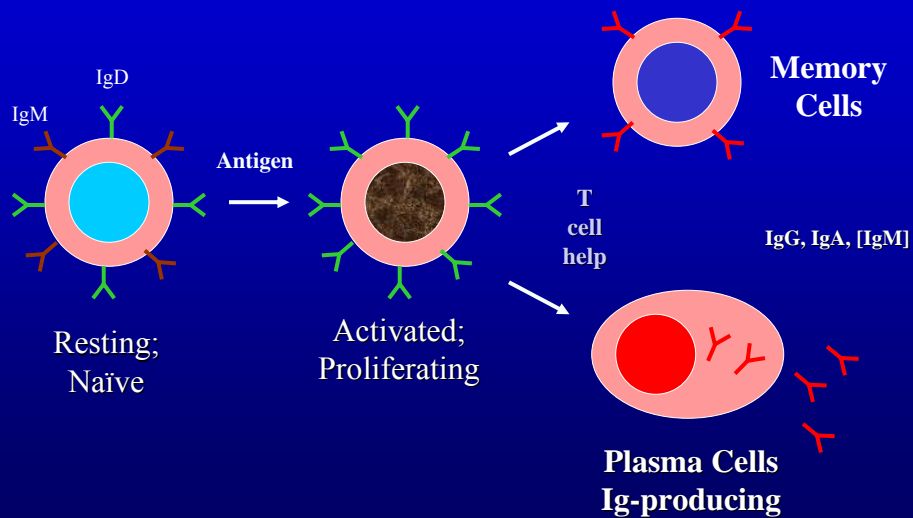
Similar in elderly, except perhaps fewer naïve B cells

CD19+ B cell Activation

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

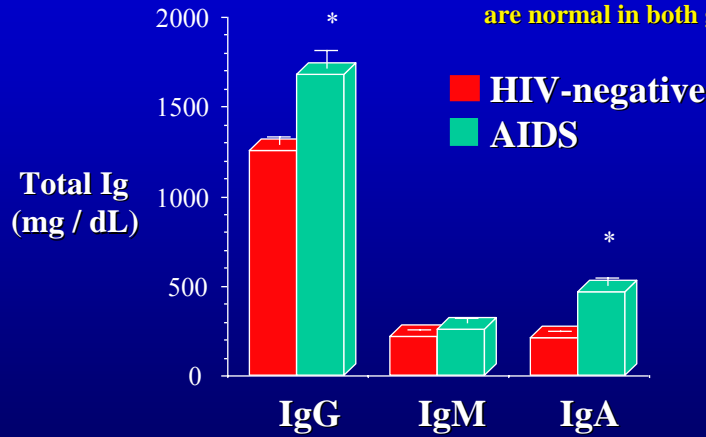
T-independent B cell activation is relatively well-preserved
With HIV infection, including response to IL-2

B cell Maturation



Total Serum Immunoglobulin Levels

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



Janoff. JID 1988; 158:983.

Problem in Adults

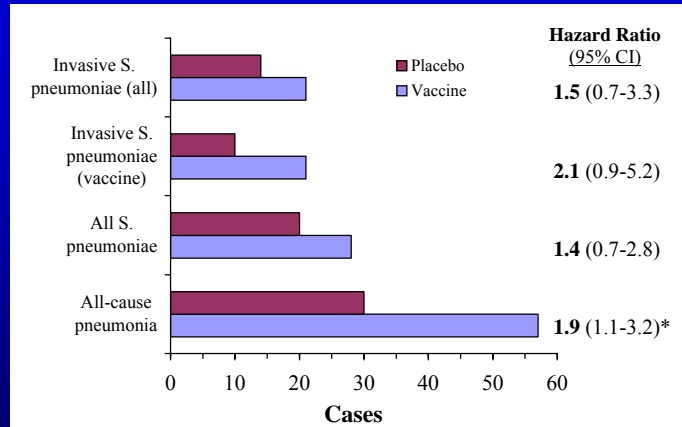


23-valent pneumococcal vaccine:

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

L. Jackson. NEJM 2003; 348:18.

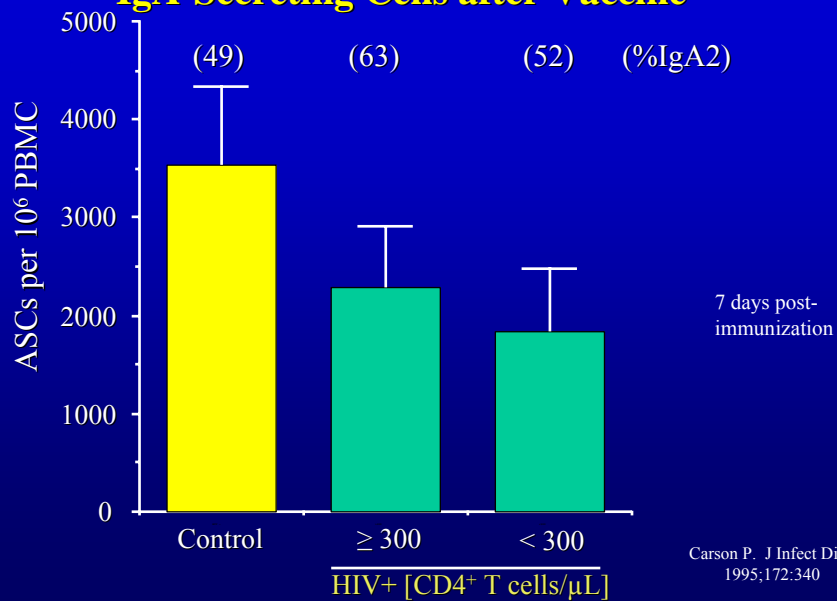
Efficacy of 23v Pneumococcal Vaccine Entebbe, Uganda 1995-8



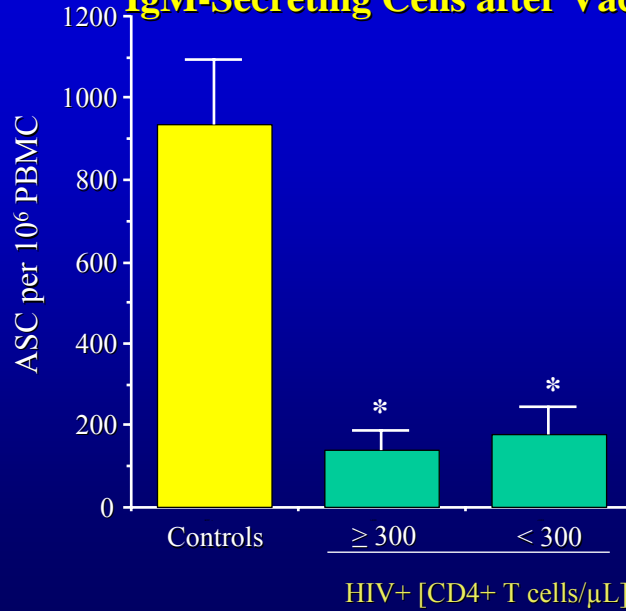
1,320 patients; >1,600 PY f/u

French. Lancet 2000; 355: 2106

Pneumococcal Polysaccharide-specific IgA-Secreting Cells after Vaccine

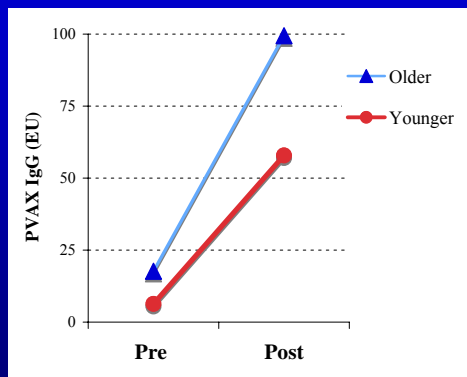


Pneumococcal Polysaccharide-specific IgM-Secreting Cells after Vaccine



Carson P. J Infect Dis. 1995;172:340

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



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

Carson. Arch Int Med 2000; 160:2017

B cell Physiology in HIV and Aging

<u>Variable</u>	<u>Older</u>	<u>HIV</u>
Naïve B cells	Normal-low	Normal-low
Memory B cells	±Increased	±Increased
Resting B activation	Normal	Increased
Cytokine production	Normal	Increased
Total IgG / IgA	± High	High
V _H gene utilization	Normal	Normal
V _H mutation freq.	Normal	
Primary responses	??	Low
Memory responses	Normal	Normal-low

How to Evaluate HIV and Aging?

Clinical variables

In vitro stimulation

Vaccines

Primary

KLH
Phage
Influenza
Hepatitis B
Hepatitis A

Memory

Tetanus/Diphtheria
Varicella
Pneumococcal
(23v/conjugate)
Influenza

Mucosal

Influenza
Typhoid

Mucosal

Influenza
Polio