Infection & Vaccination in PID

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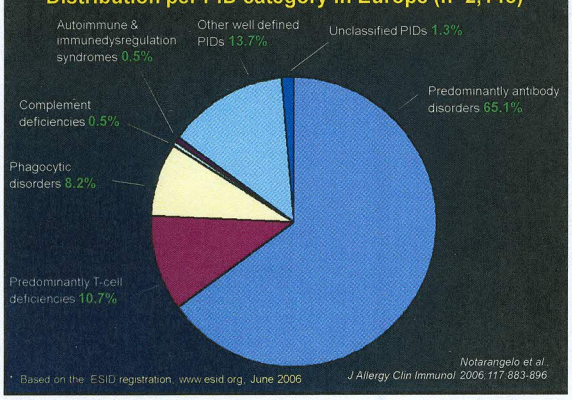
What makes infectious disease so fascinating?

- Challenge of the puzzling?
- Urgent need to find answer & treat?
- Interaction of biology & caring for children?
- Effect of population, places behaviour & fauna?
- Delight seeing very ill children fully recover?

Distribution per PID category in Europe (n=2,148)*



* Based on the ESID registration, www.esid.org, June 2006

Notarangelo et al.
J Allergy Clin Immunol 2006;117:883-896

Diagnosing immunodeficiency in childhood

- Infections are common in childhood!
- Toddlers Day care Deprivation
- "The system is maturing"

Clues for diagnosing PID in childhood

- Age
- Respiratory
- Gastroenterology
- Organism
- Haematology
- Other features
- Family history

Immunodeficiency in childhood

< 6 months

- Severe combined immunodeficiency
- T lymphocyte disorders
- Di George
- Wiskott Aldrich
- Chronic mucocutaneous candidiasis

Immunodeficiency in childhood

6 months to 5 years

- "Antibody" disorders
  - X linked agammaglobulinaemia
  - CD40 ligand deficiency
  - Hyper IgE
  - IgA deficiency
- Phagocyte disorders (Chronic Granulomatous Disease; Chediak Higashi)
- Ataxia telangiectasia

Immunodeficiency in childhood

> 5 years

- Common variable immunodeficiency
- Specific antibody failure
- Complement disorders

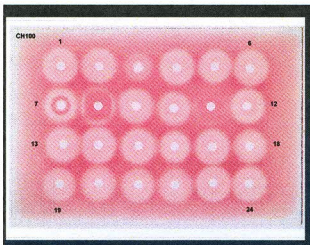
CASE 1

- Boy
- Well until 1 year
- Fever, vomiting, drowsy
- LP – Pneumococcus
- Rx Cefotaxime – good response
- Deaf – cochlear implant

- Well until 7 years
- Left LL pneumonia & empyema
- Pneumococcus in blood culture
- Rx Cefuroxime & surgical drainage

- IgG, A & M Ń
- IgG2 0.65g/L [Ń 1.4 - 4.5 gm/L]

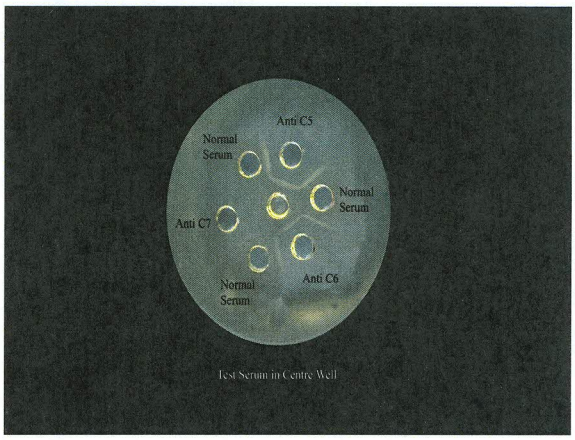
- Pneumococcal antibodies Ń
- B cell numbers Ń
- Class switched memory B cells present
- [CD27+ IgM- IgD-]

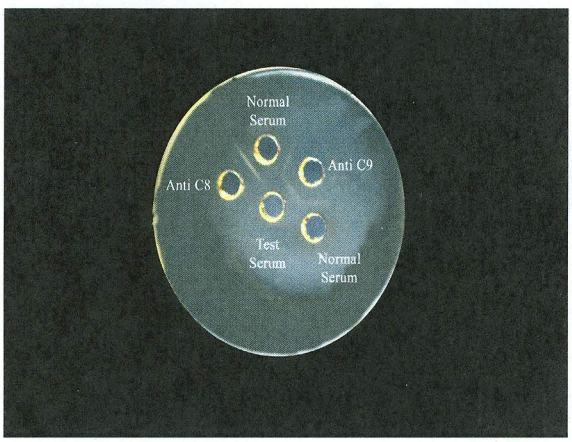


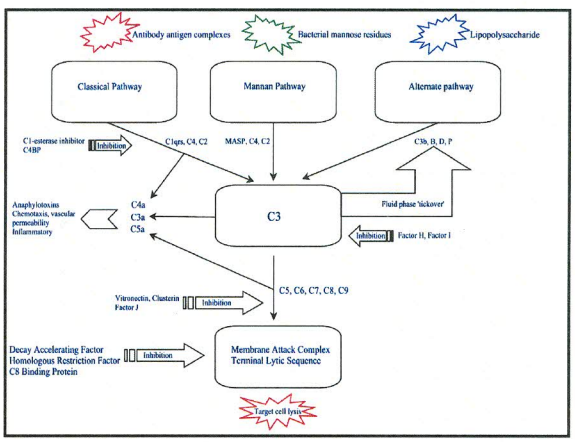
CH100 gel

(Control plus 23 test samples)

1 = Normal Serum Control.
3 = Reduced lytic zone [often related to consumption of component(s)].
7 = Target Zone Phenomena. Indicates the presence of a diffusible serum factor protecting the indicator red cells from lysis. Variously ascribed to heterophile antibodies or rheumatoid factor but is not a consistent association.
8 = Evidence of a complement component deficiency. In this case C8. The slender lytic zone around the perimeter results from the diffusion of the missing component from the surrounding samples.
11 = Evidence of a complement component deficiency. In this case C2. The lytic zone resulting from the diffusion of the missing component from the surrounding samples is evident but is less clear than in sample no. 8.







- Final Δ - C2 deficiency
- Amoxycillin prophylaxis
- Pneumococcal & Meningococcal vaccination

Complement defect Rx

- Conjugate & non conjugate Pneumococcal vaccine
- How often non conjugate Pneumococcal vaccine without inducing tolerance?
- Meningococcal A, C, Y, W135 vaccine – conjugate if possible
- How often check antibody levels & boost vaccinate? Every 1, 3 or 5 years?

- Remember to measure CH100 & AP100 not just C3 & C4

We found 1 complement deficiency from 297 cases so when measure CH100 & AP100?

- Recurrent meningococcal infection
- Serotype W135 or Y
- Previous invasive bacterial infection
- +ve family history

CASE 2

- Boy
- Well until 5 months of age
- Then decreased feeding & weight loss
- Dry cough, respiratory difficulties
- Ventilated

Results

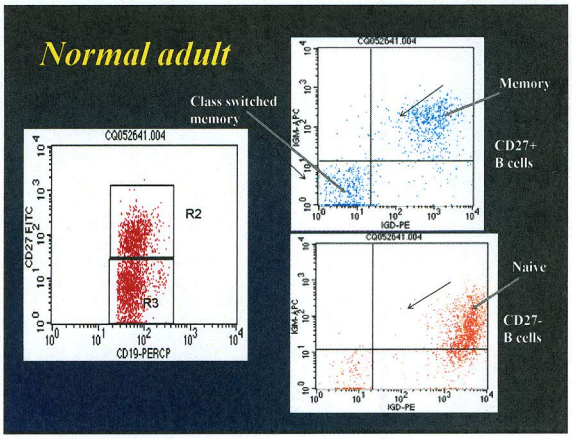
- NPS -ve for viruses, bacteria & fungi
- BAL - PCP by PCR & on microscopy
- What is significance if by PCR alone?

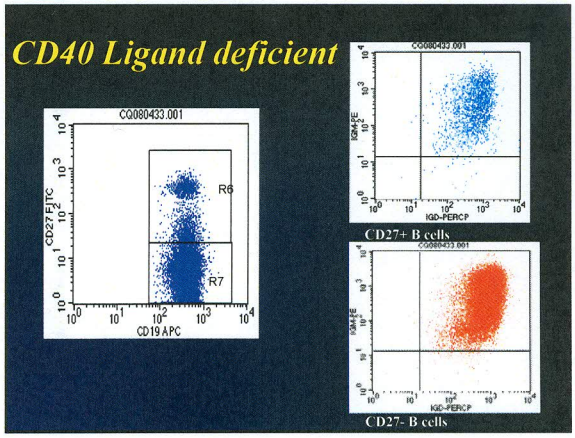
Immune test results

- HIV -ve
- IgG 0.5 gm/L; IgA < 0.3 gm/L; IgM 0.24 gm/L
- Anti B $^{1}/_{1}$
- ° Tetanus antibody
- CD3+ 6412 CD19+ 2011 NK 152
- CD8+ 704 CD4+ 5553
- CD27+ IgM- IgD- 0%
- DR expression Ń

Causes of PCP

- Malignancy & immunosuppression
- HIV
- SCID etc
- CD40L
- MHC II
- ICF
- NEMO
- Hyper IgE





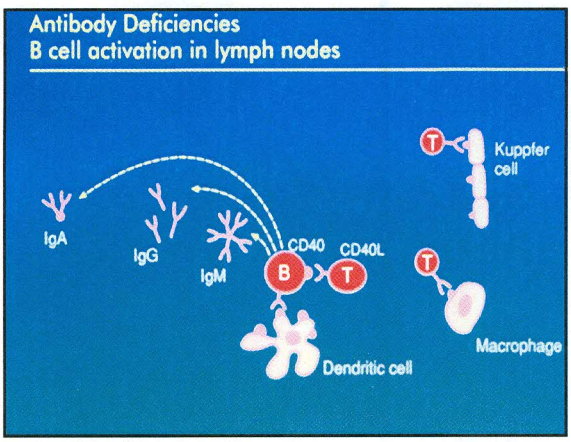
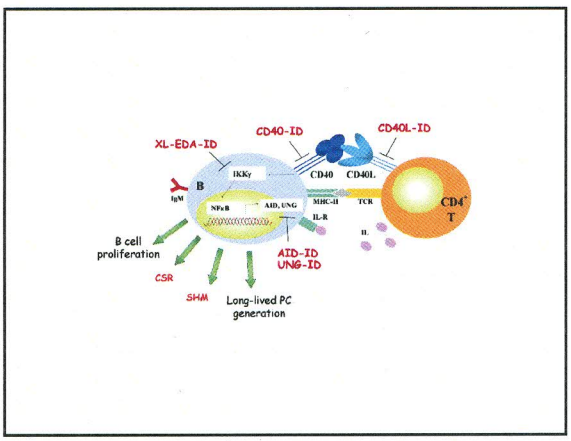


TABLE I. Clinical and immunologic features of hyper-IgM syndromes

	CD40L defect	CD40 defect	XL-EDA-ID	AR-AID	AID-C ter	AID$^{\Delta C}$	UNG defect	Defect of CSR: Upstream from DNA cleavage	Defect of CSR: Downstream from DNA cleavage
Protein affected	CD40L	CD40	NEMO	AID	AID	AID	UNG	?	?
Inheritance	XL	AR	XL	AR	AR	AD	AR	AR	AR
Clinical features									
Bacterial infections	+	+	+	+	+	+	+	+	+
Opportunistic infections	+	+	−	−	−	−	−	−	−
Lymphadenopathy	−	−	−	++	++	++	+	+	+
Autoimmunity	±	±	+	+	+	+	−	−	+
Tumors	+	− (?)*	−	−	−	−	−(?)†	−	+
Immunologic features									
Serum IgG	↓↓	↓↓	Variable	↓↓	↓↓	N − ↓	↓↓	↓↓	↓↓
Serum IgA	↓↓	↓↓	Variable	↓↓	↓↓	N − ↓	↓↓	↓↓	↓↓
Serum IgM	N or ↑	N or ↑	N or ↑	↑↑‡	↑↑‡	↑	↑↑‡	N − ↑‡	N − ↑‡
CD40-induced CSR	N	Undetected	Variable	Undetected	Undetected	Undetected	Undetected	Undetected	Undetected
CD27$^+$ B cells	↓	↓	↓	N§	N§	N§	N§	N	↓
SHM	↓	↓	Variable	↓↓	N	N	N but biased	N	N

XL, X-linked; AR, autosomal recessive; *AID-C ter*, patients with mutations in the C-terminal region of AID; AID$^{\Delta C}$, patients with AID C-terminal deletions; AD, autosomal dominant; N, normal.
*Not observed in the few patients reported thus far.
†Not observed in the few patients with UNG deficiency reported thus far; however, tumors are common in ung$^{-/-}$ mice.
‡IgM levels before Ig substitution therapy.
§CD27$^+$ B cells from these patients express sIgM and sIgD only.



Newcastle CD40 Ligand HSCT

Year	Age	Donor	Outcome	CD40L %	CSM B%
1996	4	URD	Died GvHD, Adeno		
1997	12	MSD	Died GvHD, Crypto		
1997	2	URD TCD	Alive Off all	56	5
1999	12	URD TCD	Died Adeno, Crypto		
1999	14	MSD	Died VOD/GvHD Post liver biopsy		
1999 2002	6 9	URD TCD URD	↓ Chimerism ↓ Alive & well Septrin	78	6
1999 2002	4 7	URD TCD URD TCD	↓ Chimerism Alive & well Penicillin	9	< 1
2000	1	URD TCD	Alive & well Off all	55	12
2001 2002 2003	3 4 5	URD TCD URD URD	Failed Adeno, recipient T cells Alive & well Off all	67	6
2004	1	URD	↓ Chimerism	25	< 1
2004	4	URD	Alive & well Septrin	79	4
2004	3	URD	Alive & well Off all	80	2
2009	1	URD	Alive & well Off all	67	5

XLA: Skin features

Furuncles Staphylococcus aureus

Cellulitis Group A Streptococci

Eczema without IgE

Dermatomyositis like echoviral infection

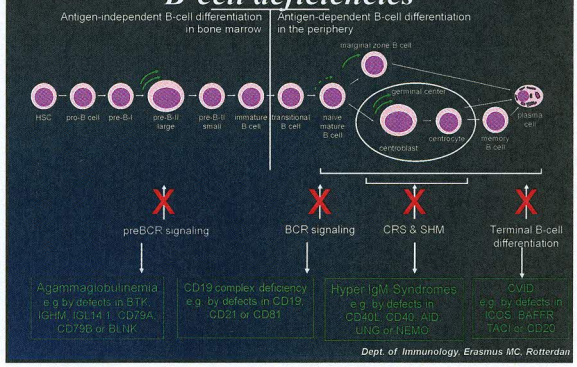
XLA: Clinical features

- Onset 6-12 months
- Diagnosis 2.5-3.5 years
- Invasive bacterial infections
  - Pulmonary & ENT 60%
  - Gastroenteritis 30%
  - Pyoderma 25%
  - Meningitis 10%
- Fatal echovirus encephalomyelitis

Antibody deficiency

- Early childhood
- B lymphocyte failure
- Most common serious PID
- Sinopulmonary infection
- XLA common - often no molecular Δ
- IgG replacement very effective

B-cell differentiation & B-cell deficiencies

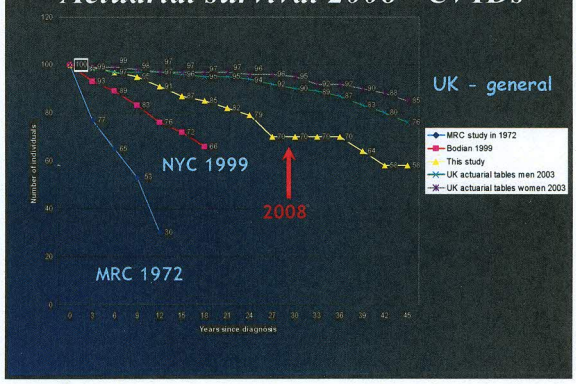


Dept. of Immunology, Erasmus MC, Rotterdam

Partial antibody deficiency

- Sinopulmonary infection
- IgA IgG2 +/- Pneumococcal AntiB ↓
- Measure vaccine responses
- Post Prevenar or post Pneumovax?
- Whole antiB or Serotype specific?
- Prophylaxis or Ig Rx?

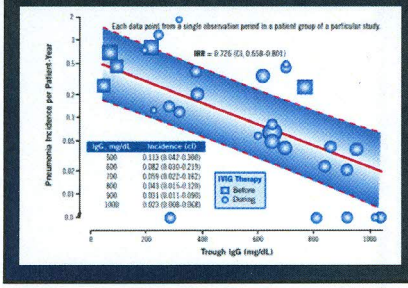
Actuarial survival 2008 - CVIDs



Reduction in pneumonia incidence [0.82 – 0.12 pneumonia / patient yr (p = 0.006)] for patients starting IVIg for first time *Aghamohammadi et al. 2004*

Continuing risk of pneumonia if trough level is <4.5 g/l *Quinti et al 2010*

Trough IgG levels related to pneumonia incidence in meta-analysis *Orange et al Clin Immunol 2010*



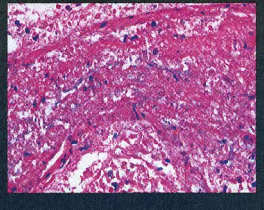
Case 4

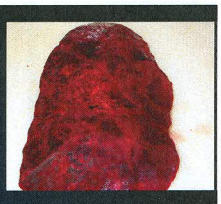
Burkholderia cepacia

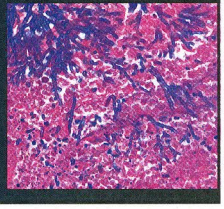
- Chronic Granulomatous Disease

Post mortem

- Lungs: granulomatous inflammation response to *Aspergillus fumigatus*







- Multiple organs (lungs, liver, kidneys, spleen): widespread vascular invasion & infarcts by zygomyces *Absidia corymbifera*

CGD complications

♦ FTT	31%
♦ Short stature	23%
♦ Stomatitis	28%
♦ Chronic diarrhoea	15%
♦ Chronic ileocolitis	13%
♦ Pulmonary fibrosis	10%

Liese, et al. J Pediatr 2000;137:687-93

Haematopoietic stem cell transplant

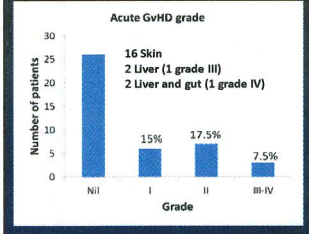
42 HSCTs in 40 patients

Median age 8.38 years (range 0.75-27.2)

Chemotherapy		HLA mismatch	
Myeloablative*	25	0	22
Reduced intensity	18	1	12
Serotherapy		2	6
Yes	33	3	2
No	10	Stem cell source	
Donor		Bone marrow	24
Sibling	11	Peripheral blood	13
Matched parent	2	Umbilical cord blood	2
Unrelated	29	Mixed	1 – BMT/UCBSC
		Not known	3

*Busulphan/cyclophosphamide

Transplant complications



- 16 acute GvHD
- 6 chronic GvHD (4 significant multiorgan/liver)

- 5 invasive fungal infections
- 26 viral infections/ reactivation
- 1 Pneumocystis jiroveci pneumonia
- 2 acute rejection → further transplant
- 4 required top up infusions