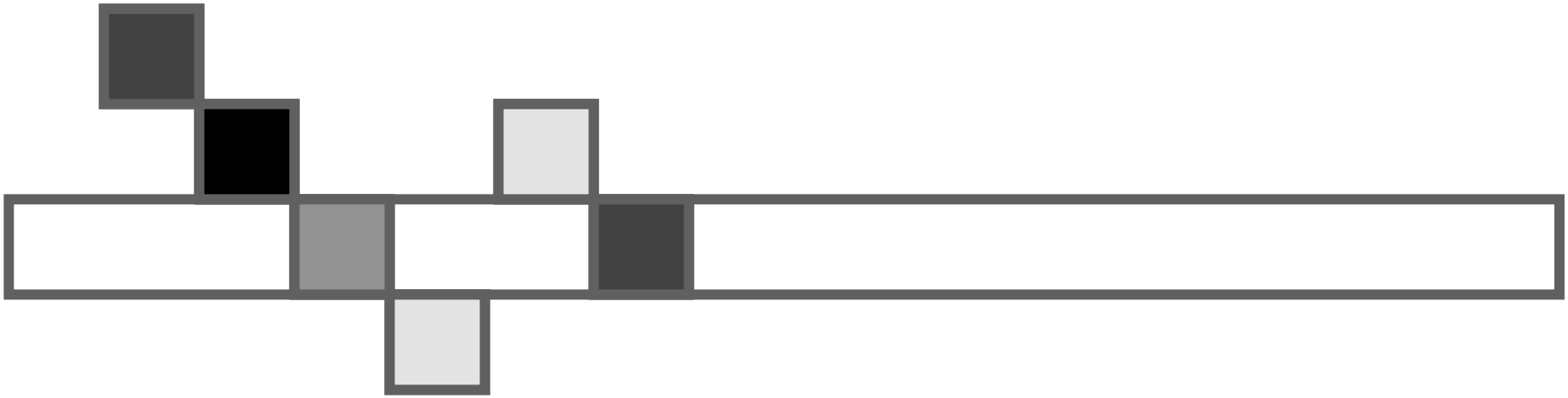


Does this adult patient suddenly have an impaired immune system ?

ESIM Winter School in Saas-Fee

January 20 to January 26, 2013

Verena Briner, M.D. FACP
Department of Medicine
Luzern, Switzerland

Does this patient have an immunodeficiency ?

Skin and mu

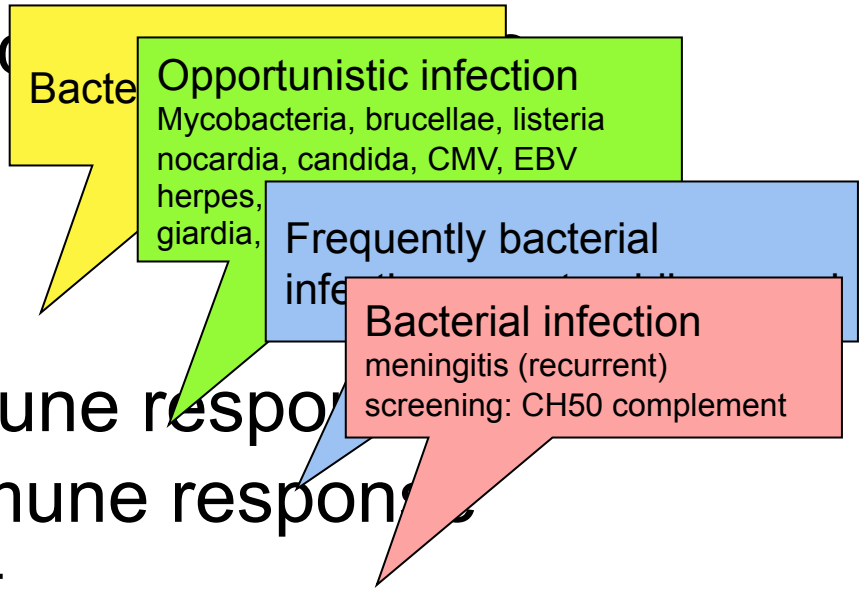
Stasis

Neutrophils

Cellular immune respo

Humoral immune respon

Complement



Typical cases with infection one easily might miss !

acquired immune deficiency
congenital immune deficiency

Man borne in 1931

1956 Diabetes mellitus, arterial hypertension
1995 Check up: MGUS IgG kappa
1998 Coronary heart disease
PTCA: stenting of RIVA

2003 M. Waldenström

2003 Chlorambucil

2004 Cladribine (Litak®)
2005 CHOP, Rituximab (Mabthera®)

Man borne in 1931

2005/06	Severe bronchitis
	2 months cough, sputum production ↑
Sept. 2006	Bronchitis
Nov. 2006	Cough, sputum, fever -39.5°C
	Sputum culture: Pseudomonas aeruginosa
	Ciproloxacin p.o.
	Symptoms improved but persisted
26.01.07	Daily fever, cough, tired
	Maintenance therapy: Rituximab

Man borne in 1931

Chest X-Ray no sign of pneumonia or bronchitis

Laboratory results

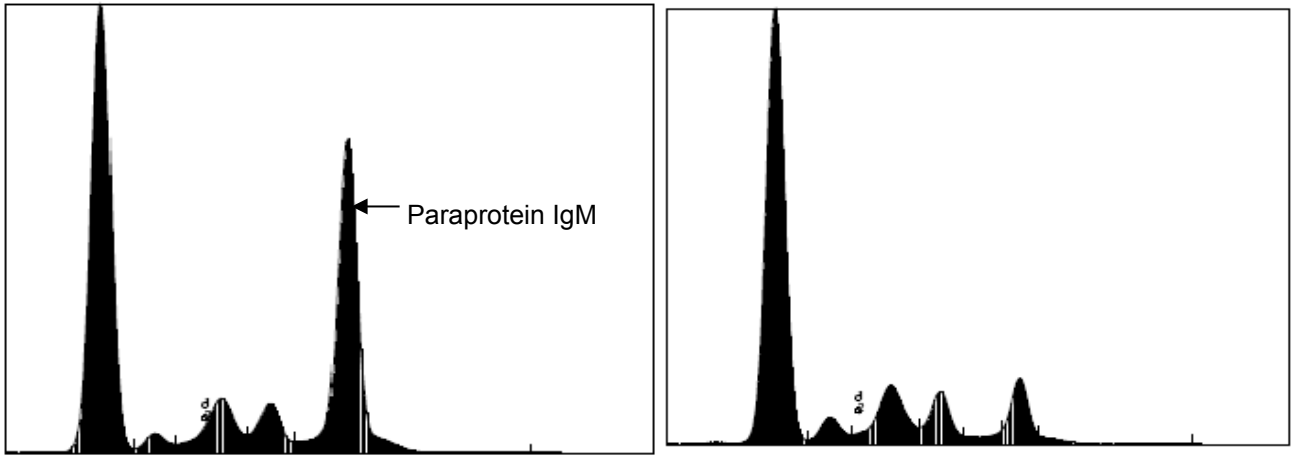
Leucocytes	6.7 G/l
Hemoglobin	134 g/l, MCV 105 fl
Platelet	127 G/l
CRP	33 ng/l

Blood- and urine culture: negativ

Therapy Piperacillin and tazobactam

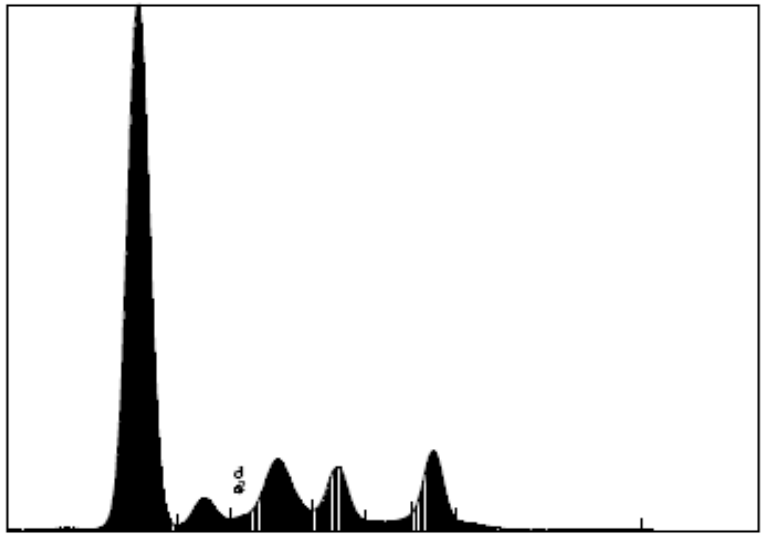
Follow up no improvement
still mild fever, tiredness

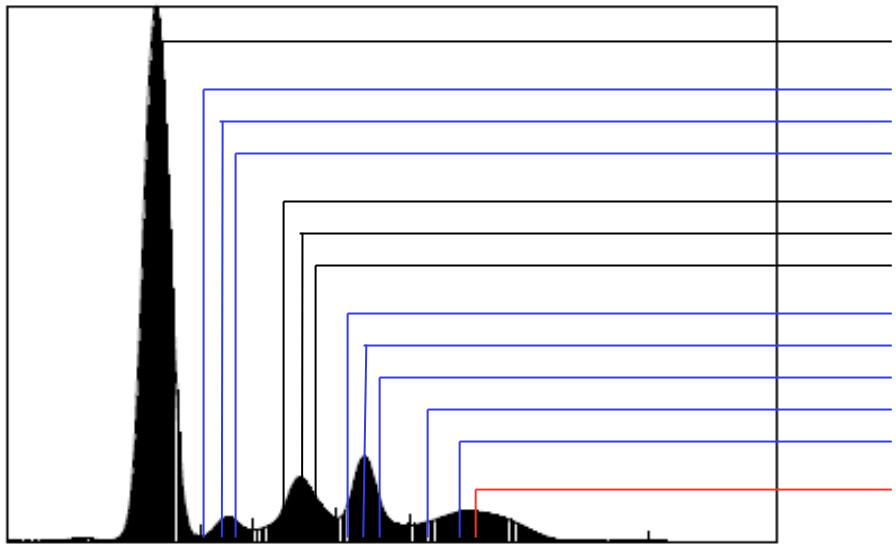
Man borne in 1931



	June 17, 2004	January 26, 2007
Protein	89.0 g/l	64.0 g/l
Paraprotein	28.5 g/l	7.2 g/l

Protein Electrophoresis

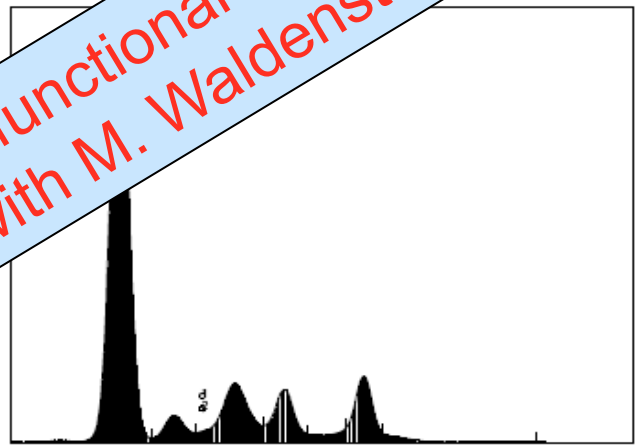




above: electrophoresis of the patient
below: normal protein fractions

Man borne in 1931

There is IgG and probably also functional IgM antibody deficiency in the patient with M. Waldenström



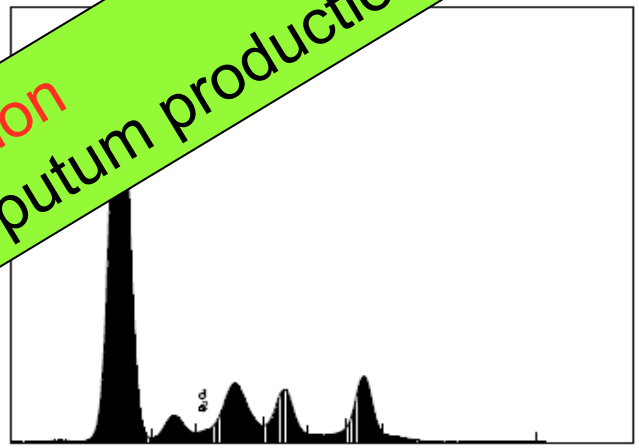
January 26, 2007

			normal	
Protein	64.0	g/l		
Paraprotein	7.2	g/l		
Total IgG	2.8	g/l	7-16	g/l

Man borne in 1931

IgG substitution

condition improves, no fever, sputum production stops



January 26, 2007

			normal	
Protein	64.0	g/l		
Paraprotein	7.2	g/l		
Total IgG	2.8	g/l	7-16	g/l

It might be that antibiotics are not enough to treat
‚simple' respiratory tract infections

Think of immunoglobulins !

Woman borne in 1932

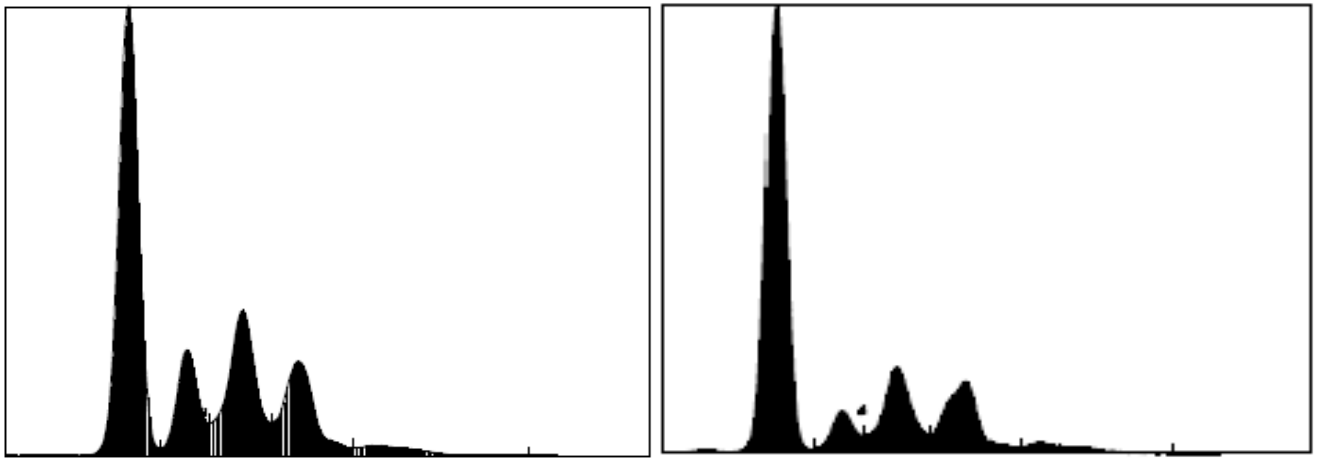
1998	CLL
2001	Hysterectomy
2003	Arterial hypertension
Winter 2004	Twice bronchitis
Oct. 2005	Long lasting episode of bronchitis
Aug. 2006	Pneumonia
Oct. 2006	Pneumonia, patchy infiltration right>left despite several antibiotics condition deteriorate

Woman borne in 1932

Laboratory	
Hemoglobin	104 g/l, MCV 93 fl
Leucocytes	36.7 G/l,
Neutrophils	3.2 G/l
Platelet	107 G/l
CRP	129 ng/l
Therapy	Ceftacidime 3x1g
Microbiology	Sputum day 3: negative
	Blood culture steril

IgG deficency in a patient with CLL

IgG substitution
rapid improvement, fever disappeared



October 17, 2006 November 10, 2006

Total IgG 2.5 g/l

Two cases with

1) acquired Ig deficiency and
2) recurrent and long lasting infections

... and now ?

Substitution for ever ?

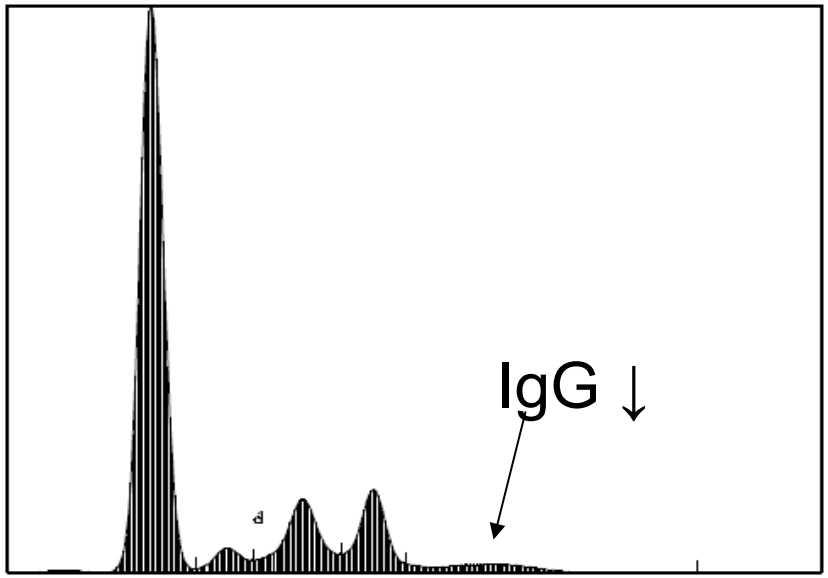
Goal IgG level ?

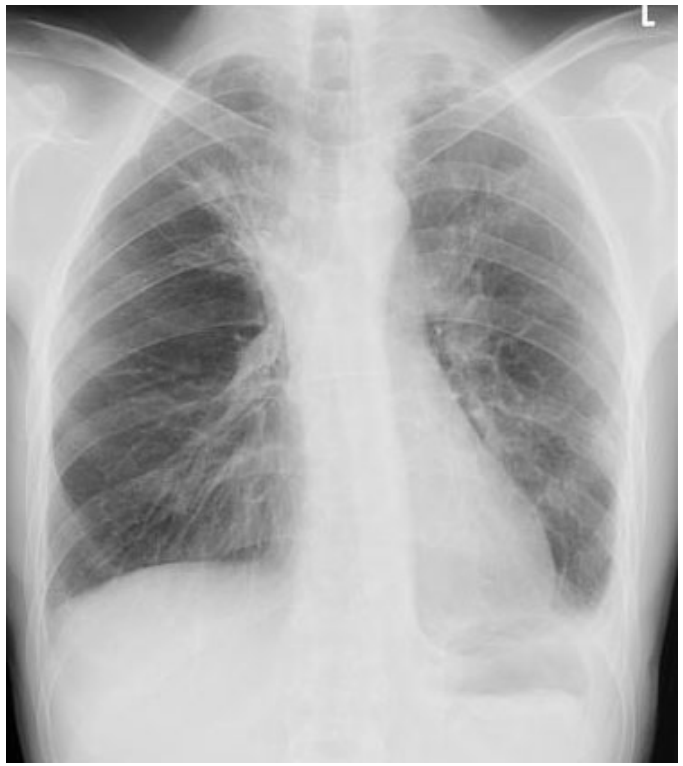
We come back to these questions

Man borne in 1965

Childhood	normal
In school	several infections of upper respiratory tract
Since 1995	Bronchitis every winter Antibiotics
2000	Pneumonia of left lower lobe
2001	Chronic coughing in winter
12/2002	Bilateral pneumonia (St. pneumoniae) Respiratory failure, mechanical ventilation

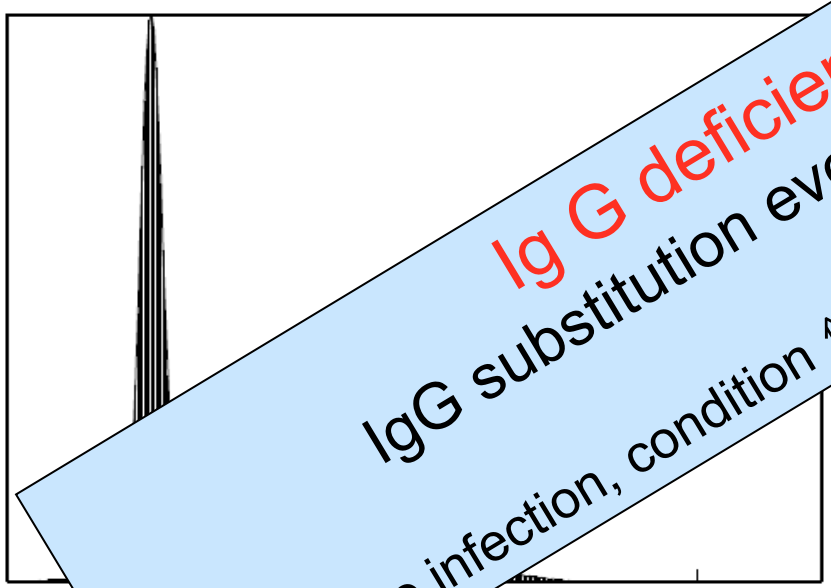
Man borne in 1965

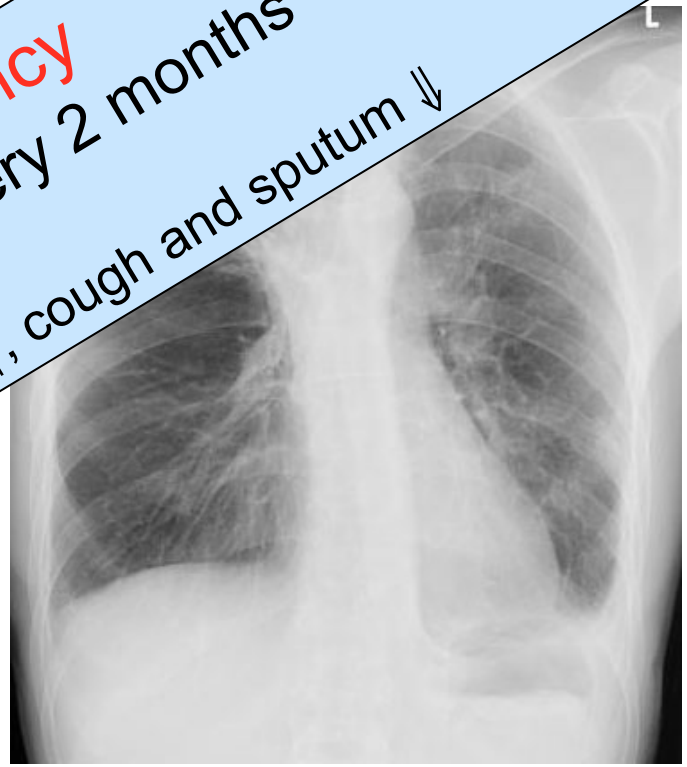




Total protein	normal
Total IgG (normal: 7-16g/l)	2.5 - 3.2 g/l
IgA (normal: 0.7-4 g/l)	0.27 g/l

Man borne in 1965





Ig G deficiency

IgG substitution every 2 months

no infection, condition ⇑, cough and sputum ⇓

Total prote	normal
Total IgG (n al: 7-16g/l)	2.5 - 3.2 g/l
IgA (normal: 0.7-4 g/l)	0.27 g/l

Man borne in 1978

Childhood	normal
since 1991	Flue like illnesses 3-4x/year
	Allergy ?
1999	Maxillary sinusitis
	Twice antibiotics
2001	Operation of maxillary sinus
	Recurrent flue like illness, sinusitis, hyposmia
2005	Bronchitis and maxillary sinusitis

Man borne in 1978

Laboratory results before discharge

Leucocytes	6.5 G/l (fractions normal)
Platelet	125 G/l
Hemoglobin	139 g/l, MCV 89 fl
CRP	17 mg/l
Electrolytes	normal
Auto-antibodies	negative
Complement	normal
Total IgG	normal

CT Scan Maxillary chronic sinusitis

Ultrasound No pathology

Man borne in 1978

During 15 years
more infections than the average population

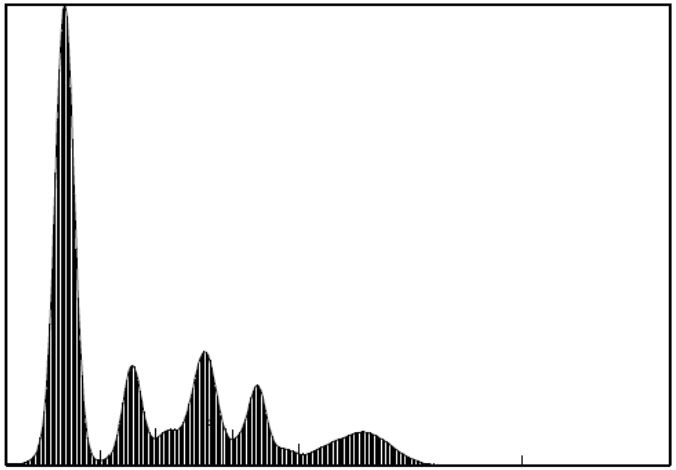
Laboratory results h ge

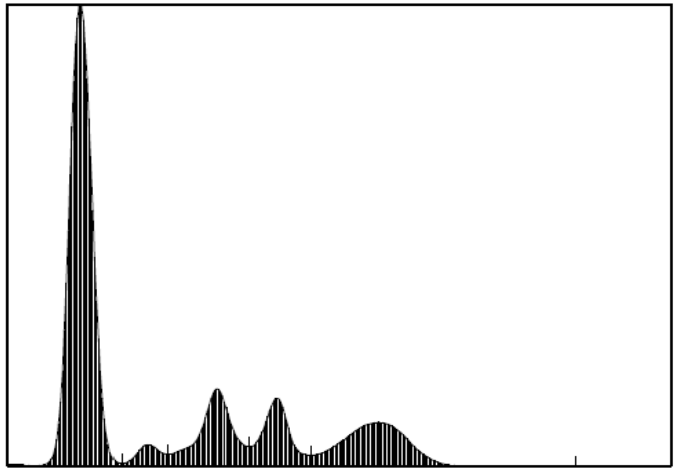
Leuc	G/l (fractions normal)
	125 G/l
	139 g/l, MCV 89 fl
	17 mg/l
lytes	normal
to-antibodies	negative
Complement	normal
Total IgG	normal

CT Scan Maxillary chronic sinusitis

Ultrasound no pathology

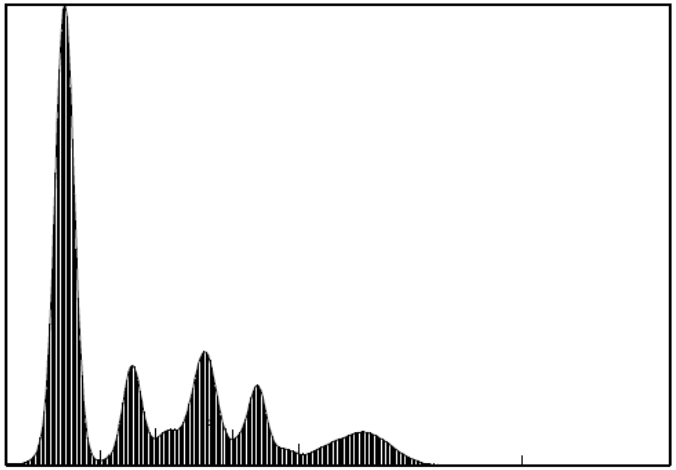
Man borne in 1978

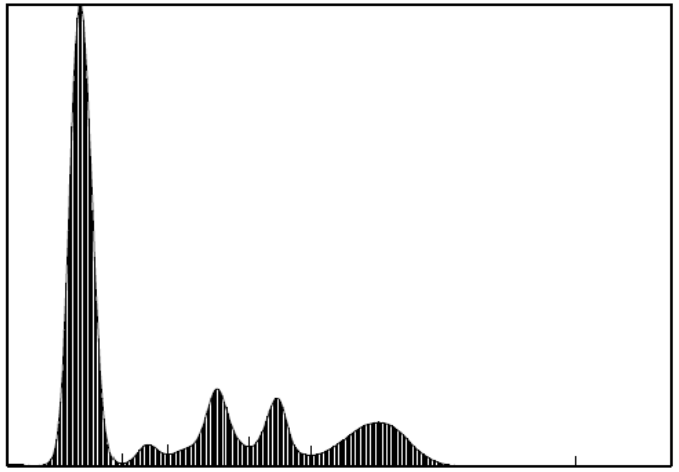




	18.12.05	5.1.2006
IgG total	7.8g/l	8.4g/l

Man borne in 1978

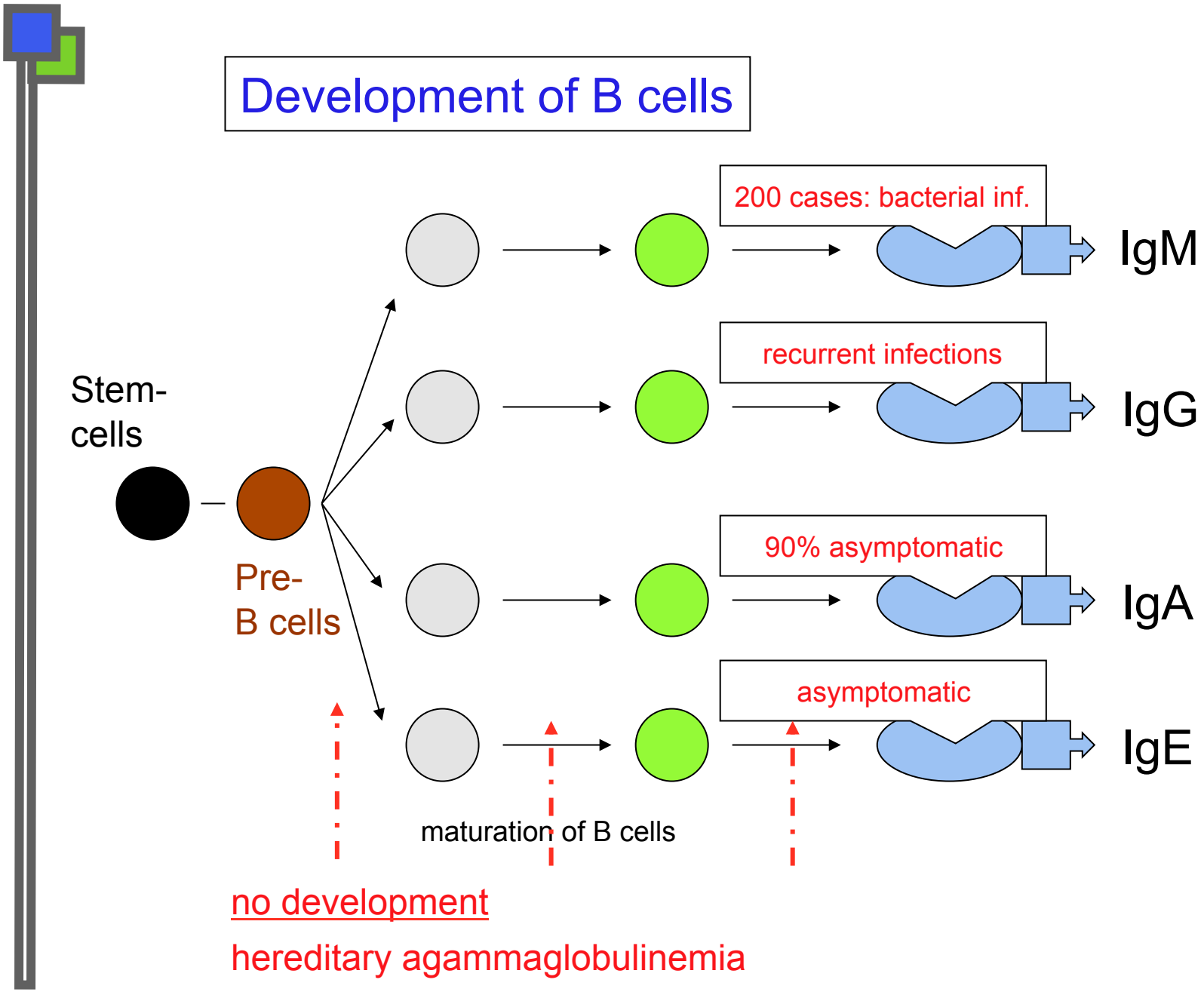




Ig G subclasses and IgA deficiency
What shall we do ?

IgG2	⇓	⇓
IgG4	⇓	⇓
IgA	<0.25	<0.25
IgM	normal	normal

Development of B cells



All 4 patients have an antibody deficiency syndrome

Congenital forms multiple regulatory defects

Common variable Immunodeficiency
Selective IgG Subclass deficiency
X-chrom. hypogammaglobulinemia
IgA deficiency
Hyper-IgM-immunodeficiency

Acquired forms

Malignancy (lymphoma)
  Myeloma, **CLL**, leucemia, **M. Waldenström**
Infection
  EBV, HIV, Parvovirus B19, CMV
  congenital: toxoplasmosis, rubella
Drugs
  IS, sulfasalazine, antiepileptics, gold
  antimalariy drugs, etc.
Protein loosing diseases
  nephrotic syndrome, protein-loosing-enteropathy

Common variable immunodeficiency syndrome (CVID)

Most frequent & ‚classic' form of antibody deficiency syndrome (IgG <4g/l and low IgA and IgM; lymphocyte count normal)

Prevalence 1:10'000

heterogeneous patient group
variable deficiency of immunglobuline

major symptom	recurrent infection		
	Bronchitis	98	%
	Pneumonia	77	%
	Viral hepatitis	6.5	%
1. Manifestation	Age 25 to 40		
Complications	Bronchiectasis	27	%

Subpopulation with CVID

Noncaseating granuloma	20 %
Autoimmune diseases	20 %
Malignancy (lymphoma)	

Deficiency of IgG Subclass

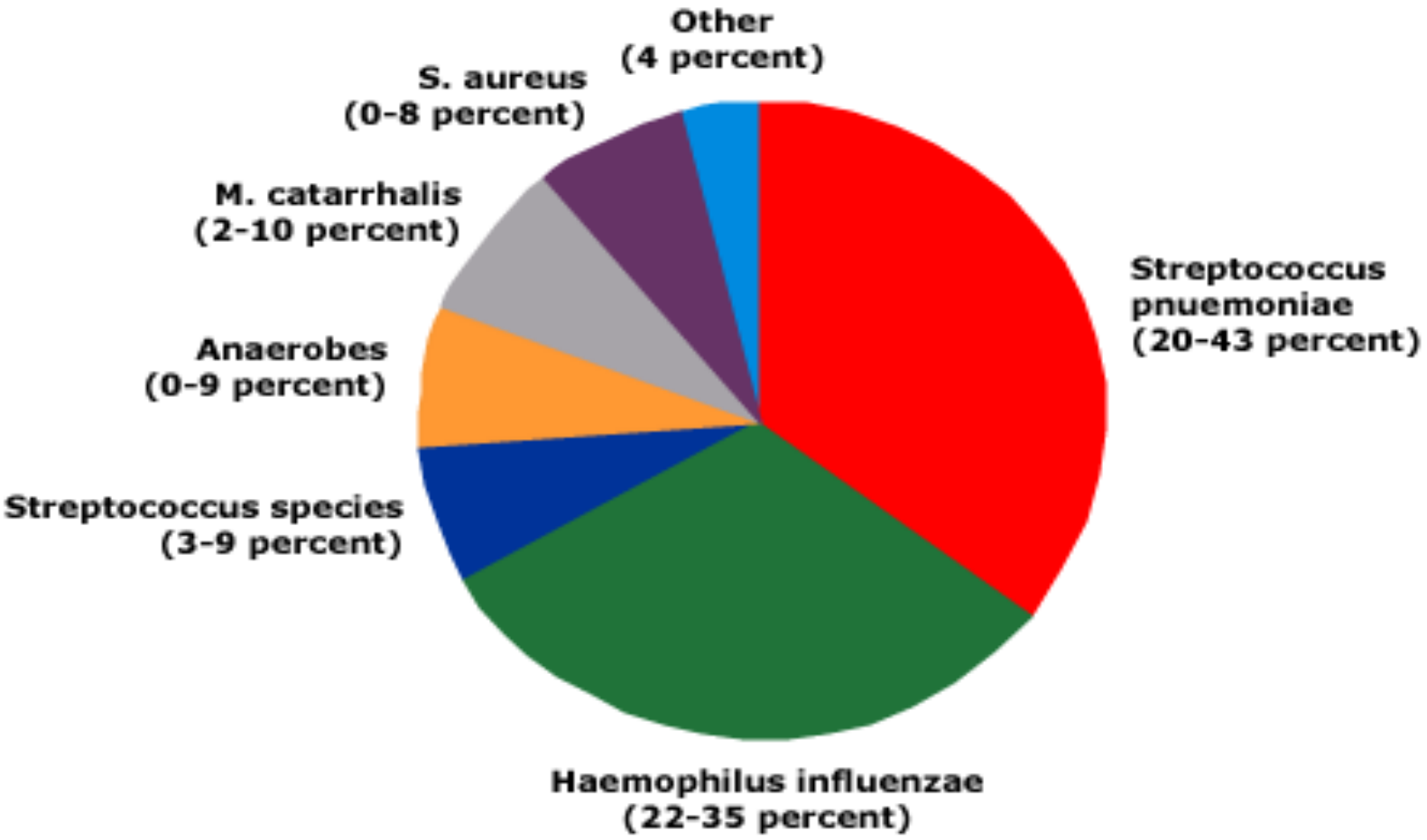
Ig	Amount	IgG_{total}	Response Polysacch.	Response Protein Vac	Normal g/l
Ig G1*	60-80%	⇓	(⇓)	⇓	3.0-10.0
Ig G2	20-30%	(no-⇓)	⇓	normal	1.0-3.5
Ig G3	5-8 %	normal	normal	normal	0.3-1.0
Ig G4	1-4 %	normal	normal	normal	0.2-0.5
				Total IgG	5.0-15.0

Combinations
Ig G1+3 oder Ig G1+others
Ig G2+4 oder Ig G2+Ig G4+Ig A (Pre-CVID?)

*Ig G1 = CVID: 3005 patients with recurrent, bacterial infections
119 patients had Ig G1 deficiency ! (2 tests without infection)

Clin ImmImmunopath 84:194;1997

Common variable immunodeficiency syndrome (CVID)



Therapy in patients with CVID: Ig

Indication for immunglobuline substitution

< 2.5 g/l	‚always'
2.5-5 g/l	if there is increased rate of infection and there is no response to vaccine

Immunglobuline i.v.	0.4-0.6 g/kg body weight
Goal IgG total	5 g/l before next substitution

⇒ Incidence rate for pneumonia decreases ! All Clin Imm 109:1001;2002

⇒ Progression of lung destruction / bronchiectasis is diminished

50 patients with CVID

before IgG substitution

≥1 pneumonia/y 42 patients

with IgG substitution

≥1 pneumonia/y 11 patients

rate of autoimmune diseases and malignancy not ⇓

since not all the patients improve, evaluation is required after 2y of therapy !

Summary

1. Recurrent respiratory infections might be the result of an congenital or acquired immunodeficiency syndrome

Recommendations for IgG deficiency syndrome

1. Treatment of infections

2. Evaluating prophylaxis with antibiotics

   Conjugiated vaccine St. pneumoniae Prevnar, Wyeth-Ayerst

3. Ig G substitution when
   1. response to vaccine is ⇓
      (Tetanus, Diphtherie, Pneumovacc without antibody rise)
      and
   2. insufficient protection with antibiotic prophylaxis

   3. Re-evaluation if infection rate is dropping with substitution of Ig G !