

A photograph of the Tower Bridge in London, viewed from the River Thames. The bridge's two massive stone towers are prominent, with their Gothic-style architecture and blue-painted steel suspension cables. The sky is a clear, pale blue. In the background, the London skyline is visible across the water.

Breaking News in therapies

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Breaking News in therapies

Steady progress...

.....nothing dramatic

Immunoglobulins

- Ivig- new formulations
- Scig-



Grazeby pump



Crono super PID pump

Safety: purification and virus inactivation

- **At least 3 safety steps in each immunoglobulin preparation:**
 - Cohn fractionation
 - Precipitation of plasma fractions by cold ethanol
 - Solvent-detergent treatment
 - Kills viruses by damaging their lipid coat
 - Pasteurisation
 - Heating at moderate temperature (60°C for 10 hours)
 - pH4/ pepsin
 - Digestion of viral protein
 - Low pH incubation
 - pH 4 for 24 hours at 37°C
 - Nanofiltration
 - Passing through a very fine filter to remove microbes and other impurities
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High concentration ivig

- Kiovig 10%
 - Sandoglobulin liquid 12%
-

Product	Concentration	Form	Storage	Vial sizes (g)	Stabiliser	Viral removal steps	IgA content (mg/ml)	Max infusion rate (mg/kg/hr)
Flebogamma	5%	Liquid	4 °C	0.5, 2.5, 5, 10	Sucrose	1. Solvent/detergent 2. Nanofiltration	<0.05	3.5
Gammagard SD	5%/10%	Powder	4 °C	1, 2.5, 5, 10	Glycine, glucose, albumin	1. Solvent/detergent 2. Nanofiltration	0.002	3.3/13.3
Kiovig	10%	Liquid	4 °C or 25 °C	1, 2.5, 5, 10, 20	Glycine	1. Solvent/detergent 2. Nanofiltration 3. Low pH incubation	0.03	13.3
Octagam	5%	Liquid	25 °C	1, 2.5, 5, 10	Maltose	1. Solvent/detergent 2. Low pH incubation	<0.1	2.5/4.2
Sandoglobulin NF	12%	Liquid	4 °C or 25 °C	6, 12	Nicotinamide, L-proline, L-isoleucine	1. Nanofiltration 2. Low pH/pepsin	<0.015	2.0
Vigam	5%	Liquid	4 °C or 25 °C	2.5, 5, 10	Sucrose, glycine	1. Solvent/detergent	<0.01	2.5

Baby A
X-linked agammaglobulinaemia
Small- but growing fast

Mrs B anti IgA antibodies-
previous reaction to ivig

Mrs C
Elderly, cannot tolerate large fluid volumes

Subcutaneous immunoglobulin



Given by infusion pump

- Start at 10ml/hr increase 1-2.5ml/h each week to max 30-40 ml/hr
- Infusion every 1-2 weeks

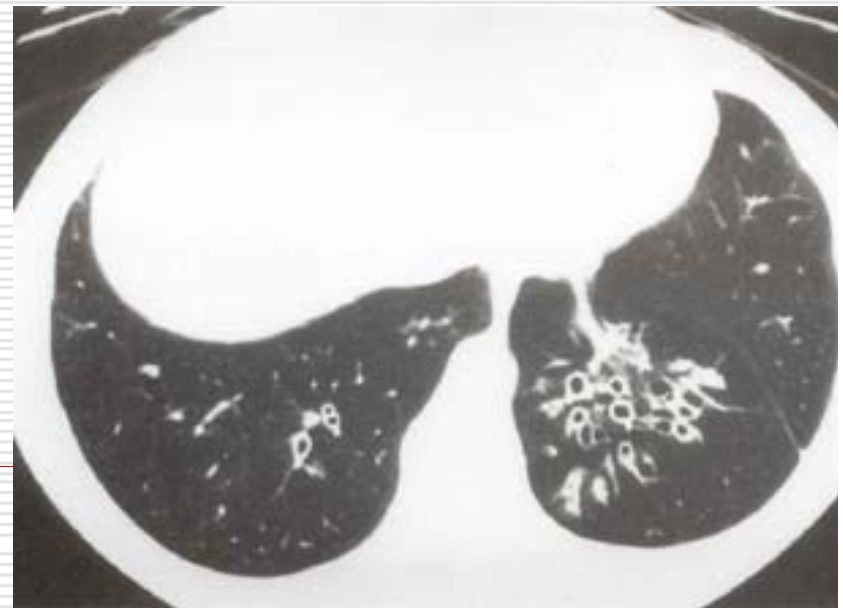
Infusion time 1-2 hours

Local reactions occasionally a problem; major reactions extremely rare



Ms J- CVID

- Started on ivig
 - Fewer infections, no cough/sputum
 - Better general health and energy
- BUT*
- Flu-like symptoms, headache, nausea: 24-48 hours after infusion
- Tendency to infection in week prior to infusion

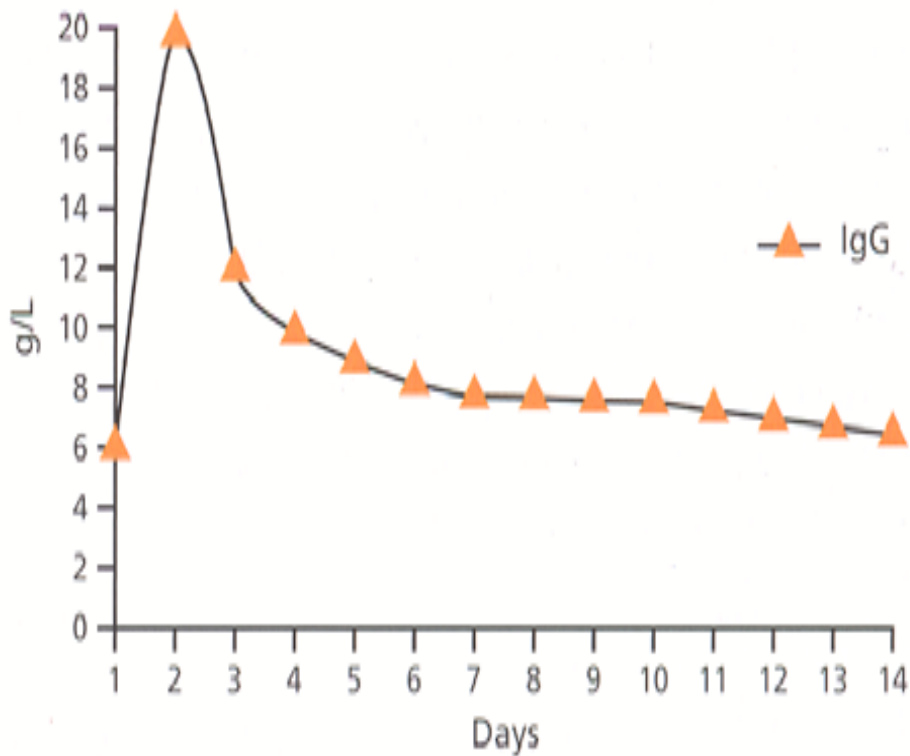


Ms J-management

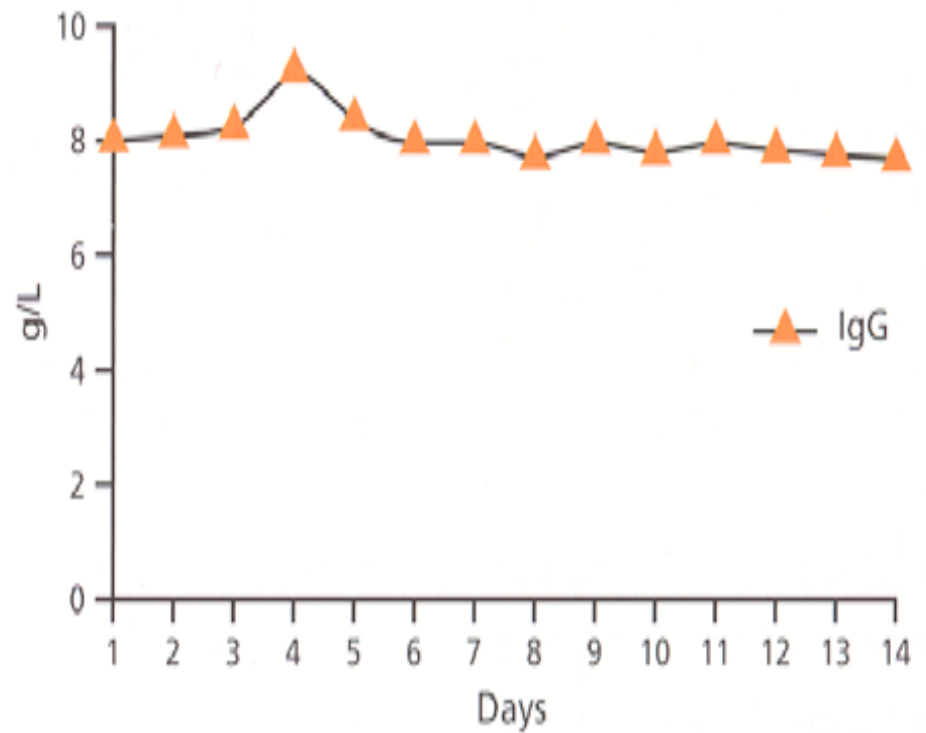
- ❑ Changed to subcutaneous treatment
- ❑ Equivalent monthly dose given weekly
- ❑ 0.16 mg/mL (16% vs 5% for ivig)
- ❑ Flu-like symptoms abolished
- ❑ Reports great improvement in quality of life
- ❑ Breakthrough infections infrequent



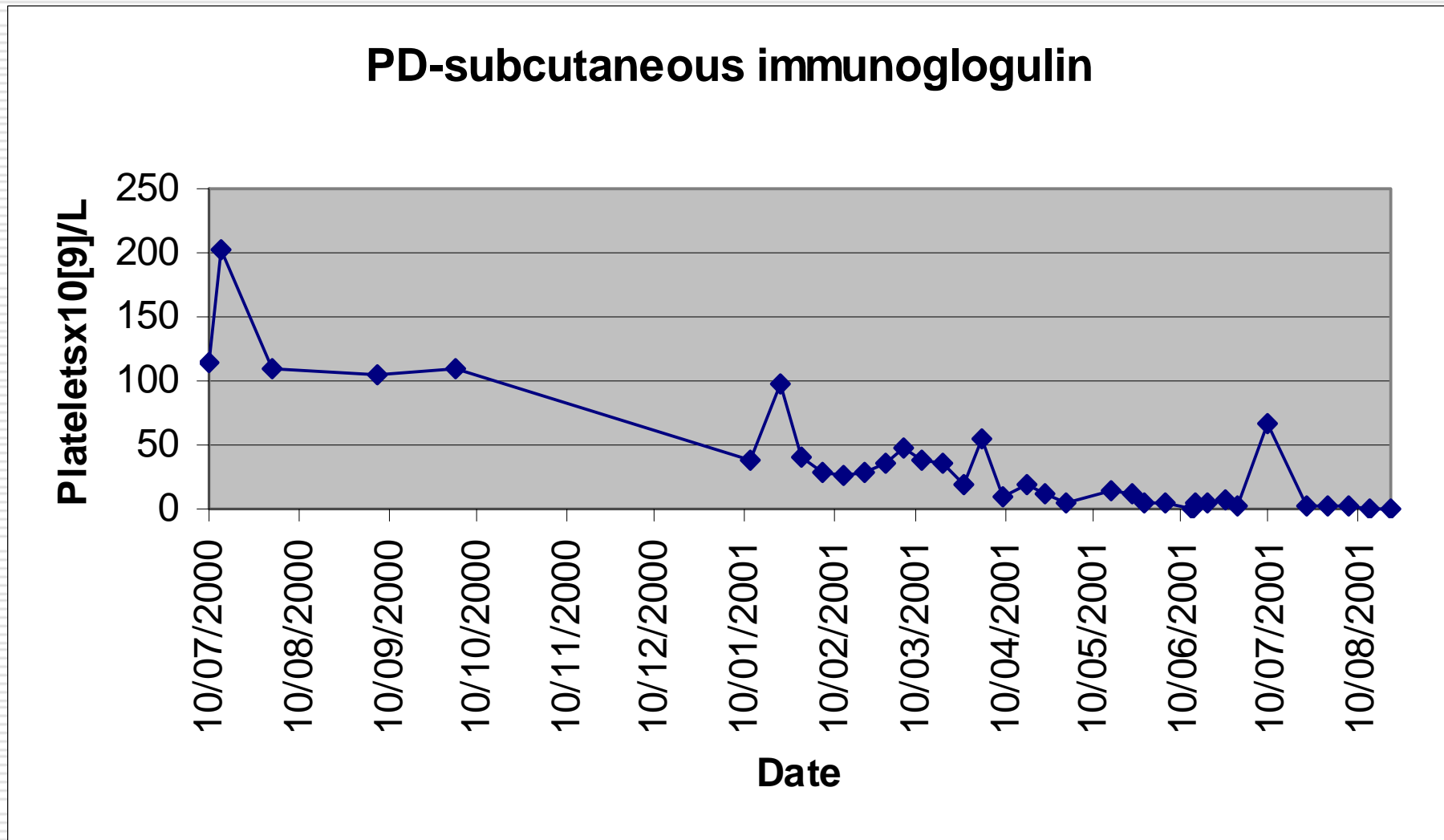
Levels of IgG following IVIG



Levels of IgG following rSCIG



Sc Immunoglobulin treatment- a note of caution



PD

- ❑ Subcutaneous IgG suitable for replacement but may not be suitable for immunomodulation, where high peak levels may be required.
 - ❑ High doses may be technically difficult via subcut route
 - ❑ Studies ongoing in neurological conditions
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Reasons for subcutaneous therapy: Barts patients

- Convenience
- Problems with iv access
- Reactions to ivig
- Trial
- Safety concerns

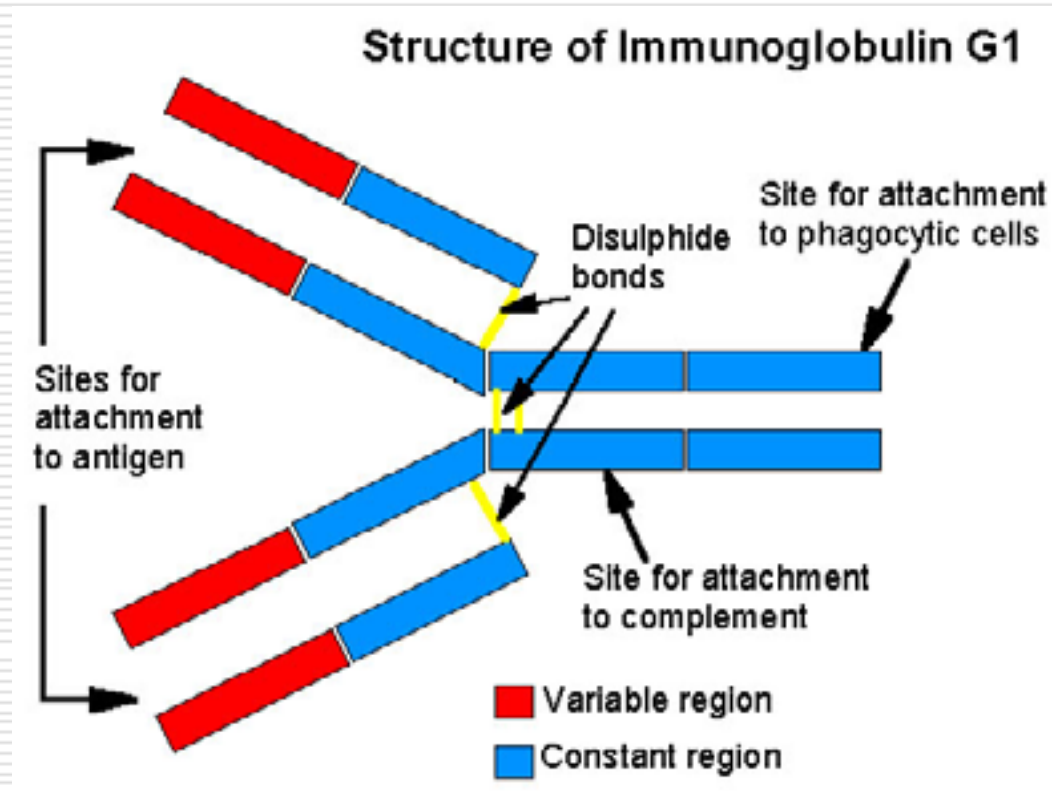
Reasons for IV therapy: Barts patients

- Convenience
 - Other immune problems
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Unbalanced immune system

□ Monoclonal antibodies

- Can target & destroy single part of immune system
- More potent treatments?
- Fewer side-effects?



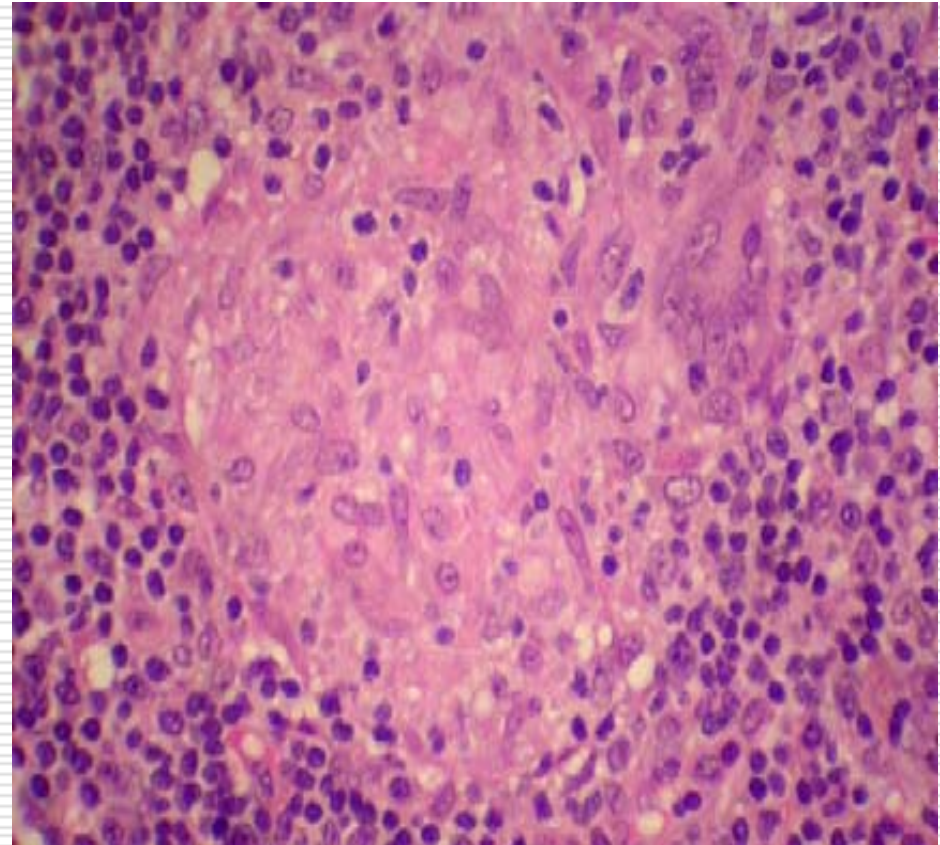
Rituximab

- ❑ Removes B cells (antibody-making cells)
 - ❑ Antibody levels usually unaffected

 - ❑ *Immune thrombocytopenia (ITP)*
 - ❑ *Autoimmune lymphoproliferation syndrome (ALPS)*
 - ❑ *X-linked proliferation syndrome (XLP)*
-

Infliximab

- Anti-TNF α
- TNF α activates white blood cells (lymphocytes & macrophages)
 - causes local inflammation & fever
 - More TNF produced when antibody production is suppressed
 - 'Granulomatous CVID'
- Infliximab may reduce need for steroids (prednisolone)



Dacluzimab & infliximab

Anti T-lymphocyte
activation (anti IL2)

Anti- macrophage (anti
TNF)



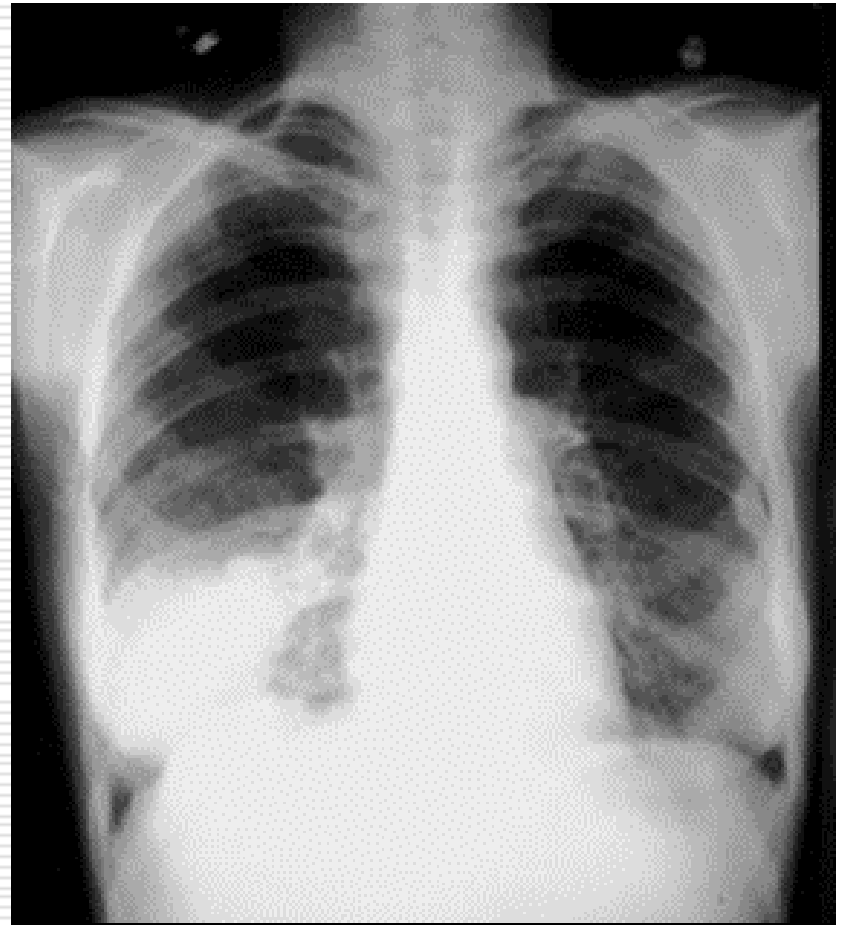
- 162 Bone Marrow Transplants for PID
 - Graft vs host disease
 - Ciclosporin/ +- Mycophenolate (MMF)
 - prednisolone
 - 9/13 children with GvHD survived
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Better bone marrow transplants?

- 'Reduced intensity conditioning'
 - Bone marrow not completely destroyed
 - Immune responses suppressed
 - Less GvHD, less toxicity.....Better survival
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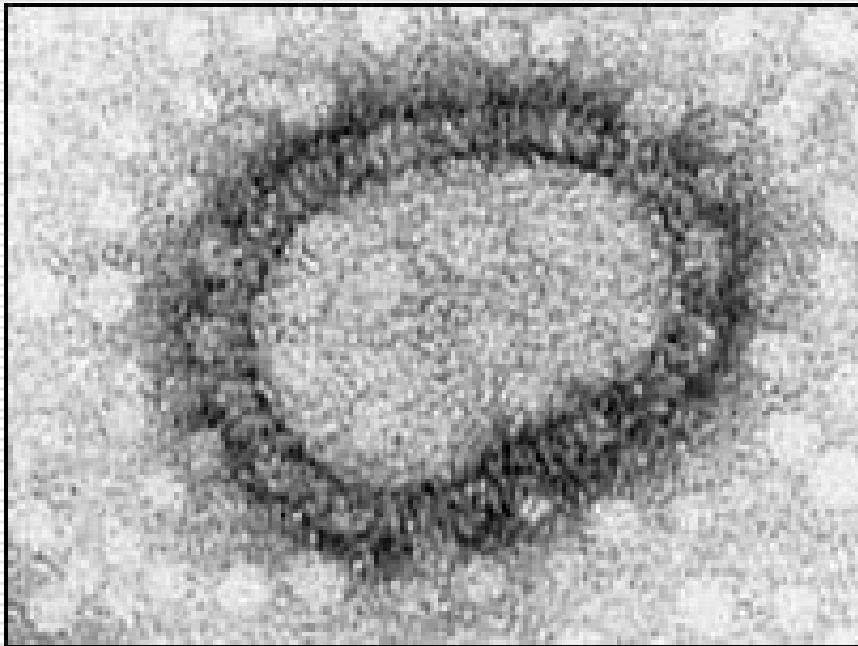
Vaccination news

- Prevenar
 - 'conjugated' pneumococcal vaccine
 - Long lasting immunity to pneumococcus
 - Can be used for babies
 - Routine in US
 - Routine in for babies UK since Sept 2006



Vaccination news..

- ❑ **One 'cure all' flu jab for life?**



- ❑ Immune response to flu is to surface proteins-which can mutate
 - Haemagglutinin
 - Neuraminidase
 - H1N1, H5N1 etc.
 - ❑ Vaccines need to be changed every year
 - ❑ M2 protein-does not mutate
-

Hereditary angioedema (C1 inhibitor deficiency): New treatments

- ❑ Berinert P (C1 inhibitor)
- ❑ Recombinant C1 inhibitor
- ❑ Icatibant
- ❑ DX88



Icatibant

- 15 patients with 20 HAE episodes treated with Icatibant:
 - 10 skin swellings, 3 abdominal pain, 7 combined skin/abdominal episodes
 - 12 patients intravenous (i.v.) infusion, 8 patients subcutaneous (s.c.) injection

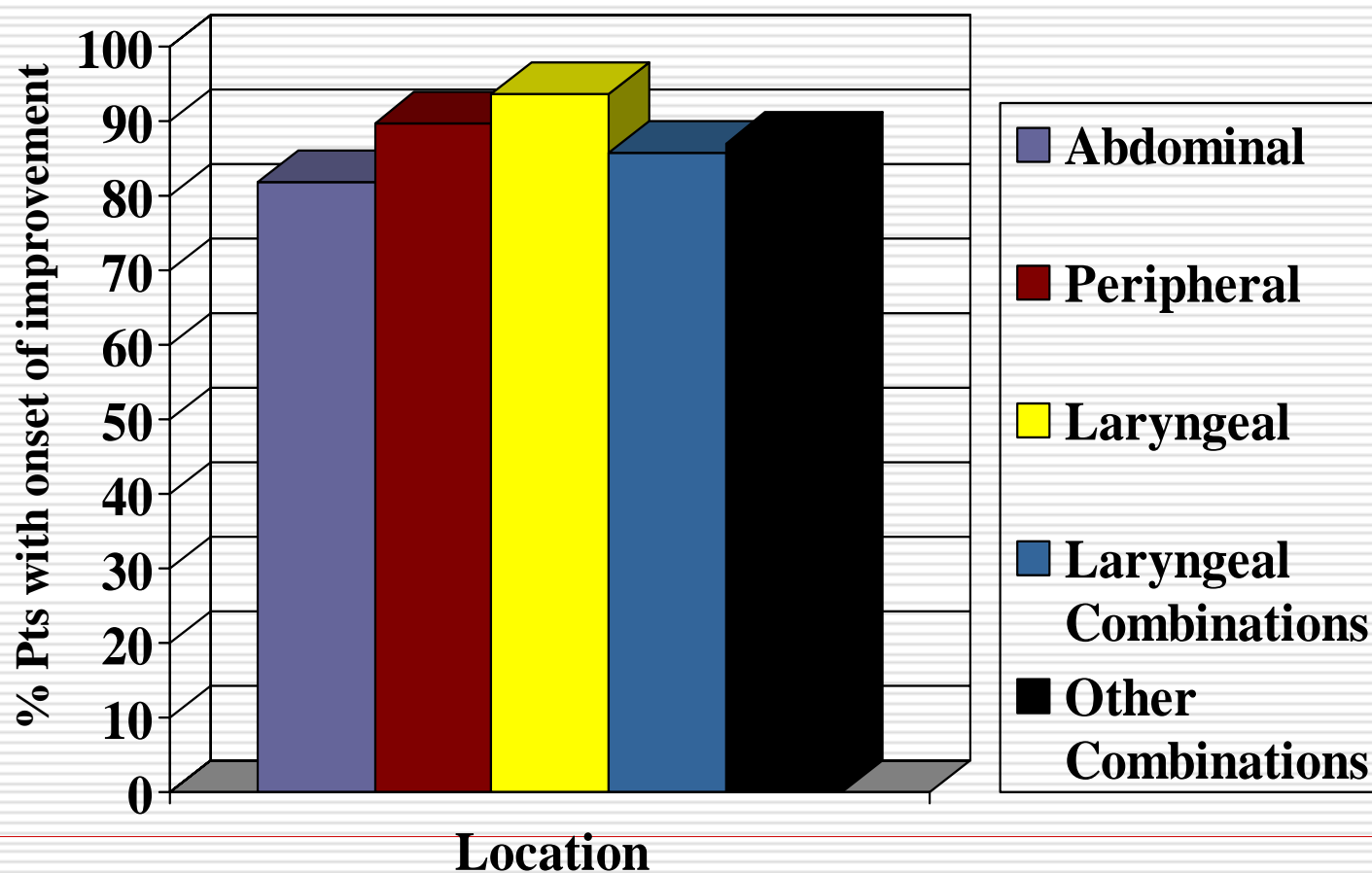
Route	Dose	Median time to onset of symptom relief	Median time to onset of symptom relief
		Treated	Untreated
<i>s.c.</i>	<i>30 mg</i>	35 min	35 h

100% response rate and rapid symptom relief

DX-88 Response by 4 hours

Response is independent of location of HAE attack

Median time to response ranges 19 - 52 min



Data as of 14 Feb 2006

What the patients say...

□ Icatibant

- 'it hurts (...but not a major issue)'
- rebound attacks may be a problem

□ DX88

- '....mostly helpful. But there are some non-responders'
- rebound attacks may be a problem

□ Overall

- '.... newer drugs may be useful, but none of them have the durability of the plasma concentrate'
- Very keen to have new treatment options

Thank you

- David Watters
(IPOPI)
- Dr Sharon Choo
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Street)
- Dr Graham Davies
(Great Ormond
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- Dr Sofia Grigoriadou
(Barts)
- Dr Christine Kinnon

