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Knowledge-based healthcare

UK CLL Forum
Clinical Sciences Day 22/09/10

Immunology Support for CLL

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- Educational grants and honoraria to support attendance and presentations at scientific meetings from Baxter, Beckman Coulter, Boehringer Ingelheim, CSL, Grifols
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- Monies & conflict of interest managed by employer
- This session is sponsored by Baxter

Immunology Support for CLL

- Clinical, Lab, (and Radiology) assessment
  - Immunodeficiency : Current status, prognosis
- Antimicrobials
  - Prophylaxis, Early treatment, Early escalation
- Immunoglobulin replacement
  - Case selection Rx status
  - Mode of delivery
  - Dosing

Case 1

- 64 F Rec LRTIs 5 yrs, worse last 2 yrs
- Stage A CLL
- 9 mth later – Night sweats + Weight loss
- WCC 56.7 (L 43.7, N 13) Hb 11.7, plts 133
- BM >79% Lymphocytes, Hepar, Spleen 13.5 cm
- Pred 50mg + Chlorambucil 8mg
- WCC 4.9 (N 1.03), Hb 11.2,
- IgG 4.6, IgA 0.26, IgM 0.09 g/L
- Pneumococcal pneumonia, +ve blood cultures

Case 1 - Referral

- Recurrent LRTIs despite IVIG
- Coincident with national shortage of IVIG
- Aim for lowest effective dose of IVIG
- "Adjust dose by serum IgG or symptoms?"

- Co-morbidities
  - IHD incl previous coronary stent for Angina
  - Diverticulitis

Case 1: Management

- CT chest - Bronchiectasis
- MBL deficiency A/0 52Cys
- Few normal B cells
- Monthly IVIG (400 mg/kg/mth)
  - Trough serum IgG 7.6, IgA 0.2, IgM <0.3 g/L
- Transfer to weekly SCIG 660 mg/kg/mth

Case 1: Progression

- New LNs – Groins, Axillae
- Hb11.3, pl 103, WCC 29.9 (L 23.3, N 6.3)
- Superficial dermatosis - Ringworm
- Amoxil 500mg bd prophylaxis
- SCIG IgG 13, IgA <0.4, IgM <0.3 g/L
- Treatment = FCx3
- LRTIs – ~3 mthly, Amoxil responsive
  - Haemophilus influenzae
- Amoxil treatment 1g tds x14

Annual Review 12 months Post FCx3

Case ZN	Lymphs %	Counts	Controls x10^6/L
CD19+	51.8%	1049	90 – 300
Few normal cells			
CD3- CD56+	16%	324	90 - 260
CD3+	29.1%	589	840 – 1710
CD3+ **CD4+**	10.9%	**221**	530 - 1350
CD3+CD8+	10.5%	213	220 – 650
Naive CD4+		**13**	154 - 700
Naïve CD8+		20	54 – 358
Naïve B		3	58 - 338

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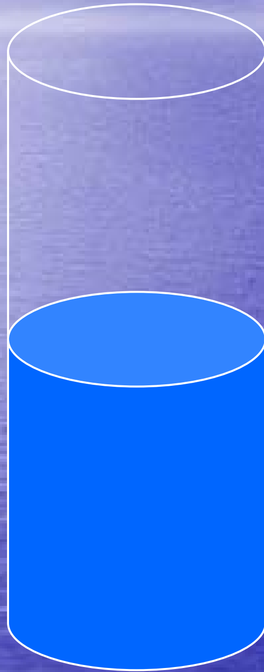
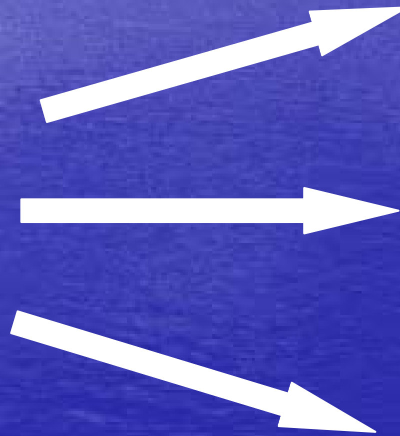
Infection

- Pneumocystic pneumonia (PCP)
- Cytomegalovirus infection (CMV)
- "Infections of Childhood"
  - Molluscum contagiosum
  - Warts
  - Superficial fungal infections
- Respiratory virus infections
  - Influenza, RSV, Adenovirus
- Bacterial infections
  - H.influenzae, Strep. Pneumoniae
- Sequelae
  - Autoimmune disorders

Immunodeficiency: Current Status & Prognosis





Immune Status

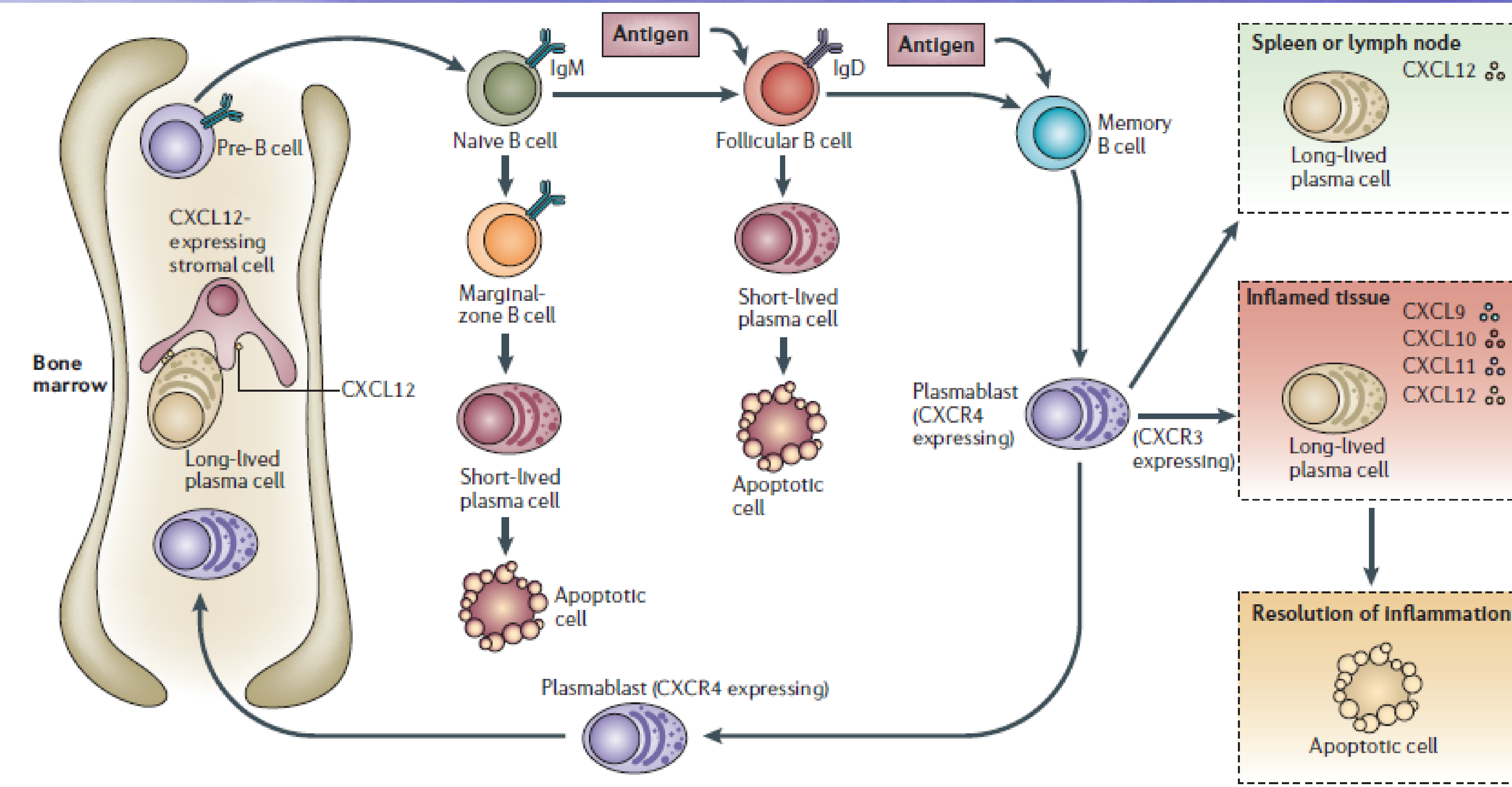
Progress

Time

Immunodeficiency in CLL – Multi-factorial

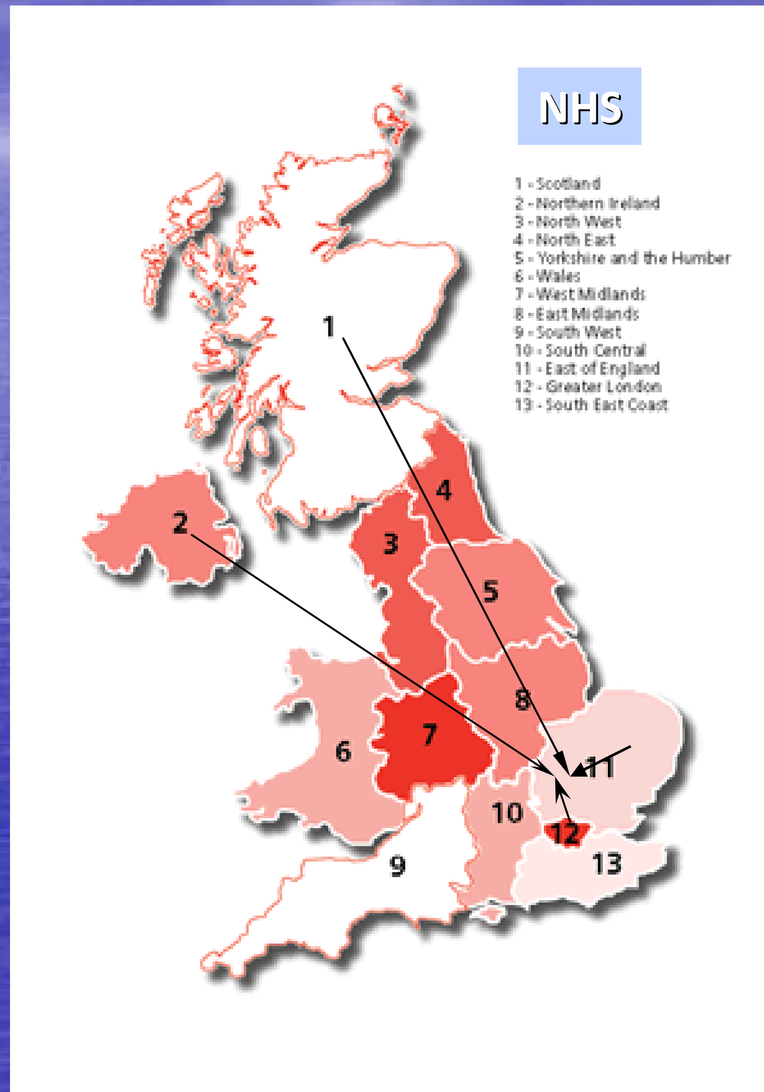
- **Intrinsic immunosuppression** of CLL
  - Bone marrow involvement
  - Maturation arrest
  - Hypogammaglobulinaemia
- **Comorbidities**
- Previous exposure to **CMV**
- **Complications of therapy**
  - History of immunosuppressive agents
  - Novel agents used in the salvage setting

Heritage and Dynamics of Plasma Cell Life

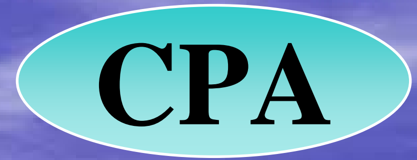


Radbruch 2006

Supra-Regional Service for Serotype Specific AntiPneumococcal Antibody Levels



Cellular Phenotyping



CPA Reference No. 2383

- Naïve CD4+ T cells
- Naïve CD8+ T cells
- Naïve B cells
- NK cells
- Regulatory T cells
- Indices of peripheral expansion
  - Cytokine receptor expression
- T + B cell differentiation
- TCRVβ cell receptor repertoires

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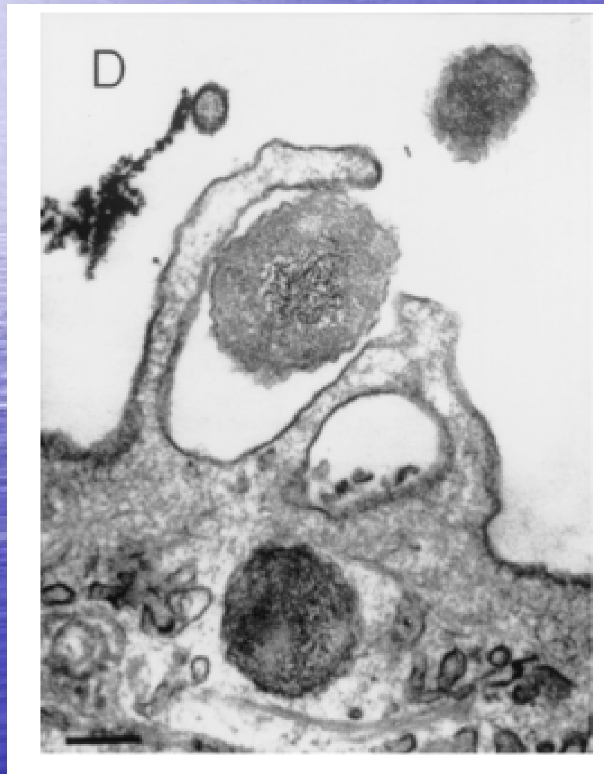
Macropinocytosis as a Mechanism of Airway Epithelial Cell Entry by NTHI

NTHI initiate cytoskeletal re-arrangement within human airway epithelium



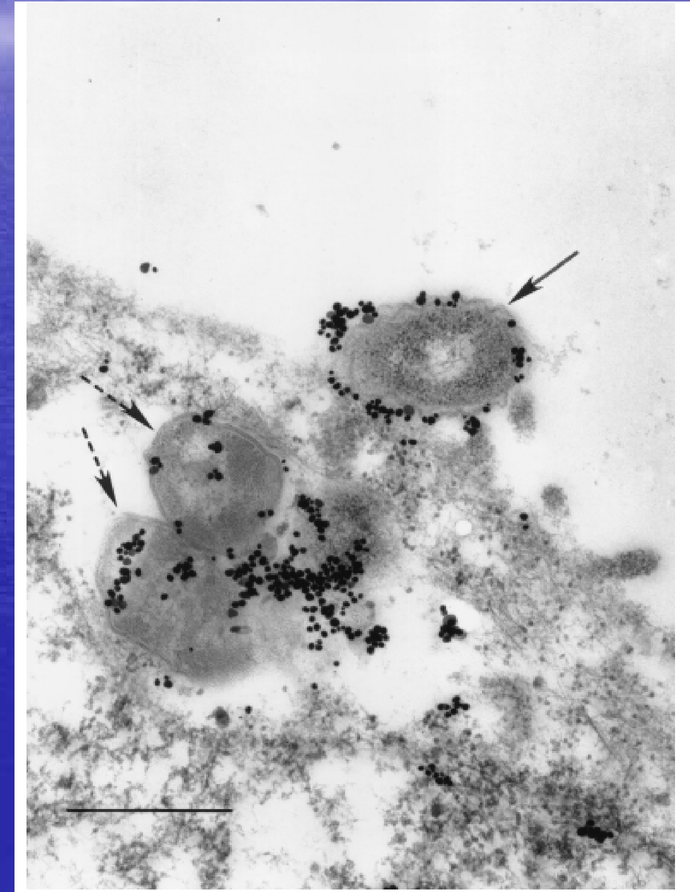
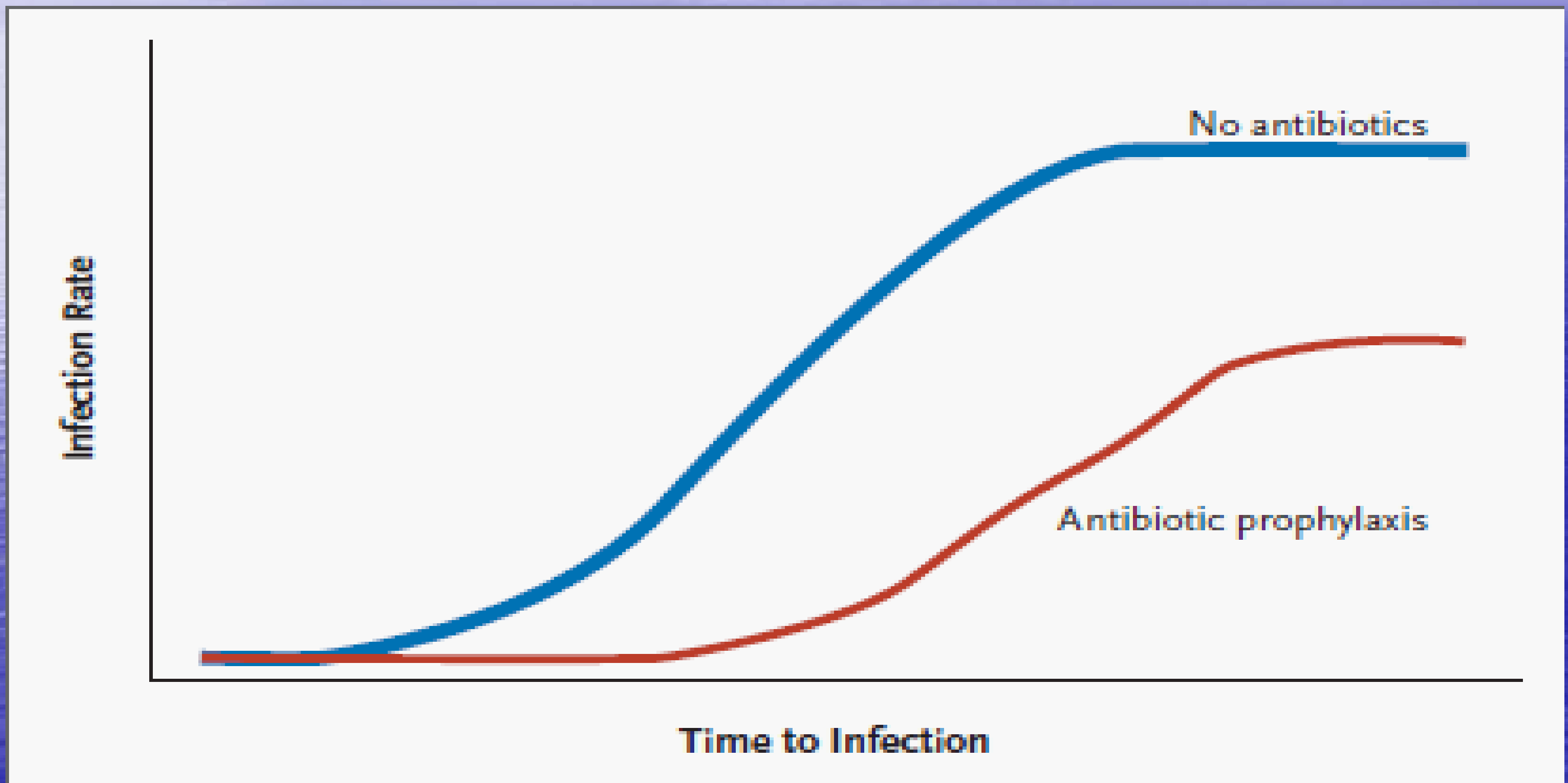


FIG. 7. 16HBE14 cells infected for 24 h with NTHI 2019. The specimen was

Ketterer M 1999

Antimicrobial Prophylaxis : Diminishes & Delays Onset of Infections



Baden L 2006

Influenza Prophylaxis
Annex A : Serious Underlying Condition

- **A :** Depleted immunity less able to cope with secondary bacterial infection after 'flu
- **B :** Advanced Chronic Illness likely to be destabilised by a severe viral illness
- **C :** Patients recently discharged from hospital, having been treated for a serious illness, whose recovery would be destabilised by a severe viral illness

DOH Oct 2009, Prophylaxis for H1N1

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Summary of recommendations

Condition	Recommend?		Recommendation/ Evidence grade	Alternatives
	Short-term	Long-term		
Immunology				
Primary immunodeficiencies	SELECTED	YES	B, IIb	None
Haemato-oncology				
Low serum IgG levels following HSCT for malignancy	YES	SELECTED	B, IIb	None
Chronic lymphocytic leukaemia	NO	SELECTED	A, Ib	Prophylactic antibiotic
Haemophagocytic lymphohistiocytosis/ haemophagocytic syndrome	SELECTED	NO	C, III	Corticosteroids + immunomodulation + antimicrobial agents
Multiple myeloma	NO	SELECTED	A, Ib	Antibiotics (therapeutic/ prophylactic), immunisation

1st National Audit Ig Database Haemato-oncology

- **55%** **CLL**
- 15% MMyeloma
- 9% Low serum Igs post BMT
- 3% Infection post BMT
- 18% Other

1st National Audit Ig Database

Cooperative Group Study IVIG in CLL 1988

- 84 cases
  - Low serum Igs AND / OR
  - History of infection
- RCT placebo vs IVIG 400 mg/kg/month
- Bacterial infections 23 vs. 42 $p = 0.01$

  1 year of IVIG 14 vs. 36 $p = 0.001$
- Delays time to first infection $p = 0.026$

IVIG in CLL and M Myeloma

- 9 Trials Benefit RR (95% C.I.)
- Survival 1.36 (0.58-3.19, *2 trials*)
- Major infections 0.45 (0.27-0.75, *3 trials)*
- Clinical infections 0.49 (0.39-0.61, *3 trials*)
- IVIG not for routine use even with low serum Igs and/or recurrent infections
- IVIG - consider on an individual basis

Raanani 2009

Binet Staging of CLL

- Areas
  - Head & Neck, Axillae, Groins, palpable Liver or Spleen
- Stage A
  - <3 areas of enlarged LNs
  - Hb $\geq$ 10g/dl / Platelets $\geq$ 100 $x10^9/L$
- Stage B
  - ≥ 3 areas of enlarged LNs
  - Hb $\geq$ 10g/dl / Platelets $\geq$ 100 $x10^9/L$
- Stage C
  - CLL with Hb $<$ 10g/dl / Platelets $<$ 100 $x10^9/L$

Case Selection

- All cases referred with recurrent infection

- <50% of require IVIG / SCIG

- IVIG / SCIG used
  - Post-chemotherapy
  - To support further chemotherapy

Is it Too Late for Ig Replacement?

- Christmas
- Daughter's wedding
- Keep me out of hospital
- Reduce need for blood products
- Keep me well whilst other treatments work

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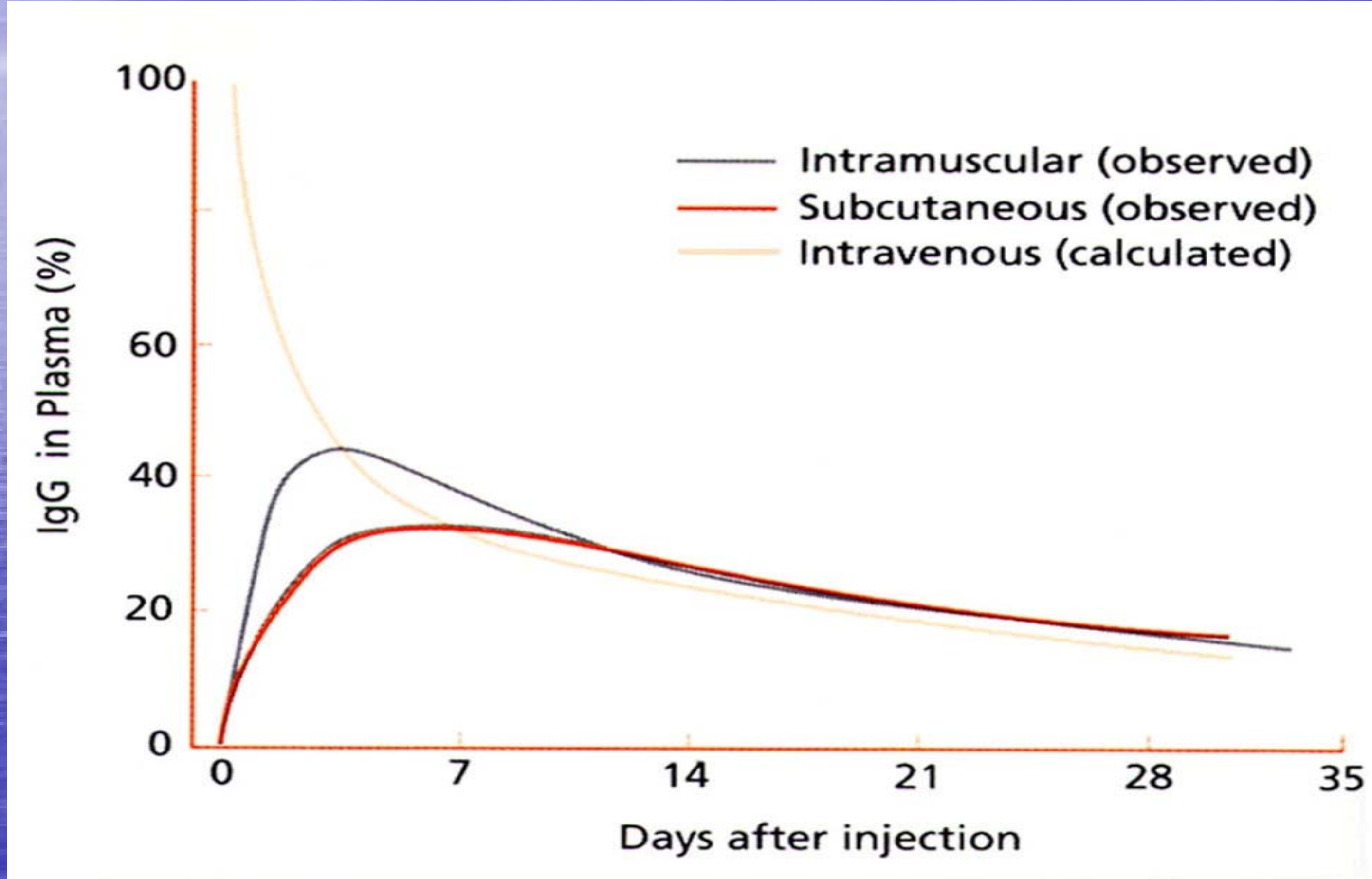
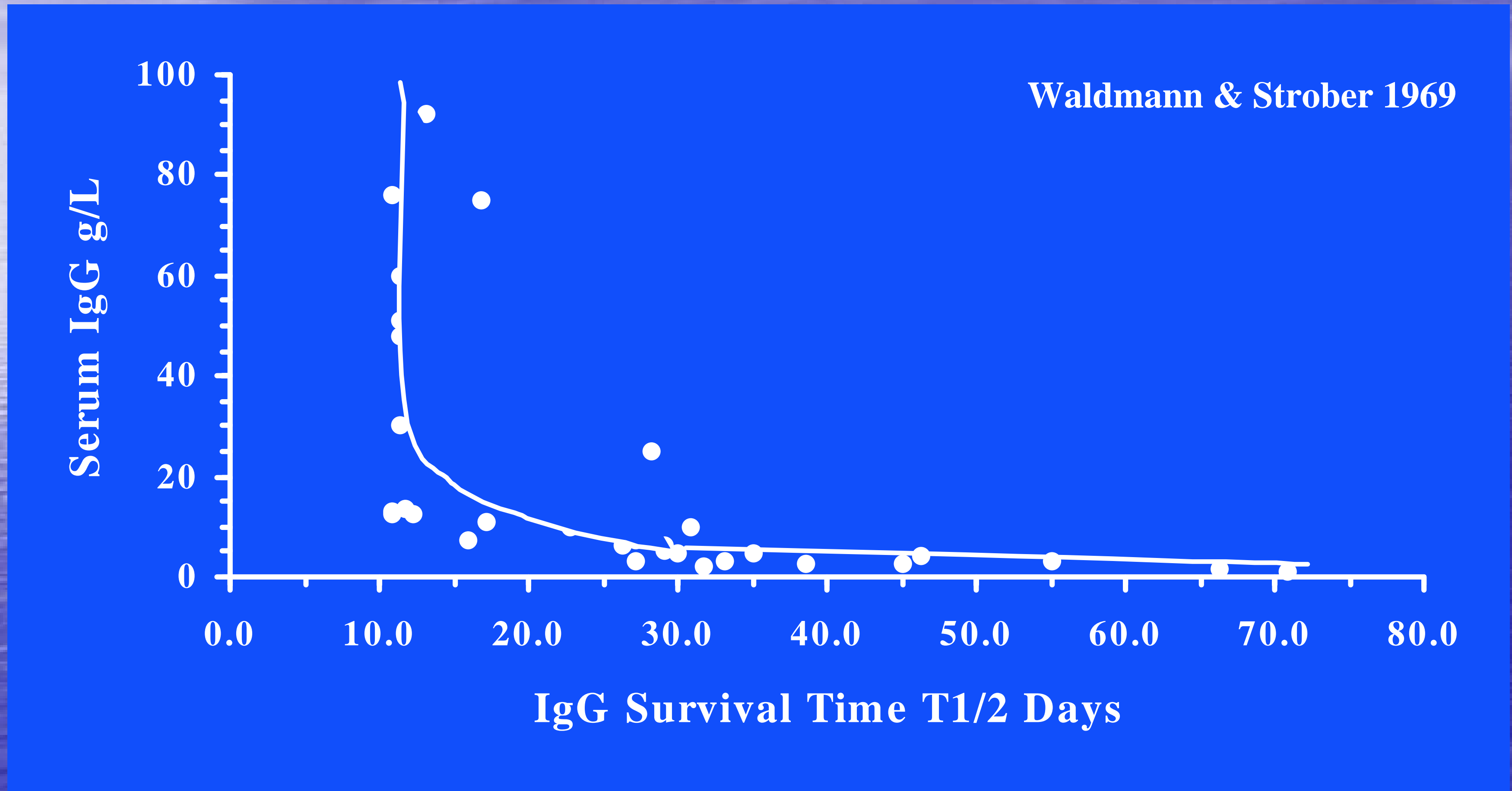
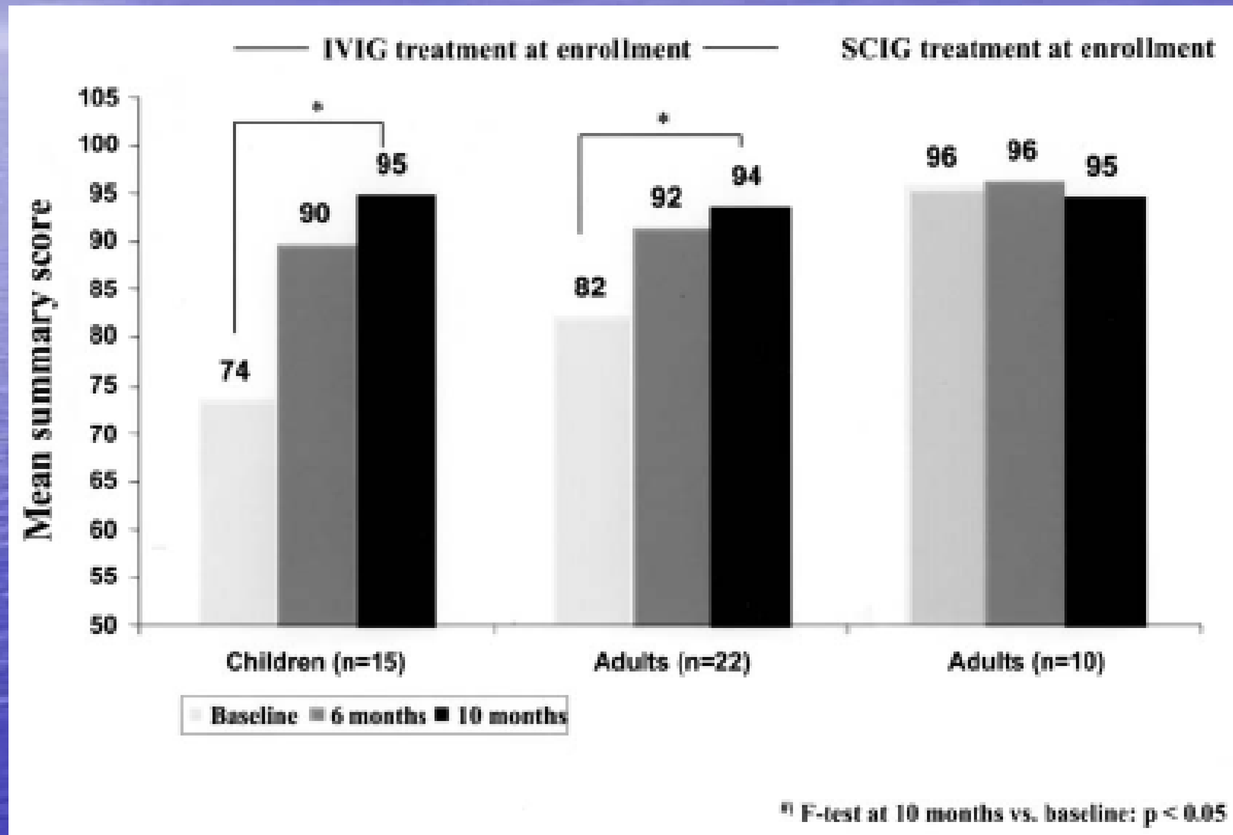
Pharmacokinetics of IgG
IVIG / IMIG / SCIG



IgG Survival T $^{1}/_{2}$ versus Serum Level



Gain in Quality of Life on Transferring from IVIG in Hospital to SCIG at Home



Gardulf JACI 2004

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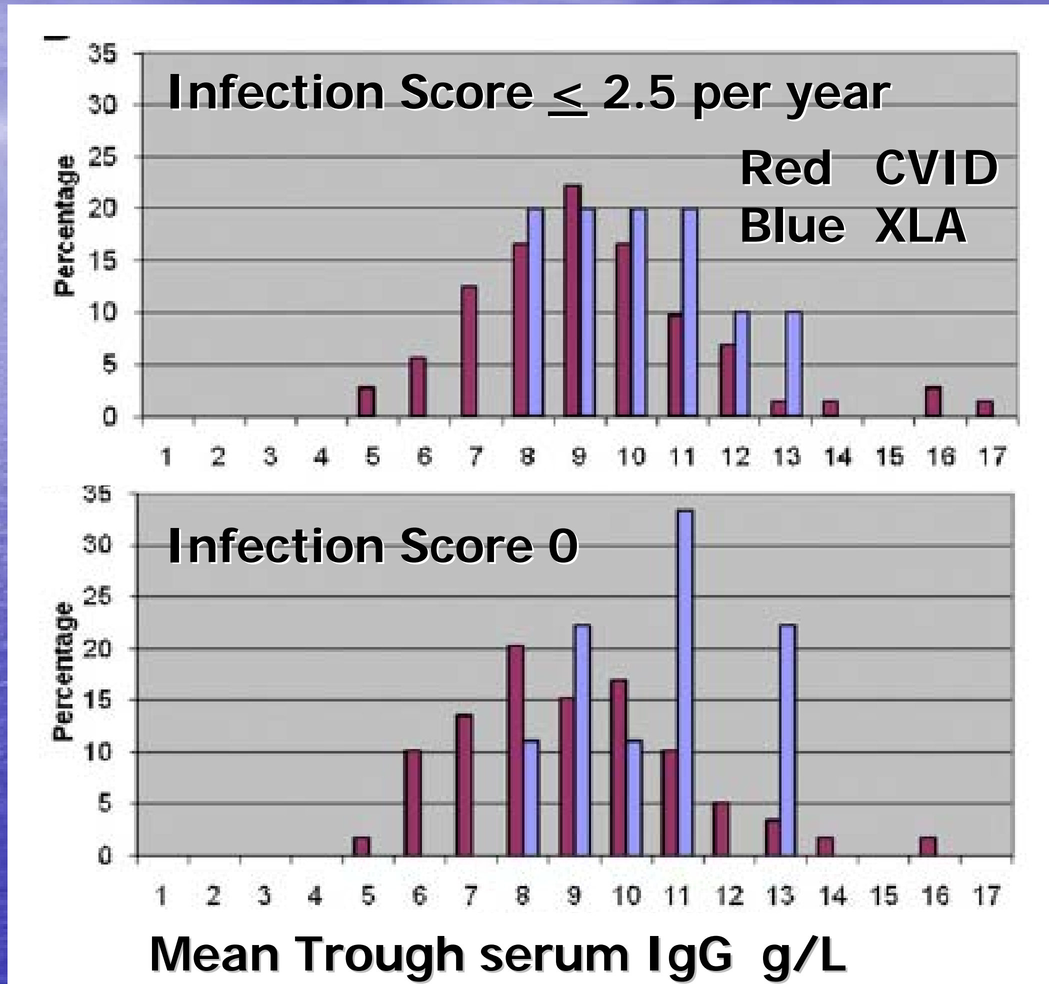
Immunoglobulin replacement: Dose

"Adjust dose by serum IgG
or symptoms?"

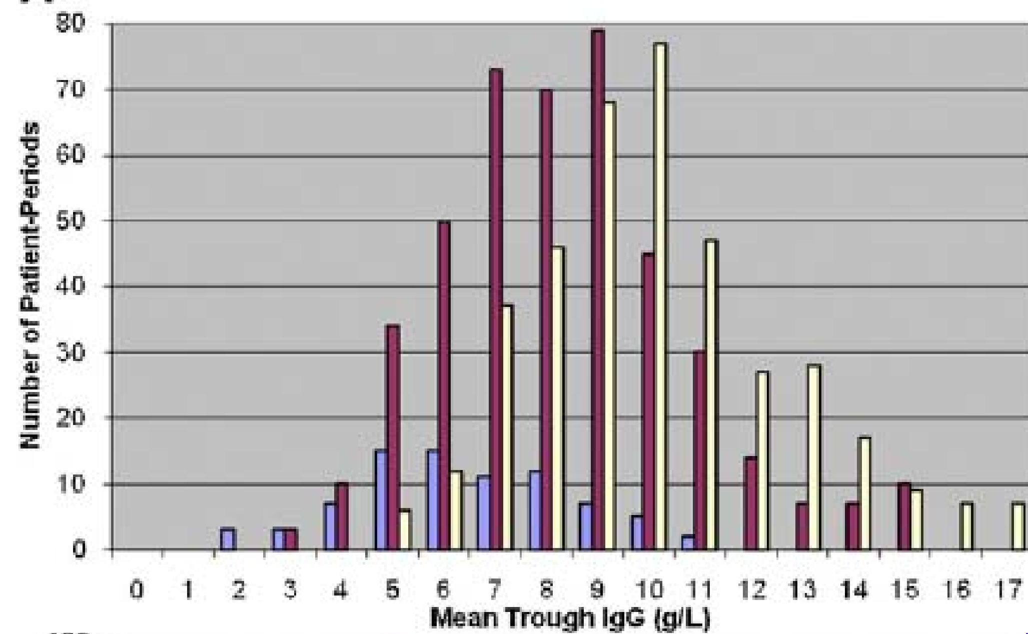
Immunoglobulin Replacement Therapy

- Dose
  - 400 – 800 mg/kg per month
  - Revise dose if bodyweight changes
- Interval
  - IVIG 2 – 3 weeks
  - SCIG 1 – 2 weeks
- Mode IVIG vs SCIG
- Monitoring Clinical $\pm$ Lab

Goal of IVIG/SCIG Replacement: CVID / XLA

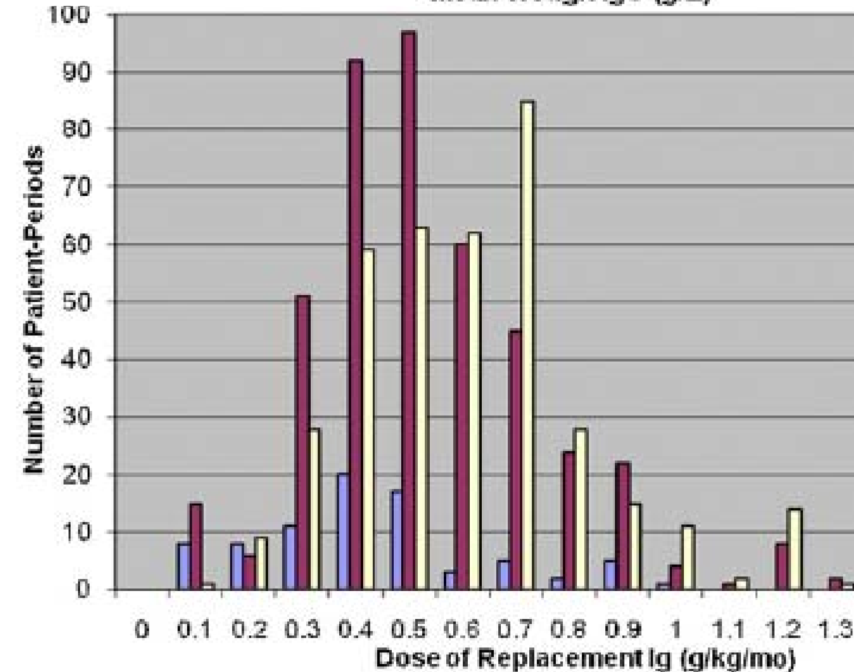


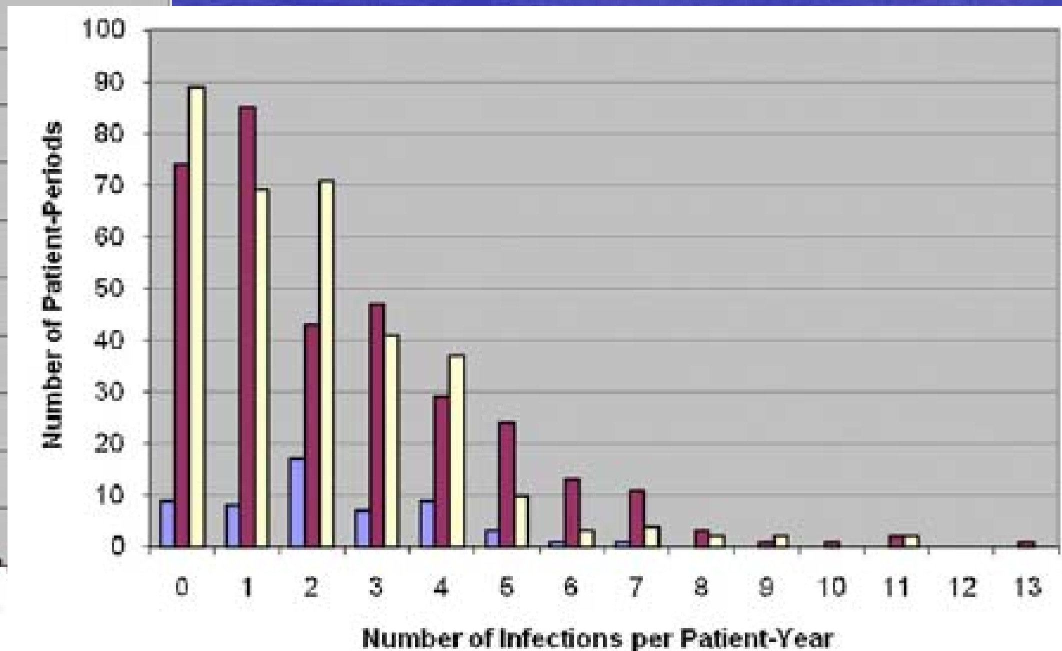
Lucas 2010



Time Trends

Blue 1980s
Red 1990s
Yellow 2000 - 07





Lucas 2010

Immunoglobulin Dose: CVID with Bronchiectasis

- Dose g/kg/month

  0.70 ± 0.29 vs **0.53** ± 0.20 $p<0.01$
- Trough serum IgG g/L

  9.2 ± 2.4 g/L vs **8.9** ± 2.6   n.s.d.
- 2x increase in dose for same increase in IgG

- Infection scores   n.s.d

  83% had infection scores <2.5

Lucas 2010

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References

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Knowledge-based healthcare

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