HTA and PID treatments: a physician perspective

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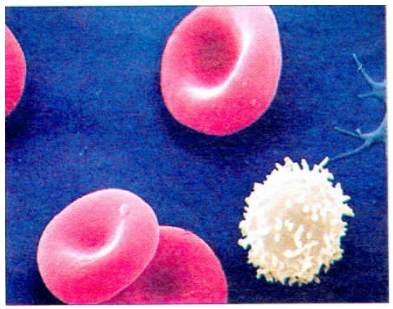
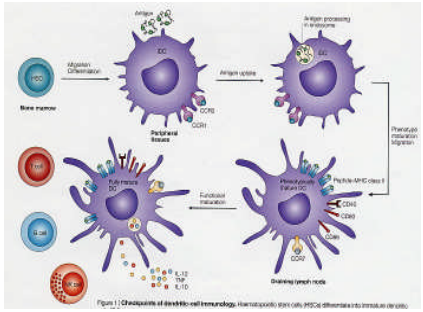
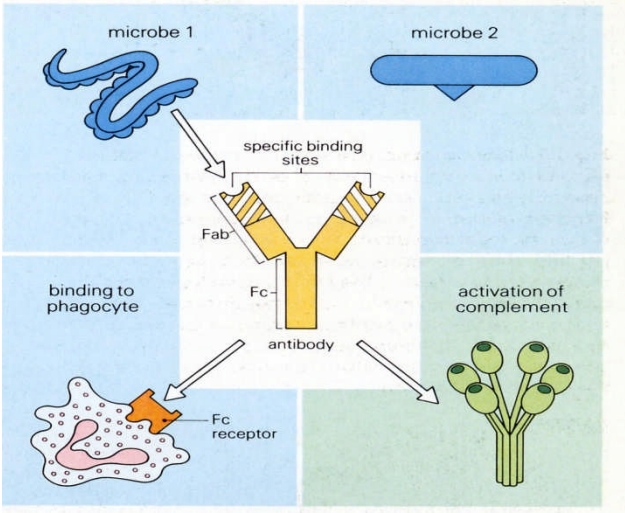
The Immune Response (IR), the body´s defence mechanism against external and internal "aggressions", is mediated by :

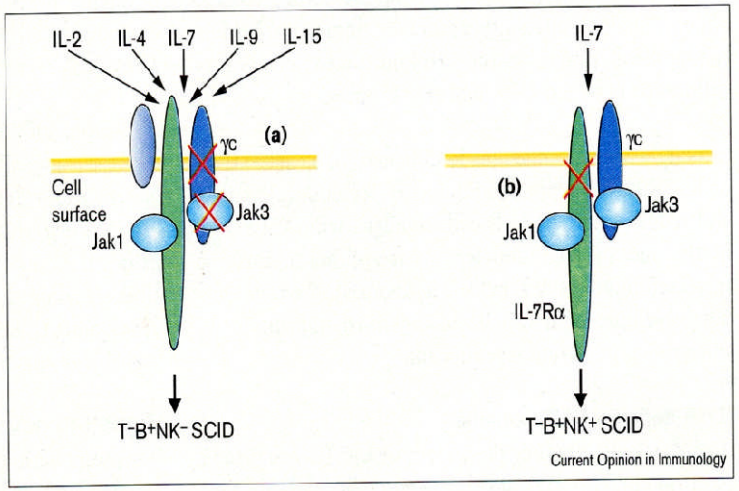
- **<u>Cells</u>: lymphocytes, neutrophils, dendritic cells, eosinophils, etc**



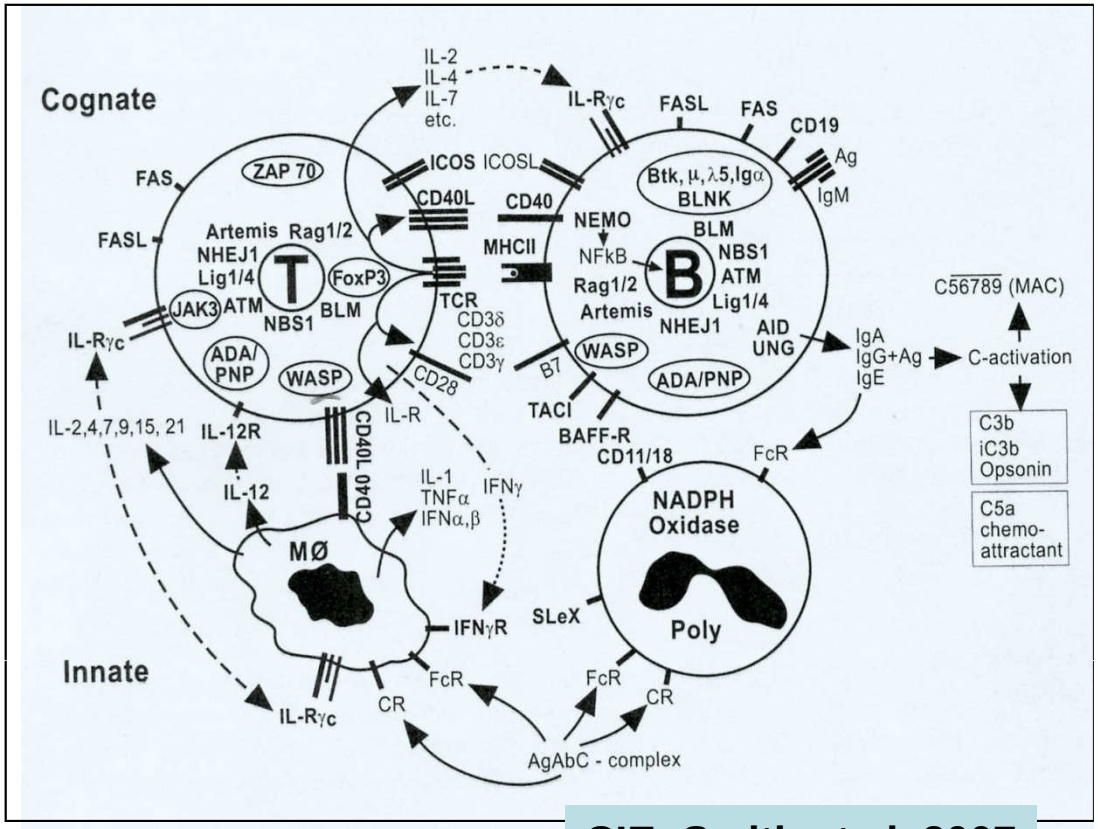


-and <u>Proteins</u> synthesised by these cells: immunoglobulins (or antibodies), cytokines, etc





Malfunction of some of the mechanisms of the IR causes different Immunodeficiencies which number almost 200 and have different manifestations, therapies and prognosis .



CIE: Smith et al. 2007

<u>Cell defects</u> are usually severe, with very poor prognosis if no adequate therapy is provided in many cases in the early months of life. In these cases, as for the "bubble" boy, a bone marrow or cord blood transplant (haematopietic precursor transplant- HPT), is required.

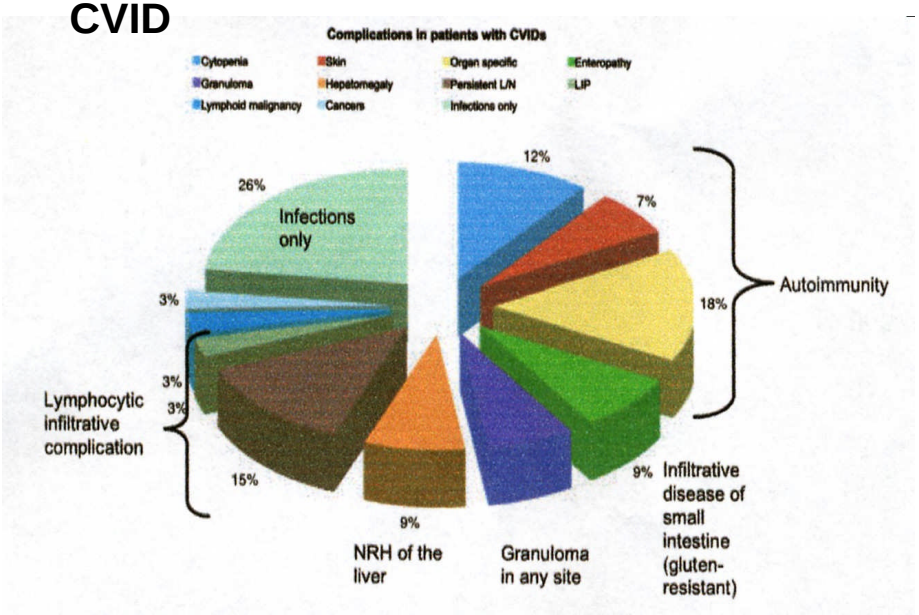
The <u>indications and protocols</u> for these therapies are indisputable

Therapy for Predominantly Antibody Deficiency Diseases:

REPLACEMENT with gammaglobulins (GG), either iv. or subcutaneously, is the ONLY and LIFE-SAVING therapy

If these patients are NOT TREATED, they have a short life-span owing to repeated infections, secondary bronchiectases, malabsorption, autoimmune cytopenias, lymphomas, etc

CVID



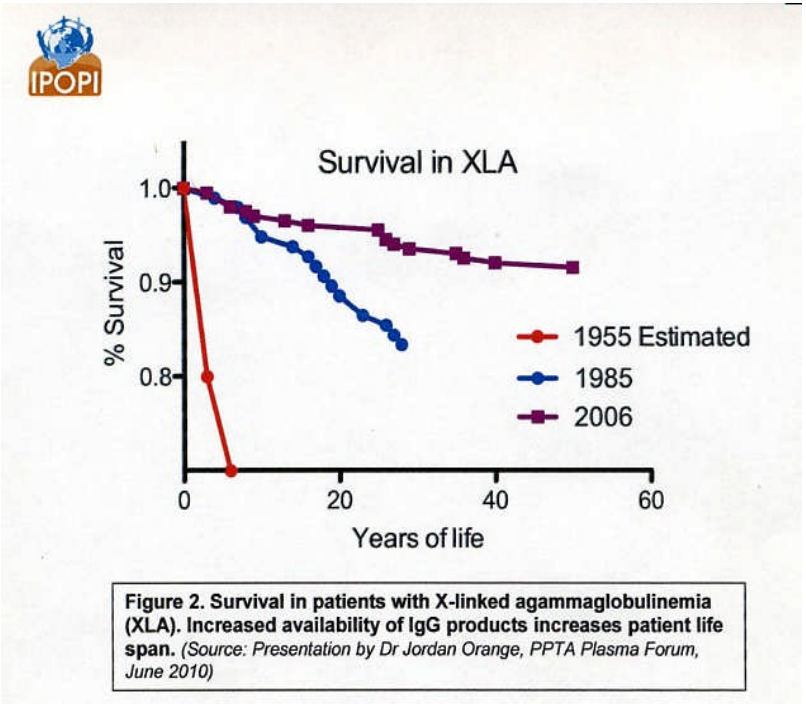


Figure 2. Survival in patients with X-linked agammaglobulinemia (XLA). Increased availability of IgG products increases patient life span. *(Source: Presentation by Dr Jordan Orange, PPTA Plasma Forum, June 2010)*

If treatment is INSUFFICIENT, patients could remain alive for some years, but ILL !!

infections, bronchiectasis, gastrointestinal problems , etc and most cannot lead a normal life (work, school, family life, etc), as we experienced with i.m. administration and low IgG trough levels in the past

Normal IgG levels : 7 to 16 gr/L

Thus, good replacement therapy MUST achieve, as far as possible, normal IgG levels

Table 1. **Infections in Patients with Primary Hypogammaglobulinemia Treated with Two Different Dosages of Intravenous Immunoglobulin**

Variable	Standard-Dose Therapy (n = 41)	High-Dose Therapy (n = 43)	Difference (95% CI)	P Value
Patients with infections, n	37	36		
Total infections related to immunodeficiency, n*	134	100		
Mild	54	38		
Moderate	17	11		
Severe	63	51		
Mean total immunodeficiency-related infections per patient ± SD (95% CI), n†	3.5 ± 2.6 (2.7–4.3)	2.5 ± 2.4 (1.8–3.2)	1.1 (0.4 to 1.8)	0.004
Median duration of immunodeficiency-associated infections (range), d†	33 (1–185)	21 (1–125)		0.015
Total respiratory infections, n	61	50		
Mean respiratory infections per patient ± SD (95% CI), n†	1.5 ± 1.6 (1.0–2.0)	1.2 ± 1.7 (0.7–1.7)	0.46 (−0.18 to 0.78)	0.18
Median duration of respiratory infections (range), d†	29 (5–178)	22 (2–125)		0.16

* Type of infection was categorized according to the criteria described in reference 18.
† Results are based on data from 41 patients. Two patients did not receive standard-dose intravenous immunoglobulin; therefore, no results were obtained for them during their respective standard-dose periods. Results were compared by using the paired t-test.

Eijkhout et al. 2001

A 32 year-old woman on EFFECTIVE replacement therapy told me :

“I AM NOW A NORMAL PERSON”

There is a some discussion (mainly due to the price of these therapies) as to which the best trough levels are for these patients, and we can say :

those that make them feel NORMAL: no severe infections, no autoimmunity... and a normal life..!!)

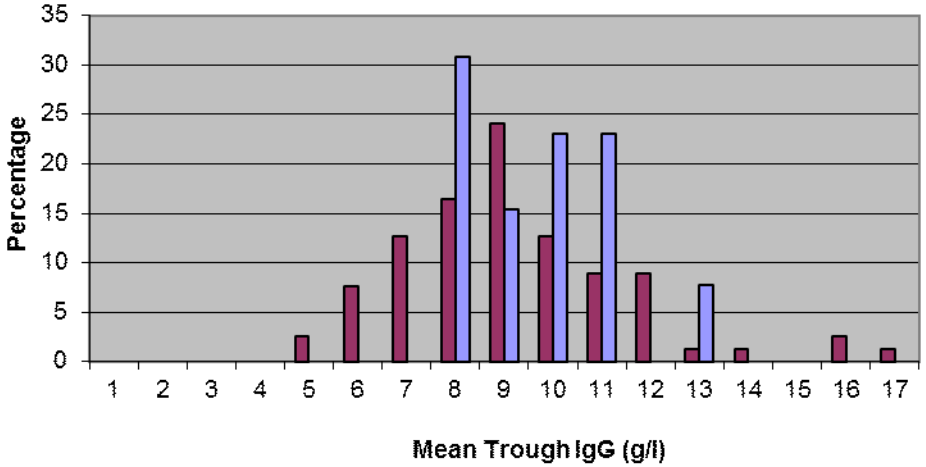
TROUGH levels are the measurement of IgG in plasma just prior to the new GG administration. However, there is no measurement of IgG in tissues, except a LACK of symptoms. Relying on IgG trough levels is not sufficient.

And trough levels depend on:

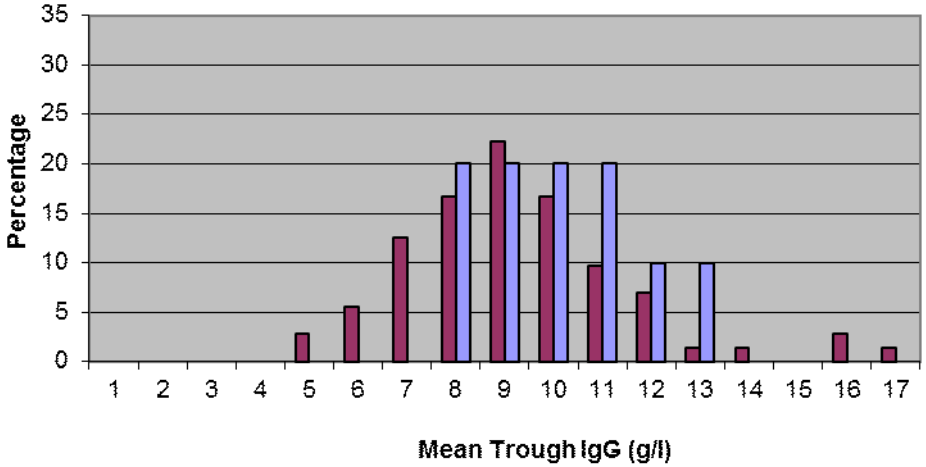
- **patient variability : - kind of infections suffered or present**
  - sequelae of delayed diagnosis, etc

- time variability: if there are acute infections, during pregnancy, etc

% trough IgG levels in 885 "infection free" periods in CVIDs & XLA

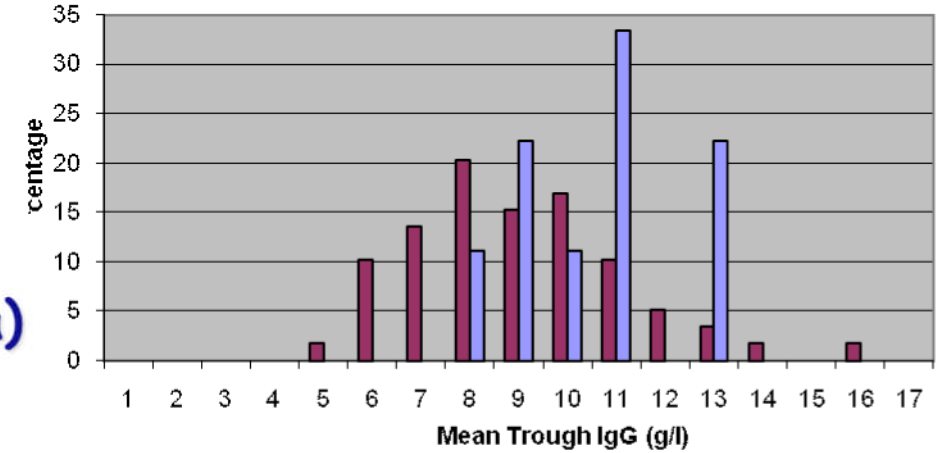


Infection-free (≤2 infections pa)



Infection-free (≤1 infections pa)

Infection-free (no infections pa)



CVIDs

XLA

Data from Lucas et al 2010 (JACI in press)

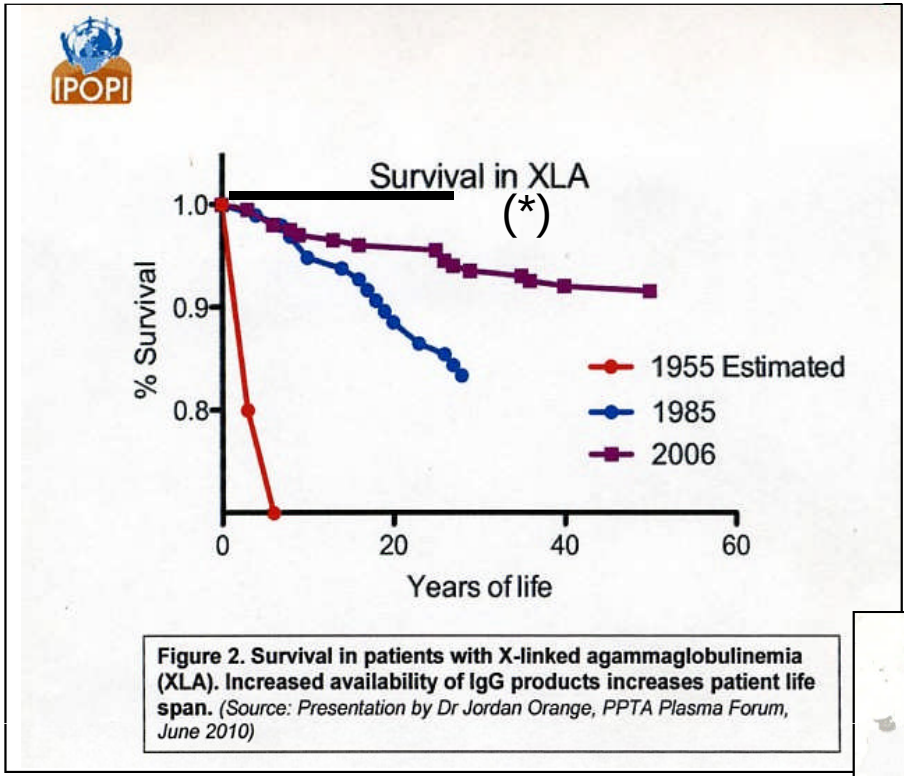
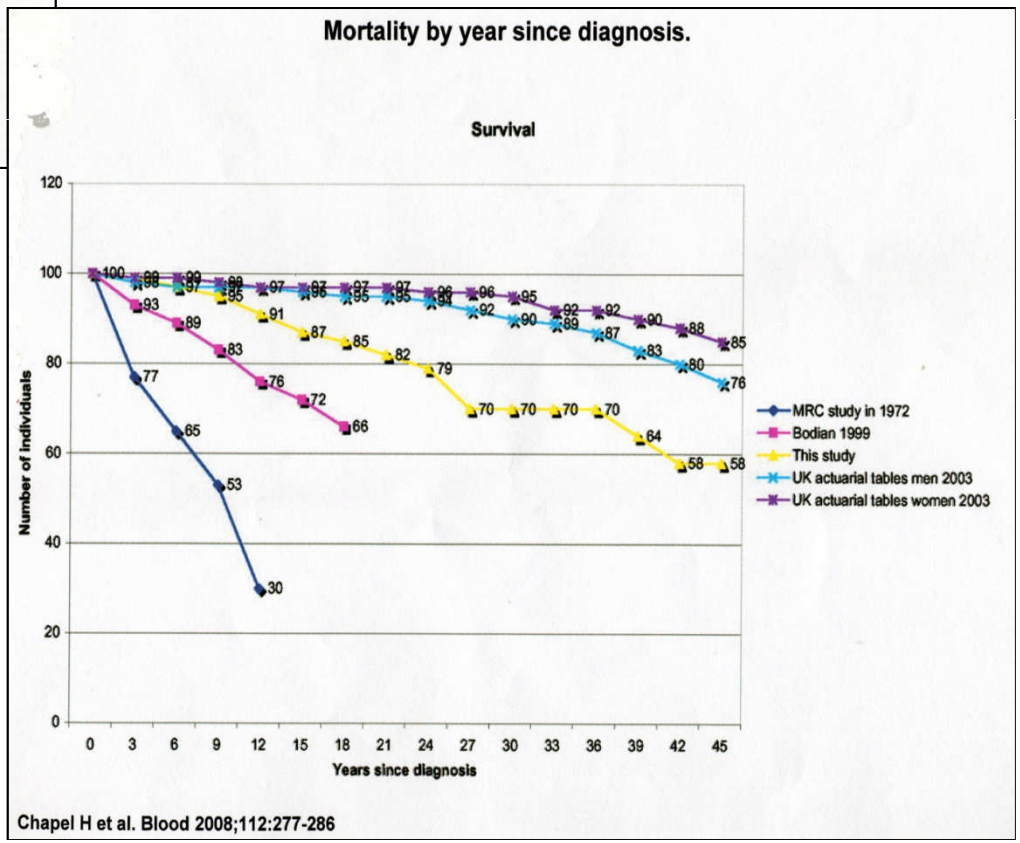
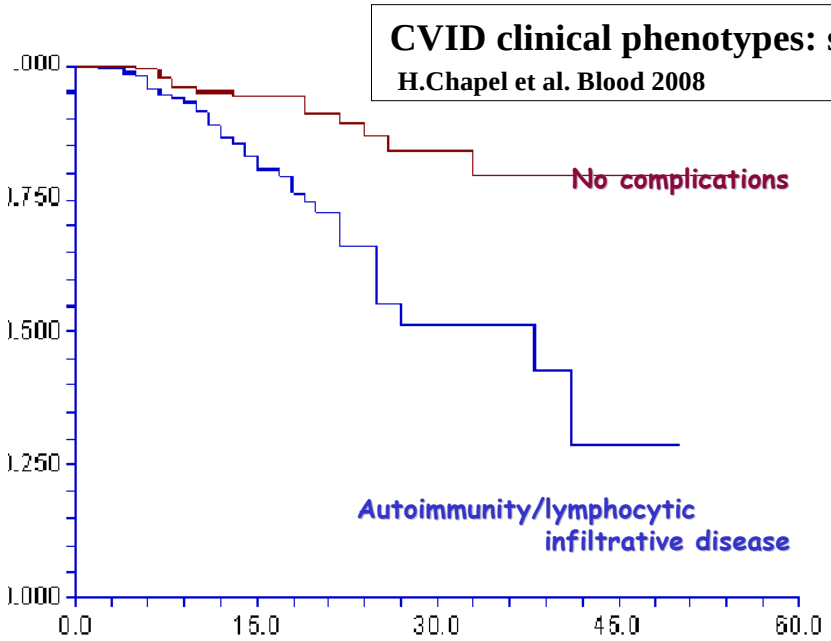


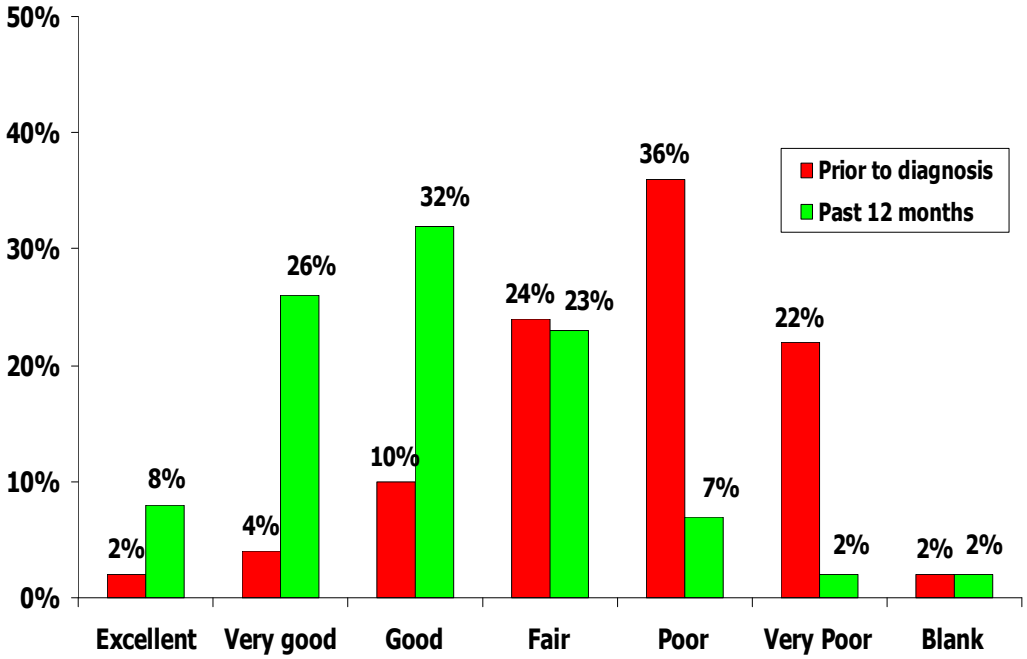
Figure 2. Survival in patients with X-linked agammaglobulinemia (XLA). Increased availability of IgG products increases patient life span. *(Source: Presentation by Dr Jordan Orange, PPTA Plasma Forum, June 2010)*

(*) XLA patients treated with IVIG from diagnosis.
My experience. Barcelona





Kaplan-Meier plot of survival Mortality by years since diagnosis and by clinical phenotype

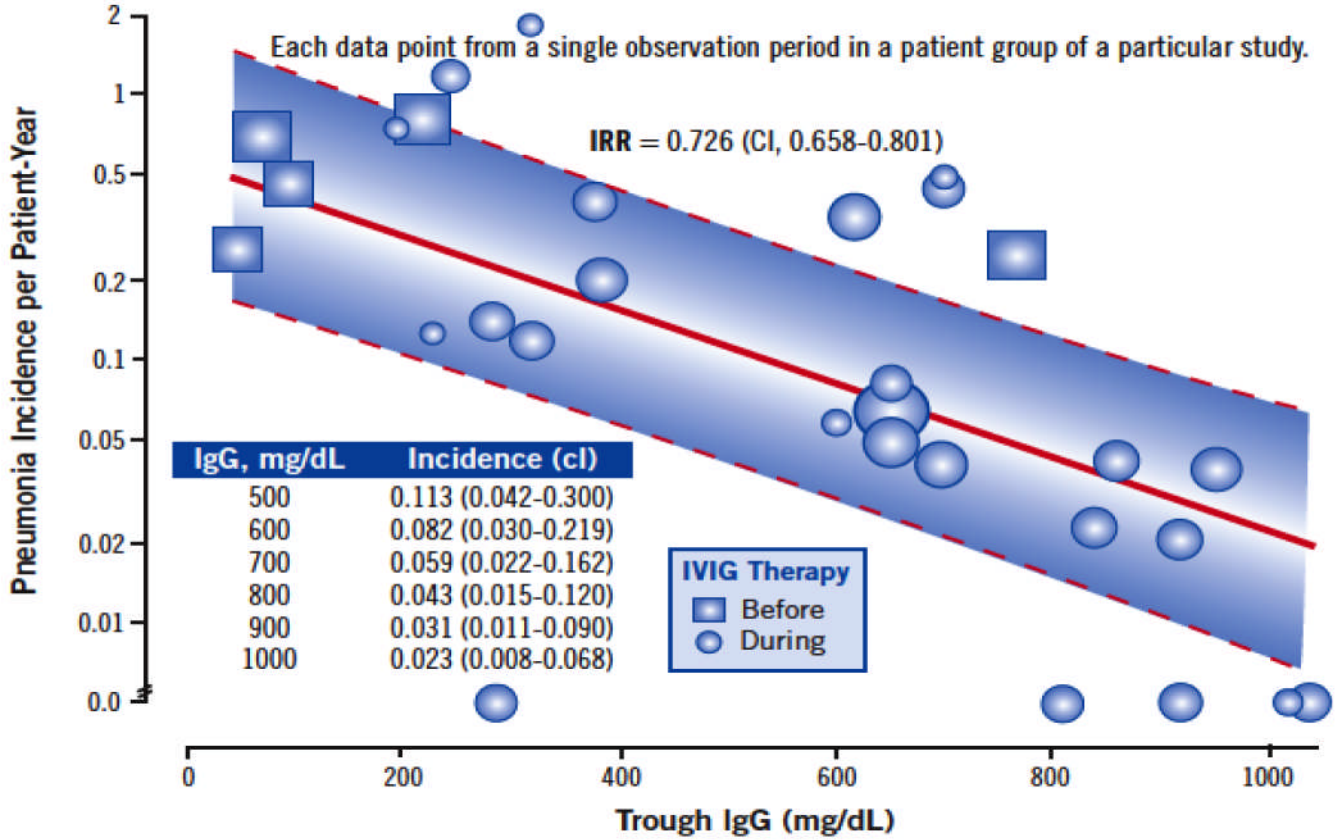


Source: 2008 IDF National Patient Treatment Survey

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



Ig therapy is COST- EFFECTIVE

Annual cost per patient pre-Dx	**$138,760**
Annual cost per patient post-Dx (excluding costs for IgG therapy)	**$30,297**
Annual savings per patient (excluding costs for IgG therapy)	**$108,463**
Annual % Cost of Diagnosed vs. Undiagnosed (excluding costs for IgG therapy)	**21.80%**
Annual cost per patient for IgG therapy (average)	**$30,000**
Annual cost per patient post-Dx (including costs for IgG therapy)	**$60,297**
Annual savings per patient that requires IgG therapy	**$78,166**
Annual % Cost of Diagnosed vs. Undiagnosed (including costs for IgG therapy)	**43.40%**

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Jeffrey Modell Foundation

If we treat DIABETES, HYPOTHYROIDISM, etc with the correct amount of insulin, thyroid hormones, etc. to reach normal levels and good quality of life with the minimum sequelae....

IMMUNODEFICIENT patients NEED to have the best therapy to become healthier, happier and more active members of society.

Vall d'Hebron
Hospital

Thank you for your understanding