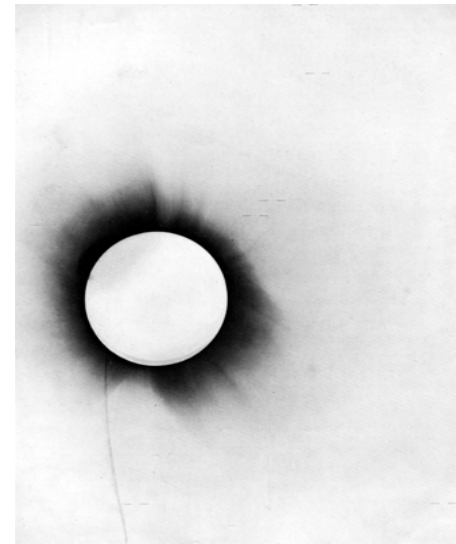


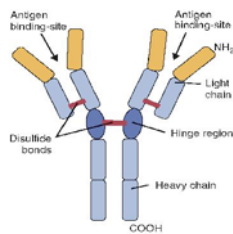
IgG Subclass Deficiency – Is it an Indication for IVIG?

David Gillis Pathology QLD



Background

- IVIG decreases infection in patients who have encapsulated bacterial infection and low serum IgG
- IgG exists in some variable forms - IgG subclasses
- IgG subclasses have slightly different functional characteristics
- If only one IgG subclass is deficient and patient infection----- Does IVIG work here?



Assessing Patients with Infection for IVIG

- **Low total IgG** -patients respond to IVIG
- **Low IgG Subclass** -do patients respond to IVIg?



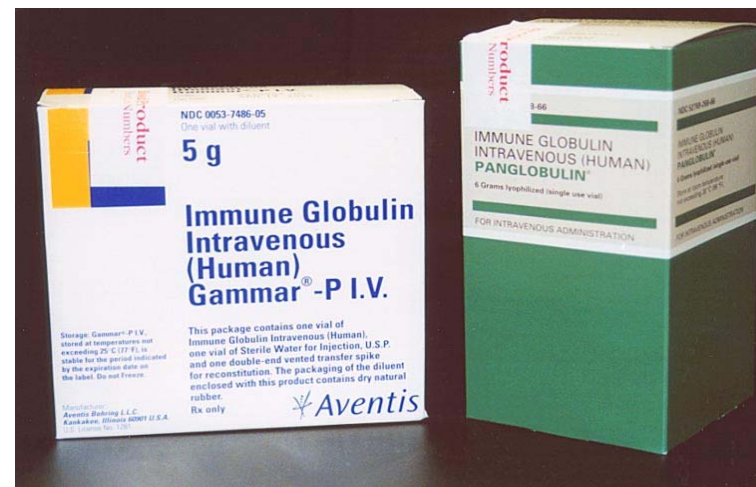
Assessing Patients with Infection for IVIG

- Should Intravenous Immunoglobulin be used in patients with **IgG Subclass deficiency**?



Assessing Patients with Infection for IVIG

Does **IgG subclass deficiency** define patients with infections who have **less infection on IVIG**?



Assessing Patients with Infection for IVIG

Is IgG subclass deficiency associated with infection?

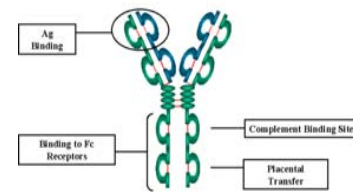
Is IgG subclass deficiency the cause of infection in those patients with and IgG subclass deficiency infection?

Does use of Intravenous Immunoglobulin in IgG subclass deficiency decrease infection?

Is IgG Subclass deficiency associated with infection?

- Early 70s - IgA deficiency with infection have low IgG2 subclass (IgG4)
 - Case reports
- 1970s - Normal Serum IgG with infection have low IgG subclasses
 - Case Reports
- 1980's - Recurrent otitis media , pneumonia , sinusitis, bronchitis
 - Case series
- 1985 - Automation of assay
- Natural infection with strep pneumoniae antipolysaccharide
IgG2 subclass specific

Immunoglobulin Fragments:
Structure/Function Relationships



Doubts - IgG Subclass Deficiency and infection !!

Problems with normals

- Schackleton – series of normal children with low IgG subclasses and no infection
- 10-20% of healthy adults have IgG4 deficiency
- 1-2% of healthy adults have heavy chain deletions - heterozygote deficiency
- Healthy children have low levels of IgG2 but normal response to polysaccharide



Doubts - IgG Subclass Deficiency and infection !!

Problems with Studies

- All studies of patients referred with infection
- Secondary to disease/ transient
- No controls without infection



Doubts - IgG Subclass Deficiency and infection !!

Problems with the Method

- Insufficient data for young children
- Difficulty with specificity of monoclonal
- Large discrepancies between laboratories
- Numerous errors in diagnosis
- Differences in results from different commercial laboratories



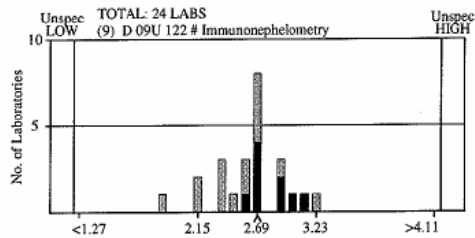
Due Date : 21/11/2008

Specimen 10-08 IgG2

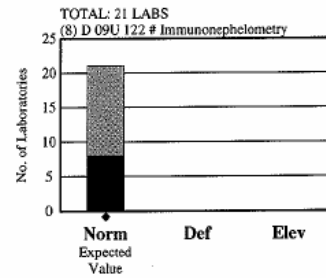
Laboratory Number 649

Your Data(^): IgG2 Quantitative: 2.69 g/L Your Method: D 09U 122: Immunonephelometry, Beckman Coulter Immage, The Binding Site
 IgG2 Qualitative: Norm Your Method: D 09U 122: Immunonephelometry, Beckman Coulter Immage, The Binding Site

IgG2 g/L



IgG2 Qual



Result Commentary:

Designated Result IgG2: Normal (Consensus)

Sample: Neat serum.

Clinical: 69 year old male with Common Variable Immune Deficiency.

Summary Data

(L) Late, (A) Amended, (B) Late and Amended

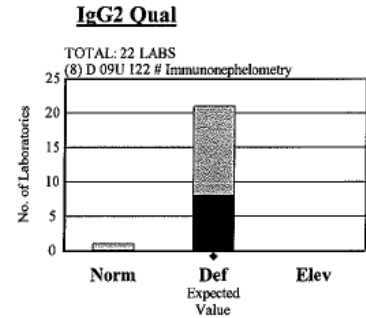
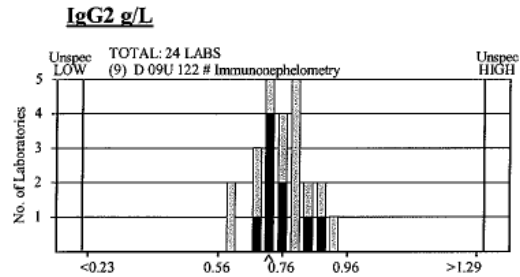
Spec.	IgG2 g/L Method Code	Result	IgG2 Qual Target	Result
10-01	D 09U 122	0.72	Def	Def
10-02	D 09U 122	4.83	Norm	Norm
10-03	D 09U 122	4.72	Norm	Norm
10-04	D 09U 122	1.01	Def	Def
10-05	D 09U 122	1.14	Def	Def
10-06	D 09U 122	1.94	Norm	Norm
10-07	D 09U 122	1.75	No target set	Norm
10-08	D 09U 122	2.69	Norm	Norm

Due Date : 15/02/2008

Specimen 10-01 IgG2

Laboratory Number 649

Your Data(^):	IgG2 Quantitative: 0.72 g/L	Your Method: D 09U 122: Immunonephelometry, Beckman Coulter Immage, The Binding Site
	IgG2 Qualitative: Def	Your Method: D 09U 122: Immunonephelometry, Beckman Coulter Immage, The Binding Site



Result Commentary:
Designated Result IgG2: Deficient (Mode)
Sample: Serum minimally diluted with human albumin solution.
Clinical: 74 year old male with Waldenström's Macroglobulinaemia, in remission.

Summary Data

(L) Late, (A) Amended, (B) Late and Amended

Spec.	IgG2 g/L Method Code	Result	IgG2 Qual Target	Result
10-01	D 09U 122	0.72	Def	Def
10-02				
10-03				
10-04				
10-05				
10-06				
10-07				
10-08				

Doubts - IgG Subclass Deficiency !!

Problems with the Method --2009

- IgG1 useful to confirm total IgG really low
- IgG2 useful???
- IgG3 transient – analytical problems
- IgG4 normal population

Is IgG subclass deficiency the cause of infection in patients with IgG subclass deficiency and infection?

Rebecca Buckley

All patients with infection / IgG Subclass deficiency- decreased antibody response to Pneumococcal Vaccine



Is IgG subclass deficiency the cause of infection in patients with infection?

- Almost all patients with infection and IgG subclass deficiency - abnormal vaccine responses (shackleton)
- Pneumococcal Antibody Vaccine responses actually measure well defined defects in immune response
- Pneumococcal antibodies better standardised test
- Pneumococcal antibody cut offs correspond to protection

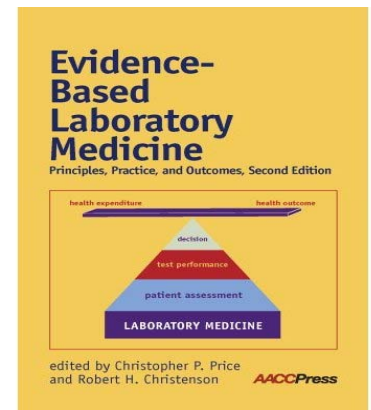
Is IgG subclass deficiency the cause of infection in patients with infection?

- BUT is pneumococcal antibodies the answer.....
- Significant problems with pneumococcal vaccine response measurement (different methodologies)
- Do not measure protective antibody
- Effects of previnar vaccination
- Only 73% sensitivity and 57% specificity for pneumococcal antibody assay at identifying immunodeficiency



Does use of Intravenous Immunoglobulin in IgG subclass deficiency decrease infection?

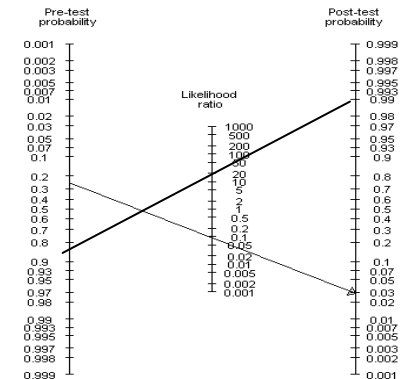
- Three recent studies (2007, 2009, 2010)
- Two retrospective
- One prospective - 6 patients improved on IVIG
- All studies dealt with patients with infection plus IgG subclass deficiency
- No studies had relevant controls –
Patients with infection without subclass deficiency , treated with IVIG
Patients with IgG subclass deficiency not treated with IVIG
- Gupta(2010), Halsey(2009), Bjorkender(2007)



No evidence for treating
IgG Subclass Deficiency with IVIG

What are we actually doing?

- Patient population – recurrent infection
- Purpose of Test – if positive- increased risk of further serious infection
- Purpose of Test – if positive - risk of infection decreased if treated with IVIG



What are we actually doing?

- Recurrent Infection
- Prediction of more serious infection
- Prediction of end organ damage

- Compare – heart disease / DVT / Rheumatoid



What are we actually doing?

Are there better ways of predicting further infection?

-

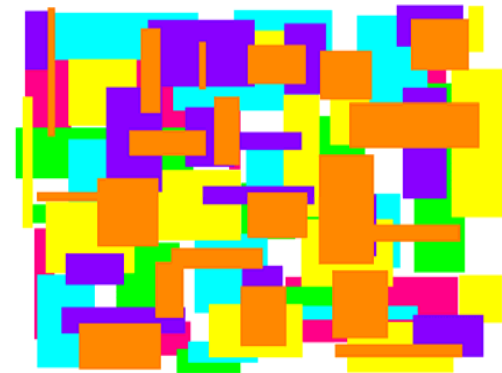
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it is the infection stupid!!

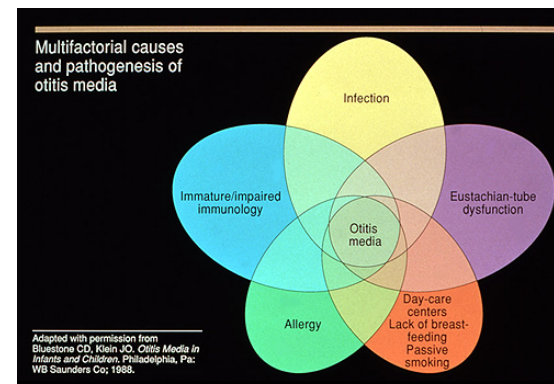
Other Factors may contribute

- Multiple other factors increase risk of further infection
- Total IgG, Vaccine Responses, MBL etc
- AND also IgG subclasses



A Breath of Fresh Air - Bossuyt!!!!

- The more risk factors the more risk of infection
- How much IgG subclass deficiency predicts increased risk of infection is unclear but may be quite small and not independent of other risk factors



How does this relate to selection of patients who respond to IVIG?

- First severe recurrent infection
- If low total IGG then qualify
- Unknown how much any other factor including IgG subclass or Pneumococcal antibody response predicts recurrence or response to IVIG



Conclusion – Diagnostic Use

- IgG subclasses not as primary screen
- In conjunction with other responses
- In conjunction with vaccine responses
- Always in association with clinical presentation
- **IT IS THE INFECTION STUPID?**

IgG Subclasses and IVIG -- A proposed trial

Do patients who have infection and have low IgG subclasses have a response to IVIG?

- Stratified controlled trial, double blind cross over
- Infection with IgG subclass deficiency given IVIG
- Infection without IgG subclass deficiency given IVIG
- Numbers needed to exclude an 25% reduction in those selected on basis of IgG subclass deficiency -20 each arm
- Numbers needed to exclude an 50% reduction in those selected on basis of IgG subclass deficiency -10 each arm

