Congenital Immunodeficiencies I
2014
-Antibody/Neutrophils/Complement

Dr Joanne Smart
BSc, MBBS, PhD, FRACP

Department of Immunology
Royal Children’s Hospital
Melbourne, Australia
Immunodeficiency

• Acquired immune deficiency most common worldwide
  • malnutrition
  • HIV
  • iatrogenic immunosuppression - cancer, transplant etc

• Primary immunodeficiencies rare
  • recent discoveries genetic defects allow increased understanding immune development and function
Components of the Immune system

- Innate
- Specific

- T cell
- B cell

Complement
PID is Rare but ... IUIS 2011
Congenital Immunodeficiencies

- Prevalence in Australia is ~1:10,000
  - does not include IgA deficiency (1:500)
- XLA 1:103,000
- Di George 1:66,000
- SCID 1:66,000
- CVID 1:83,000
- CGD 1:181,000
Congenital Immunodeficiency at RCH
Early Diagnosis

- Relies on increasing awareness of PID
- Education of broader medical community as well as the public
- “10 Warning signs of PID”
‘10 Warning Signs of PID’

1. Eight or more ear infections within one year
2. Two or more serious sinus infections within one year
3. Two or more months on antibiotics with little effect
4. Two or more pneumonias within one year
5. Failure of an infant to gain weight or grow normally
6. Recurrent deep skin or organ abscesses
7. Persistent thrush in mouth or elsewhere on skin after age one
8. Need for intravenous antibiotics to clear infections
9. Two or more deep seated infections such as sepsis, meningitis or cellulitis
10. Family history of primary immune deficiency
Congenital Immunodeficiencies

• Age at diagnosis
  • 40% diagnosed in first year
  • 40% by 5yr
  • 5-10% in adulthood
  • Overall 75% by 15yr

• Majority adults - CVID
Congenital Immunodeficiencies

- Overall Males 72% vs Females 28%
- In children - Males 5:1 Females
- Male prevalence lost in adulthood
  - Males 1:1.4 Females
- Family history in 25% (males 33%, females 5%)
- Sex difference relates to X-linked disease
Case 1- History

- 18 month male
- 1st child; non-consanguinous parents
- well until 12 months
- recurrent febrile illness (> monthly)
- URTI Sx; ‘ear’ /’ throat’ infections
- multiple courses antibiotic - variable response
- thriving
- in creche 5/7
Case 1- Examination
Case 1 - Investigations

- Is further investigation warranted?
Normal Rates of Infection

- 6-8 respiratory infections/yr for 1st 10yr life
- 6 otitis media/yr for 1st 2-3 yr life
- 2 gastroenteritis/yr for 1st 2-3 yr life

- may exceed these for 1-2 yr if high exposure to viruses
  - some day care settings
  - older siblings at school
Infections are Common In Normal Children!

<table>
<thead>
<tr>
<th>Location</th>
<th>Number of Children</th>
<th>OR for Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Home</td>
<td>1.4</td>
<td>1</td>
</tr>
<tr>
<td>Nanna</td>
<td>1.5</td>
<td>1.24</td>
</tr>
<tr>
<td>Day Care</td>
<td>2.3</td>
<td>1.77</td>
</tr>
<tr>
<td>Creche</td>
<td>3.4</td>
<td>2.61</td>
</tr>
<tr>
<td>Kindergarten</td>
<td>19</td>
<td>3.8</td>
</tr>
</tbody>
</table>
Case 1 - Investigations

• Is further investigation warranted?
• ??FBE
• ??IgG, A, M
Immunodeficiency

- Major feature = increased susceptibility to infections
  - increased frequency - >8 otitis, >2 sinus, >2 pneumonia
  - increased severity
  - prolonged duration
  - poor response to usual therapy - need for IV antibiotic
  - unusual or opportunistic organism - thrush >1yr
  - increased deep seated infections - cutaneous or organ abscesses, bone etc.
Immunodeficiency

• Other important clues
  • growth and development - failure to thrive, slowing
  • timing of infection - transplacental IgG in 1st 3-6 mos
  • chronic skin rash - 1st few mos life
  • other congenital anomalies - face, skeletal, heart, pigmentation, hair etc
  • family history of primary immunodeficiency
<table>
<thead>
<tr>
<th>Pathogens</th>
<th>Bacteria</th>
<th>Viruses</th>
<th>Fungi/Parasite</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>T Cell</strong></td>
<td>Sepsis</td>
<td>CMV, EBV, severe Varicella, resp &amp; intestinal</td>
<td>Candida P. carinii</td>
</tr>
<tr>
<td><strong>B Cell</strong></td>
<td><em>Strep, Staph H. Influenza</em></td>
<td>Enteroviral encephalitis</td>
<td>Severe intestinal Giardiasis</td>
</tr>
<tr>
<td><strong>Granulocyte</strong></td>
<td><em>Staphylococcus, Pseudomonas, Catalase +ve</em></td>
<td>NA</td>
<td>Candida Aspergillus Nocardia</td>
</tr>
<tr>
<td><strong>Complement</strong></td>
<td>Neisseria, pyogenic bacteria</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>
# Tuesday full immune function tests

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Tests</th>
<th>Clinical indications</th>
<th>Bloods needed</th>
</tr>
</thead>
</table>
| **Tuesday 1** | IgG, IgA, IgM, IgE  
Lymphocytes: WB PHA & markers (cd3, cd4, cd8, cd19, NK)  
FBE | Recurrent respiratory tract infections, cutaneous warts, Pre heart transplant, BM transplant workup | 1 ml EDTA  
3 mls plain blood  
2 mls Lithium heparin |
| **Tuesday 2** | IgG, IgA, IgM, IgE  
Specific IgG to Hib, Tet and Dip  
Isoagglutinins, Blood Group  
ASOT, DNase B  
Lymphocytes: WB PHA & markers (cd3, cd4, cd8, cd19, NK)  
FBE | Recurrent purulent respiratory infections and/or discharging ears | (1 ml EDTA) X 2  
4 mls plain blood  
2 mls Lithium heparin |
| **Tuesday 3** | IgG, IgA, IgM, IgE, C3, C4  
Neutrophil Function tests  
Lymphocytes: WB PHA & markers (cd3, cd4, cd8, cd19, NK)  
FBE | Cutaneous boils, recurrent staph infections, ? neutrophil problems | 1 ml EDTA  
3 mls plain blood  
7 mls Lithium heparin |
| **Tuesday 4** | IgG, IgA, IgM, IgE, C3, C4  
Specific IgG to Hib, Tet and Dip  
Isoagglutinins, Blood Group  
ASOT, DNase B  
Neutrophil Function tests  
Lymphocytes: WB PHA & markers (cd3, cd4, cd8, cd19, NK)  
FBE | See Tuesday 2 and Tuesday 3 combined | (1 ml EDTA) X 2  
4 mls plain blood  
7 mls Lithium heparin |
| **Tuesday 5** | IgG, IgA, IgM, IgG subclasses, IgE, C3, C4  
Specific IgG to Hib, Tet and Dip  
Isoagglutinins, Blood Group  
ASOT, DNase B  
Neutrophil Function tests  
Lymphocytes: WB PHA & markers (cd3, cd4, cd8, cd19, NK)  
FBE | See Tuesday 2 and Tuesday 3 plus IgG subclasses | (1 ml EDTA) X 2  
4 mls plain blood  
7 mls Lithium heparin |

**Other tests which may be ordered in parallel include:**

1. Pneumococcal antibodies which can be performed on the serum already taken.
2. and cd40 ligand, and/or separated lymphocyte stimulation. These occur more rarely and require extra Lithium heparin sample. It is best to contact the laboratory about the extra blood required in these instances.
## Antibody properties

<table>
<thead>
<tr>
<th>Major characteristic</th>
<th>IgG</th>
<th>IgA</th>
<th>IgM</th>
<th>IgD</th>
<th>IgE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most abundant in internal body fluids</td>
<td>Major Ig in secretions</td>
<td>Produced early in immune response</td>
<td>Predominantly surface Ig</td>
<td>Protects external surfaces</td>
<td></td>
</tr>
<tr>
<td>Major defense against m/o and toxins</td>
<td>Defends mucosal surfaces</td>
<td>1st line defence against bacteria</td>
<td></td>
<td>Elevated in -Allergy</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Effective agglutinator</td>
<td>-Parasitic infections</td>
<td></td>
</tr>
<tr>
<td>Normal serum levels (Adult)g/L</td>
<td>5</td>
<td>0.33</td>
<td>0.32</td>
<td>(&lt;100IU/L)</td>
<td>(0-200kU/L)</td>
</tr>
<tr>
<td>% total Ig</td>
<td>75</td>
<td>15</td>
<td>5-10</td>
<td>0-1</td>
<td>0.0002</td>
</tr>
</tbody>
</table>
# Antibody properties

<table>
<thead>
<tr>
<th></th>
<th>IgG</th>
<th>IgA</th>
<th>IgM</th>
<th>IgD</th>
<th>IgE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum T1/2</td>
<td>23</td>
<td>6</td>
<td>5</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>No. 4 peptide basic units</td>
<td>1</td>
<td>1,2</td>
<td>5</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Valency for Ag binding</td>
<td>2</td>
<td>2,4</td>
<td>5-10</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Special features</td>
<td>Crosses placenta</td>
<td>Blood group reactions</td>
<td></td>
<td>Sensitizes mast cells and basophils</td>
<td></td>
</tr>
<tr>
<td>Fixes complement - classical</td>
<td>++</td>
<td>-</td>
<td>+++</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>- alternative</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
# IgG Subclasses

<table>
<thead>
<tr>
<th></th>
<th>IgG1</th>
<th>IgG2</th>
<th>IgG3</th>
<th>IgG4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major characteristic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Most abundant</td>
<td>Polysaccharide Ab responses</td>
<td>Allergy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Major defense against m/o and toxins</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal serum levels (Adult)g/L</td>
<td>4.2</td>
<td>1.2</td>
<td>0.41</td>
<td>0.01</td>
</tr>
<tr>
<td>% total Ig</td>
<td>67</td>
<td>22</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Serum T1/2 (days)</td>
<td>23</td>
<td>23</td>
<td>8</td>
<td>23</td>
</tr>
</tbody>
</table>
Antibody Deficiencies

• X-linked Agammaglobulinaemia (XLA)
• Autosomal recessive Agammaglobulinaemia
• Common Variable Immune Deficiency (CVID)
• IgA Deficiency
• IgG Subclass Deficiency
• Transient Hypogammaglobulinaemia of Infancy
• Specific Antibody Deficiency
{Secondary Antibody Deficiency}
Antibody Defects

- Recurrent sinopulmonary infections
- Septicaemia with encapsulated bacteria
- Conjunctivitis, Bronchiectasis
- Enteroviral infection
- Lymphoid tissue
  - absent XLA & μ heavy chain deficiency
  - increased with HSM in CVID
- Age at presentation
  - XLA & μ heavy chain deficiency - ~ 6 mos
  - CVID - later childhood or adulthood
Ontogeny of Antibody production
Laboratory Assessment
B Cell Defects

• Initial tests
  • IgG, IgA, IgM, IgE
  • Isoagglutinins, ASOT
  • Tetanus, Diphtheria, HIB Ab

• Further investigation
  • Booster immunization and repeat tet/dip/HIB Ab
  • Specific antibody response to Pneumococcal Ag
  • ? IgG subclasses
  • B cell enumeration
Primary and secondary Ab responses
Case 2-History

- 2 yo male
- previously well & thriving
- 18/12 ‘glue ear’ - gromets
- discharging ears since
Case 2 - Investigations

• Is further investigation warranted?
• FBE, IgG, IgA, IgM
• tetanus, diphtheria and HIB serology
• ASOT/anti-DNAse B
• isoagglutinins
• ??Pneumococcal antibody responses
Case 3 - History 1

- Charlie, 11 months
- Elective ‘cold’ LUSCS at 37 weeks
- NICU - ventilated 2 days; Home day 8
- Breast fed 7 weeks
- Well until 6 months - creche
- Recurrent suppurative otitis media - 8 perforations; both ears; antibiotics help
- Occasional yellow green nasal discharge
- Chesty cough last 3 weeks
- Gastro X1 - prolonged diarrhoea 2-3 weeks
- Settled on lactose free formula
Case 3 - History 2

- FHx - 3 1/2 yo brother - well
- FHx - obscure Hx (maternal side) of early childhood death ?sex
- Fully immunized
Case 3 - Examination

• Well
• Ht 73cm (25th)
• Wt 10.2kg (50-75th)
• shotty Cx LN/small amt tonsillar tissue
• ears dry (on augmentin)
• moist cough/ chest clear
• abdo -NAD
Case 3 - Investigations

• Is further investigation warranted?
HANDBOOK 2
Case 3(a)

CASE HISTORY

A 5-year-old girl presents with a history of recurrent sinopulmonary infections and episodes of otitis media.

DIAGNOSIS

Recurrent Sinopulmonary Infections
Otitis Media

LAB RESULTS

IgG: 5.19 g/L (2.02 - 11.76)
IgA: 0.14 g/L (0.16 - 1.77)
IgM: 0.80 g/L (0.36 - 1.60)
IgE: 5.60 kU/L (0 - 250)
Add: 440 IU/ml (10 - 200)
Tetanus toxoid IgG antibody: Negative
Diphtheria Tox T1 IgG antibody: 0.06 IU/ml (0.0 - 1.0)
Staphyloc occi IgG antibody: 0.22 IU/ml (0.0 - 10)
Mib IgG antibody: Negative
Neutrophil function tests

Neutrophil function tests

Chemoattract distance moved: 77
Chemoattractin % normal: 77 % (65 - 100)
BHT slide test: 300 %
BHT slide test comment: normal
PMA induced oxidative burst: 5.66 (4.1 - 7.9)
Staph (Panorama) oxid burst: 5.05 (4.1 - 7.1)
Staph (Panorama) phagocytosis: 5.12 (5.0 - 7.7)

LYMPHOCYTE FUNCTION TESTS

Whole blood PMA stimulation index: 197.0 (200 - 300)
Patient T-kg/ml: 84/184
Control T-kg/ml: 84/184

CD3 T: 81 % [+H(43 - 72)]
CD4 T: 62 % [+H(31 - 60)]
CD8 T: 16 % [-H(13 - 25)]
CD15 B: 10 % [+H(13 - 37)]
CD16 NK: 6 % [-H(0 - 12)]

FBE

White cell count: 9.0 10^9/L (6.0 - 10.0)
Neutrophils: 2.4 10^9/L (1.0 - 8.5)
Lymphocytes: 7.2 10^9/L (4.0 - 10.0)
Monocytes: 0.1 10^9/L (0.1 - 1.0)
Eosinophils: 0.1 10^9/L (0.0 - 0.8)

IMMUNOLOGY DR. M. TAYAB
Case 3 - Results

• FBE - NAD
• IgG- N, IgA- low(not absent), IgM - N
• tetanus, diphtheria and HIB serology -negative
• ASOT/anti-DNAse B - negative
• isoagglutinins - absent
• PNABs - not done (Pt < 2 yrs)
• Lymphocyte subsets - reduced B cells
Case 3 - Now What?

• Booster Immunise - Infanrix/Hib
• Re-evaluate tet/dip/HIB Ab response 4 weeks later
Case 3 - Outcome 1

- Good serological response to booster immunization
- IgG, IgA, IgM - N
- isoagglutinins - now present
- ASOT - low positive
- Lymphocyte markers - normal

- No further Ix required
**LABORATORY SERVICES, APA**

**HANDOUT 4**

**Case 3(c)**

---

For information regarding this result, please phone:

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### IMMUNE FUNCTION TESTS

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG</td>
<td>1.12</td>
<td>0.1 - 1.4</td>
</tr>
<tr>
<td>IgA</td>
<td>0.13</td>
<td>0.1 - 0.4</td>
</tr>
<tr>
<td>IgM</td>
<td>0.32</td>
<td>0.1 - 1.35</td>
</tr>
<tr>
<td>IgD</td>
<td>0.82</td>
<td></td>
</tr>
<tr>
<td>IgE</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>ANA</td>
<td>20</td>
<td>0 - 200</td>
</tr>
<tr>
<td>Tetanus toxoid IgG antibody</td>
<td>0.12</td>
<td></td>
</tr>
<tr>
<td>Pertussis toxoid IgG antibody</td>
<td>0.27</td>
<td></td>
</tr>
<tr>
<td>Diphtheria toxoid IgG antibody</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Mumps IgG antibody</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Hib IgG antibody</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Isocytokinetic (anti-A)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Isogalactokinetic (anti-A)</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Blood Group</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td>CD3</td>
<td>1.19</td>
<td>0.65 - 1.66</td>
</tr>
<tr>
<td>CD4</td>
<td>0.16</td>
<td>0.18 - 0.66</td>
</tr>
<tr>
<td>CH50 (Complement)</td>
<td>48</td>
<td>34 - 98</td>
</tr>
</tbody>
</table>

### LYMPHOCYTE FUNCTION TESTS

Whole blood EMA stimulation index: 151.0

Patient had EMA 16/10/07

Control 16/10/10 19/10/07

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>T4</td>
<td>80</td>
<td>50 - 75</td>
</tr>
<tr>
<td>T8</td>
<td>15</td>
<td>30 - 52</td>
</tr>
<tr>
<td>CD4</td>
<td>20</td>
<td>10 - 50</td>
</tr>
<tr>
<td>CD8</td>
<td>13</td>
<td>10 - 27</td>
</tr>
<tr>
<td>NK</td>
<td>4</td>
<td>5 - 15</td>
</tr>
</tbody>
</table>

### WBC COUNT

<table>
<thead>
<tr>
<th>Cell Type</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutrophil</td>
<td>2.1</td>
</tr>
<tr>
<td>Lymphocyte</td>
<td>1.1</td>
</tr>
<tr>
<td>Monocyte</td>
<td>0.3</td>
</tr>
<tr>
<td>Basophil</td>
<td>0.3</td>
</tr>
</tbody>
</table>

**COMMENT:**


---

**Dr: Joanne Grant**

**Immunology, 3rd Floor**

**Royal Children's Hospital**

**Parkville, Vic 3052**

Ref: Dr. John SV

For information regarding this result, please phone:
Case 3 - Outcome 2

- No serological response to booster immunization
- IgG - waning, IgA - low, IgM - N
- isoagglutinins - absent
Case 3 - Differential Diagnosis

• Common Variable Immune Deficiency
• X-linked Hyper IgM (CD40 Ligand Deficiency)

• Transient Hypo-gamma globulinaemia of Infancy
Transient Hypogammaglobulinaemia of Infancy

- Low IgG with recurrent viral/bacterial infections esp respiratory
- Delay normal synthesis immunoglobulins until after maternal IgG catabolized
- Resolves spontaneously by 4 yrs
- Specific antibody production normal
- Serious infections not significant problem
- Seen in relatives patients with SCID
- Males (60%)
- Associated with atopy
Transient Hypogammaglobulinaemia of Infancy

- Mx
- Antibiotic prophylaxis
- Rarely IVIG –3-6 months
Case 4 - History

• Mitchell
• 4 week old male, first child
• N preg/FVD at term; BW 3850g
• Well, settled, breast feeding well, thriving
• slight weepy R eye since D1
• Known FHx of X-Linked Agammaglobulinaemia (XLA)
• Mother never investigated for carrier status
Case 4 - Examination

- Well
- Ht/Wt 97th centile
- slight sticky R eye
- no tonsillar tissue or palpable LN
Case 4 - Family Tree

13 months
Case 4 - Investigations

• Will early investigation help diagnose/exclude XLA?
• FBE, IgG, IgA, IgM
• Lymphocyte subsets
HANDOUT 5
Case 4

For information regarding the result, please phone.

**Immunoglobulin Tests**

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG</td>
<td>5.06 g/L</td>
<td>5.21 - 16.24</td>
</tr>
<tr>
<td>IgA</td>
<td>0.07 g/L</td>
<td>*H 0.00 - 8.00</td>
</tr>
<tr>
<td>IgM</td>
<td>&lt;0.04 g/L</td>
<td>0.00 - 0.10</td>
</tr>
<tr>
<td>IgD</td>
<td>&lt;0.1 g/L</td>
<td>0.1 - 0.6</td>
</tr>
</tbody>
</table>

**Whole Blood FNA Response**

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>CD3</td>
<td>60%</td>
<td>*H 33 - 75%</td>
</tr>
<tr>
<td>CD4</td>
<td>56%</td>
<td>*H 23 - 60%</td>
</tr>
<tr>
<td>CD8</td>
<td>28%</td>
<td>14 - 25%</td>
</tr>
<tr>
<td>CD19</td>
<td>6.5%</td>
<td>*L 12 - 36%</td>
</tr>
</tbody>
</table>

**White Cell Count**

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphocytes</td>
<td>6.9 x 10^3/L</td>
<td>5.0 - 13.5</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>1.9 x 10^3/L</td>
<td>1.0 - 7.0</td>
</tr>
<tr>
<td>Monocytes</td>
<td>0.6 x 10^3/L</td>
<td>0.2 - 1.2</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>0.0 x 10^3/L</td>
<td>0.0 - 0.8</td>
</tr>
</tbody>
</table>

**Whole Blood Procalcitonin Index**

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Index</td>
<td>46 (20 - 70)</td>
<td></td>
</tr>
</tbody>
</table>

**Comment**

Low T4 & T8. Marked reduction in B cells. Consistent with x-linked agammaglobulinaemia.

**IgG, IgA & IgM CORRELATIVE REPORT**

<table>
<thead>
<tr>
<th>Date</th>
<th>IgG</th>
<th>IgA</th>
<th>IgM</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOW</td>
<td>5.44</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>HIGH</td>
<td>16.94</td>
<td>6.00</td>
<td>0.18</td>
</tr>
<tr>
<td>11/09/02</td>
<td>9.45</td>
<td>-0.07</td>
<td>0.11</td>
</tr>
<tr>
<td>05/10/02</td>
<td>9.16</td>
<td>-0.07</td>
<td>0.12</td>
</tr>
<tr>
<td>04/11/02</td>
<td>10.60</td>
<td>-0.07</td>
<td>0.10</td>
</tr>
<tr>
<td>04/12/02</td>
<td>8.99</td>
<td>-0.07</td>
<td>0.09</td>
</tr>
<tr>
<td>05/01/03</td>
<td>8.00</td>
<td>-0.07</td>
<td>0.10</td>
</tr>
<tr>
<td>28/01/05</td>
<td>8.40</td>
<td>-0.07</td>
<td>0.10</td>
</tr>
<tr>
<td>16/02/03</td>
<td>10.00</td>
<td>-0.07</td>
<td>0.11</td>
</tr>
</tbody>
</table>

**Days 1 of 2 pages, more to follow...**
Case 4 - Results

- FBE - NAD
- IgG - reduced, IgA - absent, IgM - absent
- Lymphocyte subsets - absent B cells (CD19)

- Diagnosis = XLA
X-linked Agammaglobulinaemia

• Diagnosis
  – Immunoglobulins - very low or absent
  – No or very few circulating B cells
  – Pre B cells present in BM
  – High % T cells, normal CD4:8 ratio
  – Intestinal biopsy - absence of plasma cells

• Mutation Bruton’s Tyrosine Kinase (BTK)
Agammaglobulinaemia

Absent serum immunoglobulin & absent B cells
5 genetic defects which block BM B cell development at pre-B cell stage
• XLA – Brutons Tyrosine Kinase (BTK) 80-90%
• IgM heavy chain gene (12 reports)
• Light chain (CD179b) (n=1)
• Ig α component of B cell receptor (CD79a)
• B cell linker protein (BLNK)
X-linked Agammaglobulinaemia

- Otitis media, pneumonia, sinusitis, conjunctivitis, septic arthritis, osteomyelitis, septicaemia, meningitis
- Pyogenic encapsulated organisms
- Onset ~3-6 months when maternal IgG wanes
- Susceptibility to chronic enteroviral infection
  - encephalitis or dermatomyositis-like syndrome
X-linked Agammaglobulinaemia

• Associated conditions
  • Rheumatoid arthritis ~20%
  • Lymphoreticular malignancy (5%)
  • Sarcoid

• Rare variant is associated with GH deficiency
• Absent lymph nodes, tonsils

• Treatment
  • lifelong monthly IVIG - does not prevent Enterovirus
  • antibiotics
Case 5 - History

• Justin, 10 yo male

• ‘always sick’
  • recurrent OM - initially non-discharging
  • grommets X4 - 1st aged 1yr - recurrent drainage since
  • decreased hearing
  • long term purulent nasal discharge
  • Aged 3yr - prolonged diarrhea - giardia
  • recurrent ‘gastro’ since
  • last 2 yrs - recurrent chest infections
    o RUL pneumonia X 3 Rx IV antis 7/7
    o chronic productive cough since 5yrs
    o poor exercise tolerance
    o thriving initially h/e recent poor weight gain
Case 5 - History

• FHx - Father had recurrent OM
• 8yo sib corrosive ingestion aged 5yr - oesophageal stricture Mx RCH
Case 5 - Examination

- Well, moist cough, not clubbed
- Ht/Wt 50th
- ears - purulent D/C
- nose - purulent D/C (no facial tenderness)
- no tonsils (past T’s & A’s)
- Chest - RUL creps
- Abdo - no splenomegaly
Case 5 - Investigations

- What further investigations are indicated?
- FBE, IgG, IgA, IgM
- tetanus, diphtheria, HIB serology; ASOT/anti-DNAse B; isoagglutinins
- pneumococcal antibody responses - pre and post pneumovax
- lymphocyte subsets; lymphocyte function
- CD40 Ligand expression
# Handout 7
## Case 5(b)

**Date:** 12/02/03

**Dr:** Joanne Smith

**Immunology Department, 6th Floor Royal Children's Hospital, Parkville Vic 3052**

**Contact:** Impact Team, Immunology, 5445 5725

---

## Immunodeficiency Tests

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG</td>
<td>0.76</td>
<td>(5.10 - 17.60)</td>
</tr>
<tr>
<td>IgM</td>
<td>&lt;0.07</td>
<td>&lt;0.33 - 1.38</td>
</tr>
<tr>
<td>IgA</td>
<td>0.31</td>
<td></td>
</tr>
<tr>
<td>IgE</td>
<td>&lt;0.5</td>
<td></td>
</tr>
<tr>
<td>ASOT</td>
<td>&lt;30</td>
<td></td>
</tr>
<tr>
<td>Textracted IgG antibody</td>
<td>0.31</td>
<td></td>
</tr>
<tr>
<td>Repeat extracted IgG antibody</td>
<td>Weak positive</td>
<td></td>
</tr>
<tr>
<td>Diagaphus for IgG antibody complex</td>
<td>0.60</td>
<td></td>
</tr>
<tr>
<td>MNP IgG antibody</td>
<td>0.42</td>
<td></td>
</tr>
<tr>
<td>MIP IgG antibody</td>
<td>0.36</td>
<td></td>
</tr>
<tr>
<td>Inosogukulin 1 (anti A)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Inosogukulin 2 (anti B)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Blood Group</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

**C3**

- Value: 1.27 g/L (0.85 - 1.66)

**C4**

- Value: 0.32 g/L (0.18 - 0.88)

**CH50 (Complement Splitting)**

- Value: 0.098 (48 - 94)

---

**Please note:** 49% of whole blood PNA (usually 72 hrs):

- **Whole blood PNA stimulation index**: 420.0 (200 - 1000)

**Control blood PNA index**: 441/1044

**Patient blood index**: 577/2328

**CD3**

- Value: 76 (%) (68 - 74)

**CD4**

- Value: 62 (%) (50 - 62)

**CD8**

- Value: 24 (%) (18 - 19)

**CD19**

- Value: 13 (%) (12 - 27)

**NK**

- Value: 12 (%) (5 - 13)

**PNA**

- **White cell count**:
  - Neutrophils: 30.9 (10^3/L) (6.5 - 13.5)
  - Lymphocytes: 2.6 (10^3/L) (1.5 - 4.0)
  - Monocytes: 0.5 (10^3/L) (0.6 - 1.0)
  - Eosinophils: 6.1 (10^3/L) (0.6 - 0.1)
  - Basophils: 6.8 (10^3/L) (0.6 - 0.1)

**Comment:**

Very low IgG, IgA and IgM. Normal blood cell numbers. Low titres to protein antigens. Immunisation status suggest boost and retreat. Paramyxovirus antibody testing pending. Findings suggestive of CVI.8.
Case 5 - Results

• FBE- neutrophilia/thrombocytosis
• IgG 0.07, IgA <0.07, IgM 0.21
• tetanus - weak, diphtheria - neg, HIB - short term
• ASOT neg anti-DNAse B neg
• isoagglutinins (blood group O) anti-A 16 anti-B 0
• pneumococcal antibody responses - pre and post pneumovax - absent
• lymphocyte subsets - N
• lymphocyte function - N
• CD40 ligand - N
Sample: Serum/plasma

Pneumococcal IgG antibodies

Date of immunisation: 12/02/02

<table>
<thead>
<tr>
<th>Sample</th>
<th>12/02/02</th>
<th>12/02/03</th>
<th>Value of 30% adult reference pool</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample 1</td>
<td>342</td>
<td>432</td>
<td>(400) mg/mL</td>
</tr>
<tr>
<td>Sample 2</td>
<td>534</td>
<td>654</td>
<td>(500) mg/mL</td>
</tr>
</tbody>
</table>

Interpretation of results:

A protective response for a serotype is defined as a pre or post immunisation titre of greater than 30% of the normal adult reference pool (see above).

Animals responses to pneumococcal polysaccharides are age dependent. The number of normal children who have antibodies to 2 or more serotypes with levels greater than 30% of adult reference range and set of 2 to 3 years, 63% of 5 to 8 years and 50% of 8 to 13 years.
Case 5 - Results

• RFT - obstructive defect; FVC 71%, FEV1 60% MMEF 33%
• CXR ?RUL bronchiectasis
• CT Chest - chronic collapse RUL

• Diagnosis: Common Variable Immune Deficiency
CVID’s

• Diagnosis
  – immunoglobulins - low or absent IgG, IgA, IgM
    • may have normal IgM or IgA in some
  – B cell numbers - normal or reduced
  – normal T cell numbers, reversed CD4:8 ratio
  – normal T cell proliferative responses in most
    • reduced in some ?Intrinsic T cell defect
    • may have progressive attrition T cell function with time
CVID’s

- Heterogeneous group of conditions
- Clinically defined – (low IgG +/-IgA)
- Unknown aetiology – molecular defect not yet defined
- Males and females equally affected
- Onset late childhood and adulthood
- Variable spectrum
  - agammaglobulinaemia, hypogammaglobulinaemia, specific antibody deficiency
  - autoantibodies, autoimmune disease, cytopoenias
CVID’s

• Recurrent infection
  • *haemophilus, pneumococcus, staphylococcus*
  • sinopulmonary - sinus usually precedes chest
  • bronchiectasis - many present to pulmonary clinics

• Autoimmune disease
  • autoimmune cytopenias (haemolytic anaemia, leukopenia, thrombocytopenia)
  • alopecia areata, pernicious anaemia, gastric atrophy
  • Seronegative arthritis, rheumatoid arthritis, dermatomyositis, vasculitis, scleroderma
  • lupus evolving into CVID

• Autoimmune symptoms may precede infections
CVID’s

• Malabsorption
  • Sprue like syndrome - steatorrhea, malabs B12 folate, lactose intolerance, protein losing enteropathy
  • Nodular follicular lymphoid hyperplasia
  • Giardia lamblia - most respond to Metronidazole

• Benign lymphoproliferative disease (30%)

• Lymphoid interstitial pneumonia

• Non-caseating granulomata lung/spleen/skin/liver

• Increased incidence lymphoreticular malignancy
  • 8-13X overall
  • 438X increase in lymphoma in females >40yr
CVID’s

• High incidence in extended family of
  • autoimmunity
  • immunodeficiency - IgA deficiency and CVID
  • malignancy

• Asthma/rhinitis (without elevated IgE) (10%)

• Association with IgA deficiency
  • susceptibility gene on Chrom 6 in MHC III region
  • linkage with “ancestral haplotype”
CVID’s

• Lymph nodes - normal or enlarged
• Splenomegaly - hypersplenism ~25%

• Diagnosis
  • immunoglobulins - low or absent IgG, IgA, IgM
    • may have normal IgM or IgA in some
  • B cell numbers - normal or reduced
  • normal T cell numbers, reversed CD4:8 ratio
  • normal T cell proliferative responses in most
    • reduced in some ?Intrinsic T cell defect
    • may have progressive attrition T cell function with time
CVID’s

• IVIG
  • will not reverse chronic lung disease
  • will improve joint symptoms

• Antibiotics
  • prophylaxis and aggressive treatment infections

• Physiotherapy, drainage

• Avoid corticosteroids - AIHA, Sarcoid

• Prognosis
  • many develop chronic lung changes
  • 8% develop lymphoreticular malignancies
Case 6 - History

- 2 1/2 yo girl
- previously well and thriving
- last 6/12 recurrent episodes of spurious diarrhea
- Coeliac screen - IgA deficient
- no significant infections
- fully immunised
- FHx - nil significant
- Examination - Well, thriving
Case 6 - Investigations

• Is further Ix of immune status indicated?
• Consider:
  • FBE, IgG, IgA, IgM
  • Functional Ab responses ie
    • tet/dip/HIB
    • ASOT/AntiDnase B
    • isoaggs
    • PNABs
  • lymphocyte subsets
  • Evaluation of other family members
Selective IgA Deficiency

- IgA <0.07g/l (N IgG and IgM) > 4yrs
- common 1:300 to 1:700, males > females
- strong familial association - ?AD α penetrance
- strong association with CVID
  - CVID & IgA deficiency often found in same pedigree
  - IgA deficiency may evolve into CVID
Selective IgA Deficiency

• may develop 2° to
  • phenytoin, carbamazepine, valproic acid, d-penicillamine, gold, sulfasalazine, hydroxychloroquine, NSAIDs
  • congenital rubella or CMV

• may be seen in association with other immunodeficiency syndromes
  • ataxia telangiectasia, Di George syndrome

• normal secretory IgA with deficiency serum IgA
  • rare 3%
Selective IgA Deficiency

• increased incidence
  • allergic disease - more refractory to treatment
  • coeliac disease
  • autoimmune disease
    • SLE, RA, Thyroiditis, Addissons
    • autoantibodies without disease

• CVID

• anti-IgA antibodies in 33%
  • risk transfusion reactions (IgE anti-IgA)
Selective IgA Deficiency

• most individuals asymptomatic
  • low MW IgM in secretions increased IgM and IgG in serum
  • mount IgG and IgM response to intranasal polio virus

• high incidence IgG subclass deficiency
  • IgG2 deficiency
    • 9% of IgA deficient healthy blood donors
    • 31% of IgA deficient with recurrent infections
Selective IgA deficiency

• GI disorders
  • coeliac disease
    • childhood or adult
    • responds to gluten free diet
  • steatorrhoea, disaccharidase deficiency
  • ulcerative colitis and crohns disease

• Malignancy
Selective IgA Deficiency

• IVIG is not indicated for isolated IgA deficiency
  • little IgA in IVIG
  • patients may develop IgE to IgA - risk anaphylaxis
  • up to 40% have IgE anti-IgA Ab
  • antibiotic therapy if indicated

• IVIG only if defective specific antibody responses
  • check for IgE anti-IgA, use IgA depleted product

• All blood products should be washed in saline before infusion to deplete IgA
IgG Subclass Deficiency

• Reduction of 1 or more IgG subclasses (=/- low IgA) (N IgG &M)
• Significance is uncertain/controversial

• Individuals with complete deletions of IgG subclasses remain healthy (2.3% population)

• Patients with IgA deficiency who have associated subclass defects have increased incidence infections

• Most patients with absent or very low IgG2 have IgA deficiency
IgG Subclass Deficiency

• More relevant question is
  • “what is the ability of patient to make specific antibodies to protein and polysaccharide antigens?”

• May have marked deficiency specific antibody responses with completely normal IgG subclasses

• Low levels IgG subclasses may be a marker for evolving immunodeficiency
Specific Antibody Deficiency

• Up to 23% of immunodeficiency diagnoses (1 centre)
• Normal immunoglobulins IgG, A, M)
  • distinct from other antibody syndromes
• Normal T cell numbers, phenotype, function
• Poor or no antibody response to antigens
  • Pneumococcal polysaccharides
  • blood group, tetanus, diphtheria
  • bacteriophage φX174
Specific Antibody Deficiency

- Recurrent infection with high grade pathogens
- Candidal infection in some cases
- May represent early stage of CVID
Pneumococcal Responses

• 23 valent unconjugated vaccine Pneumovax® (not 7 valent conjugated vaccine Prevenar®)
• Measure preimmunisation and post immunisation levels (4 weeks later)
• ??adequate response >1.3mcg/ml or 4 fold increase
• ??normal response –depends on age
• Poor<2years; 50% serotypes 2-5yrs; 70% serotypes > 5yrs
Secondary Antibody Deficiency

• Protein loosing enteropathy

• Drugs
  • Steroid
  • Rituximab
Case 7 - History

• Damon, 3 yo boy
• recurrent life threatening pneumococcal sepsis
  • 11/12 pneumonia (flu A)
  • 18/12 pneumococcal meningitis - ICU
    • Cx prolonged seizure
    • prolonged recovery
  • 23/12 pneumococcal bacteraemia
  • 36/12 pneumococcal meningitis
• well b/t episodes
• mild asthma
Case 7 - History

- Fully immunised
- FHx - nil signif; older brother well
Case 7 - Examination

- Normal
- Ht 75th/Wt 50th
Case 7 - Investigation

• What investigations are indicated?
• FBE - ?signs of asplenia; IgG, IgA, IgM
• Functional Ab responses
  • tetanus, diphtheria, HIB serology
  • ASOT/Anti-DNAse B
  • isoagglutinins
  • pneumococcal serology
• C3, C4, CH100
HANDOUT 13
Case 9(b)

For information regarding this result, please phone: 5345 5725

BLOOD FUNCTION TESTS

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG</td>
<td>5.58 g/L</td>
<td>(4.10 - 16.61)</td>
</tr>
<tr>
<td>IgA</td>
<td>0.41 g/L</td>
<td>(0.25 - 1.53)</td>
</tr>
<tr>
<td>IgM</td>
<td>1.31 g/L</td>
<td>(0.29 - 9.60)</td>
</tr>
<tr>
<td>IgD</td>
<td>37 g/L</td>
<td>(0 - 150)</td>
</tr>
<tr>
<td>ANA</td>
<td>&lt;10 IU/mL</td>
<td>(0 - 200)</td>
</tr>
<tr>
<td>CA</td>
<td>1.21 g/L</td>
<td>(0.02 - 1.66)</td>
</tr>
<tr>
<td>CR</td>
<td>0.22 g/L</td>
<td>(0.10 - 0.66)</td>
</tr>
<tr>
<td>CH50 (Complement Component)</td>
<td>80</td>
<td>(50 - 80)</td>
</tr>
</tbody>
</table>

LYMPHOCYTE FUNCTION TESTS

Whole blood PHA stimulation index

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient blood/serum:</td>
<td>149,132</td>
<td>(20 - 75)</td>
</tr>
<tr>
<td>Control blood/serum:</td>
<td>122,372</td>
<td>(20 - 75)</td>
</tr>
</tbody>
</table>

CD4  | 76% | 71 (5 - 73) |
CD8  | 24% | 24 (9 - 54) |
CD19 | 23% | 22 (9 - 52) |
NK   | 5%  | 3 (5 - 53) |

WBC

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutrophils</td>
<td>7.3 x10^9/L</td>
<td>(4.9 - 7.7)</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>4.0 x10^9/L</td>
<td>(3.0 - 9.0)</td>
</tr>
<tr>
<td>Monocytes</td>
<td>0.3 x10^9/L</td>
<td>(0.1 - 1.0)</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>0.3 x10^9/L</td>
<td>(0.0 - 0.8)</td>
</tr>
<tr>
<td>Basophils</td>
<td>0.0 x10^9/L</td>
<td>(0.0 - 0.1)</td>
</tr>
</tbody>
</table>

Comment:

Acute CLL69 consistent with hypogammaglobulinemia deficiency of a complements component.
Sample: Serum

COMPLEMENT STUDIES

CH50

ND 1/16  (16 - 32)

ND = not detected.

CH50 measures the function of classical complement pathway components C1 to C9.

Class activity is underestimmable in congenital deficiency of components C1 to C9
and reduced but may be present in C9 deficiency.
### Handout 15

**Case 9(d)**

**Sample:** Serum/Plasma

<table>
<thead>
<tr>
<th>Component</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1q 78 mg/L (124 - 198)</td>
<td></td>
</tr>
<tr>
<td>C4a 155 mg/L (72 - 216)</td>
<td></td>
</tr>
<tr>
<td>C4b 74 mg/L (74 - 166)</td>
<td></td>
</tr>
<tr>
<td>C8 66 mg/L (9.0 - 15.6)</td>
<td></td>
</tr>
<tr>
<td>C9 543 mg/L (90 - 173)</td>
<td></td>
</tr>
<tr>
<td>C1-INH activity 115 mg/L (85 - 119)</td>
<td></td>
</tr>
<tr>
<td>C3 1.25 mg/L (1.13 - 277)</td>
<td></td>
</tr>
<tr>
<td>C5 245 mg/L (223 - 240)</td>
<td></td>
</tr>
</tbody>
</table>

Tests performed by:
South Eastern Laboratory Services,
Authorised Hospital,
South Sydney

**Comment:** Consistent with total C1 deficiency.

Reviewed by Doctor:  
S. Printer 10/12/03  
Val Br: Prof. A. Kemp 11/12/03  
Rev Br:  

[Handout 15 Case 9(d) page 1]
3 Complement Pathways

CLASSICAL PATHWAY
Antigen-Antibody Complexes

MANNOSE BINDING LECTIN PATHWAY
Mannan-Containing Microbes

ALTERNATIVE PATHWAY
Microbial Components

C1 → C2 → C3

MBL → MASP-1, -2

C3 → Opsonization

C5 → Inflammation

C6, C7, C8, C9 → Membrane Attack Complex
3 Complement Pathways

THE COMPLEMENT CASCADE

Activated by Microbial cell surfaces Microbial surface sugars Antibody

Major components
- C3b
- Factor B
- Factor D
- Properdin

Central event
- MBP
- C1
- C4
- C2
- C3 CONVERTASE
- C3
- C3b
- C3a

Biological effects
- (with phagocytes) Phagocytosis
- C5
- C6
- C7
- C8
- C9
- Lysis
- C5a
- (with mast cells) Inflammation
- Neutrophil chemoattractant
Complement Defects

• Deficiency of almost all components described exception is Factor B deficiency

• Autosomal recessive inheritance for all but 2
  • C1 esterase inhibitor deficiency AD
  • Properdin deficiency XL

• Complement deficiencies are rare

• C2 deficiency most common
Complement Defects

• Early components
  • autoimmune disease (SLE, RA, PNH etc)
  • recurrent infection (gram positive organisms)

• C5 - C9
  • recurrent neisserial infections

• C3 - similar to antibody defect
  • recurrent pyogenic sinopulmonary infections

• Mannose binding lectin deficiency
  • Increased frequency of infection in adults and children
C1 Esterase Inhibitor Deficiency

Hereditary Angioneurotic edema (HANE)
• Autosomal dominant
• Type I – reduced protein (85%)
• Type II – dysfunctional protein (15%)
• Recurrent episodes of subepithelial swelling (non-painful or pruritic) involving extremities, genitalia, intestinal mucosa (abdo pain), larynx

Mx
antifibrinolytics- tranexamic acid/e amino caproic acid
Androgens
C1 Esterase concentrate
### ACTION PLAN FOR Hereditary Angioedema (HAE)

#### MILD HAE SYMPTOMS
- Peripheral swelling, mild facial swelling
- Mild abdominal pain

**ACTION**
- Pain relief:
- Observe for progression

#### MODERATE TO SEVERE HAE SYMPTOMS - PERIPHERAL SWELLING
- Severe facial, genital or peripheral swelling, causing significant discomfort or disability

**ACTION**
- In adults administer Ixazyvel (Firazyr)\(^{1,2}\), subcutaneously or C1 INH (Berinert\(^{1,2}\)) 20 U/Kg IV or Cinryze\(^{3}\) 1,000 U IV\(^{1,2}\)
- In children administer C1 INH (Berinert\(^{1,2}\)) 20 U/Kg IV or Cinryze\(^{3}\) 1,000 U IV\(^{1,2}\)

#### MODERATE TO SEVERE HAE SYMPTOMS - ABDOMINAL SYMPTOMS
- Moderate to severe abdominal pain
- Vomiting
- Dehydration (e.g., dry mouth, thirst, confusion)

**ACTION**
- In adults administer Ixazyvel (Firazyr)\(^{1,2}\), subcutaneously or C1 INH (Berinert\(^{1,2}\)) 20 U/Kg IV or Cinryze\(^{3}\) 1,000 U IV\(^{1,2}\)
- In children administer C1 INH (Berinert\(^{1,2}\)) 20 U/Kg IV or Cinryze\(^{3}\) 1,000 U IV\(^{1,2}\)
- Seek urgent hospital treatment if symptoms worsen or last longer than 2 hours

**ADDITIONAL HOSPITAL TREATMENT:**
- Give 2nd dose of specific treatment

#### MODERATE TO SEVERE HAE SYMPTOMS - AIRWAY SWELLING
- Tongue swelling
- Throat swelling
- Difficulty with breathing, swallowing, talking (hoarse voice)

**ACTION**
- In adults administer Ixazyvel (Firazyr)\(^{1,2}\), subcutaneously or C1 INH (Berinert\(^{1,2}\)) 20 U/Kg IV or Cinryze\(^{3}\) 1,000 U IV\(^{1,2}\)
- In children administer C1 INH (Berinert\(^{1,2}\)) 20 U/Kg IV or Cinryze\(^{3}\) 1,000 U IV\(^{1,2}\)
- Phone ambulance - 000 (AU) or 112 (mobile)
- Seek urgent hospital treatment

**ADDITIONAL HOSPITAL TREATMENT:**
- Prepare for emergency intubation or tracheotomy
- Give 2nd dose of specific treatment if inadequate response after 1 hr

---

**NOTE:**
1. Ixazyvel (Firazyr) is approved for use in adults with HAE.
2. Patient's own supply either at home or at hospital
3. C1 INH (C1 Inhibitor concentrate) is approved for use in children and adults with HAE
4. Products cited in this Action Plan are TSA registered hence this information is specific for HAE treatment in Australia
5. Adrenergics, antihistamines and corticosteroids are not effective for HAE attacks.
Laboratory Diagnosis
Complement Defects

• CH50 is best screen
  • will detect >50% reduction in complement component

• C3, C4
  • C3 parallels CH50
  • low in inflammatory conditions
  • C4 low in CINH deficiency

• Other
  • opsonic assays
  • complement component assays
Case 8 - History

• Michael
• 20/12 boy
• first child, N preg, NVD at term
• recurrent infections
  • chest
  • skin- impetigo/boils
  • ears- bilateral discharging ears
  • thrush - oral/perineal
Case 8 - Examination

- Growth - Falling off centile chart
- coarse facies, eczema - staph superinfection
- ears - purulent D/C
- crusted nose
- shotty adenopathy - cervical/axillary
- moist cough, scattered creps
- abdominal distension
- splenomegaly
Case 8 - Investigations

- FBE, IgG, IgA, IgM
- Functional Ab responses
- Lymphocyte markers
- Lymphocyte function
- Neutrophil function
- BMA
Case 8 - Investigations

• FBE- neutrophilia, thrombocytosis, microcytic anaemia
• IgG, IgA, IgM all elevated
• Functional Ab responses- normal
• Lymphocyte markers -normal
• Lymphocyte function-normal
• BMA - normal
### IMMUNE FUNCTION TESTS

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**Comment:**
Correlation with CVID.

### ING. IGA & IGM CUMULATIVE REPORT

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Neutrophil Defects

- Neutropenia
- Chronic Granulomatous Disease (CGD)
- Leucocyte Adhesion Molecule Deficiency (LAD)
- Neutrophil specific granule deficiency
- Chediak-Higashi syndrome
Neutropaenia

Alloimmune
Autoimmune
Cyclic
• Deficiency of elastase
• Regularly (21d) fluctuating neutrophil counts
• Fever, stomatitis, gingivitis

Congenital agranulocytosis (Kostmann syndrome)
• Mutation in G-CSF gene
• Pneumonia, otitis media, gingivostomatitis, perineal abscesses
Chronic Granulomatous Disease

- Inability phagocytes to kill catalase positive microorganisms (Staph aureus, Gram negative) and fungi (Infections Aspergillus, Candida etc)
- recurrent bacterial pyogenic skin and soft tissue infections,, Lymphadenitis, Bone and Joint infections
- Gingivitis
- Granuloma formation causes GI and GU obstruction
- XL (75%) and AR forms
Chronic Granulomatous Disease

- Mutations affecting elements of phagocyte NADPH oxidase complex
- Required for oxygen dependent intracellular killing mechanism
Chronic Granulomatous Disease
X-linked CGD

• Mutation $\beta$ subunit cytochrome $b_{558}$ catalytic redox entity of NADPH oxidase, gp91 phox
• X-CGD gene is $Cybb$, on Xp21.1
• 30kb, 13 exons
• integral membrane flavoprotein that transports electrons across the plasma membrane to generate superoxide
Chronic Granulomatous Disease

• Mx
• Prohylaxis:
  • Antibiotic : bactrim
  • Antifungal : Itraconazole
  • IFN-g 3X/week
• Aggressive Rx of infection
• Granulocyte transfusions
• Cure: BMT
Laboratory Diagnosis
Phagocytic Defects

• Initial tests
  • FBE - neutrophilia, neutropoenia

• Oxidative Metabolism
  • FACS, NBT – nitroblue tetrazolium test

• Adhesion molecule expression

• Other
  • Chemotaxis
  • Phagocytosis
  • Bactericidal assays
Neutrophil Migration

Rolling adhesion

Firm adhesion

Diapedesis

Leucocyte integrin

SLex

ICAM/VCAM

Inside out signalling

Fibrinogen crosslinking

Selectin
Adhesion Molecules

• Surface bound molecules
• Cell-cell interaction
• Direct migration, phagocytosis, cellular cytotoxicity
Leucocyte adhesion deficiency

LAD 1
• Mutation in gene encoding CD18 or B2 integrin
• Delayed separation umbilical cord (4 weeks) (not a feature of LADII)
• High WBC, no pus
• Poor wound healing, severe scarring skin infections, gingivitis, systemic bacterial infections
• BMT curative

LAD 2
• Absence of sialyl lewis X (CD15s) = ligand for E selectin
• Leucocytes unable to make initial attachment to vascular endothelium
• Facies, growth and developmental delay, mantel retardation
• Pulmonary infections, severe periodontitis
• Rx oral fucose supplementation
Summary

Congenital Immunodeficiency disorders
• are rare
• can be diagnosed by a relatively small number of tests

Critical for physicians to have an index of suspicion

Early diagnosis
• offers best chance for reduced morbidity and survival
• Critical for accurate genetic counselling
Remember....... 

“there’s NO such thing as BAD LUCK!”
-Steve Holland NIH

“If in doubt check it out”
-Jo Smart
Recommended Reading

• Practice Parameters for the diagnosis and management of Primary Immunodeficiency
  • Annals of Allergy, Asthma and Immunology May 2005; 94, 5. S1-S62
  • FA Bonilla et al
Recurrent infection in children: When and how to investigate for primary immunodeficiency?

Paul EA Gray,¹,² Mahila Namasivayam¹,² and John B Ziegler¹,²

¹Department of Immunology and Infectious Diseases, Sydney Children’s Hospital, Randwick and ²School of Women's and Children’s Health, University of New South Wales, Sydney, New South Wales, Australia