Immunology and the middle ear
Andrew Riordan
The Immune system is NOT there;

• To baffle medical students
• To keep Immunologists in a job
• To encourage experiments on mice
The Immune system IS there as a defence against infection.

If some or all of it is not working there is a high risk of infection.
The immune system

Needs to fight variety of infectious agents (10^{-5} \text{ to } 10^{3} \text{ mm}). Needs variety of mechanisms:

• Cells and chemicals (Cell-mediated & humoral)
• Specific and non-specific
• Intracellular and extracellular
# The immune system

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Non-specific, cellular immunity

Polymorphs

- Main role is phagocytosis
- Adhere to endothelial cells then extravasate
Phagocytes

← Micro-organism
Phagocytes

Micro-organism

Adherence

Migration
Phagocytes

Micro-organism

Adherence

Migration
Phagocytes

Adherence

Micro-organism

Phagocytosis

Migration
Phagocytes

Adherence

Micro-organism

Phagocytosis

Migration
Adherence → Phagocytosis → Killing

Micro-organism → Phagocytes
Non-specific, cellular immunity

• Problems if:
  Neutropoenia, deficient adhesion, chemotaxis or killing
• Staphylococcal or fungal infections

Treatment:
  Antibiotics, antifungals,(BMT)
Non-specific, humoral immunity

Complement

• Helps adherence (C3b)
• Biologically active (C3a, C5a)
• Membrane Attack Complex

Acute Phase Proteins (eg CRP)

• Bind to organisms, helps C3b adherence
Complement cascade

ag/ab complexes

Microorganisms
Complement cascade

ag/ab complexes

Classical C1,4,2

Micro organisms

C3
Complement cascade

ag/ab complexes

Classical C1,4,2

Alternative Properdin, B,D,H,I

Micro organisms

C3

Terminal C5-9

MAC

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Non-specific, humoral immunity

- Problems if:
  - deficient complement components
- Early - vasculitis
- Late - sepsis (meningo/ pneumo)

Treatment
- Vaccine, Antibiotics
Specific, humoral immunity

Organisms may avoid complement or prevent cell activation. Thus need a SPECIFIC response, which can:

• Stick to the microbe
• Activate complement
• Stimulate phagocytosis
The antibody molecule

Microbe

Recognition site

Variable

Antibody receptor

Activate complement

Constant

Phagocyte

Activate phagocyte
Antibody

- Specific protection against infection
- IgM produced early, short lived
- IgG produced later, lasts longer
- IgA protects mucosal surfaces
B cells

• Each B cells makes a specific antibody. Preformed & expressed on the surface.
• When it meets the correct antigen, this clone proliferates to make antibody & memory cells. Takes a few days.
• Next response to that specific antigen, more rapid, more antibody and more effective.
Lymphocyte selective activation, clonal expansion and maturation of B cells.
Lymphocyte selective activation, clonal expansion and maturation of B cells.
Specific, humoral immunity

- Problems if
  - Deficient B cells or antibody
- Pyogenic bacteria

Treatment

Immunoglobulin
Specific, cellular immunity

- Organisms may “hide” in cells
- Need to recognise cells (MHC) and the SPECIFIC antigen
Cytotoxic T cell

Virus infected cell
Cytotoxic T cell

Virus infected cell
Cytotoxic T cell

Virus infected cell

MHC class 1
Cytotoxic T cell

Virus infected cell

Cytotoxic T cell
Cytotoxic T cell

Virus infected cell

CD8
Cytotoxic T cell

Virus infected cell

Cytotoxic T cell

CD8
Cytotoxic T cell

Virus infected cell

CD8
Cytotoxic T cell

Apoptosis
T cells

• Cytotoxic to cells infected with viruses
• Produce lymphokines to activate macrophages to kill ingested organisms
Macrophage activation

Macrophage → T cell
Macrophage activation

Macrophage → IL-12 → IFN gamma → T cell
Macrophage activation

Macrophage

IL-12

IFN gamma

T cell

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Specific, cellular immunity

- Problems if:
  - Deficient T cells or poor cell signalling
- Viral, fungal, intracellular bacterial infections

Treatment
- Antibiotics (Septrin), BMT
The Immune System

Non-specific and Specific

Polymorph → Complement → Antibody

B cell → Antibody
The Immune System

- Non-specific
- Specific

- Polymorph
- Complement

- B cell
- Antibody

Humoral immunity
The Immune System

- Non-specific
- Specific

- Polymorph
- Complement

- B cell
- Antibody

- Humoral immunity

- Extracellular organisms
The Immune System

Non-specific and Specific

Polymorph \rightarrow Complement \rightarrow Antibody

B cell \rightarrow Antibody

Humoral immunity

Extracellular organisms

NK-cell

Cytokines \rightarrow Macrophage

T cell
The Immune System

Non-specific and Specific

Polymorph → Complement → NK-cell

Cytokines → Macrophage

B cell → Antibody → Humoral immunity

T cell → Cell-mediated immunity

Extracellular organisms
The Immune System

Non-specific and Specific

Polymorph → Complement

NK-cell

Cytokines → Macrophage

B cell → Antibody → Humoral immunity → Extracellular organisms

T cell → Intracellular organisms

Humoral immunity

Cell-mediated immunity
The Immune system IS there as a defence against infection.
Immunodeficiencies

• Primary Immunodeficiencies are not common 1:10,000
• Secondary Immunodeficiencies are commoner; prematurity, malnutrition, Haem/Onc, transplants, steroids, HIV
• Susceptibility to infection depends on which part(s) of the immune system are affected
Clues to immunodeficiency;

S evere infections
- disseminated chickenpox

P rolonged infections
- chickenpox for >1 week

U nusual infections
- pneumocystis pneumonia

R ecurrent common infections
10 warning signs of primary immunodeficiency

www.info4pi.org

1. 4 new ear infections within 1 year;
2. 2 serious sinus infections within 1 year;
3. 2 months of oral antibiotic treatment with little effect;
4. 2 episodes of pneumonia within 1 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 fungal infection on skin;
8. need for intravenous antibiotics to clear infections;
9. 2 deep-seated infections, including septicaemia;
10. a family history of PID.
Immunologic screening of children with recurrent otitis media.

**Immunologists**

- Up to 98% of patients with antibody deficiency have otitis, sinusitis, bronchitis
- Many have established bronchiectasis when diagnosed
Immunologic screening of children with recurrent otitis media.

**Immunologists**
- Up to 98% of patients with antibody deficiency have otitis, sinusitis, bronchitis
- Many have established bronchiectasis when diagnosed

**Non-Specialist**
- 5% to 10% of infants and toddlers suffer ≥ 4 episodes of otitis/ year.
- Antibody deficiency is rare among these patients.
- IgA, IgG2 or specific antibody deficiency may occur

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Case 1 – born 1997

1998 ottorhoea
2000 Ts&As+grommets
  ottorhoea
2001 grommets
  ottorhoea
2003 grommets
  ottorhoea
2007 grommets
  ottorhoea
Case 1 – born 1997

1998 otterhoea
2000 Ts&As+grommets otterhoea
2001 grommets otterhoea
2003 grommets otterhoea
2007 grommets otterhoea

1999 “recurrent LRTI”
Case 1 – born 1997

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1999 “recurrent LRTI”
2002 “recurrent LRTI”
Case 1 – born 1997

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1999 “recurrent LRTI”
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2006 L pneumonia
Case 1 – born 1997

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1999 “recurrent LRTI”
2002 “recurrent LRTI”
2006 L pneumonia
2009 R pneumonia
Case 1 – born 1997

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1999 “recurrent LRTI”
2002 “recurrent LRTI”
2006 L pneumonia
2009 R pneumonia
Case 1 – aged 12
Case 1 – aged 12

- Chronic suppurative otitis media since 19 months of age
Case 1 – aged 12

- Chronic suppurative otitis media since 19 months of age
- Two episodes of pneumonia – previous “chest infections”
Case 1 – aged 12

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- Two episodes of pneumonia – previous “chest infections”
- Parents consanguinous
Case 1 – aged 12

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Case 1 – aged 12

- Chronic suppurative otitis media since 19 months of age
- Two episodes of pneumonia – previous “chest infections”
- Parents consanguinous

Could this child have immune deficiency?
Investigations
Investigations

FBC:
Hb 12
WBC 8.1 (N 4.3, L 2.4)
Plts 275
Investigations

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Hb 12
WBC 8.1 (N 4.3, L 2.4)
Plts 275
Investigations

FBC:
Hb 12
WBC 8.1 (N 4.3, L 2.4)
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Immunoglobulins
Investigations

FBC:
Hb 12
WBC 8.1 (N 4.3, L 2.4)
Plts 275

Immunoglobulins
IgG <1.1  (7.4-14)
Investigations

FBC:
Hb 12
WBC 8.1 (N 4.3, L 2.4)
Plts 275

Immunoglobulins
IgG <1.1  (7.4-14)
IgA <0.05  (0.6-3.3)
Investigations

**FBC:**
Hb 12  
WBC 8.1 (N 4.3, L 2.4)  
Plts 275

**Immunoglobulins**
IgG <1.1  (7.4-14)  
IgA <0.05  (0.6-3.3)  
IgM 8.26  (0.5-2.3)
Investigations

FBC:
Hb 12
WBC 8.1 (N 4.3, L 2.4)
Plts 275

Immunoglobulins
IgG <1.1  (7.4-14)
IgA <0.05  (0.6-3.3)
IgM 8.26   (0.5-2.3)

- Diagnosis – “Antibody deficiency”
- Treatment – immunoglobulin replacement

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Further tests
Further tests

If FBC and immunoglobulins normal;
Further tests

If FBC and immunoglobulins normal; check specific antibodies to:
Further tests

If FBC and immunoglobulins normal;
check specific antibodies to:
Pneumococcal polysaccharide
Further tests

If FBC and immunoglobulins normal; check specific antibodies to:

- Pneumococcal polysaccharide
- *Haemophilus influenzae* type b (Hib)
Further tests

If FBC and immunoglobulins normal; check specific antibodies to:
- Pneumococcal polysaccharide
- *Haemophilus influenzae* type b (Hib)
- Tetanus
Further tests

If FBC and immunoglobulins normal; check specific antibodies to:
- Pneumococcal polysaccharide
- *Haemophilus influenzae* type b (Hib)
- Tetanus

If low, give vaccines and recheck
Response to polysaccharide

Age >2yrs

No memory
Response to polysaccharide
Age >2yrs
No memory

Response to protein conjugate
Any age
Memory
Hierarchy of vaccine responses

1. Polysaccharide (pneumovax)

2. Conjugate (Hib)

3. Tetanus
Hierarchy of vaccine responses

1. Polysaccharide (pneumovax)
2. Conjugate (Hib)
3. Tetanus
Hierarchy of vaccine responses

1. Polysaccharide (pneumovax)
2. Conjugate (Hib)
3. Tetanus

Poor response
Hierarchy of vaccine responses

1. Polysaccharide (pneumovax)
2. Conjugate (Hib)
3. Tetanus
Hierarchy of vaccine responses

1. Polysaccharide (pneumovax)
2. Conjugate (Hib)
3. Tetanus

Poor response

- <4-fold increase in titre following 23-valent unconjugated pneumococcal immunisation (Pneumovax)
- Associated with history of otitis media, particularly in association with chronic otorrhoea (RR 4·64)
- Found in 6–14% of children evaluated for recurrent infection
Overlapping conditions

IgA deficiency
Overlapping conditions

IgA deficiency

Ig G2 deficiency
Overlapping conditions

IgA deficiency

Specific antibody deficiency

Ig G2 deficiency
Immunologic screening of children with recurrent otitis media.

- Recurrent otitis media with chronic otorrhoea
- Recurrent otitis media with other respiratory infections
- Family History
Immunologic screening of children with recurrent otitis media.

- Recurrent otitis media with chronic otorrhoea
- Recurrent otitis media with other respiratory infections
- Family History

FBC
Immunoglobulins (Ig G, Ig A, Ig M)
Specific Antibody responses (Pneumo, Hib, Tet)
The Immune system is NOT there;

- To baffle medical students
- To keep Immunologists in a job
- To encourage experiments on mice
The Immune system IS there as a defence against infection.

If you think it is not working SEEK ADVICE