# Table of Contents

## Immunology

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunology</td>
<td>1</td>
</tr>
<tr>
<td>Immunity</td>
<td>2</td>
</tr>
<tr>
<td>Innate Immunity</td>
<td>2</td>
</tr>
<tr>
<td>- Soluble Factors of Innate Immune System</td>
<td>2</td>
</tr>
<tr>
<td>- Cellular Factors of Innate Immune System</td>
<td>3</td>
</tr>
<tr>
<td>Complement</td>
<td>4</td>
</tr>
<tr>
<td>Adaptive Immunity</td>
<td>6</td>
</tr>
<tr>
<td>- Subclassification of Adaptive Immunity</td>
<td>6</td>
</tr>
<tr>
<td>- B lymphocytes</td>
<td>6</td>
</tr>
<tr>
<td>- T lymphocytes</td>
<td>7</td>
</tr>
<tr>
<td>- Soluble Factors of Adaptive System</td>
<td>8</td>
</tr>
<tr>
<td>- Immunoglobulins (Ig)</td>
<td>8</td>
</tr>
<tr>
<td>- Tumor Necrosis Factor (TNF-α)</td>
<td>10</td>
</tr>
<tr>
<td>- Cytokines</td>
<td>10</td>
</tr>
<tr>
<td>- Interferons</td>
<td>11</td>
</tr>
<tr>
<td>- Cellular Factors of Adaptive System</td>
<td>11</td>
</tr>
<tr>
<td>- Macrophages</td>
<td>11</td>
</tr>
<tr>
<td>- T-Lymphocytes</td>
<td>12</td>
</tr>
<tr>
<td>- B Lymphocytes</td>
<td>12</td>
</tr>
<tr>
<td>- Dendritic Cells</td>
<td>12</td>
</tr>
<tr>
<td>Overview of Immune Response</td>
<td>12</td>
</tr>
<tr>
<td>- Factors Determining Immune Response</td>
<td>12</td>
</tr>
<tr>
<td>- Primary Response</td>
<td>13</td>
</tr>
<tr>
<td>- Secondary Response</td>
<td>13</td>
</tr>
<tr>
<td>- Tolerance</td>
<td>13</td>
</tr>
<tr>
<td>Anaesthesia on Immune Functions</td>
<td>13</td>
</tr>
<tr>
<td>Histocompatibility Molecules</td>
<td>13</td>
</tr>
<tr>
<td>Systemic Inflammatory Response Syndrome</td>
<td>14</td>
</tr>
<tr>
<td>- Definitions</td>
<td>14</td>
</tr>
<tr>
<td>- Causes</td>
<td>14</td>
</tr>
<tr>
<td>- Pathophysiology</td>
<td>15</td>
</tr>
<tr>
<td>Hypersensitivity Reactions</td>
<td>17</td>
</tr>
<tr>
<td>- Classifications</td>
<td>17</td>
</tr>
<tr>
<td>- Type I (immediate) Hypersensitivity</td>
<td>18</td>
</tr>
<tr>
<td>- Type II (Antibody Mediated) Hypersensitivity</td>
<td>21</td>
</tr>
<tr>
<td>- Type III (Immune Complex-Mediated) Hypersensitivity</td>
<td>22</td>
</tr>
<tr>
<td>- Type IV (cell mediated) Hypersensitivity</td>
<td>23</td>
</tr>
<tr>
<td>- Delayed Type Hypersensitivity</td>
<td>24</td>
</tr>
<tr>
<td>- T Cell Mediated Cytotoxicity</td>
<td>25</td>
</tr>
<tr>
<td>Transplant Rejection</td>
<td>26</td>
</tr>
<tr>
<td>- Recognising Allografts – (Sensitisation Phase)</td>
<td>26</td>
</tr>
<tr>
<td>- Graft Destruction Phase</td>
<td>27</td>
</tr>
<tr>
<td>- Types of Rejection</td>
<td>27</td>
</tr>
<tr>
<td>- Transplant Haematopoietic Cells</td>
<td>28</td>
</tr>
</tbody>
</table>

By Adam Hollingworth
**Immunity**

- **Innate** =
  - mechanisms present & already synthesised prior to infection
  - physical, biochemical & cellular factors (limited)
  - static resistance, no memory
    - specifically good at working against microbes

- **Adaptive (aka acquired):**
  - microbes stimulate mechanisms which are capable of recognising non-microbial substances eg antigens
  - more powerful, 2nd line defense
  - memory, with subsequent enhanced response
  - immune response refers to adaptive

**Innate Immunity**

- 1st line defence
- main components:
  - Physical defences:
    - epithelial barriers
    - commensural flora, gastric fluid acidity, fever, lung surfactant
  - biochemical defences:
    - soluble factors:
      - lysosomes
      - acute phase reactants eg CRP
      - complement
      - fibronectin
      - interferon
    - cellular:
      - phagocytic cells eg neutrophil & MPs
      - NK (natural killer) cells

**Soluble Factors of Innate Immune System**

1. **Lysozymes**
   - Distributed widely in many secretions
   - Act by cleaving bacterial cell wall proteoglycans

2. **Fibronectin**
   - Family of closely related glycoproteins
   - Synthesised by endothelial cells & fibroblasts
   - Actions:
     - Non specific opsonisation
     - Facilitation of phagocytosis
     - Wound healing & tissue repair
   - Levels ↓ed by: major burns, surgery, trauma, DIC

3. **Complement**
   - see separate section below

4. **Interferons**
   - From virally infected cells & malignant cells
   - Transmit information to adjacent cells
   - Activate NK cells ⇒ ↑cytotoxic action
5. Acute Phase Reactants

• Eg CRP:
  o Recognises & binds wide variety of bacteria & fungi
  o Acts as an opsonin ie ↑phagocytosis & complements action

Cellular Factors of Innate System

Natural Killer Cells

• ≈10-15% blood lymphocytes
• non thymic
• aka large granular lymphocytes
• don’t have TLRs (no antigenic surface markers of T/B cells)
• part of innate immune system – but are regulated by T cells . also role in adaptive immunity
• Different cytokines/interferons regulate NK cells – proliferate or kill
• role to kill with no presensitisation:
  o tumour cells
  o virally infected cells
  o some normal cells
• activity mediated by balance of activating & inhibitory receptors:
  o inhibition by recognition of self class I MHC molecules
  o killer inhibitory receptors
• all nucleated normal cells express class I MHC
  o virally infected cells ↓s expression of class I MHC ⇒ NK cell lysis (in conjunction with activating receptors
• NKs also secrete cytokines:
  o IFN-γ ⇒
    ▪ activate macrophage
    ▪ differentiate CD4+ cells ⇒ T_{H1} cells
  o TNF
  o Granulocyte macrophage colong stim factor (GM-CSF)

Neutrophils

• 80-90% of circulating polymorphs
• contain: lysozymes, phagosomes, ingested organisms, phagolysozomes
• are able to penetrate endothelial surface under influence of chemotactic factors

Eosinophils

• can phagocytose
• can degranulate adjacent large foreign bodies (which too large for phagocytosis) eg worms
• attracted by eosinophil chemotactic factor
• attach to Ig’s & foreign particles
• release:
  o major basic protein
  o eosinophil cationic protein
  o anti-inflam enzymes
• may have role in immune down regulation

Basophils & Mast Cells

• limited no in circulation
• predominantly assoc with epithelial cells esp mast cells
• may play role in immunity to parasitic infections ie ↑ed response

Phagocytes

• Phagocytes recruited to site of infection ⇒ inflam
• Phagocytes recognise microbes by receptors for:
  o mannose residues
  o not produced by host cells

Immunology - 3

By Adam Hollingworth
N-formyl methionine containing peptides
- Toll like receptors

Examples of cells:
- Macrophages in alveolar, splenic, lymph node, kidney
- Blood monocytes
- Brain microglia
- Hepatic Kupffer cells
- Synovial A cells

## Complement

- Series ~25 plasma proteins made in liver
- Present as inactive forms C1-C9
- Activated to become proteases that cleave each other in an amplifying cascade
- Key step = activation of C3
- C3 & C5 are most important mediators
  \[ \text{can also be activated by proteolytic enzymes within exudate eg plasmin & lysosomal enzyme from neutrophils} \]

### Activation

- Pathways to activate C3:
  - Classical:
    - Antibody-antigen interaction (IgG & IgM)
    - Part of adaptive immune system
    - C1 fixes to antigen-antibody complexes ➔ C3 convertase
  - Alternative:
    - Triggered by
      - Microbial surface molecules (eg endotoxin) &
      - Complex polysaccharides
    - Part of innate system
  - Lectin:
    - Plasma mannose binding lectin binds to microbe carbohydrate ➔ activates C1
    - Innate system

### Effector Functions

- Cell lysis of bacteria (MAC):
  - C5b binds components of C6-9 ➔ membrane attack complex (MAC)
- Inflammatory functions (C3a, C5a):
  - Degranulation of mast cells ➔ histamine release ➔ VD & ↑permeability
  - Neutrophil aggregation
  - Stim arachidonate metabolism
  - Chemotaxis
- Opsonisation (C3b): opsonin = binding enhancer for phagocytosis ➔ ↑phagocytosis

### Regulation

- Complement activation regulated by
  - Cell associated proteins eg DAF (decay accelerating factor)
    - Defect ➔ paroxysmal nocturnal haemoglobinuria (=rbc lysis & anaemia)
  - Circulating proteins eg C1 inhibitor
    - Deficiency ➔ hereditary angioneurotic oedema (=episodic oedema)
Adaptive Immunity

- 2\textsuperscript{nd} line
- activated once innate system penetrated or overwhelmed
- specific against infective agent
- predominant mediated by lymphocytes & their products eg antibodies
- lymphocyte receptors much more diverse than innate immunity
  \(\Rightarrow \): capable recognising many foreign substances
- has soluble & cellular factors

Subclassification of Adaptive immunity

- 2 main subclassifications:
  - cell mediated (cellular) –
    - T (thymus derived) lymphocytes
    - Ig’s play a minor role
    - Impt in host defence against:
      - TB, fungi, protozoans
      - Viruses, intracellular organisms
      - Tumour cells, allografts
  - humoral –
    - defense of extracellular microbes & toxins
    - B (bone marrow) lymphocytes and their secreted antibodies

\begin{figure}
\centering
\includegraphics[width=\textwidth]{immunology_diagram.png}
\caption{Diagram of the adaptive immune system showing B lymphocytes, CD4+ helper T lymphocytes, and CD8+ cytotoxic T lymphocytes.}
\end{figure}

B lymphocytes

- Found:
  - Blood – ~10% circulating lymphocyte popn
~50% splenic lymphocyte popn
also seen other lymphoid tissue ie nodes, tonsils
~75% bone marrow lymphocyte popn
• differentiate in 3rd trimester in utero + neonatal period
• Recognise antigen via B-cell antigen receptor complex
  made by IgM & IgD present on B cell surface
• Other surface molecules essential for function:
  o Fc receptors
  o CD40
  o Complement component - CD21
  also EBV receptor ∴ EBV infects B cells
• Each B cell complex has unique antigen specificity

B cell Activation
• 2 methods of activation:
  o thymus independent ⇒ IgM only
  o thymus dependant:
    ▪ Require help from CD4+ T cells
    ▪ CD4+ binds CD40 on B cell
    ▪ Capable of producing all types of Ig
• Different cytokines stim B cells to clonally expand & differentiate (activate):
  o Plasma cells
  o Memory cells
• Plasma cells =
  o Specific antibody secreting cells eg IgG, IgA, IgE ie 1 class only
  o May reside in
    ▪ lymphoid organs
    ▪ mucosal tissues
    ▪ bone marrow – may live many years
• Memory cells:
  o Can become plasma cells with a repeat challenge
    ▪ Ig-Fab portion attaching specific antigen
    ▪ Ag presented + pre-processed by macrophages
    ▪ Modulatory signals from other cells esp T4 cells
• Antibodies mobilise to area of foreign material

T Lymphocytes
• Originate in bone marrow ⇒ migrate to thymus late in utero/early neonatal
• Maturation regulated by thymopoietin
• = main effectors of cell mediated immunity
• Mature, naïve T cells found:
  o circulating – 70-80% of lymphocytes = T lymphocytes
  o T cell zones eg
    ▪ Lymphatics ~90% lymphocytes in ductus thoracicus
    ▪ Deep cortical areas of lymph nodes
    ▪ periarteriolar white matter of spleen
• each T cell genetically programmed to recognise specific cell bound antigen
  by a Tcell receptor (TCR)
• antigen presenting cell (APC):
  o processes antigens on infected cells
  o presents antigen to T lymphocyte TCRs
  by major histocompatibility complex (MHC) molecules
• T cells cannot be activated by soluble antigens.
  ↩ Need antigen to be presented by MHC on APC
• TCRs are capable of recognising many antigens
  ↩ BUT MOSTLY T cell expresses one type of TCR
• Variety in TCRs occur in thymus from germ line from embryo
  ↩ lymphoid malignancies classified into polyclonal (non neoplastic) & monoclonal (neoplastic)

T cell proliferations

CD Molecules
• = accessory molecules
• co-receptors in T cell activation
• CD4 molecules ⇒ class II MHC
• CD8 ⇒ class I MHC

T cell Activation
• T cells need 2 signals to activate:
  o 1 = TCR, antigen-MHC, & CD4/8 binding
  o 2= CD28-T cell binding
• T cell activation ⇒ secrete local cytokines eg IL2
• IL2 ⇒ proliferation of T cell numbers
• Differentiation of activated T cells:
  o Effector cells
  o Memory cells

T Cell Effector Cells
• Examples & function:
  o CD4+ (65% in circ):
    ▪ Orchestrator of cellular immunity via cytokine release
    ▪ Sub category:
      • T\textsubscript{H}1 = Synthesises IL2 & IFN-y which:
        o Facilitate delayed hypersensitivity
        o MP activation
        o Opsonising & complement ficed antibodies
      • T\textsubscript{H}2 = synthesises IL4, IL5, IL13 which involved in:
        o IgE synthesis
        o Activation of eosinophils
      • MHC class II ONLY
  o CD8+ (25% in circ):
    ▪ Cytotoxic cells
    ▪ Secrete cytokines
    ▪ Virus killins
    ▪ MHC Class I ONLY

Soluble Factors of Adaptive System
• Immunoglobulins
• Cytokines
• TNF
• Interferons

Immunoglobulins (Ig)
• Main action is antigen recognition ⇒ outcome determination
• Different regions on Ig structure:
  o Fraction antigen binding (Fab) =
    ▪ highly variable area between diff Ig’s
- determines specificity
  - fraction crystalline (Fc) =
    - determines what occurs once Ig-Ag interaction has occurred

**Types of Igs**

- **IgG (76%)**:
  - Most abundant & broadest role
  - 4 subclasses:
    - IgG1 + IgG3 ⇒ *activate complement*
    - IgG2 + IgG4 ⇒ are Ig receptors on macrophages / phagocytes
  - Can cross placenta –
    - Deliver immunity for neonate
    - Rh incompatibility
- **IgA (16%)**:
  - Main Ig in secretions eg resp, GIT, urinary tract, saliva, colostrums
  - Monomer in serum, dimmer in secretions (joined by J chain)
  - Storage:
    - taken up by epithelial cells
    - secretory piece added ↳ resistant to enzyme degradation
  - congen IgA deficiency
    - ~1:900.
    - More common in Caucasians
    - Resp infections more common
  - Plasma expression of anti-IgA ~20-60%
- **IgM (7%)**
  - Occurs mainly in circulating volume
  - Part of early immune response ie IgM ⇒ then IgG after
  - IgM = thymus independent antibodies
    - all other Ig types = thymus dependant
  - = a pentamer. Capable of forming spont pentamers
  - ~10% circulating Ig
  - major class of Antibody involved in ABO, Rh, cold agglutinins
- **IgD**:
  - Mainly IV on surface of resting B cells with IgM
  - Impt in B cell antigen binding & activation to plasma cells
- **IgE (1%)**: 

![Diagram](image)

Fab = Antigen binding
Fc = effect site ie MP & complement binding
o Hypersensitivity role eg type I: mast cells via Fc fragment
o Antigen must cross link 2 IgE’s to start degranulation

Tumor Necrosis Factor (TNF-α)
- Aka cachectin
- = macrophage produced polypeptide hormone
- effects:
  o IL-1 release from monocytes & endothelial cells
  o Fever inducing via direct effects on hypothalamus
  o Enhances granulocyte adhesions & phagocytosis
  o Directly toxic to endothelial cells ⇒ DIC, ARDS, ARF, gut ischaemia
- Most potent stimulant to ↑TNFα = endotoxin
- Related TNF-β produced by T lymphocytes following specific antigen challenge

Cytokines
- = hormone like chemical messengers which affect immune response ie immunoregulatory
- Many cytokines produced by many cell types eg lymphocytes, monocytes, macrophages, glial cells, neurons
- Cytokine secreted by lymphocyte = lymphokine
- Cytokine = generic name; once aa sequence known they are called interleukins
- IL1-10 = lymphokines & monokines which influence other lymphocytes
- React with specific cell surface receptors & are active at low concentrations
- Any cytokine can act on many cell types and mediate many different actions
- Methods of effect:
  o Autocrine – acts on self
    - eg IL2 from antigen stimulated T cell stims growth of same cell
  o Paracrine – acts on cells close by
    - eg IL7 from bone marrow promotes maturation of B cell progenitors
  o Endocrine – acts on systemic cells
    - eg IL1 & TNF ⇒ acute phase response
- Functional classes:
  o Mediate innate immunity – eg IL-1, TNF
  o Regulate lymphocyte growth, activation & differentiation – eg
    - IL2 – growth factor T cells
    - IL4 – stim CD4+ ⇒ T_{H2} pathway,
    - IL12 – stim CD4+ ⇒ T_{H1} pathway
    - IL15 – growth & activity NK cells
  o Activate inflam cells eg
    - IFN-y – activate MPs
    - IL5 – activated eosinophils
    - TNF
  o Chemokines:
    - CC – from T cells
    - CXC – from MPs
  o Stim haematopoesis:
    - Colony stimulating factors eg GM-CSF & G-CSF
      - act on committed progenitor cells

IL1
- Polypeptide produced by monocytes + tissue macrophages
- Cause wide variety of inflam stimuli:
o Fever
o ↑skeletal mm catabolism
o slow wave sleep
o bone marrow release of neutrophils
o T cell + neutrophil chemotaxis
o CD4+ mediated production of IL-2
o B cell proliferation & Antibody production
o ↑hepatic production of acute phase reactants
o ↓production of albumin, prealbumin & transferrin

**IL2**
- polypeptide growth factor
- stim prolif of:
  - activated B cell
  - T cells
  - NK cells

**Interferons**
- Interferons – little use clinically in management of viral infections except:
  - α interferon –
    - chronic hep B &C
    - cytotoxic agent in hairy cell leukaemia, CML, HIV
  - γ interferon – in wound sepsis
- α interferon:
  - >17 subtypes
  - secreted by blood mononuclear cells
  - effects:
    - antiviral effects
    - induction of class 1 MHC on all somatic cells
    - activation of MPs & NK cells
- β interferon:
  - secreted by fibroblasts + epithelial cells
  - similar function to α interferon
- γ interferon:
  - secreted by lymphoid cells
  - effects as α & β but also:
    - class 2 MHC expression
    - ↑cell mediated immunity

**Cellular Factors of Adaptive System**

**Macrophages**
- Role in inducing immune system
  - MPs phagocytose microbe
  - process & present antigens to T cells – an APC
  - opsonise
- imp effector cells eg in delayed hypersensitivity reaction:
  - MPs activated by cytokines ⇒ ↑microbicidal properties ⇒ ↑killing tumor cells
    - eg IFN-γ from CD4+ cells
- (Also imp effectors in humoral immunity:
  - Opsonisation of microbe by IgG or C3b ⇒ phagocytosis)
T-Lymphocytes
• See prev
• Principle effector cell

B Lymphocytes
• See above
• Cellular components with soluble product

Dendritic Cells
• 2types:
  o dendritic cells:
    • Important in initiating primary immune responses
    • Key role in antigen presentation because:
      o Located at site of microbe entry eg epithelium
      ▲Langerhans cells =immature dendritic in epidermis
      o Express cellular immunity receptors eg TLRs, mannose receptors
      o have same chemokine receptor as T cells – drawn to Tcell zones
      o high levels of MHC II molecules
      ▲all mechanisms required to present antigen to & activate CD4+
      o follicular dendritic cells
        ▪ Fc – IgG, and C3b receptors
        ▪ Present antigens to B cells

Overview of Immune Response
• Immunogen = something which initiates an immune response
• Immunogenicity = ability to produce an immune response
• Antigen = substance reacting with either available antibodies or sensitised lymphocytes
• Hapten = smaller molecules (<1kD mw) which cannot induce an immune response by themselves but can do if combined with a carrier molecule

Factors Determining Immune Response
• Route of entry
• Dose – v high or low levels may induce tolerance
• Genetic factors:
  o Response to given immunogen
  o MHC gene locus
  o Genes code for initiation, stimulation, suppression
• Cell cooperation:
  o Thymus dependant/independent immunogen
• Other factors:
  o Foreign surfaces
  o Coexisting infection or disease of immune system
  o Fever
  o Nutritional status of host
  o Immunomodulatory agents administered to host
Primary Response

- Thymus dependant:
  - IgM – 1st to appear – peak at 2 weeks
  - Then switch IgM ⇒ IgG/IgA/IgE
  - Requires T cell cooperation
- Thymus independent:
  - IgM only Antibody to appear

Secondary Response

- Occurs within 4-5 days
- Marked proliferation of antibodies & effector T cells
- Antibody is usually IgG – more specific
- Requires immunological memory in both T & B cells
  - ie prev exposure to same pathogen

Tolerance

- = physiological process producing immunological unresponsiveness to an immunogenic substance
- need to inhibit adaptive immune system (humoral & cell mediated)
- depends on both dose & presentation:
  - high dose produces tolerance in T & B cells
  - low dose produces tolerance in T cells only
- requires repeat exposure
- easier to produce in neonate than adult

Anaesthesia on Immune Functions

- anaesthesia causes reversible depression of immune function
- features:
  - physico-chemical barriers impaired during & after anaesthesia
  - ↓ tracheal ciliary activity
  - depression of phagocytosis – proportional to degree of surg stress
  - ↓ ed adaptive immunity post op:
    - surg stress response ⇒ ↑ cortisol ⇒ depressed lymphocyte function
  - ↓ T lymphocyte numbers & ↓ activity
  - NK cells – biphasic response:
    - Initial rapid ↑ numbers by recruitment from extravascular space, lymph nodes & spleen
    - Post op: ↓ ed activity due to supressor monocytes

Histocompatibility Molecules

- Primary function of cell surface histocompatibility molecules is to bind peptide fragments of foreign proteins and present them to antigen specific T cells
- In Humans most impt ones on chromosome 6
  - = MHC or human leukocyte antigen (HLA) complex
- In humans the major histocompatibility antigens = HLA’s
- HLA’s are found on surface of all nucleated cells
- Each human inherits one set of alleles of MHC gene
- MHC class 1 & II = cell surface glycoprotein involved in antigen presentation
• MHC Class III = encode components of complement system

MHC class 1
• Found on all nucleated cells & platelets
• Encoded by HLA-1, HLA-B, HLA-C
• Bind peptides derived from proteins eg viral antigens
• CD8+ interactions only
  ➣ class restricted to MHC I
  ➣ imp action is virus killing :: good that MHC I expression is so widespread

MHC Class 2
• Restricted to antigen presenting cells eg MPs, dendritic cells, B cells
  ➣ although IFN-γ ⇒ expression of MHC II on endothelial cells & fibroblasts
• Coded in region HLA-D
• In general MHC II present exogenous antigen. These first:
  o process in endosome or lysosome
  o class II molecules assembled in ER
  o peptides from proteolytic cleavage assoc with class II molecules
  o peptide – MHC complex associate and transport to cell surface
• CD4+ interactions only

Recognising Self
• Self MHC molecules = those that grew up with during maturation in thymus
• In thymus: Only T cells that can recognise self-MHC are allowed to move to periphery
  ➣ ∴ type MHC molecules T cell encounters during development influences reactivity in periphery

HLA & Diseases
• Diseases assoc with HLA locus
• Eg anky spondylitis – people with HLA-B27 have x90↑ chance of getting disease
• Categories:
  o Inflam diseases – B27 eg anky spond, postgonococcal arthritis, acute anterior uveitis
  o Inherited errors of metabolism – hereditary haemochromatosis HLA-A
  o Autoimmune – auoimmune endocrinopathies eg RA, DM, sjogren HLA – DR locus

Systemic Inflammatory Response Syndrome

Definitions
• SIRS - at least 2 of the following:
  o temp <36 or >38
  o HR >90
  o RR >20 or PaCO2 <32 or IPPV
  o WCC <4 or >12 or >10% immature bands
• sepsis = SIRS + confirmed or presumed infection
• Severe Sepsis =
  o Sepsis + organ hypoperfusion or dysfunction
• Septic Shock=
  o Sepsis with:
    o refractory hypotension (SBP <90mmHg or MAP <70mmHg) or
    o vasopressor dependancy after adequate volume resuscitation

Causes
• non specific:
ischaemia
inflammation
trauma incl massive transfusion
infection
insults combined

Pathophysiology

- generally has same pathophysiological properties with minor differences depending on causing factor
- many consider it a self defence mechanism
- complex process involving inflammation cascade involving:
  - humoral & cellular responses
  - complement
  - cytokine cascade
- Classification into stages by Bone:
  - stage 1:
    - local cytokine production ⇒ initiate inflam reaction
    - promotes wound repair & recruitment of reticular endothelial system (RES)
  - stage 2:
    - local cytokines released into systemic circulation – with goal to improve local response
    - macrophages & platelets recruited
    - acute phase response generally controlled by:
      - ↓ proinflam mediators
      - ↑ endogenous antagonists
        ⇒ goal = homeostasis
  - stage 3:
    - failure of homeostasis ⇒ significant systemic reaction
    - cytokine action flips to destruction (rather than protection) ⇒
      - activation of humoral cascades
      - activation of RES
        ⇒ loss of circulatory integrity ⇒ end organ dysfunction
- Multihit theory:
  - further explains progression SIRS ⇒ MODS
  - SIRS cascade = primer
  - each additional event ⇒ exaggerated response ⇒ progressive illness
    ⇒ must identify cause of SIRS & resuscitate in order to prevent downward spiral
- inflam cascade:
  - if sepsis – usually initiated by endotoxin or exotoxin
  - cytokine producers: tissue macrophages, monocytes, mast cells, platelets, endothelial cells
  - key cytokines = TNF-α & IL-1 ⇒ cleavage of nuclear factor-kβ inhibitor ⇒ ↑↑NF-kβ levels
  - NF-Kβ initiates production of mRNA which induces other proinflam cytokines esp IL6 & IL8
  - IL1 & TNFα cause:
    - fever
    - release of stress hormones
      - ↑ expression of endothelial tissue factor ⇒ coagulation ⇒ +/- DIC
  - IL6 cause release of acute phase reactants:
    - CRP
    - procalcitonin
  - proinflam ILs generally ⇒
    - act directly on tissue
    - cause 2nd mediators to:
      - activate coag cascade
      - complement cascade
• release of nitric oxide, PAF, prostaglandins, leukotrienes
# Hypersensitivity Reactions

## Classifications

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Immune Mechanism</th>
<th>Pathologic Lesions</th>
<th>Disease types</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type I</strong></td>
<td>• IgE antibody⇒basophil &amp; mast cell degranulation</td>
<td>• vasoD</td>
<td>• anaphylaxis</td>
</tr>
<tr>
<td>• immediate hypersensitivity</td>
<td>• Histamine</td>
<td>• bronchoconstriction</td>
<td>• atopy</td>
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<tr>
<td>• IgE mediated</td>
<td>• Recruitment of other inflam cells</td>
<td>• mucus production</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• tissue injury</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Hypersensitivity Reactions</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Type II</strong></td>
<td>• direct phagocytosis or cell lysis</td>
<td>• phagocytosis &amp; lysis of cells</td>
<td>• blood transfusions</td>
</tr>
<tr>
<td>• cell cytotoxicity</td>
<td>• activation of complement</td>
<td>• inflam (some diseases)</td>
<td>• Goodpasteur's synd.</td>
</tr>
<tr>
<td>• Antibody (IgG, IgM) mediated</td>
<td>• recruitment of leukocytes</td>
<td>• functional rearrangement without cell or tissue injury</td>
<td>• autoimmune cytopaenias</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Hypersensitivity Reactions</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Type III</strong></td>
<td>• tissue deposition of Ag-Ab complexes⇒accumulation of PMN's, macrophages &amp; complement⇒release of enzymes &amp; toxic molecules</td>
<td>• inflam</td>
<td>• SLE</td>
</tr>
<tr>
<td>• immune complex</td>
<td></td>
<td>• necrotising vasculitis (fibrinoid necosis)</td>
<td>• serum sickness</td>
</tr>
<tr>
<td>• IgG, IgM, IgA mediated</td>
<td></td>
<td></td>
<td>• arthus reaction</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• necrotising vasculitis</td>
</tr>
<tr>
<td><strong>Type IV</strong></td>
<td>• T-cell induced mononuclear cell accumulation</td>
<td>• perivascular cellular infiltration</td>
<td>• TB, sarcoid</td>
</tr>
<tr>
<td>• delayed hypersensitivity</td>
<td>• release of lymphokines &amp; monokines</td>
<td>• oedema</td>
<td>• Type I DM</td>
</tr>
<tr>
<td>• T-cell mediated</td>
<td>• often with granuloma formation</td>
<td>• granuloma formation</td>
<td>• RA, IBD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• cell destruction</td>
<td>• MS</td>
</tr>
</tbody>
</table>
Type I (immediate) Hypersensitivity

Eg anaphylaxis

- Immune response releases
  - vasoactive & spasmonogenic substances
  - cytokines
  - Act on vessels, smooth mm and recruit inflam cells

- Features:
  - IgE mediated - which are directed against specific antigens (allergens)
  - eosinophils
  - CD4+ helper T cells
  - Th2 cells
  - IgE B cells
  - Mast cells – already present in all tissues
  - Basophils – similar to mast cells APART only found in circulating blood

IgE Synthesis & Mechanism of Action [sensitisation]

- Dendritic cell present antigen to naïve CD4+ cell
- CD4+ differentiate into Th2 cell
- Cytokine release:
  - IL4 ⇒
    - ↑IgE synthesis from IgE B cells
    - sustain development of Th2 cells
  - IL3, IL5 & GM-CSF ⇒ ↑production & survival of eosinophils
  - IL13 ⇒
    - ↑IgE production
    - ↑mucus secretion epithelial cells

- IgE produced by B cells
- IgE bound to mast cells & basophils via Fc receptor

Mast Cell (Basophil) Degranulation

- re-exposure ⇒
  - allergen bind & cross link 2 IgE on mast cell/basophil ⇒
    - calcium enters mast cell
    - degranulation of preformed vesicles containing primary mediators
    - synthesis & release of secondary mediators

- other causes of mast cell/basophil degranulation:
  - complement C3a, C5a (anaphylatoxins)
  - drugs eg codeine, morphine, adenosine
  - mellitin (bee venom)
  - sunlight
  - trauma
• Heat/cold

2 phases of Response seen:
• Initial rapid
• Second delayed response

Primary rapid response
• 5-30 mins of allergen exposure
• Resolution within 30 mins
• Mediators which induce response:
  o Biogenic amines eg histamine, heparin, 5-HT, PAF, anaphylactoxin:
    ▪ Bronchial smooth mm contraction
    ▪ Vasc permeability & VD
    ▪ Mucuous gland secretion
  o Chemotactic mediators eg
    ▪ Eosinophil chemotactic factors AND
    ▪ Neutrophil chemotactic factors
  o Enzymes in granule matrix eg chymase, tryptase ⇒
    ▪ Kinins
    ▪ Activate complement
  o Proteoglycans eg heparin

Second Delayed Response
• 2-24 hours after allergen exposure
• Can last for days
• Intense inflam cell infiltration ⇒ tissue damage – typically mucosal epithelial cell damage
  ▲ eg Eosinophils, neutrophils, Basophil, monocytes & CD4+ T cells
• Driven by activated mast cell release of:
  o Lipid mediators:
    ▪ Leukotriene B4 = highly chemotactic for neutrophils, monocyte & eosinophils
    ▪ Leukotriene C4, D4, E4:
      ▪ x1000 more potent than histamine at vasc perm & bronchial smooth mm constriction
    ▪ Prostaglandin D2: histamine like response
    ▪ Platelet activating factor:
      ▪ Platelet aggregation
      ▪ Histamine release & effects
      ▪ Proinflammatory eg chemoattraction & degranulation of neutrophils
  o Cytokine mediators:
    ▪ TNF-α:
      ▪ Recruits many additional inflam cells which release further cytokines
      ▪ Activates epithelial cells ⇒ secrete chemokines eg eotaxin & RANTES
        ▲ Recruit eosinophils
    ▪ IL1, IL3, IL4, IL5, IL6
    ▪ GM-CSF
    ▪ Chemokines
• Eosinophils ONLY impt in delayed response – they release:
  o Major basic protein
  o Eosinophil cationic protein
  ▪ Tissue damage to epithelial cells
• Large positive feedback loop eg
  o Eosinophils & activated leukocytes also produce leukotriene C4 & PAF ⇒ ed mast cell degranulation
Atopy
- susceptibility to type I response to genetically determined
- Atopic people have:
  - Higher serum IgE level
  - More IL4 producing T_{H2} cells
- Cause not fully understood
- Genes suggested
  - 5q31 – codes for many ILs & GM-CSF
  - 6p – close to HLA complex

Anaphylaxis
- symptom complex which follows exposure of a sensitised person to an antigen
- symptoms result of type 1 reaction assoc with IgE mediated mast cell degranulation
  - need to have seen antigen before to create antigen specific IgE which has then attached to mast cells + basophils
- full blown reaction with any dose
  - anaphylactoid reaction = more dose dependant
- exposure ⇒ mast cell & basophil degran ⇒ release
  - histamine, kinins, serotonin, PAF heparin
  - activatin of phospholipase A ⇒ PGs, leukotrites, PAF
- 5 grades clinical classification:
  - 1) cutaneous
  - 2) above + hypotension, tachycardia, bronchospasm
  - 3) above but more severe eg CVS collapse
  - 4) cardiac +/- resp arrest
  - 5) death

Anaphylactoid Reactions
- pathology:
  - exposure + combination of antigen with IgG, IgM +/- Hapten
  - does not require Ig cross linkage
  - activation of complement – classical & alterative pathways
  - formation of anaphylatoxins, C3a & C5a
  - ⇒ mast cell + basophil degranulation
- does not require prior exposure to causative agent
- usually less severe than anaphylaxis but may be indistinguishable

Local Immediate Hypersensitivity Reactions
- atopic allergens
- = hereditary response affecting 10% popn
- maps to 5q31 gene (where many T_{H2} type cytokines are located)
- type I response to inhaled/ingested allergens
- symptoms eg urticaria, angioedema, rhinitis, asthma
Type II (Antibody Mediated) Hypersensitivity

- mediated by antibodies against intrinsic & extrinsic antigens:
  - absorbed on cell surface
  - extracellular matrix
- then follow 3 pathways:
  - opsonization killing & phagocytosis
  - complement & Fc receptor mediated inflammation
  - antibody mediated cellular dysfunction

Opsonization killing & Phagocytosis
- mediated by:
  - opsonisation & complement:
    - directly lysed via C5-C9 complement membrane attack complex (MAC) OR
    - opsonised for phagocytosis by:
      - antibodies
      - C3b fragments
  - Fc receptor mediated phagocytosis
- Antibody dependent cell mediated cytotoxicity (ADCC):
  - Low concentrations of bound IgG/IgE to foreign cell ⇒ attract non sensitized cells with Fc receptor ⇒ cell lysis without phagocytosis
  - Cells capable of ADCC eg NK cells, MPs, eosinophils
- Clinically occur in
  - Transfusion reactions – host preformed antibodies opsonise foreign cells
  - Erythroblastosis foetalis – IgG crosses placenta ⇒ destruction fetal rbcs
  - Autoimmune haemolytic anaemia – antibody to own blood cells
  - Drug reactions – antibody produced which react with drug

Complement & Fc receptor mediated inflammation
- Antibodies deposited in ECM ⇒ complement activation ⇒ recruitment of non specific inflam cells

- Activated inflam cells release:
  - Proteases
  - ROS
    -⇒ tissue damage

- Damage via complement & Fc interactions
- Clinically:
  - Glomerulonephritis
  - Vascular rejection in organ grafts

Antibody Mediated Cellular Dysfunction
- Certain antibodies can wrongly activate or block normal cell or hormonal functions
  - Eg - antibody stimulates TSH receptor without hormone eg Graves disease
    - antibody inhibits binding of ACh neurotransmitter eg myasthenia gravis
Type III (Immune Complex-Mediated) Hypersensitivity

- Antigen-antibody complexes (= immune complexes) form in circulation or at site of antigen deposition
  - complexes also formed in norm immune response.
  - whether pathological process will develop is not fully understood
- Antigens can be exogenous or endogenous
- Immune complex mediated disease can be systemic or local

**Systemic Immune Complex Disease**
- Circulating immune complexes which systemically deposited
- Eg acute serum sickness:
  - 3 phases to reactions:
    - formation immune complex- takes 7 days
    - deposition of complex in tissues
    - inflam reaction at sites of deposition @approx 10days
  - Caused by administration large amounts foreign material ie too much antigen for RES system to remove
  - New antibodies synthesized which complex with antigen ⇒ circulating complexes
    - takes about a week
  - Small antigen complexes (↑antigen:antibody) circulate:
    - Live for long time as low affinity for mononuclear phagocytes ↓. not cleared well
    - Prone to deposition with capillary/arteriolar wall ⇒ vasculitis
    - enhanced as small complex also binds to Fc or C3b receptors ⇒ recruit inflam cells ⇒ release vasoactive mediators ie cytokines
  - Eg affected tissues:
    - Renal glomeruli ⇒ GN
    - Joints
    - Skin
    - Heart
    - Serosal surfaces
  - As antibody production increases: small complex ⇒ large complex (↑antibody:antigen):
    - ↑affinity to phagocyte binding ⇒ end process
  - deposition of immune complexes activates
    - neutrophils & MPs via Fc receptor
    - complement cascade
  - immune complexes also
aggregate platelets $\Rightarrow$ degranulation
activate factor XII $\Rightarrow$ coag cascade

- Morphology:
  - acute necrotising vasculitis predominates:
    - fibrinoid deposition within vessel walls
    - neutrophil infiltration with surrounding haemorrhage & oedema

Local Immune Complex Disease (Arthus Reaction)
- localised tissue vasculitis & necrosis
- occurs instead of systemic reaction because of:
  - formation & deposition of immune complexes is localised eg
    - intracutaneous antigen injection in previously sensitised hosts
    - diff to type I response as takes $>4$hrs lesion develop
    - oedema $\Rightarrow$ haemorrhage $\Rightarrow$ ulceration
  - relevant antigen is planted/deposited within particular tissue eg renal glomerulus

<table>
<thead>
<tr>
<th>Disease</th>
<th>Antigen Involved</th>
<th>Clinicopathologic Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic lupus erythematosus</td>
<td>Nuclear antigens</td>
<td>Neuritis, skin lesions, arthritis, others</td>
</tr>
<tr>
<td>Pseudolipidsic glomerulonephritis</td>
<td>Streptococcal cell wall antigen(s); may be &quot;planted&quot; in glomerular basement membrane</td>
<td></td>
</tr>
<tr>
<td>Polyarteritis nodosa</td>
<td>Hepatitis B virus antigens in some cases</td>
<td>Systemic vasculitis</td>
</tr>
<tr>
<td>Reactive arthritis</td>
<td>Bacterial antigens (e.g., Yersinia)</td>
<td>Acute arthritis</td>
</tr>
<tr>
<td>Serum sickness</td>
<td>Various proteins, e.g., foreign serum protein (horse anti-thymocyte globulin)</td>
<td>Arthritis, vasculitis, nephritis</td>
</tr>
<tr>
<td>Arthus reaction (experimental)</td>
<td>Various foreign proteins</td>
<td>Cutaneous vasculitis</td>
</tr>
</tbody>
</table>

Type IV (cell mediated) Hypersensitivity
- initiated by specifically sensitized T lymphocytes
  - ie antibodies not involved
- includes:
  - 1. delayed type hypersensitivity - CD4+ T cells
  - 2. T cell mediated cytotoxicity – CD8+ T cells
- Overview:
  - Antigen/hapten introduced to body
  - Combines covalently with receptors on lymphocyte membrane
  - $\Rightarrow$ Lymphocyte mitosis
  - $\uparrow$ ed release of lymphokines & $\uparrow$ vascular permeability
  - local inflame reaction within 24-48hrs eg erythema, blistering, exfoliation
  - Many autoimmune disorders
Delayed Type Hypersensitivity

- Reaction to eg:
  - TB
  - Viruses, fungi, protozoa & parasites
  - Skin sensitivity to chemical agents or contact dermatitis
  - DM & MS (also involve some CD8+)
  - Allograft Graft sensitivity

- APC process antigens, present to CD4+
- CD4+ recognise antigens & MHC II molecules on surface ⇒ CD4+ ⇒ T\(_H\)1 cells
- T\(_H\)1 cells:
  - Secrete cytokines – main IFN-\(\gamma\)
  - Some into circulation & remain in memory pool of T cells for many years
- On re-exposure to antigen T\(_H\)1 cells recognise antigen and are activated

Cytokines:
- IL12
  - Critical for induction of T\(_H\)1 response
  - secreted from activated MPs & dendritic cells
  - MPs encounter antigen ⇒ secrete IL2 ⇒ drive CD4+ into T\(_H\)1
- IFN-\(\gamma\):
  - Key mediator delayed type hypersensitivity
  - Also CD4+ ⇒ T\(_H\)1
  - Powerful activator of MPs:
    - ↑ability to kill & phagocytose microorganisms
    - ↑MHC II on surface ⇒ ↑ antigen presentation
    - ↑PDGF secretion ⇒ ↑ fibroblast proliferation & ↑ collagen synthesis
    - ↑TNF, IL1, chemokines ⇒ ↑inflammation
    - ↑IL12 ⇒ ↑T\(_H\)1 response
- IL2:
  - Autocrine & paracrine prolif of T cells
    - incl T\(_H\)1 cells
- TNF & lymphotoxin – effect endothelial cells:
By Adam Hollingworth

- ↑secretion prostacyclin ⇒ local VD
- ↑expression P-E selectins = adhesion molecules allow movement of lymphocytes into tissues
- ↑chemokines eg IL8
  - together allow ↑extravastion of lymphocytes & monocytes at site of type IV reaction
- With persistent or nondegradeable antigens eventually see nodule of activated ‘epitheloid’ MPs
  - form a granuloma
- Granuloma = epitheloid cells surrounded by collar of lymphocytes

T Cell Mediated Cytotoxicity

- Eg Viral infection & tumour cells
- Virus associates with MHC I in cell ⇒ to cell surface ⇒ recognised by TCR of cytotoxic CD8+ (CTLs) ⇒ lysis
- CTLs also involved in allograft rejection
- CTL killing via:
  - Perforins & granzymes:
    - perforin drills hole in target cell plasma membrane
    - granzymes then released through perforin pore
    - granzymes activate intracellular caspases ⇒ apoptosis of target cell
    - perforin also allow water [in] ⇒ osmotic lysis
  - Fas-FasL pathways – via apoptosis
Transplant Rejection

- Allograft = transplant of cells/tissue/organ to a recipient from non-identical donor of same species
- Xenograft = graft from different species
- Isograft = transplant from genetically identical donor ie identical twin
- Autograft = own tissue transplanted from one site to another on same pt

- Foreign allografts elicit both types of class IV Cell mediated Hypersensitivity
  $\leftrightarrow$ = delayed or T cell mediated
- Host immune system triggered by foreign histocompatibility molecules (HLAs) on donor epithelium & parenchymal cells
- HLAs exist in class I & class II forms
  $\leftrightarrow$ie MHC class I & II
- Process of graft rejection:
  - Sensitisation phase – recognising foreign donor antigens
  - Graft destruction phase

Recognising Allografts – (Sensitisation Phase)

- Host T cells recognise in 2 ways:
  - Direct
  - Indirect

  Direct
- Host T cells recognise donor HLA on donor APCs
- Donor dendritic cells (ie the APCs) most impt cells in process
- Immune response:
  - Donor MHC I HLA + CD8+ $\Rightarrow$ CTLs
  - Donor MHC II HLA + CD4+ $\Rightarrow$ T_{H1} effector cells

Indirect
- Host T cells recognise donor HLA after processing by host APCs
  $\leftrightarrow$ie same process for any exogenous processed antigen
- Main immune response = delayed type (IV) hypersensitivity mediated by CD4+ lymphocytes
  $\leftrightarrow$ also activate $\beta$ lymphocytes $\Rightarrow$ plasma cells $\Rightarrow$ any Ig secretion
Graft Destruction Phase

- Mediated by cellular & humoral mechanisms
- Include:
  - Direct CTL mediated cytolysis
  - MP mediated destruction — promoted by lymphokine release
  - Interleukin (IL) 1 $\Rightarrow$ activate CD8+ & Cd4+ $\Rightarrow$
    - release TNF & IFN$\gamma$ AND
    - $\uparrow$graft expression of HLA class II
  - soluble antigens from graft stim B lymphocytes $\Rightarrow$ antibody secretion
    - $\Rightarrow$ Complement activation
    - $\Rightarrow$ endothelial injury & vasculitis
  - Activation NK cells

Types of Rejection

Hyperacute Rejection
- minutes
When recipient prev sensitized to antigen in a graft eg blood transfusion or pregnancy

Preformed circulating antibody binds to graft endothelial HLA class I antigens

Immediate:
- Complement
- ADCC mediated injury

Result is:
- Coagulation
- Microvascular thrombosis
- Graft infarction

**Acute Rejection**
- Within first month of transplant or stop immunosuppressive therapy
- Cellular & humoral mechanisms contribute
- See interstitial mononuclear cell infiltrate ie MPs, plasma, CD4 & CD8 T cells:
  - CTL damage to endothelium & parenchymal cells
  - CD4+ ⇒ delayed hypersensitivity (IV) response

**Acute Humoral Rejection or Accelerated Rejection**
- Aka rejection vasculitis
- Mediated by antidonor antibodies
- First few months ⇒ necrotising vasculitis & consequent thrombosis
- May also see subacute vasculitis ⇒ infarction

**Chronic Rejection**
- Months to years
- Progressive organ destruction
- Cellular immune response or antibody mediated or combo
- Arterties dense intimal fibrosis ⇒ narrowing of lumen ⇒ allograft ischaemia

**Transplant Haematopoietic Cells**
- Host irradiated to
  - eradicate malignant cells
  - suppress host immune system – to minimise rejection of donor marrow
- host NK cells or radiation resistant T cells may survive ⇒ transplant rejection

**GVHD**
- =unique problem with marrow transplant
- donor immunocompetent cells introduced into immunosuppressed HLA nonidentical host
- ⇒ donor immune cells engraft and flourish THEN recognise host as foreign and mount response
  - CD4+ & CD8+ T cell mediated injury
- signs:
  - most effected: bilary epithelium, skin & GI mucosa
  - reactivation CMV infection
- methods to decrease incidence GVHD:
  - HLA matching
  - Selective donor marrow T cell depletion
    - but ↓T cells in donor ⇒
      - ↓chance of engrafting
      - ↑chance relapse
- acute GVHD <4 weeks transplant:
  - dermatitis
  - jaundice
  - hepatosplenomegaly
  - overwhelming infection
- chronic >100days post:
- hepatitis
- pericarditis
- myositis
- death from opportunistic infection