Pathology of Infectious Diseases

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**host response vs. microbial pathogens**

- **Important host response factors**
  - Intrinsic host defenses and innate immunity
  - Adaptive immunity and immune competence
  - Genetic background

- **Important bacterial factors**
  - Route of entry
  - Ability to gain access to host
  - Size of inoculum, ability to use host substrates
  - Ability to circumvent host responses
  - Bacterial products that damage cells or tissues, or alter host physiology
  - Evolutionary adaptation to host

**Respiratory tract entry**

- Eyes
- Nasal cavity
- Sinuses
- Lung
- Macrophages
  - Resident flora

**Gastrointestinal tract entry**

- Mouth
- Stomach
- Small intestine
- Large intestine
- Colon
- Faeces
The earliest cellular event in inflammation is an influx of neutrophils beginning after a few hours. Monocytes and macrophages characterize the later stages of inflammation. Eventually, fibroblasts may repair the site and endothelial cells provide new blood vessels.
Mononuclear phagocytes
monocytes and macrophages (histiocytes)

- Phagocytic
- Participates in induction of immune reactions (antigen presentation)
- Source of proinflammatory cytokines

Lymphocytes and Plasma cells

- Not a frequent component of acute inflammation
- Initiators and effectors of immune response
- T lymphocytes (helper, cytotoxic, natural killer)
- B lymphocytes and plasma cells produce antibody
- Natural killer (NK) cells produce proinflammatory cytokines and lyse target cells

Inflammation definitions

- Edema – accumulation of extravascular fluid
- Effusion – accumulation of fluid in a body cavity (e.g. peritoneum or pleura)
- Transudate – edema fluid with low protein content (s.g. <1.015)
- Exudate – edema fluid with high protein content (s.g. >1.015), often with inflammatory cells
  - Serous exudate – exudate lacking large number of inflammatory cells; usually pale yellow
  - Serosanguinous – exudate or effusion containing erythrocytes (usually red-tinged)
  - Fibrinous exudate – contains large amount of fibrin after coagulation of clotting factors
  - Purulent exudate or effusion – contains high inflammatory cell content; often seen with bacterial infections
  - Suppurative inflammation – purulent exudate accompanied by significant liquefactive necrosis (pus).

Edema and fibrinous exudate (bronchopneumonia)

Fibrinous pericarditis
Purulent exudate
Bronchopneumonia

Purulent exudate: Meningitis

Purulent and suppurative inflammation

Suppurative Myocardial Inflammation

Ulcers

Ulcer
Artery
Gastric Ulcer
### Pseudomembranous Inflammation

- **Pseudomembrane**

  - **Pseudomembranous (Clostridium difficile) colitis**

### Histopathology with bacterial infections

- **Extracellular bacteria**
  - Incite acute inflammation with edema
  - Depending upon bacterial species, may cause necrosis → suppuration (pus) or abscess
    - Exudative with necrosis
    - Abscess
  - With time, increasing chronic inflammation begins leading various degrees of mixed acute and chronic inflammation
  - Examples:
    - *Streptococcus pneumoniae*
    - *Staphylococcus aureus*
    - *Pseudomonas aeruginosa*
    - Most other bacteria

### Exudative Inflammation

- Vascular permeability, recruitment of leukocytes (esp. neutrophils), pus
- Typically caused by pyogenic, extracellular bacteria
- Usually localized
- Examples:
  - Group A strep (*Streptococcus pyogenes*) pharyngitis
  - *Staphylococcus aureus* furuncle
  - *Streptococcus pneumoniae* pneumonia and meningitis

### Exudative Inflammation

- **Streptococcal pharyngitis**
  - (strep throat)
Lobar pneumonia – *S. pneumoniae*

Meningitis – *Streptococcus pneumoniae*
**Meningitis – *Streptococcus pneumoniae***

**Necrotizing Inflammation**
- Exudative inflammation with necrosis (suppuration)
- Host damage may be caused by bacterial virulence factors
- Examples:
  - *Pseudomonas aeruginosa* pneumonia
  - *Clostridium perfringens* myonecrosis (gas gangrene)

**Necrotizing pneumonia – *Pseudomonas aeruginosa***

H&E

Gram stain
**Histopathology with bacterial infections**

- **Facultative and obligate intracellular bacteria**
  - Incite chronic inflammation ± acute inflammation
    - chronic inflammation or mixed acute and chronic inflammation
    - granulomas or granulomatous inflammation
  - Depending upon bacterial species, may cause necrosis ➔
    - caseous necrosis
    - microabcesses within granulomatous inflammation
    - host cell-specific necrosis or apoptosis
  - Examples:
    - *Mycobacterium tuberculosis* (tuberculosis)
    - *Rickettsia rickettsii* (Rocky Mountain spotted fever)
    - *Mycoplasma pneumoniae* pneumonia
    - *Chlamydia trachomatis* (lymphogranuloma venereum and urogenital infections)

**Granulomatous Inflammation and Granulomas**

- accumulations of epithelioid histiocytes (activated macrophages)
- response to bacteria that withstand destruction by neutrophil phagocytes
- dependent upon intact, appropriate cytokine responses (IL-1β, IFN-γ, CXCL and CCL chemokines, not IL-4 or IL-10)
- examples:
  - *Mycobacterium tuberculosis*
  - *Mycobacterium leprae*
  - *Coxiella burnetii*
Activated Macrophages

Macrophages can be activated by antigen-specific or by non-specific means. Activation is an operational term indicating an enhanced capacity to do inflammatory battle.

Selective inflammatory cell recruitment by activated macrophages

The many faces of macrophage activation

Resolving chronic inflammation

Mixed acute and chronic inflammation

Chronic Inflammation with infection

Plasma cell

Lymphocyte

Macrophage

Neutrophil
Granulomas and Granulomatous Inflammation

**Features**
- Inability to eliminate causative agent
- Involves specific and non-specific T cell immunity
- Recruitment of monocytes, macrophages, and lymphocytes
- Persist for long periods as aggregates

**Causes**
- Mycobacteria
- Fungi
- Parasites
- Foreign Body
- Idiopathic

Histologic features of Granulomas and Granulomatous Inflammation

- Epithelioid histiocytes (Secretory Macrophages)
- Giant Cells
- Lymphocytes
- Fibrosis

Granuloma formation

A. Recruitment of mixed inflammatory cells, driven by cytokines
B. Enrichment in mononuclear cells (macrophages, lymphocytes) organizing into a cluster
C. Fully organized granuloma with fibrosis and disruption of tissue architecture

Cytokines and chemokines in immune granuloma formation
Mycobacterium tuberculosis

Foamy macrophages (granulomatous) in lepromatous leprosy (Mycobacterium leprae)

Lepromatous leprosy
**Interstitial Inflammation**

- nonspecific morphology (chronic nonspecific inflammation)
- suggestive of viral, mycoplasmal, rickettsial, or spirochetal infections

**Cytopathic or Cytoproliferative changes**

- most typical of viral infections
- may be seen with intracellular bacterial infections (e.g. *Chlamydia trachomatis*)
- angioproliferative responses caused by *Bartonella* spp.
Human papillomavirus – condyloma acuminatum – venereal warts

Chlamydia trachomatis cytopathic effect

Papinicolou (“Pap”) stains

The “Null” reaction

- absence of inflammatory, necrotizing, or cytopathic responses
- rare with bacterial infections
- may occur with neutropenia or immune compromise due to lack of inflammatory cells or by rapid, unrestricted bacterial growth
**Bacterial Infections in Abnormal Hosts**

- **Physiologic defects**
  - Cystic fibrosis
  - Achlorhydria

- **Defective inflammatory response**
  - Leukocyte adhesion molecule deficiency
  - Chronic granulomatous disease

- **Defects in immune function**
  - Complement deficiency, asplenia, susceptibility to encapsulated bacteria
  - Hypogammaglobulinemia > defective opsonization
  - HIV, cancer therapy, corticosteroid or immune suppressive therapy diminish effective T lymphocyte responses
  - Interferon-γ receptor deficiencies (recurrent *Mycobacteria* and *Salmonella* infections)

**Bacillus anthracis (anthrax)**

- Cutaneous
- Dura mater
- Inhalational anthrax

The pathogenetic basis of the host-microbe interactions and disease
4. Evade of host defenses
   Microbial invasion to host defenses
   Evade phagocytic and immune defenses
   long enough for full cycle in host to be completed

5. Sheding/survive from body
   Transmission
   Leaves body at site and on a scale that ensures spread to fresh host

6. Cause damage in host
   Pathology, disease
   Not strictly necessary but often occurs

*Some damage may be inevitable if efficient shedding is to occur (e.g. common cold, diarrhea, skin wounds.

**Bacterial genomes by COG functional groups**

- **COG substrate**
- **COG function**

- **Respiratory tract**
  - **Mouth**
  - **Conjunctiva**

- **Alimentary tract**
  - **Scalp, injury**

- **Urogenital tract**
  - **Anus**
  - **Skin Capillary**

**eukaryotic, prokaryotic, and archaea genome sizes**

- **Homo sapiens**
- **M. tuberculosis**
- **E. coli**
- **Y. pestis**
- **V. vulnificus**
- **B. anthracis**
- **K. pneumoniae**
- **P. jirovecii**
- **S. cerevisiae**
- **C. albicans**
- **P. falciparum**
- **T. gondii**
- **B. malayi**
- **D. simulans**
- **H. sapiens**
- **C. pipiens**
- **R. norvegicus**

**n = 866**

- All graphs use log scale on x-axis.
Influenza virus (V) attached to tracheal cilia (C) and microvilli (M)

Salmonella typhimurium attached to ileal microvilli

Common bacterial adhesins
T3SSs, effector translocation and host cell invasion by Shigella

Dental microcolonies (plaque) of cocci
The biofilm

Picornavirus binding
Adherence and fusion mechanisms of HIV via gp120/gp41

Exit and spread of microbes

Mechanisms of microbial entry post-adhesion/colonization events
Endothelial cell barriers of the body

- CNS, muscle, connective tissues, skin, lung
- Renal glomerulus, intestine, choroid plexus, pancreas, endocrine glands
- Liver, spleen, bone marrow

Lymphatic drainage – spread of infection vs. initiation of adaptive immunity

- Postcapillary venules
- Thoracic lymph duct
- Lymphatic capillary
- Germinal centre
- Marginal sinus
- Basement membrane
- Epithelium at body surface

Microbial responses to evade host phagocytosis

- Initial chemotaxis
- Initial phagocytosis
- Initial intracellular fusion
- Mobilizing and multiplying in phagocytosis

Microbe dissemination
Microbial virulence mechanisms: toxins

Bacterial cell walls and microbe-associated molecular patterns (MAMPs)
Pores and hemolysins

phospholipases

Acquisition of exotoxins

Intracellular parasitism by pathogens

- Phagocytosis – opsonized pathogens bind to FcR, CR1,3,4, mannose receptors, or fMLP-receptors and must circumvent host degradation in lysosomes
- Induced endocytosis – pathogen binding to host cell surface followed by bacterial initiation of host cell internalization
- Active invasion – does not require participation of host for internalization
Induced endocytosis in *Salmonella*

A. *S. typhimurium* inducing endocytosis in Caco-2 cell

B and C. Actin rearrangements (red) with *S. typhimurium* (green)

Manipulation of the host’s cytoskeleton

- Zippering (*Listeria*)

Manipulation of the host’s cytoskeleton
Attachment without invasion

- *E. coli*
  - enteropathogenic (EPEC)
  - attachment and effacement
- *Yersinia*
  - inhibition of phagocytosis

Type III secretion mechanism
Type IV secretion systems

Eucaryotic host cell

Gene transfer to plant
Agrobacterium

Bacterial conjugation
RP4, R388, pBAD104

Pertussis toxin secretion
Bordetella

Intracellular survival
Brucella, Bartonella, Legionella

Manipulation of the host's cytoskeleton
intracellular motility - actin polymerization
Manipulation of the host’s cytoskeleton intracellular motility - actin polymerization

Shigella enterocolitis

Normal colon
enterocolitis

Shigella enterocolitis
enterocolitis
normal colon
Shigella enterocolitis

A

Epithelial cell

Pro IL-1β

M cell

Activated macrophage

LPS

Shigella

B

Apoptotic macrophage

IL-1β

IL-1R

Inflammatory cascade
(TNF-α, IL-1, IL-6, IL-8)

C

PAN

Actin tail

D

Pneumococcal meningitis

Petri dish with bacterial colonies

Histological slide of meningitis

Pneumococcal meningitis
colonization and systemic invasion

- Respiratory mucosa colonization
  bacterial factors – phosphorylcholine, CbpA;
  ↓ polysaccharide capsule; IgA protease
  host cell factors – PAF receptor; oligosaccharides

Invasion into the bloodstream
penetration through mucosal epithelial cells
penetration between mucosal epithelial cells

Pneumococcal meningitis
bacteremia / intravascular survival

- Phase shift to upregulate antiphagocytic capsule
  expression enhances survival in blood
- pneumococci with dense polysaccharide capsules do
  not adhere well to epithelial surfaces but are
  antiphagocytic
- pneumococci with less polysaccharide capsule and
  more phosphorylcholine and CbpA adhere well but
  do not resist phagocytosis well

Pneumococcal meningitis - meningeal invasion

- Need to traverse blood-brain barrier
  attachment to microvascular endothelial cells
  - mediated by CbpA, choline, ↓ polysaccharide capsule
  - attaches to PAF receptor upregulated with cytokine stimulation
  internalization via PAF receptor leads to endocytosis and:
    - intracellular destruction
    - recycling to apical surface
    - passage to basal surface into CSF
      enhanced by phase transition

Cell-cell spread of intracellular pathogens

- Cell lysis
  - Mechanical (Rickettsia prowazeki)
  - Necrotic (Plasmodia, Toxoplasma, Trypanosoma, Rickettsia, Shigella)
- Discharge from vacuoles
  - Fusion of vacuole with cell membrane (Ehrlichia, Chlamydia)
- Direct cell-cell transfer
  - Propulsion through cell membrane by actin-based motility (Rickettsia rickettsii, Shigella, Listeria)
Morphologic Tools for Identification of Microbial Infections

- inflammatory response usually stereotypical and nonspecific
- inflammation type, special staining characteristics, anatomic location, and other clues
  - neutrophils in gastric mucosa > *Helicobacter pylori*
  - abscess with "sulfur granules" > Actinomycosis (*Actinomyces* spp.)
  - caseating granulomas > *M. tuberculosis*
  - granulomas with stellate microabscesses > cat scratch disease (*Bartonella henselae*)
  - lymphocytic vasculitis > Rocky Mountain spotted fever (*Rickettsia rickettsii*)

### Table 8.2: Some Susceptibility and Resistance Genes Implicated in Prokaryotic Diseases

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<th>Gene</th>
<th>Target</th>
<th>clumsy</th>
<th>Effect</th>
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<tbody>
<tr>
<td>P40</td>
<td><em>Helicobacter pylori</em> gastritis</td>
<td>Silver stain</td>
<td>Resistance</td>
</tr>
<tr>
<td>H&amp;E</td>
<td><em>Helicobacter pylori</em> gastritis</td>
<td>H&amp;E</td>
<td>Resistant</td>
</tr>
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### Table 8.3: Some Susceptibility and Resistance Genes Implicated in Bacterial Diseases

<table>
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<th>Gene</th>
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<th>Effect</th>
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<tbody>
<tr>
<td>H &amp; E</td>
<td><em>Helicobacter pylori</em> gastritis</td>
<td>Silver stain</td>
<td>Resistance</td>
</tr>
<tr>
<td>H &amp; L</td>
<td><em>Helicobacter pylori</em> gastritis</td>
<td>H&amp;E</td>
<td>Resistant</td>
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### Table 8.4: Some Susceptibility and Resistance Genes Implicated in viral diseases

<table>
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<th>Gene</th>
<th>Target</th>
<th>LSM</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
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<td>Silver stain</td>
<td>Resistance</td>
</tr>
<tr>
<td>LR5</td>
<td><em>Helicobacter pylori</em> gastritis</td>
<td>H&amp;E</td>
<td>Resistant</td>
</tr>
</tbody>
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- *Helicobacter pylori* gastritis
- *Actinomyces* gastritis
- *M. tuberculosis* granulomas
- cat scratch disease (*Bartonella henselae*)
- *Rickettsia rickettsii* lymphocytic vasculitis

**Silver stain**

**H&E**

**Gram stain**
Caseous necrosis in TB

Sputum acid fast stain

Fluorochrome stain

H&E

H&E immunohistochemistry

Culture

Polymerase chain reaction

Culture

S. aureus PNA FISH (peptide-nucleic acid fluorescence in situ hybridization)

H. pylori in situ hybridization

Lymphocytic vasculitis

Rocky Mountain spotted fever

Immunohistochemistry

Detection of antigen-specific serological responses

Post-infection antibody kinetics

Antibody titre vs. Months

IgM

IgG
Detection of antigen-specific responses

Humoral immunity:
- antibody detection
- seroconversion or titer increase

Cellular immunity
- lymphocyte proliferation
- IFNγ production

Indirect fluorescent antibody
Agglutination

Protein (Western) Immunoblot