

**Patterns of Infectious Diseases  
(with selected examples)**

**I. Categories of Infectious Diseases**

- A. **Prions** - modified host protein - cause transmissible spongiform encephalopathy, e.g. mad cow disease
- B. **Viruses** - obligate intracellular parasites - most frequent and diverse class of human pathogens - causes such disease as herpes encephalitis, CMV inclusion disease
- C. **Bacteriophages, Plasmids, Transposons** - mobile genetic elements that encode bacterial virulence factors - may confer antibiotic resistance onto a previously antibiotic susceptible organism
- D. **Bacteria** - prokaryotes that lack nuclei and endoplasmic reticulum - invade host tissue and are capable of intracellular and/or extracellular division
- E. **Chlamydiae, Rickettsiae, Mycoplasmas** - similar to bacteria (divide by binary fission) but lack certain structures or metabolic capabilities.
- F. **Fungi** - grow as perfect sexually reproducing forms in vitro and as imperfect forms in vivo
- G. **Protozoa** - single-celled organisms endowed with motility, pliable plasma membranes and complex organelles
- H. **Helminths** - highly differentiated multicellular organisms - have definitive and intermediary host
- I. **Ectoparasites** - arthropods that attach to and live on the skin

**II. Manifestations of Infectious Diseases**

- A. Skin rashes, mucosal reddening and irritation
- B. Bloodstream invasion with septicemia (and potentially fatal shock)
- C. Tissue invasion, especially along planes of least resistance, e.g. cellulitis
- D. Serosal cavity spread, e.g., peritonitis, meningitis
- F. Lymphatic and cardiovascular system spread with dissemination to many organs producing a large variety of symptoms
- G. Localized growth of organisms - production of a "tumor", e.g., abscess, granuloma
- H. Cell-to-cell spread with destruction of the cells, e.g., viral hepatitis

### III. Pathology of Infectious Diseases

#### A. Suppurative inflammation

1. Direct response of neutrophils to chemoattractants (peptides, IL-1, TNF) released by bacteria. Neutrophil response often accompanied by fluid, e.g., pulmonary edema associated with acute pneumonia from streptococcal infection.

*Acute congestion* - bacterial proliferation, fluid exudation, neutrophils, RBCs produce "rusty" sputum.

*Red hepatization* - consolidation by cellular exudate with RBCs, neutrophils and fibrin.

*Gray hepatization* - fibrinous exudate depleted of RBCs.

*Resolution* - exudate digested and resorbed or expectorated.

2. Severe infections may result in an accumulation of neutrophils (pus) and/or, if the organism (Staphylococcus, Klebsiella) produces substances (e.g., proteases) that destroy tissue, large abscesses may form and lead to permanent damage to the tissue.

#### B. Cytopathic-Cytoproliferative

1. Damage to individual cells in the absence of inflammation
2. Viruses replicate within cell and become visible as aggregates in cell
  - a. Nuclear inclusions - e.g. Cytomegalovirus, herpes, adenovirus
  - b. Cytoplasmic inclusions - e.g. **Respiratory syncytial virus(RSV)**
3. Viruses induce fusion of cells and form polykarons, e.g. measles, **RSV**

##### Definition

**Respiratory syncytial virus (RSV)** causes upper then lower respiratory tract disease in infants and children throughout the world with virtually all persons experiencing infection within the first few years of life. Mortality, fortunately, is very low in non-immunocompromised patients but is being identified with increasing frequency in organ transplantation and HIV infected patients. The disease is manifest primarily as pneumonia, bronchiolitis, and tracheobronchitis, occasionally as otitis media (especially in infants and young children), and rarely as meningitis, myelitis and myocarditis.

##### Epidemiology

- 1). RSV infection is usually self-limited with most children exposed by age 2).
- 2). RSV presents frequently as a common cold. Presentations with greater morbidity include laryngotracheobronchitis and pneumonia. In the neonate approximately 50% of viral pneumonias are due to RSV. RSV is recognized as a frequent cause of winter outbreaks of acute respiratory infections and is estimated to be responsible for 90,000 hospital admissions (1-2% of

infected children) annually. Approximately 50% of these admissions are due to bronchiolitis and 25% due to pneumonia. A systemic illness resembling sepsis is also recognized. RSV infection accounts for about 4,500 respiratory deaths in infants and children in the United States annually.

3). High-risk groups - Most RSV infections are self-limited in children and young adults. Infants with underlying lung (bronchopulmonary dysplasia, cystic fibrosis or cardiac disease (congenital heart disease) are at increased risk. A number of high risk groups in children and adults have been identified. Children with congenital immune disorders or children or adults with acquired disorders, such as AIDS, or transplantation patients have morbidity related to their underlying disease.

### **Clinical Features**

1). The various clinical presentations of RSV are related to the age and pre-morbid condition of the host. In children <3 years old, the disease involves predominantly the lower respiratory tract. While initial symptoms including sneezing, pharyngitis, and cough indicate an upper respiratory component, more than half of infected infants will develop signs of bronchiolitis and/or pneumonia. Fever, cough and dyspnea are the most common findings in lower tract disease. The fever is usually low-grade and may be absent. Physical findings of retraction, tachypnea, wheezes, rales and rhonchi are often present.

2). The chest x-ray in children with known RSV infection and clinical pneumonia or bronchiolitis may be normal in 20-50% of cases. The most common positive x-ray findings in young children with lower respiratory tract disease include hyperinflation, interstitial infiltrates, consolidation and atelectasis. Unilateral, right-sided hilar enlargement has been reported in 1/3 of the patients in one series.

### **Pathology**

1). Gross - The pathologic changes of RSV are limited almost entirely to the lungs and descriptions of these changes are derived almost exclusively from the study of autopsy material. Grossly the lungs show areas of hyperinflation alternating with areas of consolidation and hemorrhage. Thick, mucoid material may be present in larger bronchi and expressed from small bronchioles on cut section.

2). Microscopic- The hyperinflation noted on radiographs is secondary to plugging of these terminal and respiratory bronchioles with air trapping distal to the occluded areas. The material obstructing the bronchioles is

composed of cellular debris of bronchial, bronchiolar and alveolar epithelium admixed with mucus and inflammatory cells.

The injury of the airway by RSV appears to begin as hyperplasia and squamous metaplasia of the epithelium accompanied by desquamation of the epithelial cells. Large syncytial giant cells (from which RSV derives its name) are found in and lining alveolar spaces, but may also be seen in bronchi and bronchioles. The alveolar involvement may be extensive, producing the wide areas of consolidation also noted on radiographs.

3). Viral Inclusions - Cytoplasmic inclusions, varying from 1 - 20um in diameter are present in bronchial, bronchiolar and alveolar epithelium, syncytial giant cells, and sloughed intra-alveolar cells. These globules, which stain positively with anti-RSV antibody, are often eosinophilic, homogeneous and well defined in the paranuclear area, but are granular and mildly basophilic when more peripherally located. Clear "halos" may surround the smaller inclusions. Nuclear inclusions have not been identified. In addition to the globules, staining for RSV displays cytoplasmic positivity in alveolar, bronchial and bronchiolar epithelium, syncytial giant cells and sloughed alveolar cells. The degree of staining within an alveolus varies from partial to total involvement. In bronchial and bronchiolar hyperplastic epithelium, the staining is most intense in the cells nearest the lumen.

A mild to moderate inflammatory infiltrate of mononuclear cells and neutrophils may also be present in peribronchial, peribronchiolar and interstitial tissue. The presence of a more severe acute bronchopneumonia may indicate a secondary bacterial infection.

4). Electron microscopy displays 100 nm in diameter round to elongated profiles of the virus. The viral replication is present within cytoplasmic sacs as fuzzy "budding" from the membrane.

4. Viruses induce epithelial cells to proliferate and form unusual individual and aggregate morphologic lesions

- a. Hyperplastic proliferation of venereal warts associated with human papillomavirus(HPV)
- b. Poxvirus induction of umbilicated papules (molluscum contagiosum)

5. Viruses cause dysplastic changes and malignancies

- a. Cervical squamous cell carcinoma from HPV

b. Lymphoma from Epstein-Barr virus (EBV).

### C. Mononuclear and Granulomatous Inflammation

1. Diffuse mononuclear interstitial infiltrates from cell mediated immunity (CMI).

Requires a period of time (days to weeks) from infection to development of CMI

2. Host immune response determines amount and type of mononuclear cell infiltrate

a. Lymphocytes predominate in Hepatitis B Virus infection - a disease whose severity depends on the ability of the lymphocytes (via cell-mediated immunity) to destroy the virus directly or the virus containing cells. Inability to completely do so leads to either a "carrier" state of the host or a progressive or chronic liver disease.

b. Plasma cell predominance seen in chancres of **syphilis**

1). Syphilis - Epidemiology - Worldwide disease with about 130,000 new cases reported in US each year.

2). Organism - *Treponema pallidum* is a thinly coiled, double-membraned, 6-15um long, 0.1-0.2 um wide, motile bacterium that penetrates skin and mucous membranes and invades small arteries and arterioles via its ability to adhere to endothelial cells

3). Clinical features

a). Primary stage - chancre (solitary, painless ulcer) develops 10-90 days after inoculation. Most common on external genitalia, cervix, anus or mouth. Followed 1-2 weeks later by painless regional lymphadenopathy. Primary lesion heals in 3-6 weeks; lymphadenopathy persists for months

b). Secondary stage - usually starts 2-6 weeks after chancre heals.

Hematogenous dissemination of *T. pallidum* characterized by mucocutaneous lesions(esp. on palms and soles of feet) and low-grade fever, malaise, anorexia, headache, sore throat, and generalized, nontender lymphadenopathy. Lasts for several weeks then resolves, but with 25% incidence of relapse

c). Latent stage - positive serology in absence of clinical symptoms - lasts 2-20 years, then in 30% of patients progresses to tertiary stage

d). Tertiary stage - CNS and cardiovascular involvement, gumma formation of any organ or tissue. Progressively destructive

e). Congenital syphilis - *T. pallidum* crosses placenta and infects the infant producing spontaneous abortion, stillbirth, early and late congenital syphilis.

1). Early congenital syphilis - similar to secondary stage with extensive, cutaneous lesions on palms, soles, perineum and around

mouth - lesions teeming with spirochetes. Also see osteochondritis, periostitis, fulminant pulmonary interstitial fibrosis (pneumonia alba), hepatitis with fibrosis

2). Late congenital syphilis - opacified cornea, gummas of palate and bridge of nose (collapse causes "saddle nose"), meningovascularitis, (8<sup>th</sup> nerve deafness, optic atrophy), short, screw-drive shaped teeth (Hutchinson's teeth), tibial bowing (saber shins)

3). Placenta - large, heavy and bulky, dysmaturity of villi, plasma cells in decidua, spirochetes in umbilical cord

#### 4). Pathology

##### a). Primary stage

Chancre - solitary, circular, reddened papule that erodes into a shallow ulcer with sharp, firm, raised edge and smooth, red, indurated base. Spirochetes may be seen with special stains (e.g. Warthin-Starry) in exudative fluid around blood vessels and in and around endothelial cells, leukocytes and epidermal cells.

##### b). Secondary stage

1). Skin- variable (maculopapular, papular, annulopapular) lesions of face, palms and soles with vascular and perivascular lymphoplasmacytic infiltrate, fibrosed blood vessels, proliferating endothelial cells and epidermal hyperplasia.

2). Lymph nodes with follicular hyperplasia, capsular thickening, invading spirochetes - later with noncaseating granulomas

3). GI tract - gastritis with mucosal erosions and ulcerations progressing to linitis plastica appearance. Plasma cell infiltrates

4). Liver - hepatitis with hepatocellular necrosis, and granulomatous, mononuclear or acute inflammatory cell infiltrate

##### c). Tertiary stage

1). Cardiovascular - aortic wall inflammation with obliterative endarteritis - aortic aneurysm, aortic valvular incompetence, stenosis of coronary artery ostia

2). Gumma - granuloma of untreated syphilis - affects skin, bones, subcutaneous tissues most frequently. Also liver and testes. Grey-white, rubbery lesion composed of solitary focus of necrosis surrounded by epithelioid cell and occasional giant cells, rim of lymphoplasmacytic infiltrate and "Capsule" of fibrous tissue.

3). Neurosyphilis - plasma cell and lymphocytic vasculitis of meninges and parenchyma leads to general paralysis with diffuse

cortical atrophy. Progressive destruction of lumbosacral posterior nerve roots with gliosis leads to tabes dorsalis (lose of proprioception, wide-based gait, foot slap, Charcot's joints)

5). Treatment - penicillin

3. Granulomatous inflammation consists of a central area (often of necrotic tissue) surrounded by lymphocytes and altered macrophages (epithelioid cells) which may form giant cells. Examples include **Tuberculosis**, Schistosomiasis, Histoplasmosis

1. **Tuberculosis** is a chronic, communicable disease caused principally by *M. tuberculosis hominis* that affects the lung primarily, but may infect most any organ of the body. The disease is distributed worldwide and is one of the most important diseases in humans. The *incidence* varies from as high as 450 per 100,000 in developing countries to about 12 per 100,000 in the United States. This number was decreasing gradually until 15-20 years ago, but is now increasing in many parts of the US, especially in AIDS patients, who now have a 8% per year risk of developing active tuberculosis.

The disease is *transmitted* from person to person by coughing, sneezing or talking which produces aerosolized respiratory droplets that contain the organism. Rarely, *M. tuberculosis bovis* is passed from cows to humans in infected milk, especially in countries where milk is not pasteurized.

*Primary tuberculosis* is the infection of a person who has not had prior contact with the tubercle bacillus. Inhaled bacilli are deposited in the alveoli where they are phagocytosed by and subsequently proliferate in macrophages, which in turn die and release more organisms, producing a *localized pneumonia*. Organisms are also carried to *regional lymph nodes* and from there may be disseminated throughout the body. Hypersensitivity and cell-mediated immunologic responses are initiated by the bacilli-containing macrophages and act to contain this initial infection over a period of 3-6 weeks through a vigorous *granulomatous reaction* often with characteristic cheese-like (*caseous*) *necrosis*. The primary focus in the lung and the involved hilar or mediastinal lymph nodes comprise the *Gohn complex*.

In over 90% of normal adults, the primary infection follows a *self-limited course*. In immunocompromised patients and often in children under 5 years of age, the primary focus of tuberculosis enlarges, erodes bronchi and

may spread throughout the lung or disseminate to other organs (e.g. kidneys, adrenals, spleen and liver).

**Secondary (cavitary) tuberculous** occurs when organisms proliferate in a previously infected person. The organisms may be newly acquired bacilli or may be dormant ones in a patient "newly predisposed" to reemergence of the infection by immunosuppressive therapy, AIDS, old age, cancer, etc. In lung reinfection, bacilli proliferate, incite an inflammatory response that leads to local consolidation with subsequent **necrosis, cavity formation, and granulomatous response**. Secondary effects include localized pulmonary scarring and calcification, spread to other areas, pleural fibrosis and adhesions, rupture of a caseous lesion with spilling of bacilli into the pleural cavity, erosion into a bronchus with seeding of bacilli along the airway, and "miliary" spread throughout the lymphatics and bloodstream.

4. While unable to kill the organism, some immune mediated responses to organisms may lead to isolation of the organism within macrophages or to a weak response of lymphocytes and macrophages mixed with organisms. Examples include *M. Avium* in AIDS patients, leprosy and cutaneous leishmaniasis.

#### **D. Necrotizing Inflammation**

1. Tissue damage caused by organisms that secrete toxins
2. May see liquefactive necrosis - e.g. *Entamoeba histolytica* cystic abscesses of the liver
3. May see coagulative necrosis - e.g. Massive Herpes virus infection of the liver or brain

#### **E. Chronic Inflammation and Scarring**

1. Chronic inflammation may lead to complete healing or progress to extensive scarring.
2. A consequence or progression of one of the other forms of inflammatory response
  - a. Cirrhosis following chronic HBV or HCV infection
  - b. Pipestem fibrosis induced by schistosomiasis of the liver