Staphylococci

General Characteristics

- Common inhabitant of the skin and mucous membranes
- G+ Spherical cells arranged in irregular clusters
- Lack spores and flagella
- May have capsules
- There is about 31 species

Classification

Staphylococci are divided into pathogenic and non pathogenic based on possession of the enzyme coagulase
- Coagulase +ve are usually pathogenic, example, *S. aureus*
- Coagulase -ve; frequently involved in nosocomial and opportunistic infections like *S. epidermidis* and they are less invasive

- *S. epidermidis* – lives on skin and mucous membranes; causes endocarditis, bacteremia, UTI
- *S. hominis* – lives around apocrine sweat glands

- *S. capitis* – lives on scalp, face, and external ear
- All 3 may cause wound infections by penetrating through broken skin
- *S. saprophyticus* – infrequently lives on skin, intestine, vagina

*Staphylococcus aureus*

- Grows in large, round, opaque colonies
- Optimum temperature for growth is 37oC
- Withstands high salt, extremes in pH, and high temperatures
- Produces many virulence factors
**S. aureus morphology**

Blood agar plate, *S. aureus*
Virulence factors of *S. aureus*

**Enzymes:**
- Coagulase – produced by 97% of human isolates; it is diagnostic
- Hyaluronidase – digests connective tissue
- Staphylokinase – digests blood clots
- DNase – digests DNA
- Lipases – enhances colonization on skin
- Penicillinase – inactivates penicillin

**Toxins**
- **Hemolysins** (α, β, γ, δ) – lyse RBC
- **Leukocidin** – lyses neutrophils
- **Enterotoxin** – induces gastrointestinal distress
- **Exfoliative toxin** – separates the epidermis from the dermis
- **Toxic shock syndrome toxin 1** (TSST) – induces fever, vomiting, shock, and may be complicated finally by systemic organ damage

**Pathogenesis**
- Mostly found in anterior nares, skin, nasopharynx, and intestine
- Carriage rate of *S. aureus* is about 20-60%

**Predisposing factors to infection:**
- Poor hygiene and nutrition, tissue injury, preexisting primary infection, diabetes mellitus, immunodeficiency
- Increase in community acquired methicillin resistance staph aureus (MRSA)
Staphylococcal Diseases

Localized cutaneous infections – the bacteria invade skin through wounds, follicles, or glands and may cause:

- **Folliculitis** – superficial inflammation of hair follicle; usually resolved with no complications but can progress
- **Furuncle** – boil; inflammation of hair follicle or sebaceous gland that progresses into abscess or pustule
- **Carbuncle** – larger and deeper lesion created by aggregation and interconnection of a cluster of furuncles
- **Impetigo** – bubble-like swellings that can break and peel away; most common in newborns
**Staph skin infections**

Superficial folliculitis       Deep folliculitis       Furuncle

Carbuncle
Multiple abscesses       Staph impetigo
Around many hair follicles
Cutaneous lesions of *S. aureus*

(a) Sectional view of a boil or furuncle, a single pustule that develops in a hair follicle or gland and is the classic lesion of the species. The inflamed infection site becomes abscessed when masses of phagocytes, bacteria, and fluid are walled off by fibrin.

(b) A furuncle on the back of the hand. This lesion forms in a single follicle.

(c) A carbuncle on the back of the neck. Carbuncles are massive deep lesions that result from multiple, interconnecting furuncles. Swelling and rupture into the surrounding tissues can be marked.

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Systemic infections

- **Osteomyelitis** – infection is established in the metaphysis; abscess may be found
- **Bacteremia** – primary origin is bacteria from another infected site or medical devices; endocarditis is a possible complication

**Staphylococcal osteomyelitis in a long bone**

- **Toxigenic disease**
  - **Food intoxication** – ingestion of heat stable enterotoxins.
  - **Staphylococcal scalded skin syndrome** – toxin induces bright red flush, blisters, then desquamation of the epidermis
  - **Toxic shock syndrome** – shock and organ failure
Toxic Shock Syndrome Toxin

- Non-specific binding of toxin to receptors that triggers excessive immune response

**TSS Symptoms:**
- 8-12 h post infection
- Fever
- Susceptibility to endotoxins
- Hypotension
- Diarrhea
- Multiple Organ System Failure
- Erythroderma (rash)

**TSS Treatment**

- Clean any obvious wounds and remove any foreign bodies
- Monitor and manage all other symptoms, e.g. administer IV fluids
- Administer flucloxacillin or vancomycin i.v
- For severe cases, administer methylprednisone, a corticosteriod inhibitor of TNF-a synthesis

**Identification of *Staphylococcus* in Samples**

- Frequently isolated from pus, tissue exudates, sputum, urine, and blood
- Cultivation, catalase test, biochemical testing, coagulase test
Clinical Concerns and Treatment

- **95% of S. aureus** have penicillinase and are resistant to penicillin and ampicillin
- **MRSA** – methicillin-resistant *S. aureus* – carry multiple resistance
  - Some strains have resistance to all major drug groups except vancomycin
Prevention of Staphylococcal Infections

- Universal precautions by healthcare providers to prevent nosocomial infections
- Good hygiene and cleansing

Streptococcal Diseases

- Gram-positive spherical/ovoid cocci arranged in long chains; commonly in pairs
- Non-spore-forming, nonmotile
- Can form capsules and slime layers
- Do not form catalase, but have a peroxidase system
- Sensitive to drying, heat, and disinfectants

Freshly isolated *Streptococcus*
Hemolysis on Blood Agar Plates

- Alpha hemolysis-organism excretes hemolysins which partially break down RBC (incomplete hemolysis) thus a greenish zone appears around colony.
- Beta hemolysis-organisms excretes potent hemoysins which completely lyse RBC (complete hemolysis) thus a clear zone appears around colony.
Types of Infection

- Both primary and secondary strep infections can travel from affected tissues to lymph glands, enter the bloodstream, and spread throughout the body.

Classification

- Lancefield classification system based on cell wall Ag – 17 groups (A, B, C,....)

- Classification based on hemolysis, α- hemolysis – A, B, C, G and some D

  β – hemolysis – *S. pneumoniae* and others collectively called *viridans*

GROUP A (GAS), responsible for:

- Necrotizing fasciitis
- Toxic shock syndrome.
- Strep throat.
**View of group A Streptococcus**

**GROUP B(GBS) S. Agalactiae**:
- Most often affects pregnant women, infants, elderly, and chronically ill adults.
- Most prevalent cause of neonatal pneumonia, sepsis, and meningitis
- Causes endocarditis in debilitated people

**GROUP C(GCS)** is a common source of infection in animals. It rarely causes human illness.

**GROUP D(GDS)**
*Enterococcus faecalis, E. faecium, E. durans*
- Cause wound infections in hospital patients. It is also associated with the following:
- abnormal growth of tissue in the gastrointestinal tract
- UTI
- infections in women who have just given birth
GROUP G (GGS)
- Normally present on the skin, mouth, throat, in the intestines and genital tract.
- Lead to infection in alcoholics and in people who have cancer, diabetes mellitus, rheumatoid arthritis.

Infections caused by GGS:
- bacteremia
- bursitis
- endocarditis
- meningitis
- osteomyelitis
- peritonitis

Human Streptococcal Pathogens
- *S. pyogenes*
- *S. agalactiae*
- Viridans streptococci
- *S. pneumoniae*
- *Enterococcus faecalis*

*Streptococcus pyogenes*
- Beta Hemolytic Group A Gram positive cocci in chains
- extracellular products are responsible for virulence:
  - **Pyrogenic exotoxin A**
    - Acts as a superantigen and causes STSS
  - **Exotoxin B**
    - Causes protein breakdown
Virulence factors
Streptokinase – digests fibrin clots
Hyaluronidase – breaks down connective tissue
DNase – hydrolyzes DNA

Gram Stain of *S. pyogenes*
Diseases caused by *S. pyogenes*

- Strep throat
- Impetigo
- Erysipelas
- Cellulitis
- Invasive Strep A infections:
  - Necrotizing fasciitis
  - Myositis
  - Toxic shock-like syndrome

**Erysipelas**

- Acute infection and inflammation of the dermal layer of skin.
- Bacteremia is common
- Presents as painful red patches which enlarge and thicken
- Treatment - penicillin or erythromycin
**Impetigo**

- Often occurs in epidemics in school children; also associated with insect bites, poor hygiene, and crowded living conditions
- Clinically presents as friable, golden crusts over erythematous skin.

**Treatment**
- Topical fucidin or mupirocin for 7-10d
- Oral flucloxacillin or erythromycin
  - if widespread or unresponsive
Streptococcal skin infections
Strep Throat (Streptococcal pharyngitis)

- Most common of all Strep diseases
- Spread by saliva or nasal secretions
- Incubation period is 2-4 days

Diagnosis and treatment

- Usual symptoms are slight fever associated with sore throat and visual of pus in back of throat
- Throat swab for microscopical examination and growth on blood agar (beta hemolysis)
- If the strain of S. pyogenes is lysogenic for a particular phage which expresses an erythrogenic toxin the result is Scarlet fever
- Rash appears and characteristic is the strawberry colored tongue
Strawberry Tongue

Penicillin G or Erythromycin are drugs of choice
Although the disease is self-limiting it is important to treat immediately to avoid post strep complications

Necrotizing fasciitis
Also known as “flesh eaters”
Can cause rapidly deteriorating disease and death
Common cause of wound infections
**Symptoms**

- Acute pain at the site of the wound
- Swelling
- Fever and confusion
- Overlying skin tightens and becomes discolored
- Shock and death
Pathogenesis

- Wound colonization enhanced through tissue binding proteins
- Subcutaneous fascia is destroyed in necrotizing fasciitis
  - Muscle tissue is also destroyed by bacterial penetration
- Organisms multiply and produce toxic products
  - Organisms and toxic products enter bloodstream

Prevention and Treatment

- No proven prevention measures
- Penicillin and quinolone, plus either clindamycin or metronidazole must be given early
- Urgent surgery required due to rapidity of toxin spread
  - Amputation is sometimes required in up to 50% of cases

Poststreptococcal diseases

- Rheumatic Fever- autoimmune disease follows a strep throat
- Acute glomerulonephritis or Bright’s Disease- inflammatory disease of renal glomeruli and structures involved in blood filter of kidney, due to deposition of Ag/Ab complexes
α-Hemolytic Streptococci: Viridans Group

- *Streptococcus mutans, S. oralis, S. salivarius, S. sanguis, S. milleri, S. mitis*
- Widespread residents of the gums and teeth, oral cavity, and also found in nasopharynx, genital tract, and skin
- Not very invasive; dental or surgical procedures facilitate entrance
- Can cause bacteremia, meningitis, abdominal infection, tooth abscesses, and subacute endocarditis which results when blood-borne bacteria settle and grow on heart lining or valves
  - Persons with preexisting heart disease are at high risk, colonization of heart by forming biofilms
- *S. mutans* produce slime layers that adhere to teeth, basis for plaque
- Involved in dental caries
- Persons with preexisting heart conditions should receive prophylactic antibiotics before surgery or dental procedures

Group D Enterococci and Groups C and G Streptococci

Group D:
- *Enterococcus faecalis, E. faecium, E. durans*
- Normal colonists of human large intestine
- Cause opportunistic urinary, wound, and skin infections, particularly in debilitated persons
Groups C and G:
- Common animal flora, frequently isolated from upper respiratory; pharyngitis, glomerulonephritis, bacteremia

Streptococcus Pneumonia

- Caused by infection with *Streptococcus pneumoniae*
- Gram positive, alpha hemolytic, lancefield serotype A
- Often part of normal flora of respiratory track and becomes infective once hosts resistance is lowered. Classified as an endogenous infection.

Predisposing factors: upper respiratory viral infection, diabetes, alcoholism

60-80% of all pneumonias
Cause of strep pneumonia
- Primary virulence factor is the capsular polysaccharide which protects the organism against phagocytosis
- Pathogenesis is due to rapid growth of bacteria in alveolar spaces

Symptoms of Strep Pneumonia
- Onset abrupt
- Chest pains
- Chills
- Labored breathing

Diagnosis of Strep pneumonia
- Chest Xray
- Culture and staining
- Biochemical tests of isolated organism

Treatment of Strep Pneumonia
- Typically treated with Penicillin G cefotaxime, oflaxacin or for those allergic to penicillins can be treated with erythromycin or tetracycline
- Pneumococcal vaccine (Pneumovax 23 or Pnu-immune 23) is available for the elderly
Rheumatic Fever

Definition: It is an immune complex disease affecting mainly connective tissue of heart, joint, brain and the skin

Epidemiology

- It is rare in developed world, but still common in developing countries. Peak incidence ~5-15yr.

- Acute rheumatic fever (ARF) is a major problem in the high-risk areas of the tropics, in countries with limited resources, and in communities with minority indigenous populations.

- In those less developed nations, post ARF heart disease is the most commonly acquired heart disease in hospitalized children, adolescents, and young adults. In some areas, the incidence of this entity exceeds that of congenital heart disease.

Sex

No sex predilection exists, except that Sydenham chorea occurs more often in females than in males.

Age

Although individuals of any age group may be affected, most cases are reported in persons aged 5-15 years.
Patterns of presentation of ARF.

The first pattern is sudden onset, begins as polyarthritis 2-6 weeks after streptococcal pharyngitis and is usually characterized by fever and toxicity.

If the initial abnormality is mild carditis, ARF may be insidious or subclinical.

Causes
This auto immune disease follows throat infection with group A-Beta hemolytic streptococci (Rheumatogenic strain) by about 2-3 weeks

ARF has been linked definitively with a preceding streptococcal infection, usually of the upper respiratory tract.

Predisposing factors:

- overcrowding
- poor housing
- bad ventilation
- low socioeconomic standard
Pathogenesis

2 mechanisms:

First:
Releasing toxins that causes damage to connective tissue --- release auto antigens in to circulation --- stimulation of body to form and release auto antibodies against this connective tissue --- causing rheumatic lesion

Second
Cross reaction
These strains posses an antigen immunologically similar to that in heart connective tissue so produced antibodies against streptococci can react with the heart.

Pathophysiology

ARF is a sequel of a previous group A streptococcal infection, usually of the upper respiratory tract. One beta-streptococcal serotype (eg, M types 3, 5, 18, 19, 24) is linked directly to ARF.

Evidence is very strong that the M protein in certain streptococci subtypes is responsible for antigenicity. Non–group A streptococci has never been shown to cause this disease.
The disease involves the heart, joints, central nervous system (CNS), skin, and subcutaneous tissues. It is characterized by an exudative and proliferative inflammatory lesion of the connective tissue, especially that of the heart, joints, blood vessels, and subcutaneous tissue.
Pathology

- Fibrinoid degeneration affecting connective tissue with inflammatory oedema

- Aschoff's nodules paravascular nodules consists of at centre fibrinoid degeneration surrounded with aschoff's giant cells, lymphocytes and fibroplasts

Clinical picture

Patient has history of recent streptococcal infection 2-3 weeks ago as (tonsillitis- pharyngitis -scarlet fever) Rheumatic manifestations are divided into major and minor criteria

Major criteria

* Carditis

* Arthritis

* Chorea

* Subcutaneous nodules

* Erythema marginatum

Minor criteria

Clinical: Fever, arthralgia

Laboratory: Acut phase reactants (leucocytosis – increased ESR , C reactive protein)

Prolonged PR interval
Rheumatic carditis (pan carditis)
Involves all layers of the heart

Endocarditis, affects the heart valves mainly mitral valve causing valvitis in 70% of cases. Mitral stenosis presents early due to inflammatory oedema, leading to mid diastolic rhumbling murmer over apex and localized with accentuated S1.

Mitral incompetence, due to destruction and deformity of the valve, leading to pansystolic blowing murmer over apex and propagated to axilla with muffled S1.

Aortic valvitis, causing incompetence due to destruction and deformity of the valve, leading to early diastolic soft murmer over aortic area and propagated to apex.

Myocarditis, presents as:
*Tachychardia, not proportional to the fever and continous with sleep
  ■ Myocardial dilatation causing poor quality heart sounds

■ prolonged PR interval

■ Heart failure

■ Arrhythmia
- **Pericarditis, presents as:**
  - Chest pain: stitchy and localized
  - Pericardial rub: superficial, scratchy sound, heard near to sternum and not related to respiration

- **Pericardial effusion, presents as:**
  - Increase cardiac dullness
  - Distant heart sounds

- **Rheumatic arthritis**
  - Affecting big joints (knee-ankle-elbow) usually 2 or more joints
  - It is migratory with signs of inflammation (red-hot-swollen-limitation of movement)
  - Fleeting arthritis migrate from one to the other joint
  - Characterized by dramatic response to salicylates.

**Rheumatic chorea (sydenham's chorea)**

Common in females (8-12y)
It is due to involvement of basal ganglia in rheumatic process and its manifestations appear late.
3 MAIN MANIFESTATIONSS
1. Involuntary movement
2. Hypotonia
3. Emotional instability

Involuntary movement

* affecting face, limb, and tongue.

* movement is involuntary, sudden, and jerky

* patient complains from falling of objects from the hands
* tongue movement interferes with speech

Hypotonia

* mainly proximal than distal

* associated with hyporeflexia

* if sever it leads to paralysis

Emotional instability

* Sudden crying  * Sudden laughing

Subcutaneous nodules

They are painless subcutaneous firm nodules freely mobile under the skin
Site : over extensor surfaces and bony prominances

Indicate sever carditis
**Erythema marginatum**

They are rings of erythema with clear center not painful, not itchy

**Site:** over trunk and proximal parts of the extremities

Diagnosis of ARF requires a high index of suspicion.

Guidelines of diagnosis used by the American Heart Association include major and minor criteria (i.e., modified Jones criteria). In addition to evidence of a previous streptococcal infection, the diagnosis requires 2 major Jones criteria or 1 major plus 2 minor Jones criteria.
Diagnosis
(history-examination-investigation)

HISTORY

-recurrent tonsillitis, pharyngitis or scarlet fever

-abnormal movements

EXAMINATION

According to modified Jones criteria

TWO MAJOR CRITERIA OR ONE MAJOR AND
TWO MINOR CRITERIA

PLUS

EVIDENCE OF STREPT. INFECTION.

Some considerations and precautions during diagnosis

- if you considered carditis as major criteria; you should not consider prolonged PR interval as minor criteria

- if you considered arthritis as major criteria; you should not consider artharalgia as minor criteria

- you can not depend on both subcutaneous nodules and erythema marginatum only as 2 major criteria as they are not pathognomonic to RF and occur in other collagen diseases.
INVESTIGATIONS

Acute phase reactants (ESR- CRP- leucocytosis)

ASO TITRE

Throat culture for group A β- haemolytic strept.

ECG (prolonged PR)

PLAIN X- RAY (cardiomegaly- pericardial effusion)

ECHO is important and diagnostic (detect pericardial effusion and degree of valvular affection)

TREATMENT

Curative treatment

Bed rest for 3 weeks or till improvement of all symptoms and signs

Diet (salt restriction in heart failure)

Eradication of streptococcal infection by:

- long acting penicillin 1,200,000 u deep im once OR
- penecilline procain 400,000 u only im, twice daily for 10 days OR
- oral penicillin v 400,000 u 4 times daily for 10 days
**Prophylactic treatment**

Long acting penicillin 1,200,000 u every 2-4 weeks deep im **Or**

Penicillin v orally 400,000 u twice daily **Or**

Erythromycin 250 mg twice daily orally

**Duration of prophylactic treatment**

- Rh fever without carditis: 5yrs or till 21yr of age

- Rh fever with carditis but without residual heart disease: 10 yrs- adulthood

- Rh fever with carditis and residual heart disease: 10 yrs at least since last episode and at least till 40 yr of age.

**Prevention of subacute bacterial endocarditis**

Tonsillectomy if large tonsils with repeated infection

- Sensitivity test must be done before any long acting penicillin
- If the patient is sensitive to penicillin we give erythromycin 50 mg /kg/day orally for 10 days

- Treatment of rheumatic symptoms as carditis and arthritis by:
Salicylates

*indications:
- rheumatic fever without carditis
- with carditis but without cardiomegaly or congestive heart failure

Dose 100 mg/kg/day in 6 divided doses orally for 3-5 days, followed by 75 mg/kg/d until ESR returns to normal.

Corticosteroids (prednisone)
*indications
- rh fever with carditis
- no response to salicylates
- rh fever with heart failure

Dose 2 mg/kg/day until ESR is normal then gradual withdrawal

■ Treatment of rheumatic chorea:
- haloperidol 1-5 mg/day orally divided in doses
- chlorpromazine

COMPLICATIONS
valvular lesion
infective endocarditis
heart failure
arrhythmias
PROGNOSIS – OUTCOME

- Those with carditis as part of the initial episode are at greater risk of developing recurrences and of sustaining further cardiac injury.

- Worldwide, approximately 60% of all patients with ARF will develop rheumatic heart disease.

- Patients without carditis during the initial episode have a relatively low risk of developing carditis during recurrences.

- An inverse relationship between severity of joint involvement and risk of carditis appears to exist.
- In approximately 75% of cases, the acute attack lasts only 6 weeks.
- Ninety percent of cases resolve in 12 weeks or less.
- Fewer than 5% of patients have symptoms that persist for 6 months or more.

- Cardiac involvement is the major cause of long-term morbidity. Valvular vegetations (endocarditis) are the cause of mitral valve regurgitation, the end result being left ventricular (LV) dilation and congestive heart failure (CHF). Myocarditis is present but not the cause of heart failure.
Bacillary Dysentery (Shigellosis)

- **Gram-negative, non-spore forming** rod-shaped bacteria.
- It is only naturally found in humans and apes.
- It typically causes **dysentery**
- Shigella species are classified by four **serogroups**:
  1. Serogroup *A*: *S. dysenteriae*
  2. Serogroup *B*: *S. flexneri*
  3. Serogroup *C*: *S. boydii*
  4. Serogroup *D*: *S. sonnei*
Pathogenesis

- Fecal–oral route; depending on age and condition of the host (ten bacterial cells can cause infection).
- Causes dysentery (destruction of the intestinal mucosa in the cecum and rectum).
- Some strains produce enterotoxin and Shiga toxin, similar to the verotoxin of E. coli O157:H7.
- Both Shiga toxin and verotoxin are associated with causing hemolytic uremic syndrome.

Clinical features

- Symptoms begin 2-4 days after ingestion, usually last for several days but can last for weeks.
- The most common symptoms are diarrhea, fever, nausea, vomiting, tenesmus, colicky abdominal pain, and flatulence.
- The stool may contain blood, mucus, or pus.
- On examination, dehydration with tenderness over the colon. Arthritis or iritis may complicate shigellosis (Reiter's syndrome)

TREATMENT

- ORT or IV fluid if severe attack.
- Ciprofloxacin 500mg 12hourly for 3 days
- Ampicillin, metheprim can also be used.
Leptospirosis

Introduction

Zoonotic infectious disease caused by pathogenic leptospires;
- Coiled, motile, hook at each end, G – darkfield microscope in korthof’s media;
  - Survive several months in water and moist soil
  - Can cause systemic infection manifested as widespread vasculitis
  - *L. interrogans* is pathogenic to man
  - 23 serogroups and more then 200 serotypes in the world;

Epidemiology

- Disease of the wild animals
- Incidental human infection by direct or indirect contact with the animal
- Epidemiologic features:
  1. season: summer and fall;
  2. young and middle age, children
  3. occupation: farmer, slaughter, fisher, veterinarian.
  4. epidemic type:
     - rice field type
     - flood type
     - rain type
Reservoirs of Infection

- Rats
- Dogs
- Live stocks
- Rodents including rabbits
- Wild animals
- Cats

Sources of Human Infections

- Contaminated Water or soil from infected urine
- Direct animal contacts
- Occupational exposure: farmers, vets, abattoir workers
- Recreational exposure: campers, swimmers, visiting graveyards

Routes of Infection

- Contact with water or soil contaminated animals
- Direct contact with the urine from infected source, farmer, vets, butchers, recreational activities
- Rodents carry scrub typhus, paratyphus, leptospirosis

Microbiology and distribution

- Mainly serogroup ictohemorrhagiae (rats) and canicola (dogs)
Pathogenesis

- Entry sites: skin wounds or abrasions in hand and feet and mm, conjunctiva, nasal, oral
- Bacteremia involving the entire body including eye, CSF
- Systemic effect and vasculitis due to endotoxin (hyaluronidase) and burrowing motility
- Hemorrhagic necrosis especially in the liver, lung, and kidneys leading to jaundice and acute renal failure

PATHOLOGY

1. Basic pathological change is infective, toxic injury of systemic capillaries;

2. In severe cases: lung, liver, kidneys, brain, exudation, hemorrhage, edema or necrosis.

Phase I (Septicemia)

- Following incubation period of 7-10 days
- High spiking fever, headaches, myalgia, arthralgias, conjunctival congestion
- Lasting 4 – 7 days
- Proteinuria and increased creatinine
- Organism detectable but serologic diagnosis not possible

Phase II (Immune)
• Induction of IgM Antibodies
• 1- 3 day freedom followed by recurrence of symptoms
• Lower fever, then appearance of CNS signs
• Maybe cultured from urine but not from blood or CSF
• Abnormal LFT

**Weil’s Disease**
• Less common but severe form
• Mild phase I, initially followed by severe Jaundice , Azotemia, and hemorrhage from lungs, GI tract, and other organs (3-6 day)
• Oliguric renal failure and liver dysfunction dominate the clinical picture

**Pulmonary Syndrome**

• Hemoptysis, lung infiltrates and respiratory failure
• ARDS in fatal cases
• High mortality

**Clinical Signs of Leptospirosis**

• Pulmonary infiltrates, pneumonitis, hemorrhages
• Conjunctival injection
• Jaundice
• Muscle tenderness
• Abdominal tenderness
• Rales
• Erythema, petechiae, neck stiffness, lymph adenopathy

**SEQUELAE**
1. After fever :1~5 days after defervescence
2. Sequeleae of eyes: 1w~1m
   • iridocyclitis, choroiditis, uveitis
3. Reactive meningitis
4. Cerebroarteritis obliterans: 2w~2m
   hemiplegia, aphasia

**LABORATORY FINDINGS**

1. Routine examination:
   1) Leucocytosis; thrombocytopenia
   2) GUE: protein (2/3)
   3) Elevated liver enzymes
   4) CSF

2. Serological examination:
   1) Microscopic agglutination test (MAT)
      It detects antibody >1:400(2nd week)
   2) ELISA: to detect serum and CSF IgM

3. Pathogenic tests:
   1) blood culture: before 10th day of dis.
   2) PCR: DNA( highly sensitive and specific)

**DIFFERENTIAL DIAGNOSES**

1. Influenza
2. Typhoid fever
3. Lobar pneumonia
4. Viral hepatitis
5. Viral meningitis
6. Epidemic hemorrhagic fever
7. Sepsis

**Chest X-rays**
   • 33 – 64 % of patients shows abnormality as:
• Bilateral nodules
• Diffuse ill-defined infiltrates
• Massive confluent consolidation
• Bilateral, peripheral predominance
• Complete resolution within 5 to 10 days

**Treatment**

• Early anti-microbial therapy is important to shorten the course and prevent carrier state
• Treatment of choice is Penicillin G 1.5 megaunit 6-h for 1w or Ceftriaxone 1g i.v daily, or Ampicillin
• May cause Jarish-Huxheimer type reaction” it is acute febrile reaction following treatment that resolves within 24h, (treated by physical cooling, sedative, and hydrocortisone).

• Mild cases are treated by oral Doxycycline( 100mg twice daily for 1w).

**Prevention**

• Vaccination of domestic animals
• Rodent control
• Protective gloves and boots
• Avoid swimming in contaminated waters
• Vaccination of man in endemic region ( multivalent vaccine).

**HIV INFECTION**

- HIV is a **lentivirus** (retrovirus family)
Causes acquired immunodeficiency syndrome (AIDS)

- A condition in humans in which the immune system begins to fail, leading to life-threatening opportunistic infections.

HIV infection in humans is considered pandemic by the WHO.

- From its discovery in 1981 to 2006, AIDS killed more than 25 million people
- It infects about 0.6% of the world's population

- Antiretroviral treatment reduces both the mortality and the morbidity of HIV infection
- HIV infects primarily helper T cells (specifically CD4+ T cells), macrophages, and dendritic cells.

HIV infection leads to low levels of CD4+ T cells by 3 mechanisms:

- first, direct viral killing of infected cells
- second, increased rates of apoptosis in infected cells
- third, killing of infected CD4+ T cells by CD8 cytotoxic lymphocytes that recognize infected cells.
This results in loss of cell-mediated immunity.

The major routes of transmission are: unsafe sex, parenteral (blood and its product), and vertical.

Most untreated people infected with HIV-1 eventually develop AIDS
HIV progresses to AIDS at a variable rate affected by viral, host, and environmental factors; most will progress to AIDS within 10 years of HIV infection

**Pathogenesis**

- Lentiviruses, which are responsible for long incubation period, are transmitted as single-stranded, enveloped RNA.
- Upon entry of the target cell, the viral RNA genome is converted to dsDNA by a virally encoded reverse transcriptase that is present in the virus particle.
- This viral DNA is then integrated into the cellular DNA by a virally encoded integrase so that the genome can be transcribed.
- After the virus has infected the cell, two pathways are possible:
  - either the virus becomes latent and the infected cell continues to function
  - or the virus becomes active and replicates, and a large number of virus particles that can then infect other cells are liberated.
Signs and symptoms

- HIV infection has four basic stages:
  - primary infection,
  - asymptomatic infection,
  - mildly symptomatic and
  - AIDS.

**Primary infection**
- 2-6w post-exposure.
- Rapid viral replication
- levels of HIV (several million viruses per mL of blood).
- Rapid decline in CD4 cells

- Viremia associated with the activation of **CD8 +T cells**, which kill HIV-infected cells, and subsequently with specific antibody production, or **seroconversion** (3-12w)
A good CD8+ cell response has been linked to slower disease progression and a better prognosis, though it does not eliminate the virus.

Clinical features

- **Fever**, cervical LAP, pharyngitis, rash, myalgia, malaise, headache, nausea and vomiting, hepatosplenomegaly, weight loss, mouth and esophageal sores, and rarely neurological symptoms.
- They are nonspecific symptoms, so they are often not recognized as signs of HIV infection and are not used for the diagnosis.
- Patient is much more infectious during this period.

Asymptomatic infection (latency stage)

- Few or no symptoms and can last anywhere from 2w-20y and beyond.
- HIV is active within LN (persistently swollen).
- Viral particles accumulate both in infected cells and as free virus.
- Sustained viremia with decline in CD4 count depending on viral load (usually 50-150 cells/y)
- Individuals are still infectious.
- During this stage of infection early initiation of antiretroviral therapy significantly improves survival, as compared with deferred therapy.

Mildly symptomatic disease

- Develop in the majority.
- Correspond to ARC.
- 7-10y from infection to this stage.
- ARC include:
  - diarrhea, w.t loss, recurrent candidiasis, PID, ITP, fever and night sweats, herpes zoster, oral hairy leucoplakia, p. neuropathy
AIDS
- When CD4 +T cell decline below 200 cells/µL, cell-mediated immunity is lost
- Defined by development of opportunistic infections and tumors.
- Typically, an increased susceptibility to oral candidiasis and tuberculosis.
- Later, reactivation of latent herpes viruses may cause worsening recurrences of herpes simplex eruptions, shingles, Epstein-Barr virus-induced B-cell lymphomas, or Kaposi's sarcoma.

STAGES OF HIV INFECTION
A. Viral TX
   sexual intercourse
   blood/blood product
   perinatal TX
- Risk of TX by needle sharing is 1 in 300, by occupational percutaneous exposure is 1 in 300-1000

B. Acute (primary) HIV infection
- 2-6 wks following TX
- Viral replication and CD4 decline
- Infect. Mono-like SX (often overlooked)
- Confirmation by high viral load and absent HIV-Abs.

C. Sero Conversion
   HIV-Abs 4 wks (usually) and invariably 6 mon (few exception)

D. Asymptomatic HIV infection
   8 – 10 yrs
   gradual decline in CD4 counts
   relatively stable viral load (HIV RNA level)
E. Symptomatic HIV infection (ARC)  
thrush/candidiasis  
cervical dysplasia/Ca. in situ  
HZ. Recurrent, multiple dermatomes  
O H L  
peripheral neuropathy  
chronic diarrhea  
Constitutional SX.

F. AIDS: CD4 < 200 (CD4% < 14 %)  
AIDS defining dis:  
  pcp  
cryptococcal meningitis  
Esoph. Candidiasis  
Recur. Bact. Pneumonia  
CNS toxoplasmosis  
TB, Salmonella  
Lymphoma (N.H.)  
Ch. Intestinal cryptospondosis  
isosporiasis  
kaposi sarcoma

G. Advanced HIV Disease  
  CD4 < 50  
  Most Aids-related deaths  
  Common Late Stage  
  CMV Retinitis, Colitis  
  Disseminated MAC

**Diagnosis**
- Initial screening with an enzyme-linked immunosorbent assay (ELISA) to detect antibodies to HIV-1.
- Specimens with a non-reactive result from the initial ELISA are considered HIV-negative unless new exposure to an infected partner or partner of unknown HIV status has occurred.
Specimens with a reactive ELISA result are retested in duplicate. If the result of either duplicate test is reactive, the specimen is reported as repeatedly reactive and undergoes confirmatory testing with a more specific supplemental test Western blot or, IFA.

Only specimens that are repeatedly reactive by ELISA and positive by IFA or reactive by Western blot are considered HIV-positive and indicative of HIV infection.

Specimens that are repeatedly ELISA-reactive occasionally provide an indeterminate Western blot result, which may be either an incomplete antibody response to HIV in an infected person or nonspecific reactions in an uninfected person.

A second specimen should be collected more than a month later and retested for persons with indeterminate Western blot results.

Nucleic acid testing (e.g., viral RNA or proviral DNA amplification method) can also help diagnosis Pneumocystis pneumonia

Caused by the yeast-like fungus which had previously been classified as a protozoan (Pneumocystis jirovecii).

It is specific to humans;

Pneumocystis is commonly found in the lungs of healthy people.

The older name Pneumocystis carinii, which now only applies to the (Pneumocystis variant that occurs in animals), is still in common usage.
Symptoms

- Fever, non-productive cough,
- Shortness of breath,
- Weight loss and night sweats.
- There is usually not a large amount of sputum with P
- Is a tumor caused by Human herpesvirus 8 (HHV8),
  also known as Kaposi's sarcoma-associated herpesvirus (KSHV). It became more widely known as one of the AIDS defining illnesses in the 1980s.
- The erythematous to violaceous cutaneous lesions seen in KS have several morphologies: macular, patch, plaque, nodular, and exophytic.
- CP unless the patient has an additional bacterial infection.
- Few signs on auscultation
- The fungus can invade the liver, spleen and kidney.
- Pneumothorax is a well-known complication of PCP.

Chest X-ray

There is bilaterally increased opacification with sparing of apex and base.
- PO2 (strikingly lower than would be expected from symptoms)
- Sputum or bronchio-alveolar lavage. Staining with toluidine blue, silver stain or PAS or IFA, which will show characteristic cysts.
The cysts resemble crushed ping-pong balls and are present in aggregates of 2 to 8.

A lung biopsy would show thickened alveolar septa with fluffy eosinophilic exudate in the alveoli.

Polymerase chain reaction.

Simple molecular detection of *Pneumocystis jirovecii* in lung fluids does not mean that a person has *Pneumocystis* pneumonia or infection by HIV.

The fungus appears to be present in healthy individuals also in the general population.
Disease course

- The disease attacks the interstitial, fibrous tissue of the lungs, with marked thickening of the alveolar septa and alveoli and leading to significant hypoxia which can be fatal if not treated aggressively; therefore, LDH levels increase and gas exchange is compromised.

Treatment

- Most commonly used medication is co-trimoxazole, but some patients are unable to tolerate this treatment due to allergies.
- Steroid is added to avoid inflammation, which causes an exacerbation of symptoms about four days after treatment begins if steroids are not used.
- Other medications that are used, alone or in combination, include pentamidine, trimetrexate, dapsone, atovaquone, primaquine, and clindamycin. Treatment is usually for a period of about 21 days.

- Pentamidine side effects include: acute pancreatitis, renal failure, hepatotoxicity, leukopenia, rash, fever, and hypoglycaemia.

Prevention

- In immunocompromised patients, prophylaxis with Bactrim or regular pentamidine inhalations may help prevent PCP.