Chapter 1

Infectious Diseases

Q. What are infectious diseases?

"Infectious diseases" is a broad term encompassing illnesses caused by pathogenic microorganisms. These diseases can spread directly or indirectly from person to person or via vectors, animals, or the environment.

Types of infectious agents:
1. Bacteria, e.g. *Mycobacterium tuberculosis* causing tuberculosis.
2. Viruses, e.g. influenza virus, SARS-CoV-2 (COVID-19).
3. Fungi, e.g. *Candida albicans* causing candidiasis.
4. Parasites, e.g. Plasmodium species causing malaria.
5. Prions, e.g. misfolded proteins causing diseases like Creutzfeldt-Jakob disease.

Q. Define the terms: Colonization, infestation, infection, bacteremia, sepsis and septic shock.

Colonization

- This is the simple presence of potentially pathogenic microorganisms on or within a host (like on the skin, mouth, intestines or airway) without causing disease. However, colonization may progress to infection.
- Example: Normal flora such as *Staphylococcus epidermidis* on the skin.
- Clinical relevance: Colonization does not require treatment unless there is a risk of progression to infection (e.g. in immunocompromised patients).

Infestation

- Infestation refers to presence of parasites inside or on the host. Examples: Head louse infestation, worm infestation.

Bacteremia

- Presence of viable bacteria in the bloodstream is called bacteremia which may or may not cause symptoms. It can result from day-do-day activities such as tooth brushing or dental procedures. Bacteremia usually does not cause any symptoms such as fever and often usually resolves on its own.
- Clinical relevance: Rarely it can progress to sepsis and septic shock.

Infection

- The invasion and multiplication of pathogenic microorganisms in the host, leading to tissue damage and eliciting an immune response, e.g. pharyngitis, pneumonia, viral hepatitis.

Sepsis

- A life-threatening condition that arises when the body's response to an infection causes widespread inflammation and organ dysfunction. Sepsis is usually associated with fever, weakness, tachycardia, tachypnea and multi-organ dysfunction.

Septic Shock

- Sepsis that causes dangerously low blood pressure is called septic shock (SBP <90 or MAP <70). It is a type of vasodilatory or distributive shock. It carries high morbidity and mortality.

Q. Discuss the serological (immunological) methods used in the diagnosis of infectious diseases.

- Serological (immunological) methods involve detection of antigen or antibody of a microorganism in a given sample. These are as follows:
  - Enzyme-linked immunosorbent assay (ELISA)
  - Rapid immunochromatographic test
  - Western blot (immunoblot) test
  - Immunofluorescence test
  - Complement fixation test
  - Agglutination test
  - Immunodiffusion
  - Immunoelectrophoresis

Enzyme-linked Immunosorbent Assay (ELISA)

- **ELISA** is a widely used laboratory technique for detecting and quantifying substances, typically antigens (proteins, peptides, or hormones) or antibodies, in biological samples such as blood, serum, or plasma.
- ELISA relies on the specific interaction between an antigen and an antibody, combined with an enzyme-

linked detection system that produces a measurable color change or signal when a substrate is added.
- ELISA tests are usually performed in microwell plates.

Steps in a Typical ELISA Test

- Antigen or antibody is immobilized on a 96-well microplate.
- Clinical sample is added into these microwells. If a specific antigen or antibody is present in the clinical specimen, it is captured by the coated antigen/antibodies on the ELISA plate.
- A second antibody to the target protein conjugated with an enzyme is then added which is captured by the target protein. The unbound material is washed out. A chromogenic substrate (to the enzyme) is then added. Development of color by the action of hydrolyzing enzyme on chromogenic substrate indicates the presence of the specific antigen or antibody. Color intensity is measured by the spectrophotometer.
- There are many variations of ELISA, but the basic principle remains the same as described above. In the first-generation ELISAs either crude antigen or single antigen is used for the test. In the second and third-generation ELISAs multiple antigens or recombinant antigen or/and specific peptides are used, which improves the sensitivity and specificity of the test.
- ELISA is routinely used to detect antibodies against HIV and hepatitis A virus.

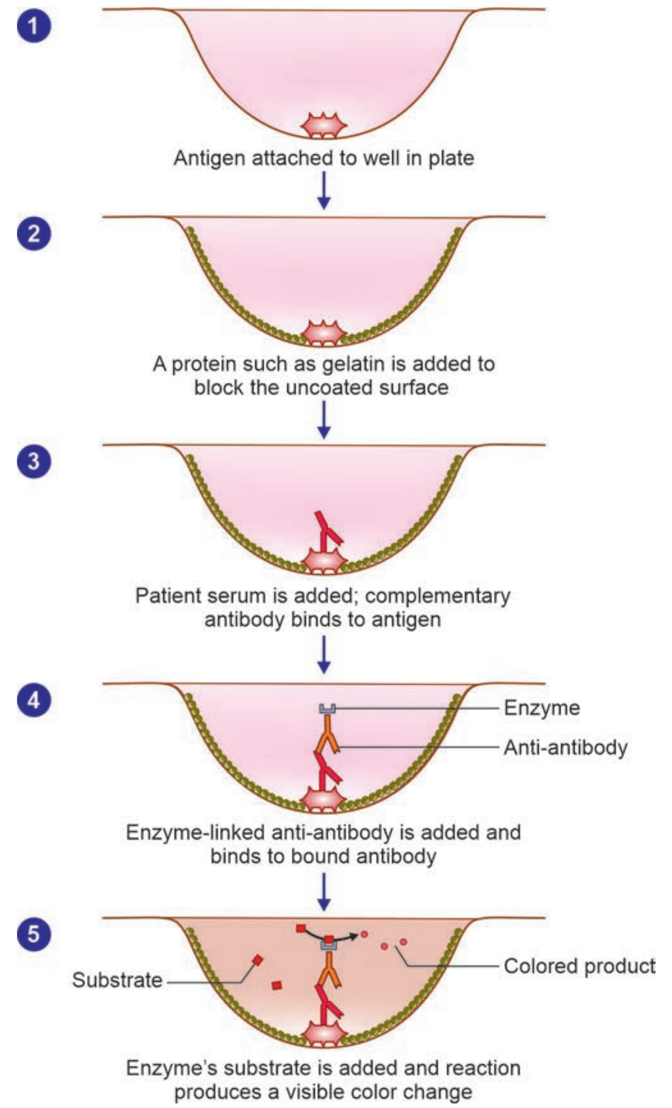

Figure 1.1: ELISA

Rapid Immunochromatographic Test

- ICT is based on the **lateral flow assay** principle, where a liquid sample flows along a nitrocellulose strip and interacts with reagents pre-applied to specific zones. Detection is achieved through visual signals, often color changes, that indicate the presence of the target analyte. This allows rapid detection of antigen or antibodies in patient's body fluids. Clinical sample (blood or urine) is added to the wells provided in the kit. The sample diffuses across the plate and the presence of specific proteins is indicated by the development of colored bands on the strip. These diagnostic strip tests are simple, rapid, cheap and reliable and can be used at home and clinics. Such kits have been developed for dengue; malaria, etc. Urine pregnancy test kit is also an example of immunochromatographic test which uses specific antibodies to selectively identify hCG in urine.

Figure 1.2: Rapid chromatographic test

Western Blot (Immunoblot) Test

- In Western blot, antibodies to multiple specific proteins are detected. Hence, it has high specificity. Microbial protein is run on gel electrophoresis to separate the ligands, which are then transferred on to a nitrocellulose membrane strip. Patient's serum is added to this nitrocellulose strip. If there are antibodies to a specific microorganism, they bind to antigens present on the strip. Enzymatically labeled anti-immunoglobulins can be added now which bind to the antibodies and visualized by the addition of an enzyme substrate to produce colored bands. This test is commonly used to confirm the diagnosis of HIV infection.

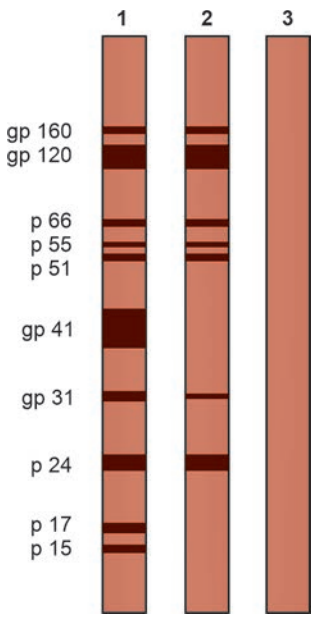

Figure 1.3: Western blot test

Test 1 is a control as it shows all the proteins tested for are present.

Test 2 is a positive result as it shows there are antibodies for 7 of the HIV proteins.

Test 3 is a negative result.

Immunofluorescence Test

- This test makes use of immunoglobulin (antibody) labeled with fluorescent dye to detect antigens or antibodies. It requires a fluorescent microscope to read the signal. It is commonly used to detect infections with herpes virus, dengue virus and rabies virus.

Direct Immunofluorescence

- Direct immunofluorescence or direct fluorescent antibody (DFA) test uses a single antibody labeled with fluorescent dye to detect the presence of a specific antigen. If a specific antigen of a microorganism is present in patient's serum, it combines with the antibody labeled with a fluorescent dye which can be detected as a fluorescent signal under a fluorescence microscope. This test is highly sensitive and specific.

Indirect Immunofluorescence

- Here two antibodies are used. The first antibody recognizes the target antigen and binds to it, and the second antibody, which is labeled with a fluorescent dye recognizes the first antibody and binds to it.
- This test is more complex than the direct immunofluorescence test and takes more time but allows more flexibility. Patient's serum is incubated with a specific microbial antigen. If specific antibodies are present in the patient serum, they combine with the antigen. Next, fluorescent-labeled antisera is added and the fluorescent signal is looked for.

Applications of Immunofluorescence

- Diagnosing autoimmune diseases (e.g. lupus with kidney biopsies).
- Detecting pathogens directly (e.g. *Treponema pallidum* in syphilis, *Plasmodium falciparum*).
- Detecting viral antigens (e.g. influenza, herpes simplex virus).

Complement Fixation Test

- Complement fixation test (CFT) is a serological method used to detect the presence of specific antigens or antibodies in a patient's serum by measuring the activity of the complement system. It is based on the principle that antigen-antibody complexes consume complement proteins, preventing them from lyzing red blood cells in a controlled test environment.
- Patient's serum is heat treated to remove any free complement. The serum is mixed with a known antigen (for antibody detection) or antibody (for antigen detection). Standardized complement proteins are added to the mixture. The mixture is incubated to allow formation of antigen-antibody complexes and complement fixation. Sensitized sheep red blood cells and hemolytic antibodies (anti-sheep antibodies) are then added.
- If antibodies are present in the patient's blood, there is formation of antigen-antibody complex and complement gets fixed to these complexes (used up), hence there is no complement left to lyse the RBCs. If there is no antibody, complement remains unused and it lyzes the sensitized sheep RBCs. Absence of hemolysis means complement fixation test is positive which means that specific antibodies are present. This test has been largely superseded by other methods such as ELISA and PCR, but still useful for the following.

Applications

- CFT is used to detect antibodies against pathogens that cause infectious diseases.
- Detection of autoimmune diseases**:** CFT can help detect autoimmune diseases by identifying autoantibodies (systemic lupus erythematosus (SLE) (anti-dsDNA antibodies), rheumatic fever.
- Screening for immunodeficiency: Identifying deficiencies in components of the complement system.
- Research applications: Studying complement-mediated immune mechanisms.

Agglutination Test

- An agglutination test detects the presence of antigens or antibodies in a sample through the clumping (agglutination) of particles such as red blood cells, latex beads, or bacteria.
- *Types of agglutination tests:* Direct agglutination test (DAT), indirect agglutination test (passive agglutination), hemagglutination test, coombs test (antiglobulin test), bacterial agglutination test.

Direct Agglutination Test (DAT)

- DAT is a diagnostic method that detects antigens naturally present on the surface of cells, such as red blood cells, bacteria, or other pathogens, by directly observing the agglutination caused by the binding of specific antibodies to these antigens.

- When antibodies specific to the antigens on the surface of a cell or pathogen are mixed, they bind to the antigens, forming cross-links between the cells. This interaction leads to visible clumping (agglutination) of the cells, which indicates the presence of the antigen.

Applications of DAT

- To determine ABO and Rh blood groups with specific anti-A, anti-B, and anti-D sera.
- Diagnosis of diseases like brucellosis, typhoid, and certain fungal infections by detecting antigens directly.
- Detection of Leishmania in visceral leishmaniasis.
- Identification of bacterial species by using antisera specific to bacterial antigens (e.g. serotyping Salmonella or Shigella species).

Indirect (Passive) Agglutination Test

- Unlike the direct agglutination test, this test uses artificially coated particles, such as latex beads, gelatin, or red blood cells, to which the antigens or antibodies are bound. These coated particles act as carriers to amplify the visible agglutination reaction.
- When antibodies (from the patient sample) interact with antigens (coated on the artificial particles) or *vice versa*, the particles clump together, forming visible agglutination. This method is termed "passive" because the antigens or antibodies are not naturally present on the particles but are artificially attached.
- In latex agglutination test, latex particles coated with specific antibody are mixed with patient's serum. If there are specific antigens in the patient's serum, there is agglutination of antibody coated latex particles. This test is used to detect toxins of *Vibrio cholerae* and staphylococci.
- In hemagglutination test, RBCs are coated with known antigens. If mixed with serum containing specific antibodies, there is agglutination of RBCs. This is used in the diagnosis of syphilis and herpes virus infections.

Immunodiffusion

- Immunodiffusion is a diagnostic test which involves diffusion through a substance such as agar gel. Here a specific antigen or antibody is placed in one well and patient's serum or body fluid is placed in another well and left for 48 hours. The antigen and antibody diffuse through the agarose gel towards each other and a precipitation line is formed between the two wells.

Immunoelectrophoresis

- It is a technique used to analyze and identify specific proteins in a sample, often serum or other body fluids. It combines the principles of electrophoresis and immunodiffusion to separate and characterize proteins based on their size, charge, and antigenic properties. This test is conducted on agarose gel.
- *Electrophoresis:* Proteins in the sample are separated based on their charge and size by applying an electric field to a gel.
- *Immunodiffusion:* After electrophoresis, a trough is cut into the gel, and specific antibodies are added. Proteins (antigens) and antibodies diffuse through the gel and form visible precipitin arcs where they interact.

Clinical Applications

- Detection of abnormal proteins: Useful in conditions like multiple myeloma and other plasma cell dyscrasias.
- Quantification of immunoglobulins: Identifies IgG, IgA, IgM, and their subtypes in cases of immune deficiency or overproduction.
- Identification of specific proteins: Useful for confirming the presence of specific proteins in serum or other fluids.

Q. Discuss the molecular methods used in the diagnosis of infectious diseases.

- Molecular methods have revolutionized the diagnosis of infectious diseases by providing rapid, sensitive, and specific detection of pathogens. These methods rely on the identification of nucleic acids (DNA or RNA) unique to the pathogen. These are polymerase chain reaction (PCR), southern blotting and northern blotting.

Polymerase Chain Reaction (PCR)

- This is the most specific and sensitive test of all molecular techniques. Here the nucleic acid sequence of a microorganism is amplified so that it becomes easily detectable. Since each microorganism has unique DNA/RNA sequences, it is possible to select a PCR primer that specifically identifies a particular microorganism.
- Multiple microorganisms can be identified in single clinical sample using 'multiplex' PCR.
- Fluorescent dyes can be attached to different primers and the final nucleic acid polymers examined by light spectroscopy.
- Reverse transcriptase (RT)-PCR amplifies very small amounts of any kind of RNA (mRNA, rRNA) and makes complementary DNA, which is then amplified with conventional PCR. HIV viral copies are estimated by this method.
- Real-time PCR (qPCR) is used to quantify the organisms and is used in estimation of HIV viral load.
- The disadvantages of PCR are its high cost and false-positive results. False positive results happen if there is any contamination from laboratory or other sources.

Applications

- Detecting bacterial (e.g. *Mycobacterium tuberculosis*), viral (e.g. HIV, influenza), fungal, and parasitic infections.
- Monitoring viral load in chronic infections (e.g. hepatitis B or C).

- Multiplex PCR is used to detect multiple pathogens in respiratory, gastrointestinal, or central nervous system infections (e.g. multiplex panels for meningitis/encephalitis pathogens).
- Most widely used method for detecting COVID-19 (reverse transcription polymerase chain reaction—RT-PCR).

Southern Blotting

- Southern blot is a method for detection of a specific DNA sequence in DNA samples. Southern blot is named after biologist Edwin Southern who developed this technique.
- DNA fragments are separated by gel electrophoresis and transferred on to a blotting paper. A DNA probe (this is a piece of single stranded DNA with known sequence labeled with a radioactive isotope or a fluorescent signal) is then added to the blotting paper. DNA probe will bind to its complementary DNA if present. This is then washed to remove any unbound DNA probe.
- Even after washing if there is radioactivity or fluorescence, it means that a specific DNA complementary to DNA probe is present. Since each microorganism has specific DNA sequences, it indicates the presence of that particular microorganism in the clinical specimen.

Applications

- **Gene detection:** Identifying the presence or absence of specific genes in an organism's genome.
- **Gene mapping:** Locating genes or mutations associated with specific genetic diseases.
- **RFLP analysis:** Studying restriction fragment length polymorphisms for genetic diversity, forensic analysis, or paternity testing.
- **Diagnosis of genetic disorders:** Detecting mutations or deletions associated with diseases like sickle cell anemia or cystic fibrosis.
- **Viral genome detection:** Identifying viral DNA in infected samples (e.g. HPV, HBV).

Northern Blotting

- This is same as Southern blotting except that RNA fragments are used to detect and quantify specific RNA molecules in a sample instead of DNA.

Applications

- Detect RNA viruses like HIV or influenza in infected samples.
- **Gene expression analysis:** Measure mRNA levels to study gene activity under different conditions or during development.

Q. Define fever of unknown origin (FUO). Enumerate the causes of FUO. How do you approach a case of FUO?

- Fever of unknown origin (FUO) or pyrexia of unknown origin (PUO) is prolonged febrile illness without an established etiology despite intensive evaluation and diagnostic testing **(Table 1.1)**.

Category-based Definitions of FUO

TABLE 1.1: Category-based definitions of FUO

Category	Commonly used definition
Classic FUO	Temperature >38.3°C (100.9°F) recorded on several occasions for >3 weeks, despite 3 outpatient clinic evaluations, 1 week of intensive outpatient investigation, or 3 days of hospital-based evaluation (*remember* 3,3,1,3).
Healthcare-associated FUO	
• ICU patient	Temperature >38.3°C (100.9°F) recorded on several occasions in an ICU patient despite ≥3 days of investigations. Fever must not have been present or incubating on admission.
• Non-ICU patient	Same definition as for ICU patient, except patient is hospitalized but not critically ill.
• Postoperative patient	Same definition as for ICU patient, except fever is usually defined as ≥38.0°C (100.4°F).
FUO in immunocompromised patients	
• Neutropenic patients	Temperature ≥38.3°C (100.9°F) sustained over a one-hour period, recorded on several occasions over at least 3 days, despite appropriate antimicrobial therapy. Neutropenia is defined as <500 neutrophils/µl or impending fall to that level within 48 hours.
• Patients with HIV and CD4 count <200 cells/µl	Temperature ≥38.3°C (100.9°F) recorded on several occasions for >3 weeks for outpatient or >3 days for inpatient despite appropriate evaluation.
Travel-associated FUO	Temperature >38.3°C (100.9°F) recorded on several occasions for >3 weeks, despite 3 outpatient clinic evaluations, 1 week of intensive outpatient investigation, or 3 days of hospital-based evaluation, in a patient who traveled to another country, typically within the prior 12 months.

Causes of FUO (Table 1.2)

TABLE 1.2: Causes of FUO

Infections (most common cause of FUO)
Bacterial
• Tuberculosis (very common cause of FUO)
• Typhoid
• Brucellosis
• Infective endocarditis
• Syphilis
• Melioidosis
• Sinusitis
• Osteomyelitis
• Prostatitis
• Dental abscesses
• Cholangitis
• Intra-abdominal abscesses (subphrenic, renal, retroperitoneal, and paraspinal abscesses)

(Contd.)

TABLE 1.2: Causes of FUO (*Contd.*)

Viral • HIV • Chronic hepatitis (B, C, D) • Infectious mononucleosis
Parasitic • Malaria • Amebiasis • Leishmaniasis • Malaria • Strongyloidiasis • Toxocariasis • Toxoplasmosis • Trichinellosis • Babesiosis
Rickettsial infections • Q fever • Rickettsial pox • Rocky Mountain spotted fever • Scrub typhus
Fungal • Candidiasis • Histoplasmosis • Mucormycosis • Blastomycosis • Cryptococcal disease
Neoplasms (second most common cause of FUO) • Lymphoma • Leukemia and other hematologic malignancies • Liver involvement with hepatoma or metastases • Renal cell carcinoma • Colon carcinoma • Atrial myxoma
Inflammatory and connective tissue disorders • Rheumatoid arthritis • Systemic Lupus erythematosus (SLE) • Sarcoidosis • Inflammatory bowel disease (IBD) • Polyarteritis nodosa (PAN) • Giant cell arteritis (common in elderly patients) • Polymyalgia rheumatica • Crohn's disease • Granulomatous hepatitis • Kikuchi disease
Miscellaneous • Drug fever • Factitious fever • Periodic fever (familial mediterranean fever)
Undiagnosed Even after extensive workup some FUOs may remain undiagnosed. Some of them may resolve spontaneously.

APPROACH TO A CASE OF FUO

Detailed History

- Since FUO has a broad range of possible causes, the history should be thorough, structured, and tailored to uncover subtle clues that may guide the diagnostic process.

Fever Characteristics

- **Onset:** When did the fever start?
- **Pattern:** Is the fever continuous, remittent, intermittent, or relapsing? Tertian fever (occurring every third day) in malaria, step ladder type fever (typhoid), undulant fever (evening fevers resolving by morning in brucellosis), week-long fever with week-long remission (relapsing fever in borreliosis), week-long high fevers with week-long remissions (known as Pel-Ebstein fever seen in Hodgkin's disease).
- **Temperature range:** Document the highest and lowest recorded temperatures.
- **Diurnal variation:** Is the fever higher in the evening or morning?
- **Response to medications:** Does the fever respond to antipyretics?

Associated Symptoms

- Weight loss, night sweats (e.g. tuberculosis, malignancy).
- Rash or skin lesions (e.g. vasculitis, lupus).
- Joint pain/swelling (e.g. rheumatoid arthritis, Still's disease).
- Lymph node enlargement (e.g. lymphoma, sarcoidosis).
- Neurological symptoms (e.g. meningitis, encephalitis).
- Cough, chest pain, dyspnea (e.g. pneumonia, fungal infections).
- Abdominal pain, jaundice (e.g. liver abscess, hepatitis).
- Diarrhea (intestinal infections, typhoid, HIV)
- Itching after a hot bath (lymphoma)
- Painful nodules on shins (tuberculosis, fungal infections, lymphoma)
- Contact with infection (tuberculosis) or animals (cat scratch disease, brucellosis) or birds (psittacosis).
- Inquire about symptoms involving all major organ systems.

Exposure History

- High-risk sexual behavior (HIV, hepatitis-B, hepatitis-C).
- Animal contact: Pets (toxoplasmosis, cat scratch disease, leptospirosis), livestock (brucellosis, Q fever).

Travel History

- Recent or past travel to endemic regions.
- Malaria, typhoid, or arboviruses (e.g. dengue, chikungunya) in tropical regions.
- Histoplasmosis or blastomycosis in the Mississippi River Valley.
- Tuberculosis or brucellosis in high-risk areas (suspect infections endemic in places visited).
- Drug therapy (suspect drug fever).

Occupational History

- Healthcare workers (tuberculosis, viral hepatitis).
- Farmers or veterinarians (zoonoses like anthrax, brucellosis, leptospirosis).
- Recent dental treatment (possibility of endocarditis).

- History of immunosuppression such as HIV infection or steroid therapy (suspect opportunistic infections).
- History of previous abdominal surgery, trauma, endoscopy, or gynecologic procedures increase the likelihood of an occult intra-abdominal abscess.

Past History

- Chronic diseases:
  - Diabetes (predisposes to infections).
  - Autoimmune diseases (e.g. lupus, sarcoidosis).
- Surgical history:
  - Prosthetic devices or implants (infection risk).
  - Splenectomy (increased susceptibility to encapsulated organisms).

Family History

- Hereditary autoinflammatory syndromes (e.g. familial Mediterranean fever).
- Genetic predisposition to autoimmune diseases or malignancies.
- Family history of TB or HIV or other infections can predispose other family members to same infection.

Treatment History

- Recent medications: Antibiotics, anticonvulsants, or antiarrhythmics can cause drug fever.
- Immunosuppressants: Increased risk of opportunistic infections.
- Recent dental treatment can lead to infective endocarditis.
- Hospitalizations: Nosocomial infections (e.g. catheter-associated infections).
- Foreign devices: Pacemakers, prosthetics, or central lines (risk of infection).
- Recent blood transfusions: Risk of HIV, hepatitis, malaria.

Personal History

- Alcohol abuse: Risk of liver abscess, TB, pneumonia.
- Diet: Raw or undercooked foods—risk of salmonellosis or toxoplasmosis. Unpasteurized milk—brucellosis or listeriosis.

Stress or Psychogenic Factors

- Factitious fever (self-induced).

Clinical Examination

- Do a complete physical examination. A meticulous, systematic physical examination can reveal subtle signs pointing toward the underlying cause. Since FUO encompasses a broad spectrum of conditions, the examination must be comprehensive and focused on detecting infectious, inflammatory, neoplastic, or other systemic causes.

Vital Signs

- Document the height and pattern of fever. Measure body temperature more than once and in the presence of a nurse to exclude factitious fever.
- BP: BP may be low in septic shock and myocarditis.
- Pulse: Pulse rate usually increases by 10 per degree Celsius rise in temperature. Relative bradycardia (i.e. pulse rate does not correspond to the raise in temperature) may be seen in enteric fever, brucellosis and some viral infections. Relative tachycardia, i.e. pulse rate more than expected to the raise in temperature may be seen in myocarditis, sepsis, hypovolemia and thyrotoxicosis.
- Respiratory rate: High respiratory rate usually points to some respiratory pathology such as pneumonia, empyema, ARDS, etc.

General Examination

- Significant weight loss: TB, HIV, malignancy.
- Pallor: May point to hematological malignancy, or a disseminated process such as TB involving bone marrow.
- Jaundice: Points to hepatobiliary disease (hepatitis, liver abscess, etc.).
- Clubbing: TB, chronic suppurative lung disease.
- Splinter hemorrhages: Infective endocarditis.
- Look for lymphadenopathy: Tuberculosis, infectious mononucleosis, HIV, lymphoma, malignancy.
- Skin and mucosal lesions
  - Maculopapular rash (rickettsial infections, viral exanthems).
  - Skin rashes in connective tissue diseases (e.g. butterfly rash in SLE, heliotrope rash in dermatomyositis).
  - Janeway lesions, Osler's nodes (infective endocarditis).
  - Petechiae or purpura (meningococcemia, vasculitis, infective endocarditis).
  - Erythema nodosum (sarcoidosis, tuberculosis, inflammatory bowel disease).
  - Eschars (rickettsial infections).
  - Oral ulcers in Behcets disease.
- Sternal tenderness: Seen in hematological malignancy due to bone marrow proliferation.
- Spinal tenderness: Pott's spine, epidural abscess.
- Signs of meningeal irritation like neck stiffness and Kernig's sign: Meningitis.
- Always examine the fundus and retina (papilloedema in meningitis, retinal leisons in CMV infection, disseminated candidiasis, tuberculosis).

Systemic Examination

- *CVS:* Carefully examine heart for any murmurs (infective endocarditis).
- *Abdomen:* look for any tenderness (deep abdominal infections) hepatosplenomegaly (enteric fever, malaria, hepatitis, hemolytic anemia, hematological malignancies), ascites (peritoneal tuberculosis, malignancy), renal angle tenderness (pyelonephritis).
- *RS:* Inspect for respiratory distress or cyanosis. Auscultate for crackles (pneumonia, pulmonary fibrosis), wheezing, or pleural rubs. Check for signs of pulmonary infections or embolism.

- *Musculoskeletal system*: Examine for joint swelling, warmth, or pain (rheumatoid arthritis, reactive arthritis, lupus), bony tenderness (osteomyelitis, malignancies), muscle tenderness (polymyositis, trichinosis).
- *Nervous system:* Altered consciousness (meningitis, encephalitis), focal deficits (abscess, stroke), neck stiffness (meningitis, subarachnoid hemorrhage).

Investigations

- Common things are common. First rule out common diseases such as enteric fever, tuberculosis, malaria, UTI, HIV infection, etc. and then only think of rare illnesses.
- Order routine investigations like Hb, total WBC count, RBC count, differential count, platelet count, ESR and peripheral smear study. Cytopenias may suggest a pathologic process involving bone marrow such as disseminated tuberculosis, hematological malignancies, etc. A high leukocyte count is common in infections. A very high leukocyte count may suggest leukemia. Eosinophilia is seen with parasitic infections and drug reactions. A very high ESR (>100 by Westergren's method) often indicates active tuberculosis, connective tissue diseases or malignancy (myeloma, leukemia, etc.).
- Urine microscopy and culture sensitivity (to R/O UTI).
- If there is cough and sputum production send it for Gram's stain, fungus stain, AFB, malignant cells and culture/sensitivity.
- Blood culture and sensitivity for both aerobic and anaerobic organisms (infecting organism may be picked up by this).
- Complete LFT and RFT to look for any liver and renal involvement.
- Culture and examination of the stool for any ova, parasites and occult blood.
- Chest radiograph (tuberculosis, pneumonia, sarcoidosis).
- Montoux test can help in diagnosing TB.
- Lumbar puncture and CSF examination if suspecting meningitis.
- Serological investigations (WIDAL test, ASO titer, HIV-Elisa, VDRL, TPHA, Paul Bunnel test, brucella agglutination test).
- Autoimmune and inflammatory markers (to rule out connective tissue diseases): Rheumatoid factor, antinuclear antibodies.
- Tumor markers: PSA (prostate cancer). CA-125 (ovarian cancer), CA-19-9 (colorectal, pancreatic cancer), alpha-fetoprotein (HCC).
- ECG, echocardiogram (to look for signs of infective endocarditis).
- Ultrasound abdomen and pelvis to R/O any intra-abdominal pathology. Ultrasound can help in many ways. It can document any organomegaly, intra-abdominal lymphadenopathy or masses, ascites, any change in the texture of organs, any intrabdominal collections of pus.
- CT/MRI scanning (intra-abdominal lymphadenopathy, tumors, abscesses).
- Tissue diagnosis (lymph node FNAC/biopsy, liver biopsy, bone marrow examination).
- Diagnostic surgical procedures like laparoscopy, exploratory laparotomy, etc. may be required in undiagnosed cases.

Treatment

- Treatment depends on the underlying cause.
- Until a diagnosis is made, it is better to use only symptomatic treatment. Blind antibiotic therapy may make diagnosis of an occult infection more difficult, and empirical steroid therapy may mask an inflammatory response without treating the underlying cause.
- Sometimes when all the tests are negative and the cause of fever remains undiagnosed, a therapeutic trial may be indicated. For example, antituberculosis therapy (ATT) in suspected tuberculosis and steroid therapy in suspected connective tissue diseases.
- Periodic review is very important in cases of FUO as development of new signs and symptoms may help in identifying the underlying cause. In some cases, a 'second opinion' by another physician can also be very helpful as different people think from different angles.
- Many undiagnosed cases of FUO will spontaneously resolve.

Q. Chemoprophylaxis.

- Chemoprophylaxis refers to the use of drugs to prevent disease or infection in individuals who are at risk. It is widely used in both infectious diseases and non-infectious conditions and is a critical public health tool to control outbreaks, prevent complications, and protect high-risk populations.
- For example, antibiotics may be administered to immunocompromised patients to prevent opportunistic infections. Antibiotics may also be given to healthy individuals to limit the spread of an epidemic, or to patients with recurrent infections (such as urinary tract infections) to prevent recurrence.

Types of Chemoprophylaxis

Primary Prophylaxis

- Prevents the initial occurrence of a disease.
- *Example*: Using isoniazid in high-risk individuals to prevent tuberculosis.

Secondary Prophylaxis

- Prevents recurrence of a disease in previously affected individuals.
- *Example*: Sulfadiazine and pyrimethamine in HIV-positive patients to prevent recurrent toxoplasmosis.

Common Situations where Chemoprophylaxis is used

Infectious Diseases

See **Table 1.3**.

TABLE 1.3: Common situations where chemoprophylaxis is used

Situation	Goal	Chemoprophylaxis
Rheumatic fever	To prevent recurrence and further cardiac damage	Phenoxymethylpenicillin 250 mg twice daily or inj Benzathine penicillin once a month for many years as recommended
Meningitis • Due to meningococci	To prevent infection in close contacts	Rifampicin 600 BD for 2 days Alternatives (single dose) ciprofloxacin 500 mg orally or inj ceftriaxone 250 mg IM
• Due to *H. influenzae* type b		Rifampicin 600 mg daily for 4 days
Tuberculosis	To prevent infection in exposed tuberculin-negative individuals, infants of infected mothers and immunosuppressed patients	Oral isoniazid 300 mg daily for 6 months
Valvular heart disease **Prosthetic heart valves**	To prevent infective endocarditis in dental, oral, or upper respiratory tract procedures:	Amoxicillin, 2 g orally. If allergic to penicllin, clindamycin 600 mg or cephalexin 2 g or azithromycin 500 mg can be used. Antibiotic should be given 1 hour before the procedure orally. If patient is unable to take orally any of these can be given parenterally.
Malaria	Prevention of malaria	Chloroquine one double strength tablet per week or mefloquine 250 mg once a week.
HIV infected patient with CD4 count below 200 cells/µl	Prevention of pneumocystis jiroveci pneumonia	Trimethoprim-sulfamethoxazole, one double-strength tablet (960 mg) daily
HIV infected patient with toxoplasma IgG antibody positive and CD4+ T cell count <100/µl	Prevention of toxoplasmosis	Trimethoprim-sulfamethoxazole, one double-strength tablet (960 mg) daily
HIV infected patient with CD4 count below 50 cells/µl	Prevention of Mycobacterium avium complex infection	Azithromycin (1200 mg orally weekly) or clarithromycin (500 mg orally twice daily)

Non-infectious Diseases

- **Thromboembolism:** Low-molecular-weight heparin (LMWH) or aspirin for individuals at risk (e.g. post-surgery or immobile patients).
- **Cancer prevention:** Tamoxifen for breast cancer prevention in high-risk individuals.
- **Cardiovascular diseases:** Statins or aspirin for prevention in high-risk individuals.

Q. Opportunistic infections (Fig. 1.4 and Table 1.4).

- Opportunistic infection is an infection by a microorganism that normally does not cause disease, but becomes pathogenic when the body's immune system is impaired. Opportunistic infections are common in following conditions:
  - Primary immune deficiency disorders
  - HIV infection
  - Steroid therapy
  - Chemotherapy for cancer
  - Immunosuppressing agents for organ transplant recipients
  - Malnutrition
  - Prolonged antibiotic therapy
- Opportunistic infections can be due to bacteria, viruses, protozoa or fungi.

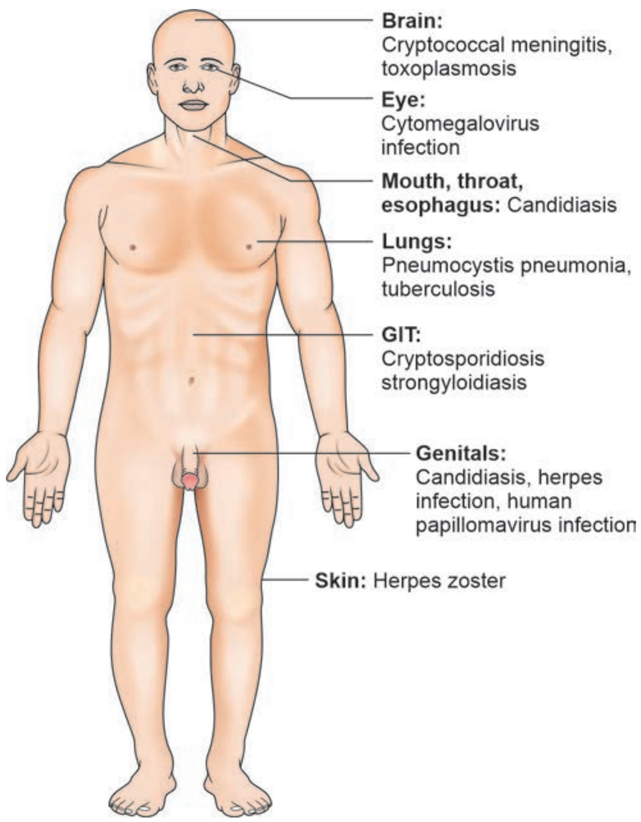

Figure 1.4: Common opportunistic infections

TABLE 1.4: Common opportunistic infections

Organism	Disease	Treatment
Viruses		
Herpes simplex virus	Encephalitis	Acyclovir
Varicella zoster virus	Disseminated herpes zoster	Acyclovir
Cytomegalovirus	Retinitis, pneumonia	Ganciclovir
Bacteria		
TB	Pulmonary or extraputlmonary involvement	Isoniazid, rifampin, pyrazinamide, ethambutol
Mycobacterium avium-intracellulare complex (MAC)	Fever, weight loss, lymphadenopathy	Clarithromycin or azithromycin + ethambutol
Fungi		
Pneumocystis jirovecii	Pneumonia	Sulphomethoxazole + trimethoprim
Candida	Mucocutaneous and esophageal candidiasis	Fluconazole, itraconazole, amphotericin-B
Cryptococcus	Meningitis	Amphotericin-B + flucytosine
Parasites		
Toxoplasma gondii	Encephalitis, pneumonia	Sulphadiazine + pyrimethamine alternative—clindamycin
Cryptosporidium	Diarrhea	Nitazoxanide
Strongyloidiasis	Diarrhea	Ivermectin, albendazole

Prevention Opportunistic Infections

- Prophylaxis in high-risk individuals
- Vaccination
- Lifestyle modifications (minimize exposure to pathogens)

Q. Nosocomial infections (hospital-acquired infections).

- Nosocomial infections (NIs), also known as hospital-acquired infections (HAIs), are infections that develop during a patient's stay in a healthcare facility and are not present or incubating at the time of admission. These infections typically appear 48 hours or more after admission or within 30 days post-discharge. The most common sites of infection are the bloodstream, lungs, urinary tract, and surgical wounds.

Common Sites of Nosocomial Infections

- *Urinary tract infections (UTIs)*: Most common HAI, often associated with indwelling urinary catheters.
- *Surgical site infections (SSIs)*: Occur at the incision site following surgery.
- *Respiratory infections*: Includes ventilator-associated pneumonia (VAP).
- *Bloodstream infections (BSIs):* Often related to central venous catheters (CVCs).
- *Gastrointestinal infections*: Most commonly caused by *Clostridioides difficile*.
- *Skin and soft tissue infections*: Can occur due to pressure ulcers or device-related infections.

Risk Factors

- *Patient-related:* Immunosuppression, comorbid conditions (e.g. diabetes, chronic lung disease), advanced age or neonatal period.
- *Procedure-related:* Indwelling devices (e.g. catheters, ventilators, IV lines), surgical procedures.
- *Environmental:* Contaminated surfaces or instruments, poor hand hygiene or infection control practices.
- *Antibiotic use:* Broad-spectrum antibiotic overuse leading to resistant organisms.

Common Pathogens in Nosocomial Infections

- Though any organism can cause a nosocomial infection, there is an increasing incidence of multidrug-resistant (MDR) pathogens causing hospital-acquired infections. Some common organisms causing nosocomial infections are as follows.
- ***Gram-positive bacteria:*** *Staphylococcus aureus* (including MRSA), Enterococcus species, gram-negative bacteria, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Acinetobacter baumannii*.
- ***Fungi:*** Candida species.
- ***Viruses:*** Respiratory viruses, such as influenza or RSV.

Transmission

- Transmission usually occurs via healthcare workers, patients, hospital equipment, or interventional procedures.

Clinical Features

- Any new onset fever or any unexplained clinical deterioration in a hospitalized patient may be due to hospital acquired infection.
- Clinical features depend on the site of infection.
- Any new infiltrate on chest X-ray may due to hospital acquired pneumonia.

Investigations

- ***Complete blood count:*** usually shows leukocytosis.
- ***Blood culture and sensitivity:*** to diagnose bloodstream infection.
- ***Urine examination:*** to diagnose urinary tract infection.
- ***Chest X-ray:*** to diagnose pneumonia.
- ***Other tests*** as per clinical suspicion.

Treatment

- Treatment will be based on the type of hospital acquired infection. However, pending investigation reports, broad spectrum antibiotics can be started.
- Intravenous cannula should be removed if there is inflammation at the insertion site.
- Indwelling urinary catheter should be removed if possible.
- Surgical-site infections should be managed with a combination of surgical care and antibiotic therapy.

Prevention Strategies

- ***Hand hygiene*:** Proper handwashing or use of alcohol-based hand sanitizers.
- ***Aseptic techniques*:** During catheter insertion, IV placement, and wound care.
- ***Minimizing device use*:** Remove indwelling devices as soon as they are no longer necessary.
- ***Antibiotic stewardship*:** Avoid overuse or misuse of antibiotics.
- ***Environmental cleaning*:** Routine disinfection of surfaces and equipment.
- ***Staff training*:** Ongoing education on infection prevention practices.
- ***Isolation protocols*:** For patients with multidrug-resistant (MDR) organisms or airborne infections.

Q. Food poisoning.

- **Food poisoning** (also known as foodborne disease) refers to an acute illness caused by consuming contaminated food or beverages. It can result from the ingestion of microorganisms, their toxins, or chemical contaminants. Symptoms usually involve the gastrointestinal tract but can vary depending on the causative agent.
- Green leafy vegetables are the most common cause of food poisoning, followed by dairy items and poultry.
- Food poisoning should be suspected when many people develop the illness after ingesting the same food and the illness bears a temporal relationship to food intake.

Causes

Microorganisms

- Bacteria
  - *Staphylococcus aureus* (*improperly stored meats, dairy, or cream-filled pastries*).
  - *Bacillus cereus* (*reheated rice, pasta, starchy foods*).
  - Salmonella (e.g. in raw poultry, eggs, or dairy).
  - *Escherichia coli* (e.g. *E. coli* O157:H7 from contaminated meat or produce).
  - *Listeria monocytogenes* (e.g. in unpasteurized dairy or deli meats).
  - Vibrio species (e.g. in raw seafood).
  - *Clostridium botulinum* (improperly canned foods, honey).
- Viruses
  - Norovirus (e.g. in contaminated water, shellfish).
  - Hepatitis A (from contaminated food or water).
- Parasites
  - *Toxoplasma gondii* (from undercooked meat).
  - Cryptosporidium and *Giardia lamblia* (waterborne).
- Fungi
  - Aflatoxins produced by molds (e.g. Aspergillus on nuts and grains).

Chemical causes

- Marine toxins: Ciguatoxin, scombrotoxin fish (e.g. barracuda, tuna, mackerel)
- Plant toxins (flava beans)
- Pesticides, herbicides, or industrial chemicals.
- Heavy metals (arsenic, thallium and cadmium)
- Naturally occurring toxins (e.g. scombrotoxin in fish, mushroom toxins).

Clinical Features

- The commonest manifestation of food poisoning is a mixture of nausea, vomiting, fever, abdominal pain and diarrhea.
- Usually symptoms occur in many persons who ingest the same food.
- Symptoms usually develop within 48 hours after ingestion of food. In case of preformed toxins (staphylococcal toxin and *Bacillus cereus*) and non-infective food poisoning symptoms develop within minutes to hours.
- Specific etiologic agent can be identified by examining the suspected food, vomitus, stool or blood.

Management

- Most cases of food poisoning are self limiting.
- Intravenous fluids and electrolytes should be given to patients with severe vomiting and diarrhea.
- Antidiarrheal agents (codeine phosphate, loperamide) can be used to control diarrhea. However, they should be avoided in young children, elderly, and patients who have fever and pain abdomen suggesting infective diarrhea.
- Antibiotics are not routinely indicated unless a specific pathogen is suspected.

Prevention of Food Poisoning

Following precautions can decrease the chances of food poisoning.

- Do not drink raw (unpasteurized) milk or foods that contain unpasteurized milk.
- Wash raw fruits and vegetables thoroughly in running water before eating.
- Use precooked, perishable, or ready-to-eat food as soon as possible.
- Avoid cross contamination; keep raw meat, fish, and poultry separate from other foods.
- Thoroughly cook raw food from animal sources. Seafood and shellfish should be cooked thoroughly to minimize the risk of food poisoning.
- Refrigerate foods promptly. Never leave cooked foods at room temperature for more than two hours.

Q. **Staphylococcal food poisoning.**

- *Staph. aureus* is a part of the normal flora of the skin, nose, and throat. *Staph. aureus* is coagulase-positive and is the most virulent of all staphylococcal species. All other staphylococci have been collectively designated as coagulase-negative staphylococci and are less virulent.
- Food handlers may transfer the bacteria via hands to foodstuffs such as dairy products, meats, eggs, and salads.
- After the food is left at room temperature, the organisms multiply and can produce a substantial quantity of enterotoxin.

Clinical Features

- Following ingestion of contaminated food, nausea, vomiting and abdominal cramps develop within 1–6 hours. Fever and/or diarrhea may also occur in a minority of patients.
- Most cases improve rapidly. Rarely severe dehydration can occur which can be fatal.

Management

- Fluid replacement and antiemetics (domperidone, ondansetron) should be given. Antibiotics are ineffective because symptoms are caused by toxins, not active bacterial infection.
- Suspected food should be tested for the presence of enterotoxin and Staphylococcus if feasible. Public health authorities should be notified if food vending is involved.
- Prevention relies on proper food handling, hygiene, and temperature control during storage and preparation.

Q. **Toxic shock syndrome (TSS).**

- Toxic shock syndrome (TSS) is a toxin-mediated acute life-threatening illness, usually caused by infection with either *Staphylococcus aureus* or group A Streptococcus (GAS, also called *Streptococcus pyogenes*). The toxins produced by these bacteria act as superantigens, triggering an excessive immune response that can lead to multisystem organ failure.
- TSS was first described in a small group of children with acute febrile illness. Subsequently, it was found in young, menstruating women who were using a highly absorbent tampon that was newly introduced to the market. This was due to multiplication of vaginally colonized *S. aureus* and production of an exotoxin known as TSST-I and enterotoxin B. However, tampon associated cases of TSS have come down, and most cases are now secondary to *S. aureus* infections of skin or other sites.

Clinical Features

- TSS usually begins with nonspecific flulike symptoms such as fever and myalgia. In menstrual cases, the onset is usually 2 or 3 days after the start of menstruation.
- As the severity of illness increases, patients develop diffuse erythematous rash, hypotension, and multiple organ dysfunction. Multiple organ dysfunction manifests as vomiting and diarrhea (GIT involvement), renal failure (kidney involvement), ARDS (lung involvement), liver enzyme elevation (hepatitis), thrombocytopenia (hematological involvement), confusion, drowsiness (CNS involvement), conjunctival erythema (mucosal involvement), etc.
- Desquamation of the skin occurs during convalescence, usually 1–2 weeks after the onset of illness.

Investigations

- Investigations typically show leukocytosis, thrombocytopenia, increased urea creatinine, hypoalbuminemia and liver function abnormalities.
- Gram staining and culture sensitivity of the infected specimen.
- Blood culture may show causative organism such as Staphylococcus or Streptococcus.

Treatment

- Patient should be admitted immediately to the hospital.
- Local measures (e.g. decontamination, debridement).
- Fluid resuscitation and circulatory support.
- Empiric antibiotic therapy (e.g. clindamycin plus vancomycin) pending culture results. In addition to antibacterial effect, clindamycin also reduces the synthesis of toxin.
- For patients with group A Streptococcus infection, a combination of penicillin-G (4 million U IV q4h) and clindamycin (600–900 mg IV q8h) is used. Intravenous immune globulin can be considered for streptococcal toxic shock syndrome (specific antibody to streptococcal exotoxins).
- Duration of antibiotic treatment is 10–14 days.

Q. **Enumerate the infections caused by streptococci. Write briefly on scarlet fever and erysipelas.**

Streptococci are gram-positive bacteria arranged in chains. They cause a variety of infections in man which are as follows:

- Skin and soft tissue infections; cellulitis, erysipelas, necrotizing fasciitis
- Bone and joint infections
- Tonsillitis
- Scarlet fever
- Glomerulonephritis
- Rheumatic fever
- Puerperal sepsis
- Endocarditis
- Urinary tract infection
- Neonatal infections including meningitis
- Female pelvic infections
- Peritonitis
- Dental infections
- Liver abscess.

Scarlet Fever

- Scarlet fever is a bacterial illness caused by *Streptococcus pyogenes* (Group A Streptococcus, GAS). It is characterized by exudative pharyngitis, fever, and bright-red exanthema *(scarlet means bright red)*.
- Exotoxin-mediated streptococcal infections range from localized skin infection (e.g. bullous impetigo) to the widespread eruption of scarlet fever to the highly lethal streptococcal toxic shock syndrome.

Clinical Features

- Common in children aged 5–15 years.
- Scarlet fever is characterized by exudative pharyngitis, fever, and *scarlatiniform rash*. Initially patient develops fever, headache, vomiting and sore throat, followed within 24 hours by a punctate erythematous rash. Erythematous rash is caused by erythrogenic toxin.
- Initially, the exanthem is seen on the tongue which becomes bright red with prominent red papillae. This appearance is called *strawberry tongue*. The rash then appears on the neck and spreads to trunk and extremities. These rashes enlarge and join together to form a generalized erythema. Usually the rash does not affect nose, lips, palms and soles. Since the lips are not affected it remains pale and stands out against the red background of flushed cheeks. Rash is more prominent in the skin folds and is called *Pastia's lines*. Usually, the rash becomes maximum by 2 days and fades by 7 days.

Differential Diagnosis

- Includes other causes of fever with generalized rash, such as:
  - Rubella, measles, and other viral exanthems
  - Kawasaki disease
  - Toxic shock syndrome
  - Systemic allergic reactions (e.g. drug eruptions).

Figure 1.5: Strawberry tongue

Complications

- Otitis media, pneumonia, septicemia, osteomyelitis, toxic shock syndrome, rheumatic fever, and post-streptococcal glomerulonephritis (PSGN).

Investigations

- Complete blood count shows leukocytosis.
- Throat swab culture is the most important test to confirm the diagnosis.
- Direct antigen detecting kits allow immediate diagnosis but have less sensitivity.
- Anti-deoxyribonuclease B and antistreptolysin-O titers (antibodies to streptococcal extracellular products).

Treatment

- Penicillin is the drug of choice and is given for 7–10 days. Cephalosporins can also be used instead of penicillin. Erythromycin (or azithromycine) is an alternative for patients allergic to penicillin.

Erysipelas

- It is an infection of skin and superficial lymphatics.
- Erysipelas usually involves the face and head but other areas may also be involved.
- The skin becomes red, edematous and firm to hard in consistency due to cuticular lymphangitis. It may spread to adjacent parts and involve large areas. The margins of the erythematous areas are raised and sometimes vesicles are also seen. The patient may appear sick.
- Erysipelas of the face has to be differentiated from cellulitis. Since cellulitis is an infection of subcutaneous tissues, it does not involve the external ear which has no subcutaneous tissue, while facial erysipelas can involve external ear (Millian's sign).
- Penicillin is the drug of choice for erysipelas. Alternatives (for penicillin-allergic patients) are clindamycin, erythromycin.

Q. Listeriosis.

- Listeriosis is a serious infection caused by *Listeria monocytogenes*. *Listera monocytogenes* is an aerobic, gram-positive rod. It is an intracellular organism and is capable of invading several cell types. Listeriosis is a rare infection and primarily affects pregnant women, newborn infants, elderly, and immunocompromised patients.
- This disease is often foodborne and can result in severe systemic illness, including meningitis and sepsis.

Transmission

- The main route of acquisition of *Listeria* is through the ingestion of contaminated food products. Other modes of transmission are contact with infected animals such as rodents or ruminants. Venereal transmission occurs occasionally. Mother-to-child transmission can occur during perinatal period.

Clinical Features

- The disease is seen mainly in neonates and young children. Mother can get infected in late pregnancy which can lead to *stillbirth*. It presents as a febrile illness. The mother recovers after delivery but, occasionally, the organism persists in the genitalia to cause *habitual abortions*. If the neonate survives, the picture is one of severe infection. Neonates die in about 3 days but survivors develop suppurative meningitis.
- Listeria infection in healthy adults is uncommon but affects immunocompromised persons like AIDS patiens, diabetics, alcoholics and those with debilitating diseases. Listeria is an opportunistic infection in AIDS. *Meningitis* is often the clinical manifestation.

Investigations

- Organism can be isolated by blood culture, and culture of any infected body fluid such as CSF.

Treatment

- The *treatment of choice is intravenous ampicillin* often in combination with an aminoglycoside (synergistic effect).
- Trimethoprim-sulphamethoxazole is second-line drug and can be used if the patient is allergic to ampicillin.
- The response to treatment is slow.

Q. Discuss the etiology, pathogenesis, clinical features and complications of diphtheria. How do you investigate and manage a case of diphtheria?

Etiology

- Diphtheria is a localized infection of mucous membranes or skin that is caused by *Corynebacterium diphtheriae*. It is associated with a characteristic pseudomembrane at the site of infection.
- *C. diphtheriae* is a gram-positive bacillus and resembles *Chinese letter patterns* on *Albert's stain*.
- There are three strains of *C. diptheriae*; mitis, intermedius and gravis. Gravis causes the most severe disease.

Epidemiology

- Diphtheria affects people all over the world. But now it is uncommon due to immunization practices. It is more common during winter. It is mainly a disease of children.
- Humans are the main reservoir of *C. diphtheriae*. However, some cases have also occurred due to transmission from livestock.
- Spread occurs in close-contact settings through respiratory droplets or by direct contact with respiratory secretions or skin lesions. Fomite transmission can also occur.

Pathogenesis

- Diphtheria is initiated by entry of *C. diphtheriae* into the nose or pharynx. It multiplies locally without blood stream invasion.

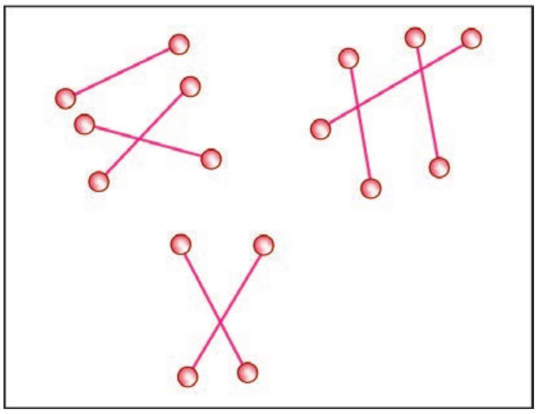

Figure 1.6: *C. diphtheriae*

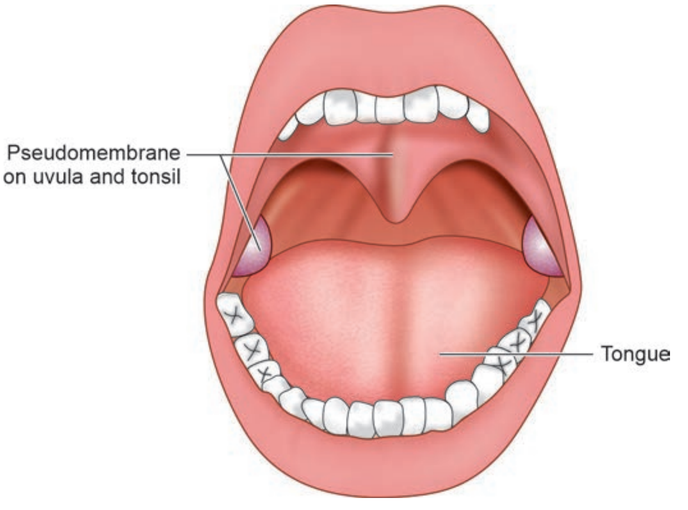

Figure 1.7: Pseudomembranes on the tonsils and uvula

- It produces a powerful exotoxin which causes local tissue necrosis and formation of a tough, adherent pseudomembrane, composed of a mixture of fibrin, dead cells, and bacteria. The membrane usually begins on the tonsils or posterior pharynx and can spread to fauces, soft palate, and into the larynx, which may result in respiratory obstruction. Toxin entering the bloodstream causes tissue damage at distant sites, particularly the heart (myocarditis), nerves (demyelination), and kidney (tubular necrosis).
- Nontoxigenic strains may cause mild local respiratory disease, sometimes including a membrane.

Clinical Features

Respiratory Diphtheria

- Nose infection presents as a chronic serosanguineous or seropurulent discharge without fever or significant toxicity. A whitish membrane may be observed on the septum.
- The **faucial (pharyngeal) form is most common**. After an incubation period of 1–7 days, the illness begins with sore throat, malaise, and mild-to-moderate fever. Grayish membrane may be present that is tightly adherent and bleeds on attempted removal. In severe cases, the patient appears toxic. Cervical

lymphadenopathy and soft tissue edema may occur, resulting in the typical *bull neck appearance* and stridor.
- Laryngeal involvement presents as hoarseness, stridor, and dyspnea.

Cutaneous Diphtheria

- Cutaneous diphtheria lesions are classically painful, deep, non-healing ulcers, which may have a grayish white membrane.

Invasive Disease

- Myocarditis presents with signs of low cardiac output and congestive failure. Conduction disturbances, ST-T wave abnormalities, arrhythmias, and heart block can occur.
- Neurologic involvement manifests as cranial nerve palsies and peripheral neuritis. Palatal and/or pharyngeal paralysis occurs during the acute phase.
- Renal failure: Due to tubular damage.

Investigations

- Gram's stain: A presumptive diagnosis of *C. diphtheriae* can be made by identifying gram-positive rods in a "Chinese letter" distribution on Gram's stain.
- Cultures from beneath the membrane, from the nasopharynx, and from suspicious skin lesions. Cultures may be negative if the patient has received antibiotics.
- Toxigenicity testing should be performed on all *C. diphtheriae* isolates.
- Polymerase chain reaction test may allow both detection of the organism and determination of toxigenicity.
- ECG may show ST-T wave changes, heart block, and dysrhythmia.

Treatment

- The goals of treatment are to neutralize the toxin by antitoxin, eliminate the infecting organism by antibiotics, provide supportive care, and prevent further transmission.

Antitoxin

- Diphtheria antitoxin is a hyperimmune antiserum produced in horses, which binds to and inactivates the diphtheria toxin.
- The antitoxin is only effective before toxin enters the cell and thus must be administered as early as possible.
- There is risk of allergic reactions to antitoxin since it contains horse serum. Hence, a test dose should be given before administration.
- The dose of antitoxin depends upon the site and severity of infection: 20,000–40,000 units for pharyngeal/laryngeal disease, 40,000–60,000 units for nasopharyngeal disease, and 80,000–120,000 units for severe disease with "bull-neck". The dose should be administered intravenously over 60 minutes.

Antibiotics

- They decrease toxin production indirectly by killing the organisms.
- Penicillin is the drug of choice. Penicillin G (25,000–50,000 units/kg IV q12 h until the patient can take orally) followed by oral penicillin V (250 mg QID) for a total of 14 days.
- Erythromycin 500 mg QID for 14 days is an alternative.

Diphtheria Toxoid Vaccine

- Patients should be given diphtheria toxoid immunization during their convalescence since natural infection does not induce immunity.

Prevention

- Isolate the patient.
- Non-immunized contacts should be given both antibiotics and diphtheria antitoxin.
- Immunized contacts are given a booster dose of diphtheria toxoid.

Q. Describe the etiology, pathogenesis, clinical features and management of tetanus. Add a note on prevention of tetanus.

- Tetanus is a serious illness caused by *Clostridium tetani* organism. It is characterized by an acute onset of hypertonia and painful muscle spasms.
- Tetanus has been described by Hippocrates and in the Indian medical writings of Sushruta.

Etiology

- *Cl. tetani* is a gram-positive, spore-forming, anaerobic bacillus. It has a drumstick appearance due to the presence of terminal spore **(Fig. 1.8)**. It is a normal commensal of human and animal gastrointestinal tracts and is widely distributed in soil. Its spores can survive for many years even in adverse conditions.
- Tetanus can occur in following situations:
  - Neonatal tetanus: Occurs when the umbilical cord is cut with an unsterile instrument or smeared with cowdung after cutting as is the practice in some areas.
  - After road traffic accidents where wounds may get contaminated easily with tetanus spores. Even a seemingly trivial injury may be able to cause tetanus.
  - People with otorrhea may develop tetanus if the ear is probed with a wire or matchstick which may carry spores on it.
  - In women after illegal abortion due to unsterile handling of the genital tract through which organisms gain entry.
  - Intramuscular injections given with contaminated needles.
  - Necrotic or gangrenous tissues due to peripheral vascular disease or any other cause.