FEVER

Definition:

- Temperature above the normal range due to an increase in the body temperature due to set point elevation (usually considered if it reaches or exceeds 38 °C).
- Normal range (36.5–37.5 °C) depends upon the age, exertion, infection, sex, time of the day, reproductive status of the subject and methods & time of measurement.

Types

1. **Continuous fever**: Temperature remains above normal throughout the day and does not fluctuate more than 1°C in 24 hours e.g. lobar pneumonia, typhoid fever.
2. **Remittent fever:** Temperature fluctuates more than 1°C in 24 hours but doesn't reach to normal level e.g., infective endocarditis, brucellosis.
3. **Intermittent fever**: Temperature fluctuates more than 1°C in 24 hours and drops to normal level, e.g. malaria, pyaemia, or septicemia.
4. **Relapsing**: Waxes & Wanes cyclically.
5. **Hyperpyrexia**: Hyperpyrexia is an extreme elevation of body temperature greater than or equal to 41.5°C .

Common Causes:

1- Infections: bacterial, viral, fungal, parasitic, etc…..

2- Collagen diseases.

3- Drug fever:
e.g (Penicillin - Cephalosporins – Sulphonamides - Phenytoin-Antihistamines - Aspirin - Theophylline intoxication - Anticholinergics)

4- Immunization reactions

5- Inflammatory disorders

Other causes:

1. Tissue injury or infarction
2. Malignancy
3. Heat illness
4. Allergic reactions
5. Thyrotoxicosis

6- Hypothalamic injury

7- Hyperactivity, seizers or vigorous exercise

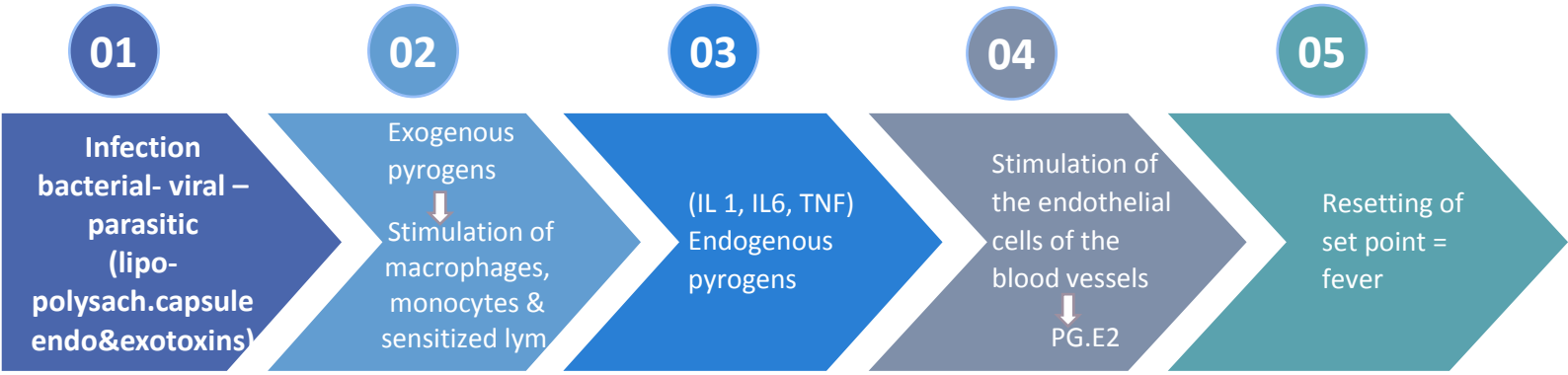
8- Neuroleptic malignant syndrome

9- Malignant hyperthermia

10- Factitious fever [Self-induced fever]

Mechanism of fever:

1) **Changing the set point** in the anterior hypothalamus by the effect of immune system stimulation through series of reactions like [infections, autoimmune reaction, malignancy, drugs, etc…]



2) **Direct effect of some drugs** like cocaine and phenothiazines and in some people dopamine antagonists.
3) **Dopamine level affects directly** the center as occurs in neuroleptic malignant syndrome.

Neuroleptic malignant syndrome

Occurs due to idiosyncrasy or overdose of certain drugs like haloperidol [safenase] & phenothiazines [e.g. chlorpromazine], it causes lead- pipe rigidity, dystonic movements and tremors of extra pyramidal origin followed by rise in body temperature that may lead to hyperthermia, Stupor or coma.
Also dopamine level decreases in the hypothalamus as mechanism of hyperthermia**.**

4) **Other medications can affect centrally** the heat regulating center like serotonin reuptake inhibitors
5) **CAMP & Na / Ca ion ratio may play a rule.**

Malignant hyperthermia

Disorder of the skeletal muscles in congenitally susceptible persons, initiated by halogenated inhalation anesthesia or depolarizing agents like succenylcholine leading to generalized muscle contraction due to increased Ca influx. The sustained muscle rigidity leads to fever and hyperthermia.

6) **Disturbance of heat loss mechanism as in heat illness.**

Adaptive value of fever:

Fever has an effect on the organisms and host defense mechanisms leading to survival of the host.

A. **Effects on the organisms:**

- **Bacteria:**

Decreases the growth of some bacteria e.g. gonococci is killed at 40 – 41°C. In the past, typhoid vaccine was used in the treatment of gonococcal infection. It inhibits the growth of some strains of

pneumococci at temperature around 40 °C. Spirochetes responsible for neurosyphilis are killed at high temp. [41 °C].
In India, it was noticed that neurosyphilis was less in malarious areas may be due to this reason.

- **Viruses:**

It inhibits the growth & activity of some viruses like polio –virus in tissues culture and activates others like herpes simplex virus.

B. Effect on the host defense mechanisms:

Fever is the nature's engine which she brings to the field to kill her enemy.

- Enhancement of the functions and process of the immune system dealing with infection, autoimmune reaction and tumor cells.
- Increases the phagocytic activity of the leucocytes and its movements.
- Temperature of (38 °C – 39 °C) increases proliferation and transport of lymphocytes in response to various types of antigens.
- Increases the production of interferons.
- The lysosomal membrane in the tumor cells is sensitive to heat, so fever causes rupture of the lysosomes leading to auto digestion of the cells. The same happens in the cells infected with viruses.
- It increases the sensitivity of tumor cells to chemotherapy. So by heat we can decrease the dose and avoid side effects.
- It increases the sensitivity of the organisms to antibiotics. So it is more than a symptom of serious disease.

Primary Requirement Of Febrile (feverish) Patients.

1- Plenty of fluids either oral or parenteral to maintain water and electrolyte balance.
2- Highly nutritious, easily digestible diet to face the increased demands of energy production and cover the needs of immune system.
3- Rest, physical and mental.
4- Keeping the temperature below the lethal level.
5- Quick diagnosis & proper therapy.
6- Reassurance & information about his illness

HEAT ILLNESS
(HEAT DISORDERS)

Represents a group of disorders, divided into:

1- **Mild:**
Sweat rash, Heat syncope, Heat edema, Heat tetany and Heat cramps (intact thermo regulatory mechanisms).

2- **Moderate:**
Heat exhaustion (intact thermoregulatory mechanisms).

3- **Severe:**
Heat stroke (failed thermo regulatory mechanisms).

Factors precipitating heat illness:

1- Increase in the atmospheric temperature & humidity.
2- Lack of acclimatization.
3- Fatigue
4- Physical conditions:
i) Extremities of age.
ii) Obesity.
iii) Alcohol consumption.
iv) Diabetes mellitus.
v) Strenuous exercise-
vi) C.V. disease.
vii) Anti cholinergic drugs
viii) Previous history.

1) Mild Heat Illness

a) Sweat rash:

Erythematous rash occurs due to excessive sweating. It is burning & itchy in character, covers the body specially the flexure points. It is claimed that sweating leads to swelling of the keratinocytes surrounding the opening of the sweat glands causing its obstruction and initiating inflammatory reaction.

Treatment:

Wearing clothes that allow sweat to evaporate, resting in a cool place part of each day, regularly bathing and drying the skin, calamine or other lotion?

b) Heat syncope:

Occurs after standing for longtime in hot weather, it is due to failure of compensatory C.V. reflexes leading to sudden drop in B.P. & brain ischemia with fainting.

Treatment: Like that of other types of fainting:

- The patient should be lying down with elevation of both legs.
- Fluid containing electrolytes, is administered slowly, and the patient is moved to a cooler area.

c) Heat tetany:

Due to respiratory alkalosis that may occur secondary to hypercapnia leading to precipitation of ionized calcium. It is a reversible condition.

Treatment:

Treated by taking the patient to a cold place.

d) Heat cramps:

Contraction of one muscle without relaxation of the opposite one usually affects the calf muscles and occurs mostly during exercise in hot weather, most probably due to salt and water depletion.

Treatment:

Putting the patient in a cool place and rest, replacement of salt & water depletion "1 liter of saline in 1 - 3 hours is usually enough or oral water and salts.

2- Moderate Heat Illness

(Heat exhaustion)

Due to water & salt loss, occurs usually to persons working for long time in hot humid weather with continuous sweating.

- Rapid course → predominant water loss.
- Gradual course → predominant salt loss.

Symptoms:

a- Headache
b- Anorexia
c- Giddiness
d- Excessive thirst
e- Nausea & Vomiting
f- Cramps may occur

Signs:

a) Profuse sweating
b) Flushing
c) Temperature is normal or between 38 °C – 39 °C.
d) Excessive thirst
e) Signs of dehydration [Low B.P., tachycardia, sunken eyes & inelastic skin.]
f) Mental changes which denotes that the condition is shifted to heat stroke.

Lab. investigation:

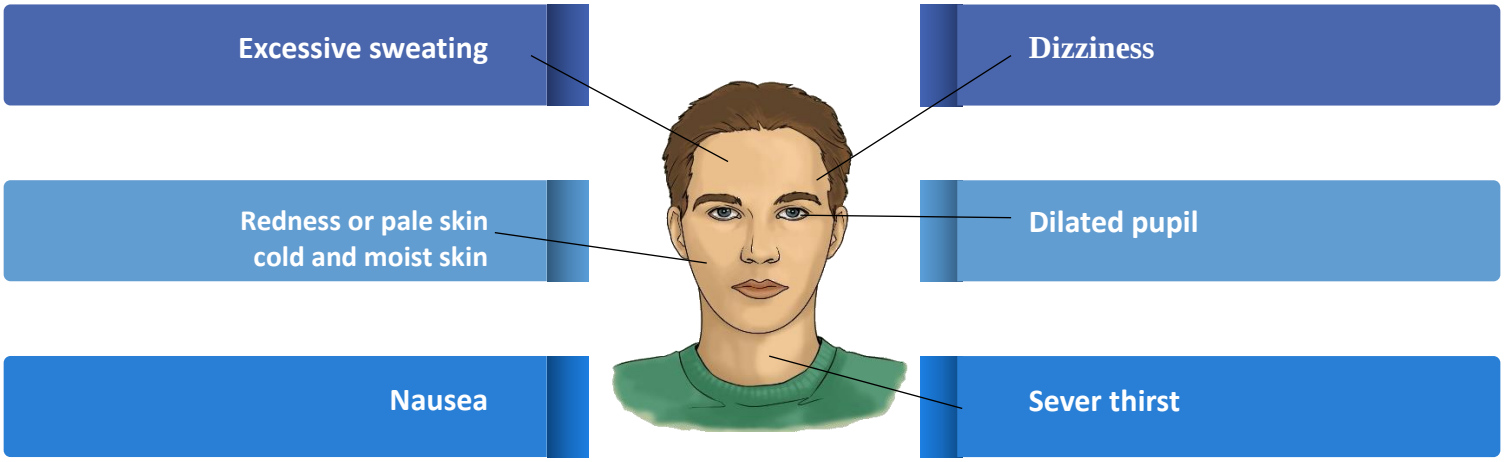
↑ Hematocrite value	↑ Sodium level (relative)
↑ Hepatic enzymes	↑ Creatinine kinase level
↓ Glucose level	Evidence of dehydration

Treatment:

- Place the patient in a dry cool place.
- Replace the water and salt loss according to the degree of dehydration.
- Dextrose 5% in half normal saline is the usual fluids needed.

  The patient may needs up to 4 liters over 6 – 8 hours especially in physically fit young patient.
- In elderly, the replacement should be gradual.

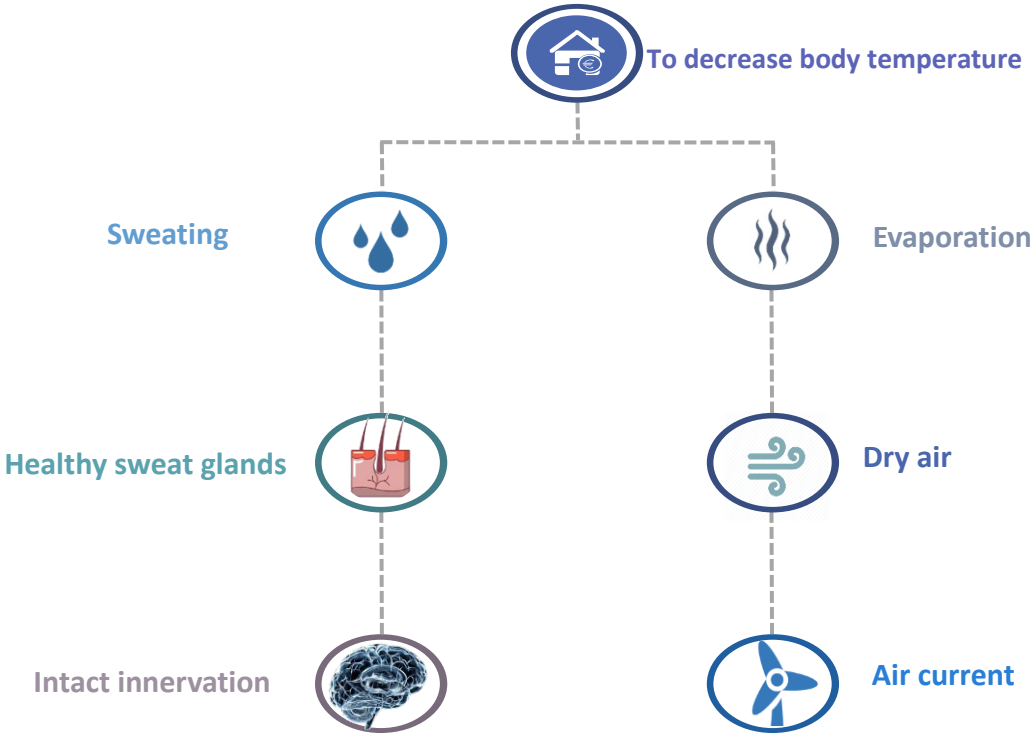
4- Sever Heat Illness



Heat stroke

[heat injury]

- It is a failure of thermoregulatory mechanisms due to hot wet weather leading to increase in body temperature to a lethal level [more than 40.6 °C] causing a wide spread cellular damage.
- It is one of the causes of hyperthermia.
- Infections per say rarely cause hyperthermia, but may initiate the condition and the environmental factors complete the picture.
- At about 32.5 °C (environmental temperature), sweating starts to share in the mechanisms of heat loss and at 35 °C, sweating and evaporation of the sweat becomes the main mechanisms for heat loss



Predisposing factors:

1- **Environmental factors:**

- Exposure to hot humid weather with decreased air current,

  N.B. When humidity reaches 75%, evaporation of the sweat nearly ceases.
- Acclimatization: Sudden exposure of non-acclimatized person to hot humid atmosphere for 48 hours or more can cause heat stroke.
- Epidemic heat stroke: Occurs when a city experiences a cold weather followed by a hot humid weather in the late spring or early summer.
- Wearing heavy clothes in a hot atmosphere.
- Military personnel's, athletes, laborers & young people doing exercise or hard work in hot humid weather is liable to develop exertional type of heat stroke.

2- **Age:**

Children and elderly is the most vulnerable group.-

3- **Obesity:**

Fat layer work as insulator for heat loss.

4- **Chronic illness:**

a) C.V. diseases.
b) Diabetes mellitus.
c) Hemiplegia or quadriplegia with autonomic dysfunction.

5- **Infection:** May initiate the condition only and the environment complete.

6- **Dehydration:** Affects the rate of sweating and interferes with heat loss (dehydration fever).
7- **Drugs:**Anticholinergic drugs, major tranquilizers phenothiazines and neuroleptic drugs may lead to heat stroke

Effects of hyperthermia on the human body:

1- The lethal effects occur when the body temperature reaches 42 degree but some considered the degree of 41 is a critical level.
2- Denaturation of proteins, enzymes & hormones with liquefaction of lipids including the brain tissue occurs at 42 degree.

Also oxidative phosphorylation ceased at this degree with loss of energy sources to different tissues including the heat regulation center. The effects depend on the duration of hyperthermia.

Effects on the brain:

- The first cell to be affected is the brain cell leading to:
  1- Mental changes, stupor & coma.
  2- Convulsions or decerbrate rigidity.
  3- Quadriplegia, hemiplegia or monoplegia.
  4- Different brain infarctions.
  5- Paralysis of centers like heat regulation center or respiratory center leading to death.
- Degeneration then necrosis to the liver cells which may lead to liver cell failure.
- Destruction of the renal cells leading to renal failure.
- Destruction of the skeletal muscle cells (rhabdomyolysis), especially in exertional type, leading to myoglobinuria with possibility of renal tubular obstruction and renal failure.
- Precipitation of Ca. & Ph. On the destructed muscle cells leads to hypocalcaemia & hypophosphatemia. Also Na enters to inside the cells & K goes outside the cells leading to hyperkalemia & hyponatremia.
- Injury to the endothelial lining of the vessels causing D.I.C.
- Affects the conductive system of the heart that may lead to different types of arrhythmias and heart failure.

Types of heat stroke:

A. Classical type:

- Occurs mainly in the extremities of age.
- Infants and children may have undeveloped heat regulating center and sweat glands, high metabolic rate and can't take care of themselves.
- Old people may have low cardiac reserve, reduced C.N.S. reflexes , may use medications that affect sweating and V.D. and can't take care of themselves.
- Gradual in onset [commonly more than 48 hours].
- Dehydration is more due to prolonged sweating.
- At presentation, skin is commonly dry.

B. Exertional type:

- Occurs commonly in middle ages healthy persons.
- Occurs in non-acclimatized persons during exercise or hard work in hot humid atmosphere.

- Rapid onset, less dehydration.

Clinical picture:

Symptoms:

Headache - Unsteadiness - Light headedness - Nausea & vomiting - Piloerection especially over the arms & chest – Paraesthesia - Change of behavior - coma.

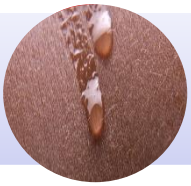
Signs

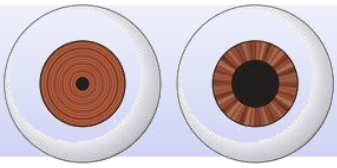
- Body temperature: Must be taken rectally, usually over 41 degree, may be cold extremities due to peripheral circulatory failure.
- Heart rate: usually tachycardia with weak pulse in case of dehydration or heart failure, in the absence of dehydration, pulse may be full & rebound irregular pulse in arrhythmia & bradycardia in heart block.
- Blood Pressure: May be low due to dehydration of low output failure (Dehydration) or high output failure (high temp).
- Respiratory rate: deep rapid respiration usually due to high temp.
  - Irregular resp. (chyne stokes) in the terminal stage.
  - Bubbling crepitation & frothy sputum in pulmonary edema.
- Skin: usually grey & dry, may be flushed and sweaty. Sweat rash is usually present.
- Coma: with dilated fixed pupils, convulsions, muscle rigidity, tremors, oculogyric crises, or transient hemiplegia may be present.

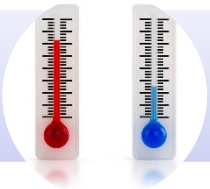
Laboratory Investigation:

- Blood gases: reveal commonly metabolic acidosis due to lactate accumulation especially in exertional type. Respiratory alkalosis may be present due to hypercapnia.
- Blood picture: Leukocytosis is common, may reach high levels [35000 – 50000 /cmm].
- A.L.T., A.S.T. & L.D.H.: Are markedly elevated .

  N.B: the A.S.T. level is prognostic, the level of 1000 i.u./ liter or more in the first 24 hours reflects a poor prognosis with serious brain, liver & renal damage.
- C.K. (creatinine kinase): Markedly elevated specially in exertional type.
- Myoglobinurea & Hyperuricemia: Usually present due to destruction of muscle fibers.
- Blood glucose level: Always there is hypoglycemia especially in exertional type and may be severe.
- Electrolytes: hyper or hyponatremia according to the type of dehydration , ↑K in first 24 hours, ↓Ca due to precipitation in the damaged fibers, ↓Ph due to the same reason.
- **E.C.G.:** S – T segment & T wave abnormalities with various arrhythmias and bundle branch block may occur and most of them are reversible after cooling.

Dry hot skin  Moist and clammy skin

Pupils constricted  Pupils dilated

Very high body temperature  Normal or subnormal temperature

Management:

- Heat stroke is one of the medical emergencies that needs rapid interference.
- The seconds are precious for the patient, so our aim is to decrease the body temperature below the harmful level, as quickly as possible, to avoid irreversible cellular damage.
- With rapid interference the mortality rate decreased from 80% to 10%.
- The rapidity of interference is more valuable than the method used for cooling.

Different methods for cooling:

The aggressive cooling measures & the slow evaporative technique.

1-Aggressive cooling measures:

- Direct application of ice on the whole body.
- Immersing the body in cold or iced water.
- Application of ice in areas of great vessels passage e.g. axilla, groin & front of the neck.
- Gastric lavage with iced fluids, Enema with iced fluid, peritoneal lavage with iced fluids.
- I.V. infusion of cold fluids.
- Inhalation of cold air.

Disadvantages of these methods:

- The cooling rate is less [about 0.1 degree/min.] except in peritoneal lavage [0.55 degree/min.].
- Difficult to be applied in comatosed patient.
- May cause shivering which increase body temp.
- Direct ice to the skin leads to vasoconstriction.
- Ice enema may cause shock and sudden death.
- Peritoneal lavage may leads to peritonitis.

2- Slow evaporative technique:

- The idea depends on the smooth cooling effect of the evaporation of water.
- This is done by spraying the body with warm water, or covering it with a blanket soaked in warm water then exposes the body to a strong dry air current.

- N.B.: Ice bag must be applied to the head only.
- This process continues until the temperature reaches 39 degree and then cooling must be stopped.

Advantages of the technique:

- Faster rate of cooling [0.33 deg./min.].
- Easily applied for comatosed patient.
- Doesn't cause shivering or peripheral v. constriction.

«This method must be done in a specialized center, the heat stroke Center».

The heat stroke & heat exhaustion center:

The center as shown in the diagram is composed of 2 suitable rooms, cooling room & observation room.

- **Cooling room:**
  - Enough number of air conditions ensure a temperature room 25 – 30 i.e. 27 and also dry air.
  - Slated beds without mattresses and opposite to each bed one fan must be fixed to wall to supply a horizontal current of air. (in the cooling room)
  - A number of suction fans in the upper part of the wall for renewal of air and removal of humid air.
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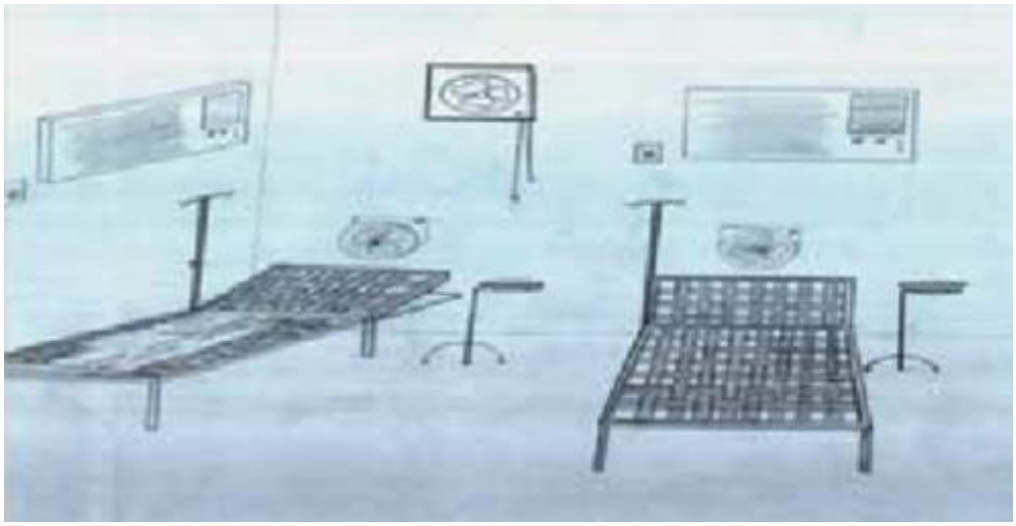
  - A number of suction fans in the upper part of the wall for renewal of air and removal of humid air.
  - A source of water & ice must be in the cooling room.

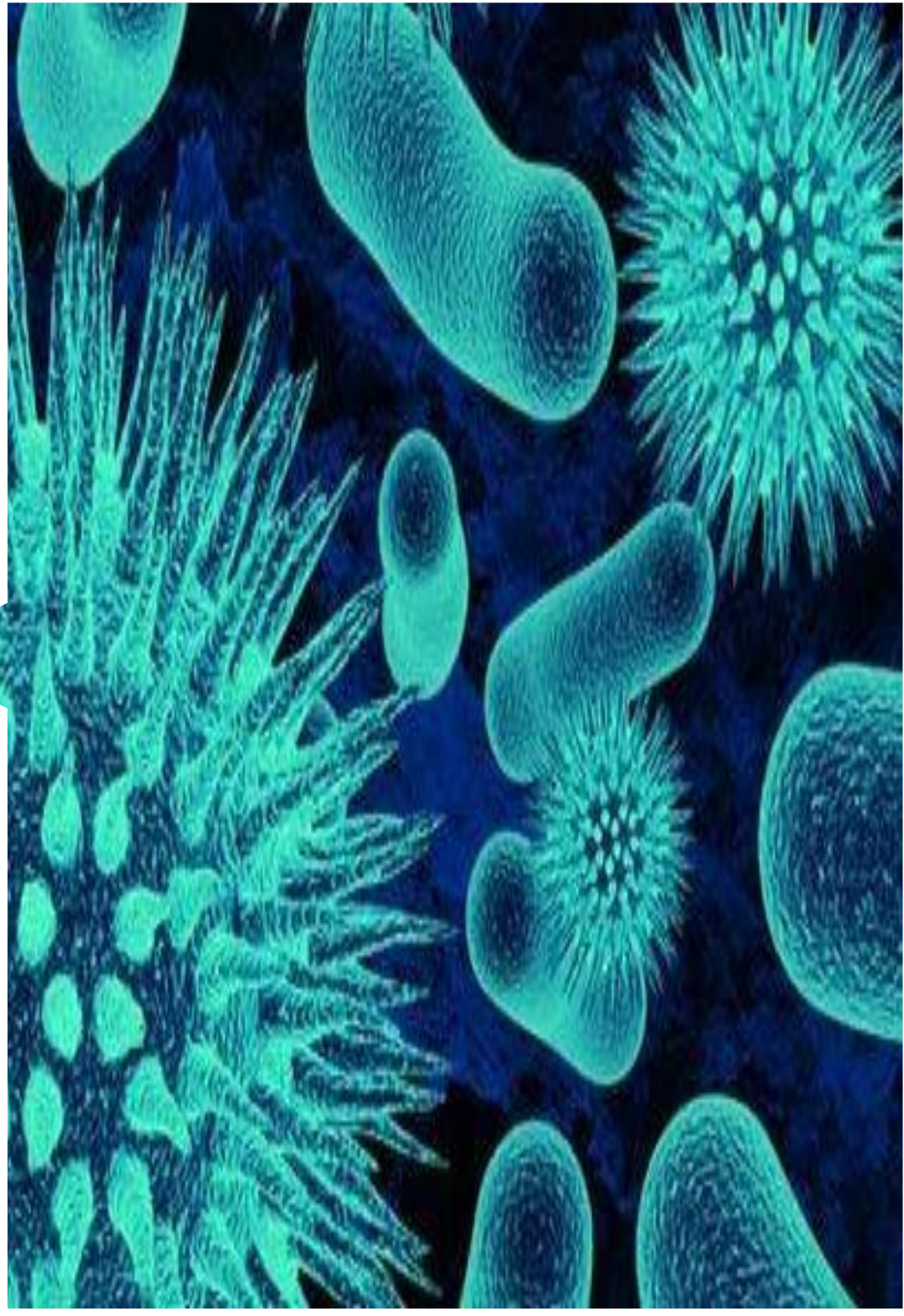
- All equipment, instruments and emergency drugs needed for comatosed patient must be supplied.



- **Observation room:**
  - Is a neighboring conditioned room containing normal bed for observation for 24 h. after cooling.
  - Once the patient arrives, his clothes must be removed quickly, and then put on the special bed.
  - In the cooling room. Get I.V. line and take enough blood samples for blood picture, blood culture, renal & liver function test blood gases, electrolytes, glucose, uric acid & bleeding & coagulation time.
  - Urinary catheter must be fixed for collection of urine. Start I.V. fluids especially saline then dextrose 5% for correction of dehydration.
  - In exertional type, 50% dextrose infusion is required as there may be severe hypoglycemia.
  - Apply ice bag over head only to the angle of the mandible and cover the body with wet blanket or spray the body directly with warm water and you have to re-wet the blanket or re-spray the body when becoming dry.
  - Temperature must be taken rectally every 3 minutes. This process must be continued until temperature reaches 39 °C then stop cooling and take the patient to the observation with light clothes.
  - Give decadron i.v. to decrease brain edema and minimize the occurrence of relapse of hyperthermia that may occur.
  - If there is convulsions give diazepam.
  - We have to search for any infection as meningitis and lumpar puncture must be done
  - According to the lab results, electrolyte imbalance, acidosis or alkalosis must be corrected accordingly.
  - Dehydration must be corrected gradually in old ages.

- If there is renal or liver cell failure, manage according to the condition.
- If there is no complications and the patient regain consciousness without relapse over 24 hours and no infection, you can discharge your patient.
- The patient must be informed about his illness and advised to avoid further attacks.
- Usually, the exertional type in young patients when treated earlier, gives rapid response without complication.
- Old people with classic type take more time to regain consciousness even with rapid interference.

Common bacterial diseases



Typhoid Fever

I-Definition

- Typhoid fever is an acute systemic illness caused by gram negative bacteria (salmonella typhi)
- Paratyphoid fevers are produced by other species named paratyphi A, B,C.

II-Modes of Transmission

- Faeco-oral transmission.
- It is transmitted through ingestion of food or drink contaminated by the faeces or urine of infected people

III-Diagnosis

1-**Incubation period:** Usually varies 3 – 21 days.

2-**Case definition**.

a) Suspected case

Any case having sustained fever 38$_{o}$c or more for 3 days or more ,decreasing but not reaching the baseline with abdominal discomfort (Abdominal pain, Diarrhea, or constipation) with 2 or more of the following symptoms:

- Dry non-productive cough.
- Relative bradycardia.
- Anorexia, Severe headache.

Blood, urine, stool culture should be done in suspected case

b) Probable case

Suspected case with tube agglutination Widal test with a titre ≥ 1/160.

c) Confirmed case

Suspected or probable case with:

- Detection of salmonella typhi or paratyphi through positive culture of blood, stool, urine or bone marrow.
- Increasing titre of tube agglutination (doubling) from acute to convalescent stage.
- Widal test alone without clinical picture and the other investigations is not diagnostic for typhoid fever.

IV- Medical treatment

1) Treatment of uncomplicated typhoid fever.

Optimal therapy

Antibiotic	Daily dose mg/kg	Days
Flouroquinolone e.g oxofloxacin or ciprofloxacin	15	5-7
Cefixime	15-20	7-14
Azithromycin of ceftriaxone	8-10 75	7 10-14

Alternative effective drug

Antibiotic	Daily dose mg/kg	Days
Chloramphenicol Amoxicillin TMP-SMX	50-75 75-100 8-40	14-21 14 14
Azithromycin Cefixime	8-10 15-20	7 7-14
Cefixime	20	7-14

2) Treatment of severe typhoid fever

Optimal therapy

Antibiotic	Daily dose mg/kg	Days
Flouroquinolone e.g oxofloxacin or ciprofloxacin	15	10-14
Ceftriaxone or Cefotaxime	60 80	10-14

Alternative effective drug

Antibiotic	Daily dose mg/kg	Days
Chloramphenicol Amoxicillin TMP-SMX	100 100 8-40	14-21 14 14
Ceftriaxone or cefotaxime	60 80	10-14
fluoroquinolone	20	7-14

3) Adjunctive Therapy (corticosteroid).

Short term, high dose corticosteroid.

- **Dexamethazone:**
  - (with specific antibiotic & supportive care reduce mortality in severe typhoid patients).
  - Adult: Start with 3mg/kg administered over 30 minutes followed by eight Doses at 1mg/kg/6h significantly reduce mortality.

- **N.B.**

1) Severe typhoid fever is defined as typhoid fever with shock and/or profound Encephalopathy manifested as delirium or obtundation.
2) Choice of antibiotics depends on culture and sensitivity and salmonella sensitivity
3) In Multi Drug Resistant *Salmonella typhi*:
   - Use of fluroquinolone or cefixime and the alternative azithromycine in uncomplicated typhoid fever.

- Use of fluroquinolone and the alternative ceftriaxone or cefotaxim in severe typhoid fever.

4) After recovery on discharging.

- Patients should be subjected to stool examination (3 successive stool cultures at least 24 hours apart) to determine if the patient developed a chronic infection (carrier state). After:
  - 15 days from Chloramphenicol therapy.
  - 10 days from Ciprofloxacin therapy.
  - 7 – 10 days from Ceftriaxone therapy.
- Cases should not be employed as food handlers until stool cultures are negative on at least 3 occasions.

V- Preventive measures:

1) Reporting
   - Weekly report Included in group B disease.
2) Isolation.
   - Where inpatient care is desirable during acute illness.
   - Enteric instructions and precautions during acute illness
3) For contacts.
   - Household and close contacts of cases should not be employed in specific occupations (e.g. food handlers) until at least 2 negative stool and urine cultures are obtained.
   - Health education should be provided and enteric precaution for persons that are household contacts of cases.
4) For carriers.
   - Oral Quinolones:
   - (Ciprofloxacin 750mg/12h Po for 28 days) (norfloxacin 400mg/12h infection (carriers) even when biliary disease exists.
   - Amoxicillin or Ampicillin (100mg/kg/day) plus TMP-SMZ (160 to 800 mg twice daily) for six weeks.
   - Follow up Cultures are necessary to confirm cure.

VI- Prophylaxis

Vaccine name	How given	No. of doses	Time between doses	Total time needed to set aside from vaccination	Minimum age	Booster needed every
Ty21a (live attenuated)	**1 capsule by mouth**	**4**	**2 days**	**1 week**	**6 years**	**5 years**
VICPS (capsule antigen poly saccharide)	**Injection (IM)**	**1**	**-**	**2 weeks**	**2 years**	**2 years**

Brucellosis

I- Definition

- Brucellosis is a systemic infection with one of the species of brucella gram negative coccobacilli (Brucella abortus , brucella melitenisis and brucella suis)
- Brucellosis is a world wide zoonosis also known as undulant fever , mediterranean fever , or malta fever

II- Modes of Transmission -:

- Ingestion of contaminated foods, main route in non endemic areas (milk and milk products raw meat, liver, spleen, bone marrow).
- Contact with infected animals and its products.
- Aerosols of infected fluid through respiratory tract or conjunctiva
- Uncommon routes: include blood transfusion, bone marrow transplantation.
- Unproved routes : transplacental , sexual , breast milk feeding

III- Diagnosis

1- History of animal contact.

2- Clinical picture.

3- Incubation period :

1-3weeks and may extend to few months, may be short and trivial without sequale or sever with serious complication classified patient into:

Acute< 8 weeks - Subacute (8-52 weeks) - Chronic > 52 weeks

- Acute brucellosis, Fever, chills, sweating, generalized boneaches
- Chronic brucellosis, Temperature may be normal lassitude, law backache, depression, and moderate splenomegaly.
- Brucella complications:Arthritis and spondylitis, endocarditis, meningitis and, Encephalitis, Epididymoorchitis, hepatitis

4- Case Definition

Suspected case

- Fever for more than 3 days with profuse night sweating and one of the following (Weight loss - headache - arthralgia)

Propable case

- Suspected case with + ve tube agglutination with titre > 1/160 in non-endemic areas & 1/320 in endemic areas.

Confirmed case

- Suspected or probable case confirmed laboratory by :-

- Isolation of brucella SPP. From clinical specimen either blood, bone marrow.
- Or a four-fold increase in brucella agglutination titre between acute and convalescent phase (serum specimen obtained 2 week apart).

VI-Lab. Investigation.

a) Standard Agglutination test

- Depends on the presence of clinical features + positive blood or tissue culture and/or detection of raised brucella agglutinins in the blood Culture (+ve in about 50 -70% of cases)
- Bone marrow culture is thought to be the standard criterion, since the reticuloendothelial system holds a high concentration of the organism. Sensitivity is usually 80-90%.
- Agglutination test is false negative in prozon phenomenon ,patients with immune suppression and hypoproteinaemia & false positive in cross reaction with other organisms , high titre of old infection remains high in risky groups like farmers , butchers and veterinarians .

b) Modified Brucella test

(mircabto ethanol test): more specific , positive in chronic brucellosis

c) A dip stick test: rapid test to detect IgM

d) Blood culture: takes about 6 weeks

e) PCR: still under evaluation

VII- Medical treatment

- Brucellosis is considered uncomplicated if there are acute non specific features in the absence of focal infection.
- Up to 30% of patients treated with monotherapy experience relapse and therefore a combination of antibiotics is routinely recommended.

1. Rifampicin

Dose: 10 – 20 mg / kgm body weight oral on empty stomach, can be used in adult and pediatric age group and pregnancy.

2. Doxycycline

Dose: 100 mg capsule twice daily used in adult only and should be avoided in children younger than 8 years and pregnancy.

3. Aminoglycosides

- Streptomycin 15 mg / kg body weight daily for 2- 3 weeks.
- Gentamicine 2 - 5 mg / kg body weight may be single daily i.m dose or i.v infusion
- Netilmicin: 4 - 6 mg / kg body weight in 2 divided doses.

4. Co-Trimoxazole

Dose: 8 -10 mg/kg body weight oral in 2 divided doses.

- Should be avoided in pregnant women preceding 13 weeks of pregnancy and after 36th weeks of pregnancy of concern about teratogenicity and kernicterus.

- **Drug Regimen**

Acute adults, without complications

1- Double Drug Regimen (Doxycycline + Rifampicin) for 6 weeks

2- Triple Drug Regimen (Doxycycline + Rifampicin + Aminoglycoside or streptomycin) for 6 weeks is more preferable.

VIII- Chronic brucellosis:

Reserved for patients whose clinical symptoms persist for 12 months or more from the time of diagnosis , Patients fall into these categories :

1- Relapse

2- Chronic localized infection

3- Delayed convalescence

Relapse is defined as the recurrence of characteristic signs and symptoms (with or without positive culture) occuring at sometime after the completion of a course of treatment and usually

treated with the same regimen as initially used.

- **Chronic brucellosis without complications**

Triple Therapy for 3 months

- **Brucellosis in pregnancy and children < 8 years**

Rifampicin + Co – Trimoxazole for at least 6 weeks

In the first trimester of pregnancy and end of pregnancy mono– therapy with rifampicin should be used.

- **Brucellosis with bone affection, Complication**

For 9-12 months and must include Doxycycline (Triple Therapy)

- **Complicated Brucellosis with neurological manifestations**

For 9-12 months and must include rifampicin (Triple Therapy) , Streptomycin or gentamicin is usually discouraged (because of the potential neurotoxicity and the questionable ability to penetrate to the CSF .

- **Complicated brucellosis in Hepatic patients**

With compensated liver diseases: as usual previous regimen

With decompensated liver disease: use ciprofloxacin 750 mg tds for one month.

- **Complicated brucellosis in Renal impairment**

Doxycycline with normal dose and minimize other drugs variated from one case to other

- **Surgical Treatment**

May be indicated with endocarditis, osteomyelitis and abscess formation.

- **N.B**

Follow up of patient is recommended after discharge from hospital to complete medical treatment and also to minimize relapse.

Stability of body temperature appear after 2-5 days from effective course of treatment.

IX- Preventive measures :

Reporting (Weekly report - Include in group b disease)

1) Hospitalization to confirm diagnosis adjust drug regimen

2) Contacts : no special precaution because no evidence of person to person transmission

3) Laboratory personnel

- There is increased risk of acquisition of brucellosis from blood culture specimen so biosafty measures should be taken.

Bacterial meningitis

I) Definition: Inflammation of the meninges covering the brain and spinal cord

II) Modes of transmission:

Differs according to the causative organism

- **In meningococcal meningitis:** Direct contact with case or carrier including respiratory droplets that may lead to subclinical infection.
- **In haemophilus meningitis and pneumococcal meningitis:** through respiratory droplets and respiratory secretion.

III) Diagnosis:

1- Case definition

[a] Suspected case.

Any patient with sudden onset of fever (Temp ≥ 38°C) with one or more of the following:

- Neck stiffness - Altered consciousness.
- Purpuric or petechial rash.
- Other signs of meningeal irritation.
- In children < 1 year of age → bulging of ant. Fontanelle.

[b] Probable case.

Suspected case + Turbid C.S.F + WBCs more than 100/ mm^3 with increase in protein more than 100/dl and decrease in glucose less than 40 mg/dl

[c] Confirmed case.

Suspected or probable case with laboratory evidence to organism by:

- Gram stain - C.S.F. culture
- Latex antigen detection - PCR.

2- Laboratory investigation.

[a] Routine lab. investigation as:

CBC, ESR , electrolytes, serum urea, creatnine , blood sugar, CRP

[b] C.S.F. examination

Agent	Pressure (mmHg)	WBCs Count (cell/µm)	Glucose (mg/dl)	Protein (mg/dl)
Normal C.S.F	**80-200**	**0-5 Lymphocytes**	**50-75**	**15-40**
Bacterial meningitis	**200-300**	**100-5000 >80% PMNL**	**<40**	**>100**
Tuberculous **meningitis**	**180-300**	**100-500 Lymphocytes**	**<40**	**>100**
Cryptococcal **meningitis**	**180-300**	**100-200 Lymphocytes**	**Reduced**	**50-200**
Viral **meningitis**	**90-200**	**100-300 Lymphocytes**	**normal**	**Normal may be slightly elevated**

[c] Imaging and radiation.

- Brain C.T scan, MRI (plain or contrasted)
- Chest x – ray.
- Abd.U/s.

[d] Others lab.

- PCR .
- Culture and sensitivity.
- Tuberculin test.

IV) Medical treatment:

(1) Empiric antibiotics treatment:

Treatment for bacterial meningitis based on clinical subgroups as follow:

1. Neonatal meningitis: (less than one month)

- Ampicillin 150 – 200 mg/kg/day [8 hours] Plus.
- Cefotaxime 100 – 200 mg/kg/day [6 – 12 hours] or
- Gentamicin 5 – 7 mg/kg/day [8 – 12 hours]

2. Infant, children, Adult meningitis:

- Cefotaxime (8 – 12 gm/day [4 – 6 hours]). or

- Ceftriaxone (4 gm/day [12 hours]) Plus
- Vacomycin (30 – 60 mg/kg/day [8 – 12 hours])

3. Above 50 years:

- Vancomycin (30 – 60 mg/kg/day [8 – 12 hours]) plus
- Ampicilline (12 gm/day [4 hours [) plus
- Cefotaxime (8 – 12 gm/day [4 – 6 hours]) or
- Ceftriaxone (4 gm/day [12 hours]) Plus

Important notes:

- Vancomycin given with normal renal functions and renal function should be followed up during treatment.
- Ampicillin added if Listeria monocytogens is suspected organism.
- If ampicillin is not available penicillin G can be used.

4. Immuno compromised patients.

- The same previous regimen can be used.

5. Recurrent Meningitis and Basilar skull fracture:

- Vancomycin plus .
- Cefotaxime or ceftriaxone as described above.

6. Neurosurgery or C.S.F. shunt.

- Vacomycin, (30 – 60 mg/kg/day) – [8 – 12 hours] plus
- Ceftazidime:
  - 50 mg/kg/8 hours in children
  - 2 gm/ 8 hours in adults.
- OR Cefepime:
  - 50 mg/kg/ 8 hours in children.
  - 2 gm / 8 hours in adults.
- OR Meropenem:
  - 20 – 40 mg/kg/ 8 hours children.
  - 2 gm/ 8 hours in adults

7. During pregnancy:

- Ampicilline 2 gm/4 hours

(2) Specific antibiotics treatment:

1. Nesseria meningtidis:

- Cefotaxime or Ceftriaxone for 7 – 14 days. and based on CSF culture and sensitivity results.
- Pencillin G or Ampicillin can be used.

2. Streptococcus pneumonia:

- Vancomycin plus Cefotaxime for 10-14 days. And can be extended to 3 weeks.

3. Haemophilus influenza:

- Ceftriaxone or Cefotaxime for 7- 14 days.

4. Listeria monocytogens:

- Ampicillin OR Pencillin G given for at least 3 weeks.

- Gentamicin which is given for at least 1st week, it can be extended to 3 weeks unless there is renal or ototoxicity.

5. Pseudomonas aeruginosa:

- Ceftazidime, Cefepime or Meropenem for 21 days.

6. Staphylococcus epidermidis:

- Vancomycin for 14 days, rifampicine may be added.

(3) Cortico – Steroid:

- Dexamethasone (0.15 mg/kg every 6 hours for 4 days),the first dose should be administered 15 - 20 minutes before the first dose of antibiotics.

(4) Supportive, Symptomatic therapy.

- Antipyretic.
- Fluids.
- Anti-convulsant.
- Anti-emetics.

V) Preventive measures.

- **Reporting**.Immediately, Group A disease
- **Isolation** for 24 hours from starting suitable abtibiotic , In Meningococcal meningitis
- **For household contacts** and other close contacts with meningococcal meningitis.

- **Rifampicine:**
  - Adults: 600 mg every 12 hours for 2 days.
  - Children: 5 – 10 mg/kg every 12 hours for 2 days.
- **Ceftriaxone.**
  - Adults: 250 mg single IM dose
  - Children: < 15 years 125 mg single IM dose
    - And this is the safest choice in pregnant female.
- **Ciprofloxacin.**
  - 500 mg – 750 mg, single oral dose for adults.

T.B. Meningitis

I) Diagnostic Criteria

The diagnosis depends on high index of clinical suspicion:-

1- Previous history of pulmonary or extra pulmonary T.B

2- Conact to a tuberculosis patient

3- Long incidious fever with non specific complaint like headache

4- Irritability , loss of weight ,altered sensorium

5- Signs of increase intra cranial pressure (vomiting – blurring of vision – papillodema)

6-Signs of cranial nerve affection (most commonly third, sixth, seventh)

- Curative course of treatment should be completed through a year or should be followed through a year.
- This course of treatment should be fulfilled through 2 consecutive phases as follow:

II) Medical treatment

1) Anti-tuberculous regimen.

First: intensive phase:

Consists of:

- 4 Drugs regimen that include: - Isoniazid – Rifampicin – Pyrazinamide - and either Ethambutol or Streptomycin.

Duration:

- This 4 drugs administerd daily for 2 months.Then ↓

Second: Continuation Phase:

Consists of:

- Isoniazid – Rifampicin.

Duration:

- These 2 drugs administerd daily or 3 times weekly for 7-10 months.

Doses and Route of administration:

1- Isoniazid: - Oral, (Tab = 50, 100 mg) 10 – 15 mg/kg/day(maximum300mg per day for adults)

- **N.B.** Pyridoxine (Vitamin B6) should be used to avoid peripheral neuropathy, side effect of isoniazid.

2- Rifampicin: - Oral, (caps = 150, 300mg) 10mg/kg/day (maximum 600 mg in adults)

- **N.B.** Liver functions and liver enzymes should be monitored

3) Pyrazinamide:- Oral (Tab = 500mg).- 15–30 mg/kg/day (Maximum 2gm dose)

4) Ethambutol: - Oral (Tab = 100, 400mg)- 15-25 mg/kg/day (maximum 1gm per dose)

- **N.B.** Renal functions should be monitored.

2) Corticosteroid Regimen

- Either dexamethasone or prednisone may be used.

1- Dexamethasone.

• Children weight < 25 kg.

- 8mg/ day for 2 weeks
- Then taper gradually over 4-6 weeks

• Adolescents and adults > 25k kt.

- 0.3 – 0.4 mg/kg/day for 2 weeks.

- Then 0.2 mg/kg/day week three.
- Then 0.2 mg/kg/day week four.
- Then 4mg per day and taper 1mg off the daily dose each week.Total duration approximately 8 weeks.

2- Prednisone.

- Children
  - 2-4 mg/kg/per day
- Adolescents and adults
  - 60 mg/day
  - Initial dose for 2 week, then tappred gradually over 4-6 weeks.

The Extra-pulmouary Tuberculosis

The proportion of patients with Extrapulmonary tuberculosis has risen over the last 40 years.
The Extrapulmonary T.B commonly affect the brain, the kidneys the bones and the cervical lymph nodes that drain the Pulmonary vessels.
Most cases of extra pulmonary TB are presented by FUO.

General Comments on Treatment of Extrapulmonary tuberculosis.

- The extrapulmonary tuberculous foci usually respond to treatment more rapidly than does cavitary pulmonary tuberculosis, owing to the lower burden of organisms.
- Therapy with 4 drugs regimens: (Isoniazide INH – Rifampicin RIF – Pyrazinamide PZA – Ethambutol EMB) for 2 Months followed by INH and RIF for 4 Months is advised in most cases caused by drug sensitive organisms.
- The Exception for this regimen. Duration include: (Bone and Joint T.B 6 to 9 Months - Tuberculous Meningitis 9 to 12 Months.)
- Adjunctive cortico-steroids are recommended for persons with: pericardial or CNS Tuberculosis.

Leprosy
(Hansen's disease)

I-Defenition

- Leprosy is a chronic disease caused by a slow multiplying bacillus ***(Myco-bacterium Leprae)***. The disease affects mainly the skin, the peripheral nerves, mucosa of upper respiratory tract, and also the eyes and other structures.
- The incubation period of the disease is about 5 years. Symptoms can take as long as 20 years to appear
- Although not highly infectious, it is transmitted via droplets, from the nose and mouth, during close and frequent contacts with untreated cases.

II- Case Definition:

A case of leprosy is a person having one or more of the following:

- Hypo pigmented or reddish skin lesion(s) with definite loss of sensation
- Damage to the peripheral nerves, as demonstrated by loss of sensation and weakness of the muscles of hands, feet, or face
- Positive skin smear

III- Types of Leprosy

Leprosy cases are divided into 2 types:

- **Paucibacillary:** characterized by one or a few hypopigmented skin macules that exhibit loss of sensation.
- **Multibacillary:** associated with multiple symmetrically distributed skin lesions that might not exhibit loss of sensation- nodules- plaques- thickened dermis- frequent involvement of the nasal mucosa resulting in nasal congestion and epistaxis

IV- Action to be taken

For cases:

A - Reporting: (group c disease)

B - Hospitalization: Refer to Leprosy hospital

Treatment:

N.B:

- Early treatment with a 6–12-month course of multi drug therapy (MDT) is highly effective, and has few side-effects and low relapse rates; there is no known drug resistance.
- Untreated, leprosy can cause progressive and permanent damage to the skin, nerves, limbs and eyes.

Multibacillary leprosy

- Rifampicin: 600 mg once a month + Dapsone: 100 mg daily + Clofazimine: 300 mg once a month and 50 mg daily (Duration= 12 months).

Paucibacillary leprosy

- Rifampicin: 600 mg once a month + Dapsone: 100 mg daily (Duration= six months).

Single Skin Lesion Paucibacillary leprosy

- Single dose of: Rifampicin: 600 mg + Ofloxacin: 400 mg + Minocycline: 100 mg.

For contacts:

- Health education for the family of the patient
- Clinical examination of contacts

Tetanus

I-Definition:

Clinical illness characterized by acute onset of hypertonia and / or painful muscular contractions (usually the muscle of the jaw and neck) and generalized muscle spasms without other apparent medical cause.

II- Modes of transmission:

Tetanus caused by a neurotoxin produced by clostridium tetani, anaerobic spore forming bacillus through infected wounds ,burns, infected syringes , infected surgical instruments

III- Diagnosis

The clinical features: rigidity, muscle spasms, autonomic dysfunction, neck stiffness and difficulty opening the mouth.

IV- Medical management:

Aim of management:

- Control muscle spasm
- Neutralization of circulating toxin
- Eradiaction of the organism
- Control autonomic dysfunction
- Wound care
- Prevent reinfection (immunization)

[A] Hospitalization:

In a dark, quite, room fitted and supplied by emergency drugs and instruments

[b] Control muscle spam to ensure patent airway

[c] Intubation: Tracheostomy or neuromuscular blocking may be needed

[d] Prophylactic measures:

Against complication:

- For deep venous thrombosis
- Gastointestinal ulcer.
- Decubitus ulcer.

[e] Maintenance of nutrition:

This is done through:

- Parenteral nutrition
- Gastrostomy tube feeding
- Nasogastric or Nasodudenal tubes.

[f] Drug treatment:

1- Tetanus antitoxin.

- Given before wound manipulation.
- It does not penetrate B.B.B
  - Human tetanus immunoglobulin (TIG)→ Dose: 3000 – 6000 units by I.M.
    Or:
  - Equine tetanus antitoxins (T.A.T) → Dose: 10,000 – 100,000 units (I.M) OR (I.V) given after hypersensitivity test.

2- Tetanus toxid. (3 doses)

- →First dose is given (1/2 cc I.M. in deltoid region) on discharge Vaccination schedules should be revised

3-Anticonvulsants.

- **midazolam (Dormicum ampoule (5mg / 1ml – 15 mg /3ml))**
  - Adult I.V dose:
    - Initial I.V dose 0.01 – 0.05 mg/kg
    - May repeat at 5 to 15 minutes interval until adequate sedation is achieved.
    - Maintenance infusion 0.02 to 0.1 mg/kg/hour

- Pediatric dose:
  - Loading I.V dose 0.05 to 0.2 mg/kg followed by continuous infusion 0.06 to 0.12 mg/kg/hour

- **Diazepam. (Valium ampoule (10 mg/ 2ml))**
  - Adult dose :
    - 0.2 mg/kg may be repeated in 4 to 12 hours if needed,
  - Pediatric dose:
    - Children 2 – 5 years → 0.5 mg/kg.
    - Children 6 – 11 years → 0.3 mg/kg
    - Children > 12 years and adolescent → 0.2 mg/kg
- **Propofol (deprivan).**
  - Continuous I.V infusion. Initial 0.3 mg/kg/hour, Increase by 0.3- 0.6 mg/kg/hour every 5 to 10 minutes until desired sedation level is achieved.
  - Usual maintenance 0.3 to 3 mg/kg/hour, reduce dose after adequate sedation achieved and adjust to response.
- **Phenoborbital.**
  - 1mg/kg/hour I.M or I.V

4- Skeletal muscle relaxants.

- Norflex → I.V 60 mg every 12 hour
- Baclofen → 5 to 10 mg/8 hours

5- Drugs reduce sympathetic overactivity:

- Magnesium sulphate: Dose: (loading dose 70 mg/kg) then infusion 1 – 4 gm/hour to maintain blood level at 2.5
- 4 mmols and increase by 0.25 – 0.5 gm/ hour till control spasm is obtained.

6- Metronidazole as Antibacterial Drug

- Adult: 500 mg/ 6 hour not exceed 4 gm/day- Paediatric: 30 mg/kg/day in 4 divded doses.

N.B (Penicillin G Potentiate effect of tetanus toxin, Therefore metronidazole has suggested as alternative)

[g] Adequate wound debridement:

- With cleaning and draining, if needed.

Tetanus Neonatorm

I-Definition: Infection with Clostridium tetani that occur during delivery due to cutting of the umbilical cord with infected instrument and characterized by (inability of the neonate for suckling) and this features may not appear in the first few days after delivery (incubation period) this is followed by difficult feeding due to trismus which progresses to generalized spasms then followed by convulsions (incubation period from 3-28 days , average 6 days)

II- Modes of transmission:

Clostridium tetani entrance with umbilical cord cutting.

III- Diagnosis.

(1) Case definition

[a] Suspected case

1- Any neonate with normal ability to suck and cry during the first 2 days of life, followed by poor feeding or inability to suck between the ages of 3 and 28 days. The condition may progress to episodes of convulsions or stiffness.(i. e. jerking of muscles).

2- Any neonatal death between age of 3 days and 28 days with no obvious case.

[b] Probable case:

None

[c] Confirmed case

No lab. Confirmation

IV- Medical treatment.

1- Tetanus anti-toxin.

[a] Human tetanus Immunoglobulin→Given 1000 units I.M.

[b] Equine tetanus antitoxin→Given 10,000 unit (I.M.) or (I.V.) after skin sensitivity test.

2- Metronidazole.

- Age

< 7 days: 15 mg/kg/day divided every 12 hours IV/ PO

> 7 days: 30 mg/kg/day divided every 12 hours IV/PO

3- Midazolam.

- Loading dose should not be used in neonates.
- Continuous infusion 0.5 mcg/kg/min I.V infusion.

4- Phenobarbital.

- Loading dose 15 mg/kg/I.V infused at a rate not to exceed 2mg/kg/minute.
- Then 3 - 5 mg/kg/day I.V/PO. In 1 – 2 divided doses.

5- Magnesium sulphate.

- 20 - 50 mg/kg/hour (Dilute 1 gm in 50 mL glucose 5%)

6- Muscle relaxant.

- Baclofen 10 – 15 mg oral divided every 8 hours, increase dose every 3 days by 5 – 15 mg/day, maximum 40 mg/day

7- Feeding through nasogastric tube

8- Sepsis work up → give proper antibiotic & revision of infection control measures

V- Preventive measures.

1- Reporting: Immediately, Group A diseases

2- Hospitalization: In dark, quite room in pediatric ICU.

3- Vaccination of pregnant female: →Tetanus toxid, one month apart.

Diphtheria

I- Definition

Diphtheria is an acute infectious disease caused by toxigenic Corynebacterium diphtheriae . it is characterized by local inflammation and the production of pseudomembrane composed of necrotic epithelium and coagulated inflammatory cells in the upper respiratory tract (nasal or oropharynx which may cause airway obstruction .

II- Modes of transmission

- Via respiratory droplets or contact with exudate from skin lesions.

III- Diagnosis

Case definition

a) Suspected case

Not applicable

b) Probable case

- Is a case of upper respiratory tract infection with adherent greyish membrane not confirmed by laboratory and not related epidemiologically to confirmed case with exclusion of other diagnosis.

C) Confirmed case

- Is a probable case that is laboratory confirmed by culture or epidemiologically linked to confirmed case.

IV- Medical Treatment

1- Anti-toxin →must be given to all probable cases immediately (I.V) or (I.M) after sensitivity test dose.

- Mild → early pharyngeal 20.000 – 40.000 units
- Moderate → nasopharyneal 40.000 – 60.000 units
- Sever → extensive disease 80.000 – 100.000 units

2- Antibiotic :Is given immediately for 10-14 days.

- Benzyl Penicillin :adult 2-3 million units I.V every 6 hours.
- Procaine Penicillin:Given (I.M) (> 10 kg. 600.000 units/day- < 10 kg. 300.000 units/day)
- Erythromycin :Given (oral) (Adult 500mg/6hours – Children 40mg/kg/day, divided every 6 hours)

3- Removal of membrane: done by laryngoscope or bronchoscope through ENT consultation.

V- Preventive measures

1- Reporting : immediately, group A disease.

2- Isolation : Patient should be isolated until 3 consecutive cultures from both throat and nose (skin lesion in cutaneous diphtheria) are negative (-ve) at the end of therapy.

3- For contacts :

- Contacts of patients with probable or confirmed disease should be restricted from work if involved in food handling.
- Close contacts should have cultures taken and kept under surveillance.
- If these cultures are positive (+ve), should consider giving Diphtheria antitoxin and follow up.

4- Prophylactic Antibiotic may be used:

- Benzathine Penicillin I.M single dose (Adult, children > 30kg → 1.2 million units , Children < 30kg 600.000 units)

Food Born Diseases
(Acute Food Poisoning)

Causative agents of acute food poisoning include bacteria, fungi, parasites, viruses, and chemicals. Bacterial food poisoning includes Salmonella, Escherichia coli, Staphylococcus aureus, Clostridium perfringens, Bacillus cereus, Shigellosis …etc.

Suspected case

- Any patient suffering from acute onset of two or more of the following (colic – nausea - vomiting – diarrhea – fever – fatigue) and usually more than one patient at the same time and from the same area .

Probable case

not applicable

Confirmed case

- The case is confirmed by isolation of the cause (the organism or its toxin from the suspected food or its source (vomitus , gastric lavage , stool , blood, water sources).

1-Salmonella

- S. Enteritidis; S. Typhimurium account for 75 % of S. infections.
- Salmonellae are one of the main causes of food borne illnesses throughout the world.
- Transmission through ingestion of food and drinks contaminated with animal faeces
- Flesh of chicken and turkey is the main source. Also contaminated duck and chicken eggs with faeces are common source of infection (Unless boiled for five minutes)

Incubation period: 12 – 24 hours but may range from 6 – 48 hours.

Pathogenesis: Two main mechanisms 1- Enterotoxin 2- Invasive inflammation

Clinical picture:

- It is that of enterocolitis i.e. involvement of both small and large intestine.
- It begins with nausea, vomiting, headache and fever.
- Soon afterwards abdominal pain and watery diarrhea lasting for a few hours in mild cases; but may be voluminous and every 30 minutes, containing blood and mucus; Leading to dehydration and renal failure.
- Recovery usually occurs by subsidence of the diarrhea within few days; it seldom persists beyond 3 weeks.
- Post infective bowel irritability may happen in the form of increased bowel frequency particularly after meals.

Diagnosis:

- Needs positive either stool or blood culture.

Treatment:

- It is short lasting self-limiting illness.
- It aims at fluid and electrolyte replacement through O.R.S.; I.V. infusions.
- Fluoroquinolones e.g. Ciprofloxacin in a dose of 500 mg. b.i.d. for 5 days have been shown to shorten the duration of the illness.
- It should be prescribed for patients who are at risk of severe disease and for septicemia e.g. the elderly and immunocompromised patients.
- Third generation cephalosporin (Cefotaxime, ceftriaxone) are the drugs of choice in children younger than 6/12;. and indicated if there is pronounced intestinal or constitutional symptoms.

- However ampicillin, chloramphenicol and co- trimoxazol can be used after sensitivity is determined.

2-Escherichia coli

Although most strains of E. coli are commensals of the intestinal tract, some have acquired virulence factors that have placed them among the leading causes of diarrhea, particularly in the developing world.

Different types of enteric E.coli infections:

1. Enteropathogenic E. Coli [EPEC] :
   - EPEC strains are most important as a cause of endemic diarrhea in developing countries.
   - They primarily infect children of age 6 -18 m.
   - Diarrheal stool often contains mucus but not blood; usually self-limited (lasting 5-15 days)
   - Incubation period: of few days, inversely related to the inoculum size.
   - Vomiting is common and may be severe and projectile.
2. Enteroaggregative E.Coli [EaggEC] :
   - Diffusely adherent E.coli (DAEC)
     - In developing countries they are the major cause of diarrhea mortality in young infants.
     - Commonly present as cases of persistent d. lasting more than 14 days.
     - EAST [enteroaggregative stable toxin] has been identified in many isolates.
3. Enterotoxigenic E coli [ETEC] :
   - Common cause of diarrhea at any age.
   - The source is usually contaminated water or unrefrigerated food.
   - The inoculum size is generally high (10m -100000m).
   - The clinical illness resembles cholera; because they produce a cholera-like heat labile toxin LT and two types of heat stable toxins ST (The sum of 3 types acts in a similar manner to cholera toxin causing luminal accumulation of Na Cl to cause diarrhea and vomiting leading to mild to severe dehydration.
4. Enteroinvasive E.coli [EIEC] :
   - Can cause food borne outbreaks in adults and children.
   - They can produce Shigella - like illness with bloody diarrhea; they possess a gene similar to that of Shigella conferring the property of invasion of epithelial cells leading to bloody diarrhea.
   - Fewer bacteria are required to cause the illness.
   - After an incubation period of 1-3 days secretory diarrhea may evolve into inflammatory colitis characterized by fever, abdominal pain, tenesmus and scanty stool containing mucus, blood and inflammatory cells.
   - Symptoms are self-limited, lasting 7-10 days.
5. Enterohaemorrhagic E.coli [EHEC] :
   - They are able to produce shiga [or Vero] toxins that is why called STEC or VTEC.
   - Incubation period is often 5-7 days with small inocula of STEC.
   - The initial watery stools become blood tinged and then grossly bloody over the course of a day or two.
   - There is abdominal cramps and tenderness.

- This is due to a diffuse inflammatory colitis with vascular leaks, rather than ulceration as shigellosis
- Mild infections remaining as a watery diarrhea.
- Patient usually improves clinically in 5 to 7 days.
- About 5-7 d later particularly in infection with O157:H7, O104:H4 microangiopathic haemolytic anemia, thrombocytopenia, and oliguric renal failure [the HUS] - develop in 5 to 10%.It is associated with shiga toxin.
- Sometimes others rapidly developing hypertension may lead to haemorrhagic strokes and death in the acute phase.
- Others develop renal failure requiring peritoneal or haemodialysis.
- Small proportion showed CKD (chronic kidney disease) manifestations
- a decade or more after the initial episode.
- STEC is found in cattle, and occasionally in other farm animals as part of normal flora.
- Ground hamburger meat prepared in large lots at slaughterhouses then quick frozen for distribution and later cooking have been implicated in outbreaks of human infection because freezing preserve the organisms.
- Organisms can also be disseminated from farm animals to ground water and adjacent crops like lettuce, apple cider and unpasteurized apple juice which have been vehicles of infection.
- Water swallowed when swimming can result in disease.
- Non-beef foods accounts for 50% of all cases in US, Like potatoes, lettuce, sprouts, fallen apples which were contaminated by animal manure used as fertilizers.
- Person to person transmission is also well documented, reflects the small inoculum size needed to cause infection which reaches between 50 -100 organisms.

Laboratory Diagnosis of E. coli:

- Can be detected on SMAC Sorbitol Mac -Conkey agar.
- ELISA can be used.
- PCR can be used.
- Can be identified in the blood by C / S in case of sepsis and circulatory shock.

Treatment:

- The most urgent need is to replace fluid and electrolyte losses.
- Infants may require parenteral fluids particularly with ETEC infection but oral rehydration is sufficient.
- With STEC, dehydration is not the prime concern as the fluid losses are not severe treatment complications: Themicroangiopathic haemolytic anaemia, thrombocytopenia and renal failure.

Prevention:

- -The safe disposal of excreta, provision of purified water, and control of flies are fundamental to the prevention.
- -Also personal and domestic hygiene, notably hand washing after defecation and before handling food.
- -Unpurified water can be made safe by boiling or by the addition of hypochlorite tablets.
- -Salads and fruits can be disinfected by soaking in water containing 80 parts per million of free chlorine from house hold bleach.

3-Staphylococcal

Symptoms:

- Usually begin 1-6 hours after ingestion of the toxin; Begin with excessive salivation, rapidly followed by nausea, vomiting, abdominal cramping and diarrhea.
- The illness is usually short, rarely lasting 24 hours.

Case Definition:

Suspected Case

Disease of sudden onset (30 min. - 8 hours, usually up to 4 hours) with:

- Severe nausea and vomiting
- Abdominal cramps
- Fatigue & prostration
- Often accompanied by diarrhea

Disease lasts for 24-48 hours.

Probable Case

None

Confirmed Case

- Isolation of Staphylococcus aureus from suspected food, vomitus, or stool
- Enterotoxin detection in the suspected food
- Suspected case among food poisoning cases sharing the same food with at least one lab confirmed case

Management:

Supportive and symptomatic

- Fluid replacement.
- Antiemetics can be given.
- Suspected food should be cultured for staphylococci and demonstration of toxin production.

Prevention:

- Proper food handling, also sanitary measures, and personal hygiene can prevent contamination of the food .
- Food should not be left to cool slowly especially in large containers, and should be taken from the refrigerators immediately before serving and reheated if required.

4-Clostridium perfringens

Etiology:

- During slow cooling the spores germinate encouraged by the relatively anaerobic environment and the rich supply of amino acids and other growth factors. Viable organisms multiply to large numbers.
- Poisoning occurs if the food is not reheated to a temperature high enough to inactivate the recently multiplying organisms which will release their enterotoxin which will cause FP when ingested.

Incubation period:

- 6 – 12 hours after eating the meal but may be as long as 24 hours.

Symptoms:

- Crampy abdominal pain and diarrhea; But nausea, vomiting and fever are much less common.
- The illness is self-limited; rarely lasting more than 24 hours.

Case Definition:

Suspected Case

Sudden onset of colic with diarrhea & nausea .Vomiting and fever are usually absent. Generally patients experience mild disease of short duration.

Probable Case

None

Confirmed Case

- Identification of the bacteria in a culture from the suspected food or patient stool
- Detection of the enterotoxin secreted by the bacteria in the stool
- Suspected case among food poisoning cases sharing the same food

Treatment:

- Rarely is necessary and should be confined to symptomatic relief.

Prevention:

- Food is best served immediately after cooking; if it is to be kept; it should be cooled rapidly.
- Cooked meat should always be kept either below 5 °C or over 60 °C.

5-Bacillus cereus

- It is a gram positive, aerobic, spore forming bacilli of universal distribution.
- It is a common cause of food spoilage, food poisoning and wound sepsis.
- Two types of food poisoning are caused by b.c.

1) C.PERFRINGENS Like Type
2) The other type is like STAPHYLO COCCAL F P

Diagnosis:

Depends on finding of counts of bacillus c. in excess of one hundred thousand in the suspected food and its detection in the vomitus and faeces of the patient.

Prevention:

Observation of correct procedures of food preparations.

6- Shigellosis

- Shigella is gram-negative bacterium. There are several species

Clinical Manifestations:

A clinical syndrome of fever, intestinal cramps, and frequent passage of small, bloody, mucopurulent stools. Shigellosis typically evolves through four phases: incubation, watery diarrhea, dysentery, and the post-infectious phase.

Laboratory Diagnosis:

- The "golden standard" for the diagnosis of Shigella infection remains the isolation and identification of the pathogen from fecal material by stool culture.
- Blood cultures are positive in <5% of cases but should be done when a patient presents with a clinical picture of severe sepsis.

Antibiotic Treatment of Shigellosis:

- Ciprofloxacin is recommended as first-line treatment.
- Other drugs have been tested and shown to be effective, including:
  - Ceftriaxone, Azithromycin and some considered Quinolones.
- Rehydration should be oral unless the patient is comatosed or presents in shock.

Prevention:

Hand washing after defecation or handling of children's feces and before handling of food is recommended. Stool decontamination (e.g., with sodium hypochlorite), together with a cleaning protocol for medical staff as well as for patients.

7- Viruses

- Viruses are common causes of vomiting and diarrhea in babies and children.
- Rotavirus & Norwalk virus are examples of causative viruses.

Diagnosis :

Is aided by enzyme immunoassay which require fresh or refrigerated stool.

Treatment:

There is no specific treatment for virus infection of the gut.

Management:

Depend on restoration of hydration and electrolyte balance by the use of ORS or IV fluids

Prevention:

By rota virus vaccine

Bacterial food poisoning		
Incubation period		
Organisms	Symptoms	Common food sources
1 - 6H		
Staphylococcus aureus Bacillus cereus	Nausea, vomiting & diarrhea Nausea, vomiting & diarrhea	Hamburger, poultry, potato, or egg, salad, mayonnaise, cream pastries Fried rice
8 - 16H		
Clostridium perfringens B. cereus	Abdominal cramps, diarrhea ± vomiting Abdominal cramps, diarrhea ± vomiting	Beef, poultry, legumes, gravies Meats , vegetable, dried beans, cereals
> 16H		
Vibrio cholera Enterotoxigenic Escherichia coli Enterohemorrhagic E. coli Salmonella spp. Shigella spp. Vibric parahacmo-lyticus	Watery diarrhea Watery diarrhea Bloody diarrhea Inflammatory d. Dysentery Dysentery	Shellfish Salad, cheese, meats, water Ground beef, roast beef, salami, raw-milk & vegetables, apple juice Beef, poultry, eggs, diary product Potato or egg salad, let-tuce, raw vegetables Mollusks, crustaceans

Botulism

I- Definition :

Botulism is a neuroparalytic illness caused by a neurotoxin made by the bacterium Clostridium botulinum.

II- Mood of transmission:

- Botulism is a food borne disease of high mortality and epidemic potential.
- Sporadic transmission occurs through the consumption of improperly processed food, low-acid preserved vegetables, and canned, fermented, salted and smoked fish.

III- Diagnosis:

Incubation period:12-36 hours after toxin ingestion, ranges from 2 hours to 10 days.

Case Definition:

Suspected Case

- (With past history of ingestion of preserved food within the previous 48 hours)
- Any patient with unexplained diplopia, blurred vision, and/or bulbar weakness accompanied by descending symmetric paralysis

Probable Case

A clinically compatible case with an epidemiologic link
(e.g., ingestion of preserved food with the previous 48 hours)

Confirmed Case

- A suspected case is confirmed in the lab. by the detection of C. botulinum toxin in blood, stool, gastric contents or suspected food.
- Bacterial isolation from stool.
- Suspected case occurs among persons who ate the same food as persons who have laboratory- confirmed botulism.

IV- Medical Treatment:

- Admission ICU (if required)
- Respiratory support (ventilation) should be anticipated.
- Botulinum antitoxin, heptavalent (HBAT) after skin testing, administration of one vial (IV) is recommended as soon as possible.
- Supportive clinical care.

V- Preventive measures

1- Reporting: Immediately (group A disease)
2- Isolation: not required

3- Refer to center of charge.
4- Laboratory procedures: Serum samples should be collected as close to the onset of illness as possible (and before antitoxin administration)
5- For contacts: Observation for clinical disease is warranted for persons who consumed common food items with the case.

Medical management of acute Diarrheal disease

Case Definition:

- 3 or more loose motions in 24 hours for up to 14 days.

Differential diagnosis:

- Food poisoning (mainly with vomiting) and coliky
- Viral infections (e.g. Rota virus)
- Bacterial Infection (shegella ,salmonella)

- Parasitic infection (amebic dysentery) with tenesmus – blood stool.
- Cholera (painless diarrhea) with rice water stool.

Cholera

I- Definition:

- It is an infectious diarrheal illness caused by ingestion of food or water contaminated with bacterial vibrio cholera . 80% of cases can be treated with rehydration solution either oral or intravenous.
- It should be considered in the differential diagnosis of all cases of painless watery diarrhea especially those associated with severe dehydration , in such cases one should inquire
- about area of arrival .
- Rehydration is considered the first and most important tool of management and should be started in the ER or in the rehydration room .

II- Clinical picture:

- Sudden severe painless watery diarrhea , usually followed by vomiting after a short time .
- Electrolyte disturbance may cause muscular spasm
- Usually the diarrhea is painless , resembling rice water not bloody and has no offensive odour .

III- Investigations:

- CBC , Electrolytes , ABG - blood chemistry - liver and kidney profile .
- Culture of stool or rectal swab if late we can put in (Carey Blair transport media)
- Serology:by antisera vibrio cholera o1- o139 after doing bio-chemical reaction or ABI - Oxidase test
- In cholera epidemics: once lab. Confirmation and antibiotics sensitivity have been established → not necessary to confirm all subsequent cases.

IV- Medical treatment:

Highly risk group is less than 18 month and old ages and must give them priority in treatement :

1- Rehydration:

- **Oral (ORS)**for mild dehydration and can drink
- **IV injection:** severe dehydration or unable to drink because of severe vomiting or mental status.

As soon as the patient can drink → ORS.

- **NG tube:** for mild dehydration and can't drink, or severe and IV injection is not possible.
- Step 1 : Assess for Dehydration
- Step 2: Rehydrate The Patient And Monitor Frequently.
- Step 3: Maintain hydration and replace ongoing fluid losses.
- Step 4: Give oral antibiotics to the Patient with severe dehydration. According to culture and sensitivity
- Step 5: Feed The Patient.

N.B:

- Children less than 18 months and the elderly patients should have a priority in treatment as they are high risk patients .
- Frequent evaluation of the patient general condition and assessment of the degree of dehydration .
- Notice the following :

- Continue the normal breast feeding .
- Don't give dextrose iv infusion .
- Discharge your patient after clinical improvement .
- Stool culture should be done 72 hours after discontinuation of the antibiotics.

Severe dehydration	Some dehydration	No dehydration
•Lethargic , unconscious • Eyes → very sunken • Tears → Absent • Mouth,Tongue very → dry , unable to drink • Skin pinch → go very slowly The Patient has severe Dehydration I.V drip for rehydration in severe cases for which ORS can not be given by mouth as shown in the next table.	• Restless , irritable • Eyes ⟶ sunken • Tears ⟶ Absent • Mouth , Tongue ⟶ dry , thirsty • Skin pinch ⟶ go slowly The Patient has some Dehydration ORS is given by mouth as shown in the next table , nasogastric tube can be inserted in persistent vomiting or inability to drink – close follow up and monitoring of the patient . • Weight in kg ×75 ml in the first 4 hours .	• Well , Alert • Eyes ⟶ Normal • Tears ⟶ Present • Mouth , Tongue ⟶ moist , drink normally • Skin pinch ⟶ go back quickly The Patient has no signs of Dehydration Oral rehydration solution is given by mouth after each diarrheal episode as shown in the next table • The child less than 2 years 50-100 ml (1/4-1/2 glass) daily • Child 2-10 years :100-200 ml ORS up to 1 liter daly. • Child more than 10 years : as required up to 2 liters ORS daily , with increased fluid intake .

Follow up:

Follow up and fluid chart and a table registering the vital signs include:

- Vital signs: T, P, BP, RR.
- Diarrhea: frequency, consistency, volume of stools, presence of blood.
- Volume of urine.
- Signs of dehydration.
- Signs of over hydration.
- Amount of ORS.
- Amount of IVI fluid .

V- Complications:

- The most important complication is dehydration .
- Dehydration → ARF → Death
- Electrolyte imbalance.
- Hypoglycemia (more in children.)
- Over hydration:

- Early → puffiness of eyelids
- Late → pulmonary oedema.

- Complications of drugs.

N.B

Early discovery of complications and treatment is very important & patient may need in severe cases to do these tests daily as a routine blood biochemistry (electrolytes / glucose / KFTs)

In severe cases the patient may need to do the following daily:

- Antibiotics according to culture and sensitivity
- tetracycline and doxycycline should not be given before 8 years
- Norfloxacine and ciprofloxacine should not be given before 18 years .
- Trimethoprim-sulfamethoxazole should not be given before 2 months .
- Zinc supplementation should be given for all children in a dose 10 mg three times daily.

Single dose of	**OR 3 days doses**
Tetracycline: 2 g	500 mg/6h for adults
Doxycycline: 300 mg	100 mg (2mg/kg) Ped or adults
Ciprofloxacin: 1 g	250 mg bid for adults
Chloramphenicol	(50-100)mg/kgm divided 6h for adults
TMP/SMZ:	15-30/kg/12h (max960mg/12h) for adults

Piperacillin - tazobactam: 4.5 gm /6 hours for adult

Plague

I) Definition:

- Plague is a zoonotic bacterial disease caused by Yersinia pestis.
- Characterized by rapid onset of fever, chills, headache, severe malaise and prostration.

II) Mode of transmission:

- It is transmitted to humans through fleabites or direct exposure to respiratory droplets or infected animal tissues.
- Plague is endemic in many countries in the region and has the potential for epidemic transmission.

III) Clinical description:

- Bubonic form: extremely painful swelling of lymph nodes (buboes).
- Pneumonic form: cough with blood stained sputum, chest pain and difficult breathing.
- Septicemic form: Both Bubonic & Pneumonic form can progress to a Septicemic form with toxemia and/or sepsis.

IV) Case Definition

Suspected case:

- A case with rapid onset of fever, chills, headache, severe malaise and prostration.
  - **-Bubonic form:** Extremely painful swelling of lymph nodes (buboes).
  - **-Pneumonic form: C**ough with bloodstained sputum, chest pain and difficult breathing.
  - **-Septicemic form :** Both **Bubonic & Pneumonic** form can progress to a **Septicemic** form with toxemia and/or sepsis.
- A suspected case may be supported by gram stain finding of gram negative bipolar coccobacilli in clinical material (bubo aspirate, sputum, tissue, blood).

Probable Case

A suspected case with any of the following

- Detection of antibodies for Y. pests in clinical specimens
- Positive indirect fluorescent antibody (IFA) test.
- Epidemiological link with a confirmed case

Confirmed Case

Suspected or probable case that is confirmed in the lab:

- Isolation of Yersinia pestis in cultures from buboes, blood, CSF or sputum.
- Passive haemagglutination (PHA) test, demonstrating at least a fourfold change in antibody titre.

V) Medical treatment

Cases should be promptly treated with appropriate antibiotics,
Duration of treatment is 10 days, or until 2 days after fever subsides.

- Streptomycin IM:

Adult: 1 g twice daily
Children: 15 mg/kg twice daily (maximum daily dose, 2 g).

- Gentamicin IM or IV:

Adult: 5 mg/kg once daily, or 2 mg/kg loading dose followed by1.7 mg/kg every 8 hours
Children: 2.5 mg/kg every 8 hours

- N.B. Gentamicin is the preferred agent in pregnancy.

Alternative agents

- Ciprofloxacin IV:

Adult: 400 mg twice daily
Children: 15 mg/kg twice daily (maximum daily dose, 1 g)

- Doxycycline IV

Adult: 100 mg twice daily or 200 mg once daily
Children≥ 8 years: Weight < 45 kg: 2.2 mg/kg twice daily (maximum daily dose, 200 mg)

VI) Preventive measures

A- Reporting: Immediately (group A disease)
B- Isolation ,Disinfection: of article soiled with patients discharge.
C-Quarantine: of contacts with patients with pneumonic plague for 7 days
For contacts:

- Contacts should be monitored for clinical disease and counseled about personal protection from sources of infection.
- **Sanitation measures** should be used to prevent increase in rodent populations.
- Duration of post-exposure prophylaxis to prevent plague is 7 days.
- **Doxycycline PO**

Adult: 100 mg twice daily
Children≥ 8 years: Weight < 45 kg: 2.2 mg/kg twice daily (maximum daily dose, 200 mg)

- **Ciprofloxacin PO**

Adult: 500 mg twice daily
Children: 20 mg/kg twice daily (maximum daily dose, 1 g).

Erysipelas

I) Definition:

Erysipelas is an inflammation of superficial layers of the skin due to streptococcal infections.

II) Clinical manifestation:

Fever, chills followed by well demarcated area of erythema sometimes with vesicles or bullae, inflammation may spread to superficial lymphatics (lymphangitis).

- **N.B:** Diagnosis based upon clinical manifestation.

III) Complications:

Hyperpigmentation of the skin, lymphedema with subsequent elephantiasis, Toxemia

IV) Action to be taken:

A-Hospitalization:

In severe cases and immunocompromised patients

B-Medical Care:

- Elevation and rest of the affected limb are recommended to reduce local swelling, inflammation, and pain.
- Dressings damped with saline should be applied to ulcerated and necrotic lesions and changed every 2-12 hours, depending on the severity of the infection.

C-Surgical Care:

Debridement is necessary only in severe infections with necrosis or gangrene.

D-Treatment:

- **N.B:** the duration of therapy should be individualized depending on clinical response, 10 days is usually appropriate but longer duration of therapy may be warranted in patients with severe disease.

Effective antibiotics include :

- Procaine benzyl penicillin

Adult dose: 0.6-1.2 million U IM /day.

Pediatric Dose:<30kg : 300,000U/day, >30 kg: Administer as in adults

- Benzyl penicillin

1–2 million IU (children: 50000–100 000IU/kg/day maximum 2 million IU) IV or IM every 6 hours

- Macrolides (e.g. Erythromycin, Azithromycin)
- First generation cephalosporin (e.g. Cephalexin, Cefradine)

Long-term prophylactic antibiotic therapy:

- Generally is accepted, but no settled guidelines are available.
- Treatment regimens should be tailored to the patient. One reported regimen is Benzathine penicillin at 1.2 MU intramuscularly every 2 or 4 weeks for several months with interval assessment for relapse.

Scarlet Fever

I) Definition:

- Scarlet Fever result from toxin-producing Group A beta haemolytic streptococci.
- Usually follow pharyngeal streptococcal infection or any other site streptococcal infection elsewhere.

II) Diagnosis:

A. Clinical Manifestation:

- Onset, Prodrome of Fever, headache, malaise, chills. rash appear 1-4 days after the onset.
- During the first days of illness, the tongue is coated heavily with a white membrane with red protruding papillae (white strawberry tongue).
- On day 4, 5 of the illness this white membrame sloughs off revealing shiny red tongue with prominent Papillae (Red strawberry tongue).
- The characteristic exanthema.
  - Formed of Punctuate erythema on a red base that blanch on pressure for sometime (scarlatina test)
  - It appear 1-4 days of onset.
  - It appear first on the upper trunk and axillae and then becomes generalized. Soles and palms are characteristically spared.
  - The rash lasts 4-5 days followed by fine desqumation.

B. Laboratory investigation:

- Swab culture of infected oropharynx or other infected areas should be obtained.
- More rapidly, latex agglutination test of the extract from throat swab.
- CBC commonly reveals leucocytosis.
- ASOT rise is a late finding.

III) Medical treatment:

Antibiotic therapy is the treatment of choice. Culture and sensitivity should be done and considered specially when other organisms are suspected.

- Long acting Penicillin.
  - 1.2 millions IU IM as single dose in adults
  - 300.000 – 600.000 IU in children < 27 kg.
  - 600.000 – 900.000 IU in children > 27 kg.
- Penicillin V: 500 mg orally /4 times daily for 10 days.
- Amoxicillin : 500 mg orally /4 times daily for 10 days.
- Erythromycin : 500 mg orally /4 times daily for 10 days in case of penicillin Hypersensitivity.
- Cephalexin: 500 mg orally /4 times daily for 10 days.

IV) Complication:

- Otitis media.
- Pneumonia.
- Septicaemia.
- Osteomyelitis.
- Rheumatic fever .
- Acute Glomerulonephritis specially in neglected cases.

Gas gangrene

I) Definition:

- Gas gangrene is produced by several clostridial species. Deep penetrating trauma & injectable drug abuse are common predisposing condition.
- Toxins produced in devitalized tissues under naerobic conditions result in shock, hemolysis & myonecrosis.
- At 1st, the wound becomes swollen & the surrounding skin is pale with a foul-smelling brownish, blood-tinged serous discharge. Later, the surrounding tissues become deeply discolored.
- Crepitus (gas in tissue) may be felt.

II) Treatment:

1- Surgical consultation for:

- -Adequate surgical debridement & exposure of infected area
- -Radical surgical excision often necessary.

2- Antimicrobial therapy:

- Intravenously for at least 7 days Penicillin G

-Adult: 300,000IU/Kg/day divided every 4hrs (20millionsIU/ day)
-Pediatric: 300,000 IU/kg/day divided every 4hrs

Alternative:- in case of penicillin allergy

- Clindamycin

- Adults: 600 mg every 6 – 8 hrs.
- Pediatric: 10 mg/Kg every 6 -8hrs

Plus:

3rd generation cephalosporin or 4th generation cephalosporin e.g.

- Ceftriaxone

- Adults: 2 g every12- 24 hrs (maximum4gm/day
- Pediatric: 50-75 mg/kg/day in 1-2 divided doses (maximum 2g/day) e.g. Cefotaxime
- Adults: 2gm every 4- 6 hrs (maximum12gm/day)
- Pediatric: 150 mg/kg/day divided every 8 hours e.g.Cefepime
- Adult: 2gm every 8-12 hrs (maximum 6 gm/day)
- Pediatric: 50 mg/kg/dose every 8 hours

Plus

- Metronidazole

- Adults: 500 mg every 6 hrs (maximum 4 g/day)
-Pediatric: 30 mg/kg/day divided every 6 hours (maximum 2 g/ day)

- N.B. Quinolones may be added in sever or resistant cases.

3- Antitetanic serum 3000-6000 units
4- Supportive measures
5- Control chronic diseases if present (as DM-Hypertension)
6- Hyperbaric oxygen therapy during wound dressing may be beneficial.

III) Preventive measures

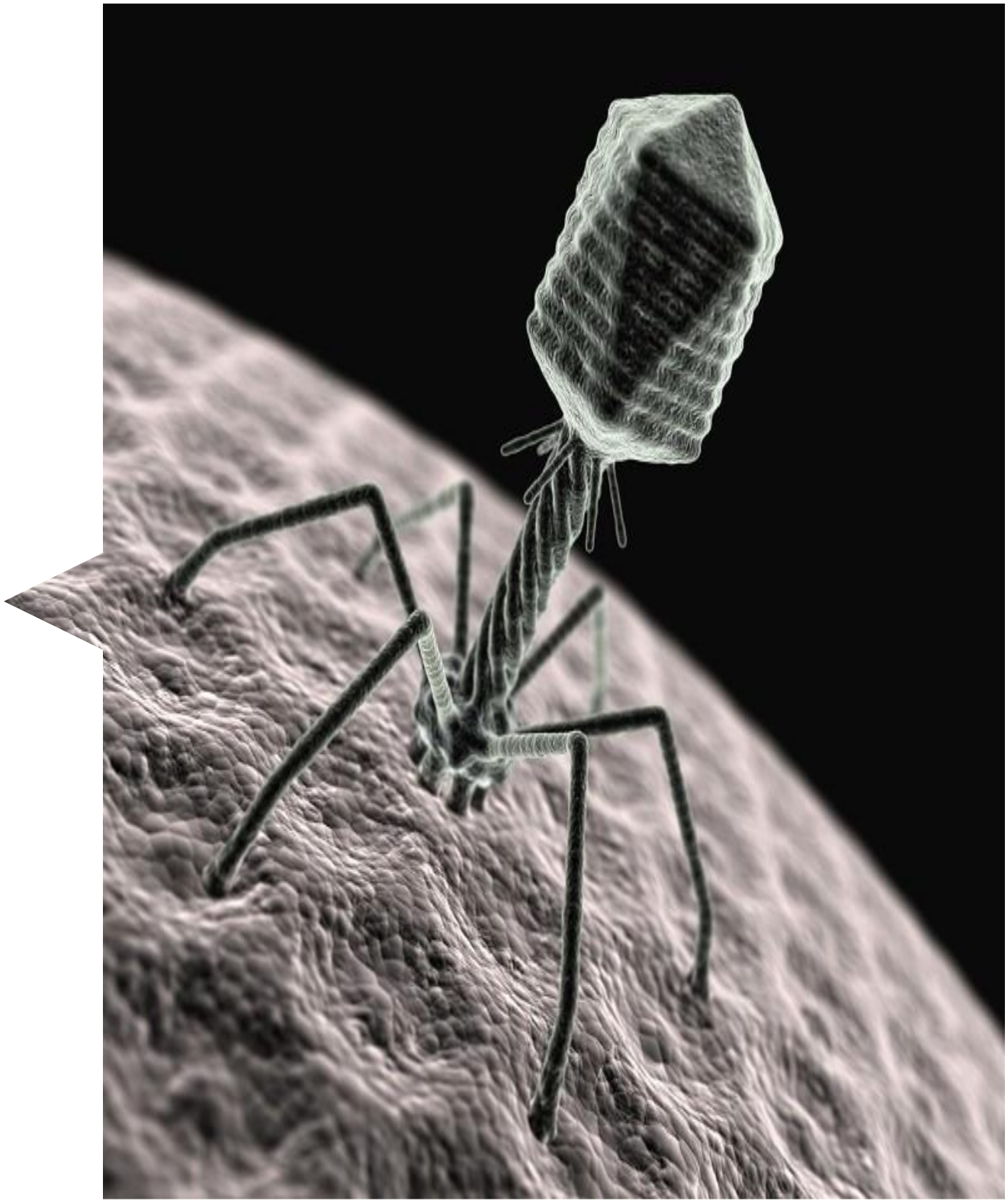
A. Reporting: Immediately (group A disease)
B. Hospitalization: cases should be admitted to the hospital.

IV) Laboratory finding:

Swab from the wound for smear & culture:

A. In the smear, absence of neutrophils & presence of G^{+ve} rods.
B. Anaerobic culture confirm the diagnosis
   - (ELISA) for rapid detection of alpha-toxin or sialidases (i.e. neuraminidases) in wound exudates, tissue samples, or serum (not available in Egypt)
   - Plain-X ray (show gas within soft tissues) it is not specific.

Common viral diseases



Cytomegalovirus

I) Definition:

- Cytomegalovirus is part of herpes virus family and like other herpes viruses may become dormant for a period and then reactivated.
- Virus affects young children mostly but all ages are susceptible

II) Mode of transmission:

- Spread through close contact with body fluid (e.g.: saliva – urine – semen – vaginal secretion – breast milk – blood transfusion – respiratory droplets – through placenta and during delivery – organ transplantation)

III) Clinical manifestation:

Incubation period: 9- 60 days

- In immunocompetent infection may be asymptomatic otherwise two clinical form recognized

1-CMV inclusion disease of newborn

- Occur in pregnant women with primary infection in 40% through vertical transmission and range in severity from being without symptoms to sever disease affecting liver splenomegaly – encephalitis – hearing loss – blindness

2-Acute acquired CMV infection:

- Which is similar to Mononucleosis with prolonged fever – fatigue – hepatitis - lymphadenopathy - splenomegaly

IV) CMV in immune-compromised:

In organ transplant – Aids CD4 T< 50

CMV retinitis - Encephalitis - pneumonia - colitis

V) Laboratory diagnosis:

- Lymphocytosis, Elevated transaminases, Anicteric hepatitis
- Serology: IgM positive in acute infection in 92% may not peak until 4-7 week of infection
- IgG denote past infection
- PCR: from tissue fluid
- Culture of tissue fluid

VI) Treatment:

- Immunocompetent: Only supportive treatment
- Immunocompromised: In AIDS with HAART therapy (see HIV/ AIDES protocol)
- Ganciclovir IV: 5mg/kg every 12 hours for 14-21 days and valganciclovir orally for prophylaxis against CMV retinitis

Epstein - Barr virus Infections

I) Definition:

- EBV infections are most common in early childhood, with a second peak during late adolescence.
- By adulthood, more than 90% of individuals have been infected and have antibodies to the virus.
- Epstein-Barr virus (EBV) is the cause of infectious mononucleosis (IM), which is characterized by fever, sore throat, lymphadenopathy, and atypical lymphocytosis.
- EBV is also associated with several human tumors, including nasopharyngeal carcinoma, Burkitt's lymphoma, Hodgkin's disease, and (in patients with immunodeficiencies) B cell lymphoma.
- EBV is also associated with oral hairy leukoplakia (an early manifestation of infection with HIV in adults. Most patients present with raised, white corrugated lesions on the tongue and occasionally on the buccal mucosa that contain EBV DNA) .

II) Pathogenesis:

- EBV is transmitted by salivary secretions. The virus infects the epithelium of the oropharynx and the salivary glands and is shed from these cells.
- The virus then spreads through the bloodstream .
- If T cell immunity is compromised, EBV-infected B cells may begin to proliferate. When EBV is associated with lymphoma, virus-induced proliferation is one step in a multistep process of neoplastic transformation .
    - N.B. EBV has been transmitted by blood transfusion and by bone marrow transplantation .

III) Clinical manifestations:

Signs and Symptoms

- Most EBV infections in infants and young children either are asymptomatic or present as mild pharyngitis with or without tonsillitis.
- In contrast, up to 75% of infections in adolescents present as IM.
- IM in the elderly presents as nonspecific symptoms, including prolonged fever, fatigue, myalgia, and malaise. In contrast, pharyngitis, lymphadenopathy, splenomegaly, and atypical lymphocytes are relatively rare in elderly patients.
- The incubation period for IM in young adults is 4–6 weeks.
- A prodrome of fatigue, malaise, and myalgia may last for 1–2 weeks before the onset of fever ; it may persist for >1 month. ;
- Then sore throat, and lymphadenopathy.
- Lymphadenopathy and pharyngitis are most prominent during the first 2 weeks of the illness, while splenomegaly is more prominent during the second and third weeks.
- Lymphadenopathy most often affects the posterior cervical nodes but may be generalized. Enlarged lymph nodes are frequently tender and symmetric but are not fixed in place.
- Pharyngitis, often the most prominent sign, can be accompanied by enlargement of the tonsils with an exudate resembling that of streptococcal pharyngitis.
- A morbilliform or papular rash, usually on the arms or trunk, develops in 5% of cases.
- Most patients treated with ampicillin develop a macular rash; this rash is not predictive of future adverse reactions to penicillins.
- Erythema nodosum and erythema multiforme have also been described.

- Most patients have symptoms for 2–4 weeks, but malaise and difficulty in concentration can persist for months.

IV) Laboratory findings:

- The white blood cell count is usually elevated and peaks at 10,000–20,000/L during the second or third week of illness.
- Lymphocytosis is usually demonstrable, with >10% atypical lymphocytes.
- Low-grade neutropenia and thrombocytopenia are common during the first month of illness.
- Liver function is abnormal in >90% of cases. Serum levels of aminotransferases and alkaline phosphatase are usually mildly elevated. The serum concentration of bilirubin is elevated in 40% of cases.

V) Complications:

(Most cases of IM are self-limited, deaths are very rare)

- Meningitis, encephalitis, splenic rupture, upper airway obstruction, or bacterial superinfection.
- Acute EBV infection has also been associated with cranial nerve palsies, Guillain-Barré syndrome, acute transverse myelitis, and peripheral neuritis.
- Other rare complications include hepatitis, myocarditis or pericarditis, pneumonia with pleural effusion, interstitial nephritis, genital ulcerations, and vasculitis.

VI) Diagnosis:

Serologic Testing (For Recent Infection)

- Tests for heterophile antibodies (Monospot Test): are positive in 40% of patients with IM during the first week of illness and in 80–90% during the third week Therefore, repeated testing may be necessary, especially if the initial test is performed early. Tests usually remain positive for 3 months after the onset of illness, but heterophile antibodies can persist for up to 1 year.
- The monospot test is 75% sensitive and 90% specific compared with EBV-specific serologies.
- False-positive monospot results are more common among persons with connective tissue disease, lymphoma, viral hepatitis, and malaria.

-EBV-specific antibody testing (EBV VCA IgM):

- **I**s used for patients with suspected acute EBV infection who lack heterophile antibodies and for patients with atypical infections.
- IgM antibody to VCA (viral capsid antigen) is most useful for the diagnosis of acute IM because it is present at elevated titers only during the first 2–3 months of the disease.

VII) Treatment: EBV-associated disease:

- Therapy for IM consists of supportive measures, with rest and analgesia.
- Acyclovir, at a dosage of 400–800 mg five times daily, has been effective for the treatment of oral hairy leukoplakia (despite common relapses).

VIII) Prevention:

- Isolation of patients with IM is unnecessary.
- A vaccine directed against the major EBV glycoprotein reduced the frequency of IM but did not affect the rate of asymptomatic infection.

Measles

I) Definition:

it is an acute viral disease ,highly contagious characterized prodromal symptoms of fever, conjunctivitis, cough, running nose and Koplik's spots most commonly seen opposite the molars on the buccal surface of the lips and cheeks , they precede the main rash by several days . after several days a rash erupts usually on the face and upper neck ,over about 3 days the rash spreads eventually reaching the hands and feet .The rash lasts for 4-6 days and then fades by desquamation ,the virus remains active and contagious in the air or an infected surfaces for up to 2 hours ,it can be transmitted by infected person for 4 days prior to the onset of the rash to 4 days after the rash erupts.

II) Modes of transmission:

- Airborne infections also
- Direct contact with upper respiratory secretion of the patients.

N.B: Measles is one of the most communicable (Contagious) acute viral diseases.

III) Diagnosis:

1. Incubation period of 10-14 days.
2. Case definition

a) Suspected case.

Any patient at any Age with fever + Maculo papulor rash and one or more of the following:

1) Cough
2) Coryza
3) Conjunctivitis

b) Probable case

None

c) Confirmed case

Any suspected case that is confirmed laboratory by serology either.

- Detection of specific IgM for measles virus.
- Virus isolation through blood culture.

IV) Medical treatment:

1- Symptomatic treatment

e.g. Antipyretic, only paracetamol.

2- Antibiotics

Is indicated if secondary bacterial infections occurred.

3- Vitamin A

Should be administered to all patients especially malnourshied and immunocompromised.

- Infants younger than 6 months.
  - 50.000 Iu/day oral for 2 days.
- Paediatric 6-11 Months
  - 100.000 Iu/day oral for 2 days.
- Children older than 1 year 200.000 Iu/day oral for 2 days.
- Children with clinical vitamin A defiency should receive 3rd dose of vitamin A after (2-4) weeks later.

N.B:

- There is No specific antiviral drugs for treatment of measles.
- Nutrition and good hydration should be optimally maintained.

V) Preventive measures:

1- Reporting

- Immediately, Group A diseases.

2- Isolation

- Respiratory Isolation, until 4th day of rash decrease exposure of others to infections.
- Children should be kept out of school for about one week.
  - N.B: Hospitalization is not necessary except in the presence of complication.

1) For contacts.

- Immunization of susptible contacts within 72 hours post exposure , this vaccine is contraindicated in:
  - Immuno compromised patients.
  - Pregnant women.
  - Infants < 1 year of Age.

Immunoglobulin:

- Can be given within 6 days of exposure to contacts of high risk complication as:
  • Immunocompromised patients.
  • Pregnant women.
  • Infants < 1 year of age.
- Later 5-6 month the live measles vaccine can be given if not contraindicated.
- And simultaneous administration of immunoglobulin with vaccine is contraindicated

VI) Complications :

More common under the age of 5 or adults over the age of 20, blindness, encephalitis, severe diarrhea and dehydration, ear infections, severe respiratory infections such as pneumonia. severe measles is common in poorly nourished young children especially those with insufficient vitamin A, or immune compromised patients, pregnant women are also at risk of severe complications, people who recover have long life immunity.

Rubella (German measles)

I) Definition:

Acute viral infectious disease characterized by mild fever with mild systemic symptoms with diffuse punctate maculopapular rash with characteristic posterior auricular, posterior cervical or occipital lymphadenopathy which precedes the rash by 5 to 10 days .

Infection during pregnancy causes serious congenital defects to the baby (congenital rubella syndrome). In more than 90% in babies born to infected mothers proved to occur during the first 10 weeks of pregnancy and the congenital defects are rare or simple after 20 weeks of pregnancy.

II) Modes of transmission:

- Air borne infection
- Also person to person contact especially with contact to naso-pharyngeal secretion.

III) Diagnosis:

1- Incubation period: Varies between 2 – 3 weeks.

2- Case definition

[a] Suspected case

- Fever 38°C or more and generalized maculopopular rash with one or more of the following:
  - Suboccipital and posterior cervical lymphadenopathy.
  - Arthralgia
  - Conjunctivities.

[b] Probable case.

None

[c] Confirmed case.

Suspected case confirmed laboratory either:

- Virus isolation.
- (+ve) Rubella IgM.

IV) Medical treatment:

- Symptomatic treatment.

V) Preventive measures:

1- Reporting

Immediately, (Group A diseases) .

2- Isolation: 7 days from the onset of rash .

3- Contacts.

- Immunoglobulins (IG) has not been shown to prevent Rubella infection after exposure and is not recommended for that purpose.
- Post exposure prophylaxis (PEP) with MMR vaccine does not prevent or alter the clinical severity of Rubella and is not recommended.

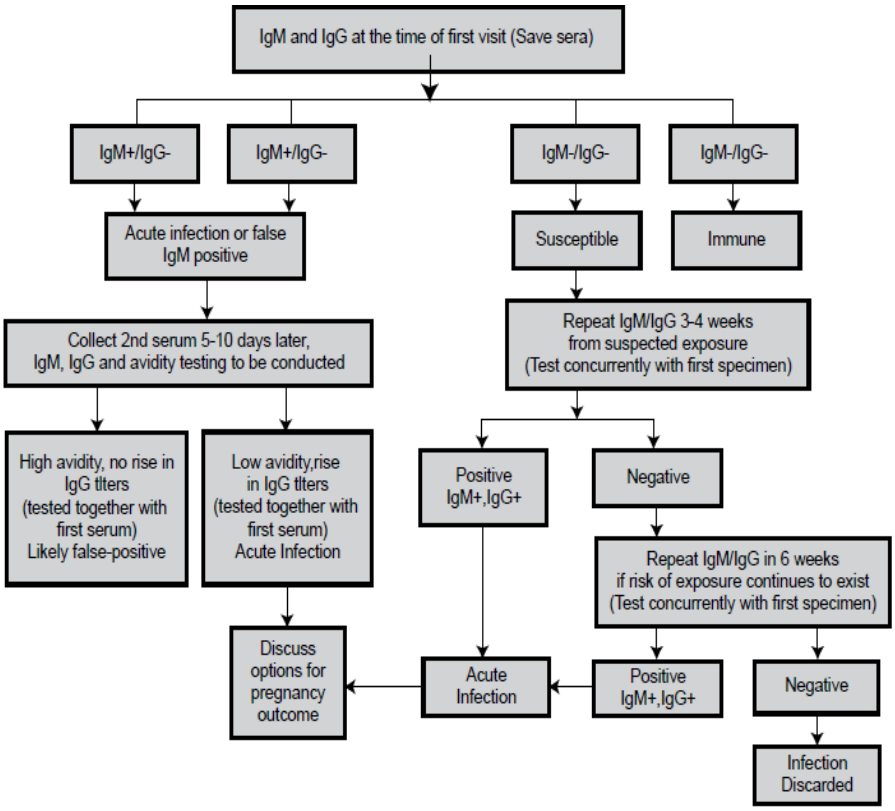
4 - Preventive health measures.

- Health education
- Immunization with one dose of MMR vaccine (But not in pregnant women).

Rubella in pregnancy:

- If a pregnant women is not immune to Rubella and catches it during the first 5 months of pregnancy, usually she passes the disease on to her fetus.

- After bearing, a child with congenital Rubella syndrome act as a source of infection for at least one year and should be cared for only by individuals who are Immune to Rubella.



- If the fetus gets rubella during the first 12 weeks of pregnancy, the baby will be borne likely with many lesions e.g visual lesions, auditory lesions, and cardiac lesions.
- If the fetus gets Rubella between 12 and 20 weeks of pregnancy, problems are usually milder after 20 weeks of pregnancy, usually no problems.

Algorithm for:

Serological evaluation of pregnant women exposed to Rubella.

Mumps

I) Definition:

An acute viral disease characterized by fever and swelling of one or more of the salivary glands commonly the parotid ,it may be complicated by orchitis or pancreatitis ,Hearing loss ,encephalitis or myocarditis also can occur

II) Modes of transmission:

- Disease transmitted by: Droplet infection and direct contact.

III) Diagnosis:

- Incubation period : usually varies from (12 – 25 days).
- Case definition.

[a] Suspected case

Acute illness of unilateral or bilateral tender, self – limited swelling of parotid or other salivary glands.

[b] Probable case

- None

[c] Confirmed case.

Any suspected case confirmed lab by:-

- Mumps virus isolation from suspected clinical case.
- Detection of increased Mumps virus IgM antibody
- Confirmed suspected case lab. by RT – PCR.

IV) Medical treatment:

- Supportive and symptomic treatment.
- NSAID is indicated in case of orchitis together with scrotal support.

V) Preventive measures:

1. Reporting

- Immediately., Group A diseases.

2. Isolation

- Respiratory isolation with droplet precautions for 5 days from the onset of swelling

Disease	Isolation precautions	Isolation time
Mumps	- Droplet - Contact	9-days from appearance of the swelling

3. For contacts.

- Post exposure prophylaxis with MMR vaccine does not prevent and is no recommended.
- Immunoglobulin has not been shown to prevent mumps infections after exposure and is not recommended.

Chicken pox

I) Definition:

- It is an acute viral illness characterized by fever and mild systemic symptoms of headache ,fatigue, loss of appetite, the disease is diagnosed by the characteristic skin rash , the patient
- first develops crops of itchy red papules , the papules form teardrop-like vesicles and blisters surrounded by a halo of erythema on the abdomen ,back and face before spreading to other parts of the body, the patient may be febrile and generally unwell.
- Serious complicatios (pneumonitis, Rey's syndrome, Guillian-Barre syndrome, thrombocytopenia, purpura, hepatitis, encephalitis) are more common in adults, pregnant women, the immunocompromised, those who have taken systemic steroids in the
- previous 3 months or those with chronic lung disease . Maternal infection in early pregnancy carries a small risk of infection for the fetus, in contrast maternal infection at term carries a great risk of infection for the newborn child .
- However for those over age of 12 or anyone who may be at greater risk of complications , oral antivirals may be considered e.g. Acyclovir, if the patient is seen within 24 hours of the onset of the rash. Any patient with chicken pox who becomes breathless should be referred to hospital.
- The CDC recommend the use of intravenous acyclovir in pregnant patients for the treatment of life threatening herpes infections, including encephalitis, pneumonitis and hepatitis. Acyclovir has also been recommended for the treatment of severe or progressive maternal varicella infection.
- However, the use of acyclovir during pregnancy for non life threatening infections or for suppressive therapy is not recommended by the CDC.

II) Modes of transmission:

- Chicken pox spread in the air through coughing or sneezing, also spread by touching or breathing of the virus particles that come from chicken pox blisters.

III) Diagnosis:

- **Incubation period:** varies between 12 – 24 days.
- **Case definition:**

[a] Suspected case

Case with acute fever (38.5°C or more) with generalized Maculo– Vesicular rash without other obvious case.

[b] Probable case

None

[c] Confirmed case.

Suspected case confirmed laboratory through RT. PCR.

IV) Medical treatment:

- Chicken pox is "self – limited" illness and most patients recover without specific treatment.

• Principally, Immuologically normal hosts directed to prevent avoidable complications.
• Obviously, good hygiene and good nutrition

(1) Oral Acyclovir.

Is indicated in complicated or sever cases in children and obligatory in adults.

- May reduce the duration of fever and active rash.

- Given 800 mg by mouth five times daily for 5 days.

Duration.

•In children < 12 years of age oral Acyclovir may be benefit if initiated early in the disease (<24) in a dose of 20mg/kg oral every 6 hour.

(2) Famciclovir.

- Is recommended for adolescents and Adults with chicken pox of 24 hour duration.
- Given in dose (250 mg three times daily) for 5 – 7 days.

(3) Valacyclovir.

- Given in a dose of 1 gm three times daily for 5 days.

(4) I.V Acyclovir.

- Used in chicken pox in severely immune compromised hosts for 7 days.

(5) Antipruritic drugs.

- Can be used to decrease pruritis and itching.

(6) In secondary bacterial infection of skin

- proper antibiotics and skin care.

V) Preventive measures:

1- Reporting.

- Weekly, Group "B" diseases.

2- Isolation.

- In hospitals, strict isolation to avoid direct contact to patient and airborne exposure to immocompromised patient about 5-7 days after skin Rash exposure.
- Children and students excluded from schools until all skin rash all crusted usually 5 days.

3- Immunization and prophylaxis

- 2 Doses of the vaccine are recommended for all children.
  - •The first → at 12 – 15 months of age.
  - •The second → at 4 – 6 year of age.
- VZV. Seronegative persons > 13 years of age should receive 2 doses of vaccine at least 1 Month apart.
- -A second approach is to administer varicella – zoster Immune – globulin (VZIG) to individual who are susptible and at high risk.
- Lastly individuals who are ineligible for vaccine or who are beyond the 96 – hour window after direct contact., Antiviral therapy can be given as prophylaxis.

Rabies

I) Definition:

Acute zoonotic viral disease , the dogs are considered the main reservoir of infection through introduction of infected saliva into the skin wound of the attacked person .

The disease is characterized by acute encephalitis which is often fatal

II) Modes of Transmission:

- Humans are usually infected by a virus-laden saliva, inoculated during the bite or scratch of a rabid animal.

III) Diagnosis:

1. Incubation Period.
   - May vary from few days to many years.
   - Usually 20 days to 90 days.
2. Case definition:

a) Suspected case.

- A case compatible with the clinical syndrome the case presents with symptoms of acute encephalomyelitis either by hyperactivity (Furious) rabies or paralytic syndromes (dumb rabies) that almost always progress to coma or death, usually be respiratory failure, within 7 to 10 days.
- Symptoms include: headache, fear, fatigue and undefined sensory changes.
- As the disease proceeds paralysis or paresis occurs, hydrophobia, followed by delirium and coma.

b) Probable Case.

A suspected case plus (+) history of contact or bite with suspected rabid animal.

c) Confirmed Case.

A suspected case that is confirmed laboratory either by:

- Detection of viral antibodies by direct florescent antibody test.
- Rabies virus isolation (either in virus tissue culture or in laboratory rats) from saliva sample or C.S.F. sample or CNS tissue specimen.

3. Laboratory investigation:

Only possible in a few laboratories that usually use their own protocols (i.e. Not available in Egypt).

a) Serum and spinal fluid can be tested for antibodies to rabies virus.

b) Saliva can be tested by virus isolation or RT-PCR.

c) Skin biopsy specimen can be examined for rabies antigen in the cutaneous nerves at the base of hair follicles at the nape of the neck.

IV) Medical Treatment:

- No specific medical treatment is available once rabies is clinically diagnosed.
- Only intensive supportive care is done.

V) Preventive measures:

1. Reporting

- Immediately, Group A diseases.

2. Isolation

- Standard contact isolation for respiratory secretion for the duration of the illness.

3. Management of Bite Wound.

- All wounds due to animal bites or scratches should be immediately and thoroughly cleaned with soap or detergent and flushed with water for a minimum of 15 minutes followed by antiseptic e.g. ethanol or Iodine povidone or aqueous solution of Iodine.
- The full dose of:
  - Human Rabies Immunoglobulin (HRIG 20 Iu/kg)
  - Or, Equine Rabies Immunoglobulin (ERIG 40 Iu/kg) Should be thoroughly infiltrated in the area around and into wound bite, any remaining volume should be injected intramuscularly at a site distant from vaccine administration.
- The wound should not be sutured unless otherwise required, if suturing required firstly wound cleaning and washing then wound infiltered with rabies immunoglobulin and suturing delayed for several hours.
- Consideration should be given to prophylaxis against tetanus.

4. Post Exposure: Prophylaxis.(PEP).

- This varies according to degrees or category of contact to rabid animal as follow:

Category of contact with rabid animal	PEP. Recommendation
Category I: Touching or feeding animal or licks intact skin.	None Specially vaccination History reliable
Category II: Nibbling of uncovered skin, Minor scratches or abrasion without bleeding.	Immediate vaccination And local treatment of the wound
Category III: Single or multipple Transdermal bites or scratches licks on broken skin, contamination of mucous membrane with saliva from licks.	Immediate vaccination and administration of rabies immunoglobulin and local treatment of the wound.

5. Vaccination:

- Vaccination done in five 1ml i.m. doses in the deltoid region (never given in gluteal region)
- Using either:
  - PCECV: Purified chick embryo cell vaccine.
  - PDEV: Purified duck embryo vaccine.
  - HDCV: Human Diploid cell vaccine.
- The first dose as soon as possible after the bite.
- Subsequent doses should be given at 3, 7, 14, and 28 days after the first dose.
- These doses and vaccination regimen is for both children and adults.
- Pre-vaccinated cases:
  - One dose should be given on days zero and 3.
  - No rabies Immunoglobulin (RIG) should be applied to pre-vaccinated cases.

6. Contacts measures

Contacts who have open wound or mucous membrane exposure to the patient’s saliva should receive antirabies specific treatment

Viral hemorrhagic fevers

I- Definition:

- -Viral HF is acute systematic febrile syndrome caused by over 30 viruses from 4 different virus families.
- Micro vascular instability with capillary leak and impaired haemostasis are the pathogenic hallmarks.
- Recent CDC VHFs are caused by viruses of 5 distinct families which are:

[1] Arena viridae family.

- VHFs caused by arena viruses:
  a. Lassa fever.
  b. Lujo HF.
  c. south American HFs.

[2] Filoviridae family.

- VHFs caused by filoviruses:
  a. Ebola HF.
  b. Marburg HF.

[3] Bunyoviridae family.

- VHF caused by bunyaviruses:
  a. Rifty valley fever.
  b. Crimean – cango HF (CCHF)
  c. Haemorrhagic fever with renal syndrome. (HFRS)
  d. Hantavirus pulmonary syndrome. (HPS).

[4] Flaviviridae family:

- VHFs caused by flaviviruses:
  a. Dengue HF.
  b. Yellow fever.
  c. Omsk HF.
  d. Kyasanw forest disease.
  e. West Nile fever.

[5] Paramyxoviridae family:

- VHFs caused by paramyxoviruses.
  a. Hendra virus diseases.
  b. Nipah virus encephalitis.
- In rare cases, other viral and bacterial infections can cause a Haemorrhagic fever.
- Viral haemorrhagic fevers should be considered in febrile patients with a compitable clinical syndrome and history of travel and exposure, especially if the patient fail to response
- to empiric treatment for the usual infectious diseases prevalent in the area.
- Despite the name, Haemorrhage is not uniformly named in viral HF. And its absence should not be used to exclude the diagnosis.
- Typical laboratory findings in viral HF at presentation include:
  c. Lymphopenia.
  d. Thrombocyopenia.
  e. Elevated hepatic transaminases wit AST > ALT.
  f. Lymphocytosis and thrombocytosis may be seen in late stages.

II- Modes of transmission:

- Varies according to the causative viruses.
- Arthropod borne (mosquito or tick borne transmitted diseases).
- Also transmit and spread from person to person (contact) according to causative viruses.

III- Diagnosis:

Case definitions.

(a) Suspected case

Acute fever does not respond to usual treatment plus one or two of the following: (Epistaxis - Haematemesis - Blood in stool- Haemoptysis – Purpuric rash - Other haemorrhagic signs) or any case of death where the patient has had contact with suspected or confirmed case ,or (any person come back from endemic area or endemic countries and showed suspecting symptoms or signs).

(b) Probable case

None

(c) Confirmed case

- A suspected case with one of the following:
  - Virus isolation from blood or tissue.
  - Detection of viral antigen.
  - Detection of genome in blood, tissue, or body fluid by PCR.
  - Presence of specific IgM antibody in titre high enough to indicate recent infection.

V- Medical treatment:

- Generally, treatment of viral HF is supportive following guideline for the management of septic shock.
- Symptomatic treatment.
- The antiviral drugs (Ribaverine and / or others). And treatment with convalescent plasma have demonstrated efficacy in few viral HFs.

V- Preventive measures:

1.**(Reporting)** Immediately

2. **(Isolation,)** Patients should be isolated.
   - Healthcare workers should be advised to use strict barriers precautions Blood, body fluids precautions.

Disease	Isolation time	Notes
Viral hemorrhagic fevers	Until the symptoms disappear	Should be immediately reported (Group A diseases)

3. For contacts

- Contacts should be monitored for clinical diseases.
- For laboratory personnel specimen should be considered highly infectious and should be sent in an appropriate protective device to the central laboratory

Dengue fever

I- Definition:

- It is an acute viral illness characterized by fever , severe headache, severe muscle and joint pain , a skin rash usually appear which may be associated with minor or major hemorrhagic manifestations.
- The disease includes 4 serological types (DeN1, DeN2, DeN3,DeN4)

II- Modes of transmission:

- Principally through bites of infected female Aedes Egyptie.

III- Diagnosis:

1. Incubation period:From 3 – 14 days. Usually 4 – 7 days.
2. Case definition.

(a) Suspected case.

Dengue fever (DF)

- Acute viral fever of sudden onset lasts for about 5 days with severe headache and retroorbital pain sometimes vomiting
- Dengue haemorrhagic fever. (DHF) 4 necessary criteria.

1- Fever of recent onset.
2. Throumbocytopenia.
   - Platlet count less than 100.000 cmm.
3. Any haemorrhagic or bleeding signs include +ve tourniquet test.
4. Evidence of plasma leakage sign.
   - Increase in haemotocrit value.
   - Fluid accumulation → acquired ascites.

Dengue shock syndrome. (DSS)

In addition to the previous 4 criteria there is shock and signs or circulatory collapse as:

- Rapid weak pulse.
- Hypotension.
- Cold periphery, calmmy skin.

(b) Probable case

Suspected case with immunoglobulin antibodies to dengue virus.

(c) Confirmed case.

Laboratory confirmation with any of the following :
(1) Isolation of the virus from blood during fever or from tissue or tissue culture .
(2) Four fold rise of antibody titre for one or more of the dengue viruses in one or more serum samples.

(3) Presence of dengue virus IgM indicates recent infection identified from 6-7 days of the onset of the disease .

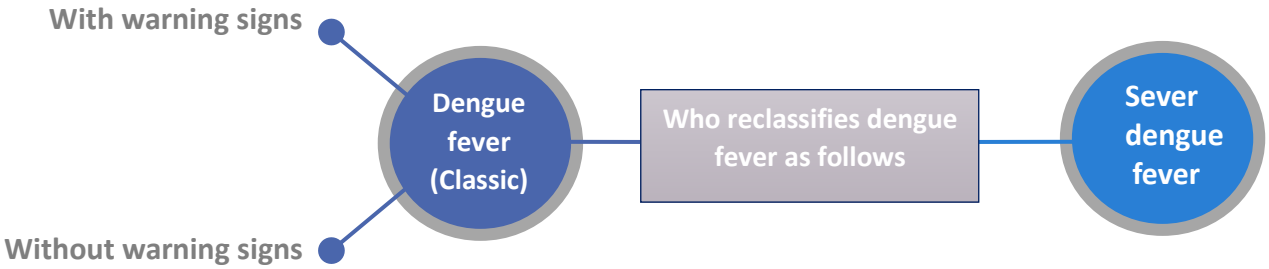
(4) Identification of the virus by RT-PCR in blood or tissues.

- Severe dengue is defined as:

(1) Severe plasma leakage, leading to fluid accumulation with respiratory distress or shock.
(2) severe organ impairement including cardiac, liver ALT > 1000 and CNS altered consciousness.
(3) Severe bleeding.
WHO reclassify dengue fever as follows:

- Warning signs:

(1) Abdominal pain or tenderness.
(2) Persistent vomiting.
(3) Clinical fluid accumulation.
(4) Mucosal bleed.
5) Lethargy / restlessness
(6) Liver enlargement > 2 cm.
(7)Laboratory increase in HCT (Haematocrite) concurrent with rapid decrease in platelet count.



IV- Medical treatment

- The initial treatment of deugue cases involves appropriate classification of severity grades with early recognition of potiential complication and warning signs.

1- Rest and supportive care.
2- Patient in shock may require ttt in ICU.
3- Symptomatic ttt .
4- Antipyretic e.g. paracetamol only .
5- No specific ttt for dengue fever.

V- Preventive measures.

1- Reporting, immediately, included in group A.
2- Isolation, patient rooms should be supplied with bedding nets and daily spraying the rooms with insecticides

Isolation precaution table

Disease	Isolation time	Isolation precau-tions	Notes
Dengue fever	Until symptoms disappear	Apply blood precautions	Should be imme-diately reported Group A diseases

3- **Contact**: untill now no vaccine, the patient's accommodation during the first 2 weeks should be determined , and search for new suspected cases.

Rift valley fever

I- Definition:

- An acute viral illness characterized by fever , headache ,muscle and joint pains , sometimes complicated by encephalitis , retinitis and acute hepatitis with hemorrhagic manifestations which may be fatal .
- The disease is classified as zoonotic disease .

II- Modes of transmission:

- Transmission of disease from animal to human is by mosquito vector also by direct contact with blood or tissues or body fluids of infected animals.

III- Diagnosis:

(1) Incubation period.

Varies 2 – 7 days (Average 3 days).

(2) Case definition.

(a) Suspected case.

Sudden onset of fever, severe headache plus one or more of the following:

- Congestion of eyes, with affection of vision ranges from decrease in visual acuity to loss of vision.
- Altered consciousness.
- General aches.
- Backaches.
- Retroorbital pain.
- Myalgia.
- Jaundice.
- Haemorrhagic signs.

(b) Probable case

Suspected case with past history of residence or travelling in area where rift valley fever is endemic or enzootic within 1 week of symptoms and signs.

(c) Confirmed case.

Any suspected or probable case confirmed laboratory by:

- Viral identification DNA by PCR.
- Detection of IgM anti-RVF in sera of suspected or probable case.
- Virus isolation tissue culture.
- Suspected case connected epidemiologically to a confirmed case.

IV- Medical treatment:

(1) Supportive clinical care and symptomatic treatment.

(2) Careful management of cerebral edema, coma, seizures is critical in RVF.

(3) Ribaverine may be effective in treatment of severe RVF.

V- Preventive measures:

1- **Reporting,** immediately as RVF included in group A diseases.

2- **Isolation**

Isolation precautions table

Disease	Isolation precautions	Isolation time	Notes
Rift valley fever	Apply blood precautions	Until symptoms disappear	Should be immediately reported Group A disease

apply blood and body fluids precaution.

3- Contact

The patient's accommodation during the first 2 weeks should be determined , and search for new suspected cases.

Yellow Fever

I- Definition:

It is an acute viral illness with variable severity from mild asymptomatic cases to moderate with fever and moderate systemic manifestations , to severe with jaundice and severe with gingival and gastrointestinal hemorrhage up to the severest manifestations with hepato-renal failure and proteinuria ..

II- Modes of transmission:

- Mosquitoes borne disease ,mostly aedes aegyptie.

III- Diagnosis:

1- Incubation period, usually varies 3-6 days.

2- Case definition.

(a) Suspected case

- A person with febrile illness who has been coming from yellow fever endemic area within 1 week and has:
  - Myalgia, sever bone aches, vomiting in mild cases.
  - In severe cases - there is jaundice, albumiuria and mucosal or GIT hemorrhages.

(b) Probable case.

None

(c) confirmed case.

- Is a suspected case that has been confirmed laboratory by one of the following:
  - Virus isolation in specific tissue culture.
  - Detection of virus RNA by RT-PCR .
  - Detection of immunoglobulins in blood by ELISA.

3- Clinical picture:

a- Asymptomatic cases:

- Most infection especially in endemic areas are asymptomatic (subclinical infection).

b- Mild form of YF:

- There is acute febrile illness, headache, myalgia, low back pain, and the characterstic bradycardia in relation to high temperature.

c- Severe form YF:

- In addition to high fever, sever constitutional manifestation, early signs of jaundice appear, mucosal bleeding and GIT haemorrhages ,this form may progress to liver, renal failure and terminally death.

IV- Medical treatment:

- Treatment is mainly supportive.
- No Specific antiviral drug should be used.
- Oral-rehydration and I.V fluids for hypotensive critical ill patient with non hepatotoxic antipyretic agents.
- In renal functions affected patients, The dialysis may be needed.
- In sever active bleeding, fresh frozen plasma is introduced.

V- Preventive measures:

1- **Reporting**, immediately (Group A. Diseases)

2- **Isolation**:

Apply blood precaution, also precaution to body fluids.

Disease	Isolation time	Isolation precautions	Notes
Yellow fever	Until complete recovery , the patient should be protected from insect bite especially during the first 5 days of isolation	Apply blood Body fluids precua-tions	Patient rooms should be supplied with bedding nets and daily spraying the rooms with insecticides

3- Contacts:

- Observation of contacts to patients.
- Vaccination of contacts (live attenuated 17D vaccine).
- Yellow fever is a vaccine preventable disease.

Where the live attenuated 17D vaccine yeilds long term protection (at last 10 Years and possibly life long).
With single dose 0.5 ml subcutaneous.

Avian Influenza (H5N1)
InfluenzaA (H5N1)

I- Definition:

virus subtype that infects mainly birds. It is highly contagious among them. It is likely that H5N1 infection among birds has become endemic in certain areas and that human infections resulting from direct contact with sick or dead infected poultry will continue to occur, most of the human cases have occurred from.

II- Mode of transmission:

- Direct or close contact with infected poultry.
- Because these viruses do not commonly infect humans, there is little or no immune protection against them in the human population and an influenza pandemic could begin.

III- Case definition:

Depends on the presence of a combination of clinical and epidemiologic criteria.

1- A Person under Investigation

An individual who was exposed to sick or dead domestic or wild birds in an area where poultry outbreaks were identified.

2- Suspected Case

-An individual presenting with signs of unexplained acute lower respiratory illness, e.g.

- Fever (temperature >38°C)
- Sore throat
- Frequent cough and shortness of breath
- Myalgia and arthralgia

Other sever unexplained illness (e.g. encephalopathy or diarrhea)

With one or more of the following exposures in the 7 days prior to symptom onset:

- Close contact with a person who is a suspected, probable, or confirmed H5N1 case.
- Exposure to poultry (domestic or on a farm) or their remains or to environments contaminated by their feces in an area where H5N1 infections in animals or human have been identified. Exposure might be through handling, slaughtering, defeathering, butchering, or preparation for consumption.
- Close contact with sick or dead birds in a location where poultry outbreaks were identified.
- Travel within one week before the onset of symptoms to an area with known avian influenza epidemic (H5NI), with direct exposure to domestic or wild birds.

3- Probable Case

A person meeting the criteria for a suspected case and laboratory evidence for influenza H5N1 as identified by RT-PCR conducted at the Central Laboratory (Ministry of Health and Population).

4- Confirmed case

A person meeting the criteria for a suspected case with laboratory evidence for Influenza H5N1 as identified by RT-PCR positive for influenza H5N1 at the Central Laboratory at the Ministry of Health and Population and confirmed by a WHO reference laboratory for H5N1

IV- Treatment:

- **Start treatment with Oseltamivir (Tamiflu)**
  immediately and for 5 days
  Adults dose: (tab=75 mg):75 mg twice daily for 5 days.
  Children (Syrup =12mg/ml):
  1-12 month: 3 mg /Kg /dose twice daily
  <15 Kg: 30 mg twice daily
  15 – 23 Kg: 45 mg twice daily
  23 – 40 Kg: 60 mg twice daily
  >40 Kg: 75 mg twice daily
- **Mechanical ventilation** for severe cases

V- Preventive measures:

For the persons under investigation, suspected, probable and confirmed cases:

A) Reporting: immediately (group A disease)

B) Hospitalization:

It's recommend that person to be hospitalized in chest hospital in case he/she experiences fever or any lower respiratory illness.

C) Isolation:

Isolate cases in special isolation rooms in the hospital (respiratory precaution)

D) Investigations:

a- Laboratory Procedures collect:

1-Two throat swabs (pharyngeal + nasopharyngeal) for PCR to be done immediately.
2- Serum samples
3-Another Two throat swabs 11 days post onset of symptoms.

- **N.B** the throat swab samples are placed in viral transport media.

b- Others: plain chest X-ray.

E) Case proved to be infected:

A throat swab is done every 5 days till negative result is obtained.

F) Case proved to be not infected:

Discharge after completing the 5 days Tamiflu treatment course.

G) For laboratory personnel

Precautions and measures applied for collecting the sample:

- The medical personnel must always wear personal protective equipment such as(gown, gloves, goggles and N-95 mask).
- Samples should be collected in a designated room in the hospital/clinic.
- Standard precautions should be used to obtain samples.
- Infection control and safety precautions such as decontamination, disinfection, sterilization, and biohazard waste removal must be applied.

Influenza virus (seasonal influnza)

I- Definition:

Influenza virus is an orthomyxovirus, influenza viruses are divided into types A, B, and C on the basis of variation in the nucleoprotein antigen.

- In types A and B the hemagglutinin (H) and neuraminidase (N) antigens undergo genetic variation, which is the basis for the emergence of new strains.
- Type C is antigenically stable.
- Influenza A viruses can be divided into subtypes on the basis of their surface proteins (H) and (N). There are 16 known (H) subtypes & 9 (N) subtypes.
- Only 3 subtypes of H (H1, H2 and H3) and two subtypes of N (N1 and N2) are known to have circulated widely from human to human.

II- Symptoms and signs of H1N1 Influenza Infection in Humans:

- The viruses are transmitted among humans by respiratory secretions through sneezing, coughing and contact with contaminated articles.
- The typical incubation period for influenza is 1-4 days.
- Typical influenza-like symptoms , diarrhea, vomiting, conjunctivitis, shortness of breath, viral pneumonia, and other severe and life threatening complications (ARDS)
- In adults, emergency warning signs that need urgent medical attention include:
    - Difficulty breathing or shortness of breath
    - Pain or pressure in the chest or abdomen
    - Sudden dizziness
    - Confusion
    - Severe or persistent vomiting
    - Flu-like symptoms improve but then return with fever and worse cough.
- In children emergency warning signs that need urgent medical attention include:
    - Rapid breathing or trouble breathing
    - Bluish or gray skin color
    - Not drinking enough fluids
    - Severe or persistent vomiting
    - Not waking up or not interacting
    - Being so irritable that the child does not want to be held
    - Flu-like symptoms improve but then return with fever and worsened cough.

The following vulnerable groups:

- Adult over 65 years old.
- Children less than 2 years old.
- Immunocompromized people.
- Pregnant females.
- People with chronic illness e.g(asthma -DM - heart failure and renal patients)

III- Treatment:

- Start treatment with Oseltamivir (Tamiflu®) immediately and for 5 days.(ministry of health protocol)

Adults dose: (tab=75 mg):75 mg twice daily for 5 days

Children(Syrup =12mg/ml):

1-12 month: 3 mg /Kg /dose twice daily
<15 Kg: 30 mg twice daily
15 – 23 Kg: 45 mg twice daily
23 – 40 Kg: 60 mg twice daily
>40 Kg: 75 mg twice daily

- Mechanical ventilation for severe cases

Case proved to be infected:

A throat swab is done every 5 days till negative result is obtained.

Case proved to be not infected:

Discharge after completing the 5 days Tamiflu treatment course.

Community-acquired pneumonia (CAP)

I- Definition:

A number of pathogens can give rise to CAP (viruses, bacteria and fungi)

🦠 Bacterial CAP:

Usually acquired via inhalation or aspiration of pulmonary pathogenic organisms into a lung segment or lobe. Less commonly, CAP results from secondary bacteremia from a distant source. Aspiration pneumonia is the only form of CAP caused by multiple pathogens. Severe CAP develops in patients with cardiopulmonary disease, diminished splenic function, and/or pathogenic virulence.

🦠 Typical CAP pathogens:

Typical bacterial pathogens include Streptococcus pneumonia (penicillin-sensitive and -resistant strains), Haemophilus influenzae (ampicillin - sensitive and - resistant strains), and, Moraxella catarrhalis (all strains penicillin-resistant). These 3 pathogens account for approximately 85% of CAP cases.

S. pneumoniae remains the most common agent responsible for CAP. In patients with an exacerbation of chronic bronchitis who develop CAP that requires hospitalization, Moraxella catarrhalis infection is the most common infecting pathogen.

Importantly, S aureus, K pneumoniae, and Pseudomonas aeruginosa are not typical causes of CAP in otherwise healthy hosts.

S. aureus may cause CAP in individuals with influenza (eg, human seasonal influenza and H1N1 influenza).

K pneumonia CAP occurs primarily in individuals with chronic alcoholism.

P aeruginosa is a cause of CAP in patients with bronchiectasis or cystic fibrosis.

🦠 Atypical CAP pathogens:

Non zoonotic atypical CAP pathogens (approximately 15% of all CAP cases) include Legionella species, Mycoplasma pneumoniae, and Chlamydophila pneumoniae. Zoonotic atypical CAP pathogens include Chlamydophila (Chlamydia) psittaci (psittacosis), Francisella tularensis (tularemia), and Coxiella burnetii (Q fever). recent close contact with the appropriate zoonotic vector is needed to develop a zoonotic CAP. Negative prognostic factors include preexisting lung disease, underlying cardiac disease, poor splenic function, advanced age, immunocompromised hosts ,multilobar involvement, and delayed initiation of appropriate antimicrobial therapy.

💡 NB:

- 💡 Overwhelming pneumococcal sepsis may occur in patients with CAP who have impaired splenic function potentially leading to death within 12-24 hours, regardless of the antimicrobial regimen used.

II- Signs & Symptoms:

- Patients with typical bacterial CAP pathogens present with pulmonary symptoms, while patients with atypical CAP pathogens present with a variety of pulmonary and 1 or more extrapulmonary findings (eg, CAP plus diarrhea).
- Patients with typical bacterial CAP present with fever, usually with a productive cough and often with pleuritic chest pain.

- With the exception of Legionella pneumonia, pleuritic chest pain and productive cough are not features of atypical CAP due to M pneumoniae or Chlamydophila pneumoniae (usually present
- with a nonproductive cough).
- Purulent sputum: is characteristic of pneumonia caused by typical bacterial CAP pathogens and is not usually a feature of that caused by atypical pathogens, with the exception of Legionnaires
- disease.
- Blood-tinged sputum: may be found in patients with pneumococcal pneumonia, Klebsiella pneumonia, or Legionella pneumonia.
- Rales: are heard over the involved lobe or segment.
- Bronchial breathing: If consolidation is present. Legionella pneumonia, Q fever, and psittacosis are atypical pneumonias that may present with signs of consolidation. Consolidation is not a feature of pneumonia caused by M pneumoniae or Chlamydophila pneumonia.
- Pleural effusion (usually due to H influenzae infection)

N.B:

- Pleural effusion in a patient with CAP and extrapulmonary manifestations should suggest Legionella infection. Empyema: is most often associated with Klebsiella, group A Streptococci, and S. pneumoniae.
- Cavitation: Is not a feature of pneumococcal pneumonia, but it is a normal part of the disease process in K pneumonia infections.

III- Investigations:

- CXR: may reveal lobar or segmental (patchy) infiltrates. Ipsilateral pleural effusion may be detected
- CBC: leucocytosis with shift to the left may be present.
- Sputum for Gram stain and/or culture.
- Blood cultures (if necessary) upon admission, because some typical bacterial pathogens, such as S pneumoniae and H influenzae, are frequently associated with positive blood cultures.

IV- Pharmacologic Therapy:

- Coverage should be divided against typical and atypical CAP pathogens.
- Combination therapy usually consists of Ceftriaxone plus doxycycline, azithromycin, or a respiratory quinolone.
- Duration of therapy is usually for 14 days .If the patient is switched to an oral regimen and is doing well, earlier discharge from the hospital is possible.
- Very healthy young adults and children may be treated for shorter periods.

N.B:

- Respiratory quinolones include Gemifloxacin (320 mg PO once daily), Moxifloxacin (400 mg PO/IV once daily) , Levofloxacin (750 mg PO-500 mg IV once daily) , Ciprofloxacin (500-750 mg PO twice daily- 400 mg IV / 8 to12 hours).

Viral Pneumonia

- Depending on the virulence of the organism, as well as the age and comorbidities of the patient, viral pneumonia can vary from a mild and self-limited illness to a life threatening signs and
- Symptoms Many viral pneumonias have overlapping clinical presentations with each other and with bacterial pneumonia and may occur together with bacterial pneumonia making diagnosis on purely
- clinical grounds difficult or impossible.
- An accurate and early etiologic diagnosis is important because specific therapies are used against certain viruses. Even with currently available tests, a causative microorganism could not be identified in 50-80% of patients.
- Pregnant women with viral pneumonia have a higher risk for severe disease than other females. Elderly persons and persons who are immunosuppressed develop severe viral pneumonia, resulting in high morbidity and mortality rates.
- The main exception to this was seen in the 2009-2010 H1N1 influenza pandemic, in which severe infection was more common in the population aged 5-59 years than in the elderly. This was thought to be from lack of exposure, and thus immunity, to the 1957 (and earlier) H1N1 influenza strain(s).

I- Etiologic viruses include:

- Adenovirus
- Coronavirus
- Hantavirus
- Influenza virus
- Parainfluenza virus (PIV), respiratory syncytial virus (RSV), human metapneumovirus (hMPV), measles virus
- Rhinovirus

Most of the members of Herpesviridae family are documented lung pathogens in hosts with compromised cell immunity and include the following:
Herpes simplex virus 1 (HSV-1) and herpes simplex virus 2 (HSV-2).Herpesvirus 6, Herpesvirus 7, and Herpesvirus 8 , Varicella-Zoster virus (VZV) ,Cytomegalovirus (CMV) , Epstein-Barr virus (EBV).
Influenza viruses are the most common viral cause of pneumonia.
Primary influenza pneumonia manifests with persistent symptoms of cough, sore throat, headache, myalgia, and malaise for more than three to five days. The symptoms may worsen with time, and new respiratory signs and symptoms, such as dyspnea and cyanosis, appear.
-Respiratory syncytial virus (RSV) is the most frequent cause of lower respiratory tract infection in infants and children and the second most common viral cause of pneumonia in adults. Patients with RSV pneumonia typically present with fever, nonproductive cough, otalgia, anorexia, and dyspnea. Wheezes, rales, and rhonchi are common physical findings.
-Parainfluenza virus (PIV) is second in importance only to RSV as a cause of lower respiratory tract disease in children and pneumonia and bronchiolitis in infants younger than 6 months.
The signs and symptoms include fever, cough, coryza, dyspnea with rales, and wheezing.

II- Laboratory studies:

- Viral culture
- Rapid antigen detection (IF, ELISA)
- Polymerase chain reaction (PCR) assay
- Serology
- Chest radiography: usually demonstrates bilateral lung involvement.

III- Management:

- Oxygen
- Rest
- Antipyretics
- Analgesics
- Nutrition
- Broad spectrum antibiotics (for concomitant bacterial pneumonia).
- Immunoglobulin
- Antiviral agents

Causative agent	Treatment
Influenza virus (e.g H1N1, H5N1)	Oseltamivir Peramivir Zanamivir
Respiratory syncytial virus	Ribavirin +RSV immunoglobulin(Palivizumab)
Parainfluenza virus	Ribavirin
Herpes simplex virus	Acyclovir
Varicella-zoster virus	Acyclovir + Varicella-zoster immunoglobulin
Adenovirus	Ribavirin or Cidofovir
Measles virus	Ribavirin +Intravenous immuno-globulin
Cytomegalovirus	Ganciclovir+Intravenous immuno-globulin or Foscarnet

Acute viral encephalitis

I) Definition:

Inflammation of the brain parenchyma

II) Modes of transmission:

Differs according to the type of virus (person to person or arthropode borne infection)

III) Diagnosis:

Case definition:

[a] Suspected case

Any patient have fever, headache and altered mental status varies from confusion to coma with 2 or more of the following:

- Seizures - Paresis
- Cranial nerve palsies - Paralysis
- Abnormal movement - Abnormal reflexes

[b] Probable case

- Suspected case + clear C.S.F
- Contain WBC 5-500 cells/cm with predominant lymphocytes with mild increase in C.S.F Protein and normal C.S.F glucose level.

[c] Confirmed case.

Suspected or probable case with:

- Detection of IgM antibody to the virus in the serum or C.S.F by ELISA.
- Detection of the virus, antigen or genome in C.S.F or serum by PCR.
- Isolation of virus from serum or C.S.F.

Investigation:-

- -Routine lab (CBC, ESR, CRP, RBS, urea, creatinine, liver funcation & electrolyte)
- CSF analysis
- CT brain
- MRI may be needed

IV) Medical treatment:

1) Empiric acyclovir I.V infusion

- Adult dose: 10 mg/kg/8 hours for 14- 21 day
- Pediatric dose: 15-20 mg/kg/8 hours for 14- 21 day

2) Empiric antibiotics

- Give Vancomycin plus Cefotaxime or Ceftriaxone as described for bacterial meningitis.

3) Cerebral dehydrating agents

- Mannitol 20% given 5 – 10 mL/kg/day in 2 – 3 divided dose. (1 gm/kg/day).Rapid I.V infusion within 20 – 30 minutes.
- **Furosemide:**

Given 1 mg/kg/Dose I.V with mannitol 20 % (with it or before) and monitoring vital signs and renal function .

- **Dexamethasone** (controversial)

Given 4-6mg/ 6 hours for 4 days or more.

4) Supportive and symptomatic treatment

V) Preventive measures:

1- Reporting: Immediately, Group A diseases.

2-Isolation: All cases should be isolated.

A public health workers should be instructed to take strict preventive and central measures.

3- Contacts: Should be observed for clinical diseases

Poliomyelitis
(Acute Flaccid Paralysis)

I- Definition:

- AFP is a symptom of several diseases, including Poliomyelitis, Guillain Barre Syndrome , Transverse Myelitis, and other neurological diseases. All cases should be detected; reported, and investigated .
- **Poliomyelitis** is a highly infectious viral disease, which mainly affects young children. The virus is transmitted through contaminated food and water, and multiplies in the intestine, from where it can invade the nervous system.

II- Symptoms:

- Initially: fever, fatigue, headache, vomiting, stiffness in the neck, and pain in the limbs. In a small proportion of cases, the disease causes paralysis, which is often permanent.
- **Only 5% of patients** exhibit different severities of nervous system involvement, from nonparalytic poliomyelitis to the most sever form of paralytic poliomyelitis (with bulbar involvement).
- **Most patients (95%)** with poliomyelitis virus infections are asymptomatic or have only mild systemic symptoms, such as pharyngitis or gastroenteritis.
- **Acute poliomyelitis** is a disease of the anterior horn motor neurons of the spinal cord and brain stem Flaccid asymmetric weakness and muscle atrophy are the hallmarks of its clinical manifestation, due to loss of motor neurons and denervation of their associated skeletal muscles.

III- Case definition:

(a) Suspected Case

Any child under 15 years of age with acute flaccid paralysis, including Guillian-Barre syndrome or any paralytic illness at any age when polio is suspected.

(b)Probable Case

A suspected AFP case with one of the following:

- No specimen obtained or specimen collected after 14 days of illness
- Residual paralysis after 60 days of illness
- Died within 60 days of illness
- Unable to trace patient conditions.

The expert committee can identify a probable case based on the above.

(c) Confirmed case

A confirmed case of polio is any suspected case from which poliovirus is isolated.

IV- Treatment:

- Avoid any medication by injection.
- Symptomatic treatment.
- Consultation of physical therapy.

V- Laboratory procedures:

- Two fecal samples (5-10 gm each) should be collected from all suspected cases,(24-48 hours apart) in a clean, dry, and sterile container

- Electromyography.
- lumbar puncture test (for bulbar poliomyelitis).
- Brain and spinal imaging (CT scan,MRI) according to presentation

VI- Prevention measures:

- Health education.
- Vaccination:

  1- Salk vaccine (inactivated poliovirus vaccine),administered through injection & is recommended for immunodeficient persons.

  2- Sabin vaccine (attenuated live poliovirus) administered orally

Reporting: Immediately (group A disease)

Isolation: of AFP or polio cases is not compulsory

Middle East respiratory syndrome coronavirus

(MERS-CoV)

I- Case definition:

(a) Suspected case

Three combinations of clinical, epidemiological and laboratory criteria can define a case :

- -A person with a febrile acute respiratory illness with clinical, radiological, or histopathological evidence of pulmonary parenchymal disease (e.g. pneumonia or acute respiratory distress syndrome) and testing for MERS-CoV is unavailable or negative on a single inadequate specimen and the patient has a direct epidemiologic-link with a confirmed MERS-CoV case.

OR

- -A person with a febrile acute respiratory illness with clinical, radiological, or histopathological evidence of pulmonary parenchymal disease (e.g. pneumonia or Acute Respiratory Distress Syndrome)and an inconclusive MERS-CoV laboratory test (that is, a positive screening test without confirmation) and a resident of or traveler to Middle Eastern countries where MERS-CoV virus is believed to be circulating in the 14 days before onset of illness ,

OR

- -A person with an acute febrile respiratory illness of any severity and an inconclusive MERS-CoV laboratory test (that is, a positive screening test without confirmation)and the patient has a direct epidemiologic-link with a confirmed MERS-CoV case.

(b) Probabole case

None

(c) Confirmed case

A person with laboratory confirmation of MERS-CoV infection

Factors predictive of ICU admission and death:-

- Advanced age.
- Male sex.
- High peak creatinine kinase.
- High lactate dehydrogenase.
- High initial absolute neutrophil count.
- Low serum sodium level.

II- Medical Treatment:

- The most effective therapeutic regimen is not known.
- Mechanical ventilation was required
- Empiric antibiotics are indicated if secondary bacterial infection is suspected.

III- Preventive measures:

A- Reporting: immediately (group A disease)

B- Isolation:

- In special isolation rooms in the hospital (respiratory precaution).

- Isolation of patient in a negative pressure room is preferred [if not available, use a single room with door closed].
- Frequent hand washing continues to be critical.

IV- Collect and send to the Central Laboratory :

1- Throat swab
2- Serum sample (5 cc)
3- Sputum
4- Nasopharyngeal swab

V- Investigations:

- Real-time RT-PCR.
- Virus isolation
- Antibody detection

Hospitals must follow infection control guidelines

- Masking of patients (surgical mask), accompanying individuals are to wear N95 mask or equivalent.
- Staff protection with N95 masks, eye protection, gowns and gloves.
- Isolation of patient in a negative pressure room is preferred [if not available, use a single room with door closed].
- Frequent hand washing continues to be critical.

Human Immune Deficiency Virus Infections (HIV/AIDS)

I- Definition:

HIV is a retrovirus transmitted by sexual, parenteral and perinatal route.

II- Case Definition:

1. HIV Infection

(a) Suspected Case

None

(b) Probable Case

None

(c) Confirmed Case

A laboratory confirmed case with:

- HIV positive serology (ELISA, two separate specimens)
- Confirmation by Western blot at the Central Laboratory

2. Acquired Immune Deficiency Syndrome (AIDS)

Case Definition in Adults

AIDS is defined as any patient who has at least 2 of the major and 1 of the minor signs listed below,or a patient infected with HIV and has CD4 cells less than 200 without symptoms.

Major signs:

- Weight loss at least 10% of body weight, Chronic diarrhea for more than1month
- Prolonged fever more than one month (intermittent or constant)

Minor Signs:

- Persistent cough more than 1 month, - Generalized pruritic dermatitis
- An episode of Herpes Zoster, - Oro-pharyngeal candidiasis
- Chronic progressive and disseminated Herpes Simplex infection
- Generalized lymphadenopathy

The presences of generalized Kaposi's sarcoma or cryptococcal meningitis are sufficient by themselves for the diagnosis of AIDS.

Case Definition of AIDS in Children

At least two major signs, and at least one minor sign, and absence of known cause of immune suppression (such as malnutrition)

Major signs:

- Weight loss or abnormally slow growth,chronic diarrhea for more than one month
- Prolonged fever for more than one month, -Generalized lymphadenopathy
- Oro-pharyngeal candidiasis

Minor signs:

- Repeated common infections , Persistent cough for more than one month
- Generalized dermatitis, Confirmed maternal HIV infection

Note: TB and HIV infections are often found together.

Suspected case

- Any patient suffering from symptoms related to HIV infection

- Children less than 18 months with positive HIV test by ELISA or infant of a mother known to have HIV and have related symptoms to the disease .

Probable case

- -The status of a suspect with the positive test for antibodies to HIV (ELISA) or the rapid test.
- -Children less than 18 months: positive test for antibody or born from infected mother and baby show symptoms.

Confirmed case

- Positive antibody test by Western blot or positive test by PCR

III- lab Investigation:

1. ELISA:- it may give few false +ve , false –ve results occur, if blood test was done during window period.
2. Western blot: if the ELISA is +ve, the result must be confirmed by western blot.
3. Qualitative or quantitative cultures (PCR: are used for diagnosis of neonatal HIV infection).
4. Others: according to clinical presentation as (CBC- urine -chest x-ray - stool etc.)

IV- Medical Treatment:

National guidelines on clinical care and antiretroviral drugs for treating and preventing HIV infection WHO 2014

When to start:

Population	Recommendations
Adult and Adolescent	Initiate ART if CD4 cell count ≤ 500cells/mm3 regardless of clinical staging: As a priority , ART should be initiated in all individuals with severe or advanced HIV clinical diseases (WHO clinical stage 3 or 4) and individuals with CD4 count ≤ 350cells/mm3 Initiate ART regardless of WHO clinical stages and CD4 cell count : • Active TB disease • HBV and/ or HCV co-infection with severe chronic liver disease
Children	Children less than 5 years: Initiate ART regardless of WHO clinical stage and CD4 cell count Children more than 5 years : • Initiate ART if CD4 cell count ≤ 500 cells /mm3 • As a priority , initiate ART in all children with severe / advanced HIV diseases (WHO clinical stage 3 or 4) or CD4 count ≤ 350 cells/ mm3 • Initiate ART in all regardless of WHO clinical stage and CD4 cell count in case of active TB disease
Pregnant and breast feeding women	Initiate ART in all HIV- infected pregnant and breastfeeding women and continue for life «option B+»

What to start:

The first line ART should consist of two nucleoside reverse transcriptase inhibitors (NRTIs) plus a non nucleoside reverse transcriptase inhibitor (NNRT)

First line ART for adults		
Preferred regimens	**Tenofovir + Lamivudine (emtricitabin)+Efavirenz**	
Alternative regimens	**- (Tenofovir+ Lamivudine (emtricitabin) Nevirapine - Lamivudine + Zidovudine + Efavirenz or Nevirapine**	
Preferred Second line ART regimen		
Adult and Adolescent (≥10years)	**If Zidovudine was used in first line ART**	**Tenofovir + lamivudine or (Emtricitabine) + Atazanavir/ritonavir (or Lopinavir/ritonavir)**
	If Tenofovir was used in first line ART	**Zidovudine + Lamivudine + Atazanavir/ritonavir (or Lopinavir/ ritonavir)**
Preferred First line Regimen for Children		
First –line ART	**Children (3 to ≤10 years) and adolescents ≤ 35 kg)**	**Adolescents (10 to 18 years) ≥ 35 kg**
Preferred regimens	**Abacavir + Lamivudine + Efavirenz**	**Tenofovir + Lamivudine (emtricitabin) + Efavirenz**
Alternative regimens	**-Abacavir+ Lamivudine +Nevirapine -Zidovudine + Lamivudine+ Efavirenz -Zidovudine+ Lamivudine+ Nevirapine -Tenofovir + Lamivudine (or Tenofovir) + Efavirenz -Tenofovir+Lamivudine(orEmtricitabine) + Nevirapine**	**-Zidovudine + Lamivudine + Efavirenz -Zidovudine + Lamivudine +Nevirapine -Tenofovir + Lamivudine (em-tricitabin) + Nevirapine**
Preferred Second line regimen for children		
NNRTI –based 1st line	**All ages**	**-Zidovudine+lamivudine+ Lopinavir/ ritonavir -Abacavir or (Tenofovir) + Lamivudine (or Emtricit-abine) + Lopinavir/ritonavir**

LPV/rbased 1st line	Younger than 3 years	No changes Younger than 3 years Address adherence issues
	3 years and older	-Zidovudine + Lamivudine + Efavirenz -Abacavir or (Tenofovir) + Lamivudine + Efavirenz

Pregnant and / or breast feeding women and their infants

- A combination of TDF+ FTC(or 3TC)+FEV is recommended as first

Summary of Maternal and Infant ARV-prophylaxis			
Scenario	Maternal ARV prophylaxis	Infant ARV prophylaxisa	Duration of infant ARV prophylaxis
Mother diagnosed with HIV during pregnancy b,c	Initiate maternal ART	NVP b	6 weeks b
Mother diagnosed with HIV during Labour or immediately postpartum and plans to breastfeed	Initiate maternal ART	NVP	6 weeks ; consider Extending this to 12 weeks
Mother diagnosed with HIV during Labour or immediately postpartum and plans replacement feeding	Refer mother for HIV care and evaluation for treatment	NVP b	6 weeks b

Infants identified as HIV exposed after birth (through infant or maternal HIV antibody testing) and is breastfeeding	Initiate maternal ART	NVP	Perform infant PCR early infant diagnosis test and then immediately initiate 6 weeks of NVP strongly consider extending this to 12 weeks
Infant identified as HIV exposed after birth (through infant or maternal HIV antibody testing) as is not breastfeeding	Refer mother for HIV care and evaluation for treatment	No drug	Do PCR test in accordance with national recommendations on early infant diagnosis ; no infant ARV prophylaxis ; initiate the treatment if the infant is infected
Mother receiving ART but interrupts ART regimen while breastfeeding (such as toxicity ,stock – outs or refusal to continue)	Determine an Alternative ART Regimen or solution ; counsel regarding adherence	NVP	Until 6 weeks after maternal ART is restarted or until 1 week after breastfeeding has ended

Pregnant and / or breast feeding women and their infants

- A combination of TDF+ FTC(or 3TC)+FEV is recommended as first line ART in pregnant and breast feeding women, including pregnant women in the 1st trimester of pregnancy and women of childbearing age.
- Infants of mothers who are receiving ART and breast feeding should receive 6 weeks of infat prophylaxis with daily NVP or twice daily AZT.
- If infant as receiving replacement feeding, they should be given 6 weeks infant prophylaxis with daily NVP or twice daily AZT.

1- If infant had NVP causes toxicity or NVP is not available, 3TC can be substituted.
2- If the mother is using replacement feeding, infant AZT can be substituted for infant NVP; if there is documented maternal viral suppression near delivery for a mother receiving ART and using replacement feeding, four weeks of infant ARV prophylaxis may be considered.

Drug	Infant age	Daily dosing
Nevirapine	Birth to 6 weeks • Birth weight 2000-2499g • Birth weight ≥2500g	 • 10 mg once daily • 15 mg once daily
	› 6 weeks to 6 months	20 mg once daily
	› 6 months to 9 months	30 mg once daily
	› 9 months until breastfeeding ends	40 mg once daily
Zidovudine	Birth to 6 weeks • Birth weight 2000-2499 g • Birth weight ≥ 2500 g	• 10 mg twice daily • 15 mg twice daily

3- If it is known that the mother has initiated ART less than 4 weeks before delivery, consider extending infant NVP for infants who are breastfeeding to 12 weeks.

Simplified infant prophylaxis dosing recommendations:

1- Infants weighing ‹ 2000 g should receive mg/kg dosing; suggested starting dose is 2 mg/kg once daily.
2- Recommended for 6 weeks, but 4 weeks may be considered in settings with replacement feeding.
3- Dosing beyond 6 weeks of age in special situation in which prolonged dosing of up to 12 weeks should be considered (such as the mother having had limited ART and not being likely to be virally suppressed; the infant is identified as HIV exposed after birth and is breastfeeding. this is based on the dosing required to sustain exposure among infants of › 100ng /ml with the least dose change.

Abbreviations					
3TC	Lamivu-dine	FTC	Emtric-itabine	LPV	Lopinavir
ABC	Abacavir	ATV/r	Atazana-vir/rito-navir	LPV/r	Lopinavir/ ritonavir
ATV	Atazana-vir	AZT, ZDV	Zidovu-dine	NVP	Nevirap-ine
EFV	Efavirenz	TDF	Tenofovir disproxil fumarate		

Prevention and treatment of AIDS-Associated Opportunistic Infections

Revise National guidelines on clinical care and antiretroviral drugs for treating and preventing HIV infection WHO 2014

Preventive measures:

A - Reporting: immediately (group A disease)

B - Isolation:

- Isolation of the HIV positive individual is unnecessary.
- The patient should be informed about his/her HIV status and provided counseling regarding options for medical treatment, prevention of transmission to others, and testing of contacts.

For contacts:

- Confidential HIV testing and counseling should be offered to sexual partners of patients with HIV infection.
- Follow-up for the patient and spouse/sexual partner is recommended every 3 months by staff from the AIDS Program.

For healthcare workers:

- **Emergency personnel** should follow standard universal precautions for potential exposures to blood.
- Masks, visors, and protective clothing are indicated when performing procedures that may involve spurting or splashing of blood or bloody fluids.

Healthcare workers who sustain a needle stick injury from an HIV-infected patient:

Should be counseled about the risk of infection (3 cases per 1000 needle sticks).

They should be offered serologic testing at periodic intervals over the following 12 months.

-Post exposure prophylaxis (PEP)

- Recommendation place emphasis on the importance of initiating occupational PEP as soon as possible, ideally within 2 hours of exposure.
- First dose of PEP should be offered while evaluation is underway.
- PEP should not be delayed while awaiting source patient or results of the exposed baseline HIV test.

- The preferred HIV PEP regimen

Raltegravir 400 mg per oral twice daily.plus Truvada per oral once daily.

(Tenolovir DF 300mg + Emtricitabine Emtriva 200mg) fixed dose combination for 28 days.

- Emergency transfusion services should use blood donations that are screened for HIV antibody.

Ebola
The Deadly African Virus

Virology:

FAMILY/GEOG-RAPHY	AGENT	CASE-FATALITY
Filoviridae (thread) Sub-saharan Africa	Ebola 1976 Marburg1967	50-80% 25%
Arenaviridae (sandy) West Africa (Lassa)	Lassa1969	Lassa:1-2% (up to 25% in hospitalized pts)
Bunyaviridae Sub-saharan Africa Egypt, Yemen, KSA SW US	Phlebovirus: Rift Val-ley 1930 Nairovirus: Crimean Congo Hantavirus	Rift Valley: <1% overall 50% in hemorrhagic renal syndrome
Flaviviridae "yellow" 100 country worldwide	Yellow fever1600 Dengue & Alkhumra	Yellow Fever: 5-7% overall 50% in hemorrhagic

Transmission of Ebola:

1-Direct contact with virus-containing body fluids (eg, blood, vomitus, urine, feces and probably sweat)

2- The ritual washing of Ebola victims at funerals

3-Dealing with laboratory animals so infection can be via ingestion or passage through breaks in the skin

4- Handling of infected chimpanzees, gorillas, fruit bats, monkeys, forest antelope found ill or dead.

5- Bushmeat, which can range from bat to monkey

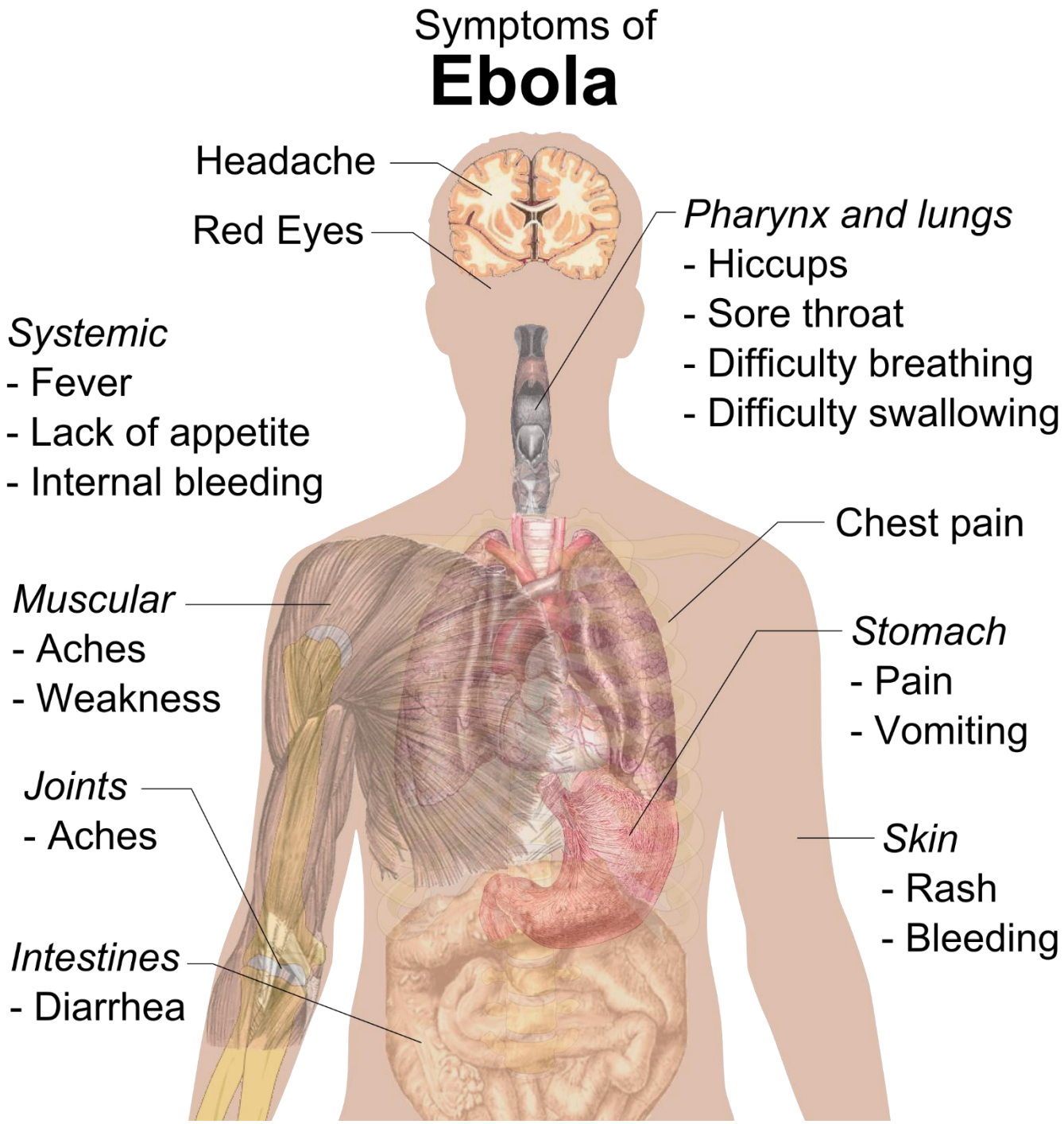
(Not by mosquito or inhalation)

Viral persistence

Virus can persist for some time in certain anatomic sites inaccessible to the immune system, such as the testes with secretion in the semen up to 3 month

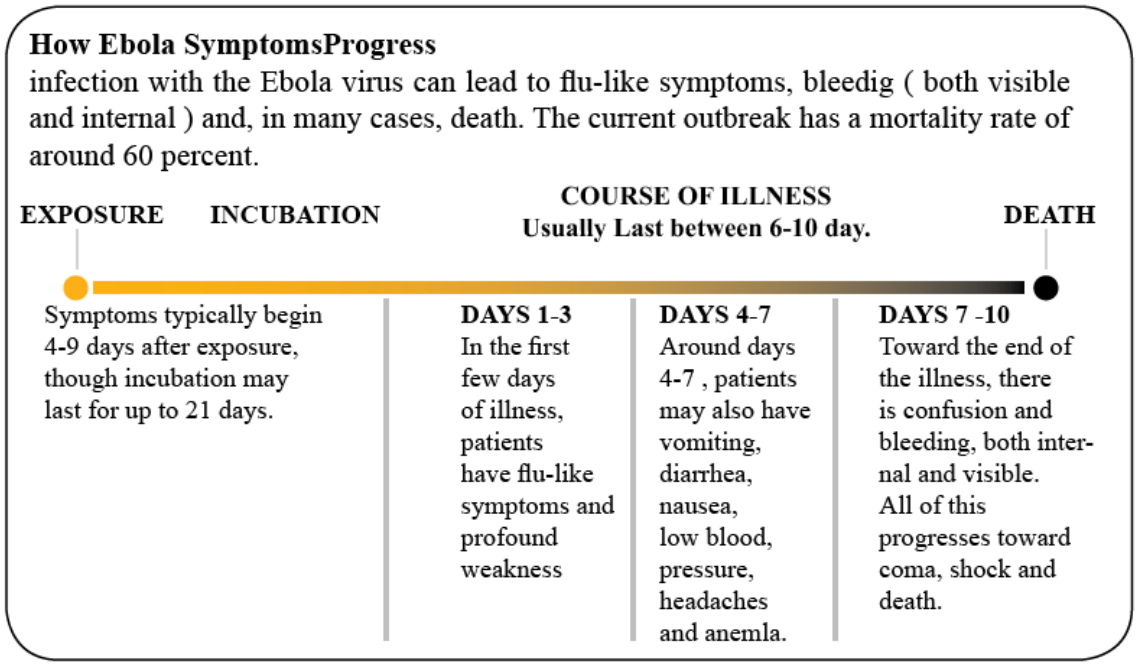
Clinical Picture:

• Stage I (as illustrated by the figure):



Stage II (Specific):

- Hemorrhage (DIC)
- Neuropsychiatric abnormalities
- Anuria
- Shock
- Impaired liver function



CDC Case Definition:

Person under Investigation (PUI)

• A person who has both consistent symptoms and risk factors as follows:

1) Clinical criteria: fever >38.5 plus symptoms as severe headache, muscle pain, vomiting, diarrhea, abdominal pain, or hemorrhage.

2) Epidemiologic risk factors within the past 21 days before the onset such as contact with blood or other body fluids or human remnants of a patient known or suspected to have EVD Residence in or travel to an area where EVD transmission is active, or direct handling of bats, rodents, or primates from disease endemic areas.

Probable Case

• A PUI who is a contact of an EVD case with either a high or low risk exposure

Confirmed Case

• Laboratory confirmed diagnostic evidence of ebola virus

High risk exposures:

- Percutaneous, e.g. the needle stick, or mucous membrane exposure to body fluids of EVD patient
- Exposure to body fluids of an EVD patient without appropriate personal protective equipment (PPE)
- Laboratory worker processing body fluids of confirmed EVD patients without appropriate PPE or standard biosafety precautions
- Participation in funerals with direct exposure to human remnants in the geographic area where outbreak is occurring without appropriate PPE

Investigations:

Rapid diagnostic tests:

1- Enzyme-linked immunosorbent assay (ELISA)

2- Reverse-transcription polymerase chain reaction (RT-PCR)

3- CBC with sever leucopenia , LFTs AST>ALT ,renal profile and proteinuria, Amylase

4- Coagulation profile (D dimer)

CATEGORIES USED TO CLASSIFY EBOLA CASES

Ebola cases are classified as suspected, probable, or confirmed depending on whether they meet certain criteria (table 3)

Table3: Ebola case-classification criteria

Classification	Criteria
Suspected	Any person, alive or dead, who has (or had) sudden onset of high fever and had contact with a suspected, probable or confirmed Ebola case, or a dead or sick animal OR any person with sudden onsetof high fever and at least three of the following symptoms: headache, vomiting, anorexia/ loss of appetite, diarrhoea, lethargy, stomach pain, aching muscles or joints, difficult swallowing. breathing difficulties, or hiccup; or any person with unexplained bleeding OR any sudden, unexplained death.
Probable	Any suspected case evaluated by a clinician OR any person who died from «suspected» Ebola and had an epidemiological link to a confirmed case but was not tested and did not have laboratory confirmation of the disease.
Confirmed	A probable or suspected case is classified as confirmed when a sample from that person tests positive for Ebola virus in the laboratory.

Treatment Protocol for Ebola Virus Disease (EVD)

For suspected and confirmed cases

Treatment:

- Supportive care should focus on maintaining circulatory function and blood pressure, correction of severe coagulopathy

Supportive Care

Non- invasive monitoring

- Non-invasive monitoring with ECG,O2 saturation (pulse oximetry) and non invasive blood pressure monitoring should be available

Oral fluid and electrolyte replacement

- First close input output chart should be done ,Oral fluid and electrolyte replacement is preferred in patients who are not critically ill (97%). Rehydration solutions should be used.

- If unable to swallow, early placement of nasogastric tube should be considered.
- Severe hypokalemia is a frequent finding in patients with EVD, has been associated with poorer outcomes and should be actively managed, ideally by enteral potassium chloride or by peripheral IV. If possible, avoid insertion of central venous catheters.

Fluid replacement and resuscitation

1-The amount of IV fluid required depends on each patient's clinical status. See chart (1)

2-It is recommended that **Ringer's lactate** be used for volume replacement.

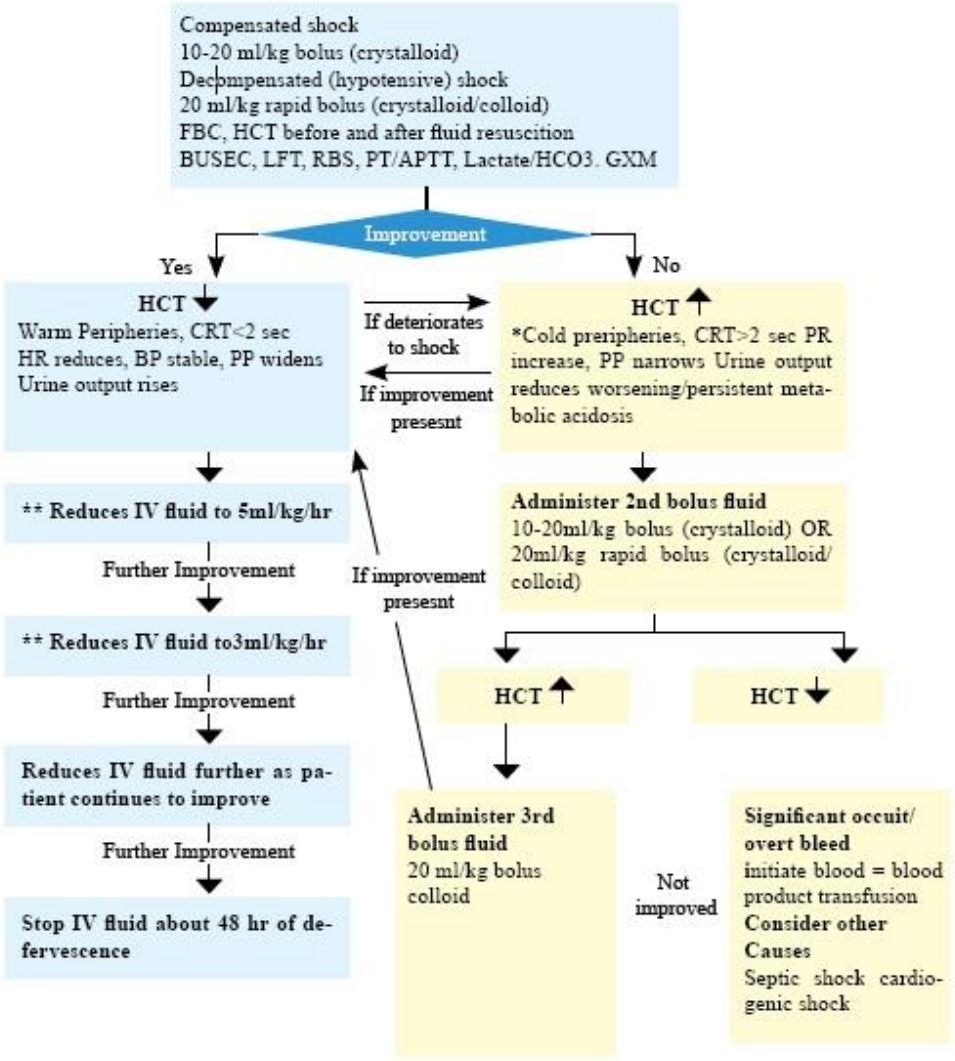
3-Starch-based colloid solutions should be avoided as their use may increase risk of coagulopathy and acute kidney injury.

4- If the patient is hypotensive following empiric crystalloid fluid resuscitation via peripheral IV, a central venous catheter should be inserted by the most experienced physician using

Haemodynamic assessment - continuum of haemodynamic changes

Parameters	Stable circulation	Compensated shock	Hypotensive shock
Conscioius level	Clear and lucid	Clear and lucid	Restless, combative
Capillary refill time	Brisk (<2 sec)	Prolonged (>2 sec)	Very prolonged, mottled skin
Extremities	Warm and pink	cool peripheries	Cold, dammy
Peripheral pulse volume	Good volume	Weak & thready	Feeble or absent
Heart rate (HR)	Normal HR for age	Tachycardia	Severe tachycardia or bradycardia in late shock
Blood pressure (BP)	Normal BP for age	Normal systolic pressure but rising dia-stolic pressure	Hypotension Unrecordable BP
Pulse pressure (PP)	Normal PP for age	Narrowing PP postural hypotension	Narrowed pulse pressure (<20 mmHg)
Respiratory rate (RR)	Normal RR for age	«Quiet» Tachypnoea	Kussmaul breathing (Metabolic acidosis)
Urine output	Normal	Reducing trend	Oliguria or anuria

* Highlighted boxes are early signs of shock



Fluid and Electrolyte (chart 1)

Vasopressors

The guidelines for vasopressors use in septic shock are:

- A mean arterial blood pressure target of 65-70 mmHg (or median for age in children) is a reasonable initial target in adults, but should be reassessed based upon individual patient factors such as hypertension.
- Norepinephrine infusion dose: 0.01-3 microgram/ kg/ minute.

Blood product replacement

1-Treatment is generally only required for those bleeding or requiring invasive procedures.
2-Standard laboratory coagulation tests (platelet count, INR, PTT, fibrinogen) should be done
3-If there is concern regarding status of patient's coagulation status and/or if an invasive procedure is planned, fresh frozen plasma to be given
4-Blood transfusion for threshold hemoglobin level <7 gm

Drugs

- **Antibiotic Therapy :**

Antibiotic should cover enteric organisms so Cefotaxime or ceftriaxone plus ciprofloxacin but in cases of sever sepsis or septic shock carbapenem plus vancomycin.

- **Antimalarial therapy**

Antimalarial therapy as directed by the infectious diseases consultant should be started early if there is a strong clinical suspicion of malaria, even it can be add on to treatment of Ebola

- **Antiviral drugs needed**

Favipiravir

- **Symptomatic support**

Symptom	Aetiology& Implications	Management
Seizure or Coma	Aetiology unclear, potentially related to liver failure. Typically ominous sign, seen typically shortly before death.	Airway management as required Benzodiazepines +/- dilantin to control seizures laboratory investigations (e.g. Na+, glucose) CT head if lateralizing features
Hypotension & Shock	frequently an early manifestation of illness severity and plausible lethal pathway. Initially, hypovolemia from profound GI losses. A component of early distributive shock remains a possibilty but has not been confirmed. Secondray sepsis remains a possibility but has not been confirmed.	close monitoring of fluid balance Aggressive repletion of fluid and electrolyte losses (potassium, bicarbonate) Consider vasopressor therapy if hypotension continues despite adequate fluid resuscitation.

Dyspnea or Respiratory failure	Respiratory involvement not a cardinal feature, Polypnea seen at all stages of illness in the context of shock and profound metabolic acidosis.	Oxygen therapy +/- mechanical ventilation
Severe diarrhoea and vomitting	Frequent early presentation, the aetiology of which remains unclear.	NG tube insertion & suction Haloperido 1mg PO/IV/SC q8h standing. (0.25 - 0.5 mg in children) Metoclopramide 10mg PO/IV/SC q6h standing. (0.1mg/kg/ dose in children).
Intolerant to oral intake	Common in severe cases Associated with chest pains so esophagitis is a plausible mechanism but unproven.	Consider enteral nutrition if tolerated if enteral nutrition are poorly tolerated, Consider TPN after 8 days of unsuccessful enteral nutrition.
RUQ pain and hepatomegaly	Common in severe cases Unproven but hepatitis plausible	Monitoring of liver biochemistry, consideration of vitamin K for early signs of INR elevation, watch for hypoglycemia.
Hemorrhage (GI & puncture sites)	Ominous sign, seen typically shortly before death Aetiology most likely DIC	Complete hematology and liver laboratory workup Cosider platelet transfusions is low, FFP if INR elevated, cryoprecipitate if fibrinogen low.
Fever, chills, headache and myalgias	Common Aetiology associated to viremia	Acetaminophen 650mg PO q4h PRN (maximum 4g in 24h) (Pediatrics 10-15 mg/kg/ dose Q4H to in children, max of 5 doses per 75mg/kg/day). Lower doses may need to be used in patients experiencing hepatic dysfunction. Non-steroidal anti-inflammatory medications should be strictly avoided due to their platelet-inhibiting effects, which could exacerbate hemorrhage
pain	Common, often involving abdomen, chest wall, headache and joint pain that are not adequately managed with acetaminophen alone	Narcotics, morphine, fentanyl, hydromorphone if renal impairment

RRT and CPR

Renal replacement therapy (RRT)

If available, intermittent hemodialysis may be preferable to CRRT(continuous renal replacement therapy) in patients with possible or proven EVD even if vasopressor therapy is required. (Decreased exposure time and no need for manual drainage of effluent bags

Cardiopulmonary resuscitation (CPR)

Patients with late stage proven EVD and progressive multi-organ failure have minimal expectation of survival and withholding CPR may be appropriate to avoid unnecessary risk to health professionals.

In the event of a 'code blue', responding staff must not rush into the room without first applying the appropriate PPE including N95 respirators for aerosol generation before entering the patient's room.

The resuscitation equipment must be appropriately decontaminated according to the equipment cleaning guidelines before it is removed from the room.

Respiratory Care

For Non- Intubated Patients:

1-Provide O2 as ordered with continuous SpO2 monitoring.

2-ET(End Tidal) CO2 for monitors is preferred

3-Nebulization, and noninvasive mask ventilation must not be employed in these patients as these may generate aerosols.

4-Bronchodilator delivery should be provided via MDI and spacer (+/- mask) only. If the patient is not improving consideration should be given to early, elective intubation and mechanical ventilation

Intubation guidelines:

1-Endotracheal intubation should be performed by the most senior responsible physician using full PPE, including an N95 respirator.

2-Direct laryngoscopic and video-laryngoscopic equipment and a difficult airway cart should be available nearby.

3-Use of rapid-sequence-induction technique as much as possible to minimize chances of cough and aerosolization. The best pharmacotherapy will be determined by the physician on a case by-case basis but in general should include significant sedation (narcotic Propofol /ketamine /benzodiazepines)

4-If difficult airway cart is utilized, do not bring entire cart into the room - only the necessary equipment.

5-Bronchoscopy should be in a negative pressure room with staff wearing full PPE including N95 respirator.

6- Ventilation parameters include the following, avoid excess tidal volume (<6ml/kg), avoid excess plateau pressures (<30 cm H2O), appropriate PEEP to avoid barotrauma ,HEBA filter of exhaled gas ,and use of Ketamine during intubation to avoid sever hypotension .

Post Exposure Prophylaxis Trials

- Interferon-alpha-2b was protective in mice when therapy was started before or soon after virus challenge
- Synthetic small-molecule drug inhibits viral RNA polymerase function

Conclusion

- Rapid diagnosis & resuscitation is very important to save lives of the patients
- Sticking to infection control policies and procedure can save not only us but the whole community.

Leptospirosis

I- Defenition :

- Is the most widespread zoonosis in the world. It is caused by pathogenic spirochetes of the **genus Leptospira.**
- Leptospirosis is endemic in tropical countries. The highest mortality rates remain among the elderly and those with Weils syndrome.
- There are 25 serogroups which are in turn comprised of nearly 250 serovars (upon the basis of antigenic characteristics).
- Although rats and mice (the typical reservoirs) are important primary hosts, a wide range of other mammals including dogs, cows, and certain marine mammals are able to carry and transmit the disease as secondary host.

II- Mode of transmission:

- Humans become infected through contact with water, food, or soil containing urine from infected animals. This may happen by swallowing contaminated food or water or through skin, eye and mucous membranes contact.
- Urine of an infected animal is contagious as long as it is still moist.
- The disease is not known to be spread from person to person.
- The symptoms in humans appear after a 4–14 days incubation period

III- Clinical description:

The usual presentation is an acute febrile illness with headache, myalgia (particularly calf muscle) and prostration associated with any of the following symptoms/signs:

- Conjunctival suffusion
- Anuria or oliguria
- Jaundice
- Cough, haemoptysis and breathlessness
- Haemorrhages (from the intestine; lung bleeding is notorious in some areas)
- Meningeal irritation
- Cardiac arrhythmia or failure
- Skin rash

N.B The clinical diagnosis is difficult where diseases with symptoms similar to those of leptospirosis occur frequently.

IV- Laboratory observations:

- Anemia (in severe cases) due to bleeding, hemolysis and uremia.
- BUN and creatinine are elevated in severe cases.
- Serum bilirubin level is elevated (in icteric type)
- Serum aminotransferase levels are frequently normal, but sometimes raised to 2-3 times normal levels.
- CPK is usually raised due to muscular involvement.
- WBC is subnormal, normal or slightly elevated; it may reach 50,000/µL in severely ill patients with jaundice.
- Thrombocytopenia is common especially in severe cases.

V- Laboratory diagnosis:

On infection the microorganism can be found in blood and CSF for the first 7 to 10 days (invoking serologically identifiable reactions) and then moving to the kidneys. After 7 to 10 days the microorganism can be found in fresh urine.

- **ELISA IgM:** (main diagnostic tool in our hospitals)

Is particularly useful in making an early diagnosis, as it is positive as early as 2 days into illness, a time when the clinical manifestation may be nonspecific. It was found to be 100% sensitive (in the second phase) and 93% specific (It is genus specific, not serovar specific).

- **PCR:** sensitive, specific, positive early in disease, and able to detect leptospiral DNA in blood, urine, CSF and aqueous humor (It is genus specific, not serovar specific). (not available)
- **MAT (microscopic agglutination test):** a serological test is considered the gold standard in diagnosing leptospirosis. As a large panel of different leptospira need to be subcultured frequently, which is both laborious and expensive, it is underused, mainly in developing countries. Fourfold or greater rise in titre or seroconversion on paired samples obtained at least 2 weeks apart. (not available)
- **Culture:** The median time to positivity is three weeks with a maximum of three months. This makes culture techniques useless for diagnostic purposes, but is commonly used in researches.(not available)

VI- Prophylaxis:

- **Doxycycline :** 200 mg once a week, to prevent infection in high risk areas.

VII- Treatment:

- Severe cases treated with intravenous Penicillin G (drug of choice). Dose: 1.5 MU every 6 hours for 1 week
- Less severe cases treated orally with antibiotics such as Doxycycline (100 mg orally every 12 hours for 1 week) Ampicillin or Amoxicillin.
- Third-generation Cephalosporin, such as (Ceftriaxone - Cefotaxime) and Quinolone antibiotics may also be effective.
- Supportive therapy measures include normalization of the hydroelectrolytic balance. Dialysis is used in renal failure. Organ specific care and treatment are essential in cases of renal, liver, or heart involvement. Corticosteroids and Intravenous immunoglobulin are beneficial in some complicated cases.

Acute Viral Hepatitis
Hepatitis A

I- Mode of transmission:

- Through the mouth (food and drinks) (hepatitis A and E viruses)

II- Clinical Description:

- An acute illness that typically includes jaundice, dark urine, anorexia, malaise, extreme fatigue, and right upper quadrant tenderness. Incupation period 2-6 weeks.
- About 40% of all viral hepatitis is caused by viral hepatitis A

III- Case definition:

(a) Suspected case

any patient suffering from yellow skin ,sclera or conjunctiva with dark urine and fatigue with or without fever with anorexia and pain in the right hypochondrium

(b) Probable case

It is a suspected case with elevated liver enzymes more than 3 folds of the average normal in blood.

(c) Confirmed case

It is a suspected or probable case confirmed by positive ELIZA antibodies for hepatitis A virus (HAV IgM) or a case linked to an epidemiologically confirmed case ..

IV- Laboratory Criteria for Diagnosis:

- Increased serum bilirubin (total / direct)
- Detection of bilirubin in urine.
- Highly elevated liver enzymes (ALT and AST)
- Detection of IgM anti-hepatitis A virus (IgM anti-HAV).

V- Medical Treatment:

- Liver support
- Others: according to C/P

VI- Preventive measures:

A - Reporting: (group C disease)

B - Isolation:- Enteric isolation during the 1st 2 weeks & no more than 1 week after onset of jaundice

Disease	Isolation time	Isolation precations
Hepatitis virus A	Children below 3 years: all time of hospital admission , - From 3-14 years : 2 weeks from the onset of the disease . - After 14 years : 7 days after appearance of jaundice .	Contact (gloves + aprons)

- Hepatitis A gives solid and long term immunity.
- -There are some cases with recurrence of the symptoms within first 6 months.
- -About10-15% will have symptoms that last long time or come back 6-9 months.
- In hepatits A there is no chronicity.

VII- Extra hepatic complication of HAV:

(Very rare, most of them are immune mediated)

1- Autoimmune hemolytic anemia (consult hematologist if necessary) .
2- Autoimmune thrombocytopenia (consult hematologist if necessary).
3- Haemophagocytic syndrome (macrophage activation syndrome).
4- Aplastic anemia (consult hematologist).
5- Encephalitis.
6- Guillain Barre Syndrome (consult neurologist).
7- Transverse myelitis (consult neurologist).
8- Mononeuropathy multiplex (consult neurologist).
9- Cranial nerve affection e.g: optic neuritis, trigeminal neuropathy.
10-Acute pancreatitis.
11-Reactive arthritis.
12-Renal complications (consult nephrologist).

- -Mesangial proliferative glomerulonephritis.
- Interstitial nephritis.
- -IgA nephropathy.
- -Acute tubular necrosis.
- -Nephrotic syndrome.

13-Auto immune hepatitis.
14-Lupus(consult rheumatologist).

Chronic Hepatitis B
Chronic HBV infection

I- Definition :

Defined as persistence of hepatitis B surface antigen (HBsAg) for six months or more after acute infection with HBV

II- Inclusion criteria for treatment:

a. Age ≥ 18 years
b. HBsAg (+ve) for more than 6 months.
c. HBV DNA ≥ 2000 IU/ML.
d. ALT elevation above upper limit of normal on 2 successive occasions within 3- 6 months.

III- Treatment:

Lamivudine:

- Oral administration
- One tabelet 150 mg once daily

Entecavir:

- Oral administration
- Patients naive to lamivudine therapy: 0.5 mg once daily
- Patients who are refractory/resistant to lamivudine: 1.0 mg once daily
- Dose adjustment needed if eGFR< 50 mL/min

Tenofovir:

- Oral administration
- 300 mg once daily
- Dose adjustment needed if eGFR< 50 mL/min

IV- Treatment failure:

May be primary or secondary

Primary antiviral treatment failure may be defined as:-

Failure of an antiviral drug to reduce HBV DNA levels by ≥1 x log10 IU/mL within 3 months of initiating therapy.

Secondary antiviral treatment failure may be defined as:-

A rebound of HBV DNA levels of ≥1 x log10 IU/mL from the nadir in persons with an initial antiviral treatment effect ≥1 xlog10 IU/mL decrease in serum HBV DNA.

V- Duration: based on clinical endpoints:

- HBeAg positive: continue treatment until HBV DNA undetectable and HBeAg seroconversion achieved; continue for ≥ 6 months after anti-HBe appearance
- Close monitoring for relapse required after treatment discontinuation
- HBeAg negative: continue treatment until HBsAg clearance

PegIFN:

- Favorable predictors of response: Low HBV DNA, High ALT, Genotype A or B > C or D, Not advanced disease, Young women wanting pregnancy in near future, Concomitant HCV infection.
- Dosage/administration
    - 180 µg /week by subcutaneous injection.

- Assessment is done at week 24 of therapy
- In case of seroconversion (patient becomes HBeAg –ve and HBeAb +ve →continue treatment for 48 weeks).
- If no seroconversion →stop treatment and shift to oral antiviral therapy according to previous guidelines.)

Lamivudine (3TC):

- Dosage 100 mgm. QD
- Extremely well tolerated
- Suppresses viral replication in almost all cases
- Appears equally effective in patients exposed to vertical transmission
- Results in sustained viral suppression in 10–20% of cases(Loss of HBeAg and HBV DNA)
- Results in YMDD drug resistant mutants in 15–70% of cases
- Resistance should be identified as early as possible by monitoring HBV DNA level: if discovered add on Adefovir 150 mgm.QD.

For Patients already on treatment:

- Patients on Lamivudine and HBV DNA is undetectable by PCR →continue treatment with monitoring of ALT every 3 months and HBV DNA every 6 months.
- Patients on combined Lamivudine & Adefovir →continue treatment or shift to Tenofovir 300 mg once daily.
- Lamivudine resistance → Shift to Tenofovir 300 mg once daily.

Special Groups:

Liver Cirrhosis:

- All cirrhotic patients should receive oral antiviral therapy if HBV DNA is detectable by PCR irrespective of the viral load.

Compensated Cirrhosis: -

- Entecavir 0.5 mg or Tenofovir 300mg once daily.

Decompensated Cirrhosis:-

- Entecavir 1 mg once daily.

The dose of antiviral needs to be adjusted in patients with low creatinine clearance (< 50ml/min)

Don’t Forget! All cirrhotic patients with HBV viremia should be treated irrespective of the viral load.

Pregnancy:

- All pregnant females should be screened for HBsAg.
- Newly diagnosed pregnant women in the last trimester showing an HBV DNA level ≥ 100,000 IU/ML are candidates for Lamivudine 100 mg or Tenofovir 300 mg once daily starting last trimester and for 3 months after delivery to decrease chance of new-born infection.
- Mothers with active CHB plus cirrhosis or severe hepatitis flare should receive treatment with Tenofovir throughout pregnancy.
- Females who become pregnant while on treatment On Lamivudine monotherapy: Continue on treatment On Other lines of treatment: shift to class B drug (Tenofovir 300 mg once daily)

- Re-evaluate the condition after delivery and consider treatment according to the previous guidelines.

For Newborns:

- -Newborns for chronic HBV mothers should receive HBIG and the first dose of HBV vaccine at birth.
  - **N.B** breast feeding is not recommended during treatment with lamivudine, Tenofovir or Entecavir.

Treatment of HCV/HBV Coinfection:

- Treatment indication for HCV infection and NO indication for HBV: treat according to HCV guidelines + follow-up HBV closely if SVR.
- Treatment indication for HCV infection and indication for HBV: consider one of the interferon based regimens (PR+ SOF / PR+SIM / PR+DCV).
- Treatment indication for HBV infection and NO indication for HCV: treat according to HBV guidelines.

HBV/HDV Coinfection:

- Active HDV infection is confirmed by HDV RNA assays.
- Peg –INF is the only effective drug against HDV.
- Efficacy of Peg –INF is assessed during treatment after 3-6 months by measuring HDV RNA levels.
- Optimal duration of therapy is not well defined but therapy for at least 72 weeks.
- Oral antiviral therapy should be used only when there is active HBV replication according to guidelines.

Renal Insufficiency, Dialysis, and Renal Transplant patients:

- All patients with renal dysfunction should be screened for HBV.
- Seronegative patients should be vaccinated.
- In patients with CHB Entecavir is preferred for treatment.
- The dose should be adjusted according to creatinine clearance.

Immunosuppressed Patients:

- All candidates for chemotherapy and immunosuppressive therapy should be screened for HBsAg and anti HBc prior to initiation of treatment.
- Vaccination is mandatory for seronegative cases. Higher vaccine doses may be needed.
- HBsAg positive patients (irrespective of the viral load) should receive oral antiviral therapy at the onset of chemotherapy and for 12 months after cessation of treatment.

Patients who are:

- HBsAg –ve, AntiHBc +ve, HBV PCR +ve should be managed in the same way as HBsAg +ve cases.
- HBsAg –ve, AntiHBc +ve, HBV PCR –ve should be followed up every 2-3 months. Start oral antiviral if HBV PCR becomes positive.
- Which oral antiviral?
  - Viral load < 2000 IU/ml and short duration of immunosuppression: use Lamivudine.
  - Viral load ≥2000 IU/ml and long duration or repeated courses of immunosuppression: use Entecavir or Tenofovir.

When to stop antiviral Therapy?

- HBeAg(+):Stop treatment 6-12 months after seroconversion
- HBeAg(-):Indefinitely, or until HBsAg seroconversion.

NCCVH Hepatitis C Treatment Protocol

Inclusion Criteria:

1- HCV RNA positivity
2- age: 18-75 years

Exclusion Criteria:

1- Total serum bilirubin > 3 mg/dl
2- Serum albumin < 2.8 g/dl
3- INR ≥1.7
4- platelet count < 50000/mm3

- If any of the criteria from 1 to 4 is not caused by liver disease, the patient can be included in the treatment protocol

5- HCC, except 4 weeks after intervention aiming at cure with no evidence of activity by dynamic imaging (CT or MRI)
6- Extra-hepatic malignancy except after two years of disease free interval. In cases of lymphomas and chronic lymphocytic leukemia, treatment can be initiated immediately after remission based on treating oncologist report.
7- Pregnancy or inability to use effective contraception
8- Inadequately controlled diabetes mellitus (HbA1c > 9%)

Patients will be categorized to:

1-Easy to treat group:

- Treatment naïve
- Total serum bilirubin ≤ 1.2 mg/ dl
- Serum bilirubin ≥ 3.5 g/ dl
- INR ≤ 1.2
- Platelet count ≥ 150000/mm3

2-Difficult to treat group:

- Peg-INF treatment experienced
- Total serum bilirubin ≥ 1.2 mg/ dl
- Serum bilirubin ≤ 3.5 g/ dl
- INR ≥1.2
- Platelet count < 150000/mm3

- Easy to treat group are eligible to be treated by the following regimen for 12 weeks: Sofosbuvir + daclatasvir
- Difficult to treat group are eligible to be treated by the following regimen for 12 weeks: Sofosbuvir + daclatasvir + ribavirin.

Treatment of special populations:

1 -Advanced liver disease (CHILD score ≥8)
2- Post – organ transplantation.
3- Chronic kidney disease (CKD)
4- Non –responders to sofosbuvir containing regimens
5- Combined HCV and HIV

1-Treatment of patients with advanced liver disease:

- Treatment is **ALLOWED ONLY** in one of several assigned specialized centers
- The following regimen is used for 12 weeks:
  - Sofosbuvir + Daclatasvir + Ribavirin
  - The dose of ribavirin is 600 mg/ day. A trial should be done to reach dose of 1000 mg/ day based on patient tolerability

2-Treatment of patients with post organ transplantation:

- Treatment will be with Sofosbuvir + Daclatasvir for 24 weeks

3-Treatment of patients with chronic kidney disease (CKD):

In patients having a serum creatinine exceeding the upper normal level, eGFR is calculated, and, accordingly,

- Patients with CKD (eGFR>30 ml/min) are treated by the usual treatment regimens.
- Patients with CKD stage (eGFR ≤ 30 ml/min) are treated by Paritaprevir-r/Ombitasvir+ ribavirin, provided the following are fulfilled:
  - Patients have compensated liver (Child A cirrchosis or no cirrhosis)
  - Hb level is at least 10 g/ dl
  - The patient has no associated uncontrolled comorbidity (Cardiac, neuro-psychic,..)

A nephrologist consultation is done. A report determining the treatment eligibility and necessity, and the exact ribavirin recommended dose (and time of administration in relation to dialysis)

- In case of dialysis the patient should be aware of the high risk of reinfection by signing a consent form.

4-Treatment of patients who failed previous Sofosbuvir containing regimen

- Treatment will be with Sofosbuvir +Daclatasvir +Ribavirin for 24 weeks
- The dose of ribavirin is 600 mg/ day. A trial should be done to reach a dose of 1000 mg/ day based on the patient tolerability

5- Treatment of patients with Combined HCV and HIV:

- Comanagement by the hepatologist and the infectious disease physician is needed.
- Sofosbuvir should not be received in combination with tipranavir

Notes on doses and modes of administration

- Dose of Sofosbuvir: 400mg once daily with or without food.
- Dose of Daclatasvir :60mg once daily with or without food
- The dose of ribavirin is 600 mg/ day. A trial should be done to reach a dose of 1000 mg/ day based on the patient tolerability

N.B

- Patients > 65 years old should undergo cardiological assessment prior to therapy by ECG, echocardiography and cardiological consultation
- An update will be released as soon as possible based on avail ability of other treatment regimens.

Scoring of patients with CKD for DAA treatment priority

Positive points:

Post-renal transplant	5 points
Regular Dialysis	5 points
Cryoglobulinemic vasculitis	5 points
Non-Hodgkin B-cell lymphoma	5 points
Biopsy confirmed MCGN with hypocomplementemia	4 points
Biopsy-confirmed MCGN without hypocomplementemia	3 points
Nephrotic syndrome regardless of histological type	2 points
Previous treatment failure	2 points
HBV/HIV/CMV co-infection	2 points
Stage of kidney disease (MDRD-4)	1 point/stage
Stage of liver disease (Fibroscan)	1 point/stage

Negative points:

Age > 70	−1 point/5 years
Decompensated cirrhosis	−3 points
Concurrent drug–drug interaction with selected Protocol	−3 points
Concomitant heart disease	−1 point/NYHA score
Concomitant pulmonary disease	−1 point/−10% FVC1
Concomitant CNS disease	−1 point/10% disabilit

	Native kidneys	Transplanted
Selected protocol	E2: Paritaprevir (150 mg) / ritonavir (100 mg) and ombitasvir (25 mg) {Querevo} + Ribavirin	B2: Ledipasvir 90 mg + Sofosbuvir 400 mg {Harvoni} + Ribavirin
Basis of recommendation	PEARL-I (GT-4); AASLD-I-LB	SOLAR-2 (GT-4); AASLD-I-LB ; EASL A1
Alternative Protocol 1	B2: Ledipasvir 90 mg + Sofosbuvir 400 mg {Harvoni} + Ribavirin	D3: Daclatasvir (Daklinza) 60 mg + Sofosbuvir (Sovaldi) 400 mg + Ribavirin
Basis of recommendation	SYNERGY (GT-4); ION-1 (GT-1); AASLD IIb-LB	ALLY-1(GT-1); AASLD-I-LB; EASL A1
Alternative Protocol 2	C2: Simeprevir (Olysio) 150 mg + Sofosbuvir (Sovaldi) 400 mg + **Ribavirin in the presence of cirrhosis**	
Basis of recommendation	COSMOS(GT1); EASL B2 EASL B2	

Ribavirin dose (4)	Protocols B,C,E 2: Body weight- based 1000 mg (< 75 kg) OR 1200 mg(>75kg) daily; Protocol D3: Daily fixed dose 600 mg	
Treatment duration with RBV	12 Weeks	
Treatment duration without RBV	12 Weeks OR 24 Weeks in the presence of cirrhosis	24 Weeks
Remarks		Modify doses of CyA, TAC, SIR, EVE according to blood levels Restrict protocol E(5)

eGFR * > 30ml /min /1.73 sqm

On Conservative Rx or Dialysis			
	No Cirrhosis	Compensated Cirrhosis(2)	Decompensated Cirrhosis(3) Decompensated Cirrhosis(3) Decompensated Cirrhosis(3)
Selected protocol	E2: Paritaprevir (150 mg) / ritonavir (100 mg) and ombitasvir (25 mg) {Querevo} + Ribavirin		D3: Daclatasvir (Daklinza) 60 mg + Sofosbuvir (Sovaldi) 400 mg + Ribavirin
Basis of recommendation	RUBY-1(GT-1); AASLD-lib-LB; EASL A1		ALLY-1(GT-1); AASLD-I-LB; EASL A1
Alternative Protocol 1 Basis of recommendation			

	C1*: Simeprevir (Olysio) 150 mg + Sofosbuvir (Sovaldi) 200 mg **without Ribavirin** Ram et al (Ref 32)		
Alternative Protocol 2 Basis of recommendation			
Ribavirin dose (4)	200 mg daily to be reduced if intolerated to 200 mg 3 times weekly. If on dialysis, 200 mg 4 hours before dialysis 3 times weekly		
Treatment duration with RBV	12 Weeks		
Treatment duration without RBV	12 Weeks	24 Weeks	24 Weeks
Remarks			avoid protocol E

* eGFR: estimated glomerular filtration rate; RBV: Ribavirin

* CyA:Cyclosporin-A; TAC:Tacrolimus; SIR:Sirolimus; EVE:Everolimus

(1) Estimated by MDRD (4) equation
(2) > F3 by fibroscan or equivalent chemical model
(3) Child pugh score class B -7 or higher
(4) Withdraw if not tolerated or hemoglobin level drops by 2 gm / dl despite Erythropoeitin treatment
(5) Use only by a transplant expert

eGFR * < 30ml /min /1.73 sqm

Transplanted			
	No Cirrhosis	Compensated Cirrhosis(2)	Decompen-sated Cirrhosis(3) Decompen-sated Cirrhosis(3) Decompensated Cirrhosis(3) De-compensated Cirrhosis(3)
Selected protocol Basis of recommen-dation	D3: Daclatasvir (Daklinza) 60 mg + Sofosbuvir (Sovaldi) 400 mg + Ribavirin ALLY-1(GT-1); AASLD-I-LB; EASL A1		
Alternative Protocol 1 Basis of recommen-dation	----------		
Alternative Protocol 2 Basis of recommen-dation	----------		
Ribavirin dose (4)	200 mg daily to be reduced if intolerated to 200 mg 3 times weekly. If on dialysis, 200 mg 4 hours before dialysis 3 times weekly		
Treatment duration with RBV	12 Weeks		
Treatment duration with-out RBV	12 Weeks	24 Weeks	24 Weeks
Remarks	Modify doses of CyA, TAC, SIR, EVE according to blood levels		
	Restrict protocol E(5)		avoid protocol E

* CyA:Cyclosporin-A; TAC:Tacrolimus; SIR:Sirolimus;EVE:Everolimus
(1) Estimated by MDRD (4) equation
(2) > F3 by fibroscan or equivalent chemical model
(3) Child pugh score class B -7 or higher
(4) Withdraw if not tolerated or hemoglobin level drops by 2 gm / dl despite Erythropoeitin treatment
(5) Use only by a transplant expert

Cirrhotic Ascites

I- Management:

- **Abstinence from alcohol consumption.**
- **Bed rest.**
- **Dietary sodium restriction:**
  - Diet containing 88 mmol/ day (2ooomg/day) is currently recommended for patients with ascites. Diets that have even lower salt contents are not well tolerated.
  - Fluid restriction in patients with ascites is usually not required. It should only be used in patients with serum sodium < 120 mmol/L.
- **Diuretics (single morning doses):**
  - The usual starting doses of diuretics are 100 mg of spironolactone and 40 mg furosemide.
  - Doses can be titrated up to a maximum of 400 mg of spironolactone and 160 mg of furosemide. A ratio of 100:40 usually maintains normokalemia compliance with and response to sodium
  - restriction and diuretics can be evaluated by daily weights and 24-hour urine collection for sodium. Completeness of urine collection is indicated by urinary creatinine levels of 15-20 mg/kg in males and 10 -15 mg/kg in female. Weight loss should be limited to 0.5 kg per day. More rapid weight loss can cause hypovolemia and renal insufficiency, as fluid resorption from the peritoneal cavity is limited to 700 mL per day. Patients with massive edema can tolerate more rapid fluid loss until the edema has resolved. Diuretics should be discontinued and consideration should be given to the use of second line therapy if there is evidence of encephalopathy, if serum sodium is < 120 mmol/L
  - despite fluid restriction, or if serum creatinine is > 2.0 mg/dL (180 micromoles [mcmol]/day).
- **Paracentesis:**

- Refractory ascites is subdivided into diuretic-resistant and diuretic-intractable ascites diuretic resistant ascites usually requires a period of observation on maximal medical therapy to ensure diuretic resistance, which may take up to several weeks. A recent study showed that a single dose of 80 mg of intravenous furosemide and subsequent random urine sodium of < 50 mmol/L is
- indicative of refractory ascites, compared with those cases of diuretic responsive ascites, where the serum sodium is always > 80 mmol/L, with no overlap between the 2 groups. Refractory ascites portends a poor prognosis and requires second-line therapy, such as large-volume paracentesis,
- transjugular intrahepatic portosystemic shunts (TIPS), or liver transplantation.
- A single large volume paracentesis followed by diet and diuretic therapy is appropriate treatment for diuretic- sensitive patients with tense ascites. Repeated large volume paracentesis (4 L-6 L) is safer and more effective for the treatment of tense ascites compared with larger than usual doses of diuretics.
- Total paracentesis has also been shown to be safe. Paracentesis > 10 L should not be performed more often than every 2 weeks.
- The only absolute contraindication to paracentesis is clinically evident fibrinolysis and disseminated intravascular coagulation.
- Severe coagulopathy and thrombocytopenia (INR > 2 or platelet count < 50) may need correction prior to the procedure to minimize the risk of bleeding. Puncture site. Albumin is

commonly used for intravenous plasma expansion after large-volume therapeutic paracentesis (> 5 L-6 L). Six to 8 g of albumin/L of ascetic fluid removed is administered intravenously during or after the procedure to prevent relative hypovolemia.

- **A peritoneovenous shunt**
  - Is a surgically inserted tube that connects the peritoneal cavity to the superior vena cava along subcutaneous tissue, allowing one-way passage of ascitic fluid from the peritoneal cavity back into the circulation. It is recommended only for diuretic resistant patients who are not candidates for transplant and who are not candidates for serial therapeutic paracentesis.
- **TIPS**
  - Is a side to side portocaval shunt, TIPS has become another option for the treatment of refractory ascites. A flexible metal prosthesis is used to bridge a branch of the hepatic and portal veins and is effective in reducing sinusoidal pressure. The procedure is performed percutaneously under radiologic guidance and obviates the need for surgery. It is recommended that coagulopathy (INR > 2 and platelet count < 50 x109/L) be corrected first if indicated, and that paracentesis be performed in patients with tense ascites prior to the procedure. Child-Pugh class C patients with ascites are less likely to respond to TIPS, and are generally not recommended for TIPS insertion.
  - Reported rates of shunt occlusion range from 23% to 87% within the first year. It is recommended that ultrasonographic screening be performed at 24 hours after TIPS insertion, at 6 weeks, 3 months, 6 months, and every 6 months thereafter. Late TIPS complications include encephalopathy in 30% of cases.
  - Absolute contraindications for TIPS insertion include serum bilirubin > 85 mcmol/L (5 mg/dL), INR > 2, functional renal disorder with serum creatinine > 250 mcmol/ (2.8 mg/dL), intrinsic renal disease with urine protein > 500 mg/24 hr or active urinary sediment, Grade III or IV hepatic encephalopathy, cardiac disease, portal vein thrombosis, noncompliance with sodium restriction, or the presence of carcinoma that is likely to limit the patient's lifespan to less than 1 year.
- **Liver transplantation**
  - Is the only definitive treatment for ascites and the only treatment that has been clearly shown to improve survival. Patients with cirrhosis who develop ascites should be assessed for possible liver transplantation because of their poor prognosis. Patients who develop renal dysfunction (GFR < 50 mL/min) do much worse after liver transplantation (80% vs 50% survival at 15 months, P< .05).Therefore, given the latter, every effort should be made to transplant patients prior to the onset of renal dysfunction. Other poor prognostic indicators include mean arterial pressure < 82 mmHg, urinary sodium excretion of < 1.5 mEq/day, plasma norepinephrine levels of > 570 pg/mL, poor nutritional state, presence of hepatomegaly, and serum albumin < 25 g/L.

Hepatic Encephalopathy

I- Definition:

Symptoms of neurologic, psychologic and motor disturbance that may occur as a complication of acute, sub-acute or chronic liver failure

II- Precipitating factor:

Hypokalemia: e.g. diarrhea, vomiting, diuretic overdose, hyponatremia, infection, GIT bleeding, constipation, dietary protein overload

III- Clinical features:

HE passes in the following stages:

Stage 0: sub clinical with minimal changes in memory, concentration, and coordination

Stage1: inversion of sleep wake pattern – insomnia – trivial lack of awareness.

Stage2: confusion – bizarre behavior – slurred speech – drowsiness– asterixis – apathy

Stage3: lethargy – disorientation in place and time

Stage4: Coma

IV- Diagnosis:

- Elevated blood ammonia level is the best characterized neurotoxin that precipitates hepatic encephalopathy. However, an elevated serum ammonia concentration is not required to make the diagnosis and is not specific for hepatic encephalopathy.
- Rapid response to specific treatment of hepatic encephalopathy supports the diagnosis.
- Brain CT and MRI rule out intracranial lesion when the diagnosis of hepatic encephalopathy in question.
- Serum laboratory testing to rule out metabolic abnormalities

Differential diagnosis:

1- Intracranial lesion e.g.: bleeding, stroke, and tumor.

2- Infection e.g.: meningitis, encephalitis, abscess

3- Metabolic encephalopathy e.g.: hypoglycemia ,uremia, hypercarpnia

4- Toxic encephalopathy from drugs as sedative ,hypnotic ,antipsychotic.

V- Treatment

1- Exclude non hepatic causes of altered mental function.

2- Correction of precipitants of encephalopathy e.g. Correction of hypovolemia, Correction of electrolyte disturbances, Management of GIT bleeding and stop diuretics

3- Treatment of infection.

E.g. Cefotaxime (2g/8hr)for 7 days Or Ceftriaxone (2g/12hr) for 7days Or Levofluxacin (750 mg IV/day) for 7 days in Spontaneous bacterial peritonitis.

4- Avoid medication that depress CNS function e.g. Benzodiazepam. Patient with sever agitation may receive Haloperidol.

5- Patient with sever encephalopathy grade 3 , 4 who are at risk of aspiration should undergo prophylactic endotracheal intubation managed in ICU

6- In acute liver failure brain edema associated with swelling of grey matter and with normal renal function treated with **Mannitol 20%:** 1 g/kg once over 30 minutes then 0.25g/kg every 4 hrs for 24-48 hrs (renal functions within normal limits)(max. 2 days because rebound intracranial tension may occur

7- Measures to decrease intestinal ammonia production

A- Diet:

- Stop animal protein till improvement.

- Patients with HE should avoid prolonged periods of dietary protein restriction and receive the maximum tolerable protein intake, aiming at 1.2 g of protein/kg/day (range 1–1.5)
- Diet containing vegetable protein better tolerated than diet rich in animal protein

B - Short chain amino acid: hepatic encephalopathy may be caused by decreased plasma ratio of branched chain amino acid, but there is no significant evidence for its beneficial effect with hepatic encephalopathy. It is used for nutritional supplement.

N.B:

Aminoleban® is contraindicated in Patients with severe renal disorder, while Kidmin ® is indicated in patients with acute or chronic renal failure

C- Lactulose: nonabsorable synthetic disaccharide inhibit intestinal ammonia production

- Dose: 30 ml orally every 6-8 hour or by nasogastric tube
- Lactulose (300 ml completed to 1 L of water) as retention enema for one hour every 6 hours.

D- Antibiotics:

- **Rifaximin**550mg tab / 12 hour
- Or **Metronidazol**e 250 mg /8hr for 7 days
- Or **Neomycin** 500mg tab/ 8hfor 7 days (not commonly used due to its nephrotoxicity)

8- Measures to increase ammonia clearance:

L- Ornithine L- aspartate (Amp = 5gm) (20gm/12hr in 500ml glucose 5%) regarding normal kidney function test.

9- Flumazenil (Anexate®): (1 mg bolus IV) a Benzodiazepam antagonist has beneficial effect if Benzodiazepam precipitate coma if used as sedative or for endoscopic evaluation

10- Zinc supplementation: has been suggested as having potential value in some patients with chronic or recurrent hepatic encephalopathy, but little evidence exists to document its effectiveness.

Hepatorenal Syndrome

Definition:

HRS is a form of acute or subacute renal failure characterized by severe renal vasoconstriction, which develops in decompensated cirrhosis or acute liver failure.

HRS is a circulatory disorder (splanchnic vasodilatation due to mediators e.g: NO with subsequent renal vasoconstriction)

Clinical presentation:

- Oliguria
- Generally benign urine sediment
- Very low rate of sodium excretion
- Progressive rise in plasma creatinine

Types of Hepatorenal Syndrome

Based upon the speed of onset of renal failure, two forms of Hepatorenal syndrome have been described:

- Type I Hepatorenal syndrome (more serious type)
- Type II Hepatorenal syndrome (less severe)

Type I Hepatorenal syndrome:

- At least a 50% lowering of the creatinine clearance to a value below 20 ml/min in less than a two week period or
- At least a two fold increase in serum creatinine to a level greater than 2.5 mg/dl (221µmol/l).
- Commonly oliguric.
- Median survival time is only 2 weeks.

Type II Hepatorenal syndrome:

- Characterized by ascites that is resistant to diuretic
- Less severe than Type I
- Associated with relatively preserved liver function
- Median survival time is about 6 months

Diagnostic criteria

Major:

- Chronic or acute liver disease
- Low GFR (plasma creatinine >1.5 mg/dl, creatinine clearance < 40 ml/min)
- Absence of any other apparent cause
  - Shock
  - Ongoing bacterial infection particularly SBP
  - Fluid loss
  - Current or recent treatment with nephrotoxic drugs
  - Ultrasonic abnormality as obstruction or parenchymal renal disease
- Lack of sustained improvement
  - Withdrawal of diuretics
  - Expansion of plasma volume (1-1.5 L of isotonic saline, albumin for ≥ 2 days)
- Low urine protein (< 500 mg/day)

Minor:

- Urine volume < 500 ml/24 hrs.
- Urine sodium < 10 meq/L
- Urine osmolality > plasma osmolality

- Urine erythrocytes < 50/ HPF
- Serum sodium < 130 meq/L

Management of Hepatorenal syndrome

Prevention

1- Prophylaxis against bacterial infections (Antibiotic Prophylaxis)

2- Volume expansion:

- To prevent the development of renal failure in patients who develop spontaneous bacterial peritonitis it is now recommended that these patients should be given plasma volume expansion with 20% albumin (1-1.5g/kg over 1-3 days) at diagnosis to prevent circulatory dysfunction, renal impairment and mortality.
- Use of salt poor albumin as fluid replacement in patients undergoing large volume paracentesis (8 g for each liter of ascitic fluid removed) is known to prevent paracentesis induced circulatory dysfunction.

3- Judicious use of diuretics:

- Identifying the lowest effective dose of a diuretic for any individual patient is important, as diuretic induced renal impairment occurs in about 20% of patients with ascites.
- Diuretic induced renal impairment is usually moderate and rapidly reversible following diuretic withdrawal.

4- Avoid use of nephrotoxic drugs (e.g. aminoglycosides,NSAID)

Treatment of Hepatorenal syndrome

1- Initial management:

- Renal function rarely recovers in the absence of hepatic recovery.
- The key goal in the management of these patients is to exclude reversible or treatable lesions (mainly hypovolemia), and to support the patient until liver recovery (e.g. from alcoholic hepatitis, hepatic regeneration (e.g. acute liver disease) or liver transplantation.
- The treatment of HRS is directed towards reversing the hemodynamic changes induced by reduced renal perfusion pressure, stimulated sympathetic NS, and increased synthesis of humoral and renal vasoconstrictor factors.
- Precipitating factors should be recognized and treated, and nephrotoxic drugs discontinued.
- All patients should be challenged with up to 1.5 liters of fluid such as normal saline or human albumin solution to assess the renal response as many patients with subclinical hypovolemia will respond to this simple measure.
- Non nephrotoxic broad spectrum antibiotics should be given regardless of evidence of sepsis, as undiagnosed delay in effective treatment of infection may increase mortality.

2- Optimize blood pressure:

- If mean arterial pressure is low (< 70 mmHg), it should be increased to about 85-90 mmHg or until urine output improves by infusing a vasopressor drug.
- Vasopressin, Ornipressin, Terlipressin or Noradrenalin infusion have all been used with some success.
- On physiological grounds it seems sensible to use either Ornipressin or Terlipressin as first line.

3- Paracentesis:

- Drainage of tense ascites may temporarily improve renal hemodynamics and renal function by decreasing renal venous pressure, there may be a modest fall in blood pressure following Paracentesis.

- The fall in renal perfusion pressure due to decreased arterial pressure may of course counteract any beneficial effect and should therefore be counterbalanced by pressor support as necessary.

4- Pharmacological treatment:

By splanchnic vasoconstriction, or directly using renal vasodilators

- -Dopamine was the first drug used due to its vasodilator effect when given in suppressor doses, it gives response in <5% of cases.
- -It is therefore better to give a 12 hours trial of dopamine and stop treatment if there is no improvement in urine output.
- -Ornipressin is a vasoconstrictor of the splanchnic vasculature thus increasing blood and renal perfusion pressure.
- -Using a combination of Ornipressin and albumin infusion resulted in an increase in mean arterial pressure and normalization of renal function.
- -HRS didn't recur after cessation of therapy in patient who finished the 15 days treatment period.
- -Terlipressin (Glypressin) is a synthetic analogue of vasopressin with intrinsic vasoconstrictor activity. Given by I.V administration every 4 hours in a total dose of 2 mg /day. Long term administration with albumin for two weeks reversed HRS in 7of 9 patients. No side effects were reported.
- -Midodrine and Octreotide:
  - Octreotide is a long acting analogue of somatostatin which has a variable effect on splanchnic hemodynamics.
  - Midodrine is a sympathomimetic drug. Combined long term administration of Midodrine and Octreotide, led to improvement of renal function.

5- Renal support:

- Renal support should only be offered where there is a realistic possibility of hepatic regeneration, hepatic recover, or liver transplantation. Renal support otherwise merely prolong the dying process.
- Renal support is generally given as continuous hemofiltration. -Intermittent hemodialysis causes hemodynamic instability in some patients.
- The molecular adsorbent recirculating system (MARS) is a modified dialysis method using albumin containing dialysate that is recirculated and perfused online through charcoal and anion exchanger columns.
- MARS enables the elective removal of albumin bound substances. it gives significant improvement in standard liver and kidney tests.

6- Surgical maneuvers, TIPS, and liver transplantation:

- -TIPS could serve as a bridge to liver transplantation allowing kidney function to recover and clinical status to improve.
- -The only effective and permanent treatment of HRS is liver transplantation.

Portal hypertension and GIT bleeding

One of the major complications of portal hypertension is bleeding from esophageal varices.
Bleeding from gastric or duodenal varices as well as bleeding from colonic varices or from portal hypertensive gastropathy is less common.

Primary prophylaxis of bleeding from esophageal varices

It is defined as a therapeutic intervention that aims at the prevention of the first variceal hemorrhage.

- Every patient with newly diagnosed liver cirrhosis should undergo upper endoscopy for screening of esophageal and/or gastric varices. In patient with esophageal varices with a diameter of more than 5 mm, prophylactic treatment should be initiated.
- Prophylactic treatment is not necessary when only small varices (diameter below 5 mm) are present.
- Nevertheless, endoscopic follow up is mandatory.

Prophylaxis / Therapy

Standard modalities are drug therapy with non-selective beta blockers and endoscopic variceal band ligation (VBL) of varices.

- Non-selective beta blockers like Propranolol and Nadolol were introduced for primary prophylaxis.
- An effective alternative treatment for primary prophylaxis is endoscopic VBL.

Acute bleeding from esophageal varices

Dependent on the amount of lost blood, patients might be hemodynamic instable and present in hemorrhagic shock.

- The management of patients with acute variceal bleeding includes not only treatment and control of active bleeding but also the prevention of rebleeding, infections and renal failure.
- Patients should be hemodynamically stabilized and receive medical treatment with vasopressors and antibiotic treatment (quinolones)
- High risk patients with advanced liver disease (ascites, encephalopathy, jaundice, malnutrition) or previous therapy with quinolones should receive ceftriaxone.
- Transfusion of blood should be done with caution with a target hemoglobin level between 8 to 9 g/dl; restrictive transfusion strategies are associated with better survival.
- Available therapy options include medical and endoscopic treatment, balloon tamponade, placement of fully covered self-expandable metallic stents, transjugular intrahepatic portosystemic
- shunts (TIPS) and surgical shunts. Nowadays, the initial approach is a combination of vasoactive drugs, antibiotics and endoscopic therapy.

Medical therapy

Drugs currently in use are vasopressin, somatostatin and Terlipressin.
Relevant adverse effects include systemic vasoconstriction with serious implications like mesenteric or myocardial ischemia. Application of vasopressin in combination with nitrates
reduces the side effects associated with vasoconstriction.

Surgery

Surgical procedures in patients with acute or recurrent variceal bleeding are limited to a very small portion of patients in whom medical and / or endoscopic control of bleeding was not achievable and TIPS was not an option because of technical or anatomical problems (e.g. complete thrombosis of the portal vein). Possible procedures are portosystemic shunt operation or staple transection of the esophagus.

Secondary prophylaxis of esophageal variceal bleeding

Prevention of rebleeding is a major goal.

- **Medical therapy**

Most of the studies found a reduction of the rebleeding risk as well as a reduction in mortality after using non selective beta blockers propranolol or Nadolol.

- **Endoscopic therapy**

The combination of VBL and medical therapy is an even more promising approach for secondary prophylaxis.

- **Transjugular intrahepatic portosystemic shunt**
- **Surgery**

Shunt surgery has been shown to be effective in the prophylaxis of rebleeding from esophageal varices.

Gastric varices and hypertensive gastropathy:

The diagnosis of gastric varices is made by endoscopy. In case of doubt of the diagnosis, endosonography with Doppler sonography allows further differentiation. If only isolated gastric varices are present, the exclusion of portal or splenic vein thrombosis as the underlying cause is mandatory.

Patients with gastric varices studied the injection of cyanoacrylate for primary prophylaxis of bleeding from large gastric varices and found the injection of cyanoacrylate to be safe and effective in primary prophylaxis.

Bleeding from gastric varices:

Therapy with Terlipressin or somatostatin is recommended. The endoscopic treatment of choice is injection with cyanoacrylate. Known complications of cyanoacrylate injection include mucosal ulcerations as well as thromboembolism. TIPS insertion is highly effective with control of bleeding in more than 90% of patients and should be considered in patients in whom endoscopic therapy fails.

Portal hypertensive gastropathy:

The diagnosis is made by endoscopy. Typical signs are mosaic, also called snakeskin, pattern of erythema. More severe forms present with red punctate erythema, diffuse hemorrhagic lesions and / or brown spots that indicate submucosal hemor-rhage. The therapy of acute bleeding from Portal hypertensive gastropathy is mainly based on drugs that decrease portal pressure (Propranolol in a dose of 24 to 480 mg per day, Octreotide, vasopressin and PPI)

Terlipressin was also shown to be effective in acute bleeding from portal hypertensive gastropathy.

If medical therapy fails, TIPS insertion or surgical shunt is an option.

In the secondary prophylaxis of bleeding from portal hypertensive gastropathy, propranolol is effective in the prevention of rebleeding.

Gastric antral vascular ectasia syndrome (GAVE):

- It accounts for 4% of non variceal upper GI bleeding.
- Linear red streaks running longitudinally in the gastric antrum are apparent (watermelon stomach).
- In patients with liver cirrhosis the mucosal pattern is often more diffuse (honeycomb stomach).
- Different drugs have been used in the treatment of bleeding from GAVE (Estrogen-progesterone, Octreotide)
- Treatment consists mainly of endoscopic measures like argon plasma coagulation (APC), or laser photoablation of the lesions using (YAG) laser.
- The efficacy of APC in the treatment of bleeding from GAVE is very high.

Ectopic varices:

- Ectopic varices are dilated Porto-venous vessels of the gastrointestinal mucosa that are located outside of the esophagus or the stomach.
- Endoscopy is the most important diagnostic tool.
- Examination of the duodenum is mandatory. Examination of the jejunum makes double-balloon enteroscopy necessary.
- Colonoscopy is the principal method for the diagnosis of colonic varices.
- Therapy of ectopic varices is mainly based on sclerotherapy or injection therapy.
- Band ligation may be useful for temporary hemostasis in duodenal varices. Additional treatment following band ligation for duodenal varices is therefore mandatory.
- Surgery and TIPS are effective therapy measures in recurrent bleeding from ectopic varices.

Common parasitic diseases

Toxoplasmosis

I- Definition:

Toxoplasmosis is caused by infection with the protozoan Toxoplasma gondii, an obligate intracellular parasite.

II- Life cycle of Toxoplasma gondii:

The only known definitive hosts for Toxoplasma gondii are cats, Unsporulated oocysts are shed in the cat's feces, oocysts take 1-5 days to sporulate in the environment and become infective.

Intermediate hosts in nature (including birds and rodents) become infected after ingesting soil, water or plant material contaminated with oocysts, oocysts transform into tachyzoites (the rapidly dividing form observed in the acute phase of infection) shortly after ingestion. These tachyzoites localize in neural and muscle tissue and develop into tissue cyst bradyzoites (the slowly growing form observed in tissue cysts)

III- Routes of infection:

Humans can become infected by any of several routes:

- Eating undercooked meat of animals harboring tissue cysts (bradyzoites).
- Consuming food or water contaminated with cat feces oocysts
- Blood transfusion (tachyzoites) or organ transplantation (bradyzoites).
- Transplacental transmission (tachyzoites) from mother to fetus.
- In the human host, the parasites form tissue cysts (bradyzoites), most commonly in skeletal muscle, myocardium, brain, and eyes; these cysts may remain throughout the life of the host.

1-Acute toxoplasmosis in immunocompetent persons

Healthy people who become infected with Toxoplasma gondii often do not have symptoms However, the parasite remains in their body in an inactive state. It can become reactivated if the person becomes immunosuppressed.

Symptomatic disease may be characterized as follows:

- Lymphadenopathy
- Fever, malaise, night sweats, and myalgias have been reported
- Retinochoroiditis is reported

2-Acute toxoplasmosis in immunodeficient hosts

The disease in these patients may be newly acquired or a reactivation

It may be characterized as follows:

- CNS toxoplasmosis:
  Brain involvement (toxoplasmic encephalitis), with or without focal CNS lesions, is the most common manifestation of toxoplasmosis in individuals with AIDS. It is almost always due to
  reactivation of old lesions.
- Patients may report visual changes
- They may have signs and symptoms similar to those observed in immunocompetent hosts (flulike symptoms and lymphadenopathy)
- Myocarditis and pneumonitis are reported.

Symptoms associated with reactivation toxoplamosis are dependent on the tissue or organ affected.

3-Congenital toxoplasmosis

- Generally if a woman has been infected before becoming pregnant, the unborn child will be protected because the mother has developed immunity.
- If a woman is pregnant and becomes newly infected with Toxoplasma during or just before pregnancy, she can pass the infection to her unborn baby.
- The damage to the unborn child is often more severe the earlier in pregnancy the transmission occurs. Potential results can be:
  - Miscarriage
  - Stillborn child
  - Infected newborns have anemia, thrombocytopenia, and jaundice at birth.
  - Microcephaly has been reported.
  - Infants infected before birth often show no symptoms at birth but may develop them later in life with potential blindness (due to retinochoroiditis), mental disability, and seizures.

IV- Laboratory diagnosis:

- Demonstration of tachyzoites in lymph node tissue sections or smears of body fluids establishes the diagnosis of acute toxoplasmosis.
- Histological demonstration of cysts containing bradyzoites confirms prior infection with T. gondii, but is nondiagnostic for acute infection
- Serologic testing has become the routine method of diagnosis :
  - -Diagnosis of acute infection with T. gondii can be established by the detection of the simultaneous presence of IgM and IgG antibodies to toxoplasma in the serum (available in Egyptian labs).
  - A negative IgM test essentially excludes recent infection, but a positive IgM test is difficult to interpret because Toxoplasma-specific IgM antibodies – beside lacking specificity-may be detected for as long as 18 months after acute acquired infection.

NB: Double sandwich IgM-ELISA method is sensitive, specific, and precludes the false positive (available in reference labs).

- Positive IgG titers can be detected as early as two to three weeks after infection. These titers peak at six to eight weeks and decline slowly to a new baseline level that persists for life. It is necessary to measure the serum IgM titer in concert with the IgG titer to better establish the time of infection.
- IgG antibodies avidity (available in Egyptian labs): are used to discriminate between recently acquired infection and that obtained in the more distant past.The presence of high avidity antibodies essentially rules out infection acquired in the recent three to four months. Low IgG avidity antibody results should not be interpreted as diagnostic of recently acquired infection.
- These low avidity antibodies can persist for months to one year or longer.
- This is most useful in pregnant women in their first months of gestation who have a positive test for both IgG and IgM toxoplasma antibodies.
- The double-sandwich IgA ELISA (available in reference labs) is more sensitive than the IgM ELISA for detecting congenital infection in the fetus (sample from cord blood) and newborn. Local antibody production in the eye has been successfully used for diagnosis of ocular infection

IgG Result	IgM Result	Report/interpretation for humans
Negative	Negative	No serological evidence of infection with Toxoplasma.
Negative	Equivocal	Possible early acute infection or false-positive IgM reaction. Obtain a new specimen for IgG and IgM testing. If results for the second specimen remain the same, the patient is probably not infected with Toxoplasma.
Negative	Positive	Possible acute infection or false-positive IgM result. Obtain a new specimen for IgG and IgM testing. If results for the second specimen remain the same, the IgM reaction is probably a false-positive.
Equivocal	Negative	Indeterminate: obtain a new specimen for testing or retest this specimen for IgG in a different essay.
Equivocal	Equivocal	Indeterminate: obtain a new specimen for both IgG and IgM testing.
Equivocal	Positive	Possible acute infection with Toxoplasma. Obtain a new specimen for IgG and IgM testing. If results for the second specimen remain the same or if the IgG becomes positive, both specimens should be sent to a reference laboratory with experience in diagnosis of toxoplasmosis for further testing.
Positive	Negative	Infected with Toxoplasma for six months or more.
Positive	Equivocal	Infected with Toxoplasma for probably more than 1 year or false-positive IgM reaction. Obtain a new specimen for IgM testing. If results with the second specimen remain the same, both specimens should be sent to a reference laboratory with experience in the diagnosis of toxoplasmosis for further testing.
Positive	Positive	Possible recent infection within the last 12 months, or false-positive IgM reaction. Send the specimen to a reference laboratory with experience in the diagnosis of toxoplasmosis for further testing.

- **NB:** Serological determination of active central nervous system toxoplasmosis in immunocompromised patients is not possible at this time. Toxoplasma-specific IgG antibody levels in AIDS patients often are low to moderate, but occasionally no specific IgG antibodies can be detected. Tests for IgM antibodies are generally negative
- PCR (available in Egyptian labs): Is highly sensitive, specific, and has clinical utility in the diagnosis of congenital, ocular, cerebral, and disseminated toxoplasmosis.
- Real time PCR of the amniotic fluid to detect the B1 gene of the parasite Peripheral blood, cerebrospinal fluid, and urine should be considered for PCR examination in any newborn, suspected to have congenital disease. PCR of vitreous or aqueous fluid is helpful in establishing diagnosis in patients with atypical retinal lesions.

V- Treatment:

Currently recommended drugs in the treatment of toxoplasmosis act primarily against the tachyzoite form of T gondii; thus, they do not eradicate the encysted form (bradyzoite).

Immunocompetent adults:

- Immunocompetent adults and children who have only lymphadenopathy do not require specific therapy unless they have persistent, severe symptoms.
- Patients with ocular toxoplasmosis should be treated for one month with pyrimethamine plus either sulfadiazine or clindamycin.

Maternal infection:

- Spiramycin should be initiated immediately after diagnosis of recently acquired maternal infection (based on serology). It is recommended for the first and early second trimesters.
- Pyrimethamine / sulfadiazine for the late second and third trimesters, for women with confirmed fetal infection(by PCR of amniotic fluid at 18 gestation weeks). Folinic acid is added to regimens to reduce bone marrow suppression.

N.B

- Maternal infection does not necessarily result in fetal infection.
- pregnant women should have monthly ultrasound examinations for the entire pregnancy
- In most countries, treatment of the fetus is followed by treatment of the new born throughout the first year of life.

Immunocompromised patients (toxoplasmosis is rapidly fatal):

Antiparasitic treatment should be considered for all symptomatic, seropositive, immunocompromised patients suspected to have toxoplasmosis.

When clinical manifestations suggest involvement of the brain, spinal cord, or both, neuroimaging studies such as CT or MRI are mandatory.

Empiric anti-T. gondii treatment is an accepted practice for patients with multiple ring enhancing brain lesions (usually established by MRI), positive IgG antibody titers against T. gondii, and advanced immunodeficiency; a clinical and radiological response to specific anti-T. gondii treatment is judged supportive of the diagnosis of CNS toxoplasmosis (Patients with cerebral toxoplasmosis usually improve by more than 50% of their baseline neurological examination in seven to ten days.)

Treatment of toxoplasmosis in immunocompromised patients is combination of pyrimethamine/sulfadiazine and folinic acid.

Clindamycin can be used instead of sulfadiazine.

Trimethoprim / sulfamethoxazole appears to be equivalent to pyrimethamine / sulfadiazine in patients with AIDS.

Treatment is recommended for 4 to 6 weeks after resolution of all signs and symptoms.
• After treatment of the acute phase (primary or induction treatment) in immunocompromised patients, maintenance therapy (secondary prophylaxis) should be started, usually with the same regimen that was used in the acute phase, but at half doses.
At present, maintenance treatment is continued for the life of the patient or until the underlying immunosuppression has ceased. In patients with AIDS, primary and secondary prophylaxis are generally discontinued when the patients' CD4 count has returned to more than 200 cells per µl and the HIV PCR peripheral blood viral load has been reasonably controlled for at least six months.

VI- Doses:

- Pyrimethamine (100 mg loading dose PO followed by 50 mg daily)
- Sulfadiazine (2 to 4 g / day PO in 4 divided doses)
- Clindamycin (300 – 600 mg PO four times daily)
- Spiramycin (1g (3,000,000 IU) orally every eight hours without food)
- Folinic acid (10 to 25 mg orally daily).

Malaria

I) Definition:

It is a parasitic disease caused by one or more of the following species : Plasmodium falciparum , plasmodium vivax , plasmodium ovale , plasmodium malariae and plasmodium knowlesi , but P. falciparum is considered the most dangerous and severe and may be fatal .

N.B:

The recently appreciated extent of human infections from plasmodium Knowlesi, a natural pathogen of Macaque Monkeys, this parasite has been proposed to be a fifth human Malaria parasite and is important cause of human Malaria in parts of southeast Asia ,also plasmodium knowlesi is responsible for significant morbidity and mortality in Malaysia.

II) Modes of Transmission :

- Malaria is transmitted by the bite of a blood-feeding female anopheles mosquito.
- Also, blood transfusion and infected syringe in drug user addicts can transmit infection.

III) Diagnosis:

Incubation period:

- Varies 10 – 14 days in P. vivax, P. ovale, P. falciparum.
- Varies 18 days up to 6 weeks in P. Malaria infection..

Case Definition :

a) Suspected case.

Patient with unexplained fever and/or other clinical symptoms for example:
(Headach- Back pain - Chills - Sweeting - Myalgia - Nousea - Vomiting – Spleno-megally- Anaemia).
And history of travel or residence in a endemic area or area where the vector of transmission is present.

b) Probable case

Is positive serological case by RDT.

c) Confirmed case

Is clinical suspected or probable case with detection of malaria parasites (plasmodium species) on smear and blood film.

d) Asymptomatic Malaria:

- A person with no recent history of symptoms and/or of malaria who shows laboratory confirmation of parasitemia.

IV) Medical treatment:

(A) If the patient is conscious and can take the tablets orally

(1) Quartum tablets (Artemether 20 mg +Lumefantrine 120mg)

Number of tablets , dosage time in a strip 24 tablets (6 doses in 3 days i.e . twice daily as shown in this table)						
	First day		Second day		Third day	
Weight/age	Date of onset	After 8 hours from the onset of treat-ment	After 24 hours from the onset of treat-ment	After 36 hours from the onset of treat-ment	After 48 hours from the onset of treat-ment	After 60 hours from the onset of treat-ment
5kg/3years	1 tab.	1tab.	1tab.	1tab.	1tab.	1tab.
15kg/5years	2tab.	2tab.	2tab.	2tab.	2tab	2tab.
25kg/9years	3tab.	3tab.	3tab.	3tab.	3tab.	3tab.
More than 35 kg /more than 15 years	4tab.	4tab.	4tab.	4tab.	4tab.	4tab.

N.B :

Tablets should be taken with milk or with fatty meal(Primaquine tablet 15 mg), unless the patient is pregnant or has G6PD deficiency must be careful and can give :

- 1 tablet daily in plasmodium vivax for 14 days.
- In plasmodium falciparum 1tablet for 3-5 days.

Advices for use of oral quartum tablets :

- The drug is used in falciparum and non-falciparum (uncomplicated malaria) – Used in adults and pediatrics unless there is vomiting or any other contraindications . – The drug is not used in empty stomach .
- If vomiting occurred shortly after dosage give another dose of quartum

(B) If the patient is unconscious or can not tolerate the oral tablets because of vomiting or in cases of severe malaria or presence of systemic complications :

- First line treatment :

1- Artesunate (vial 60mg) : given by IM or IV infusion 2.4 mg/ kg body weight (2-3 ampules according to BW)

Time schedule : 0 time / after 12 hours from the onset of treatment / after 24 hours / then daily single dose) 7 days treatment in cases of severe and complicated malaria . After improvement continue with the oral Quartum as in (A) until cure.

- Second line treatment :

2- Quinine (ampule 600 mg):

3- 10mg/kg added to dextrose 5% by iv infusion over 4 hours every 8-12 hours (maximum 2000 mg daily , after improvement continue with the oral quinine for 1 week .
4- Quinine tablets (300mg):
5- 10 mg/kg/ day (total 2 tablets ×3×7) + doxycycline 100 mg for one week

V) Malaria prophylaxis:

- Mefloquine (250mg) : is given to the traveler to endemic area:
- One tablet 5 days before travel during or after meal .
- Then one tablet every week at the same time (maximum 3 months)

VI) Preventive Measures:

1) Reporting:

Immediately, Malaria included in group A diseases.

2) Isolation:

3) Chemoprophylaxis:

- **Mefloquine (250 mg tablet)**
- **Dose**
  - : one tab. week before travel to endemic area.
  - : one tab. weekly time of staying.
  - : one tab. weekly for 4 weeks after return.
- **Doxycycline (100 mg tablet):** indicated in people traveling to China, Kamboudia, Veitnam.
- **Dose**
  - : one tab. started 1-2 days before travelling.
  - : one tab. daily time of staying.
  - : one tab. daily for 4 week after return.

Disease	Isolation time	Isolation precautions	Notes
Malaria	Until the the patient cure and symptoms disappear .	Blood precautions	

Leishmania

I- Definition:

- It is a parasitic disease caused by leishmanial species which are intracellular parasites with many types Cutaneous Leishmaniasis
- Visceral Leishmaniasis (Kala Azar).
- Mucosal Leishmaniasis (Muco-cutaneous L.)

II- Modes of transmission :

- Transmitted through bite of female sand fly and very rare through blood transfusion and infected syringe also through vertical transmission.

III- Diagnosis:

1) Incubation period Varies between 2-6 months and range 10 days up to 2 years or more.
2) Case Definition:

a) Suspected case:

- Visceral leshmaniasis
  - Person with fever (38 or more) with splenomegaly and/or hepatomegaly and/or lymphadenopathy of unexplained cause or history of travel or residence to endemic area where vector of transmission is present.
- Cutaneous Leshimaniasis .
  - Person with painless, slowly healing skin ulcer usually Not purulent (may be purulent) with history of exposure to sand fly or history of travel or residence to endemic area where vector of transmission is present.

b) Probable Case

Not available

c) Confirmed case

- Demonstration of Amastigote phase in stained Tissue scrapping specimen.

IV- Medical treatment:

1- Visceral leishmania:

Is present in Egypt especially in South and North Sinai and Canal cities , and it affects all ages with painless ulcers that heal spontaneously within a year and it leaves scars in the skin if not treated .

Treatment with Pentostam IM in a dose of 20mg/kg body weight (maximum 850 mg daily for 3-4 weeks .

- If no response tell your patient to take a rest for 2-3 weeks then restart the pentostam with the same dose and the schedule .
- The treatment is given in the ICU and under the doctor's supervision.
- Liposomal amphotericin B is the drug of choice and is given ia a total dose of 40 mg/kg (4mg/kg on days 1 to 5, 10, 17, 24, 31 and 38).
- Miltefosine: in treatment of relapse.

2- Cuteanous leishmaniasis :

1) In the presence of mild few ulcers (5 or less) treated as follows :

- Infiltration around the ulcers with pentostam 1-2 cm weekly until healing of ulcers .
- Cryo-cautry through :
- CO2 gas
- Nitrogen gas (the temperature reaches 70 under zero) repeated after 2 weeks.

2) In the presence of more than 5 ulcers or disseminated lesions

- Treatment is given as visceral leishmaniasis with pentostam IM 20mg /kg (maximum 850 mg daily for 3-4 weeks).
- Large ulcers may need surgical intervention.

V) Preventive Measures:

1) Reporting

Weekly, where leishmania is included in group B diseases.

2) Isolation:

- In cutaneous leishmania
- In visceral leishmania
- Blood precaution
- Also body fluids precautions.

Fascioliasis

I) Definition :

- Fascioliasis (hepatic fluke) is one of the zoonotic diseases as it also infects animals like buffalo, cows, goats, sheep, etc. Presence of encysted metacercaria in canal water and small rivers make it easy to be attached to raw vegetables during irrigation by this water or by washing vegetables in it.
- Mode of transmission: humans and animals eat raw vegetables (lettuce, radishes, etc.) to which encysted metacercariae are attached but unseen, and so they become infected with the liver fluke fasciola.

II) Clinical pictures:

Acute clinical symptoms:

- Appear from the time of penetration of the intestinal wall and liver tissues during the infective stage until the larva reaches the bile ducts.
- The patient feels intestinal symptoms such as vomiting, diarrhea, tenderness in the upper right quadrant, anorexia and fever.
- Liver enlargement and jaundice may also be found according to the severity of infection.

The chronic stage:

- Starts after larva reach the adult stage and lay eggs, in about three or four months.
- This stage continues for several years during which the patient suffers from abdominal pain, hepatomegaly, jaundice, dyspepsia and loss of appetite. Chronic stage is detected by the presence of fasciola eggs in the patient's stool.

Case Definition:

Suspected Case:

None

Probable Case:

None

Confirmed:

Laboratory confirmation by detection of fasciola eggs in the stool by microscopic examination.

III) Investigation:

- -Microscopic examination of Stool: to detect characteristic eggs
- ELISA & immunoblot tests are 95%-100% sensitive & specific sucessful treatment correlates with a decline AB titer.
- Ultrasonography
- Endoscopic retrograde cholangiopancreatography (ERCP): in case of jaundice

IV) Medical Treatment:

- Triclabendazole (Fasinex® for animal, Egaten® for human)
  Adults: 10mg/kg as a single dose.
  WHO recommends 20 mg per kg of body weight given in 2 divided doses 12-24 hours apart for one day for severe cases of fascioliasis
  Children: dosage has not been established. However, 10mg/kg orally as a single dose has been used.
  Dosage protocol of triclabendazole 10 mg/kg body weight

- **Advice all people** to put vegetables in an acetic (lemon) solution for about ten minutes and then wash them with pure running water, or put the vegetables in a solution of potassium permanganate (24 mg/liter for about 15 minutes), which will kill all the encysted metacercaria, and then wash them with pure running water. Also advise them to avoid washing vegetables in the infected canal water.

Filariasis

I) Definition and mode of transmission:

- The disease denotes infection with any of several nematodes as Wurchereria bancrofti, Brugia malayi, and Brugia temori.
- Wurchereria bancrofti nematodes live in most hot areas of the world, including Latin America, Africa, Asia and the Pacific Islands.
- Its presence increases in the rural areas where mosquitoes transmit the disease.
- Bancroftain Filariasis is an infection with the nematode Wurchereria bancrofti which normally resides in the lymphatic of infected people.
- Female worms produce microfilaria which is the infective stage to the female Culex pepians mosquito.
- This mosquito is the main transmitter and the secondary host of the lymphatic filaria parasite where it develops in the mosquito stomach and transforms into the third larval stage, which is the infective stage for humans.

Age in years	Number of DEC tab.	Number of alben-dazole tablets
Above 2-4 years	2 tab.	1 tab.
Above 4-8 years	3 tablets	1 tab.
Above 8-11 years	4 tab.	1 tab.
Above 11-14 years	5 tab.	1tab.
Above 14 years	6 tab.	1tab.

II) Clinical Features:

- The disease may be asymptomatic and parasitologically negative or positive.
- Some patients suffer from acute recurrent filarial fever, lymphadenitis, and retrograde lymphangitis.
- Some patients, who have low level or undetectable microfilaria, show chronic signs including hydrocele, chyluria, and elephantiasis of the limbs, breasts, and genitalia
- Some patients have Tropical Pulmonary Eosinophilia Syndrome, manifested by paroxysmal nocturnal asthmatic, chronic interstitial lung disease, recurrent low grade fever, profound eosinophilia, and degenerated microfilaria tissues in the blood stream (Occult Filariasis)

Case Definition:

Suspected case

Any patient suffering from acute cold like symptoms in endemic areas .

Probabol case

Patient in endemic areas with increased density of culex pipens .

Confirmed case

Laboratory confirmed case with:

- The presence of microfilaria in nocturnal peripheral blood sample
- Detection of filarial antibodies by serology .
- Clinically chronic cases which is laboratory negative .

III) Treatment:

- Should include albendazole 400 mg + DEC tablet (Diethyl carbamazine) 6mg/kg maximum 300 mg as follows .

- Exception from this schedule :
  - Children under 2 years .
  - Patients with chronic and debilitating diseases.
  - Pregnant women until delivery .
  - One dose yearly for 4-6 years until the adult worms die in the body of infected persons .

Miscellaneous

Fungal Pneumonia

Fungi account for only a small portion of community-acquired and nosocomial pneumonias. However, fungal respiratory infections generate concern in the expanding population of immunosuppressed patients. Fungal infection occurs following the inhalation of spores, after the inhalation of conidia, or by the reactivation of a latent infection. Hematogenous dissemination frequently occurs, especially in an immunocompromised host.

The diagnosis of fungal pneumonias is difficult to prove, and is often made on a presumptive basis. It relies on a combination of clinical, radiologic, and microbiological factors. Non molecular fungal markers in serum or other biological samples represent a noninvasive diagnostic tool, which can help in therapeutic decisions.

CXR: Pulmonary nodules

Treatment of fungal infection:

The type of antifungal drug employed must be selected based on the particular pathogen that is isolated or that is clinically suspected. Many classes of antifungal agents are now available, including the classic antibiotics; first, second, and third generation triazoles; and the echinocandins. Amphotericin B is less frequently used and, when used, is often given as a liposomal formulation to decrease toxicity According to the policy of AFH (see alsoH1N1, H5N1and corona virus)

- Cases with pneumonia should be admitted & reported
- Do Plain chest X-ray.
- Take throat swab for Real-time RT-PCR.
- Collect sputum and serum sample (5 cc).
- Give Oseltamivir (Tamiflu): Double the dose (and for longer duration if PCR is +ve for influenza viruses).
- Give broad spectrum antibiotics (combination therapy e.g Ceftriaxone plus azithromycin, or a respiratory quinolone).
- Referral to chest hospital if PCR is +ve for H5NI
- Do HIV-Ab if fungal pneumonia is suspected (from features of CXR) & give antifungal treatment (follow the protocol of HIV-AIDS if HIV-Ab is +ve)
- If one of the other causative viruses could be known, give an tiviral treatment (see the table above).

Anthrax

I) Definition:

- Anthrax is a rare but serious bacterial infection caused by the Gram-positive, spore-forming, bacterium Bacillus anthracis.
- Spores are very resistant to damage and can remain dormant in the soil for decades. It is primarily a disease of herbivorous mammals.
- Humans generally acquire the disease through contact with infected animals or contaminated animal products.
- Symptoms usually develop within two days of exposure for inhalation anthrax and 1-7 days with cutaneous anthrax.

II) Types:

Cutaneous anthrax (95% of cases):

- Direct contact with the skins or tissues of infected animals.
- Present as:
  - an inflamed itchy pimple develops, which enlarges and becomes vesicular and then ulcerates, and 2-6 days later a black eschar develops 'malignant pustule'.
  - Local erythema and induration, with local lymphadenopathy.
  - Associated systemic malaise with headache and sore throat, but often afebrile.

Inhalation anthrax:

- Breathing in anthrax spores, usually in industrial processes such as the tanning of animal skins.
- Present as:
  - Initially, there is flu like illness. Patients also develop pallor or cyanosis, dyspnea, tachycardia, and pleuritic chest pain.
  - Abrupt onset of respiratory failure may develop 2-4 days later.

Intestinal anthrax:

- Very rare and is caused by swallowing spores in contaminated meats ,present as:
  - -Severe abdominal pain with watery or bloody diarrhea.
  - -If bacteremia develops it is usually fatal, with massive gastrointestinal hemorrhage and sometimes meningoencephalitis.

Injection anthrax:

- Identified in drug users probably contracted from using heroin contaminated by anthrax spores, present as:
  - Swelling, redness and pain around injection sites.
  - Abscess or ulcers at an injection site, often with marked edema.
  - Possible late presentation with septicemia and meningitis.

N.B: terrorists may use anthrax as a 'biological weapon'.

III) Action to be taken:

A- Reporting: (Group A disease) must be notified immediately.

B- Isolation: is recommended

C- Diagnosis:

- Culture from the ulcer or eschar (in cutaneous anthrax), pleural fluid, the cerebrospinal fluid or the blood.
- The preferred diagnostic procedure for cutaneous anthrax is staining the ulcer exudate.
- ELISA serological diagnosis.

- Chest X-Ray and/or chest CT scan are indicated if inhalation anthrax is suspected. Chest X-Ray often shows a widened mediastinum, pleural effusion and pulmonary infiltrates.
- CBC shows raised white cells (predominantly neutrophils)
- Liver Function Tests show raised transaminases.

IV) Treatment:

- Inhalation Anthrax:
  - Treat initially with either Ciprofloxacin or Doxycycline combined with one or two other antibiotics - eg, Amoxicillin, Benzylpenicillin, Chloramphenicol, Clarithromycin, Clindamycin, Imipenem with Cilastatin, Rifampicin and Vancomycin.
  - When the condition improves and the sensitivity of the B. anthracis strain is known, treatment may be switched to a single antibiotic.
  - Treatment should continue for 60 days because germination may be delayed.

N.B:

1- Raxibacumab, a monoclonal antibody directed at the protective antigen of Bacillus anthracis, is available from the CDC for treatment of inhalational anthrax in adults and children. It is used as part of a combination regimen with appropriate antibiotic drugs. It is also approved for prophylaxis of inhalational anthrax when alternative therapies are not available or not appropriate.

2- Chest tube drainage of the recurrent pleural effusions, which are typically hemorrhagic, often leads to dramatic clinical improvement.

- **Cutaneous and gastrointestinal anthrax:**
  - Treat with either Ciprofloxacin or Doxycycline for 7-14 days (treatment may need to be continued for 60 days if exposure is due to aerosol).
  - Treatment may be switched to Amoxicillin or Amoxicillin- Clavulanate if the infecting strain is susceptible.
- **Injection anthrax:**
  - Timely surgical debridement is important to remove primary source of toxin
  - Empirical antibiotics to cover B. anthracis as well as other causes of soft tissue infections are needed.
  - This can involve a five drug combination - intravenous Ciprofloxacin and Clindamycin with Penicillin, Flucloxacillin and Metronidazole.

V) Prevention:

Measures to prevent anthrax infection after exposure include vaccination, decontamination, and prophylactic treatment. For people who have been exposed to anthrax but do not have symptoms, 60 days of ciprofloxacin, a tetracycline (including doxycycline),
or penicillin is given to reduce the risk or progression of disease due to inhaled anthrax.
Vaccination is recommended as part of post exposure treatment by the CDC; however, this is not a licensed use for this vaccine.

Familial Mediterranean fever (FMF)

I) Definition :

- It is a hereditary auto inflammatory disorder caused by mutations in MEFV, a gene which encodes a protein called pyrin.
- FMF affects groups of people originating from around the Mediterranean Sea.
- The disorder inherits in an autosomal recessive fashion.

II) Signs &Symptoms:

There are seven types of attacks. Ninety percent of all patients have their first attacks before they are 18 years old. All develop over 2–4 hours and last anywhere from 6 hours to 4 days. Most attacks involve fever:

1. Abdominal attacks, featuring abdominal pain affecting the whole abdomen with all signs of peritonitis, and acute abdominal pain like appendicitis. They occur in 95% of all patients and may lead to unnecessary laparotomy. Incomplete attacks, with local tenderness and normal blood tests, have been reported.
2. Joint attacks mainly occurring in large joints, mainly in the legs. Usually, only one joint is affected. 75% of all FMF patients experience joint attacks.
3. Chest attacks with pleuritis and pericarditis . Pleuritis occurs in 40% and makes it difficult to breathe or lie flat, but pericarditis is rare.
4. Scrotal attacks due to inflammation of the tunica vaginalis. This occurs in up to 5% and may be mistaken for acute scrotum (i.e. testicular torsion)
5. Myalgia (rare in isolation)
6. Erysipeloid (a skin reaction on the legs, rare in isolation)
7. Fever without any symptoms (25%)

III) Laboratory findings:

The diagnosis is mainly clinical, it is made on the basis of the history of typical attacks, especially in patients from the ethnic groups in which FMF is more highly prevalent.

Nonspecific findings during attacks:

- High C-reactive protein level. Elevated white blood cell count
- Elevated plasma fibrinogen level Elevated ESR
- Elevated indirect bilirubin Elevated amyloid A
- Elevated haptoglobin
- Proteinuria (suggests renal amyloidosis) in patient with a long history of attacks
- **A genetic test (PCR for FMF) is also available that detects mutations in the MEFV gene:**
  - Homozygous: means a patient (the presence of two copies of the mutant gene that causes FMF, one from each parent).
  - Heterozygous: means a carrier (the presence of only one copy of the mutant gene).

IV) Clinical Lab interpretation:

- -If symptoms match a typical pattern (after ruling out other possible diseases using laboratory tests, images,….etc), the diagnosis is clinically made as FMF patient even if genetic testing shows heterozygous mutation or even if it is normal (As homozygous
- mutation may be in uncommon sites).
- -If symptoms match atypical pattern (After ruling out other possible diseases), and genetic testing shows homozygous mutation, the diagnosis is FMF patient.

- -If there are no symptoms, and genetic testing shows heterozygous mutation (on doing survey or genetic counseling), the diagnosis is FMF CARRIER.

V) Differential diagnosis:

Differential diagnosis includes:

- Acute intermittent porphyria (Hypertension & urine porphyrins).
- Hereditary angioedema with abdominal attacks (Does not cause fever-low levels or improper function of a protein called C1 esterase inhibitor).
- Relapsing pancreatitis (congenital or acquired).
- Other hereditary relapsing fevers.

VI) Treatment:

- Attacks are self-limiting, and require analgesia and non-steroidal anti-inflammatory drugs (such as Diclofenac).
- Prolonged fever with muscle pain responds to systemic corticosteroids.
    - Single dose Methylprednisolone or Anakinra at the start of episodes have been reported to relieve symptoms
- Colchicine: adult dose: 1–2 mg a day, pediatric dose: 0.02mg/ kg/day.
    - Colchicine prevents the attacks in 60% of cases.
    - It decreases attack frequency in 35% of cases.5 % of cases are non responders.
    - Development of amyloidosis is delayed with colchicine treatment.
    - Some advice discontinuation of Colchicine before and during pregnancy, but the data is inconsistent and others feel that it is safe to take Colchicine during pregnancy.
        - N.B. Attacks of FMF are naturally suppressed during pregnancy.
- Alternatives in non-responders include:
    - Add on Anakinra (kineret): 100 mg subcutaneously once daily, anakinra is an interleukin-1 (IL-1) receptor antagonist (not available in Egypt).
    - Rilonacept :(a medication that binds and neutralizes IL-1) 2.2 mg/kg (maximum 160 mg) by weekly subcutaneous injection (not available in Egypt).
    - Infliximab (Remicade): 5 mg/kg IV q wk.
    - Thalidomide (Thalomid): initially 100 mg once/day.

Fever of unknown origin (FUO)

I) Definition :

In 1961, fever of unknown origin (FUO) was defined as fever higher than 101o F (38.3oC) on several occasions of greater than 3 week's duration and no diagnosis established despite 1 week of intensive evaluation.

Recent definition:

Within the past decade, a revision has been proposed that categorizes FUO into classic, hospital acquired FUO, FUO associated with low white blood counts, and HIV associated FUO (AIDS related).

(1) Classical type: it meets the original criteria of FUO, with evaluation of at least three days in the hospital, three outpatient visits, or one week of logical and intensive outpatient testing.

(2) Nosocomial: fever occurring on several occasions in a patient who has been hospitalized for at least 24 hours and has not manifested an obvious source of infection that could have been present before admission, a minimum of three days of evaluation is needed.

(3) Immune deficient (Neutropenic): is defined as recurrent fever in a patient whose neutrophil count is 500 per mm or less and who has been assessed for three days without establishing

(4) HIV – associated: it is defined as recurrent fevers over a four – week period in an outpatient or for three days in a hospitalized patient with HIV infection.

II) Diagnosis of fever of unknown origin (FUO)

Complete history & physical exam

↓

Positive findings → yes → order appropriate and specific diagnostic testing

↓

No

↓

CBC, ESR, electrolytes, liver function tests, blood culture, Uri-analysis, urine culture, tuberculin test & chest x-ray

↓

Positive results → yes → order appropriate follow up diagnostic testing

↓

No

↓

Abdomino – pelvic CT with contrast

↓

Assign to most likely category

↓

A –Infections | B-Maliganacies | C-Autoimmune Conditions | D- Miscellaneous conditions

Infections:

Urine & sputum cultures for AFB,VDRL, HIV test, serology for

CMV, EBV, ASO titre (geographically specific testing)

↓

Yes ← diagnosis is clear → No

↓

TTE (transthoracic echocardiography),
TEE (transesophageal echo.),
LP (lumber puncture),
Gallium 67 scan,
x-ray or CT on the nasal sinuses.

B. Malignancies:

1- Hematologic:

Hematologic peripheral smear, serum protein electrophoreses

↓

Yes ← Diagnosis is clear → No

↓

Bone marrow biopsy

2. Non hematologic:

Mammography, chest Ct with contrast, upper/ lower endoscopy, bone scan & gallium 67 scan

↓

Yes ← Diagnosis is clear → No

MRI of the brain,

Diagnostic laparoscopy, liver biopsy, biopsy of suspicious skin lesion or lymphnode.

C. Autoimmune conditions:

Rheumatoid factor, ANA

↓

Yes ← Diagnosis is clear → No

↓

Temporal artery biopsy

Lymph node biopsy.

Miscellaneous:

Order appropriate diagnostic tests based on information from the history.

💡 **NB:** At the end of the investigations if we can't reach a diagnosis therapeutic intervention should be done

1- Anti tuberculosis therapy for 2 weeks

2- If not responded corticosteroid therapy is given with gradual withdrawal.

Fever with Rash

I- Approach to the Patient:

A- Detailed medical history including:

1. Drug history
2. Travelling history
3. Occupational history
4. Vaccination history
5. Sexual history
6. Social history (smoking, alcohol, illicit drug, job & hoppies)

II- The medical examination:

In addition to the thoroughly medical examination, focus on the following:

1. Vital signs.
2. General appearance.
3. Signs of toxicity.
4. Presence and location of Adenopathy. i.e lymph node examination and description.
5. Presence and morphology of genital, mucosal or conjunctival lesions.
6. Detection of hepatosplenomegally.
7. Presence of Arthritis.
8. Signs of Neurologic dysfunction, Nuchal Rigidity or Meningitis

III- Skin rash lesion:

- Describe the lesion
- See distribution of lesion
- Put differential diagnosis

Description of some of skin lesion:

- Macules, flat, non-palpable lesions in the plane of the skin, not more than1cm.
- Papules: Small, Solid, Palpable lesions in the plane of the skin, not more than 1 cm.
- Nodules: Masses that are located deeper within or below the skin, more than 1 cm.
- Patches: Flat, Non Palpable lesions in the plane of the skin more than 1 Cm.
- Vesicles (Less than0.5 Cm), bullae (More than1Cm) Small and large blisters.
- Pustules: Small, Palpable lesions Filled with pus .
- Plaques: Large, Flat lesions usually greater than 1 cm in Diameter and palpable.

Table Systemic infections with Prominent Cutaneous Manifestations and Skin - Rash

Organism / Disease viruses	Macules	VESICLES, BULLAE	PETECHIAE, PURPURA
Human immunodeficiency virus type Echoviruses	√		
Echoviruses	√	√	√
Coxsackie viruses	√	√	√
Rubeola (measles)	√		
Atypical measles	√		√
Adenovirus	√		√

Lymphocytic choriomeningitis	√		
Dengue	√		√
Viral hemorrhagic fevers			√
Rubella (German measles)	√		√
Colorado tick fever	√		
Yellow fever		√	√
Varicella-zoster (disseminated)		√	
Herpes simplex (disseminated)		√	
Varicella (chickenpox)		√	
Vaccinia		√	
Variola		√	√
Cytomegalovirus	√		
Congenital Cytomegalovirus Epstein-Barr virus			√
Hepatitis B	√		√
Monkeypox	√		√

Parvovirus B 19 (erythema infectiousm)	√		
Human herpes virus 6	√		
Human herpes virus 7	√		
ORGANISM/DISEASE Bacteria	**MACULES, PAPULES**	**VESICLES, BULLAE**	**PETECHIAE, PURPURA**
Chlamydia psittaci	√	√	
Mycoplasma pneumonia	√		
Ehrlichia spp	√		
Rickettsia rickettsii (RMSF)	√		√
Rickettsia akari (rickettsialpox)	√	√	
Rickettsia prowazekii (epidemic/louse-borne typhus)	√		√
Rickettsia typhi (endemic/murine typhus)	√		
Rickettsia tsutsugamushi (scrub typhus)	√		
Bartonella henselae	√		
Bartonella quintana	√		
Salmonella enterica serotype typhi	√		
Francisella tularensis	√		
Streptobacillus moniliformis (rat-bite fever)	√		√
Treponema pallidum (secondary syphilis)	√		
Mycobacterium haemophilum	√		
Neisseria monorrhoeae	√		√
Neisseria meningitides			√

Listeria monocytogenes		√	
Leptospira spp	√		
Bartonella bacilliformis	√		
Borrelia spp. (relapsing fever)	√		√
Pseudomonas aeruginosa	√		
Spirllum minus (rat-bite fever)	√		√
Staphyloccus aureus	√		√
Streptococci - group A (Scarlet fever)	√		
Capnocytophaga canimorsus			√
Vibrio vulinificus		√	
Fungi (Disseminated Infection)			
Candida spp	√		
Cryptococcus neoformans	√		
Histoplasma capsulatum	√		
Blastomyses dematitidis	√		
Coccidioides immitis	√		
Fusarium spp. (agents of mucormycosis	√		
Protozoa			
Plasmodium falciparum (malaria)			√