MICROBIOLOGY

PARASITOLOGY

Parasite: A living organism which receives nourishment and shelter from another organism where it lives.

(Ref: K.D. Chatterjee-13th edition, P-1)

Or, Parasite cane be defined as 'A living organism which depends on living organism for food and accommodation."

A parasite cannot live independently.

(Ref: Prof. Akram-2nd, P-1)

Classification of parasites:

1. **Ectoparasite**: Lives outside on the surface of the body of the host. e,g. mite, louse.

2. **Endoparasite**: Lives inside the body of the host in the blood, tissues, body cavities, digestive tract and other organs. e,g. *Entamoeba histolytica* in liver & large intestine.

3. **Temporary parasite**: Visits its host for a short period.e,g. *Plasmodium malariae*.

4. **Permanent parasite**: Leads a parasitic life throughout the whole period of its life. e,g.
   - *Ankylostoma duodenale* (Hookworm)
   - *Ascaris lumbricoides* (Round worm)
   - *T. vaginalis*.

5. **Facultative parasite**: Lives a parasitic life when opportunity arises. e,g. *Cryptococcus neoformance*.

6. **Obligatory parasite**: Cannot exist without a parasitic life.e,g. Plasmodium, *Ascaris lumbricoides*.

7. **Occasional/Accidental parasite**: Attacks an unusual host. e,g. *Balantidium coli* in pig, In man- hydatid cyst (*E. granulosus*)

8. **Wandering/Aberrant parasite**: Happens to reach a place where it cannot live.e,g. *Trichinela spiralis*.

(Ref: K.D. Chatterjee-13th edition, P-1)

Classification of parasites according to structure:

A. **Protozoa**:
   1. Sarcodina (amoebas)
   2. Sporozoa (sporozoans)
   3. Mastigophora (flagellates)
   4. Cilliata (ciliates)

B. **Metazoa**:
   1. Platyhelminthes (flat worm)
      - Cestodae (Tape worm)
      - Trematodae (Flukes)
   2. Nemathelminthes (round worm)

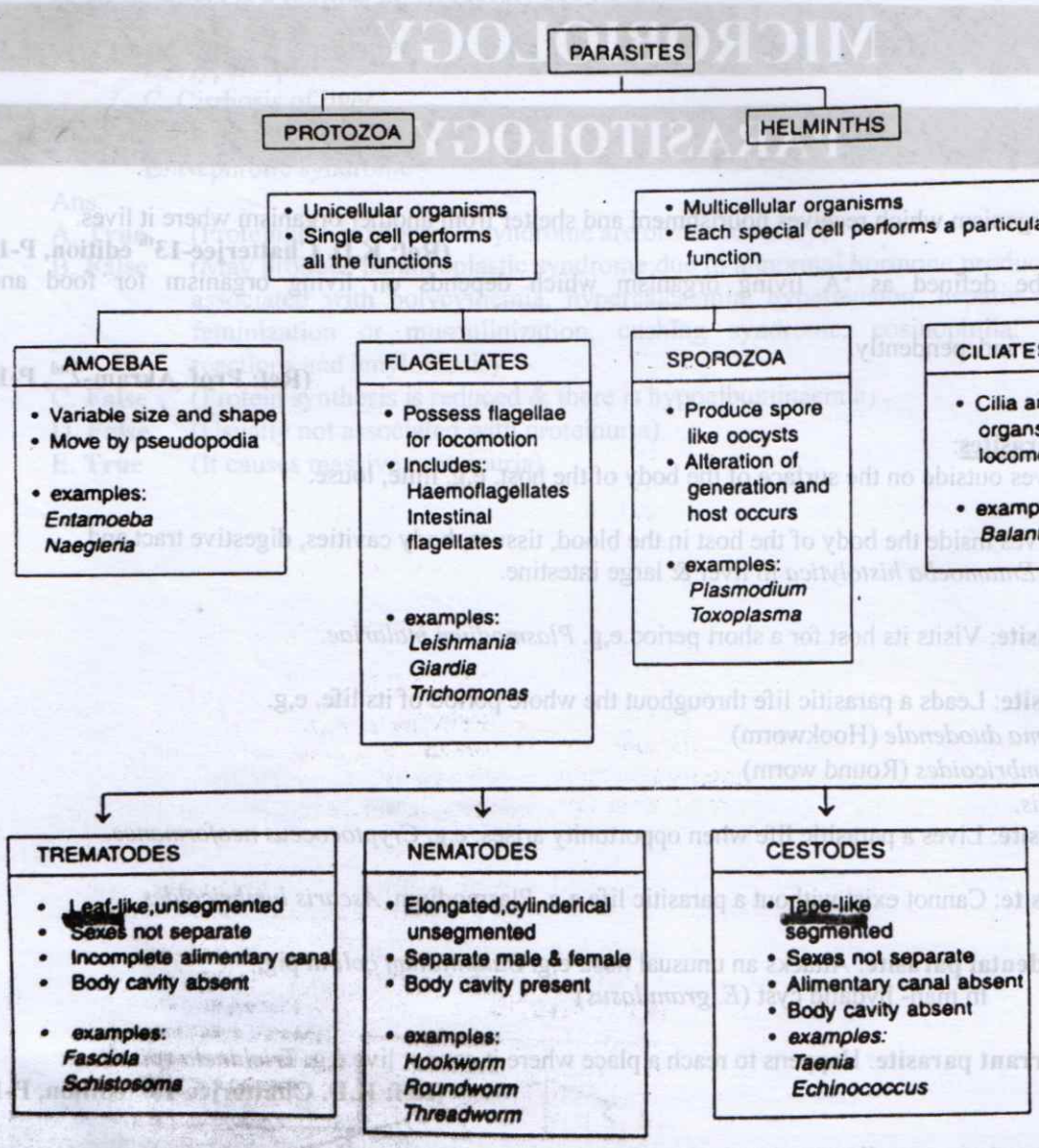


Fig. 2.1: Classification of parasites

For viva:

Criteria of parasitism: Following are some of the important criteria for parasitism –

1) Ecological relationship between two different organisms, one designated the parasite, the other the host.
2) The parasite is physiologically or metabolically dependent upon its host.
3) Heavily infected hosts may be killed by their parasites.
4) The reproductive potential of the parasite exceeds that of their hosts.

(Ref: Prof. Akram-2nd, P-2, 3)

Host: An organism which harbours the parasite. Or,
Host may be defined as living organism or animal which provide shelter to the foreign living animal or parasite.

(Ref: K.D. Chatterjee-13th edition, P-1)

■ **Classification of host**:

1. **Definitive host**: The host which harbours the adult stage or where parasite utilizes the sexual method of reproduction.
   In the majority of human parasitic infections, man is the definitive host. e,g. Man is the definitive host for *Dyphylobothrium latum*, *T. solium, T. saginata*. Leishmania, filaria.

2. **Intermediate host**: The host which harbours the larval stages of parasite. Man is an intermediate host in malaria & hydatid disease. e,g. Cyclops fish in case of *D. latum, T. solium*.

3. **Paratenic host**: A host where the parasite remains viable without further development. e,g. housefly for amebiasis.

(Ref: K.D. Chatterjee-13th edition, P-1)

Intermediate host

❑ **Where human acts as an intermediate host:**
- Plasmodium,
- *Echinococcus granulosus*,
- *Toxoplasma gondii*,
- Visceral and cutaneous larva migrans.

Question Bank

Q. Parasites that have intermediate host as part of their life cycle are *(BSMMU –Residency - **MD/MS, Basic science, Paediatrics** – March' 19)*
a) *Taenia solium*
b) *Toxoplasma gondii*
c) *Ascaris lumbricoides*
d) *Trichomonas vaginalis*
e) *Echinococcus granulosus*

Ans.
a) **True** (Definitive host man and intermediate host pig)
b) **True** (Definitive host cat and intermediate host man and other mammals)
c) **False** (involves only on host)
d) **False** (trophozoites are the infective stage and female are the reservoir of infection)
e) **True** (Dog is the definite host and sheep is the intermediate host)

Q. Man acts as intermediate host in the following parasitic infection *(BSMMU –Residency – **MD, MS, Basic Science** – March' 15)*
a) *Plasmodium ovale*
b) *Echinococcus multilocularis*
c) *Multiceps multicep*
d) *Dracunculus medinensis*
e) *Paragonismus westermanii*
Ans. a) T b) F c) F d) F e) F

Q. Parasites where man act as intermediate host are *(BSMMU –Residency - **MD/MS, Basic science** – March' 14)*

a)	plasmodium ovale	T
b)	echinococcus granulosus	T
c)	multiceps multiceps	F
d)	dracunculus medinensis	F
e)	paragonimus westermanii	F

Q.The following parasites has an intermediate host as part of its life cycle:(BSMMU-M.Phil, Diploma,July-08)

a) trichomonas vaginalis F
b) taenia solium T
c) echinococous granulosus T
d) toxoplasna gondii T
e) ascaris lumbricoides F

Q. Following parasites has an intermediate host as part of its life cycle: (MD/MS (DMC)-03Ja)

a) Trichomonas vaginalis F
b) Taenia soliurn T
c) Echinococcus granulosus T
d) Toxoplasma gondi T
e) Aascaris lumbricoides F

Q. Man acts as both definitive and intermediate host for- (BSMMU-MD/MS01Ja)

a) Taenia solium T (Ref: K.D.C)
b) Taenia saginata F
c) Trichenella spiralis T
d) Echinococcus granulosus F
e) Plasmidium vivax F

Free living amoeba

Q. Pathogenic free living amoeba are: ***(BSMMU –Residency – MD, MS, Basic Science – March' 18)***

a) *Entamoeba histolytica*
b) *Balantidium coli*
c) *Acanthamoeba*
d) *Negleria fowleri*
e) *Entamoeba coli*

Ans. a) F b) F c) T d) T e) F

Help link:

Pathogenic free living amoebae:

- Also called opportunist amoebae
- **Types**:
  1. ***Naegleria fowleri***- primary amoebic meningoencephalitis, produces death with in 5-7 days after the onset of symptoms (PAM),
  2. **Acanthomoeba** - granulomatous amoebic encephalitis(GAE), one week to months may nedded to ensure death.
  3. ***Balamuthia mandillaris***: produce granulomatous amoebic encephalitis(GAE)

- ❑ Infection produced by free living amoebia: Terramoebiasis (multiply both in host (endozoic), and free living (exozoic).
- ❑ Habitat: soil, fresh water, sewage, sludge, blackish water, sea water.
- ❑ Both are uninucleated.

Free living amoeba:

- *Naegleria fowleri*
- *Naegleria gruberi*
- *Acanthamoeba castenalli*
- *Hartmannella spp.*
- *Balamuthia mandrilaris*

Q. Free living amoeba are *(BSMMU – Residency - **MD, MS, Basic Science, Dentistry** - March' 17)*
a) *Negleria fowleri*
b) *Acanthamoeba spp*
c) *Endolimax nana*
d) *Entamoeba coli*
e) *Balamuthia mandrilaris*
Ans. a) T b) T c)F d) F e)T

Q. Free living amoeba are *(BSMMU – Residency – **MD, MS, Basic science** – March' 16)*
a) *Acanthamoeba spp.* T
b) *Endolimax nana* F
c) *Iodoamoeba butschlii* F
d) *Negleria fowleri* T
e) *Balamuthia mandrilaris* T

Q. Free living amoeba that causes human infection *(BSMMU –Residency – **MD, MS, Basic Science** – March' 15)*
a) *Entamoeba coli*
b) *Endolimax nana*
c) *Negleria fowleri*
d) *Acanthamoeba spp.*
e) *Balamuthia mandrilaris*
Ans. a) F b) F c) T d) T e) T

Parasites causing anaemia

Q. Parasites causing anemia are *(BSMMU – Residency - **MD, MS, Basic Science, Dentistry** - March' 17)*
a) *Giardia lamblia*
b) *Plasmodium vivax*
c) *Wuchereria bancrofti*
d) *Ancylostoma duodenale*
e) *Diphyllobothrium latum*
Ans. a) T b) T c)F d) T e)T

Help link:

■ **Parasites causing anaemia:**

Parasites	Types	Causes of anaemia
A. Protozoa		
1. Leishmania	Normochromic normocytic anaemia	1. Anti-RBC Ab formation. 2. Short life span of RBC (50days) 3. Lysis of RBC by spleen 4. Compromise erythropoiesis.
2. Plasmodium	Microcytic or normochromic hypochromic anaemia (Haemolytic anaemia)	Extensive haemolysis (Break down of RBC during segmentation of parasites)
3. Trypanosoma	Normochromic normocytic anaemia	1. Haemolysis 2. Removal of sensitized RBC from blood. 3. Depressed production of RBC by bone marrow.
4. Giardia		Giardia attaches on the convex surfaces of the intestinal epithelial cells by the sucking disc & prevent absorption of essential nutrients of haemopoiesis (such as iron, folic acid etc.).
B. Helminths		
1. Hook worms *Ancylostoma duodenale* *Necator americanus*	Dimorphic type (both microcytic & macrocytic)	1. Chronic blood loss due to sucking of blood by hook worm as their food. 2. Nutritional deficiency.
2. *Ascaris lumbricoids*		

3. *Diphyllobothrium latum*	Megaloblastic anaemia	• Unsaturated fatty acid released by *D. latum* interferes with the function of intrinsic factor of Castle. • *D. latum* takes up vit-B_{12} causing megaloblastic anaemia.
4. Taenia		
5. *Schistosoma haematobium*		

Q. Parasites that produce anaemia *(BSMMU –Residency – MD, MS, Basic – March' 15)*
a) *Diphylobothruim latum*
b) *Entamoeba histolytica*
c) *Wuchereria bancrofti*
d) *Ancylostoma duodenale*
e) *Leishmania donovani*
Ans. a) T b) T c) F d) T e) T

Parasites in blood

Parasites	Location in blood	Disease
1. Malaria parasite	RBC	Malaria
2. *Leishmania donovani*	Monocyte	Kala-azar (visceral leishmaniasis)
3. *Wuchereria bancrofti*	Plasma	Filariasis
4. *Brugia malayi*	Plasma	Malayan filariasis
5. *Trypanosoma brucei*	Plasma	Trypanosomiasis
6. *Babesia microti*	RBC	Babesiosis

(Ref: K.D. Chatterjee-13th, P-9 + LANGE review-14th)

Q. Haemoparasites are found in *(BSMMU – Non-Residency – MD, MS, Basic science – July' 15)*
a) diphtheria F
b) malaria T
c) tuberculosis F
d) kala-azar T
e) filariasis T

Q. Parasites found in blood are *(BSMMU –Residency – MD, MS, Basic Science – March' 15)*
a) *W. bancrofti*
b) *Loa loa*
c) *Echinococcus granulosus*
d) *Trypanosoma cruzi*
e) *Leishmania donovani*
Ans. a) T b) T c) F d) T e) T

Q. Following parasitic diseases can be diagnosed by direct microscopic examination of peripheral blood film: *(BSMMU – M. Phil, Diploma (Non-Residency)–11Ju, DMC & others – MD/MS – 11Ju)*
a) kala-azar. T
b) post Kala-azar dermal leishmaniasis F
c) hydatid cyst F
d) filariasis T
e) cryptosporodiosis F

Q. Hemoparasits are found in: (BSMMU – MS - January, 2010)

a) malaria T
b) amoebiasis F
c) dengue F
d) leishmaniasis T
e) filariasis T

Q. Following parasites are found in blood - (BSMMU - M. Phil, Diploma, July-04)

a) Trypanosoma cruzi
b) Toxoplasma gondii
c) Leishamania donovani
d) Echinococcus granulosus
e) Wuchereria bancrofti

Ans.

A. **True** (The organism migrate via blood stream & develops into amastigote forms in tissue)

B. **False** (Infection of human being with the ingestion of cysts in undercooked meat or from contact with cat feces)

C. **True** (Amstigote form of L. donovani is found in macrophages)

D. **False** (The embryo is liberated from the ovum in the small intestine and gains access to the blood stream & thus to the liver)

E. **True** (The adult worms, 4-10 cm in length, live in the lymphatics, and the females produce microfllariae which at night circulate in large numbers in the peripheral blood)

Q. Following parasites are found in blood- (BSMMU-02Ja, Basic-02Ju)

a) Leishmania donovani T
b) Echinococcus granulosus F
c) Plasmodium vivax T
d) Schistosoma mansoni T
e) Trypanosoma cruzi T

Intestinal flagellate

Q. Intestinal flagellates are *(BSMMU –Residency - MD/MS, Basic science, Paediatrics – March' 19)*

a) *Giardia lamblia*
b) *Dientamoeba fragilis*
c) *Chilomastix mesnili*
d) *Trichomonas vaginalis*
e) *Trypanosoma cruzi.*

Ans. a) T b) F c) T d) T e) F (haemoflagellates)

Help Link: Intestinal flagellates are:

1. Giardia lamblia(Duodenum, jejunum),
2. Trichomonas vaginalis(Vagia, urethra),
3. Trichomas tenax(mouth),
4. Trichomonas hominis(caecum),
5. Chilomastix mesnili (caecum),
6. Enteromonas hominis(colon),
7. Retortamonas intestinalis (colon)

Haemoflagelates

Q. Haemoflagelates are *(BSMMU – Non-Residency – **MD, MS, Basic science – July' 16**)*

a) Trichomonas F
b) Leishmania T
c) Echinococcus F
d) Trypanosoma T
e) Plasmodium F

Help link:

Haemoflagelates:

a) Trypanosoma:

- *T. brucei* (causes African trypanosomiasis/sleeping sickness)
- *T. cruzi* (causes American trypanosomiasis/chagas' disease)
- *T. rangeli* (Non-pathogenic)

b) Leishmania:

- *L. donovani*
- *L. tropica*
- *L. brasiliensis*

Q. Haemoflagellates are *(BSMMU – Non-Residency – **MD/MS, Basic science** – July' 14)*

a) *Wuchereria bancrofti*
b) *Trichomonas vaginalis*
c) *Leishmania donovani*
d) *Trypanosoma cruzi*
e) *Trichomonas hominis*

Ans. a) F b) F c) T d) T e) F

Oncogenic parasites

Q. Parasites causing cancer in human are *(BSMMU – Residency – **MD, MS, Basic science** – March' 16)*

a) *Trichenella spiralis* F
b) *Schistosoma haematobium* T
c) *Diphylobothrium latum* F
d) *Clonorchis sinensis* T
e) *Onchocerca vovulus* F

Help link:

Parasites	Name of disease
Clonorchis sinensis	Cholangiocarcinoma
Opisthorchis (flukes)	Cholangiocarcinoma
Schistosoma hematobium	SCC of UB

Liver flukes

- Also known as fascioasis
- ❑ **Agent:**
  - mainly-
    - F. hepatica,
    - F. gigantica
  - Others:
    - Chlonorchis sinensis,
    - Opisthorchis viverrini and felneus,

Q. Parasites causing surgical jaundice are *(BSMMU – Non-Residency – MS, Basic Science – July' 17)*
a) *Entamoeba histolytica*
b) *Echynococcas granulosus*
c) *Clonorsis sinensis*
d) *Ascaris lumbricoids*
e) *Schistosoma haematobium*

Ans. a) F b) F c) T d) T e)F

Helplink:
Liver flukes are associated with surgical jaundice:
1. Fasciola hepatica
2. Fasciola gigantica
3. Clonorchis sinensis
4. Opisthorchis viverreni

Others: Ascaris lumbricoides

Q. Parasites infecting the human liver are *(BSMMU – Non-Residency – **MD, MS, Basic science, Dentistry** – July' 15)*
a) *Entamoeba histolytica* T
b) *Leishmania donovani* T
c) *Fasciolopsis buski* F
d) *Toxoplasma gondii* T
e) *Cryptosporidium hominis* F

Q. Liver flukes are *(BSMMU –Residency – **MD, MS, Basic Science** – March' 15)*
a) *Heterophytes heterophytes*
b) *Ophisthorchis felineus*
c) *Strongyloides stercoralis*
d) *Clonorchis sinensis*
e) *Paragonimus westermani*

Ans. a) F b) T c) F d) T e) F

HELP LINK: Parasitic and helminthic infections are major causes of morbidity worldwide, and the liver is frequently involved. These diseases include malaria, schistosomiasis, strongyloidiasis, cryptosporidiosis, leishmaniasis, echinococcus, and infections by the liver flukes Fasciola hepatica, Clonorchis sinensis, and Opishorchis viverrini.

Q. Parasite which can infect liver are: *(BSMMU – Residency – MD/MS – March'13)*
a) W. bancrofti
b) Loa loa
c) Plasmodium
d) Echinococcous
e) Entamoeba histolytica

Ans: a) F b) F c) T d) T e) T

Q. The following parasites may infect the liver: *(BSMMU – M. Phil, Diploma (Non-Residency)–March-2012, DMC & others – MD/MS – March-2012)*
a) Entamoeba histolytica T
b) Leishmania donovani T
c) Fasciolopsis buski F
d) Toxocara Canis T
e) Cryptosporidium hominis F

Parasite in urine & sputum

Parasite that can be diagnosed by examination of urine & sputum:

a. Urine:

- *Schistosoma haematobium*
- *Trichomonas vaginalis*
- *Wuchereria bancrofti*

b. Sputum:

- Eggs of paragonimus (*Paragonimus westermoni*)
- Larva of strongyloides,
- Larva of ascaris,
- Hydatid cysts (protoscolices and brood capsules) - *Echinococcus granulosus*
- *Entamoeba histolytica* and gingivalis.

❑ **Perianal and vaginal swabs:**

- Enterobius,
- T. saginata,
- T. vaginalis,
- E. histolytica(trophozoites detected in vagina)

(Ref: K.D. Chatterjee-13th, P-10)

Q. Parasitic structure may found in urine *(BSMMU –Residency - **MD/MS, Basic science** – March' 14)*

a) microfilaria of B. malayii F
b) microfilaria of W. bancrofti T
c) trophozoite of T. vaginalis T (Ref: Bhatia parasitology)
d) eggs of S. haematobium T
e) eggs of S. japonicum F

Q. Eggs or larvae of parasites found in the sputum are *(BSMMU – Non-Residency - **MD/MS, Basic science** – 13Ju)*

a) *Paragonismus westermani* T
b) *Wuchereria bancrofti* F
c) *Ascaris lumbricoides* T
d) *Strongyloid stercoralis* T
e) *Ascaris lumbricoides* T

Q. Examination of urine specimen is used to diagnose following parasitic diseases: (BSMMU – MS - January, 2010)

a) Entamoeba histolytica F
b) Schistosoma haematobium T
c) Leishmania donovani F
d) Plasmodium falciparum F
e) W. bancrofti T

Parasites in stool

Visible to nacked eye in stool

- Ascaris
- Taenia proglottids
- Diphylobothrium proglottids
- Enterobiasis
- Hook worms

Parasites in stool specimen

- Adult parasites: round worm, pinworm, tapeworm
- Trophozoites:
  - E. histolytica,
  - Balantidium coli,
  - Giardia intestinalis,
  - Trichomonas hominis

Cyst or ova in iodine preparation/wet preparation:

1. E. histolytica,
2. G. lamblia,
3. Ascaris, Trichuris,
4. Taenia, Hook worms

Concentration method for helminths egg:

1. Hookworms, roundworms,
2. Thread worms, schistosomes,
3. Clonorchis, opisthorchis,
4. Fasciola,

Protozoan cysts found in stool (by concentration method)

E. histolytica, hartmanni, coli
Giardia intestinalis

Coccidian cysts and sporozoites found in stool (by concentration method)

- Isospora beli

Q. Cysts found in stool are following: *(BSMMU – Residency – MD/MS – March'13)*

a) Toxoplasma gondii
b) Giardia intestinalis
c) Entamoeba histolytica
d) Fasciola hepatica
e) Balantidium coli

Ans: a) F b) T c) T d) F e) F

Parasites causes clinical manifestation

Pathogenicity of parasites

- Trauma: Hookworm, round worm, taeniasis
- Lytic necrosis: amoebiasis
- Inflammation: leishmaniasis, trichinellosis
- Toxins: amoebiasis
- Allergic manifestation: Visceral larva migrans, round worm.

Parasites causes clinical manifestation

- **CNS manifestation**
  - ❑ Encephalopathy:
    - ❑ Cerebral malaria
    - ❑ Trypanosomiasis
    - ❑ Toxoplasmosis
    - ❑ Trichinosis

- ❑ SOL:
  - ❑ Hydatid cyst(larval cestodes),
  - ❑ amoebic brain abcess(E. histolytica, Acanthomoeba, Cysticercus),
  - ❑ Paragonimiasis(ectopic trematodes),
  - ❑ Toxocara(migrating nematodes),
- ❑ Meningitis: Naegleria, angiostrogylus

Parasite causes meningitis

1. N. fowleri,
2. Acanthomoeba
3. Angiostrogylus

➢ CSF may invaded by :
- Trypanosoma,
- Free living amoeba.

❑ Ocular manifestation:

- Choroidoretinitis:
  - ➢ Onchocerciasis,
  - ➢ Toxoplasmosis,
  - ➢ Toxocariasis
- Space occupying lesion:
  - ➢ Cysticercosis
  - ➢ Schistosomiasis
  - ➢ Brugiasis
- Orbital oedema
  - ➢ American trypanosomiasis
  - ➢ Trichinosis
  - ➢ Loaiasis(Loa loa)
  - ➢ Larval cestodes

➢ GIT manifestation:

- **Dysentery:**
  - ➢ E. histolytica, Balantidium coli, Trichuris, Schistosoma,
- **Malabsoption syndrome:**
  - ➢ Giardia, strongyloides, isospora
- **Intestinal obstruction:** (surgical problem producing parasite)
  - ➢ Ascaris, E. histolytica, Schistosoma (granuloma), taeniasis, Strongyloidosis.
- **Intestinal perforation** (surgical problem producing parasite) : Ascaris, Strongyloides

❖ Prasite causes diarrhoea

- ❑ E. histolytica
- ❑ G. intestinalis/lamblia
- ❑ Microsporidium
- ❑ Isospora belli
- ❑ Crytosporidium parvum
- ❑ Balantidium coli

➢ Duodenal aspirates:

- Giardia, eggs or larva of strongyloides,

➢ Pulmonary disease:

- **Interstitial pneumonia:**
  - ➢ Pneumocystis carinii, Toxoplasma gondii

- **Pulmonay eosinophilia:** Larval nematodes
- **Focal lesion In lung parenchyma:**
  - Echinococcus, E. histolytica
- **Pulmonary oedema**: Plasmodium falciparum

Question Bank

Q. Protozoa producing infections in the CNS are *(BSMMU – Non-Residency – **MS, Basic science** – July' 18)*
a) tyrpanosoma
b) negleria
c) giardia
d) toxoplasma
e) microsporidium

Ans. a) T b) T c) F d) T e) F

Help Link:

Microsporidium: Chronic diarrhea and wasting are the most common symptoms of microsporidiosis, but different species invade different sites including the cornea, biliary track and muscles.

Q. Parasites causing surgical complication are *(BSMMU – Non-Residency – MS, Basic science, Dentistry – July' 16)*

a) Echinococcus granulosus	T
b) Myco bacterium tuberculosis	F
c) Salmonella typhi	F
d) Schistosoma haematobium	T
e) Wuchereria bancrofti	T

Q. Following parasites infect various tissue: (BSMMU – MS - January, 2010)

a) Toxoplasma	T
b) T. cruzi	T
c) Malarial parasite	T
d) Loa. Loa	F
e) N. fouleri	F

Q. Parasites affecting eye are: (BSMMU - M. Phil, Diploma, July-09)

a) Leishmania donovani	F
b) Loa Loa	T
c) Trypanosome	T
d) P. vivax	F
e) Toxoplasma gondi	T

Q. Medically important protozoa are: (BSMMU - M. Phil, Diploma, July-'09)

a) Echinococcus granulosus	F
b) Trypenosome cruzi	T
c) Toxoplasma gonddi	T
d) Loa loa	F
e) Leishmania donovani	T

Q. Parasites which infect nervous tissue are as follow - (BSMMU - M. Phil, Diploma, July-05)

A. toxoplasma	T
B. trypanosomia cruzi	T
C. malarial parasite	T
D. Loa loa	F
E. N. fowleri	T

HELP LINK:

- Toxoplasma causes intracranial calcification, mental retardation & blindness.
- Trypanosomia cruzi multiply in the ganglionic cells of autonomic nervous system and may cause megacolon & megaoesophagus.
- Malarial parasite may produce cerebral malaria caused by occlusion of the capillaries with aggregrates of parasitized red cells leading to life-threating haemorrhage and necrosis in the brain.
- E. N. fowleri causes meningoencephalitis.

Intracellular parasites

Intracellular parasites:

- Plasmodium
- Leishmania
- *T. gondii*
- *Trypanosoma cruzi*

Q. The following are intracellular parasites - (BSMMU – MS - January, 2010,DMC – MD/ MS - January, 2010)

a. *Echinococcus granulosus*	F
b. *Leismania donovani*	T
c. *Trypanoma gambiense*	F
d. *Plasmodium vivax*	T
e. *Toxoplasma gondi*	T

Ans.

a) **False** Echinococcus granulosus is a cestode (tapeworm) infestation which gives rise to hydatid disease. The dog is the intermediate host between sheep and man. In the latter the chief pathological lesion is the formation of hydatid cysts. These are most commonly found in the liver, lung, and brain, in descending order of frequency. The worms themselves are extracellular and infection develops when ova are accidently eaten. These are shed in the faeces of the dogs which harbour the adult worm in the small intestine.

b) **True** Leishmania donovani, a protozoon, 'is the causative agent of systemic leihmaniais,, kala-azar, a disease in which the protozoa are generally found Within the macrophages in the amastigote form called the Leishmán—Donovan bodies. These are particularly common in the bone marrow and spleen. Leishmania parasites are cleared from the body by cell-mediated immune mechanisms. Hence the diagnosis can be made by eliciting a delayed type of hypersensitivity reaction to an extract of Leishmania injected into the skin, the Leishmanin test.

c) **False** The trypanosomes, T. gambiense and T. rhodesiense are flagellated parasites which are found freely circulating in the blood. Both cause sleeping sickness in cattle and the human and are transmitted from man to man or from animals to man by the tsetse fly (Glossina).

d) **True** Plasmodium vivax is one of a group of parasites of the genus Plasmodium. This particular species is responsible for benign tertian malaria. The diagnosis is confirmed by the examination of a blood smear when various forms of the life cycle including trophozoites, merozoites and schizonts can be seen within. infected erythrocytes.

e) **True** Toxoplasma gondil, the cause of toxoplasmosis, multiplies within the Cytoplasm of the cells of the mononuclear phagocyte system causing the lymph nodes to enlarge and become packed with large cells which are probably macrophages. In severe cases cysts may form and in the brain necrotic nodules may be found which may calcify. Severe damage can also occur in the eye leading to choroidoretinitis and uveitis. The definitive host is the cat and infection occurs through faecal contaminatioh of the human either by inhalation or ingestion. In the cat oocysts are discharged into the lumen from their site of development in the gastrointestinal membrane **(Ref: Smiddy)**

Entamoeba Histolytica

Q. Infection with entamoeba histolytica: *(BSMMU - M. Phil, Diploma – July '10)*

a) Usually affects the ileum F
b) Is often asymptomatic T
c) Is usually diagnosed by serological test F
d) Only tröphozoite are found is hepatic abscess T
e) Excystation and encystation occur in intestinal environment of human T

HELP LINK:

Amoebiasis is caused by Entamoeba histolytica, which is spread between humans by its cysts.

The life cycle of *E. histolytica*:

- **Host:** Only man
- **Infective form**: The mature quadrinucleate cyst
- **Habitat**: Mucosa and submucosa of large intestine.
- **Route of entry**: Faeco-Oral
- **Incubation period**: 4 to 5 days.

■ **Cycle**:

Cysts are swallowed with the contaminated foods & drink
↓
pass unaltered through stomach
↓
reach caecum, lower part of ileum, colon
↓
Excystation
↓
Tetranucleate amoeba
↓
Division of nuclei with successive division
↓
8 amoebulae (metacyclic trophozoites)
↓
They are highly active
↓
They invade the mucosa & lodge into submucosa of large gut
↓
Multiplication by binary fission
↓
Secretes proteolytic ferment (histolysin in nature)
↓
Destruction & necrosis of tissue
↓
Ulceration colitis (attack of acute dysentery)
↓
Trophozoites may enter into the deeper layer through portal vein into liver
↓
Effects of parasites gradually toned down & increase in host tolerance
↓
Lesions begin to heal
↓
Trophozoites discharge into lumen

↓

Encystation

↓

Cysts pass through faeces

↓

Cysts can survive in the environment for long

↓

Cysts may be ingested with foods & drinks due to faeco-oral contamination.

(Ref: K.D. Chatterjee-13th edition, P-22)

Q. Intestinal Amoeba: (BSMMU – MS - January, 2010)

a) commonly parasitise the jejunum and ileum	F
b) consist mostly of pathogenic species	T
c) may cause dysentery	T
d) are sensitive to metronidazole	T
e) may cause liver disease	T

HELP LINK:

Entamoeba histolytica causes amebic dysentery and liver abscess.

Important Properties

The life cycle of *E. histolytica* has two stages: the motile **ameba (trophozoite)** and the nonmotile **cyst**. The trophozoite is found within the intestinal and extraintestinal lesions and in diarrheal stools. The cyst predominates in nondiarrheal stools. These cysts are not highly resistant and are readily killed by boiling but not by chlorination of water supplies. They are removed by filtration of water.

The cyst has **four nuclei,** an important diagnostic criterion. Upon excystation in the intestinal tract, an ameba with four nuclei emerges and then divides to form eight trophozoites. The mature trophozoite has a single nucleus with an even lining of peripheral chromatin and a prominent central nucleolus (karyosome).

Antibodies are formed against trophozoite antigens in invasive amebiasis, but they are not protective; previous infection does not prevent reinfection. The antibodies are useful, however, for serologic diagnosis.

Pathogenesis & Epidemiology

The organism is acquired by ingestion of cysts that are transmitted primarily by the **fecal–oral** route in contaminated food and water. Anal–oral transmission, e.g., among male homosexuals, also occurs. There is **no animal reservoir.** The ingested cysts differentiate into trophozoites in the ileum but tend to colonize the cecum and colon.

The trophozoites invade the colonic epithelium and secrete enzymes that cause localized necrosis. Little inflammation occurs at the site. As the lesion reaches the muscularis layer, a typical **"flask-shaped" ulcer** forms that can undermine and destroy large areas of the intestinal epithelium. Progression into the submucosa leads to invasion of the portal circulation by the trophozoites. By far the most frequent site of systemic disease is the **liver,** where abscesses containing trophozoites form.

Infection by *E. histolytica* is found worldwide but occurs most frequently in tropical countries, especially in areas with poor sanitation. About 1–2% of people in the United States are affected. The disease is widely prevalent among male homosexuals.

Clinical Findings: Acute intestinal amebiasis presents as **dysentery** (i.e., bloody, mucus-containing diarrhea) accompanied by lower abdominal discomfort, flatulence, and tenesmus. Chronic amebiasis with low-grade symptoms such as occasional diarrhea, weight loss, and fatigue also occurs. Roughly 90% of those infected have asymptomatic infections, but they may be carriers, whose feces contain cysts that can be transmitted to others. In some patients, a granulomatous lesion called an **ameboma** may form in the cecal or rectosigmoid areas of the colon. These lesions can resemble an adenocarcinoma of the colon and must be distinguished from them.

Amebic abscess of the liver is characterized by right-upper-quadrant pain, weight loss, fever, and a tender, enlarged liver. Right-lobe abscesses can penetrate the diaphragm and cause lung disease. Most cases of amebic

liver abscess occur in patients who have not had overt intestinal amebiasis. Aspiration of the liver abscess yields brownish-yellow pus with the consistency of **anchovy-paste.**

Dysentery

Q. Characteristic features of the stool in amoebic dysentery are *(BSMMU – Non-Residency – MD, MS, Paediatrics, Basic Science – July' 19)*

a) abundant cellular exudate
b) RBC in clumps
c) presence of eosinophils
d) presence of macrophages
e) presence of Charcot-Leyden crystals

Ans. a) F (Cellular exudate is scanty) b) T c) T d) F e) T

(Ref: Bhattia Parasitology-6th, P-41)

Help Link:

Dysentery: Passage of blood in faeces is called dysentery. Or,

Dysentery may be defined as an acute inflammation of large intestine characterized by diarrhoea with blood and mucus in stool.

Organisms that cause dysentery:

1. **Bacillary dysentery**: Shigella group of organism mainly *S.flexneri, S. sonnei.*
2. **Amoebic dysentery**: *E. hisiolytica*
3. **Protozoal dysentery**: *Giardia intestinalis, Balantidium coli.*
4. **Helminthic dysentery**: Round worm, thread worm.

■ **Differences between examination of stool in amoebic dysentery and bacillary dysentery**:

Traits	Amoebic dysentery	Bacillary dysentery
Macroscopic		
1.Number	6-8 motions a day	Over 10 motions a day
2.Amount	Relatively copious	Small
3.Odour	Offensive	Odorless
4.Colour	Dark red	Bright red
5.Nature	Blood & mucus with faeces	Blood and mucus: no faeces
6.Reaction	Acidic	Alkaline
7.Consistency	Not adherent to container	Adherent to the bottom of the container
Microscopic		
1.RBC	In clumps: reddish-yellowish in color	Discrete or in rouleax: bright red in color.
2.Pus cells	Scantly	Numerous
3.Macrophages	Very few	Large and numerous; many of them contain RBC
4.Eosinophils	Present	Scare
5.Pyknotic bodies	Very common	Nil
6.Ghost cells	Nil	Numerous
7.Parasite	Trophozoites of E. histolytica	Nil
8.Bacteria	Nil	Many motile bacteria
9.Charcot-Leyden (C.L.) crystals	Present	Nil

(Ref: K.D. Chatterjee-13th edition, P-29)

Trichomonas

Q. Trichomonas vaginalis *(BSMMU–Residency-**Dentistry** - March' 17; BSMMU - M. Phil, Diploma – July '10)*

a) is sexually transmitted
b) found as commensal in the gut
c) may cause urethritis
d) can be treated by quinolones
e) found only in trophozoite form

Ans. a) T b) F c) T d) F e) T

HELP LINK:

Trichomonas vaginalis is a prototoza. They exist only in the trophozoite phase and there is no cystic phase. The flagellates are pear-shaped bodies.

■ **Morphology**:

1. Pear – shaped
2. Only trophozoite form and no cystic stage.
3. A Central nucleus and four anterior flagella.
4. It has an undulating membrane that extends about two-thirds of its length.

■ **Sites**: They live in female genital tract. It is also found in urinary tract of both male & female.It is sexually transmitted.

■ **Pathogenecity of *T. vaginalis***:

1. In female: A watery, foul-smelling, greenish vaginal discharge accompanied by itching and burning sensation.
2. In male: Infection is asymptomatic. About 10% of man have urethritis.

Mosquito

Q. Mosquitoes transmit the following diseases *(BSMMU –Residency - **Basic science** – March' 19; **MD, MS, Basic science** – March' 16)*

a) schistosomiasis
b) leishmaniasis
c) dengue
d) yellow fever
e) malaria

Ans.

a) **False** (The mosquito plays no part in the life cycle of the schistosoma, the intermediate host of this parasite is a snail found in fresh water.)

b) **False**

c) **True** (Dengue fever is a severe but usually short lived febrile illness which is caused by a toga virus transmitted by the mosquito Aedes aegypti)

d) **True** (Yellow fever is also caused by a toga virus transmitted by Aedes aegypti. Both the virus of dengue fever and yellow fever belong to the group collectively known as arthropod borne virus, hence the generic name arbovirus.)

e) **True** (Malaria is protozoal disease transmitted by the female anopheles mosquito. The various protozoal species are Plasmodium vivax, falciparum, maiariae and ovale. The most severe form of malaria is caused by P1. Falciparum which causes both malaria and blackwater fever. The latter is so named because of the haemoglobinuria whiëh follows the severe intrvascular haemolysis.)

(Ref: Smiddy)

KALA-AZAR

Life cycle: Flagellar promastigotes (10-20 μm) are introduced by the feeding female sandfly. Sandfly saliva helps Leishmania evade immunity. The promastigotes are taken up by macrophages where they lose their flagellae and transform into amastigotes (2-4 μm). These multiply, ultimately causing lysis of the macrophages and infection of another cell. Sandflies pick up amastigotes when feeding on infected patients or animal reservoirs. In the sandfly, the parasite transforms into a flagellar promastigote which multiplies by binary fission in the gut of the vector and migrates to the proboscis to infect a new host.

(Ref. Davidson-23rd, P-282)

Vector:

Sandflies live in hot and humid climates in the cracks and crevices of mud or straw houses and lay eggs in organic matter. People living in such conditions are more prone to acquire the disease. Female sandflies bite during the night and preferentially feed on animals: humans are incidental hosts.

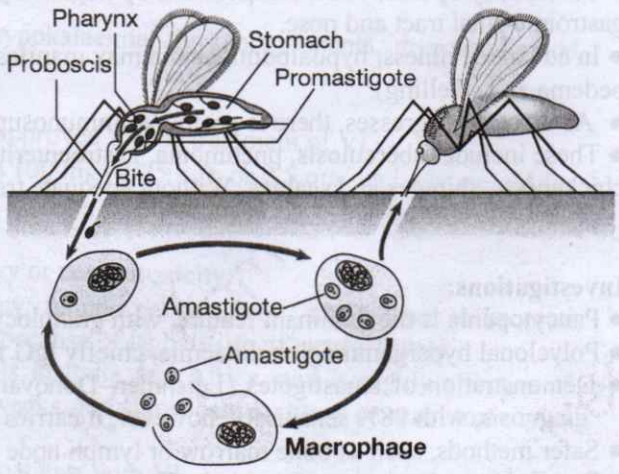
(Ref. Davidson-23rd, P-282)

■ **Mode of infection**:

1. Transmission by sandfly during blood meal.
2. Congenital infection of a child in utero.
3. Transmission by blood transfusion.
4. Transmission by inoculation of cultures of L. donovani.
5. Possible transmission during coitus.

■ **Pathogenesis**:

Sandfly bite human
↓
Microwound
↓
Promastigote enters into the body
↓
Metacyclic promastigote faces body's defense mechanism
↓
It attaches on the surface of macrophage through receptor
↓
Invade the reticulo-endothelial system (R.E.S.)
↓
Phagosome formation
↓
fused with lysosome to form phagolysosome
↓
Whether they multiply or die
↓
If multiply, they make the environment of RES suitable by proton pump mechanism (to change the pH of the RE cells)
↓
Detoxify the metabolites
↓
Scavange the oxidative free radicals
↓
Multiply by binary fission & form amastigote
↓



Dermis only	Dermis and mucosae	Viscera and dermis
L. tropica	(sometimes)	(sometimes)
L. mexicana etc.	*L. brasiliensis*	*L. donovani*

Fig. 11.40 Life cycle of *Leishmania*. *From Knight R. Parasitic disease in man. Churchill Livingstone, Elsevier Ltd; 1982.*

Rupture of macrophages & release of amastigotes
↓
Amastigotes are taken up by new cells & the cycle is repeated
↓
Formation of granulomatous tissue (dermal lesion) or hyperplastic lesion (visceral lesion).

(Ref: Davidson-23rd, P-2832+ K.D.)

[R.E cell: Macrophage & the precursor (monocyte), specialized endothelial cell of liver, spleen, bone marrow, reticular cell of lymphatic tissue & bone marrow (fibroblasts).]

■ **Incubation period**: 6 weeks to 6 months.

■ **Clinical features**:

In the Indian subcontinent, adults and children are equally affected; elsewhere, VL is mainly a disease of small children and infants, except in adults with HIV co-infection.

- The incubation period ranges from weeks to months (occasionally, several years).
- The first sign of infection is high fever, usually accompanied by rigor and chills.
- Fever intensity decreases over time and patients may become afebrile for intervening periods ranging from weeks to months. This is followed by a relapse of fever, often of lesser intensity.
- Splenomegaly develops quickly in the first few weeks and becomes massive as the disease progresses.
- Moderate hepatomegaly occurs later.
- Lymphadenopathy is common in Africa, the Mediterranean and South America but is rare in the Indian subcontinent.
- Blackish discoloration of the skin, from which the disease derived its name, kala-azar (the Hindi word for 'black fever'), is a feature of advanced illness but is now rarely seen.
- Pancytopenia is common.
- Moderate to severe anaemia develops rapidly and can cause cardiac failure.
- Thrombocytopenia, often compounded by hepatic dysfunction, may result in bleeding from the retina, gastrointestinal tract and nose.
- In advanced illness, hypoalbuminaemia may manifest as pedal oedema, ascites and anasarca (gross generalised oedema and swelling).
- As disease progresses, there is profound immunosuppression and secondary infections are very common.
- These include tuberculosis, pneumonia, gastroenteritis, severe amoebic or bacillary dysentery, boils, cellulitis, chickenpox, shingles and scabies. Without adequate treatment, most patients with clinical VL die.

(Ref: Davidson-23rd, P-282)

Investigations:

- Pancytopenia is the dominant feature, with granulocytopenia and monocytosis.
- Polyclonal hypergammaglobulinaemia, chiefly IgG followed by IgM, and hypoalbuminaemia are seen later.
- Demonstration of amastigotes (Leishman–Donovan bodies) in splenic smears is the most efficient means of diagnosis, with 98% sensitivity; however, it carries a risk of serious haemorrhage in inexperienced hands.
- Safer methods, such as bone marrow or lymph node smears, are not as sensitive but are frequently employed.
- Parasites may be demonstrated in buffy coat smears, especially in immunosuppressed patients.
- Sensitivity is improved by culturing the aspirate material or by using PCR for DNA detection and species identification, but these tests can only be performed in specialised laboratories.
- Serodiagnosis, by ELISA or immunofluorescence antibody test, is employed in developed countries. In endemic regions, a highly sensitive direct agglutination test using stained promastigotes and an equally efficient rapid immunochromatographic k39 strip test have become popular. These tests remain positive for several months after cure has been achieved, so do not predict response to treatment or relapse.

The vast majority of people exposed to the parasite do not develop clinical illness but may have positive serological tests thereafter.

- Formal gel (aldehyde) or other similar tests based on the detection of raised globulin have limited value and should not be employed for the diagnosis of VL. **(Ref: Davidson-23rd, P-282)**

ANTI KALA-AZAR DRUGS:

1. **Pentavalent antimonials:** Traditionally, pentavalent antimony is available as sodium stibogluconate (100 mg/ ml) in English- speaking countries and meglumine antimoniate (85 mg/ ml) in French ones. The daily dose is 20 mg/ kg body weight, given either intravenously or intramuscularly for 28-30 days..

Side-effects:

- Arthralgias
- Myalgias
- Raised hepatic transminases
- Pancreatitis (especially in patients co-infected with HIV)
- ECG changes:
  - T wave inversion and reduced amplitude
  - Manifested by concave ST segment elevation
  - Prolongation of QT> 0.5 msec
- Severe cardiotoxicity
- Ventricular ectopics
- Runs of ventricular tachycardia
- Torsades de pointes
- Ventricular fibrillation
- Sudden death

2. Amphotericin B: The antifungal drug, amphotericin B deoxycholate given once daily or on alternate days at a dose of 0.75-1.00 mg/ kg for 15-20 doses, is used in patients with Sb failure or as a first-line drug in regicns with a significant level of Sb unresponsiveness. It has a cure rate of nearly 100%.

Side effects:

- Infusion-related side-effects, e.g. high fever with rigor, thrombophlebitis, diarrhoea and vomiting, are extremely common.
- Serious adverse. events, such as renal or hepatic toxicity, hypokalaemia, thrombocytopenia, myocarditis and occasional death, are not uncommon.

3. Miltefosine: This oral drug, an alkyl phospholipid, has been approved for the treatment of VL.

Dose: A daily dose of 50 mg (patient's body weight < 25 kg) to 100 mg (≥ 25 kg), or 2.5 mg/ kg body weight for children, for 28 days cures over 90% of patients.

Side effects:

- Mild to moderate vomiting and diarrhoea and rarely skin allergy or nephrotoxicity.
- Since it is a teratogenic drug, it cannot be used in pregnancy; female patients are advised not to become pregnant for the duration of treatment and another 2 months, because of its half-life of nearly 1 week.

4. Paromomycin: An aminoglycoside, this has undergone trials in India and Africa, and is highly effective if given intramuscularly at 15 mg/ kg body weight daily for 3 weeks. No significant auditory or renal toxicity is seen.

5. Pentamidine isetionate: This was used to treat Sb-refractory patients with VL.

Side effects:

- Type 1 diabetes mellitus
- Hypoglycaemia
- Hypotension

(Ref: Davidson-23rd, P-282)

Question Bank

Q. In Kala azar *(BSMMU –Residency - MD/MS, Basic science, Paediatrics – March' 19)*

a) anemia is microcytic and hypochromic
b) vector is a female mosquito
c) PKDL is a sequele
d) etiological agents exist in two morphological form
e) hypergammaglobulinemia occurs

Ans. a) F b) F (sand fly) c) T d) T e) T (also occurs in malaria)

Help Link:

✓ **Anemia (normocytic and normochromic):**
- Appears early and may become severe enough to cause congestive heart failure

✓ **Causes of anaemia in Kala-azar (Ref. short case abdullah sir + KD chaterjee)**
- Hypersplenism(sequestration and splenic pooling)
- Short lifespan of RBC
- Hemolysis
- Ineffective erythropoisis
- Marrow hypoplasia(crowding out of erythopoietic tissue)
- Anti RBC antibody
- Positive coombs test(autoimmune hemolysis)

Q. A pt. with HIV symptoms develops Kala azar.--- (FCPS – Medicine – 19Ja)

a) HIV induced immunosupression increases the risk of VL 10 times
b) Low CD4 count may have atypical presentation
c) ART causes decline in the coinfected cases
d) Tendency to relapse within 5yrs
e) chemotherapy with monthly liposomal amphotericin B is useful.

Ans. a) F b) T c) T d) F e) T **(Ref. Davidson-23rd, P-283-284)**

Q. Regarding PKDL (FCPS – Medicine – 19Ja)

a) In Sudan children, spontaneous healing occurs in 3/4 cases.
b) Amastigote form remains in female sand fly
c) occurs in infected skin
d) Diagnosed by rk 39 Strip test.
e) No systemic symptoms

Ans. a) T b) F c) T d) T e) T

Help Link:

Post-kala-azar dermal leishmaniasis

After treatment and apparent recovery from VL in India and Sudan, some patients develop dermatological manifestations due to local parasitic infection.

Clinical features

- In India, dermatological changes occur in a small minority of patients 6 months to at least 3 years after the initial infection.
- They are seen as macules, papules, nodules (most frequently) and plaques, which have a predilection for the face, especially the area around the chin.
- The face often appears erythematous.
- Hypopigmented macules can occur over all parts of the body and are highly variable in extent.
- There are no systemic symptoms and little spontaneous healing occurs.
- In Sudan, approximately 50% of patients with VL develop post-kala-azar dermal leishmaniasis (PKDL), experiencing skin manifestations concurrently with VL or within the following 6 months.
- In addition to the dermatological features, a measles-like micropapular rash may be seen all over the body.

- In Sudan, children are more frequently affected than in India.
- Spontaneous healing occurs in about three-quarters of cases within 1 year.

Investigations:

- The diagnosis is clinical, supported by demonstration of scanty parasites in lesions by slit-skin smear and culture.
- Immunofluorescence and immunohistochemistry may demonstrate the parasite in skin tissues. In the majority of patients, serological tests (direct agglutination test or k39 strip tests) are positive.

Management:

- Treatment of PKDL is difficult.
- In India, Sb for 120 days, several courses of amphotericin B infusions, or miltefosine for 12 weeks is required.
- In Sudan, Sb for 2 months is considered adequate.
- In the absence of a physical handicap, most patients are reluctant to complete the treatment. PKDL patients are a human reservoir, and focal outbreaks have been linked to patients with PKDL in areas previously free of VL.

Prevention and control

Sandfly control through insecticide spray is very important. Mosquito nets or curtains treated with insecticides will keep out the tiny sandflies. In endemic areas with zoonotic transmission, infected or stray dogs should be destroyed. In areas with anthroponotic transmission, early diagnosis and treatment of human infections, to reduce the reservoir and control epidemics of VL, is extremely important. Serology is useful in diagnosis of suspected cases in the field. No vaccine is currently available.

(Ref. Davidson-23rd, P-284)

Q. *Leishmania donovani* *(BSMMU –Residency – **MD, MS, Basic Science** – March' 18)*
a) has a amastigote form present in sandfly
b) induces hypergammaglobulinemia
c) has erythrocytic and exoerythrocytic cycles
d) is absent in skin nodule of PKDL
e) infection is diagnosed by rk39 antibody test
Ans. a) F b) T c) F d) F e) T

Q. Promastigate form of Leishmania donovani are detected in *(BSMMU – Non-Residency – **MD, MS, Basic science, Dentistry – July' 16)***
a) bone marrow aspirate F
b) buffy coat smear F
c) blood culture T
d) infected sand fly T
e) polymorphonuclear leucocyte F

Q. In Kala-azar *(BSMMU –Residency – **MD** – March' 15)*
a) sand fly is the vector
b) culture done in L-J media
c) Kedrowsky's bacilli are conventionally used for CFT
d) aldehyde test may be strongly positive
e) always there is monoclonal gammopathy
Ans. a) T b) F c) T d) T e) F

Q. In Kala azar *(BSMMU – Residency –**Basic Science** – March' 15; Non-Residency – **MD, Basic Science** – July' 14)*
a) sand fly is the vector
b) culture of the organism is not possible
c) Kedrowasky's bacilli is conventionally used for CFT
d) Aldehyde test may be strongly positive
e) always there is monoclonal gammopathy
Ans. a) T b) F c) T d) T e) F (hypergammaglobulinemia)

Help link: In Kala-azar, there is hyper gammaglobulinaemia.

Q. Facts about *Leishmania donovani* *(BSMMU –Residency – **MD, MS, Basic Science** – March' 15)*

a) Phlebotomus argentipes is the vector
b) amastogote from is the pathogenic form
c) cultured in NNN media
d) produce black water fever
e) survive in clamastocyte Ans. a) T b) F c) T d) F e) T

Q. Following statements are true regarding Leishmaniasis *(BSMMU – Non-Residency – **MD, Basic science** – 13Ju)*

a) transmitted by anopheles mosquito
b) is a protozoal disease
c) is a self limiting condition
d) affects liver and spleen only
e) demonstration of LD bodies confirms diagnosis

Ans. a) F b) T c) F d) F e) T

Q. The followings are hematological findings in visceral leishmaniasis: *(BSMMU – Residency – MD – March'13)*

a) Monocytosis
b) Lymphopenia
c) Leucopenia
d) Eosinophillia
e) Thrombocytopenia

Ans : a) T b) F c) T d) F e) T

Q. Amastigote form of leishmania donovani are detected in: *(BSMMU – M. Phil, Diploma (Non-Residency)– March-2012, DMC & others – MD/MS – March-2012)*

a) spleenic aspirate	T
b) bone marrow aspirate	T
c) epitrochlear lymph node	T
d) polymorphonuclear leukocytes	T
e) infected sandfly	F

HELP LINK: Demonstration of amastigotes (Leishman - Donovan bodies) in splenic smears is the most efficient means of diagnosis, with 98% sensitivity; however, it carries a risk of serious haemorrhage in inexperienced hands. Safer methods, such as bone marrow or lymph node smears, are not as sensitive. Parasites may be demonstrated in buffy coat smears, especially in immunosuppressed patients. Sensitivity can be improved by culturing the aspirate material or by PCK for DNA detection and species identification, but these tests can only be performed in specialised laboratories.

Q. Causes of anaemia in Kala-azar are: *(BSMMU – M. Phil, Diploma (Non-Residency)–11Ju, DMC & others – MD/MS – 11Ju)*

a) increased sequestration of RBC in spleen	T
b) increased destruction of RBC in liver	F
c) invasion of bone marrow by LD body	T
d) development of anti red cell antibody	T
e) intravascular haemolysis.	T

HELP LINK:

In the early course of the disease there may be no or minor nospecific changes in blood counts. In more advanced disease there is usually pancytopenia- anemia, leukopenia (neutropenia, marked eosinopenia, relative lymphocytosis and monocytosis). There is thrombocytopenia. Anemia may be due to bone-marrow infiltration, hypersplenism, autoimmune hemolysis, and bleeding.

Q. Following are true about Kala-azar: (BSMMU – MD/MS - January, 2009)

a) anaemia is microcytic hypochromic type F
b) is transmitted by female mosquito F
c) PKDL is caused by Leishmania donovani T
d) they exist in two morphological form T
e) hyper gammaglobulenimia T

Q. Following statements are true about Leishmania: (BSMMU - M. Phil, Diploma, July-07)

a) exist in two morphological forms T
b) causes lymphatic obstruction F
c) transmitted by female anopheles mosquito F
d) causes hypergammaglobulenimia T
e) can be transmitted sexually F

Malaria

■ **Species of protozoa found in the erythrocytes of human:**

Species of protozoa	Diseases
1. *Plasmodium vivax*	Tertian malaria
2. *Plasmodium falciparum*	Aperiodic malaria
3. *Plasmodium ovale*	Tertian malaria
4. *Plasmodium malariae*	Quartan malaria

Pathogenesis:

Life cycle of the malarial parasite:

The female anopheline mosquito becomes infected when it feeds on human blood containing gametocytes, the sexual, forms of the malarial parasite. Development in the mosquito takes from 7-20 days. Sporozoites inoculated by an infected mosquito disappear from human blood within half an hour and enter the liver. After some days merozoites leave the liver and invade red blood cells, where further asexual cycles of multiplication take place, producing schizonts. Rupture of the schizont releases more merozoites into the blood and causes fever, the periodicity of which depends on the species of parasite.

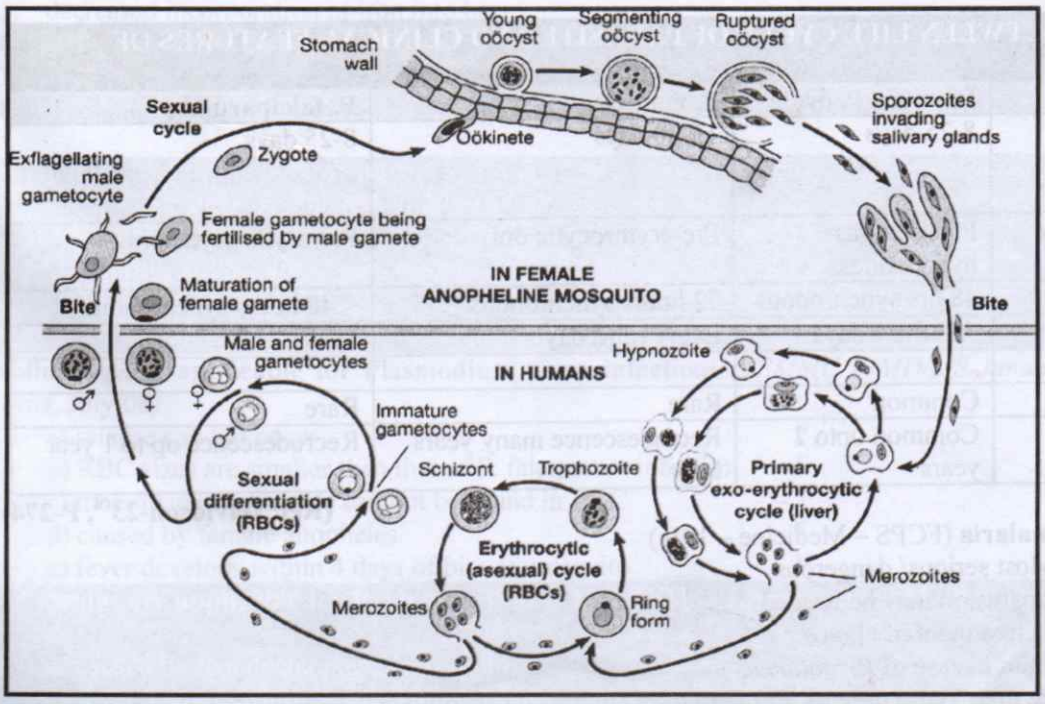


Fig: **Malarial parasites: life cycle.**

P vivax and P. ovale may persist in liver cells as dormant forms, hypnozoites, capable of developing into merozoites months or years later. Thus the first attack of clinical malaria may occur long after the patient has left

the endemic area, and the disease may relapse after treatment with drugs that kill only the erythrocytic stage of the parasite.

Hypnozoites (*) are present only in *P. vivax* and *P. ovale* infections.

P. falciparum and P malariae have no persistent exoerythrocytic phase but recrudescences of fever may result from multiplication in the red cells of parasites which have not been eliminated by treatment and immune response.

■ **Differences:**

Traits	P. vivax	P. falciparum
1. Size of infected RBC	Larger than non-infected RBC	Similar to non-infected RBC
2. Ring form of parasite	One present in one RBC	More than one present in one RBC
3. Achole	Not formed	Formed
4. Most common form under microscope	Syzont	Signate ring
5. Trophozoite (ring form)	2.5 μm	1.25- 1.5 μm
6. Schizont	Almost completely fills an enlarged RBC	Fills 2/3 of non-enlarged RBC.
7. Merozoite	12-24. Arranged in an irregular grape-like cluster.	18-24. Same
8. Malarial pigments	Yellowish-brown	Dark brown or blackish.
9. Infected RBC	• Enlarged • Pale • Schuffner's dots present	• Usually unaltered • Reddish violet • Maurer's dots
10. Gametocyte	• Spherical or globular • Much larger than a RBC. •Host cell enlarged with Schuffner's dots	• Crescentic • Larger than a RBC. • Host cell hardly recognizable.

RELATIONSHIPS BETWEEN LIFE CYCLE OF PARASITE AND CLINICAL FEATURES OF MALARIA:

Cycle/ feature	P. vivax, P. ovale	P. malariae	P. falciparum
Pre-patent period (minimum incubation period)	8-25 days	15-30 days	8-25 days
Exo-erythrocytic cycle	Persistent as hypnozoites	Pre-erythrocytic only	Pre-erythrocytic only
Asexual cycle	48 hrs synchronous	72 hours synchronous	< 48 hours synchronous
Fever Periodicity	Alternate days	Every third day	None
Delayed onset	Common	Rare	Rare
Relapses	Common upto 2 years	Recrudescence many years later	Recrudescence up to 1 year

(Ref: Davidson-23rd, P-274)

Q. Regarding severe malaria (FCPS – Medicine – 19Ja)

a) *P. Malaria* Most serious/ dangerous
b) Exchange transfusion may be needed.
c) I/V quinine is treatment of choice
d) relapse common in case of *P. malariae*
e) recrudescence upto 1yr in case of *P. falciparum*

Ans. a) F b) T c) F d) F e) T **(Ref. Davidson-23rd, P-274-276)**

Q. Characteristics of Plasmodium falciparum are *(BSMMU – Residency - **MD, MS, Basic Science** - March' 17)*

a) it invades only young, immature erythrocyte
b) multiple sporozoites can infect single erythrocytes
c) noninfected RBCs form rosettes around the infected RBC
d) the distinctive crescentic gametocytes are found in peripheral blood film
e) relapse of falciparum malaria can occur

Ans. a) F b) T c) F d)T e) F **(ref. K. D Chatterjee, 100 page, 13th ed)**

Q. The following statements are true about P. vivax infection: *(BSMMU – Residency – MD – March'13)*

a) Persists as hypnozoite in liver
b) Duration of asexual cycle is less than 48 hours
c) Fever comes at every second day
d) Recrudescence occurs many years later
e) Incubation period is more than two months

Ans : a) T b) F c) T d) F e) F

Q. In malaria, anaemia is due to: *(BSMMU – M. Phil, Diploma – 11Ju, DMC & others – MD – 11Ju)*

a) folic acid deficiency T
b) haemolysis T
c) marrow suppression T
d) iron deficiency F
e) hyperspienism T

HELP LINK:

Causes of anaemia in malaria:

1. Destruction of parasitised and non parasitized RBC,
2. hypersplenism,
3. antimalarial therapy in glucose-6-phosphate dehydrogenase deficiency,
4. Autoimmuno lysis,
5. decreased incorporation of iron into haem,
6. increased fragility of RBC,
7. decreased RBC production from bone marrow suppression.
8. Depletion of folate stores

Q. Followings are applicable for P. vivax: *(BSMMU – MD/MS – January, 2010)*

a) Sexual cycle is completed within 24 hours F
b) Fever develop within 4 days of bite of mosquito F
c) Relapse can occur T
d) RBC sizes are larger T
e) More than one parasite can be found in one RBC F

Q. Following are applicable for Plasmodium vivax infection: *(BSMMU – MD/MS-January, 2009,* M. Phil, Diploma, July-08*)*

a) relapse can not occur F
b) RBC sizes are smaller than that of P. falciparum infection F
c) more than one parasite can not be found in RBC T
d) caused by female anopheles T
e) fever develops within 4 days of bite of mosquito F

Q. Followings are applicable for P. vivax: (BSMMU – MD/MS - January, 2008, M. Phil, Diploma, July-07, MS-07Ja)

a) caused by female anopheles mosquito T
b) fever develop within 4 days of bite of mosquito F *(Incubation period is 8-25 days)*
c) relapse can occur T
d) RBC sizes are smaller than that of P. falciparum F
e) More than one parasite can be found in one RBC. F

Q. Form of plasmodia that is transmitted from mosquito to human is: (M. Phil, Diploma-07July)

a) sporozoite T
b) gametocyte F
c) merozoite F
d) hypnozoite F
e) schizont F

Q. Following are applicable for plasmodium vivax infection - (BSMMU - M. Phil, Diploma, July-06)

a) Caused by female anopheles T
b) Fever develops within 4 days of bite of mosquite F
c) Relapse can not occur F
d) RBC sizes are larger than that of P. falciparum T
e) More than one parasite can be found in RBC F

HELP LINK:

■ **Mosquito born parasitic diseases**:

Parasitic disease	Mosquitoes
1. Malaria	Female anopheline mosquitoes
2. Bancroftian Filariasis	Female culicine mosquitoes.
3. Malayan filariasis	Mansonoids

■ **Incubation period**:

P. vivax, falciparum, ovale: 10-14 days.
P. malariae: 18 days - 6 wks.

■ **Differences**: see before

Recurrent fever pattern in malaria is caused by –

A. **Recrudescence**:

- It is the clinical manifestation which results from **persistence of malarial parasites in blood** in which the surviving population of erythrocytic forms are increased.
- It is the renewed clinical attack of malaria after a short interval due to surviving & multiplying population of erythrocytic stage of plasmodia.
- During this period there is very low paracytaemia.
- In case of *P.fatciparum* and *P. malariae* → It occurs due to drug resistance when a person's immunity is destroyed.
- It may occur mostly upto 1 year. (in *P. falciparum*); upto 40 years (in *P. malariae*)

B. **Relapse**: It is the clinical manifestation which results from persistence of hypnozoite form in the liver in which erythrocytic schizogony commences again which leads to recurrence of clinical attack of malaria.

- There was no paracytemia in blood.
- Relapse is capable of maintaining infection for 3 to 5 years. It occurs in –
  - *P. vivax* → 3 years
  - *P. ovale* → 1 - 3 years
- In *P.fatciparum* and *P. malariae*, there is no hypnozoite → no relapse.

(Ref: KDC-13th, P-113)

Prophylaxis

Q. In Chloroquine resistant cases, which drugs are/ is used for malaria prophylaxis – (FCPS – Medicine – 19Ja)

a) Mefloquine
b) Doxycycline
c) Malarone
d) Chloroquine
e) Proguanil

Ans. a) T b) T c) T d) F e) F

Help Link:

11.56 Chemoprophylaxis of malaria

Antimalarial tablets	Adult prophylactic dose	Regimen
Chloroquine resistance high		
Mefloquine[2]	250 mg weekly	Started 2–3 weeks before travel and continued until 4 weeks after
or Doxycycline[3,4]	100 mg daily	Started 1 week before and continued until 4 weeks after travel
or Malarone[4]	1 tablet daily	From 1–2 days before travel until 1 week after return
Chloroquine resistance absent		
Chloroquine[5] *and* proguanil	300 mg base weekly 100–200 mg daily	Started 1 week before and continued until 4 weeks after travel

[1]Choice of regimen is determined by area to be visited, length of stay, level of malaria transmission, level of drug resistance, presence of underlying disease in the traveller and concomitant medication taken. [2]Contraindicated in the first trimester of pregnancy, lactation, cardiac conduction disorders, epilepsy, psychiatric disorders; may cause neuropsychiatric disorders. [3]Causes photosensitisation and sunburn if high-protection sunblock is not used. [4]Avoid in pregnancy. [5]British preparations of chloroquine usually contain 150 mg base, French preparations 100 mg base and American preparations 300 mg base.

(Ref. Davidson-23rd, P-278)

Toxoplasmosis

Q. Toxoplasmosis: *(BSMMU – M. Phil, Diploma (Non-Residency)–March-2012, DMC & others – **MS** – March-2012)*
a) is spread by dogs
b) show serological evidence of previous infection in over 29% of cases
c) may be asymptomatic
d) may cause fetomaternal transmission in 10% of the fetuses
e) can cause respiratory distress syndrome in fetus.

Ans. a) F (cats) b) T c) T d) F e) F

HELP LINK:

Toxoplasma gondii.

- **Agent**: Toxoplasma gondii
- **Importance:** Severe disease in developing foetus, important pathogen in AIDS.
- Intracellular protozoa
- **Morphology:** Trophozoites, tissue cyst and oocyst.
- **Trophozoite:**
  - ❑ crescent or oval shaped,
  - ❑ staine by Giemsa or wright stain.
  - ❑ Found in: tissues during acute stage of infection and invade all mammalian cells except non nucleated RBCs. Can be seen in extracellularly
  - ❑ Killed by: dessication, freezing, thawing and gastric secretion
- **Tissue cysts:**
  - ❑ found in- chronic phase of infection.
  - ❑ Organ involved: skeletal and heart muscle, brain.
  - ❑ Cyst remain viable for several years.
- **Oocyst:**
  - ❑ develop only in definitive host(cat and member of feline family),
  - ❑ freshly oocysts are not infective,
  - ❑ infective after developments in the soil or water.
  - ❑ Mature cyst contains eight sporozoites in the infective form.
- **Mode of transmission:**
  - ❑ a) ingestion,
  - ❑ b) transplacental,
  - ❑ c) others: occupational, organ transplantation, blood transfusion.

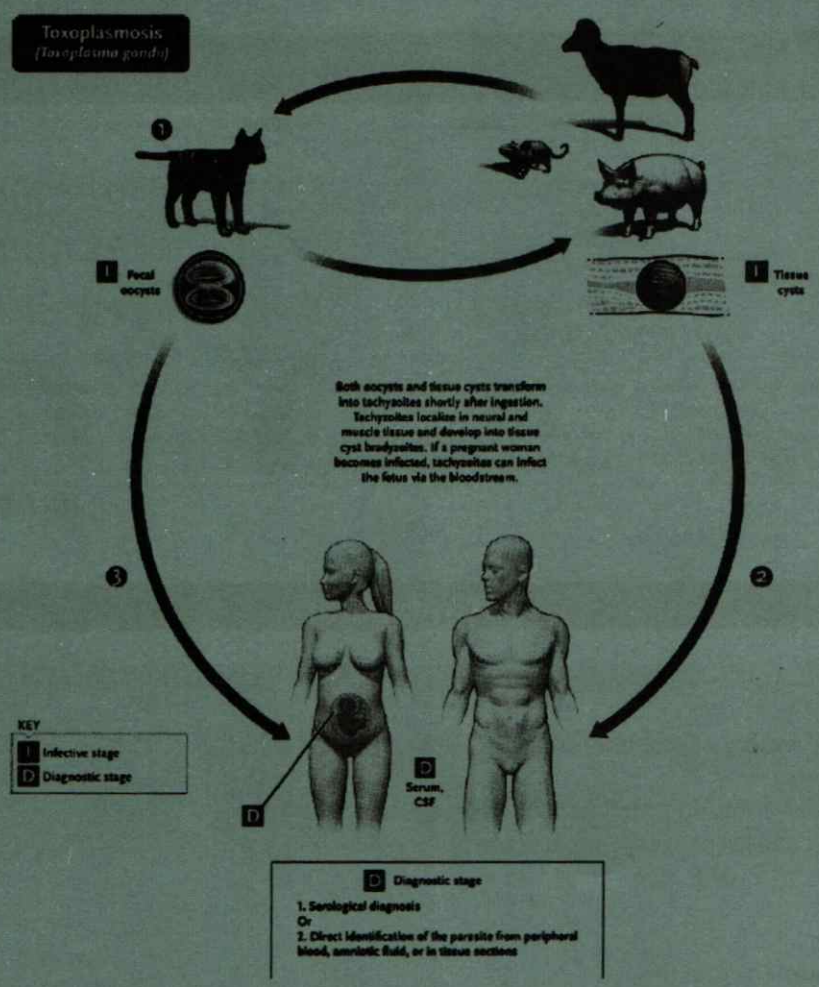


Fig: ***Toxoplasma gondii***. Life cycle. Top red arrows show the natural life cycle as T. gondii circulates between cats (#1), which excrete oocysts in the feces that are eaten by mice, but also by domestic animals such as pigs and sheep. Cysts form in tissue such as muscle and brain. The natural cycle is completed when cats eat mice. Humans are accidental hosts. They can be infected by the ingestion of undercooked pork and lamb (blue arrow #2) containing tissue cysts in muscle or by ingestion of food contaminated with cat feces containing oocysts (blue arrow #3). **(Ref: LANGE Review-14th, P-439)**

Definitive host: Domestic cat and other felines.

Intermediate host: Humans and other mammals.

Pathogenesis:

Toxoplasma gondii is usually acquired by ingestion of cysts in uncooked meat or cat faeces.

Transplacental transmission from an infected mother to the fetus occurs also. Human-to-human transmission other than transplacental transmission does not occur.

After infection of the intestinal epithelium, the organisms spread to other organs, especially the brain, lungs, liver and eyes. Progression of the infection is usually limited by a competent immune system. When contained, the organisms persist as cysts within tissues. Immunosuppression allows activation of organisms in the cysts.

Congenital infection of the fetus occurs only when the mother is infected during pregnancy.

Diagnosis:

- Painless lymphadenopathy
- No heterophil antibody

- Scanty or absent atypical lymphocytosis
- IgG antibody
- ELISA (confirm)
- Lymph node biopsy
- DNA

- **Congenital toxoplasmosis: asymptomatic after birth.**
  - ❑ Chorioretinitis, blindness,
  - ❑ epilepsy, mental retardatin,
  - ❑ abortion or still birth,
  - ❑ eye lesion, hepatosplenomegaly.
- **Toxoplasma in pregnant women:**
  - ❑ acquired in pregnancy,
  - ❑ symptoms present only in 10-20 % mothers,
  - ❑ risk of foetus does not depends upon maternal symptoms.
- **Ocular toxoplasma:**
  - ❑ Chorioretinitis- uveitis, choroiditis, chorioretinitis.
- **Disseminated infection**:
  - ❑ In AIDS pts, Organ transplant recipients, malignancy,
  - ❑ C/F: CNS involvement, diffuse encephalitis, meningitis, chorioretinitis, myositis, pneumonitis, orchitis.
- **Lab diagnosis:**
  - ❑ a) isolation,
  - ❑ b) identification of trophozoites in the tissues or body fluids,
  - ❑ c) Lymph node histology,
  - ❑ d) serodiagnosis (four fold rise of antibody titre in two sera).
- **Histopathlogy:** reactive hyperplasia with epithelioid histiocytes.

Complications of toxoplasmosis:

1. **Congenital infection** can result in-
   - Abortion
   - Still-birth
   - Neonatal disease with encephalitis, chorioretinitis, and hepatosplenomegaly.
   - Fever, jaundice and intracranial calcifications are also seen.

2. In patients with reduced cell-mediated immunity (AIDS patients)
   - life-threatening disseminated disease
   - encephalitis

(Ref: LANGE Review-14th, P-438)

Congenital infection by toxoplasma: Congenital infection of the fetus occurs only when the mother is infected during pregnancy. If she is infected before the pregnancy, the organism will be in the cyst form and there will be no trophozoites to pass the placenta. The mother who is re-infected during pregnancy but who has immunity from a previous infection will not transmit the organism to her child. Roughly one-third of the mothers infected during pregnancy give birth to infected infants, but only 10% of these infants are symptomatic.

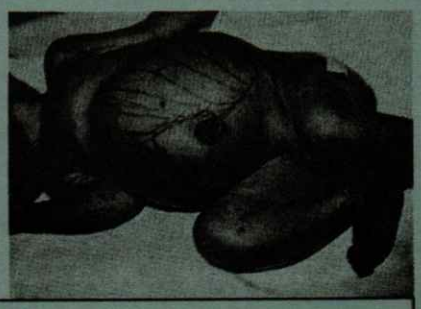


Fig: Congenital infection by toxoplasma

■ **Diseases produced by Toxoplasma gondii in a female of Child bearing age**:

Cerebrospinal:	Encephalomyelitis Cerebral calcification
Eye:	Focal chorio-retinitis Anterior uveitis
Lymphatics	Slim's disease
Skin	Exanthematous lesion
Lungs	Interstitial pneumonia
Heart:	Myocarditis
Liver-spleen	Hepatosplenomegaly
Uterus:	Abortion

Fig: Chorio-retinitis

TORCH: These are the congenital infections of neonates:

- **T**oxoplasmosis
- **R**ubella
- **C**ytomegalovirus
- **H**uman (alpha) herpes virus 1 or 2
- **H**uman (beta) herpes virus, and
- **S**yphilis.

CESTODES

Q. Following are Tapeworm: (BSMMU – MD/MS - January, 2009)

a) Strongyloid stercoralis F
b) Echinococcus granulosus T
c) Enterobius vermicularis F
d) Wuchereria bancrofti F
e) Diphylobothrium latum T

HELP LINK:

The various cestodes which cause human diseases are:

	Pseudophyllidean cestodes	Cyclophyllidean cestodes
1. Adult worms in intestine (Tapeworm)	• Genus Diphyllobothrium: D. latum.	• Genus Taenia: T. saginata, T. solium • Genus Hymenolepis: H. nana, H. diminuta • Genus Dipylidium D. canium
2. Larval stages in man	• Sparganum mansoni • Sparganum proliferum	• Genus Echinococcus: Hydatid cyst of E. granulosus. • Genus Taenia: Cysticercus cellulosae of T. solium. • Genus Multiceps: Coenurus cerebralis of M. multiceps.

■ **General features of cestodes**:

1. Cestodes are segmented and tape like.
2. Sizes vary from a few millimeters to several meters.
3. Adult worms are found in the intestinal canal of man and animal.
4. "Head" is provided with suckers (slit- like or cup-like) and sometimes with hooks which serve as organs of attachment.
5. There are three regions in an adult worm: "head" (scolex), "neck" and a strobila (a body or trunk) consisting of a series of segments (proglottides).
6. Sexes are not separate
7. Body cavity is absent.
8. Alimentary canal is entirely absent.
9. Excretory and nervous systems are present.
10. Reproductive system is highly developed and complete in each segment.

Nice to know:

- Fish tapeworm: *Diphylobothrium latum.*
- Beef tape worm: *Taenia saginata*
- Pork tapeworm: *Taenia solium*
- Dog tapeworm: *Echinococcus granulosus*
- Dwarf tapeworm: *Hymenolepis nana*
- Rat tapeworm: *Hymenolepis diminuta*

(Ref: Akram's Parasitology-2nd, P-156)

Features of medically important cestodes:

Name of cestode	Mode of transmission	Intermediate host	Main sites affected in human body	Diagnosis	Treatment
1. Diphylobothrium latum	Ingested larvae in undercooked fish.	Copepods and fish	Intestine	Opreculated eggs in stool.	Praziquantel
2. Taenia saginata	Ingested larvae in undercooked beef.	Cattle	Intestine	Proglottids in stool	Praziquantel
3. Taenia solium	a. Ingested larvae in undercooked pork	Pigs	Intestine	Proglottids in stool	Praziquantel
	b. Ingested eggs in food or water contaminated faeces	Pigs	Brain & Eye (Cysticerci)	Biopsy CT scan	Praziquantel or surgical removal of cysticerci.
4. Echinococcus granulosus	Ingested eggs in food or water contaminated with dog faeces.	Sheep	Liver, lungs and brain (Hydatid cyst)	Biopsy, CT scan, serology	Albendazole or surgical removal of cyst.

(Ref: LANGE Review-15th)

Echinococcus

Q. Regarding Echinococcus *(BSMMU – Residency – **MD, MS, Basic science** – March' 16)*

a) man is the definitive host
b) transmission by ingestion of contaminated eggs
c) transplacental transmission occurs
d) cyst may be found in brain and kidney
e) adult tapeworm is found in domestic animals like sheep

Ans. a) F b) T c) F d) T e) F

Help link:
Infective form: Eggs of *E. granulosus*
Portal of entry: Alimentary tract
Sites of localization - Viscera (Liver, lungs and other organs).

Definitive host of *E. granulosus*: Dog, wolf, fox and jackal.
Intermediate host of *E. granulosus*: Sheep, pig, cattle, horse, goat and man.
Dead-end intermediate host: Man

■ **Transmission**: The eggsin the dog's faeces are ingested by man. This occurs in the following ways:

1. By a direct contact (handling & fiooding) with infected dogs.
2. By allowing the dog to feed from the same dish.
3. By taking uncooked vegetables contaminated with infected canine faeces.

Infection is generally acquired in childhood (due to intimate association with dogs) though the disease does not become manifest before adult.

(Ref: K.D. Chatterjee-13th, P-162)

Hydatid cyst

Q. Hydatid cyst - (BSMMU - M. Phil, Diploma, July-04)

a) Contains the adult the parasite	F
b) Is found most commonly is liver	T
c) Is transmitted on contact with dog feces	T
d) Can produce malignancy in liver	F
e) Can produce hypersensitivity if rupture	T*(if the cyst ruptures spontaneously or during trauma or surgical procedure, life threatening anaphylaxis can occur)*

HELP LINK:

■ **Hydatid cyst**: The larval stage of *E. granulosus* in man causes uniocular hydatid cyst.

■ **Structure**:

A. **Cell wall**: The cyst wall has 2 layers-

1. ***Outer cuticular layer (Ectocyst)***:

- It is a laminated hyaline membrane.
- It is thick (upto 1 mm).
- Its appearance is of the white of a hard-boiled egg.
- It is elastic and when incised or ruptured curls on itself exposing the inner layer containing the brood capsules and daughter cysts.

2. ***Inner or germinal layer (Endocyst)***:

It is cellular.

It is thin (22-25μm).

It is the vital layer of the cyst and –

- It gives rise to brood capsules with scolices
- secretes the specific hydatid fluid
- forms the outer layer.

(Ref: K.D. Chatterjee-13th, P-162)

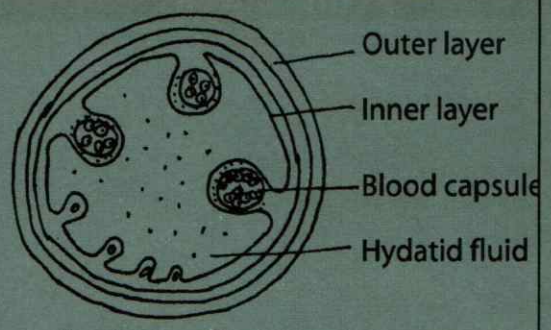


Fig: Structure of hydatid cyst

Composition and character of hydatid fluid:

1. Clear colorless fluid.
2. Specific gravity low, 1.005-1.010
3. Reaction slightly acid, pH 6.7
4. Contains NaCl, $NaSO_4$, Na_3PO_4 and Na & Ca salts of succinic acid
5. Antigenic, being used for immunological tests.
6. Highly toxic, when absorbed gives rise to anaphylactic symptoms.
7. Hydatid sand- Agranular deposit found to settle at the bottom. It consists of liberated brood capsules, free scolices and hooklets.

(Ref: K.D. Chatterjee-13th, P-162)

■ **Sites**: It occurs in -

- Brain
- Heart
- Lungs
- Liver
- Kidney
- Urinary bladder
- Uterus, fallopian tube & ovary
- Muscle
- Long bones

Composition of Hydatid cyst:

A. **Cell wall**: The cyst wall has 2 layers-

1. ***Outer cuticular layer (Ectocyst)***: It is a laminated hyaline membrane. Its appearance is of the white of a hard-boiled egg. It is thick.
2. ***Inner or germinal layer (Endocyst)***: It is cellular. It gives rise to brood capsules with scolices, secretes the specific hydatid fluid and forms the outer layer. It is thin.

B. **Inner component**:

1. NaCl, $NaSO_4$, Na_3PO_4 and Na & Ca salts of succinic acid
2. Hydatid sand - Agranular deposit found to settle at the bottom.

■ **Pathogenesis of Hydratid Cyst:**

The larval form of worm *Echinococcus granulosus* causes cystic hydratid disease. By handling a dog or drinking contaminated water, human may ingest eggs of *E. granulosus*. Larvae released from the eggs penetrate the gut and enter the blood stream and disseminate to deep organs (Liver, lung, skeletal muscle, brain etc) where they grow to form hydrated cyst.

The clinical features may depend on the site of the cyst & its size:

- As the cyst continues to grow & expand, pressure symptoms & necrosis of infected tissue may result
- Rupture of a cyst (During biopsy or naturally), may produce anaphylactic shock, eosinophilia or allergic reaction.

■ **Complications of hydatid cyst**: Rupture of a hydatid cyst is associated with

1. Anaphylactic symptoms
2. Formation of localized or generalized secondary echinococcosis.

Lab. diagnosis of hydatid cyst:

Principle:

The diagnosis of Echinococcosis relies mainly on findings by ultrasonography and/or other imaging techniques supported by positive serologic tests for detection of antibody. Microscopy can be done but there is risk of hypersensitivity and dissemination to other organs.

(Ref: Prof. Akram-2nd, P-263)

Specimen collection:

- Blood.
- Aspirated fluid.

A. ***Direct evidence***:

-Exploratory cyst puncture followed by microscopic examination of hydatid cyst.

-We look for hooklets & scolices.

B. ***Indirect evidence***:

1. **Casoni's reaction**: It is a hypersensitivity reaction. It is not done due to chance of severe anaphylactic reaction.
2. **Radiological examination** of hydatid cyst: we look for radio-opaque shadow of calcified hydatid cyst.
3. **Hepatic photoscan**: we localize the site of hydatid cyst in liver.
4. **Blood examination**: TC- ↑ (leukocytosis). DC- Eosinophilia. (20-25%)
5. **Serological tests**: Detection of anti E. granulosus Ab by
   - Indirect haemagglutination test
   - Indirect flourescent antibody
   - Floculation test
   - Immunoelectrophoresis

(Ref: K.D. Chatterjee-13th, P-163)

NEMATODES

Features of medically important nematodes

Primary Location	Species	Common Name of Disease	Mode of Transmission	Endemic Areas	Diagnosis	Treatment
Intestines	Enterobius	Pinworm	Ingestion of eggs	Worldwide	Eggs on skin	Mebendazole or pyrantel pamoate
	Trichuris	Whipworm	Ingestion of eggs	Worldwide, especially tropics	Eggs in stools	Mebendazole
	Ascaris	Ascariasis	Ingestion eggs	Worldwide, especially tropic	Eggs in stools	Mebendazole or pyrantel pamoate
	Ancylostoma and Nector	Hookworm	Larval penetration of skin	Worldwide, especially tropics (Ancylostoma) united states (Necator)	Eggs in stools	Mebendazole or pyrante
	Strongyloides	Strongyloidiasis	Larval penetration of skin, also autoinfection	Tropics primarily	Larvae in stools	Ivermectin
	Trichinella	Trichinosis	Larvae in undercooked meat	Worldwide	Larvae encysted in muscle; serology	Thiabendazole against adult worm
	Anisakis	Anisakiasis	Larvae in undercooked seafood	Japan, United States, Netherlands	Clinical	No drug available
Tissue	Wuchereria	Filanasis	Mosquito bite	Tropics primarily	Blood smear	Diethylcarbamazine
	Onchocerca	Onchocerciais Blackfly bite	Black fly bite	Tropical Africa	Skin biopsy	Ivermectin
	Loa	Loaiasis	Deer fly bite	Tropical Africa	Blood smear	Diethylcarbamazine
	Dracunculus	Guinea worm	Ingestion of Copepods in water	Tropical Africa and Asia	Clinical	Thiabendazole prior to extracting worm
	Toxocara larvae	Visceral larvae migrans	Ingestion of eggs	Worldwide	Clinical and serologic	Albendazole or mebendazole
	Ancylostoma larvae	Cutaneous larva migrans	Penetration of skin	Worldwide	Clinical	Thiabendazole

Q. Nematodes having lung infiltrative phase in their life cycle are *(BSMMU – Non-Residency – MD, MS, Paediatrics, Basic Science – July' 19)*

a) *Ascaris lumbricoides*
b) *Necator americanus*
c) *Strongyloides stercoralis*
d) *Wuchereria bancrofti*
e) *Trichuris trichiura*

Ans. a) T, b) T c) T d) F e) F

Help Link:

Nematodes passing through the lungs of the host:

- Strongyloides stercoralis
- Ankylostoma duodenale
- Necator americana
- Ascaris lumbricoides

Q. Larva of following nematodes cause disease *(BSMMU –Residency - MD/MS, Basic science, Paediatrics – March' 19)*

a) *Toxocara canis*
b) *Dracunculus medinensis*
c) *Trichuris tichiuara*
d) *Ankylostoma duodenale*
e) *Strongyloides stercoralis*

Ans.

a) **False** (Infective form is embryonated eggs)
b) **True** (Infective form is filariform larva)
ç) **False** (Infective form is embryonated eggs)
d) **True** (Infective form is filariform larva)
e) **True** (Infective form is filariform larva)

Q.The parasite which enter through skin penetration are *(BSMMU–Non-Residency–MD, MS, Basic science–16Ju)*

a) Wuchereria bancrofti F
b) Ascaris lumbricoides F
c) Necator americanus T
d) Strongyloides stercoralis T
e) Enterobius vermicularis F

Q. Following organisms can penetrate skin *(BSMMU – MD/MS (Residency) – January, 2011)*

a) Necator americanus T
b) Onchocerca volvulus F
c) S. stercoralis T
d) W. brancrofti F
e) A. duodenale T

Q. Following diseases are caused by nematodes: (BSMMU - M. Phil, Diploma, July-07)

a) hydatid disease F
b) giardiasis F
c) ascariasis T
d) trichomoniasis F
e) toxoplasmosis F

Q. Following nematodes pass via lung during their life cycle - (MD/MS (DMC)-09Ja)

a. *Trichuris trichiura* F
b. *Ascaris lumbricoides* T
c. *Enterobius vermicularis* F
d. *Stongyloides stercoralis* T
e. *Ancylostoma duodenale* T

Q. Nematodes penetrating intestinal mucosa are- (MD/MS (DMC) – January,2008)

a) *Aascaris lumbricoides*
b) *Strongyloid sterocoralis*
c) *Ancylostoma duodenale*
d) *Enterobius vermicularis*
e) *Trichuris trichiura*

Ans.
a) F *(habitat is intestine but they do not penetrate intestine)*
b) T *(female are buried in mucosa)*
c) F *(habitat is intestine but they do not penetrate intestine)*
d) F *(habitat is caecum & appendix but they do not penetrate)*
e) F *(habitat is caecum & appendix but they do not penetrate)*

HELP LINK:

■ **According to habitat of adult worms:**

Intestinal	**Somatic** (Inside the tissues & organs)
Small intestine only • Ascaris lumbricoides (round worm) • Ancylostoma duodenale (Old world worm) • Necator americanus (American hookworm) • Strongyloides stercoralis • Trichinella spiralis (Trichina worm) • Capillaria philippinensis Caecum & vermiform appendix • Enterobius vermicularis (Thread/pin worm) • Trichuris trichuria (Whipworm)	Lymphatic system • Wuchereria bancrofti • Brugia malayi Subcutaneous tissues • Loa loa (African eye worm) • Dracunculus medinensis (Guinea worm) • Onchocerca volvulus Lungs • Strongyloides stercoralis Mesentery • Mansonella ozzardi • Dipetalonema perstans

(Ref: K.D. Chatterjee-13th edition, P-200)

■ **Mode of infection of Nematode:**

1. **By ingestion of-**
•Embryonated eggs - eg. A. lumbricoides, T. trichiura, E. vermicularis.
•Encysted embryos in infected pig's flesh- eg. T. spiralis.
•Growing embryos in an intermediate host (infected cyclops)- e.g. D. medinensis.
2. **By penetration of the skin** - e.g. A. duodenale, N. americanus, S. stercoralis.
3. **By blood-sucking insects**: eg. Filarioidea.
4. **By inhalation of infected dust containing embryonated eggs**. eg. A. lumbricoides, E. vermicularis.

(Ref: K.D. Chatterjee-13th edition, P-200)

Q. Nematodes found in lymphatic system: (MD/MS (DMC)-04Ja)

a) Wuchereria bancrofti T
b) Brugia malayi T
c) Loa loa F
d) Onchocerca volvulus F
e) Trichinella spiralis F

ASCARIASIS

Q. Clinical manifestations of ascariasis are: (BSMMU – MD - January, 2009)

a) Loeffler's syndrome T
b) Iron-deficiency anemia F
c) Ground itch F
d) Intestinal obstruction T
e) Obstructive jaundice T

HELP LINK:

Pathogenic lesions produced by *Ascaris lumbricoides*: Infection of *A. lumbricoides* in man is known as Ascariasis. The pathogenic lesions produced by *A. lumbricoides* infection may be divided into following two groups:

MEDICAL CONDITIONS:

A. **Symptoms produced by adult worm**:

1. **Spoliative action**:
   - PEM- by robbing the host of its nutrition (protein & vitamin)
   - Vit-A deficiency (Night blindness).
   - Malnutrition by liberating antienzymes (antipepsin & antitrypsin)

2. **Toxic action**: When body fluid of Ascaris (Ascarease) is absorbed by host, it gives rise to -
   - Typhoid like fever
   - Allergic manifestations: Urticaria, oedema of the face, conjunctivitis and irritation of upper respiratory tract, hypersensitivity reaction → Ascaris encephalopathy.

B. **Symptoms due to eggs**:
   - Eggs do not cause any lesion in the intestine.
   - Ova in the biliary canaliculi and liver may produce inflammatory changes.

C. **Symptoms due to migrating larvae**:
   1. **In the lung**: ***Ascaris pneumonia/ Loeffler's syndrome*** - Fever, cough, dyspnoea, blood-tinged sputum,urticarial rash, eosinophilia (20%).
   2. **In general circulation**: larvae can reach brain, spinal cord, heart, kidney, liver, eye causing organ dysfunction.
      - Meningitis, epilepsy, retinitis, palpebral oedema.

SURGICAL CONDITIONS: These conditions are caused by adult worm.

A. **Mechanical effects**:
   - Intestinal obstruction by bolus of parasites.
   - Intussusception- specially in children. (recurrent)
   - Perforation of intestinal ulcer.

B. **Ectopic ascariasis**: Due to migration
   - Suffocation: Ascaris may accidentally enters into respiratory passage & block rima glottidis or may enter into bronchus resulting in suffocation.
   - Ascaris may come out through mouth & nose.

C. **Wandering ascariasis**:
   - **Enter into appendix**: Acute appendicitis.
   - **Enter lumen of billiary passage**: may cause obstructive jaundice.
   - **Enter lumen of pancreatic duct**: causes acute haemorrhagic pancreatitis.
   - Penetrates the liver & cause liver abscess.

(Ref: K.D. Chatterjee-13th, P-233 + Akram-2nd, P-172)

Auto infection

Q. Parasites that cause auto infections are *(BSMMU-Residency - MD, MS, Basic Science - March' 18)*

a) *Cryptosporidium parvum*
b) *Entamoeba histolytica*
c) *Strongyloides stercoralis*
d) *Ascaris lumbricoides*
e) *Toxoplasma gondii*

Ans. a) T b) F c) T d) F e) F

Q. The parasites causing autoinfection are - *(BSMMU – Non-Residency – MD, MS, Basic Science & Dentistry – July' 17)*
a) *Cryptosporidium parvum*
b) *Giardia lamblia*
c) *Strongyloides stercoralis*
d) *Ascaris lumbricoides*
e) *Enterobius vermicularis*

Ans. a) T b) F c) T d) F e) T

Helplink:

Few intestinal parasites may be transmitted to the same person by contaminated hand(external autoinfection) or by reverse peristalsis(internal autoinfection). It is observed in

1. Cryptosporidium parvum
2. Taenia solium
3. Enterobious vermincularis
4. Strongyloides stercoralis
5. Hymenolepsis nana

(Ref: Medical parasitology by Apurbo sankar page 05)

Diseases transmitted by mosquito

Q. Diseases transmitted by mosquito are *(BSMMU –Residency – MD, MS, Basic Science, Dentistry – March' 18)*
a) rickettsia
b) lymphatic filariasis
c) cerebral malaria
d) chikungunia
e) kala azar

Ans. a) F b) T c) T d) T e)F

Q. The following helminthic diseases are transmitted by the bite of a mosquitoes- (MD/MS (DMC)-03Ja)

a) Filariasis	T
b) Onchocerciasis	F
c) Taeniasis	F
d) Schistosomiasis	F
e) Visceral larva migrans	F

HELP LINK:

■ **Parasites which are transmitted by insect vectors:**

Parasite	Insect vector	Diseases
1. *Giardia intestinalis*	House fly	Giardiasis
2. *Entamoeba histolytica*	House fly	Amoebiasis
3. *Trypanosoma brucei*	Tsetse flies.	Trypanosomiasis
4. *Trypanosoma cruzi*	Reduvid bug	Trypanosomiasis
5. *Leishmania donovani*	Sandflies	Kala-azar
6. *Plasmodium species*	Female anopheline mosquitoes.	Malaria
7. *Wuchereria bancrofti* 8. *Brugia malayi*	Female culex mosquitoes.	Filariasis
9. *Onchocerca volvulus*	Female black fly	Onchocerciasis
10. *Loa loa*	Deer fly	Loiasis.

(Ref: Microbiology)

Others

Q. Parasites reside in human intestine are *(BSMMU –Residency – MD, MS, Basic Science, Dentistry – March' 18)*
a) *Schistosoma haematobium*
b) *Fasciolopsis buski*
c) *Heterophytes heterophytes*
d) *Fasciola hepatica*
e) *Schistosoma mansoni*
Ans. a) F b T) c) T d) F e) F

Q. Following parasites infect man through oral route: (BSMMU – MD/MS - January, 2008)

a) Dracunculus medinensis	T
b) Strongyloid stercoralis	F
c) Enterobius vermicularis	T
d) Schistosoma haematobium	F
e) Ancylostoma duodenale	F

HELP LINK:

■ **Routes of various parasitic infection/ portal of entry**:

1. **Contamination of food and drink**:

a) Egg (e.g. egg of *Ascaris lumbricoides*) or Cyst (e.g. cyst of *Entamoeba histolytica*) containing food or drink.
b) Flesh of intermediate host containing Infective form of parasite:
- Beef containing cysticercus bovis (larval stage of *Taenia saginata*)
- Pork containing cysticercus cellulosae (larval stage of *Taenia solium*)
- Fish containing plerocercoid larvae of *Diphylobothrium latum*.

c) Intermediate host as a whole harbouring Infective form.
- Cyclops infected *Diphylobothrium medinensis*.

d) Aquatic plant containing Infective form of parasite.
- Metacercarial form of *Fasciolopsis buski* & *Fasciola hepatica*.

2. **By contamination of skin or mucous membrane**:

a) By direct penetration of skin:
- *Ancylostoma duodenale*
- *Necator americanas*
- *Strongyloides stercoralis*
- *Schistosoma haematobium*
- *Schistosoma mansoni*
- *Schistosoma japonicum*

b) By blood sucking arthropods:
- Plasmodium species
- Wuchereria
- Leishmania species
- Trypanosoma

c) By inhalation of dust containing egg:
- Ascaris lumbricoides
- Enterobius vermicularis

d) By blood transfusion: e.g.- plasmodium species.
e) By sexual contact: e.g.- Trichomoniasis.

f) Transplacental / congenital:
- Toxoplasma gondii
- Plasmodium.

3. **By vector or insects**:
- Leishmania donovani
- Plasmodium species.

(Ref: K.D. Chatterjee-13th, P-4)

Q. Parasitic diseases of skin are: (BSMMU - M. Phil, Diploma-07July)

a) scabies	T
b) moluscum contagiosum	F
c) filariasis	T
d) creeping eruption	T
e) erythema induratum	F

Q. Following parasites infect man by penetrating the skin - (BSMMU - M. Phil, Diploma, July-06)

a) Dracunculus medinensis	F
b) Strongyloid stercoralis	T
c) Enterobius vermicularis	F
d) Schistosoma haematobium	T
e) Necator americanus	T

Q. Following parasites infect man through oral route - (BSMMU - M. Phil, Diploma, July-05)

A. dracunculus medinensis
B. strongyloid sterocoralis
C. entrobius vermicularis
D. schistosoma haematobium
E. necator americanus

Ans.
a) T *(Ingestion of copepods in water)*
b) F *(Auto-infection, Larval penetration of skin)*
c) T *(Ingestion of eggs)*
d) F *(Pentration of skin)*
e) F
(Larval Penetration of skin)

(REF: LANGE Review-14th)

Q. Following parasites enter the body through skin: (BSMMU-MD/MS-06Ja)

A. Necator americanus
B. Dracunculus mediasis
C. Schistosorna haematobium
D. Enterobius vermicularis
E. Strongyloid sterocoralis.

Ans. a) T b) F *(Ingestion .of copepods in water)* c) T d) F *(Ingestion of eggs)* e) T

HELP LINK:

Parasites enter the body through skin
• Ancylostoma duodenale
• Necator americanus
• Strongyloides stercoralis (filariform larvae)
• Larva migrane (cutaneous)
• Schistosomes: S. haematobium, S. mansoni, S. japonicum

Q. Following are protozoal infections (BSMMU-05Ja)

A. Hydatid disease
B. Trypanosomiasis
C. Giardiasis
D. Schistosomiasis
E. Filariasis

Ans.

A. F *(Echinococcus granulosus—dog tapeworm)*
B. T C. T
D. F *(Trematode)*
E. F *(Caused by W. bancrofti, a tissue nematode)*

Q. Following parasites enter the body penetrating the skin- (BSMMU-05Ja)

A. Necator americanus T
B. Enterobius vermicularis F
C. Strongyloid stercoralis T
D. Schistosoma mansoni T
E. Dracunculus medinensis F

Q. Parasites which usually infect young RBC is/are- (BSMMU-MD/MS-05Ja)

A. P. malariae
B. P. ovale
C. P. vivax
D. P. falciparum
E. L. donovani

Ans.

a) F *(invades normoblasts)*
b) F *(invades reticulocytes)*
c) F *(invades reticulocytes)*
d) T *(invades RBCs of all ages but especially young cells —so anemia is most severe)*
e) F *(Invades macrophages)*

Q. Malabsorption syndrome is the primary character of disease which is caused by: (MD/MS-(DMC)-01Ja)

A. Trypanosoma bruci.
B. Microaerophilic streptococci.
C. Entamoeba histolytica.
D. Giardia lamblia
E. Toxoplasma gondii.

Ans.

a) F (fever, severe headache, infection of blood stream,)
b) F
c) F (perianal pruritis)
d) T (chronic enteritis & acute entero-colitis)
e) F (cerebrospinal, eye, lymph, skin, lung, breast, arterys affected)

Q. An insect vector can infect human with - (BSMMU-MD/MS-01Ja)

a) Wuchereria bancrofti T
b) Diphylobothrium latum F
c) Brugia malayi T
d) Onchocere volvulus T
e) Strongyloides stercoralis F

For Dentistry

Q. The saprophytic parasites of the oral cavity that produce severe, progressive periodontal disease in immunocompromised patients are *(BSMMU – Residency – Dentistry – March' 19)*

a) *Entamoeba gingivalis*
b) *Giardia lamblia*
c) *Trichomonas tenax*
d) *Entamoeba histolytica*
e) *Toxoplasma gondii*

Ans. a) T b) F c) T d) F e) F

SOME IMPORTANT TOPICS

Table: Portal of entry of infectious parasites

Portal of entry	Infectious parasite
1. Ingestion, Alimentary tract	• Taenia solium • Taenia saginata • Trichinella spiralis • Spirometra larval stage • Balantidium coli. • E. granulosus • Toxoplasma gondii. • Diphyllobothrium latum • Fasciola buski • Fasciola hepatica • Entamoeba histolytica • Ascaris lumbricoids • Hymenolepsis nana • Trichuris trichiura
2. Penetration of skin	• Ancylostoma duodenale • Necator americanus • Strongyloides stercoralis (filariform larvae) • Larva migrane (cutaneous) • Schistosomes: S. haematobium, S. mansoni, S. japonicum
3. Inoculation of skin	• Trypanosoma brucei • Leishmania donovani • L. tropica. • L. brasiliensis • Plasmodium
4. Contamination, skin	Trypanosoma cruzi
5. Dropped on skin	• Wuchereria bancrofti • B. malayi • Loa loa • O. Volvulus
6. By blood sucking insect	• Trypanosoma • Leishmania • Wuchereria • Plasmodium
7. By inhalation of dust containing eggs	• A. lumbricoides

	• E. vermicularis
8. By sexual contact	• Trichomonas
9. Congenital/ vertical transmission	• Plasmodium • Toxoplasma gondii
10. By blood transfusion	• Plasmodium • Toxoplasma
11. Direct contact	• Sarcopti scabei • Pthyrus pubis
12. Autoinfection	• Enterobius vermicularis • S. stercorales

IMPORTANT MCQ OF PARASITOLOGY

[Ref: Smiddy]

Q. Which among the following are protozoal infections:

a) hydatid disease
b) trypanosomiasis
c) giardiasis
d) schistosomiasis
e) filariasis

Ans.

a) **False** Hydatid disease is caused by a cestode, (tapeworm) known as *Echinococcus granulosus* which is transmitted by dogs to man by faecal—oral contamination. The dog is infected by the eating of infected sheep, cattle or pig offal. Man ingests the ova which have a chitinous coat which is digested by the gastric juice thus liberating the embryos. These then invade the veins of the gastrointestinal tract and reach the liver via the portal blood, where most of them lodge to develop into unilocular or multilocular cysts.

b) **True** The trypanosomes, T. gambiense and rhodesiense are both flagellated protozoa. Both are a cause of sleeping sickness, a disease transmitted by the tsetse fly. In South America another species, T. cruzil, which is transmitted by the blood sucking bugs of the family Triatomidae, causes a condition known as Chagas disease in which severe myocardial damage may occur.

c) **True** Giardiasis is caused by the flagellate protozoa Giardia lamblia. This parasite causes an intestinal infection which leads to chronic diarrhoea and possible malabsorption.

d) **False** Schistosomiasis is caused by a group of trematode worms which infect man after they have been released from their intermediate host. Schistosoma tiaematobium has as its intermediate host the snail, Bullnus, which lives in fresh but stagnant water. From the snail free swimming cercariae emerge which enter the human host chiefly through the skin of the legs and also through the mucous membrane of the mouth and pharynx. The adult worms finally reach the vesicle plexus of veins where they settle and pair. The major causes of damage are the ova which are produced. A granulomatous reaction is provoked with the result that fibrosis of bladder wall occurs. In addition squamous metaplasia of the urothelium may be followea by a squamous carcinoma. Another variety, the Schistosoma mansoni, inhabits the venules of the lower gastrointestinal tract provoking a granulomatous reaction with subsequent ulceration and melaena. Both may cause pipe-stem periportal fibrosis of the liver which may finally terminate in the development of portal hypertension and oesophageal varices.

e) **False** Filanasis is a nematode infection, four different species of filaria can be found in human tissues. The diagnosis of filariasis is made by demonstrating the presence of microfilariae in blood films at night in the case of *Wuchereria bancrofti* or in skin snip biopsies in the case of Onchocerca volvulus. Infestation with the former cause elephantiasis due to low grade inflammation which the parasite induces in the lymphatics and the latter causes subcutaneous nodules, looseness of the skin and blindness. Wuchereria bancrofti is transri,itted by a female mosquito, usually of the Culex genus and onchocerca is transmitted by the fly, Simulium amnosum.

Q. Mosquitoes transmit the following diseases: (BSMMU – MD/MS – 06Ja, DMC-02Ja)

A. Schistosomiasis.
B. Leishmaniasis.
C. Dengue
D. Yellow fever.
E. Malaria.

Ans.

A. **False** (The mosquito plays no part in the life cycle of the schistosoma, the intermediate host of this parasite is a snail found in fresh water.)

B. **False** (Leishmaniasis is protozoal disease transmitted by the bite of the sandfly, Phiebotomus papatasi. The condition is endemic throught the Middle East, South Asia, Africa and Latin Ameica. The infective agent is slender, flagellated parasite which is introduced into the host together with the sandfly saliva. It is then phagocytosed by the mononuclear cells and transformed into a round amastigote which divides in the phagolysosomes of the macrophages, rupturing the cells nd infecting others. The extent of the spread of the amastigotes is determined by the species of Leishmania. Thus the cutaneous form is caused by several varieties including L. major and braziliensis whereas visceral leishmaniasis is caused by L. donovani in the New world.)

C. **True** (Dengue fever is a severe but usually short lived febrile illness which is caused by a toga virus transmitted by the mosquito Aedes aegypti).

D. **True** (Yellow fever is also caused by a toga virus transmitted by Aedes aegypti. Both the virus of dengue fever and yellow fever belong to the group collectively known as arthropod borne virus, hence the generic name arbovirus.)

E. **True** (Malaria is protozoal disease transmitted by the female anopheles mosquito. The various protozoal species are Plasmodium vivax, falciparum, maiariae and ovale. The most severe form of malaria is caused by *Pl. Falciparum* which causes both malaria and blackwater fever. The latter is so named because of the haemoglobinuria whiëh follows the severe intrvascular haemolysis.)

Q. The following are mainly intracellular parasites: (BSMMU – MS - January, 2010)

a) Echinococcus granulosus
b) Leishmania donovani
c) Trypanosoma gambiense
d) Plasmodium vivax
e) Toxoplasma gondii

Ans.

a) **False** Echinococcus granulosus is a cestode (tapeworm) infestation which gives rise to hydatid disease. The dog is the intermediate host between sheep and man. In the latter the chief pathological lesion is the formation of hydatid cysts. These are most commonly found in the liver, lung, and brain, in descending order of frequency. The worms themselves are extracellular and infection develops when ova are accidently eaten. These are shed in the faeces of the dogs which harbour the adult worm in the small intestine.

b) **True** Leishmania donovani, a protozoon, 'is the causative agent of systemic leihmaniais,, kala-azar, a disease in which the protozoa are generally found Within the macrophages in the amastigote form called the Leishmán—Dpnovan bodies. These are particularly common in the bone marrow and spleen. Leishmania parasites are cleared from the body by cell-mediated immune mechanisms. Hence the diagnosis can be made by eliciting a delayed type of hypersensitivity reaction to an extract of Leishmania injected into the skin, the Leishmanin test.

c) **False** The trypanosomes, T. gambiense and T. rhodesiense are flagellated parasites which are found freely circulating in the blood. Both cause sleeping sickness in cattle and the human and are transmitted from man to man or from animals to man by the tsetse fly (Glossina).

d) **True** Plasmodium vivax is one of a group of parasites of the genus Plasmodium. This particular species is responsible for benign tertian malaria. The diagnosis is confirmed by the examination of a blood smear when various forms of the life cycle including trophozoites, merozoites and schizonts can be seen within infected erythrocytes.

e) **True** Toxoplasma gondii, the cause of toxoplasmosis, multiplies within the Cytoplasm of the cells of the mononuclear phagocyte system causing the lymph nodes to enlarge and become packed with large cells which are probably macrophages. In severe cases cysts may form and in the brain necrotic nodules may be found which may calcify. Severe damage can also occur in the eye leading to choroidoretinitis and uveitis. The definitive host is the cat and infection occurs through faecal contaminatioh of the human either by inhalation or ingestion. In the cat oocysts are discharged into the lumen from their site of development in the gastrointestinal membrane.

GENERAL BACTERIOLOGY

Prokaryotes and Eukaryotes

Q. Prokaryotic cells have *(BSMMU –Residency - **Dentistry** – March' 19)*
a) processed mRNA
b) both exons and introns
c) coupled transcription and transaction
d) nucleoid rather than nucleus
e) golgi apparatus
Ans. a) F b) F(bacterial DNA has no introns, whereas eukaryotic DNA does) c) T d) T e) F

Help link:
Nucleoid
- ✓ The DNA of prokaryotes is a single, circular molecule that has a molecular weight (MW) of approximately 2 × 109 and contains about 2000 genes. (By contrast, human DNA has approximately 100,000 genes.)
- ✓ Because the nucleoid contains no nuclear membrane, no nucleolus, no mitotic spindle, and no histones.
- ✓ bacterial DNA has no introns.

(Ref: LANGE-14th, P-10)

Q. Prokaryotic cells *(BSMMU – Diploma - **Dentistry** – July' 18)*
a) have no true nucleus
b) poses single circular DNA
c) contain sterol in their cytoplasmic membrane
d) reproduce both sexually and asexually
e) do respiration by cytoplasmic membrane
Ans. a) T b) T c) F (eukaryote has sterol not prokaryote except Mycoplasma) d) F
e) T (cellular respiration occurs either in the cytoplasm or in the cytoplasmic membrane)

Q. Prokaryotic cells have *(BSMMU –Residency – **Dentistry** – March' 18)*
a) processed mRNA
b) both exons and introns
c) coupled transcription and translation
d) nucleoid rather nucleus
e) golgi apparatus
Ans. a) F (It is a feature of eukaryotes) b) F c) T d) T e) F

Help link:
■ **Prokaryote**: 'Pro' means primitive & 'karyotes' means nucleus. So, literally prokaryotes means the cells having a primitive nucleus.

Prokaryotes are cells having a primitive nucleus or nucleoid consisting of a single circular molecule of **loosely organized DNA** lacking a nuclear membrane, nucleolus, nucleoplasm and mitotic apparatus.
Example: All and only bacteria.

Features of prokaryotes:
- Cells have no nucleus but nucicoid.
- Lacking nuclear membrane, neucleoplasm and mitotic apparatus.
- Single circular chromosome.
- No membrane bound organdies.
- 70S (50S + 30S) ribosome.
- Reproduce asexuaily or by binary fission.
- Cell wall has peptidoglycan.

■ **Eukaryote**: 'Eu' means normal & 'karyotes' means nucleus. So, literally eukaryotes means the cells having a normal nucleus.

Eukaryotes are cells having a true nucleus with multiple chromosomes, nucleolus & nucleoplasm surrounded by a nuclear membrane and using mitotic apparatus for their division.

Example: Human cells, protozoa. fungi, plant cells etc.

Features of eukaryotes:

- Cells have organised nucleus with DNA, nuclear membrane, nucleolus & nucleoplasm.
- Many linear chromosomes.
- Membrane bound organdies present.
- 80S (60S + 40S) ribosome.
- Reproduce sexually or asexually.
- Cells may or may not have cell walls. If cell wall is present, it is made up of cellulose chitin.

■ **Differences**:

Traits	Prokaryotic cell	Eukaryotic cell
1. DNA within a nuclear membrane	No	Yes
2. Mitotic division	No, binary fission	Yes
3. DNA associated with histones	No	Yes
4. Chromosome number	One	More than one
5. Mitochondria	No	Yes
6. Lysosome	No	Yes
7. Size of ribosome	70S	80S
8. Cell wall containing peptydoglycan	Yes	No
9. Cell type	Primitive	More advance
10. Example	Bacteria, Mycoplasma	Protozoa, fungi.
11. Sterol	Absent (except mycoplasma)	Present
12. Plasmid	Present	Absent

(Ref: LANGE Review-14th, P-02)

Basic bacteriology

- Bacteria are classified by shape into three basic groups: cocci, bacilli, and spirochetes
- The cocci are round, the bacilli are rods, and the spirochetes are spiral-shaped.
- Certain cocci occur in pairs (diplococci), some in chains (streptococci), and others in grapelike clusters (staphylococci).
- Size from about 0.2 to 5 μm
- The smallest bacteria Mycoplasma: same size as the largest viruses (poxviruses)
- The longest bacteria rods are the size of some yeasts and human red blood cells (7 μm).
- Metachromatic granules: characteristic feature of Corynebacterium diphtheriae, the cause of diphtheria.

General characteristics of bacteria

- All cocci are Gram posive, except: neisseria
- All rods are Gram negative , except:
  - bacillus,
  - clostridium,
  - corynebacterium,
  - listeria,
  - actinomyces
- All pathogens are facultative anaerobes, except: clostridium and bacteroids

Gram resistent organisms:

- Mycobacterium,
- Nocardia (wax like outer layer),
- Mycoplasma(no cell wall),
- Rickettsia,
- Coxiella, chlamydia,
- Treponema, borrelia

Question Bank

Q. Gram positive bacteria are *(BSMMU – Non-Residency – **MD, MS, Basic science** – July' 18)*
a) Mycobacterium tuberculosis
b) Neisseria gonorrhoeae
c) Acinetobacter spp.
d) Coagulase negative Staphylococcus
e) Treponema pallidum Ans. a) F b) F c) F d) T e) F

Q. Gram positive cocci are *(BSMMU – Residency - **Dentistry** - March' 17)*
a) Neisseria gonorrhoeae
b) Streptococcus pneumoniae
c) Kiebsiella pneumoniae
d) Staphylococcus aureus
e) Pseudomonas aeruginosa
Ans. a) F b)T c) F d) T e)F

Help link:

Classification of Medically Important Bacteria.		
Characteristics	**Genus**	**Representative Diseases**
I. Rigid, thick-walled cells		
A. Free-living (extracellular bacteria)		
1. Gram-positive		
a. Cocci	*Streptococcus*	Pneumonia, pharyngitis, cellulitis
	Staphylococcus	Abscess of skin and other organs
b. Spore-forming rods		
(1) Aerobic	*Bacillus*	Anthrax
(2) Anaerobic	*Clostridium*	Tetanus, gas gangrene, botulism
c. Non-spore-forming rods		
(1) Nonfilamentous	*Corynebacterium*	Diphtheria
	Listeria	Meningitis
(2) Filamentous	*Actinomyces*	Actinomycosis
	Nocardia	Nocardiosis
2. Gram-negative		
a. Cocci	*Neisseria*	Gonorrhea, meningitis
b. Rods		
(1) Facultative		
(a) Straight		

(i) Respiratory organisms	*Haemophilus*	Meningitis
	Bordetella	Whooping cough
	Legionella	Pneumonia
(ii) Zoonotic organisms	*Brucella*	Brucellosis
	Francisella	Tularemia
	Pasteurella	Cellulitis
	Yersinia	Plague
(iii) Enteric and related organisms	*Escherichia*	Urinary tract infection, diarrhea
	Enterobacter	Urinary tract infection
	Serratia	Pneumonia
	Klebsiella	Pneumonia, urinary tract infection
	Salmonella	Enterocolitis, typhoid fever
	Shigella	Enterocolitis
	Proteus	Urinary tract infection
(b) Curved	*Campylobacter*	Enterocolitis
	Helicobacter	Gastritis, peptic ulcer
	Vibrio	Cholera
(2) Aerobic	*Pseudomonas*	Pneumonia, urinary tract infection
(3) Anaerobic	*Bacteroides*	Peritonitis
3. Acid-fast	*Mycobacterium*	Tuberculosis, leprosy
B. Non-free-living (obligate intracellular parasites)	*Rickettsia*	Rocky Mountain spotted fever, typhus, Q fever
	Chlamydia	Urethritis, trachoma, psittacosis
II. Flexible, thin-walled cells	*Treponema*	Syphilis
(spirochetes)	*Borrelia*	Lyme disease
	Leptospira	Leptospirosis
III. Wall-less cells	*Mycoplasma*	Pneumonia

(Ref: LANGE Review-14th, P-25)

Q. Gram positive cocci are *(BSMMU – Residency – **Dental surgery** – March' 14)*

a) neisseria F
b) veilonella F
c) enterococci T
d) streptococci T
e) staphylococcus T

Q. Followings are gram negative bacilli: (BSMMU - M. Phil, Diploma, July-09)

a) Pseudomonas aeruginosa T
b) Treponema pallidum F
c) Yersinia enterocollitica T
d) Helicobacter pylori T
e) Vibrio cholerae T

Q. Following bacteria are Gram positive cocci- (BSMMU-MD/MS-07Ja)

a. Streptococcus pneumoniae T
b. H. influenzae F
c. N. meningitides F
d. Viridans streptococci T
e. Staphylococcus T

Q. Followings are gram positive bacteria- (BSMMU-MD/MS-06Ja)

A. Bacillus cereus
B. Leptospira
C. Lactobacillus
D. Actinomycetes
E. Yersinia pestis

Ans. a) T *(spore forming rod)* b) F *(It is a spirochete)*
c) T d) T e) F *(gram negative facultative straight zoonotic organism causing plague)*

Facultative anaerobes

- Utilize oxygen, if present, when absent, use fermentation pathway to synthesize ATP.

Hemophilus	Bordetella	Brucella	pasteurella	Legionella
Bartonella	Franciella	Vibrio	Campyobacter	E. coli
Klebsiella	Proteus	Serratia	Citrobacter	Enterobacter
Salmonella	Shigella	Yersinia	fusobacterium,	acinetobacter

Important intracellular pathogens are:

- Brucella
- Histoplasma
- Legionella
- Listeria
- Mycobacteria
- Chlamydia
- Rickettsia
- Viruses: Parovirus
- Plasmodium
- Toxoplasma

Obligate intracellular pathogens are:

o Chlamydia o Rickettsia o Viruses

- Mycobacterium tuberculosis is not obligate intracellular parasite.

- **Obligate aerobes :** M. tuberculosis, pseudomonas
- **Obligate anaerobes:** Clostridium tetani, bacteroids, cannot grow in the presence of oxygen because they lack either superoxide dismutase or catalase, or both

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Question Bank

Q. Facultative intracellular microorganisms are *(BSMMU –Residency - MD/MS, Basic science, Paediatrics – March' 19)*

a) *Salmonella pararyphi*
b) *Bacillus cereus*
c) *Mycobacterium bovis*
d) *Vibrio cholerae*
e) *E. coli*

Ans. a) T b) F c) T d) F e) F

Q. Intracellular organisms are *(BSMMU –Residency - **Dentistry** – March' 19)*
a) Epstein-barr virus
b) mycobacteria
c) shigella
d) pseudomonas
e) streptococcus
Ans. a) T b) T c) F d) F e) F

Q. Facultative intracellular bacteria are *(BSMMU –Residency – **MD, MS, Basic Science** – March' 18)*
a) *Salmonella typhi*
b) *Mycobacterium tuberculosis*
c) *Listeria monocytogenes*
d) *Chlamydia trachomatis*
e) *Mycoplasma pneumonia*
Ans. a) T b) T c) T d) F e) F

Q. Facultative intracellular organisms are *(BSMMU –Residency - **MD/MS, Basic science** – March' 14; – MD/MS (Residency) – January, 2011)*
a) L. monocytogenes T
b) nocardia F
c) brucella T
d) pseudomonas F
e) salmonella T

Q. The obligate intracellular bacteria are: *(BSMMU – M. Phil, Diploma (Non-Residency)–12Ju, DMC & others – MD/MS – 12Ju)*
a) Chlamydia trachomatis T
b) Rickettsia prowazekii T
c) Legionella pneumophilia F
d) Mycobacterium leprae F
e) Mycoplasma pneumonae F

Q. Facultative intracellular organisms are: *(BSMMU - M. Phil, Diploma – July '10)*
a) Rickettsia F
b) Legionella T
c) Chlamydia F
d) Brucella T
e) Yersenia T

Q. Following are obligate intracellular organism: (BSMMU – MD – January, 2010)
a) Mycobacterium tuberculosis F
b) Chlamydia T
c) Rickettesia app. T
d) Brucella spp. F
e) Yersinia spp. F

Q. Intracellular pathogens are – (MD/MS (DMC)-08Ja)
a) Legionella T
b) Streptococcus pyogens F
c) Parvovirus T
d) Chlamydia T
e) Brucella T

Q. Obligatory intracellular parasites are - (BSMMU - M. Phil, Diploma, July-06)
a) Mycoplasma pneumoniae F
b) Rickettsia prowazoki T
c) Chlymedia trachomatis T
d) Coxiella burneti T
e) M. tuberculosis F

Q. Obligate aerobes are: (BSMMU-MD/MS-06Ja)
A. Pseudomonas
B. E.coli
C. Mycobacterium tuberculosis
D. Kiebsiella
E. Streptococcus beta haemolyticus

Ans.
a) T b) F *(Facultative anaerobe)*
c) T *(It causes ↓ in highly oxygenated tissues such as the upper lobe of lung & kidneys)*
d) F *(Facultative, gram negative rods)*
e) F *(Facultative anaerobs)*

Q. Followings are intracellular bacteria - (BSMMU-MS-04Ja)

a) M. tuberculosis	T
b) Listeria monocytogens	T
c) Pseudomonas	F
d) Bacillus anthracis	F
e) Chlamydia	T

Others

Q. Following bacteria can not be stored in the refrigerator- (BSMMU-MD/MS-06Ja)

A. Pseudomonas	F
B. Neisseria mningitidis	T
C. Bacillus cereus	F
D. Staphylococcus aureus	F
E. Neisseria gonorrhoeae	T

Components of bacterial structure

Q. Following are the essential components of bacterial structure: (BSMMU - M. Phil, Diploma, July-'08)

a) cytoplasmic membrane	T
b) plasmid	F
c) nucleoid	T
d) mesosome	T
e) flagella	F

HELP LINK:

Structure	Chemical Composition	Function
Essential components		
Cell wall		
Peptidoglycan	Sugar backbone with peptide side chains that are cross-linked	Gives rigid support, protects against osmotic pressure, is the site of action of penicillins and cephalosporins, and is degraded by lysozyme
Outer membrane of gram-negative bacteria	Lipid A	Toxic component of endotoxin
	Polysaccharide	Major surface antigen used frequently in laboratory diagnosis
Surface fibers of gram-positive bacteria	Teichoic acid	Major surface antigen but rarely used in laboratory diagnosis
Plasma membrane	Lipoprotein bilayer without sterols	Site of oxidative and transport enzymes
Ribosome	RNA and protein in 50S and 30S subunits	Protein synthesis; site of action of aminoglycosides, erythromycin, tetracyclines, and chloramphenicol
Nucleoid	DNA	Genetic material
Mesosome	Invagination of plasma membrane	Participates in cell division and secretion
Periplasm	Space between plasma membrane and outer membrane	Contains many hydrolytic enzymes, including β-lactamases
Nonessential components		
Capsule	Polysaccharide[1]	Protects against phagocytosis
Pilus or fimbria	Glycoprotein	Two types: (1) mediates attachment to cell surfaces; (2) sex pilus mediates attachment of two bacteria during conjugation
Flagellum	Protein	Motility
Spore	Keratinlike coat, dipicolinic acid	Provides resistance to dehydration, heat, and chemicals
Plasmid	DNA	Contains a variety of genes for antibiotic resistance and toxins
Granule	Glycogen, lipids, polyphosphates	Site of nutrients in cytoplasm
Glycocalyx	Polysaccharide	Mediates adherence to surfaces

(Ref: LANGE REVIEW-14th, P-06)

Q. The component of gm- lipopolysaccharide which is responsible for most of its effects are: (MD/MS (DMC)-01Ja)

a) Core polysaccharide. F
b) Lipid- glucose fragment F
c) Lipid A. T
d) 'O' antigen. T
e) Lipoprotein subunit. F

HELP LINK:

■ **Lipopolysaccharide(LPS)**: It is called endotoxin. It is firmly bound to cell surface and is released only when the cells are lysed. It consists of

- lipid A (phospholipid).
- a core polysaccharide of five sugars linked through ketodeoxyoctulonate (KDO) to lipid A.
- an outer polysaccharide containing up to 25 repeating units of 3 to 5 sugars.

■ **Function**:

1. Lipid A is responsible for the toxic effect of endotoxin.
2. Polysaccharide is the important somatic or 'O' Ag of several gram negative bacteria that is used frequently in lab. diagnosis.

Nice to know:

Bacterial cell wall

- **The cell wall**: Outermost component, common to all bacteria (except Mycoplasma species, which are bounded by a cell membrane, not a cell wall).
- **Periplasmic space**: lie beteen the outer membrane and the cytoplasmic membrane.
  - ➢ **Importance**: contains beta lactamase that degrade penicillin, other beta lactum drugs.
- **Porin proteins**: control diffusion of sugar, ion and amino acids, vitamins, and metals as well as many antimicrobial drugs such as penicillins, beta lactums, fluoroquinonoles.
- Can develop resistence by mutating the gene.

LPS (Lipopolysaccharide):

- Composed of three distinct units
  (1) A phospholipid called lipid A: for the toxic effects.
  (2) A core polysaccharide of five sugars linked through ketodeoxyoctulonate (KDO) to lipid A.
  (3) An outer polysaccharide consisting of up to 25 repeating units of three to five sugars. This outer polymer is the important somatic, or O antigen of several gram negative bacteria that is used to identify certain organisms in the clinical laboratory.
- Neisseria, have an outer lipo-oligosaccharide (LOS) containing very few repeating units of sugars.

Teichoic acid:

- Fibers located in the outer layer of the gram-positive cell wall.
- Composed of polymers of either glycerol phosphate or ribitol phosphate.
- **Importance**: ability to induce septic shock.

Cytoplasmic membrane:

- Inside the peptidoglycan layer of the cell wall composed of a phospholipid bilayer
- Mycoplasma: have sterols in their membranes.
- **Functions:**
  1. active transport of molecules into the cell,
  2. energy generation by oxidative phosphorylation
  3. synthesis of precursors of the cell wall, and
  4. secretion of enzymes and toxins

Nucleoid:

- The DNA of prokaryotes is a single, circular molecule that has about 2000 genes. (By contrast, human DNA has approximately 100,000 genes.)
- The nucleoid contains no nuclear membrane, no nucleolus, no mitotic spindle, and no histones, there is little resemblance to the eukaryotic nucleus.
- One major difference between bacterial DNA and eukaryotic DNA is that bacterial DNA has no introns.

Transposons:

- Pieces of DNA that move readily from one site to another either within or between the DNAs of bacteria, plasmids, and bacteriophages.
- They are nick named "jumping genes."
- Transposons can code for drug-resistant enzymes, toxins, or a variety of metabolic enzymes and can cause mutations in the gene

Capsule

- Gelatinous layer
- composed of polysaccharide, except in the anthrax bacillus, which has a capsule of polymerized D-glutamic acid.
- **Function**:
  1. Prevents phagocytes to engulf the bacteria. Negative charges on the capsular polysaccharide that cause neutrophil to prevent.
  2. **Quellung reaction:** Specific identification of an organism by capsular swelling.
  3. As the antigens in certain vaccines. Example: capsular polysaccharides of 23 types of S. pneumoniae vaccine.
  4. Role in the adherence of bacteria.

Flagella:

- Flagella are long, whiplike appendages that move the bacteria toward nutrients and other attractants, a process called **chemotaxis.**
- Many rods have flagella but most cocci do not and are therefore nonmotile.
- Spirochetes move by using a flagellum like structure called the **axial filament**
- **Importance:**
  (1) Motile bacteria (e.g., E. coli and Proteus species) can cause urinary tract infections.
  (2) Salmonella species are identified in the laboratory by using of specific antibodies against flagella.

Pili (Fimbriae):

- Hair like filaments
- They are shorter and straighter than flagella and composed of pilin,
- found mainly on gram-negative organisms
- **Importance**:
  (1) attachment of bacteria to specific receptors on the human cell surface. Mutants of Neisseria gonorrhoeae that do not form pili are nonpathogens.
  (2) sex pilus: attachment between the male (donor) and the female (recipient) bacteria during conjugation

Glycocalyx (Slime Layer):

- Polysaccharide coating , secreted by many bacteria
- Adhere firmly to various structures (e.g., skin, heart valves, prosthetic joints, and catheters).
- The glycocalyx is an important component of biofilms
- **Examples**:
  - *Pseudomonas aeruginosa* cause respiratory tract infections in cystic fibrosis
  - *Staphylococcus epidermidis* and *viridans streptococci* that cause endocarditis.
  - *Streptococcus mutans* adhere to the surface of teeth, role in the formation of plaque, the precursor of dental caries.

Biofilm:

- Composed of polysaccharides and proteins.
- **Sites:** Foreign bodies such as prosthetic joints, prosthetic heart valves, and intravenous catheters, heart valves
- **Importance:**
- It protects bacteria from both antibiotics and host immune defenses such as antibodies and neutrophils.
- They also retard wound healing resulting in chronic wound infections, especially in diabetics.
- Persistence of Pseudomonas in the lungs of cystic fibrosis patients and in the formation of dental plaque, the precursor of dental caries.

Curli: *E. coli* and Salmonella have surface proteins and binds to endothelium and extracellular proteins such as fibronectin.

Importance: play a role in the production of the thrombi seen in the DIC.

Cell wall

Q. Cell wall of gram positive bacteria contains *(BSMMU –Residency - MD/MS, Basic science, Paediatrics, Dentistry – March' 19)*

a) peptidoglycan
b) periplasmic space
c) lipopolysaccharide
d) teichoic acid
e) porin protein

Ans. a) T b) F c) F d) T e) F(because Gram negative bacteria has outer membrane and porin protein is a part of outer membrane)

HELP LINK:

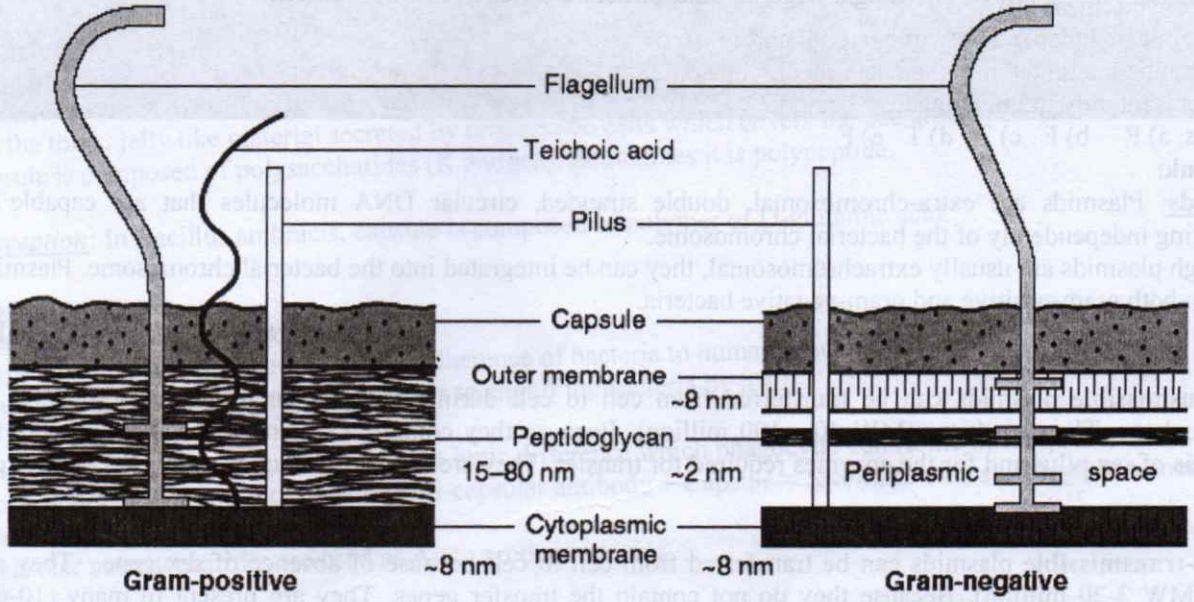

Fig: Gram positive & Gram negative cell wall (Ref: LANGE Review-14th, P-07)

■ **Components of cell wall:**

Gram positive cell wall	Gram negative cell wall
• **Peptideglycan** (Thicker, multilayer; 40 sheets) • **Techoic & Teichoronic acids** • Polysaccharides	• **Peptidoglycan** (thinner, single layer; 1-3 sheets) • Lipoprotein (LP) • Lipopolycysaccharides (LPS): endotoxin • **Outer membrane** • Periplasmic space

(Ref: LANGE REVIEW-14th, P-07)

Q. Gram positive bacteria differ from gram negative bacteria by: *(BSMMU – MD/MS (Residency) – 11Ja)*

a) cell membrane F
b) outer membrane T
c) pilli F
d) capsule F
e) lipopolysaccharide T

Help link:

■ **Differences:**

Component	Gram positive	Gram negative
1. Peptidoglycan layer	Thick, 40 sheets	Thin, 1-3 sheets
2. Teichoic & Teichuronic acids	Present	Absent
3. Lipoprotein	Absent	Present
4. Outer membrane	Absent	Bilayer outer membrane present outside peptidolgycan layer
5. Lipopolysaccharide (endotoxin)	Absent	Present - which act as endotoxin
6. Periplasmic space	Absent	Present
7. Gram staining	Violet	Red
8. L- form	Protoplast	Spheroplast

Plasmid

Q. Plasmid *(BSMMU – Non-Residency – **MS, Basic science** – July' 18)*
a) is chromosomal DNA
b) contain linear DNA
c) replicate independently of bacterial chromosome
d) can be integrated into the bacterial chromosome
e) present only in gram negative bacteria
Ans. a) F b) F c) T d) T e) F

Help link:

Plasmids: Plasmids are extra-chromosomal, double stranded, circular DNA molecules that are capable of replicating independently of the bacterial chromosome.
Although plasmids are usually extrachromosomal, they can be integrated into the bacterial chromosome. Plasmids occur in both gram-positive and gram-negative bacteria.

(Ref: LANGE Review-14th, P-10)

Types: 2 types.
1. **Transmissible** plasmids can be transferred from cell to cell during cell division through conjugation by bacteriophage. They are large (MW 40 - 100 million). Because they contain a dozen of genes responsible for synthesis of sex pilus and for the enzymes required for transfer. They are usually present in a few (1-3) copies per cell.

2. **Non-transmissible** plasmids can be transferred from cell to cell because of absence of sex gene. They are small (MW 3-20 million). Because they do not contain the transfer genes. They are present in many (10-60) copies per cell.

■ **Functions**:
1. Antibiotic resistance, which is mediated by a variety of enzymes, coded by plasmid DNA.
2. Resistance to heavy metals such as mercury (Hg) and silver (Ag), which is mediated by reductase enzyme.
3. Resistance to UV light, which is mediated by DNA repair enzymes.
4. Synthesis of pili (fimbriae) which mediate the adherence of bacteria with epithelial cells.
5. Production of exotoxins, including several enterotoxins. **(Ref: LANGE Review-14th, P-10)**

Q. Plasmid *(BSMMU –Residency - **MD/MS, Basic science** – March' 14)*
a) is chromosomal, ds DNA
b) contains circular DNA
c) replicate independently of the bacterial chromosome
d) can be integrated in to the bacterial chromosome
e) contain only gram positive bacteria
Ans. a) F b) T c) T d) T e) F

Capsule

Q. Organisms possess capsules are *(BSMMU –Residency – **MD, MS, Basic Science** – March' 18)*
a) *Haemophilus influenzae*
b) *Cryptosporidium spp.*
c) *Streptococcus pneumoniae*
d) *Staphylococcus saprophyticus*
e) *Klebsiella pneumoniae*
Ans. a) T b) F c)T d) F e) T

Q. Polysaccharide capsulated organisms are: (BSMMU - M. Phil, Diploma, July-07)

a) *Streptococcus pneumonae*	T
b) *B. anthracis*	F [Poly D glutamate]
c) *N. meningitidis*	T
d) *S. aureus*	T [contains microcapsule]
e) Salmonella	T

HELP LINK:

■ **Capsule**: Capsule is the bacterial end product condensed as gelatinous extracellular polymer giving rise to a well defined outer covering layer that immediatey in contact with cell wall.

- It is the thick, jelly like material secreted by prokaryotic cells which covers the bacterial cell wall.
- Capsule is composed of polysaccharides (K antigen). Sometimes it is polypeptide.

■ ***Exception***: In Bacillus anthracis, capsule is composed of polymer of D-glutamic acid.

■ **Importance**:

1. Capsular organism is pathogenic.
a. Capsule may play an important role in adherence of bacteria to human tissues.
b. Capsule limits the ability of phagocytosis to engulf the bacteria by it's
   i. Slippery action.
   ii. + ve or -ve charge that neutralizes the ionic difference which phagocytic cell (ionic interception)
2. Specific identification of organism: Anti-capsular antibody + Capsule = Swelling. This swelling phenomenon is called 'Quellung reaction'.
3. Capsular polysaccharides are used as Ag to produce vaccine.

Capsulated Gram negative bacteria***

1. *E.coli* (some stains)
2. ***Neisseria meningitidis***, *Neisseria gonorrhoea*
3. ***Klebsiella pneumonie***
4. ***H. influenzae***
5. *Pseudomonas aeroginosa*
6. *Salmonella*
7. *Yersinia pestris*
8. Bordetella
9. Pasturella

Capsulated Gram positive bacteria:

1. *Strptococcus pyogenes* (hyaluronic acid capsule)
2. *Sterptococcus pneumoniae*
3. *Streptococcus agalactiae*
4. *Staph. aureus*
5. *Bacillus megaterium, anthracis*
6. *Clostridium perfringens*

Fungus - *Cryptococcus neoformans* has a similar capsule.

Q. Capsulated organisms are - (BSMMU - M. Phil, Diploma, July-06)

a) Streptococcus pneumonia	T
b) Clostridium tetani	F
c) Closttidium welchii	F
d) Haemophilus infiuenzae	T
e) Staphylococcus aureus	T

Q. Following bacteria are motile: (BSMMU – MD/MS - 05Ja)

A. Kiebsiella pneumoniae
B. Pseudomonas
C. Shigella
D. Clostridium tetani
E. Proteus

Ans.

A. **False** *(Kiebsiella are non-motile, gram negative rods)*
B. **True** *(non-sporing, non-capsulated, and motile each with a polar flagellum)*
C. **False** *(gram negative rods, aerobic & non motile)*
D. **True** *(gram positive, non-acid fast, & may be motile)*
E. **True** *(motile)*

HELP LINK:

Motile bacteria	
• E. coli	• Proteus
• Vibrio	• Pseudomonas
• Salmonella	• Clostridium tetani
• Campylobacter	
• Helicobacter	
• Aeromonas	
• Pleomonus	

Q. Bacterial surface structures that show antigenic diversity include each of the following (M. phil, Diploma (DMC) – 03Ju)

a) Pili F
b) Capsule T
c) Flagella F
d) Peptidoglycan F
e) Loss of N. gonorrhoea F

Q. Bacterial pili are involved in: *(BSMMU – MD/MS – January, 2010)*

a) Adherence to host cells T
b) Transfer of genetic material T
c) Resistant to heat F
d) Endotoxic activity F
e) Motility F

HELP LINK:

PILI (FIMBRIAE)

Pili are hair-like filaments that extend from the cell surface. They are shorter and straighter than flagella and arc composed of subunits of a protein, pilin, arranged in helical strands. They are found mainly on gram-negative organisms.

Pili have two important roles:

1. They mediate the attachment of bacteria to specific receptors on the human cell Surface, which is a necessary step in the initiation of infection for some organisms. Mutants of *Neisseria gonorrhoeae* that do not form pili are nonpathogens.
2. A specialized kind of pilies, the sex pilies, forms the attachment between the male (donor) and the female (recipient) bacteria during conjugation.

Virulance of bacteria

Q. Bacterial structures which show antigenic property are *(BSMMU –Residency - MD/MS, Basic science, Paediatrics – March' 19)*

a) capsule
b) plasmid
c) pili
d) flagella
e) spore

Ans. a) T b) F c) T (pili or fimbria are antigenic, antibodies against fimbrial antigens are not protective) d) T e) T

Q. Virulance of bacteria is related to - (DMC – MD/ MS - January, 2010)

a) their number in the tissues	F
b) production of toxin	T
c) resistance of the host	F
d) their ability to resist phagocytosis	T
e) their ability to produce spreading factors	T

Help link:

1. **Adherence factors**: Certain bacteria have specialized structures that allow them to adhere to the surface of human cells. Thereby, they enhance their ability to cause disease.
   - Pili : in case of *Neisseria gonorrhoeae*
   - Capsules
   - Glycocalyx

2. **Invasion of host cells and tissues:** Ability of bacteria to enter into host cells and tissue and to spread within the body. e,g. Salmonella species invades tissues through the junction between epithelial cells.
   - Enzyme: e.g. Collagenase, hyaluronidase (of *Streptococcus pyogens)*
   - By breaking mucous membrane - *N. gonorrhoeae.*
   - Through intact mucous membrane — Shigella.

3. Antiphagocytic factors:
   - Capsule (Capsular polysaccharide of pneumococci.)
   - Pili
   - Protein A of *Staphylococcus areus*
   - Coagulase enzyme

4. Enzymes:
   - **Tissue degrading enzymes**: Hyaluronidase, Lecithinase etc.
   - **IgA protease**: Produced by & *pneumoniae. N meningitidis, H influenzae* etc.

5. Toxins:
   - **Exotoxins**: Enterotoxin. tetanospasmin. botulinum toxin, pyogenic toxin etc.
   - **Endotoxins**: It is the constituent of cell wall of Gram-negative bacteria and responsible for fever, shock. leucopenia, hypoglycemia, hypotension. DIC etc.

6. Others: M-protein of *Streptococcus pyogens:* interfere with ingestion by phagocytes.

(Ref: LANGE Review-14th, P-33-43)

Stages of bacterial pathogenesis: A generalized sequence of the stages of infection is as follows:
(1) Transmission from an external source into the portal of entry.
(2) Evasion of primary host defenses such as skin or stomach acid.
(3) Adherence to mucous membranes, usually by bacterial pili.
(4) Colonization by growth of the bacteria at the site of adherence.
(5) Disease symptoms caused by toxin production or invasion accompanied by inflammation.
(6) Host responses, both nonspecific and specific (immunity), during steps 3, 4, and 5.
(7) Progression or resolution of the disease.

(Ref: LANGE Review-14th, P-33)

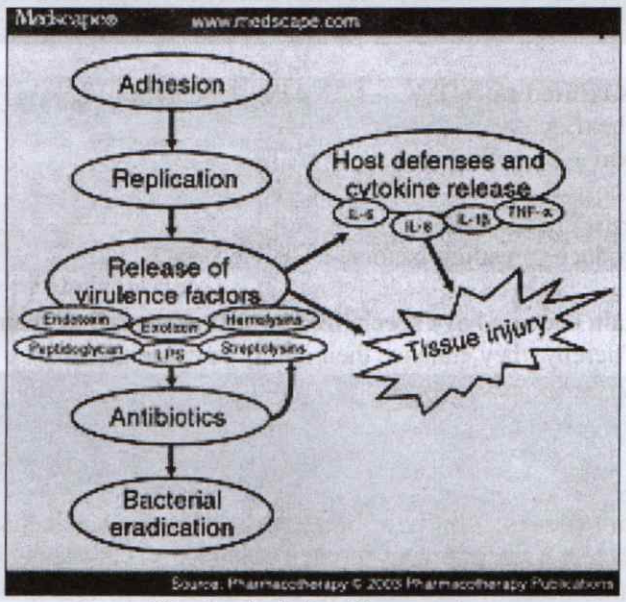

Fig: bacterial pathogenesis

Nice to know:

Bacterial virulence mechanisms:

1. Enzyme mediated tissue damage
2. Adherence
3. Toxin induced local and systemic effects
4. Invasion
5. Circulation from and spread from primary infection site
6. Evasion of host immune response

SPORE

Bacterial Spores:

- Highly resistant structures
  - eg: Bacillus, agent of anthrax, and
  - Clostridium causes tetanus and botulism.
- **Sporulation**: when nutrients, sources of carbon and nitrogen, are depleted.
- **The spore forms:** inside the cell and contains bacterial DNA, a small amount of cytoplasm, cell membrane, peptidoglycan, very little water, and most importantly, a thick, keratin like coat for the resistence to heat, dehydration, radiation, and chemicals mediated by **dipicolinic acid, a** calcium ion chelator found only in spores.
- **Spore can be killed by**: autoclaving, tyndallization, conc. H_2O_2.
- **Endospore killed by**: alkylating agents (ethylene oxyde and 10% bleach), ionizing radiation, X-ray, gamma ray.

- **Importance:**
  - Sterilization cannot be done by boiling.
  - Done by steam heating under pressure (autoclaving) at 121°C, usually for 30 minutes.

■ **Properties of spore:**

Important features of spore	Medical application
1. Highly resistant to heating; spores are not killed by boiling (100^0C) but are killed at 121^0C.	
2. Highly resistant to many chemicals; including most disinfectants. This is attributed to the thick keratinlike coat of the spore.	Only solutions designated as sporicidal will kill spores.
3. They can survive for many years, especially in the soil.	Wounds contaminated with soil can be infected with spores and cause diseases such as tetanus (*C. tetani*) and gas gangrene (*C. perfringens*).
4. They exhibit no measurable metabolic activity.	Antibiotics are ineffective against spores because antibiotics act by inhibiting certain metabolic pathways of bacteria. Also, spore coat is impermeable to antibiotics.
5. Spores form when nutrients are insufficient but germinate to form bacteria when nutrients become available.	Spores are not often found at the site of infections because nutrients are not limiting. Bacteria rather than spores are usually seen in Gram-stained smears.
6. Spores are produced by members of only two genera of bacteria of medical importance, ***Bacillus*** and ***Clostridium***, both of which are gram positive rods.	Infections transmitted by spores are caused by species of either ***Bacillus*** or ***Clostridium***.

(Ref: LANGE Review-14th)

Q. Endospore formation is seen in *(BSMMU –Residency - **MD/MS, Paediatrics, Dentistry** – March' 19)*
a) *Clostridium difficile*
b) *Bacillus subtilis*
c) *Brucella melitensis*
d) *Coxiella burnetti*
e) *Bacteroides fragilis*
Ans. a) T b) T c) F(Brucella do not produce spore, flagella or capsule) d) T e) F

(Ref. LANGE Review-15th, P-131 + Text book of Microbiology by Satish Gupta-10th, P-24)

Q. Bacterial spores are *(BSMMU –Residency – **MD, MS, Basic Science, Dentistry** – March' 18)*
a) antibiotic sensitive
b) thermostable
c) reproductive stage in bacterial multiplication
d) easily destroyed by gamma radiation
e) sensitive to antiseptics
Ans. a) F(resistent) b) T c) F d) T e) F

(Ref. LANGE Review-15th, P-12)

Q. Non sporing aerobic bacteria are *(BSMMU – Residency – **MD, MS, Basic science, Dentistry** – March' 16)*
a) *Lactobacillus spp.* F
b) *Actinomyces spp.* F
c) *Nocardia spp.* T
d) *Bacteroides fragilis* F
e) *Prevotola spp.* F

Help link:

The Aerobic spore bearers:

Bacillus Species:

- B. anthracis
- B licheniformis
- B subtilis.
- Bacillus alvei
- B brevis
- B circulans
- B coagulans
- B macerans
- B pumilus
- B sphaericus
- B thuringiensis
- Sporpsarcina

Anaerobic spore forming bacteria: Anaerobic spore forming bacteria are the species of the genus clostridium. They are-

- *Clostridium tetani*
- *Clostridium botulinum*
- *Clostridium perfringens*
- *Clostridium difficile*
- *Clostridium septicum*

Q. Endospore formation is seen in: (BSMMU – MD/MS - January, 2009)

a) Clostridium difficile T
b) Bacillus subtalis T
c) Brucella melitensis F
d) Coxiella burnetti T
e) Bacteroids fragilis F

(Ref: Apurbo sankar-6th, P-21)

Q. Following are the spore bearing bacilli- (BSMMU – MD/MS - 02Ja)

a) Bacillus circus T
b) Clostridium butulinum T
c) Bacillus subtilis T
d) Pseudomonas F
e) H influenzae. F

HELP LINK:

Spore forming bacilli		Diseases
Bacillus	*Bacillus anthracis*	Anthrax
	Bacillus cereus	Food poisoning
Clostridium	*Clostridium tetani*	Tetanus
	Clostridium botulinum	Botulism
	Clostridium perfringens	Gas gangrene, Food poisoning
	Clostridium difficile	Pseudomembranous colitis

Microbial growth

Q. Multiplication of microbes include *(BSMMU –Residency – MD/MS, Basic science – March' 14)*

a) bacteria by binary fision
b) fungus by sexual and asexual methods
c) protozoa by replication
d) yeast by spore germination
e) virus by replication

Ans. a) T b) T c) F d) F e) T

Help link: Bacterial growth:

1. **Lag phase**: metabolic activity occurs but cells do not divide. Duration: few minutes up to many hours.
2. **Log (logarithmic) phase/ exponential phase:** rapid cell division occurs. β-Lactam drugs, such as penicillin, act during this phase.
3. **The stationary phase**: occurs when nutrient depletion or toxic products cause growth to slow until the number of new cells produced balances the number of cells that die, resulting in a steady state.
4. **Death phase**: decline in the number of viable bacteria.

Sterilization

Sterilization

- **Sterilization**: is the killing or removal of all microorganisms, including bacterial spores, which are highly resistant
- Disinfection is the killing of many, but not all, microorganisms
- **Antiseptics**: Chemicals used to kill microorganisms on the surface of skin and mucous membranes.
- Death of microorganisms depends on two variables- the concentration of the killing agent and the length of time the agent is applied.

Methods of sterilization:

A. Physical methods:

a) Heat:	b) Radiation:	c) Filtration:
Dry heat: 1. Red heat 2. Flaming 3. Hot air oven **Moist heat:** **Below100^{0}C** 1. Pasteurization 2. Water bath 3. Vaccine bath 4. Inspissator **At 100^{0}C:** 1. Boiling 2. Steaming 3. Tyndallization **Above 100^{0}C:** Autoclave	1. X-ray 2. γ-ray 3. β-ray 4. UV-ray 5. Infrared rays	1. Berkefeld 2. Chamberland 3. Seitz 4. Sintered glass 5. Membrane filters 6. HEPA (High efficiency particulate air) filter

B. Chemical methods:

1. Alcohols
2. Phenols
3. Heavy metals
4. Dyes
5. Detergents
6. Ethylene oxide
7. Oxidizing agents
8. Halogens

PHYSICAL AGENTS:

➢ In the form of heat or radiation or filtration.

- ❑ **Dry heat**: requires temperatures in the range of 180°C for 2 hours. This process is used primarily for glassware.
- ❑ **HEAT**: moist heat (either boiling or pasturization or autoclaving). Heat kills by denaturing proteins, but membrane damage and enzymatic cleavage of DNA may also be involved. Moist heat sterilizes at a lower

temperature than dry heat, because water aids in the disruption of noncovalent bonds (e.g., hydrogen bonds).

- **Autoclaving**: most frequently used, spores are resistant to boiling (100°C at sea level), autoclave chamber is used in which steam, at a pressure of 15 lb/in^2, reaches a temperature of 121°C and is held at that temperature for 15 to 20 minutes.
- **Pasteurization**: used for milk, consists of heating the milk to 62°C for 30 minutes followed by rapid cooling. ("Flash" pasteurization at 72°C for 15 seconds is often used.) This is sufficient to kill the vegetative cells of the milkborne pathogens (e.g., Mycobacterium bovis, Salmonella, Streptococcus, Listeria, and Brucella), but not to sterilize the milk.

- **RADIATION**: ultraviolet (UV) light and X-rays. The greatest antimicrobial activity of UV light occurs at 250 to 260 nm, causes absorption by the purine and pyrimidine bases of DNA. The most significant lesion caused by UV irradiation is the formation of thymine dimers. Because UV radiation can damage the cornea and skin. It is used in hospitals to kill airborne organisms, especially in operating rooms.
  - **X-rays**: have higher energy and penetrating power than UV radiation and kill mainly by the production of free radicals. But spores are remarkably resistant, probably because of their lower water content. Other use- heat-sensitive items, such as sutures and surgical gloves, and plastic items, such as syringes.

- **FILTRATION:**
  - In the past, solutions for intravenous use were autoclaved, but heat-resistant endotoxin in the cell walls of the dead gram-negative bacteria caused fever.
  - Therefore, solutions are now filtered to make them pyrogen-free prior to autoclaving.
  - The most commonly used filter is composed of nitrocellulose and has a pore size of 0.22 μm. This size will retain all bacteria and spores.

CHEMICAL AGENTS:

- Chemical agents act:
  - disruption of the lipid-containing cell membrane,
  - modification of proteins, or
  - Modification of DNA.

DISRUPTION OF CELL MEMBRANES:

1. Alcohol-used to clean the skin before immunization or venipuncture. 70% is commonly used.
2. **Detergents**: are "surface-active" agents. Quaternary ammonium compounds (e.g., benzalkonium chloride) are cationic detergents widely used for skin antisepsis. Benzalkonium chloride is the active ingredient in Lysol, a commonly used disinfectant for floors and other surfaces.
3. **Phenols**: Phenol was the first disinfectant used in the operating room. Chlorhexidine is a chlorinated phenol that is widely used as a hand disinfectant prior to surgery ("surgical scrub") and in the cleansing of wounds. Hexachlorophene, which is a biphenol with six chlorine atoms, is used in germicidal soaps, but can cause neurotoxicity. Phenols not only damage membranes, but also denature proteins.

MODIFICATION OF PROTEINS:

- **Chlorine:** disinfectant to purify the water supply and to treat swimming pools. It is also the active component of hypochlorite (bleach, Clorox). Chlorine is a powerful oxidizing agent.
- **Iodine:** Iodine is the most effective skin antiseptic used in blood culture and installing intravenous catheters. Iodine, like chlorine, is an oxidant that inactivates sulfhydryl-containing enzymes. Iodine is in two forms:

  (1) **Tincture of iodine** (2% solution of iodine and potassium iodide in ethanol) is used to prepare the skin prior to blood culture. Because tincture of iodine can be irritating to the skin, it should be removed with alcohol.

(2) Iodophors are complexes of iodine with detergents that are frequently used to prepare the skin prior to surgery because they are less irritating than tincture of iodine.

- **Heavy Metals:** Mercury and silver have the greatest antibacterial activity of the heavy metals. Thimerosal (Merthiolate) and merbromin (Mercurochrome), which contain mercury, are used as skin antiseptics. Silver nitrate drops are useful in preventing gonococcal ophthalmia neonatorum. Silver sulfadiazine is used to prevent infection of burn wounds.
- **Hydrogen Peroxide:** used as an antiseptic to clean wounds and to disinfect contact lenses.
- **Formaldehyde & Glutaraldehyde:** Formaldehyde, as a 37% solution in water (formalin), denatures proteins and nucleic acids. Glutaraldehyde, which has two reactive aldehyde groups, is 10 times more effective than formaldehyde and is less toxic. In hospitals, it is used to sterilize respiratory therapy equipment, endoscopes, and hemodialysis equipment.
- **Ethylene Oxide:** is used extensively in hospitals for the sterilization of heat sensitive materials such as surgical instruments and plastics.
- **Acids & Alkalis:** Strong acids and alkalis kill by denaturing proteins. Mycobacterium tuberculosis and other mycobacteria are relatively resistant to 2% NaOH, which is used in the clinical laboratory to liquefy sputum prior to culturing the organism. Weak acids, such as benzoic, propionic, and citric acids, are frequently used as food preservative because they are bacteriostatic.

MODIFICATION OF NUCLEIC ACIDS:

- **Crystal violet (gentian violet)**: used as a skin antiseptic. Malachite green, a triphenylamine dye like crystal violet, is a component of Löwenstein-Jensen's medium. The dye inhibits the growth of unwanted organisms in the sputum.

Spores can be killed by

- **Physical method:**
  - **Dry heat**: red heat, flamming, Hot air woven
  - **Moist heat**: Autoclave
  - **Filtration**: cellulose membrane filter
  - **Ionizing radiation**: gamma ray, beta ray.
- **Chemical methods:**
  - **Alkylating agents:**
    - Formladehyde
    - Glutaraldehyde
    - Ethylene oxide
- **Peroxygenes:**
  - H_2O_2,
  - ozone,
  - peracetic acid.

Sterilization method	Materials
Red heat	Inoculating wire loops, tips of forceps & needle
Flaming	Glass slide, cover slip, scissor, scalpel, platinum loops, needles, forcep's tip, mouth of culture bottle & test tube
Hot-air oven (160^0C/hour)	**Glass wares**: petridish, **glass syringe**, test tube, test tube with swab stick, flasks, glass pipettes, **powder**, oil, fat.
Pasteurization	Milk
Water bath	Fluid containing protein e,g. serum
Vaccine bath	Bacterial vaccine
Inspissator	Loeffler's serum slope Lowenstein-Jensen media
Boiling (100^0C)	Glass syrings, glass pipette, rubber stopper, blunt metallic forceps & trays.

Steaming	**Media** containing serum, egg, sugar.
Tyndalization	**Media** containing serum, egg, sugar, any other heat labile substance (peptone water with1% CHO)
Autoclaving	•Linen substances such as operation theatre mask, gown, cap, draping sheet, bed cover •**Agar based culture media** •**Blunt surgical instruments**: Forceps, retractor •Bottle with rubber cap •Suture materials e,g. silk
γ - radiation	•Disposable plastic materials (**plastic syringe**, plastic tube),surgical gloves, transfusion equipments (cannula, catheter) •Arterial grafts and other biological material
UV- ray	•Laboratory safety cabinate •**Operation theatre**
Gluteryldehyde, Ethylene oxide	**Endoscope**, cystoscope, Heart-lung machine, drain tube
Formaldehyde	**Operation Theatre**
Formaldehyde fumigation	Metress
Filtration	•Aqueous liquid •Solution of heat labile substance e,g. Peptone water with sugar Culture media containing sugar Serum Antibiotic solution •Blood product (eg. factor IX) •Water purification in the lab •Preparation of toxins •Preparation of antisera •Isolation of viruses •Determination of sizes of viruses.

Regarding time and temp:

Method	Temp	Time
Dry heat	160-180	1-2 hour
Pasturization(holder method)	63	30 min.
Pasturization (flash method)	72	15-20 seconds
Pasturization (ultra high temp. method)	133	1-2 sec
Boiling	100	15 min
Tyndallization	100	20-45 min
Autoclave (15 lb/m2)	121-124 115-118 134-138	15-20 min 30 min 3 min

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Question Bank

Q. Bacterial spores are killed by *(BSMMU – Non-Residency – MD, MS, Paediatrics, Basic Science, Dentistry – July' 19)*

a) moist heat at 121°C for 15 minutes
b) dry heat at 180°C for 30 minutes
c) 10% providone iodine
d) ethylene oxide gas
e) chlorhexidine

Ans. a) T (Autoclave) b) F (2 hours) c) F d) T e) F (clorinated phenol that is used as a hand disinfectant prior to surgery, not only damage membrane but also denature protein)

(Ref: LANGE-15th, P-99)

Q. Chemicals act as high level disinfectant include *(BSMMU – Non-Residency – **Dentistry** – July' 19)*

a) 37% formaldehyde
b) 2% gluteraldehyde
c) 70% isopropyl alcohol
d) 10% providone iodine
e) chlorhexidine gluconate

Ans. a) b) T c) F (intermediate level of disinfectatnt) d) F (intermediate level of disinfectatnt) e) F

Help Link:

Methods of Disinfection	
Method	**Concentration (Level of Activity)**
Heat	
- Moist Heat	75C to 100C for 30 min (high).
Liquid	
- Glutaraldehyde	2% (high).
- Hydrogen Peroxide	3% to 25% (high)
- Formaldehyde	3% to 8% (high/intermediate).
- Chlorine Dioxide	Variable (high).
- Peracetic Acid	Variable (high).
- Chlorine Compounds	100 to 1000 ppm of free chlorine (high)
- Alcohol (ethyl, isopropyl)	70% to 95% (intermediate).
- Phenolic Compounds	0.4% to 5.0% (intermediate/low).
- Iodophor Compounds)	30 to 50 ppm of free iodine/L (intermediate).

Q. Disposable syringes are sterilized by *(BSMMU –Residency - **MD/MS, Basic science, Paediatrics, Dentistry** – March' 19)*

a) ethylene oxide
b) formaldehyde
c) ionizing radiation
d) ultraviolet radiation
e) hexachloride

Ans. a) T b) F c) T d) F e) F

Help link:

Materials	Methods of sterilization/disinfection
Infective materials like soiled dressings, beddings, animal carcasses	Burning (incineration)
Metal instruments	Autoclaving, hot air oven, infrared radiation
Serum, body fluids, bacterial vaccines	Water bath, at 56°C for 1 hour, vaccine bath for 1 hour
Milk	Pasteurization, 63°C × 30 min, or 72°C × 20 sec
Cystoscope and endoscope and other anaesthetic equipment	Glutaraldehyde (glider 2%) or ethylene oxide
Most of the culture media	Autoclaving at 121°C × 15 minutes
Culture media containing egg, serum, or sugar	Tyndallisation (steam for 30 min each on 3 consecutive days)
Toxin, ascetic fluid, serum, sugar and antibiotic solutions	Filtration by seitz filteror chamber land filter, membrane filter
Rubber, plastic and polythene tubes including disposable syringes	Gamma radiation, ethylene oxide gas
Dressings, aprons, gloves, catheters, surgical instruments except sharp instruments	Autoclaving at 121°C × 15 minutes
Sharp instruments	5% cresol
Suture materials except catgut	Autoclaving at 121°C × 15 minutes
Catgut	Lonising radiation (dose of 2.5 M rad)
Rubber or plastic disposable goods, disposable syringes, bone and tissue grafts, adhesive dressings	Lonising radiation (dose of 2.5 M rad)
Antitoxic sera, serum, urine	Merthiolate (1: 10,000)
Polythene tubing, fabrics, Heart-lung machine	Ethylene oxide
Facces and urine, vomitus, sputum	Bleaching powder, cresols, formalin, burring, autoclaving
Woolen blankets, wool and hides	Formaldehyde gas
Sterilization of operation theatre	Formaldehyde gas (50 cc formalin and 25 gm KMnO4 per 100 cu it space)
Wards and laboratory or operation theatre floor space	Formaldehyde gas and cresols (Lysol) Sodium hypochlorite (1%)
Water	Chlorine as hypochlorite 0.2%
Skin	Tincture iodine, spirit (70 % ethanol), Savlon (phenol derivative)

(Ref: Subash chandra parija)

Q. In sterilization *(BSMMU –Residency – **MD, MS, Basic Science, Dentistry** – March' 18)*

a) boiling is an important means of sterilizing rubber materials
b) surgical gloves are sterilized by dry heat
c) gamma radiation is a sterilizing agent
d) culture media is sterilized by autoclave
e) pasteurization kills *M. bovis*

Ans. a) F b) F c) T d) T e) T

Q. In sterilization *(BSMMU –Residency – **Dentistry** – March' 18)*

a) glutaraldehyde kills spores
b) hot-air oven causes sharp instruments blunt
c) glass bead sterilizer is a dry heat method
d) autoclave can kill viruses
e) dry heat method is ideal

Ans. a) T b)F c) T d) T e) F

Q. Endoscopes are sterilized by *(BSMMU – Non-Residency – MS, Basic Science – July' 17)*

a) plasma sterilization
b) formaldehyde solution
c) hydrogen peroxide
d) boiling
e) 2% gluteraldehyde solution

Ans. a) F b) F c) F d) F e) T(usually used 0.1-1% for disinfection)

Help link:

Spores can be killed by

- **Physical method**:
  - Dry heat: red heat, flamming, Hot air woven
  - Moist heat: Autoclave
  - Filtration: cellulose membrane filter
  - Ionizing radiation: gamma ray, beta ray.
- **Chemical methods**:
  - Alkylating agents:
    - Formladehyde
    - Glutaraldehyde
    - Ethylene oxide
- **Peroxygenes**:
  - H_2O_2,
  - ozone,
  - peracetic acid.

Q. Spores are killed by exposure to: *(BSMMU – Residency - **Dentistry** - March' 17; M. Phil, Diploma – July '10)*

a) moist heat at 110°C for 15 minutes
b) dry heat at 160°C for 1 hour
c) ethylene oxide
d) hydrogen peroxide
e) gentian violet

Ans.

a) **False** Bacterial spores require exposure to moist heat at a temperature of 121°C for at least 15 minutes and preferably 30 minutes before they are destroyed. Resistant spores such as the spores of *Clostridium botulinum* can resist autoclaving at the lower temperature of 115° C for up to 40 minutes.

b) **True** The majority of spores are killed by exposure to dry heat at 160°C for 1 hour. In practice this is an unacceptable method of sterilization because slight charring of paper and cotton occurs at this temperature.

c) **True** Ethylene oxide is highly lethal to all kinds of microbes and spores. It is of particular value for sterilizing particles liable to damage by heat. e.g. plastic and rubber articles. Sterilization time depends upon the temperature of the reaction and the relative humidity.

d) **False** Hydrogen peroxide has been used as an antiseptic but has little or no action on bacterial spores. **True** (Ref: MATRIX desk)

e) **False** Gention violet will kill some vegetative forms of bacteria particularly Gram-positive organisms. It is much less active against Gram-negative bacteria and virtually useless against spores of any kind.

(Ref: Smiddy)

Q. Physical methods of sterilization include *(BSMMU – Residency – **MD, MS, Basic science, Dentistry** – March' 16)*

a) radiation	T
b) sterilization by ethylene oxide	F
c) filtration	T
d) boiling	T
e) pasteurization	T

Q. Following are sterilized by autoclaving *(BSMMU –Residency – **MS, Basic Science** – March' 16)*

a) draping sheet	T
b) gauze piece	T
c) needle holder	T
d) surgical blade	F
e) suture material	T

Q. Chemical agents that destroy spores *(BSMMU –Residency – **MD, MS, Basic** – March' 15)*
a) phenol
b) alcohol
c) formaldehyde
d) ethylene oxide
e) peracetic acid
Ans. a) F b) F c) T d) T e) T

Q. Endoscopes are sterilized by *(BSMMU –Residency – **MS, Basic Science** – March' 15)*
a) 2% gluteraldehyde
b) H_2O_2
c) formaldehyde solution
d) autoclaving
e) γ-radiation
Ans. a) T b) F c) F (irritating) d) F e) F

(Ref. P. Chakraborti-1st, P-39)

Q. Endoscopic instruments can be sterilized by:
a) UV- light
b) autoclaving
c) ethylene oxide gas
d) gluteraldehyde solution
b) lysol
Ans. a) F b) F c) T d) T e) F

Q. Bacterial sterilization: *(BSMMU – Residency – MS – March'13)*
a) Dry heat is more effective than moist heat
b) Milk is pasteurized by the process of sterilization
c) Vegetative bacteria are more readily killed than bacterial spores
d) The presence of protein increases the resistance of bacteria to heat
e) Moist heat is most effective at a neutral pH
Ans. a) F b) T c)T d) F e) T

Q. Following are the high level disinfectants: *(BSMMU – M. Phil, Diploma (Non-Residency)–March-2012, DMC & others –**MS** – March-2012)*

a) Glutaraldehyde	T
b) Quarternary ammonium compound	F
c) Hydrogen per-oxide	T
d) Alcohol	F
e) Formadehyde	T

Q. Regarding sterilization: *(BSMMU – M. Phil, Diploma –11Ju, DMC & others – MD – 11Ju)*

a. In autoclave, temperature should be 121^{0}C for 20 minutes	T
b. to kill all spores, 160^{0}C temperature for 60 minutes is essential without steam	T
c. gluteraldehyde kills all spores & viruses	F
d. degree of disinfection by gluteraldehyde is proportional to the concentration of solution.	F
e. peracetic acid (STERIS) is used for flexible objects	T

Q. Article are sterilized by the following methods: *(BSMMU - M. Phil, Diploma – July '10)*

a) sharp instruments by boiling	F
b) endoscope by chemicals	T
c) blunt instruments by boiling	T
d) cloth by autoclaving	T
e) telescope by boiling	F

Q. Disposable syringe are sterilized by: (BSMMU – MD/MS (Residency) – January, 2010)

a) Ethylene oxide T
b) Formaldehyde F
c) Ionizing radiation T
d) Ultraviolet radiation F
e) Gluteraldehyde F

Q. In surgical instrument sterilization the methods of choice are (BSMMU –MS– 09Ja)

a) fiber optic instrument by autoclave F
b) sharp instrument by autoclave F
c) proctroscope by heat & savion F
d) artery forcep by autoclave T
e) rough instrument by autoclave T

Q. Materials sterilized by following methods: (BSMMU - M. Phil, Diploma, July-08)

a) scissors by boiling F
b) catheter by gamma radiation T
c) cloths by chemicals F
d) endoscope by chemicals T
e) blunt instruments by autoclaving T

Q. Endoscope is sterilized by the following: (BSMMU - Basic Science, July-07)

a) flaming F
b) γ-ray T
c) chemical substances T
d) boling F
e) autoclave F

Q. Spores are killed by exposure to: (BSMMU - M. Phil, Diploma, July-08)

a) moist heat at 110^{0}C for 15 minutes F
b) dry heat of 160°C for 15 minutes F
c) ethylene oxide T
d) H_2O_2 T
e) gentian violet F

Q. The following are the absolute method of sterilization: (DMC - M. Phil, Diploma, July-06)

a) autoclave T
b) hot air woven T
c) tyndalization T
d) chlorination F
e) formaldehyde gas T

Q. Tyndallization method of sterilization applies to following. (BSMMU – MD/MS - 02Ja)

a) Temp at below 100° C for 3 consecutive days F
b) Temp at 100^0 C for 3 consecutive days T
c) Temp at below 100^0 C for one day. F
d) Temp 71^0 C for 15 seconds F
e) Especially used for destruction of spore. T

HELP LINK:

■ **Tyndallization**: It is the process in which articles to be sterilized are repeatedly exposed to steaming at 100^{0}C for 20-45 min for 3 successive days with incubation of the articles at 37^{0}C for 24 hours in between.

■ **Process**: First exposure to 100^{0}C for 30 min → Vegetative bacteria are destroyed, but spores remain → Incubation (not freezing) for overnight. May be 37^{0}C →Germination of spores → Second exposure to 100^0 C for 30 min → Vegetative bacteria are destroyed → But, few spores may remain → Incubation → Germination → 3rd exposure → All are destroyed.

■ **Articles**: Media containing
- Serum
- Egg
- Sugar
- Any other heat labile substance (peptone water with 1% CHO)

Hospital infection

Hospital infection/ Nosocomial infection: Nosocomial infection is the result of transmission of pathogenic organisms to a previously uninfected patient from a source in the environment of hospital.
They occur in 5 - 15% of pt. admitted to hospital.

Classification of Nosocomial infection: Nosocomial infection is either endogenous or exogenous.
A. **Endogenous/Autoinfection**: Organisms originate from the patient
B. **Exogenous/Cross infection**: Organisms originates from the following sources-
1. Operation room and theater environment
2. Surgical team: Surgeon and assistants
3. Unsterile instrument
4. Postoperative ward:
   a) From the other patients
   b) From hospital staffs: Ward boy, nurses, etc.
   c) From visitors.

Common organisms responsible for nosocomial infection:
A. **Autoinfection**: Gram negative bacilli are the important cause of autoinfection (Escherichia coli), such as-
1. Urinary tract infection
2. Respiratory tract infection
3. Septicaemia/septic shock
4. Wound infection (particularly after abdominal surgery).

B. **Cross infection**: Mainly by air borne infection.
i. *Staphylococcus aureus, Staphylococcus epidermidis*
ii. *Streptococcus pyogens, streptococcus faecalis, pneumococci.*
iii. Gram negative bacilli: *Escherichia coli*, Pseudomonas
iv. Anaerobic organism: Bacteroids, *Clostridium tetani, Clostridium perfringens* etc.

Most common nosocomial infections:
1. Wound infection
2. Pneumonia
3. Septicaemia
4. Urinary tract infection.

Most commonly occurs in patients:
1. Patient in ICU
2. Patient with severe underlying disease, e.g. Renal failure, COPD, Liver disease
3. Transplant patients
4. Patient with AIDS
6. Polytrauma patients.

Q. Common bacterial agents of hospital acquired infections are *(BSMMU –Residency – **MD, MS, Basic Science, Dentistry** – March' 18)*
a) Acinetobacter spp.
b) *Streptococcus pneumoniae*
c) *Haemophilus influenzae*
d) *Pseudomonas aeruginosa*
e) *Enterococcus spp.*

Ans. a) T b) F c) F d) T e) T

Help link:

Organisms responsible for hospital infection:

A) Bacterial causes:

1. *Staphylococcu aureus*
2. *Streptococcus pyogens*
3. *Streptococcus faecalis*
4. Peptostreptococcus
5. *Staphylococcus epidermidis*
6. *Clostridium tetani*
7. *Clostridium perfringes*
8. *E. coli*
9. Klebsiella
10. Proteus
11. Bacteroids
12. Pseudomonas
13. Pncumococci

B) Viral causes: Respiratory viruses.

C) Fungal causes: *Candida albicans*

STAINING

Importance of staining in diagnostic microbiology:

1. Identification of different bacterial species.
2. To know about the details morphology of the bacteria by different types of staining.
3. To select proper antibiotics, as we know there are wide variation of antibiotic sensitivity between Gram positive, Gram negative & acid-fast bacteria. For example- Gram positive bacteria are more sensitive to β-lactam antibiotics than Gram-negative bacteria. So, identification of bacteria whether it is Gram positive or Gram negative is important prior to start treatment.

Utility of staining in diagnostic microbiology:

1. Staining is necessary for the study of bacterial morphology.
2. Staining of a bacterial cell wall may help in establishing its identity.

Classification of staining used in microbiology:

1. **Simple stains**: In this technique, a single staining substance is used.

Example:

- Methylene blue
- Crystal violet
- Basic fuchsin etc.

2. **Differential stains**: Two stains with differing affinities to different bacteria are used in differential staining techniques.

Example:

- Gram stain.
- Ziehl – Neelsen's stain/ acid fast stain.
- Alberts stain — To see metachromatic granules of *C. diphtheriae.*
- Giemsa stain - To detect *Chlamydia*
- Waysow's stain — to detect *Yersinia pestis.*

3. Negative stain:

Example: • India ink stain for detection of capsule of *Cryptococcus neoformens* fungus.

4. Fluorescent stains:

Example: • Auramine and rhodamine to detect mycobacteria.

5. Impregnation stain:

Example:

• Silver impregnation for *Treponema pelidum.*

6. Special stains:

Example:

• Stain to see endospore.

• Stain to see flagella.

Common staining methods adapted for bacterial study:

Technique	Staining
1. Gram	Cell wall
2. Ziehl – Neelsen	Mycobacterium
3. Giemsa	Blood parasites, Chlamydia, Borrelia
4. Albert	*C. diphtheriae* (volutin or metachromatic granules), Other corynebacterium.
5. Wayson's	*Yersinia pestis* (plague)
6. Hiss	Capsule around the bacteria
7. Methylene blue	Basic morphology of bacteria Leucocytes in faeces
8. Auramine blue	Mycobacterium
9. Acridine orange	DNA (green) RNA (orange red)

Gram Staining

This staining procedure, developed in **1884** by the Danish physician **Christian Gram**, is the most important procedure in microbiology. It separates most bacteria into two groups: the gram-positive bacteria, which stain blue, and the gram-negative bacteria, which stain red.

Principle of Gram's staining:

- Gram staining depends on bacterial cell wall & cytoplasmic membrane.
- When bacteria are stained with crystal violet & mordant with lugols I_2, some bacteria resist decolorization by alcohol & others do not.
- The bacteria which resist are called gram positive (Gram-positive bacteria have thick peptidoglycan layer on their cell wall, so they can resist decolourization of primary stain) & those which are decolorized are gram negative (Gram-negative bacteria have a thin peptidoglycan layer, so they cannot prevent decolourization).
- Gram positive bacteria stains blue & gram negative bacteria stains red.

Procedure of gram staining:

1. **Fixation**: The slide is flamed 3-4 times on the opposite side of the smear. Thus the smear is fixed.

2. **Primary staining**: Crystal violet is coated over the smear & kept for 1 minute. It is then washed with tap water.

3. **Mordanting**: Lugols I_2 is coated over the smear & kept for 1 minute. It is then washed with tape water. It is done to increase the penetration power of lugols I_2.

4. **Decolorization**: It is done by alcohol & is continued till the violet color comes out from the smear. The slide is then washed with tap water.

5. **Counter staining**: Carbol fuschin (1 in 10 dilution) is coated over the smear & is kept for 30 sec. The slide is then washed with tap water & allowed to dry at room temp.The slide is then examined under microscope with oil immersion to observe the gram reaction, morphology & arrangement of bacteria.

(Ref: LANGE Review-14th, P-8)

Dyes used in gram stain:

1. Crystal violet
2. Carbol fuschin

Q. Bacteria that are stained by Grams stain are *(BSMMU –Residency – **MD, MS, Basic Science** – March' 18)*

a) *Treponema pallidum*
b) *Mycoplasma*
c) *Corynebacterium diphtheria*
d) *Mycobacterium bovis*
e) *Helicobacter pylori*

Ans. a) F b) F c) T d) F e) T

Help link:

Medically Important Bacteria that Cannot Be Seen in the Gram Stain.

Name	Reason	Alternative Microscopic Approach
Mycobacteria, including *M. tuberculosis*	Too much lipid in cell wall so dye cannot penetrate	Acid-fast stain
Treponema pallidum	Too thin to see	Dark-field microscopy or fluorescent antibody
Mycoplasma pneumoniae	No cell wall; very small	None
Legionella pneumoniae	Poor uptake of red counterstain	Prolong time of counterstain
Chlamydiae, including *C. trachomatis*	Intracellular; very small	Inclusion bodies in cytoplasm
Rickettsiae	Intracellular; very small	Giemsa or other tissue stains

(Ref: LANGE Review-14th, P-8)

Q. Bacteria that are not visualized microscopically by gram stain includes *(BSMMU – Residency - **MD, MS, Basic Science, Dentistry** - March' 17)*

a) Borrelia
b) Mycobacteria
c) Yersinia
d) Chlamydia
e) Acinetobacter

Ans. a)T b) T c) F d) T e)F

Q. Bacteria that can not be seen under microscope in Gram stain smear are *(BSMMU – Residency – **MD, MS, Basic science** – March' 16)*

a) *Treponema palladium* T
b) *Mycobacterium leprae* T
c) *Streptococcus pyogens* F
d) *Mycoplasma pneumonia* T
e) *Clostridium tetani* F

Bacterial exotoxin & endotoxin

■ **Differences between exotoxin & endotoxin:**

Traits	Exotoxin	Endotoxin
1. Source	Certain species of some Gram + ve & Gram -ve bacteria	Cell wall of most Gram - ve bacteria
2. Secreted from cell	Yes	No
3. Chemistry	Polypeptide	LPS
4. Solubility	Soluble substance	Insoluble substance
5. Toxicity	High (fatal dose: 1 mg)	Low fatal dose: (100 micro-organisms)
6. Mode of action	Various modes	Include TNF (Tumour necrosis factor) & IL-1
7. Clinical effects	Various effects	Fever & shock
8. Antigenicity	Highly antigenic	Poorly antigenic.
9. Vaccines	Toxoids used as vaccines.	No toxoid, no vaccine.
10. Formation of toxoid	Yes	No
11. Heat stability	Destroyed rapidly at 60^0C (except staph. aureus en terotoxin)	Stable at 100^0C for an hour
12. Location of gene that produces the toxin	Plasmid or bacteriophage (virus) DNA produce the exotoxin.	Bacterial chromosome produces the endotoxin.
13. Typical diseases	Tetanus, Diphtheria, Botulism	Menigococcaemia, Gram –ve sepsis.

(Ref: LANGE Review-14th, P-39)

Exotoxin

Exotoxin: Exotoxins are highly toxic chemical substances, protein or polypeptide in nature, which are actively secreted by certain species of some Gram positive & Gram-negative bacteria and contribute a major part to bacterial virulence.

Criteria of exotoxin:

- Protein in nature.
- Actively secreted by bacteria
- Heat labile, i.e. destroyed by heat.
- Highly antigenic.
- Produces neutralizing antitoxin.
- Have specific tissue selecting property with specific pattern of effects.
- Toxoid can be produced from them, so vaccination against them is possible.

Important exotoxin producing bacteria with the diseases:

- *Corynebacterium diphtheria* ⇒ Diphtheria
- *Clostridium tetani* ⇒ Tetanus
- *Clostridium botulinum* ⇒ Botulism
- *Clostridium difficile* ⇒ Pseudomembranous colitis
- *Clostridium perfringens* ⇒ Gas gangrene
- *Bacillus anthracis* ⇒ Anthrax
- *Staphylococcus aureus* ⇒ Toxic shock syndrome, food poisoning, scalded skin syndrome
- *Streptococcus pyogenes* ⇒ Scarlet fever
- *Escherichia coli* ⇒ Watery diarrhoea, bloody diarrhoea
- *Vibrio cholera* ⇒ Cholera
- *Bordetella pertussis* ⇒ Whooping cough. **(Ref: LANGE Review-14th, P-40, Table 7-10)**

For Viva:

Exotoxin producing Bacteria:

A. Gram +ve bacteria:

- *Corynebacterium diphtheriae*
- *Clostridium tetani.*
- *Clostridium botulinum*
- *Clostridium defficile*
- *Clostridium perfringens*
- *Staphylococcus aureus*
- *Streptococcus pyogens*
- *Bacillus anthracis*

B. Gram -ve bacteria:

- Enterotoxigenic *E. coli* (ETEC)
- *Vibrio cholera.*
- *Bordetella parteusis*
- Pseudomonas
- *Yersinia enterocolitica.*
- *Campylobacter jejunae*
- Aeromonas

Table: Important Bacterial Exotoxins.

Bacterium	Disease	Mode of Action	Toxoid Vaccine
Gram-positive rods			
Corynebacterium diphtheriae	Diphtheria	Inactivates EF-2 by ADP-ribosylation	Yes
Clostridium tetani	Tetanus	Blocks release of the inhibitory neurotransmitter glycine by proteolytic cleavage of releasing proteins	Yes
Clostridium botulinum	Botulism	Blocks release of acetylcholine by proteolytic cleavage of releasing proteins	Yes[1]
Clostridium difficile	Pseudomembranous colitis	Exotoxins A and B inactivate GTPases by glucosylation	No
Clostridium perfringens	Gas gangrene	Alpha toxin is a lecithinase. Enterotoxin is a superantigen	No
Bacillus anthracis	Anthrax	Edema factor is an adenylate cyclase. Lethal factor is a protease that cleaves MAP kinase, which is required for cell division	No
Gram-positive cocci			
Staphylococcus aureus	1. Toxic shock syndrome	Is a superantigen; binds to class II MHC protein and T-cell receptor; induces IL-1 and IL-2	No
	2. Food poisoning	Is a superantigen acting locally in the gastrointestinal tract	No
	3. Scalded skin syndrome	Is a protease that cleaves desmoglein in desmosomes	No
Streptococcus pyogenes	Scarlet fever	Is a superantigen; action similar to toxic shock syndrome toxin of *S. aureus*	No
Gram-negative rods			
Escherichia coli	1. Watery diarrhea	Labile toxin stimulates adenylate cyclase by ADP-ribosylation; stable toxin stimulates guanylate cyclase.	No
	2. Bloody diarrhea	Verotoxin is cytotoxic to enterocytes by degrading 28S ribosomal RNA	No
Vibrio cholerae	Cholera	Stimulates adenylate cyclase by ADP-ribosylation	No
Bordetella pertussis	Whooping cough	Stimulates adenylate cyclase by ADP-ribosylation; inhibits chemokine receptor	Yes[2]

[1]For high-risk individuals only.
[2]The acellular vaccine contains pertussis toxoid and four other proteins.

Question Bank

Q. Following bacteria produces exotoxin: *(BSMMU – Residency – MD/MS – March'13)*
- *a) S. aureus*
- *b) N. meningitidis*
- *c) S. viridans*
- *d) Cl. botulinurn*
- *e) H. nifluenzae*

Ans : a) T b) F c) F d) T e) F

Q. Preformed toxins are *(BSMMU – Non-Residency – MD, Basic science – July' 16)*

a) staphylococcal enterotoxin	T
b) botulinum toxin	T
c) diphtheria toxin	F
d) cholera toxin	F
e) verotoxin	F

Q. Following organisms can produce heat stable exotoxin - (BSMMU-MS-04Ja)

a) Escherichia coli	T
b) Staphylacoccus aureus	T
c) Clostridium botullinum	F
d) Vibrio cholerae	F
e) Corynebactrium diphtheriae	F

Q. Exotoxin producing organisms are: (MD/MS (DMC)-05Ja)

a) Cl. Tetani	T
b) S. Typhi	F
c) C. Diphtheriae	T
d) N. Meningitidis	F
e) Ps. Aeruginosa.	T

HELP LINK:

■ **Exotoxin producing organisms**:
1. Gram positive cocci: Staphylococcus. aureus, Streptococcus. pyogens
2. Gram positive rods: C. diphtheriae, Clostridium tetani, Cl. welchi, Bacillus anthacis
3. Gram negative rods: E. coli, V. cholerae, Shigella, Bordetella pertussis, H. influenzae

Q. The main host defense against bacterial exotoxins are- (MD/MS (DMC)-03Ja)

a) Activated macrophages secreting proteases	T
b) IgG and IgM antibodies	T
c) Helper T cells	T
d) Eosinophils	F
e) Modulation of host cell receptors in response to the toxin	T

Q. Exotoxins are produced by- (BSMMU – MD/MS - 01Ja)

a) Vibrio cholerae.	T
b) Bordetella pertussis	T
c) ETEC	T
d) Proteus mirabilis	F
e) Klebsiella	F

Endotoxin

Endotoxin: Endotoxins are lipopolysaccharides, an integral part of cell wall of most Gram negative bacteria, liberated when bacteria are disintegrated: and perform various toxic effects to the host.

Properties of endotoxin:

- Lipopolysaccharide in nature.
- Integral part of bacterial cell and liberated only after the death of bacteria.
- Relatively heat stable.
- Less antigenic.
- Not produces neutralizing antitoxin.
- No specific tissue selecting property and all endotoxins have almost similar pattern or effects.
- Toxoid can not be produced from them, so vaccine can not be produced against them.

Important endotoxin producing bacteria:

- *E. coli*
- Klebsiella
- Salmonella
- Shigella
- Proteus

Mode of action of endotoxin:

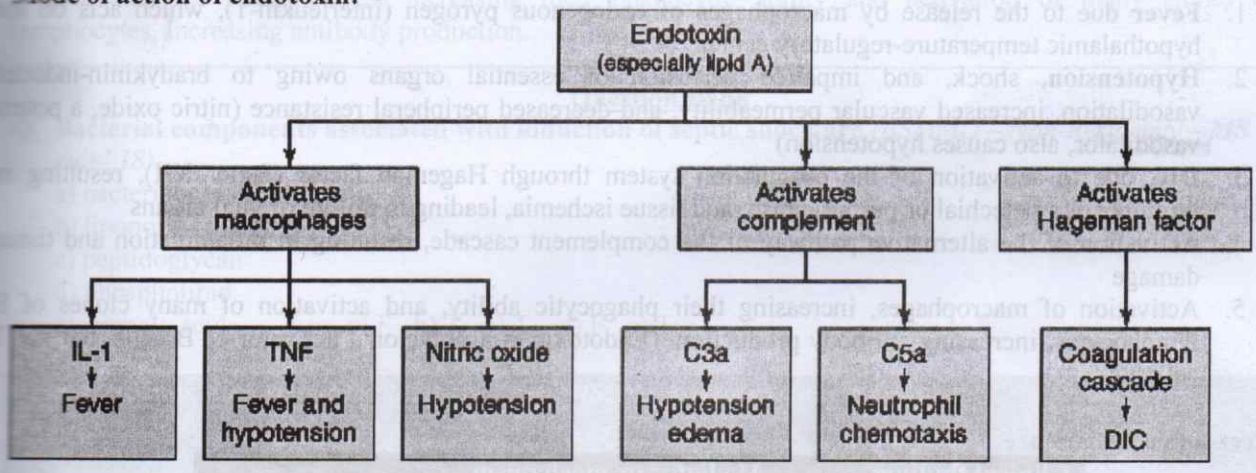

Fig: Mode of action of endotoxin

(Ref: LANGE Review-14th, P-45)

Endotoxin is the most important cause of septic shock, which is characterized primarily by fever, hypotension, and disseminated intravascular coagulation (DIC). Endotoxin causes these effects by activating three critical processes: (1) activating macrophages to produce interleukin-1 (IL-1), tumor necrosis factor (TNF), and nitric oxide; (2) activating complement to produce C3a and C5a; and (3) activating Hageman factor, an early component of the coagulation cascade.

Endotoxins are **LPS**, whereas exotoxins are polypeptides; the enzymes that produce the LPS are encoded by genes on the bacterial chromosome, rather than by plasmid or bacteriophage DNA, which usually encodes the exotoxins. The toxicity of endotoxins is low in comparison with that of exotoxins. All endotoxins produce the same generalized effects of **fever** and **shock,** although the endotoxins of some organisms are more effective than those of others. Endotoxins are weakly antigenic; they induce protective antibodies so poorly that multiple episodes of toxicity can occur. No toxoids have been produced from endotoxins, and endotoxins are not used as antigens in any available vaccine.

The findings of fever and hypotension are salient features of **septic shock.** Septic shock is one of the leading causes of death in intensive care units and has an estimated mortality rate of 30–50%. The endotoxins of gram-

negative bacteria are the best-established causes of septic shock, but surface molecules of gram-positive bacteria (which do not have endotoxins) can also cause septic shock.

Two features of septic shock are interesting:

1. Septic shock is different from toxic shock. In septic shock, the bacteria are in the bloodstream, whereas in toxic shock, it is the toxin that is circulating in the blood. The clinical importance of this observation is that in septic shock, blood cultures are usually positive, whereas in toxic shock, they are usually negative.
2. Septic shock can cause the death of a patient even though antibiotics have killed the bacteria in the patient's blood, that is, the blood cultures have become negative. This occurs because septic shock is mediated by cytokines, such as TNF and interleukin-1 (see below), that continue to act even though the bacteria that induced the cytokines are no longer present.

The toxic portion of the molecule is **lipid A,** which contains several fatty acids. β-Hydroxymyristic acid is always one of the fatty acids and is found only in lipid A. The other fatty acids differ according to species. The polysaccharide core in the middle of the molecule protrudes from the surface of the bacteria and has the same chemical composition within members of a genus. The repeat unit of sugars on the exterior differs in each species and frequently differs between strains of a single species. It is an important antigen of some gram-negative rods ("O" or somatic antigen) and is composed of 3, 4, or 5 sugars repeated up to 25 times. Because the number of permutations of this array is very large, many antigenic types exist. For example, more than 1500 antigenic types have been identified for *Salmonella.*

The biologic effects of endotoxin include

1. **Fever** due to the release by macrophages of endogenous pyrogen (interleukin-1), which acts on the hypothalamic temperature-regulatory center
2. **Hypotension,** shock, and impaired perfusion of essential organs owing to bradykinin-induced vasodilation, increased vascular permeability, and decreased peripheral resistance (nitric oxide, a potent vasodilator, also causes hypotension)
3. **DIC** due to activation of the coagulation system through Hageman factor (factor XII), resulting in thrombosis, a petechial or purpuric rash, and tissue ischemia, leading to failure of vital organs
4. Activation of the alternative pathway of the complement cascade, resulting in inflammation and tissue damage
5. Activation of macrophages, increasing their phagocytic ability, and activation of many clones of B lymphocytes, increasing antibody production. (Endotoxin is a polyclonal activator of B cells, but not T cells.)

Effects of endotoxin are:

Clinical findings	Mediator or mechanism
Fever	**Interleukin- I**
Hypotension (shock)	**Bradykinin, nitric oxide**
Inflammation	**Alternative pathway of complement (C3a, C5a)**
Coagulation (DIC)	**Activation of Hageman factor**

(Ref: LANGE Review-14th, P-45; Table 7-14)

Biological effects of endotoxin:

1. **Fever:**

Endotoxin activates macrophage
↓
Release of endogenous pyrogen (IL-1)
↓
IL-1 acts on temperature regulating center in hypothalamus
↓
Fever.

2. Hypotension, shock & impaired perfusion of essential organs: owing to

a. Bradykinin: causes
- Vasodilatation
- Increased vascular permeability
- Decreased peripheral resistance

b. Nitric oxide: a potent vasodilator, also causes hypotension

3. Disseminated intravascular coagulation (DIC):

Activation of Hageman factor (factor XII)
↓
Coagulation cascade
↓
Thrombosis, a petechial or purpuric rash and tissue ischaemia (Disseminated intravascular coagulation)
↓
Failure of vital organs

4. Activation of alternative pathway of complement cascade: resulting in Inflammation & tissue damage-

a. C3a → Hypotension & edema
b. C5a → Neutrophil chemotaxis
c. Membrane attack complex → Tissue damage.

5. Activation of macrophages, increasing their phagocytic ability and activation of many clones of B lymphocytes, increasing antibody production.

Question Bank

Q. Bacterial components associated with induction of septic shock are *(BSMMU – Non-Residency – **MS** – July' 18)*

a) bacterial capsular protein
b) lipopolysaccharide
c) peptidoglycan
d) phospholipid
e) teichoic acid Ans. a) F b) T c) T d) F e) T

Q. Endotoxin is *(BSMMU – Non-Residency – **MD, MS, Basic science – July' 16**)*

a) composed of glycoprotein F
b) firmly bound to the cell surface T
c) heat labile F
d) responsible for causing fever and hypoglycemia F
e) released after death of the bacteria T

Q. Characteristics of endotoxin are *(BSMMU – Residency – **MD, MS, Basic science, Dentistry** – March' 16)*

a) highly antigenic F
b) lipopolysaccharide in nature T
c) used as vaccine in toxoid form F
d) stable at 100^0 C for 1 hour T
e) secreted from cell F

Q. Endotoxin producing bacteria *(BSMMU –Residency – **MD, MS, Basic** – March' 15)*

a) *Staphylococcus saprophyticus*
b) *Bacillus anthracis*
c) *Salmonella typhi*
d) *fusobacterium spp.*
e) *Clostridium perfringens*

Ans. a) F b) F c) T d) T e) F

Q. Following are the characteristics of endotoxin: *(BSMMU – Residency – MD/MS – March'13)*

a) Causes non specific enhancement of immune response
b) Cause induction of growth factor production
c) Highly antigenic in nature
d) Causes leukocytosis
e) Decrease plasma cortisol

Ans : a) T b) F c) F d) T e) F

Q. Following are toxin mediated disease (BSMMU - MD - January - 11)

a) scarlet fever	T
b) plague	F
c) dengue	F
d) staphylococcal food poisoning	T
e) diphtheria	T

Q. Endotoxin are - (BSMMU - M. Phil, Diploma, July-05)

A. protein in nature	F
B. lipopolysaccharide complex	T
C. secreted by living bacteria	F
D. highly antigenic	F *(Poorly antigenic)*
E. heat stable	T

Q. The effects of endotoxin include- (MD/MS (DMC)-03Ja)

a) Opsonization	F
b) Fever	T
c) Activation of coagulation cascade	T
d) Hypotension	T
e) Activation of complement.	T

Q. Endotoxin is- (BSMMU-Sur-04Ja)

a) Heat stable	T
b) Strong antigenic	F
c) Can produce disseminated intravascular coagulation	T
d) Liberated when the organism is destroyed	T
e) Protein in nature.	F

Q. Endotoxin- (BIRDEM-04)

a) Is part of the Gram-negative bacterial cell wall	T
b) Heat labile	F
c) Can be converted to toxoids	F
d) Is secreted by living bacterial cells	F
e) Stimulates release of interleukin-I	T

HELP LINK:

■ **Important endotoxin producing bacteria:**

1. E. coli
2. Klebsiella
3. Salmonella
4. Shigella
5. Proteus
6. Neisseria
7. V. cholerae
8. Brucella
9. Pseudomonas

Q. Endotoxins are- (BSMMU – MD/MS - 05Ja)

A. protein in nature	F
B. highly antigenic	F
C. heat stable	T
D. produced by Gram negative bacteria	T
E. used for formation of toxoid	F

Normal flora

Normal flora:
Normal flora is the term used to describe the various micro-organisms (bacteria and fungi) that are permanent residents of certain body sites, especially the skin, oropharynx, colon, and vagina.

(Ref: LANGE Review-14th, P-26)

Types of normal flora: There are 2 types of normal flora —

1. **Resident flora**: These are micro-organisms regularly present in the region. e.g. *Viridans streptococci* in mouth and throat, *E. coli* in intestine.
2. **Transient flora**: The micro-organisms are present only of hours to weeks, e.g. *Streptococcus pyogens* in throat.

	Important organisms	Less important organisms
Skin	• *Staphylococcus epidermidis*	• *Staphylococcus aureus* • Streptococci • Corynybacterium (Diptheroids) • *Pseudomonas aeruginosa* • Anaerobes (e.g. Propionibacterium) • Yeast (e.g. *C. albicans*)
Nose	• *Staphylococcus aureus*	• *Staphylococcus epidermidis* • Streptococci • Corynybacterium (Diptheroids)
Mouth	• *Viridans streptococci*	• Various streptococci • *Eikenella corrodens*
Dental plaque	• *Streptococcus mutans*	• *Prevotella intermedia* • *Porphyromonas gingivalis*
Gingival crevices	Various anaerobes, e.g. Bacteroides, Fusobacterium, streptococci, Actinomyces	
Throat	• *Viridans streptococci*	Various streptococci (including *Strep. Pyogens* & *Strep. Pneumoniae*), Neisseria species, *Haemophilus influenza*, *S. epidermidis*
Colon	• *Bacteroides fragilis* • *Escherichia coli*	Bifidobacterium, Eubacterium, Fusobacterium, Lactobacillus, Various aerobic gram-negative rods, *Enterococcus faecalis* and other streptococci, Clostridium
Vagina	• Lactobacilus • *E. coli* • *S. agalactiae*	Various streptococci, Various gram-negative rods, Bacteroids fragilis, Corynebacterium (dipiitheroids), *C. albicans*
Urethra		*S.epidermaditis*, Corynebacterium diphtheroids), Various streptococci, Various gram-negative rods, e.g. *E. coli*

(Ref: LANGE Review-14th, P-26)

Importance of normal flora: Normal flora has got both beneficial & harmful role to their host.

Beneficial Role:

1. **Prevention of colonization of pathogenic organisms**: They prevent colonization of pathogenic bacteria by occupying the receptor sites at a particular anatomical area. This is called bacterial interference.
2. **Production of antimicrobial substances**: Many of the normal flora produce bacteriocidal substances which inhibit the other pathogenic bacteria. eg.-E. coli in gut produce colicin which is a bacteriocidal substance.
3. **Nutritional function**: Normal flora also produce some substances which are essential for the host. ex -vit B_{12} & K produced by the E. coli of the gut.
4. **Antigenic stimulation by normal flora**: In new born, bacteria act as powerful stimulus for the development of the immune system. It leads to production of IgA that is secreted through mucus membranes & give protection.
5. Lactobacilli of the vagina produce lactic acid, resulting in acid pH of the vaginal fluid which destroy many pathogens there.

(Ref: Lippincott-2nd, P-9)

Harmful effect:

1. Many of normal flora of one anatomical site can produce diseases in other anatomical structure. e. g *E coli* of the gut produce UTI & most of the etiological agents of the UTI is E. coli coming from endogenous route i.e. GI tract.
2. When the organisms are displaced from their normal site in the body to an abnormal site. An example is the introduction of the normal skin flora *S. epidermidis* into the bloodstream where it can colonize catheters and heart valves, resulting in bacterial endocarditis.
3. When potential pathogens gain a competitive advantage due to diminished populations of harmless competitors. For example, when normal bowel flora is depleted by antibiotic therapy leading to overgrowth by the resistant *Cl. difficile,* which can cause severe colitis.
4. When harmless commonly ingested food substances are converted into carcinogenic derivatives by bacteria in the colon.
5. Some normal flora can produce diseases in immuno-compromized pt.

Major bacteria found in the colon:

Bacterium[1]	Number/g of Feces	Important Pathogen
Bacteroides, especially *B. fragilis*	10^{10}–10^{11}	Yes
Bifidobacterium	10^{10}	No
Eubacterium	10^{10}	No
Coliforms	10^{7}–10^{8}	Yes
Enterococcus, especially *E. faecalis*	10^{7}–10^{8}	Yes
Lactobacillus	10^{7}	No
Clostridium, especially *C. perfringens*	10^{6}	Yes

(Ref: LANGE Review-14th, P-29)

Question Bank

Q. Normal flora of the conjunctiva are *(BSMMU – Non-Residency – MS, Basic Science – July' 19)*

a) Chlamydia
b) Streptococcus viridans
c) Streptococcus epidermidis
d) Staphylococcus aureus
e) Nocardia

Ans. a) F b) F c) F (Staph. epidermidis) d) T e) F

(Ref: Subash chandra parija-2nd, P-622)

Q. Normal microbial flora in oral cavity are *(BSMMU – Non-Residency – **Dentistry** – July' 19)*
a) Streptococcus mutans
b) Acinetobacter baumannii
c) Lactobacillus spp
d) Fusobacterium nucleatum
e) Escherichia coli
Ans. a) T b) F c) T (in vaginal delivery, predominant bacteria) d) T e) F

(Ref: P. Chakroborti-3rd, P-696)

Help Link:
- ✓ **Acinetobacter baumannii** is a typically short, almost round, rod-shaped (coccobacillus) Gram-negative bacterium.
- ✓ Opportunistic pathogen in humans, affecting people with compromised immune systems, and nosocomial infection.

Q. Flora of the vagina that cause meningitis in newborn are *(BSMMU –Residency – **MD, MS, Basic Science** – March' 18)*
a) *Candida albicans*
b) *Escherechia coli*
c) diphtheroids
d) group B streptococcus
e) *Enterococcus spp.*
Ans. a) F b) T c) F d) T e) F

Q. Normal flora of the mouth are *(BSMMU –Residency – **Dentistry** – March' 18)*
a) viridians group of streptococci
b) *Staphylococcus epidermidis*
c) Diphtheroids
d) *Staphylococcus aureus*
e) Chlamydia spp
Ans. a)T b)T c) F d)F e) F

Q. Microorganisms which are normal flora of vagina and cause meningitis in newborn are *(BSMMU – Residency - **MD, MS, Basic Science** - March' 17)*
a) *Candida albicans*
b) *E. coli*
c) *Ureaplasma urealyticum*
d) *Staphylococcus epidermidis*
e) *Streptococcus agalactiae*
Ans. a) F b) T c) F d) F e) T

Q. Normal flora of throat are *(BSMMU – Residency - **Dentistry** - March' 17)*
a) Streptococcus mutans
b) Streptococcus pyo genes
c) Streptococcus agalacriae
d) Streptococcus salivarius
e) Streptococcus foecalis **Ans.** a) T b)T c) F d)T e)F

Q. Candida albicans are normal flora of *(BSMMU – Residency - **Dentistry** - March' 17)*
a) mouth
b) nasopharynx
c) colon
d) vagina
e) urethera
Ans. a) T b) F c) T d) T e) F

Q. Normal flora of skin is/ are *(BSMMU – Non-Residency – **MD, MS, Basic science, Dentistry – July' 16**)*

a) staphylocoocus aureus T
b) streptococcus pneumonae F
c) moraxella catarrhalis F
d) malassezia furfur T
e) streptococcus viridians F

Q. Normal vaginal flora includes *(BSMMU – Non-Residency – **MS** – July' 15)*

a) anerobic streptococci F
b) *E. coli* T
c) *staphylococcus aureus* T
d) lactobacillus T
e) *streptococcus pyogenes* F

Q. Normal flora of the conjunctiva include *(BSMMU –Residency - **MD/MS, Basic science** – March' 14)*

a) chlamydia F
b) *streptococcus viridians* F (hemolytic)
c) *streptococcus epidermidis* F
d) *staphylococcus aureus* T
e) nocardia F

Help link:

Normal flora of the conjunctiva:

- *Chlamydia trachomatis*
- *Chlamydia pneumonia*
- *Haemophilus aegyptius*
- *Haemophilus influenza*
- Moraxella spp
- Neisseria spp
- *Streptococcus epidermidis*
- *Streptococcus viridans*
- *Staphylococcus aureus*

Q. Following statements are correct: (MD/MS (DMC)-04Ja)

a) Most common normal flora in skin is *Staph. epidermidis.* T
b) Most common normal flora in throat is *Strep. viridians* T
c) *E. coli* is a prominent member of normal flora of throat. F
d) Most common site as carrier of Staph. Aureus is in nose. T
e) Major site of bacteroides fragilis is in vagina. F (major site – colon; minor site – vagina)

Q. Following bacteria are normal flora of throat- (BSMMU-MS-04Ja)

a) *Haemophilus influenzae* T
b) *Streptococcus viridens.* T
c) *Streptococccus pneurnoniae* T
d) *Streptococcus pyogenes* T
e) *Streptococcus agalactiae* F

Drug Resistance

■ **Definition**: It is the ability of bacteria to resist the deteriorous effect of anti-microbial agent on them. If the concentration of drug requires to inhibits or kill the microorganism is greater than the concentration that can safely be achieved then the microorganism is considered to the resistant to the drug.

■ **Types**:

1. ***Natural***:
   - M. tuberculosis is resistant to penicillin.
   - Streptococci is impervious to aminoglycosides.
2. ***Acquired***:
   - Staphylococcus is now penicillin resistant through previously it was sensitive.

■ **Mechanisms of drug resistance**:

1. Micro-organisms produce enzymes that destroy the active drug. e.g.
   - Staphylococci resistant to penicillin G produce β-lactamase that destroy the drug.
   - Phosphorylase destroy aminoglycoside.
   - Acetyl transferase destroy chloramphenicol.
2. Micro-organisms change their permeability to the drug. eg. Tetracycline cannot accumulate in the resistant bacteria.
3. Micro-organisms develop an altered structural target for the drug. eg. chromosomal resistant to aminoglycosides is associated with the loss or alteration of a specific protein receptor on the 30S subunit of bacterial ribosome.
4. Micro-organisms develop an altered metabolic pathway that bypasses the reaction is inhibited by the drug. eg. some sulfonamide resistant bacteria do not require extracellular PABA but can utilize preformed folic acid.
5. Microorganisms develop an altered enzyme that can still perform the metabolic function is less affected by drug. eg. in trimethoprim resistant bacteria, dihydrofolate reductase is far less inhibited.

■ **Origin of drug resistance**:

A. **Genetic origin**:

I. **Chromosome mediated resistance**: Spontaneous mutation in a locus of chromosome that controls susceptibility of a drug. Mutation:

- Change in structural protein receptor.
- Loss of structural protein receptor of a drug. e.g. Aminoglycosides.

II. **Extrachromosomal resistance/ Plasmid mediated resistance**: The extra-chromosomal genetic material is called plasmid. Plasmid that carries gene for drug resistance is called **R** factor (resistant plasmids). This plasmid genes control the formation of enzymes, capable of

- destroying the drug (β-lactamase)
- altering structure of drugs (aminoglycosides)
- altering function of drug (tetracycline)

R factor may be transported from one microbes to another by-

1. **Transduction**: Bacteriophage infect bacteria → R factors ingested by phage → Phage attack new bacteria→ Transfer of resistant plasmid.
2. **Transformation**: Direct uptake of R factors from environment or in lab.
3. **Conjugation**: During conjugation, R factors are transferred from resistant cell to sensitive cell through sex pili. Multi-drug resistance (MDT) spread through this method.
4. **Transposon mediated resistance**: Transfer of transposon (a short segment of DNA) occurs between one plasmid & another or between a plasmid & chromosome within a bacterial cell.

Resistance of different drugs

- **Extended-spectrum β-lactamases (ESBLs):**
  - Produced by E. coli, Klebsiella, Enterobacter, and Proteus.
  - Causes resistance to all penicillins, cephalosporins, and monobactams.
- **Resistance to penicillins:** Changes in the penicillin-binding proteins (PBPs) in the bacterial cell membrane
- Some of S. aureus causes another form of resistance, called tolerance,

- **Aminoglycosides:**
  1. Modification by plasmid-encoded phosphorylating, adenylylating, and acetylating enzymes (the most important mechanism);
  2. chromosomal mutation (e.g., a mutation in the gene that codes for the target protein in the 30S subunit of the bacterial ribosome;
  3. decreased permeability of the bacterium to the drug.
- **Chloramphenicol**: plasmid-encoded
- **Erythromycin**: plasmid encoded
- **Tetracyclines**: plasmid-encoded
- **Sulfonamides**: a plasmid-encoded
- **Quinolones**: chromosomal mutations that modify the bacterial DNA gyrase
- **Rifampin:** chromosomal mutation in the gene encoding the bacterial RNA polymerase,
- **Isoniazid**: mutations in the organism's catalase–peroxidase gene
- **Ethambutol**: mutations in the gene that encodes arabinosyl transferase,
- **Pyrazinamide**: mutations in the gene that encodes bacterial amidase

B. **Non-genetic origin**:

1. Bacteria can be walled off within an abscess cavity that the drug can not penetrate effectively.
2. Bacteria can be in a resting state, i.e. not growing; they are therefore insensitive to cell wall inhibitors such as penicillin & cephalosporins. Similarly, *M. tuberculosis* can remain dormant in tissues for many years,during which time it is insensitive to drugs.
3. Under certain circumstances, organisms that would ordinarily be killed by penicillin can lose their cell walls, survive as **protoplasts** and be insensitive to cell-wall-active drugs.

Medically important bacteria that exhibit significant drug resistance:

Type of Bacteria	Name of Bacteria	Clinically Significant Drug Resistance
Gram-positive cocci	*Staphylococcus aureus*	Penicillin G, nafcillin
	Streptococcus pneumonias	Penicillin G
	Enterococcus faecalis	Penicillin G, aminoglycosides, vancomycin
Gram-negative cocci	*Neisseria gonorrhoeae*	Penicillin G
Gram-poisitive rods	None	
Gram-negative rods	*Haemophilus influenzae*	Ampicillin
	Pseudomonas aeruginosa	β-Lactams, aminoglycosides
	Enterobacteriacea	β-Lactams, aminoglycosides
Mycobacteria	*M. tuberculosis*	Isoniazid, rifampin
	M. avium-intracelluiare	Isoniazid, rifampin and many others

Table: R-factor-mediated resistance mechanisms:

Drug	Mechanism of Resistance
Penicillins and cephalosporins	β-Lactamase cleavage of β-lactam ring
Aminoglycosides	Modification by acetylation, adenylylation, or phosphorylation
Chloramphenicol	Modification by acetylation
Erythromycin	Change in receptor by methylation of rRNA
Tetracycline	Reduced uptake or increased export
Sulfonamides	Active export out of the cell and reduced affinity of enzyme

(Ref: LANGE Microbiology)

4. The presence of foreign bodies makes successful antibiotic treatment more difficult. This applies to foreign bodies such as surgical implants and catheters as well as materials that enter the body at the rime of penetrating injuries, such as splinters and shapnel.
5. Several aircrafts can make it appear that the organisms are resistant, e.g administration of the wrong drug or the wrong dose or failure of the drug to reach the appropriate site in the body.
   Example – poor penetration into spinal fluid by several early generation cephalosporins.

Question Bank

Q. Antibiotic resistance *(BSMMU –Residency - **Dentistry** – March' 19)*
a) results from irrational use of antibiotics
b) to vancomycin resistant enterococci can be treated with carbapenem
c) is mostly plasmid mediated
d) to MRSA can be treated with aminoglycosides
e) is associated with urease formation
Ans. a) T b) F c) T d) F e) F

Q. Bacterial mechanisms of resistance development against lactum drugs are *(BSMMU – Residency - **MD, MS, Basic Science, Dentistry** - March' 17)*
a) production of β lactumase enzyme
b) mutation in transpeptidase enzyme
c) efflux pump
d) altered porins
e) alteration of metabolic pathway
Ans. a) T b) F c) F d) T e) F

Q. Genetic material transfer among bacteria occurs through *(BSMMU –Residency – **MD/MS, Basic science** – March' 14)*
a) transduction
b) sporulation and spore germination
c) transformation
d) replication
e) conjugation
Ans. a) T b) F c) T d) F e) T

Q. The following statements regarding mechanism of development of resistance are correct: *(BSMMU – M. Phil, Diploma (Non-Residency)–12Ju, DMC & others – MD/MS – 12Ju)*
a) by increasing uptake of the drug within the bacteria
b) by conformational alteration in the binding site
c) by synthesizing enzyme
d) by forming new cell wall
e) by developing efflux mechanism
Ans. a) F b) T c) T d) F e) T

Q. The following bacteria are used as probiotics *(BSMMU – MD/MS (Residency) – January, 2011)*

a) lactobacillus	T
b) peptostreptococcus	F
c) sacchromyces cerevisiae	F
d) bifidobacterium	T
e) fusobacterium	F

HELP LINK:
Probiotics are live, non-pathogenic bacteria that may be effective in the treatment or prevention of certain human diseases. The suggested basis for the possible beneficial effect lies either in providing colonization resistance by which the non-pathogen excludes the pathogen from binding sites on the mucosa, in enhancing the immune response against the pathogen, or in reducing the inflammatory response against the pathogen.

For example, the oral administration of live Lactobacillus rhamnosus strain GG significantly reduces the number of cases of nosocomial diarrhea in young children. Sacchromyces cerevisiae is a yeast.
Adverse effects: few; however, serious complications have arisen in highly immunosuppressed patients and in patients with indwelling vascular catheters.

Q. Mechanisms of transferring genetic materials by micro-organisms are- (MD/MS (DMC)-08Ja)

a) transcription F
b) transposition F
c) mutation F
d) transduction T
e) translation F

Q. β-Lactamase producing bacteria are- (BSMMU - MD - 06Ja)

A. Streptococcus pyogen
B. M. Tuberculosis
C. Ecoli
D. Pseudomonas
E. C. diphtheriae

Ans.
a) F *(Staph. aureus may produce β-lactamase)* b) F
c) T *(E. coli & other coliform can produce β-1actamase)*
d) T *(Kiebsiella can produce β-lactamase)* e) F

ANTIBIOTIC SENSITIVITY TESTING

- **Minimal Inhibitory Concentration (MIC)**: the lowest concentration of drug that inhibits the growth of the organism. After incubation at 35°C for 18 hours,
- **Disk diffusion method**: disks impregnated with various antibiotics are placed on the surface of an agar plate that has been inoculated with the organism isolated from the patient
- **Minimal Bactericidal Concentration (MBC)**: concentration of drug that actually kills the organism rather than the concentration that merely inhibits growth, eg: endocarditis.

❖ Bactericidal drugs usually have an MBC equal or very similar to the MIC, whereas bacteriostatic drugs usually have an MBC significantly higher than the MIC.
❖ **Beta lactamase produce**: *S. aureus, H. influenzae*

❑ USE OF ANTIBIOTIC COMBINATIONS:

(1) To treat serious infections.
(2) To achieve a synergistic inhibitory effect.
(3) To prevent the emergence of resistant organisms.
Eg: combination of a penicillin and an aminoglycoside causes a synergistic action against enterococci (E. faecalis),

Antitoxins (immune globulins)

- Tetanus antitoxin
- Botulinum antitoxin
- Diphtheria antitoxin
- Pertusis

❑ **Passive active immunity**: Tetanus, rabies, HBV

IMPORTANT MCQ OF GENERAL BACTERIOLOGY

[Ref: Smiddy]

Q. When using an autoclave to sterilize surgical drapes and instruments It is essential that:

a) the load should be tightly packed.
b) the containers in which the loads are packed should be impervious to steam
c) air should be completely removed from the chamber prior to the admission of steam
d) a vacuum must be made at the end of the cycle
e) an adequate indication of autoclave efficiency should be included in the load.

Ans.

a) **False** The loads should not be tightly packed because tight packing hinders the passage of steam into and through the loads thus interfering with sterilization.

b) **False** Until recently materials to be sterilized were packed in metal drums and if these remain in use the vents to allow the admission of steam must be opened before placing the drums in the sterilizer. The more modern technique is to wrap materials in paper or Steriseal and place the packs in cages or racks.

c) **True** This is a pre-requisite for the correct functioning of the modern autoclave which does not depend on gravity displacement. By moving 98% of the air from the chamber penetration of the load occurs almost instantly so that efficient sterilization is obtained and the cycle time is shortened, Normal sterilizing time is 3 minutes at 134^0C.

d) **True** The creation of a vacuum at the end of the cycle in a chamber still warm from the presence of steam in both the chamber and the surrounding jacket, ensures that the contents of the autoclave are dry before removal.

e) **True** In most departments the Bowie Dick test has been replaced by Lantor Testing daily. This test is performed prior to the days work in the sterilizing unit, after which the efficacy of the procedure is judged by an automatic recording device which indicates the temperatures reached and the duration of the cycle.

Q. Spores are killed by exposure to: *(BSMMU – Residency - **Dentistry**-March' 17; M. Phil,Diploma–July '10)*

a) moist heat at 110^0C for 15 minutes
b) dry heat at 160°C for 1 hour
c) ethylene oxide
d) hydrogen peroxide
e) gentian violet

Ans.

a) **False** Bacterial spores require exposure to moist heat at a temperature of 121^0C for at least 15 minutes and preferably 30 minutes before they are destroyed. Resistant spores such as the spores of *Clostridium botulinum* can resist autoclaving at the lower temperature of 115^0 C for up to 40 minutes.

b) **True** The majority of spores are killed by exposure to dry heat at 160^0C for 1 hour. In practice this is an unacceptable method of sterilization because slight charring of paper and cotton occurs at this temperature.

c) **True** Ethylene oxide is highly lethal to all kinds of microbes and spores. It is of particular value for sterilizing particles liable to damage by heat. e.g. plastic and rubber articles. Sterilization time depends upon the temperature of the reaction and the relative humidity.

d) **False** Hydrogen peroxide has been used as an antiseptic but has little or no action on bacterial spores.

e) **False** Gention violet will kill some vegetative forms of bacteria particularly Gram-positive organisms. It is much less active against Gram-negative bacteria and virtually useless against spores of any kind.

Q. Differenced between disinfectants and antiseptics are: (FCPS – Surgery – 08Ja)

a) the latter are more harmful to living tissue cells.

b) antiseptics free inanimate objects from vegetative organisms whereas disinfectants are used for the local removal of pathogenic bacteria from the tissues.

c) the former are more readily inactivated by contact with proteinaceous material such as blood.

d) the speed of action of disinfectants can be accelerated by raising the temperature whereas the action of antiseptics can only be intensified by increasing their concentration.

e) there are specific differences in the mode of action of both groups of compounds.

Ans.

a) **False** The converse is correct.

b) **False** The converse is correct. Disinfectants are used to free inanimate objects from vegetative organisms but not necessarily from spores whereas antiseptics are primarily bacteriostatic agents for the removal of pathogenic bacteria from the tissues.

c) **False** Both are equally affected by proteinaceous material.

d) **False** The speed of action of both groups of substances can be accelerated by raising the temporature and/ or their concentration.

e) **False** Both groups of agents may have a variety of actions including disruption of the cytoplasmic membranes,enzyme systems or cellular proteins.

Q. Chemical agents used as disinfectants and anti-septics include the following compounds: (FCPS-Surgery-08Ja)

a) the phenols

b) isopryl alcohol

c) the halogens

d) the soaps

e) derivatives of salicylic acid

Ans.

a) **True** Phenol, which is carbolic acid, was used by Lister over 100 years ago, to prevent wound infection. This group of chemical compounds act by coagulating protein. Phenol is effective against both bacteria and viruses but it is no longer used because of its toxicity. However, a variety of derivatives such as lysol. Dettol and hexachlorophine are in common use.

b) **True** This compound is in common use for sterilization of the skin and is most effective in 70% concentration The alcohols act by coagulating cell proteins thus killing bacteria and some viruses.

c) **True** The halogens, or any substance capable of releasing them, such as sodium hypochlorite, are lethal to bacteria, viruses, fungi and spores. Their action is to oxidise SH groups but a disadvantage is their susceptibility to quenching by organic matter.

d) **True** Soaps have weak disinfectant activity although they are active against *Strep. pyogenes*, *Strep. pneumoniae*, *Haemophilus influenzae* and the virus of influenza. They have no action on *Staph. pyogenes*, mycobacteria or Gram-negative bacilli. The main effect of soap is a mechanical one removing the transient skin flora.

e) **False** Salicylic acid and the salicylates have no disinfectant or antiseptic action.

Q. Infection within a hospital may be:

a) dust-borne

b) waler-borne

c) food-borne

d) hand-borne

e) endogenous

Ans.

a) **True** Infected particles redistributed from a static position by dusting or bed making may lead to respiratory tract infections. A further possibility is the distribution of such particles through inadequate or imperfectly maintained ventilation systems. Droplet nuclei 1-10 μm in diamter formed by the

evaporation of small droplets may remain in the air for long periods and are accountable for some virus infections such as the common cold.

b) **True** Water-borne infection may occur due to contamination of a water supply with excreta. This is the common method of spread of cholera and typhoid fever.

c) **True** Food-borne infection is usually the result of infection of the food supplied to patients by foodhandlers who are carrying an intestinal pathogen. Alternatively if infected water is used for washing food infection may be transmitted.

d) **True** Hand-borne infections are usually due to poor personal hygiene. Patients and carriers with intestinal pathogens can contaminate their hands with traces of faeces when cleansing themselves after defaecation.

e) **True** Endogenous infection is common particularly in patients in whom the original disease was the result of bacterial intection, e.g. peritonitis following appendicitis or diverticulitis.

Q. The virulerce of bacteria is related to:

a) their number in the tissues
b) the production of toxins
c) their ability to produce spreding factors
d) their resistance to phagocytosis
e) decreased resistance of the host

Ans.

a) **False** The number of bacteria does not affect their virulence, only their potential for producing an infective lesion. About 10 coagulase positive staphylococci are required to produce a superficial infective lesion such as a boil.

b) **True** Bacterial toxins are of two main types, exotoxins and endotoxins. Both play a large part in determining bacterial virulence. The former, which are mainly produced by Gram-positive organisms, diffuse freely from the organisms into the surrounding tissues although some, like the exotoxin of *Clostridium tetani* have an affinity for specific tissues. Endotoxins, however, are an integral part of the cell. Typical examples are the glyco-lipid complexes of the Gram-negative organisms such as *Escherichia coli*.

c) **True** Spreading factors, such as streptokinase which is produced by *Streptococcus pyogenes*, are important factors in determining bacterial virulence. This enzyme activates a proteolytic enzyme precursor in the plasma and causes the lysis of fibrin clots. Another factor of similar importance is hyaluronidase which is produced by *Clostridium perfringens* and other organisms. This enzyme splits hyaluronic acid, the muco-polysaccharide, intercellular cement substance, thus enabling the clostridia to spread along the tissue planes.

d) **True** Resistance to phagocytosis chiefly depends upon the presence of surface components on the bacteria which make it difficult for the phagocytic cells to ingest them. Virulent strains of pneumococci, for example, possess polysaccharide capsules, whereas rough mutants which have lost their capsules are readily engulfed by phagocytes.

e) **False** Decreased resistance of the host does not affect the inherent virulence of the organism. It does, however, affect the number required to produce a clinical lesion. In an experimental animal, the minimum lethal dose of organisms would also be reduced.

Q. Bacteria are normally found on or in the:

a) blood
b) urinary tract
c) lower bronchi
d) gastrointestinal tract
e) skin, sebaceous glands and hair follicles

Ans.

a) **False** In a normal individual bacteria are only transiently found in the blood stream, e.g. following tooth brushing. Such bacteria do not multiply and are rapidly eliminated.

b) **False** The urinary tract is normally sterile. Infection of the female urethra with Gram-negative cocci, however, is the common cause of the urethral syndrome, often mistakenly referred to as 'cystitis' although the bladder urine is sterile.

c) **False** The lower bronchi are normally sterile.

d) **True** The gastrointestinal tract is inhabited by an abundant bacterial flora from the level of the duodenojejunaljunction onwards. It has only recently been appreciated, however, that obligate anaerobes belonging to the bacteroides group constitute a majority of the intestinal flora. Prior to culture of the small bowel contents using anaerobic techniques, it was thought that this part of the bowel was sterile.

e) **True** *Staphylococcus albus, Staphylococcus aureus*, diphtheroid organisms, lactobacilli and a variety of obligate anaerobes colonise the skin and its appendages.

SYSTEMIC BACTERIOLOGY

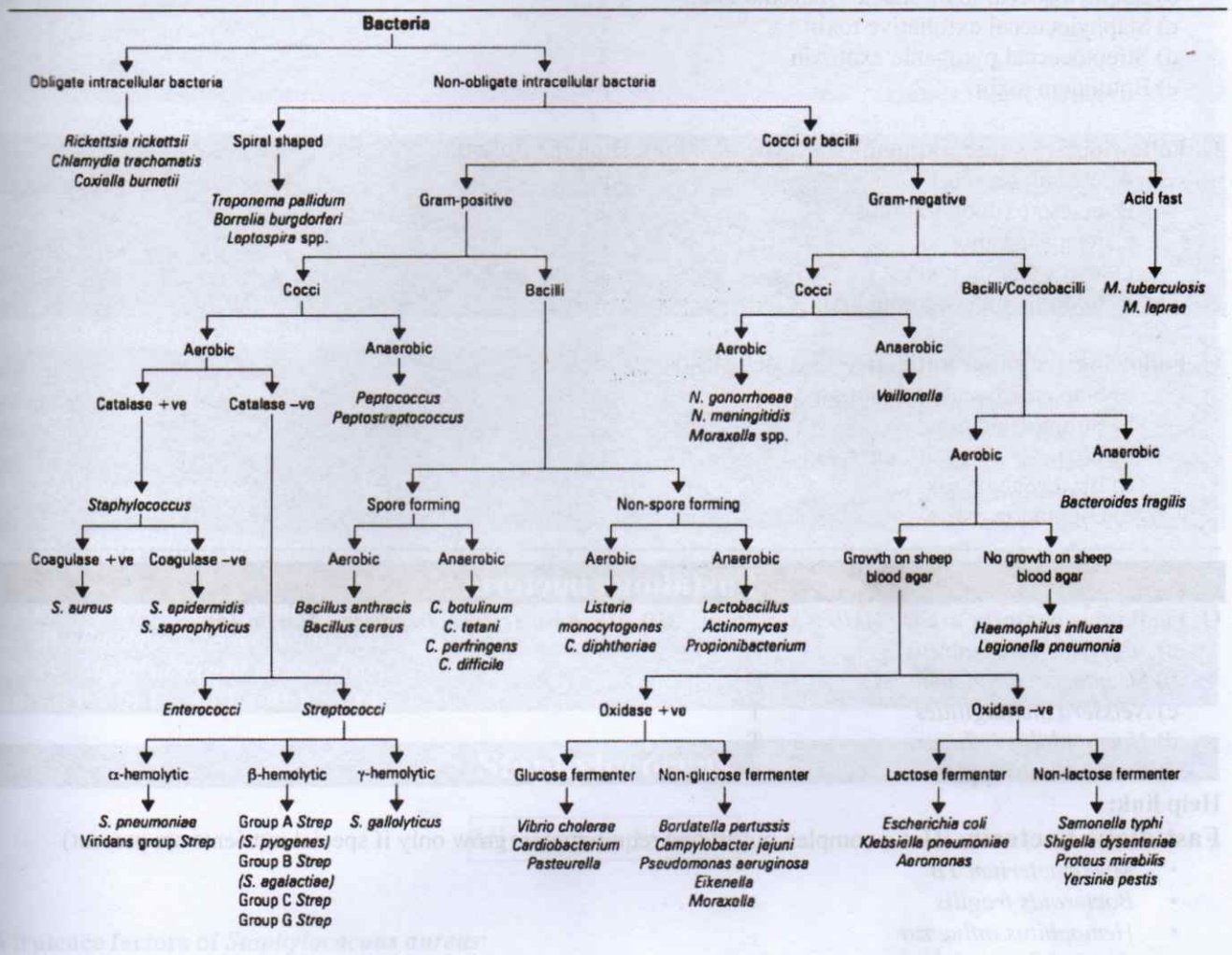

Fig: Classification of bacteria

Super antigen

Q. Toxins acts as superantigen are *(BSMMU – Residency - **MD, MS, Basic Science** - March' 17)*

a) erythrogenic toxins
b) toxic Shock Syndrome Toxin
c) staphylococcal enterotoxin
d) botuinum toxin
e) cholera toxin

Ans. a) T b)T c) T d) F e)F

Help link:

Superantigens:

- Toxic shock syndrome toxin (S. areus)
- Staphylococcal enterotoxin (S. aureus)
- Erythrogenic toxin (S. pyogens)
- Bacillus toxin (Bacillus cercius)
- Cl. perfringens enterotoxin

Q. Super antigens are: *(BSMMU – Residency – MD, MS, Basic science, Dentistry – March' 16)*
a) Staphylococcal entertoxin T
b) Staphylococcal toxic shock syndrome toxin T
c) Staphylococcal exfoliative toxin T
d) Streptococcal pyrogenic exotoxin T
e) Botulinum toxin F

Q. Following are super antigen: (BSMMU - M. Phil, Diploma, July-05)
A. coagulase F
B. enterotoxin of S aureus T
C. tetanospasmin F
D. erythrogenic toxin T
E. toxic shock syndrome toxin T

Q. Following are super antigen- (BSMMU-MS-04Ja)
a) Staphylococcal enterotoxin T
b) Streptolysin O F
c) Toxic shock syndrome toxin T
d) Erythrogenic toxin T
e) Diphtheria exotoxin F

Fastidious bacteria

Q. Fastidious bacteria are *(BSMMU – Residency – MD, MS, Basic science, Dentistry – March' 16)*
a) *Staphylococcus aureus* F
b) *Streptococcus pneumonia* F
c) *Neissera meningitides* T
d) *Haemophilus influenza* T
e) *Enterococcus spp.* F

Help link:

Fastidious bacteria: (Has a complex nutritional requirements, grow only if special nutrients are present)
- *Mycobacterium TB*
- *Bacteroids fragilis*
- *Hemophilus influenza*
- *Campylobacter jejuni*
- *Spirochates*
- *Helicobacter pylori*
- *Neisseria gonorrhea*
- *Neisseria meningitidis*

Q. The following are fastidious bacteria *(BSMMU – MD/MS (Residency) – January, 2011)*
a) H. influenzae T
b) S. aureus F
c) N. meningitides T
d) H. pylori T
e) N. gonorrhoeae T

Q. The following are fastidious organism: (BSMMU - M. Phil, Diploma, July-04)
A. Streptococcus pneumonia F
B. Neisseria meningitides T
C. Escherichia coli F
D. Proteus F
E. Mycobacterium tuberculosis T

Q. Post infectious non infective inflammatory diseases are *(BSMMU – Residency - **MD, MS, Basic Science, Dentistry** - March' 17)*
a) rheumatoid arthritis
b) acute rheumatic fever
c) acute glomerulonephritis
d) systemic lupus erythematosus (SLE)
e) cervical spondylitis
Ans. a) F b) T c)T d)F e)F

Q. Followings are encapsulated bacteria that can cause respiratory tract infections *(BSMMU – Non-Residency - **MD/MS, Basic science** – 13Ju)*
a) *Streptococcus pneumoniae* T
b) *Mycoplasma pneurnoniae* F
c) *Kiebsiella pneumoniae* T
d) *Haemophilus influenzae* T
e) *chlamydiae pneumoniae* F

Q. Followings are the organisms that can cause latent infections *(BSMMU – Non-Residency - **MD/MS, Basic science** – 13Ju)*
a) *Plasmodium falciparum*
b) *Toxoplasma gondii*
c) *Histoplasma capsulatum*
d) *Pneumocystis jerovecii*
e) *Mycobacterium tuberculosis*
Ans. a) F b) T c) T d) T e) T

Staphylococcus

Virulence factors

Virulence factors of *Staphylococous aureus*:

A. Cell wall components & antigens: *S. aureus* has several important cell wall components and antigens.

1. **Protein A** is the major protein in the cell wall. It is an important virulence factor because it binds to the Fc portion of IgG at the complement-binding site, thereby preventing the activation of complement. As a consequence, no C3b is produced, and the opsonization and phagocytosis of the organisms are greatly reduced. Protein A is used in certain tests in the clinical laboratory because it binds to IgG and forms a "coagglutinate" with antigen–antibody complexes. The coagulase-negative staphylococci do not produce protein A.
2. **Teichoic acids** are polymers of ribitol phosphate. They mediate adherence of the staphylococci to mucosal cells and play a role in the induction of septic shock.
3. **Polysaccharide capsule** is also an important virulence factor. There are 12 serotypes, but types 5 and 8 cause 85% of infections. The capsule is poorly immunogenic, which has made producing an effective vaccine difficult.
4. **Surface receptors** for specific staphylococcal bacteriophages permit the "phage typing" of strains for epidemiologic purposes. Teichoic acids make up part of these receptors.
5. Most strains of *S. aureus* are coated with a small amount of polysaccharide capsule (microcapsule) that is antiphagocytic. There are 11 serotypes based on antigenicity of the capsular polysaccharide.

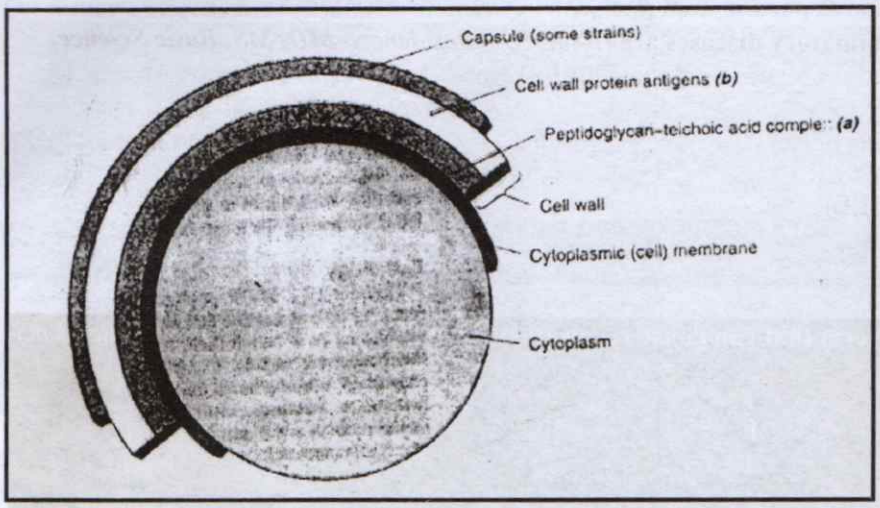

Fig: Antigenic structures of Staphylococcus.

6. The **peptidoglycan** of *S. aureus* has endotoxin-like properties; i.e., it can stimulate macrophages to produce cytokines and can activate the complement and coagulation cascades. This explains the ability of *S. aureus* to cause the clinical findings of septic shock yet not possess endotoxin.

B. **Toxins**:

1. **Enterotoxin**: It causes food poisoning (characterized by prominent vomiting and watery non- bloody diarrhea).
2. **Toxic shock syndrome toxin (TSST)**: It causes toxic shock, especially in tampon-using menstruating women or in individuals with wound infections.
3. **Exfoliatin** (Epidermolytic toxin): It causes 'Scalded-skin" syndrome (SSS) in young children.
4 **Haemolysins**: α-toxin, β-toxin, γ-toxin & δ-toxin.
5. **Leukocidins**: They can kill leukocytes.
6. **Other toxins**: They cause tissue necrosis in vivo. Of these, the most important is Alpha toxin, which causes marked necrosis of skin and hemolysis.

C. **Enzymes**:

- **Catalase**: It converts H_2O_2 into water and oxygen.
- **Coagulase**: It clots oxalated or citrated plasma.
- **β-lactamase**: It causes breakdown of β-lactum antibiotics. e.g.-Penicillin.
- **Hyaluronidase** (or spreading factor): It destroys the ground substances of connective tissue.
- **Staphylokinase** (or fibrinolytic factor): It lyses thrombi.
- **Proteases**: They cause breakdown of proteins.
- **Lipases**: They cause breakdown of tissue lipids.
- **DNA-ase**: It causes breakdown of cellular DNA.

(Ref: LANGE Review-14th, P-112, 113)

Question Bank

Q. Exotoxins produced by *Staphylococcus aureus* are *(BSMMU – Residency - MD, MS, Basic Science, Dentistry - March' 17)*

a) erythrogenic toxins
b) enterotoxin
c) exfoliative toxin
d) neurotoxin
e) toxic shock syndrome toxin

Ans. a) F b)T c)T d) F e)T

Help link:

1. **Cytolytic toxin (Haemolysins)**: alpha, beta, gamma, delta
   - Alpha toxin- destroy RBC
   - Beta toxin-destroy sphingomyelin in RBC
   - Gamma- destroy RBC
   - Delta-destroy RBC and WBC.

2. **Leukocidins**:
   - Kill leukocyte
   - P-V leukocidin- severe skin and soft tissue infection by MRSA, severe necrotising pneumonia.
3. **Enterotoxin** (preformed):
   - Causes Food poisoning (CHO food, rice and pudding) - characterized by vomiting & watery, non-bloody diarrhoea.
   - produce toxin when food kept overnight,
   - resist boiling for 30 minutes.
   - Act as super antigen, stimulate release of IL-1,IL-2 from macrophage, helper T cells, cytokine released, from lymphoid cells lining in the small intestine
   - stimulate vomiting center due to stimulating enteric nervous system, prevent water reabsoption, leads to prominent vomiting and diarrhoea.(I.P- 1-6 hour), called bacteriophage/ lysogenic toxin,
   - No antibiotic is effective.
4. **Exfoliatin/ epidermolytic toxin:** Saclded Skin syndrome (SSSS). It cleaves desmoglein, and causes detachment of the superficial layers of the skin.
5. **Toxic shock syndrome toxin** (5- 25 % pt):
   - produce toxic shock syndrome characterized by fever, shock, skin rash (desquamative), hypotension,
   - super antigen (IL-1, IL-2, TNF),
   - conditions where TSS occurs (main site of colonization): contaminated nasal pack, vaginal tampons
   - Mechanisms: produced by *Sta. aureus and* certain strains of *Str. pyogenes. It binds directly to class II* (MHC) of (macrophages) without intracellular processing. Release of large amounts of IL-1,2 that produce toxic shock. TSST is induces T cells to multiply which contributes to the overproduction of cytokines.

Q. Coagulase positive staphylococci are *(BSMMU – Residency - **Dentistry** - March' 17)*
a) S. aureas
b) S. epidermidis
c) S. intermedius
d) S. hyicus
e) S. haemolyticus
Ans. a) T b) F c)F d)F e)F

Q. Staphylococcus aureus *(BSMMU – Diploma – Dentistry-July' 16)*
a) coagulates human serum
b) can survive a week or more in dried pus
c) may produce an enterotoxin
d) is part of the normal flora of the skin
e) acquires resistance to antibiotics by transduction
Ans. a) T b) F c) T d) T e) F

Q. Virulence factors of *Staphylococcus aureus* are *(BSMMU – Residency – **MD, MS, Basic science, Dentistry** – March' 16)*

a) protein A	T
b) lipase	T
c) M protein	F
d) endotoxin	F
e) exfoliative toxin	T

Q. Toxins produced by *Staphylococcus aureus* *(BSMMU –Residency – **MD, MS, Basic Science** – March' 15)*
a) erythrogenic toxin b) enterotoxin
c) toxic shock syndrome toxin (TSST)
d) endotoxin
e) exfoliative toxin Ans. a) F b) T c) T d) F e) T

Q. Staphylococcus aureus has following toxins & enzymes: (BSMMU – MD – January, 2010)

a) Erythrogenic toxin F
b) Pyrogenic toxin F
c) Exfoliative toxin T
d) Endotoxin F
e) Enterotoxin T

Q. Staphylococcal enterotoxin: (BSMMU – MD – January, 2010)

a) Preformed T
b) Heat labile F
c) Exotoxin T
d) Acid stable T
e) Common agent of food poisoning T

HELP LINK:

Enterotoxin of staphylococcus aureus: Causes food poisoning characterized by prominent vomiting and watery, non-bloody diarrhea. It acts as a superantigen within the gastrointestinal tract to stimulate the release of large amounts of interleukin-1 (IL-1) and interleukin-2 (IL-2) from macrophages and helper T cells, respectively. The prominent vomiting appears to be caused by cytokines released from the lymphoid cells, which stimulate the enteric nervous system to activate the vomiting center in the brain.

Enterotoxin is fairly heat-resistant and therefore is usually not inactivated by brief cooking. It is resistant to stomach acid and to enzymes in the stomach and jejunum. There are six immunologic types of enterotoxin, types A-F.

Q. The following toxins are produced by *S. aureus*: (BSMMU - M. Phil, Diploma, July-09)

a) Enterotoxin T
b) Erythrogenic toxin F
c) Dermonurotoxin F
d) Endotbxin F
e) Toxic shock syndrome toxin T

Q. Following toxins are produced by Staph. aureus: (BSMMU - Basic Science; M. Phil, Diploma– 07Ju)

a) Erythrogenic toxin F
b) Dermonecrotoxin F
c) Enterotoxin T
d) Toxic Shock Syndrome Toxin T
e) Myocardiotoxin F

Q. Staphylococcal enterotoxin is- (BSMMU – MD/MS - 07Ja)

a. Preformed T
b. Heat labile F
c. Exotoxin T
d. Acid labile F
e. Common agent of food poisoning T

Q. *Staphytococcus aureus* has following toxins and enzymes - (BSMMU - M. Phil, Diploma, July-06)

a) Erythrogenic toxin F
b) Pyrogenic exotoxin F
c) Exfoliatin toxin T
d) Endotoxin F
e) Enterotoxin T

Q. Toxic shock syndrome toxin: (PG-96Ja)
A. Is produced by Strep beta hemolyticus T
B. In indistinguishable from enterotoxin A F
C. In indistinguishable from enterotoxin F T
D. Causes shock by releasing IL1 and IL2 T

Diseases caused by Staphylococcus

Q. *Staphylococcus aureus* causes *(BSMMU – Non-Residency - MD – July' 19)*
a) toxic epidermal necrolysis
b) erysipelas
c) boil
d) eschar
e) chancre

Ans. a) T b) F (suppurative cause of streptococcus) c) T d) F (***Eschar*** is ***caused*** by burning or cauterizing) e) F (occurs in primary syphilis)

(Ref: LANGE-15th, P-109)

Help link:
Diseases produced by Staphylococcus:
A. **Inflammatory**:
1. Skin infections: Impetigo, furuncles, carbuncles, boils, abscess, paronychia, cellulites, folliculitis, hydradenitis suppurativa, conjunctivitis, eyelid infections (blepharitis and hordeolum), postpartum breast infections (mastitis).
2. Septicemia (sepsis): it can originate from any localized lesion, especially wound infection, or as a result of intravenous drug abuse.
3. Endocarditis: It may occur on normal or prosthetic heart valves.
4. *Osteomyelitis and arthritis (common in children)*
5. Postsurgical wound infections.
6. Pneumonia: can occur in postoperative patients or following viral respiratory infections, especially influenza. It may lead to empyema or lung abscess.
7. Conjunctivitis (in new born)
8. Abscess can occur in any organ. (Brain abscess)
9. Secondary infections of wounds, ulcers, burns & skin disorder.
10. Cross infection in hospitals
11. Antibiotic associated enteritis.

B. **Toxin mediated**:
1. Food poisoning (gastroenteritis) – caused by enterotoxin
2. Toxic shock syndrome – caused by Toxic shock syndrome toxin -1 (TSST-1)
3. Scalded skin syndrome – caused by Exfoliatin

(Ref: LANGE Review-14th, P-113, 114 + Lecture of DMC)

Q. Staphylococcal infection can cause *(BSMMU-Non-Residency-Paediatrics-July'19)*
a) pneumonia
b) scarlet fever
c) increased ASO titre
d) toxic shock syndrome
e) transplacental transmission of infection

Ans. a) T (Necrotising Pneumonia by MRSA) b) F (streptococcus pyogens) c) F(streptococcus pyogens) d) T e) F

(Ref: LANGE-15th, P-109)

Q. Toxin mediated diseases are *(BSMMU –Residency - MD/MS, Basic science, Paediatrics – March' 19)*
9) scarlet fever
b) plague
c) dengue
d) staphylococcal food poisoning
e) diphtheria

Ans. a) T b) F c) F d) T e) T

Q. *Staphylococcus aureus* causes the following toxin mediated diseases *(BSMMU – Non-Residency – MD/MS Basic science – July' 14)*
a) scarlet fever
b) food poisoning
c) scalded skin syndrome
d) acute rheumatic fever
e) toxic stock syndrome

Ans. a) F b) T c) T d) F e) T

Q. *Staphylococcus aureus* can produce – (MD/MS (DMC) – July '08)
a) toxic shock syndrome
b) pneumonia
c) infective endocarditis
d) erysipelas
e) scarlet fever

Ans.
a) T b) T c) T
d) F *(caused by Streptococcus pyogens)*
e) F *(caused by Streptococcus pyogens)*

Q. Following are applicable about Staph. aureus: (BSMMU – MD/MS - January, 2008)

a) produce coagulase	T
b) can cause food poisoning	T
c) causes scarlet fever	F (Scarlet fever is caused by streptococci)
d) causes cellulites	T
e) causes neonatal meningitis	F (Causes meningitis in older children & adults)

Methicillin-resistant Staph. aureus (MRSA)

Q. Methicillin resistant Staphylococcus aureus (MRSA) *(BSMMU –Residency – MD, MS, Basic Science, Dentistry – March' 18)*
a) are sensitive to vancomycin
b) causes deep seated infection
c) is resistant to conventional antistaphylococcal antibiotics
d) is sensitive to linezolid
e) phase typing is done for epidemiological purpose

Ans. a) T b)T c) T d) T e) T

Help Link:
1. Phage typing has been used for differentiating between MRSA outbreak strains.
2. It is also invaluable in monitoring the emergence and dissemination of MRSA strains in hospitals and the community.
3. Phage typing, PCR amplification for mecA gene, and antibiotic resistance patterns as epidemiologic markers in nosocomial outbreaks of methicillin resistant Staphylococcus aureus

Q. Methicillin resistant Staphylococcus aureus has the following characteristics: *(BSMMU – Residency – MD/MS – March'13)*

a) Presence of efflux pump
b) resistance to oxacillin
c) Chromosome mediated drug resistance
d) Susceptible to vancomycin
e) High prevalence in ICU

Ans: a) F b) T c) T d) T e) T

HELP LINK:

Methicillin-resistant Staph. aureus (MRSA):

Resistance to methicillin, due to penicillin-binding protein mutation, has been recognised in **Staph. aureus** for more than 30 years. The recent recognition of resistance to vancomycin/ teicoplanin (glycopeptides) in either glycopeptide intermediate Staph. aureus (GISA) or rarely, vancomycin-resistant (VRSA strains threatens the ability to manage serious infections produced by such organisms.

MRSA is now a major world wide health care-acquired pathogen accounting for up to 40% of staphylococcal bacteraemia in developed countries. Community-acquired MRSA (c-MRSA) currently accounts for 50 % of all MRSA infections in the USA. These organisms have also acquired other virulence factors such as Panton—Valentine leukocidin (PVL), which can cause rapidly fatal infection in young people. Clinicians must be aware of the potential danger of these infections and be prepared to take whatever appropriate infection control measures are locally advised.

Treatment should always be based on the results of antimicrobial susceptibility testing since resistance to all these agents occurs. Milder MRSA infections may be treated with clindamycin, tetracyclines or co-trimoxazole, Clycopeptides, linezolid and daptomycin are reserved for treatment of more severe infections. PVL producing Staph. aureus infections should be treated with protein-inhibiting antibiotics (clindamycin, linezolid).

VRSA:

- Vancomycin resistant S aureus.
- VR genes are located in enterococci.
- **Location of gene**: transpososn on a plasmid.
- **Treatment**:
  - Daptomycin,
  - 2nd line- quinopristin, dalfopristin

VISA: intermediate resistance to vancomycin.

Laboratory test

Q. The single most important laboratory test for determining the virulence of staphylococcus is: (MD/MS (DMC)-01Ja)

A. Mannitol fermentation. F
B. Hemolysis of sheep RBC. F
C. Detection of coagulase. T
D. Catalase test F
E. Detection of penicillinase. F

Help link:

Biochemical tests:

Test	S. aureus	S. epidermidis, S. saprophyticus
1. Catalase test	+ ve	+ ve
2. Coagulase test	+ ve	- ve
3. Manitol fermentation test	+ ve	- ve
4. DNase test	+ ve	- ve
5. Sensitivity test		

Q. Staphylococci pathogenic to man: (MD/MS (DMC)-01Ja)

A. Grow in irregular cluster in culture	T
B All produce an enterotoxin.	F (50%)
C. Are resistant to penicilin.	T
D. Produce coagulase.	T
E. Produce a capsular polysaccharide.	T

Help link:

■ **Characteristics:**

- Staphyle: Berry, Coccus: Round
- Aurus: Comes from aurum as it produce golden yellow pigment.
- Gram positive , aerobic or facultative anaerobic
- Non motile
- Non spore forming
- Arrange in irregular grape like clusters
- Catalase positive(all staphylococcus, no streptococcus can do)
- Coagulase positive (Thick Pus), other species are negative
- Ferment menitol
- Normal flora of nose and skin
- Produce golden yellow colour in culture
- Haemolysis RBC (Beta Haemolysis)

Catalase positive in:

- Staphylococcus
- E. Coli
- Klebsiella
- Neisseria
- Hemophyllus
- M. TB

Catalase negative: Streptococcus

Coagulase positive: Staph. Aureus

Coagulase negative:

- Staph. Epidermidis,
- Staph. Saprophyticus.

Oxidase positive:

- Neisseria,
- vibrio,haemophyllus,
- pseudomonas

Oxydase negative:

- Staphylococcus,
- Steptococcus,
- Enterobacteriacae.

Pigment producing bacteria

Q. Pigment producing bacteria are *(BSMMU –Residency – MD, MS, Basic Science – March' 18)*
a) *Pseudomonas aeruginosa*
b) *Streptococcus pyogenes*
c) *Corynebacterium diphtheriae*
d) *Escherechia coli*
e) *Staphylococcus aureus*

Ans. a) T b) F c) F d) F e) T

Help link:

Pigment producing bacteria

- Staph. Aureus- golden yellow
- Pseudomonas:
  - pyocyanin- blue,
  - pyoverdin- green,
  - pyorubrin- red,
  - pyomelanin- black.
- Serratia rubidae: red pigment
- Atypical mycobacteria: yellow orange pigment
  - Photochromogen(produce colony in presence of light):
    - eg; M. kansasii- produce lung disease,
    - M. marinum- produce swimming pool granuloma/fish tank granuloma
  - Scotochromogen (produce colony in darkness):
    - M. scrofulaceum- causes cervical granulomatous lymphadenitis

Streptococcus

- Gram positive
- Non motile
- Arrange in chain
- Catalase negative

Classification: produce zone of hemolysis in blood agar

1. **α-haemolytic/ Partial:**
   - produce greenish zone,
   - S. pneumoniae,
   - S. viridens
2. **β-haemolytic/ complete:**
   - produce clear zone,
   - S. pyogens,
   - S. agalactie
3. **Gamma haemolytic/non haemolysis**: S. bovis, E, faecalis

Cell wall of all hemolytic streptococus contains polysaccharide capsule (another classification).

- **Group A:** beta hemolytic –S. pyogenes
- **Group B:** beta hemolytic – S. agalactiae
- **Group C:** beta hemolytic – S. dysagalactiae
- **Group D:** either beta or gamma- Enterococcus (E. faecalis, E. faecium)

Causes of beta hemolytic bacteria

- Strep. Pyogenes
- Strepto. Agalactiae
- Some strains of S. aureus
- Some strains of E. coli that cause UTI
- Pseudomonas

Peptostreptococci:

Grow under anerobic and microaerophilic conditions. Normal flora of gut, mouth and female genital tract. Along with viridens streptococci ofter found in brain abscess following dental surgery.

Streptococcus pyogens:

- Normal flora of skin and oropharynx.
- With the help of pilli bacteria adhere to the mucosa of the pharynx and produce pharyngitis.
- Prevent opsonization by preventing C3b.

Pathogenesis:

Virulance factors:

1. M-protein : main antiphagocytic component, rheumatogenic and nepgritogenic
2. C-carbohydrate: determines the group of beta hemolytic streptococci.
3. Polysaccharide capsule

Toxins:

1. **Erythrogenic toxin**: rash of scarlet fever, acts as a super antigen, mechanism similar as TSST. Nonlysogenic bacteria do not cause scarlet fever, although they can cause pharyngitis.
2. **Streptolysin O**: Causes beta haemolysis. It is antigenic.
3. **Streptolysin S:**
4. **Pyrogenic exotoxin A**: TSS, superantigen
5. **Exotoxin B**: Necrotizing fasitis

Enzymes (Steptococcus pyogenes):

1. Hyaluronidase(spreading factor): causes rapid spread of cellulitis
2. Streptolonase/ fibrinolysin: activates plasminogen to plasmin, that dissolves fibrin in clots, thrombi and emboli. Used to lyse thrombi in ischaemic heart disease.
3. DNAase/ Streptodornase: degrades DNA in exudates or necrotic tissue
4. Proteinase
5. Lipoproteinase
6. Amylase
7. Phosphatase
8. Diphosphopyridine nucleotidase

Question Bank

Q. Diseases caused by group A streptococcus *(BSMMU –Residency - **Basic science** – March' 19)*

a) scarlet fever
b) toxic shock syndrome
c) impetigo
d) acute glomerulonephritis
e) Sydenham's chorea

Ans. a) T b) T c) T d) T e) T

Help link:

Diseases: (Streptococcus pyogens)

1. **Enzymic/Pyogenic:**
   a) tonsilitis, peritonsilar abscess,
   b) pharyngitis,
   c) Impetigo/pyoderma,
   d) cellulitis, Puerperal sepsis
   e) necrotising fascitis,
   f) otitis media, Mastoiditis
   g) sinusitis, Endometritis
   h) endocarditis,
   i) Erysipelas
   j) Wound infection
   k) Osteomyelitis, lymphangitis, lymphadenitis
   l) Endometritis, Septicaemia and bacteremia
2. **Toxin:** Scarlet fever, necrotising fascitis
3. **Post streptococcal complication:** Rheumatic fever, AGN (2-3 wks after skin infection)

Q. Non suppurative sequelae of *Streptococcus pyogens* infection are *(BSMMU – Non-Residency – **MD, MS, Basic science** – July' 18)*
a) erythema nodosum
b) subacute bacterial endocarditis
c) acute rheumatic fever
d) scarlet fever
e) acute glomerulonephritis
Ans. a) F b) F c) T d) F e) T

Q. Non typeable Streptococci are *(BSMMU –Residency – **MD, MS, Basic Science** – March' 18)*
a) *Streptococcus pyogenes*
b) *Chlamydia trachomatis*
c) *Mycoplasma genitalium*
d) *Staphylococcus saprophyticus*
e) *Streptococcus agalactiae*
Ans. a) F b) F c) F d) F e) F
Help Link: Only ***Sterptococcus pneumoniae*** and ***Streptococcus viridans*** are non typeable.

Q. ASO test *(BSMMU – Non-Residency – MD, MS, Basic Science & Dentistry – July' 17)*
a) is raised in majority of cases of streptococcal pyoderma
b) can be false positive in liver diseases
c) is diagnostic in rheumatic fever(can be important in the diagnosis of Rheumatic fever but not diagnostic)
d) becomes positive within 3 days of streptococcal infection
e) measures antibody against streptolysin 'O'
Ans. a) F b) T c) F d) T e) T

Help link:

What is pyoderma:

- ✓ Pyoderma or impetigo is a localized infection of the skin, primarily affecting face, arms, legs and other exposed parts of the body.
- ✓ Infection s acquired by direct contact and caused by S. pyogens(serotype: 49, 53-55, 59-61)
- ✓ Mainly seen in young children
- ✓ Impetigo is one of the important causes of AGN in children.
- ✓ Titres of anti DNAs B are high in group A streptococcal skin infections and serve as an indicator of previous streptococcal infection in pts with suspected of having AGN

What is Streptolysin O:

✓ Is an oxygen labile and heat labile protein with a molecular weight 50000-75000 Da.
✓ It causes beta hemolysis only when colonies are grown under the surface of blood agar plate

Antistreptolysin O titer (ASLO titer):

- is a measure of the blood plasma levels of antistreptolysin O antibodies
- Are high soon after infection

Used in:

- diagnosis of a streptococcal infection or indicate a past exposure to streptococci.
- helps direct antimicrobial treatment
- used to assist in the diagnosis of scarlet fever, rheumatic fever, and post infectious glomerulonephritis.
- Demonostration of antibody is important for the determination of a recent group A streptococcal infection and also the late complication of streptococcal infections after the organisms have been eliminated from the host

✓ A positive test usually is >200 units/mL, but normal ranges vary from laboratory to laboratory and by age.
✓ The false negatives rate is 20-30%.
✓ If a false negative is suspected, then an anti-DNase B titre should be sought.
✓ False positives can result from liver disease and tuberculosis.

(Ref: Lange review 14th page 120, 122, Text book of Microbiology by subash chandra page 187, Wikipedia)

Q. Streptococcal skin infection may cause *(BSMMU – Non-Residency - MD – 13Ju)*

a) acne F
b) melasma F
c) erysipelas T
d) impetigo T
e) cellulitis T

HELP LINK:

Disease produced by Strept. Pyogenes:

A. ***Suppurative***:

1. Respiratory tract	•Sore throat •Tonsilitis •Peritonsillar abscess •Pharyngitis
2. Skin & soft tissue	•Impetigo (Strep. Pyoderma) – superficial infection of abraded skin that forms pus or crusts. • Necrotizing fascitis •Erysipelas •Cellulitis
3. Genital tract	Puerperal sepsis
4. Ear infection	•Otitis media •Mastoiditis
5. Deep infection	•Acute endocarditis •Lymphadenopathy •Septicaemia.

B. ***Non- suppurative***:

1. Rheumatic fever (following throat infection)
2. Acute glomerulonephritis (following skin infection)

C. **Toxigenic diseases**:

1. Scarlet fever
2. Toxic shock syndrome.

Q. Diseases caused by *Streptococcus pyogenes* include: *(BSMMU – M. Phil, Diploma (Non-Residency)–12Ju, DMC & others – MD/MS – 12Ju)*

a) erysipelas T
b) necrotizing fasciitis T
c) scalded skin syndrome F
d) toxic shock syndrome T
e) food poisoning F

Q. Streptococcal infection of the skin includes - (MD/MS (DMC)-09Ja)

a. scarlet fever
b. bullous impetigo
c. erysipelas
d. Mycosis vulgaris
e. Toxic shock syndrome

Ans.

a. F (it is not an infection of skin) b. T
c. T d. F
e. F (it is not an infection of skin)

Q. Following organisms produce IgA protease- (BSMMU-MS-04Ja)

a) Staphylococcus aureus F
b) Streptococcus pyogenes F
c) Streptococcus pneumoniae. T
d) Haemophillus influenzae T
e) Neisseria gonorrhoeae T

Q. Streptococcus beta hemolyticus may produce: (MD/MS (DMC)-01Ja)

A. Peritonsillar abscess T
B. Chronic retropharyngeal abscess F
C. Glandualr fever F
D. Furunculosis of external ear F
E. Acute parenchymatous tonsillitis T

Nice to know:

Traits	Staphylococcus	Streptococcus
Clinical		
1. Infection (Abscess)	Localized	spreading
2. Pus	Thick	Thin
Laboratory test		
3. Gram staining	Cluster arrangement	Chain arrangement
4. Culture	Grows in 7.5% NaCl	Grows in blood agar + crystal violet
5. Colony	Larger; resembling pin head	Smaller resembling pin point
6. Zone of hemolysis	Small	Large
7. Biochemical test	Catalase positive	Catalase negative

Sore throat

Q. Pharyngitis is caused by *(BSMMU – Non-Residency – **Dentistry** – July' 19)*
a) Adenovirus
b) Coxackie virus
c) Epstein-Barr virus
d) Norovirus
e) Rotavirus

Ans. a) T b) T c) T (causes mononucleosis) d) F (causes Gastroenteritis) e) F (causes Gastroenteritis)

(Ref: Lange-15th, P-308+326)

HELP LINK:

Causes of sore throat:

- Bacteria:
  - S. pyogenes,
  - H. influenzae,
  - C. dipththeriae ,
  - C. trachomatis
  - Borrelia vincentii
- Virus:
  - Rhinovirus, corona virus, Parainfluenza
  - adenovirus, influenza virus, HSV, Coxsackie
- Fungus: Candida albicans

Q. Following are the expected organism of bacterial pharyngitis: *(BSMMU – MD/MS – 10Ja)*

a) Kiebsiella spp	F
b) E. coli	F
c) S. pyogenes	T
d) Proteus spp	F
e) Acinebacter spp	F

Lysogenic conversion

Q. Bacteriophage mediated toxins are *(BSMMU – Non-Residency – MD, MS, Basic Science & Dentistry – July' 17)*
a) cholera toxin
b) tetanospasmin
c) botulinum toxin
d) erythrogenic toxin
e) exfoliative toxin

Ans. a) T b) F c) T d) T e) F

Help link:

Lysogenic toxin:

1. Enterotoxin of S. aureus
2. Erthrogenic toxin of Strep. Pyogenes
3. Diphtheria
4. Botulinum
5. Choleragen
6. Heat labile toxin of E. coli

Q. Lysogenic conversion is responsible for toxin production in: *(BSMMU – MD/MS – January, 2010)*

a) *Corynebacterium diphtheriae*	T
b) Streptococcal species causing Scarlet fever	T
c) Salmonella species	F
d) *Clostridium tetani*	F
e) Heat labile toxin of *E. coli*	F (plasmid coated)

HELP LINK:
During the growth of the virus within the cell, a piece of a bacterial DNA is incorporated particle and is carried into the recipient cell at the time of infection. Within the recipient cell, the phage (bacterophage). DNA can integrate into the cell DNA and the cell can acquire a new trait, a process called **lysogenic conversion**. This process can change a non-pathogenic organism in to a pathogenic one. Diphtheria toxin, botulinum toxin, choleratoxin & erythrogenic toxin (streptococcus poygenses) are encoded by bacteriophages and can be transferred by transduction.

Organism:

1. *C. diphtheriae*
2. *Cl. botulinum*
3. E. coli
4. *S. pyogens* causing TSS & scarlet fever
5. *V. cholerae*

Scarlet fever is caused by streptococcus pyogenes. Other disease caused by streptococcus pyogenes:

- Skin & joint infection
- Bone & joint infection
- Tonsillitis
- Puerperal sepsis
- Glomerulonephritis
- Rheumatic fever

Q. Lysogenic conversion is responsible for toxin production in: (BSMMU - M. Phil, Diploma, July-09, MD/MS-09Ja, 06Ja)

a) Corynebacterium diphtheriae T
b) Streptococcal pecies causing Scarlet fever T
c) Salmonella species F
d) Aeromonas species F
e) E. coli T

Neisseria

- Gram negative cocci.
- All neisseria are oxidase positive (posses enzyme cytocrome C)
- Non spore forming, non motile, Human are the only natural host

Neisseria Gonorrhoae

- Non capsulated
- Ferment only glucose
- **Virulence factor:**
  - **Pili**: attached host cells and antiphagocytic. Piliated cocci r virulent. Have marked antigenic variation.
  - **IgA protease**: invade mucosa
  - **Lipooligosaccharides**: causes endotoxic shock.
  - **Capsule**: Usually no capsule, some strains has capsule
- **Transmission:**
  Sexual contact
  During birth
  Quite sensetive to dehydration and cool environment
- **Risk of gonococcal infections:**
  - Complement deficiency(late component), c6-c9 deficiency.
  - Women during mens and pregnancy

- Other STD

Diseases caused by N. gonorrhoea

Primary lesions: In male
- Acute anterior urethritis
- Pharyngitis
- Proctitis

Primary lesions: In female
- Acute anterior urethritis
- Acute endocervicitis

Primary lesions: In children
- Valvovaginitis
- Acute anterior urethritis

Primary lesion: In newborn: Opththalmia neonatorum

Secondary lesion:

By direct spread:
- **In male:** Prostatitis, epididymitis, Cowperitis
- **In female**: Salpingitis, Bartholinitis, Endometritis, Pyosalpinx, Tuboovarian abscess, Pelvic peritonitis, Oophoritis

By hematogenous spread: Ulcerative endocarditis, Septic arthitis, Tenosynovitis, Iritis

By lymphogenous route: Cystitis, pyelitis, Pyelonephritis.

Lab Diagnosis:

- **Gram staining**: Gram negative intracellular and extracellular diplococci with plenty of pus cells and neutrophils.
- **Culture-**

  a) Blood agar media

  b) Selective media:
  - Thayer martin media/ chocolate agar medium.
  - Modified New york city media. (positive <50% case)
  - Stuart transport media

✓ **Serological test:**
- Ag or Ab can be detected in the serum, but it is useless
- it undergo rapid antigenic mutation.
- other microbes with antigenic variation :
  - Influenza virus type A, HIV

- Coinfection with chlamydia trachomatis(10-30%) cases should be treated concomittently

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Question Bank

Q. ***Neisseria gonorrhoeae*** *(BSMMU –Residency - MD/MS, Basic science, Paediatrics – March' 19)*

a) is gram positive
b) is oxidase positive
c) causes septic arthritis
d) may cause pharyngitis
e) grow on blood agar media

Ans. a) F b) T c) T d) T e) T

Q. Complication(s) of gonorrhoea include(s) *(BSMMU –Residency - MD, Basic science – March' 19)*
a) prostatitis
b) erythema nodosum
c) arthritis
d) circinate ballanitis
e) stricture urethra

Ans. a) T b) F c) T d) F (balanitis not circinate balanitis) e) T

Help link:

Table 35–3. Clinical manifestations of gonococcal infection

Group	*Common diseases*	*Less common diseases*
Male	Acute gonorrhoea Urethral stricture Epididymitis Prostatitis	Septicaemia Peritonitis Meningitis Dermatitis Arthritis Pharyngitis Proctitis
Female	Acute gonorrhoea Pelvic inflammatory disease	Proctitis Arthritis Dermatitis DIC Meningitis Pharyngitis
Children	Gonorrhoea Conjunctivitis Ophthalmia neonatorum	Arthritis Vulvovaginitis

(Ref. Essential of Microbiology, Rajesh Bhatia-4th, P-207)

Q. Neisseria gonorrhoeae *(BSMMU – Residency – MD, MS, Basic science – March' 16)*

a) can penetrate	F
b) is a fastidious bacteria	T
c) has many antigenic diversity	T
d) usually cause bacteremia	F (rarely cause bacteremia)
e) infection can be prevented by vaccine	F

HELP LINK:

NEISSERIA GONORRHOAE

Pathogenesis & Epidemiology:

Gonococci, like meningococci, cause disease only in humans. The organism is usually transmitted **sexually;** newborns can be infected during birth. Because the gonococcus is quite sensitive to dehydration and cool conditions, sexual transmission favors its survival. Gonorrhea is usually symptomatic in men but often asymptomatic in women. Genital tract infections are the most common source of the organism, but anorectal and pharyngeal infections are important sources as well.

Pili constitute one of the most important virulence factors, because they mediate attachment to mucosal cell surfaces and are antiphagocytic. Piliated gonococci are usually virulent, whereas non-piliated strains are avirulent. Two virulence factors in the cell wall are **LOS** (a modified form of endotoxin) and the outer membrane proteins. Note that the endotoxin of gonococci is weaker than that of meningococci, so less severe disease occurs when gonococci enter the bloodstream than when meningococci do. The organism's **IgA protease** can hydrolyze secretory IgA, which could otherwise block attachment to the mucosa. Gonococci have no capsules.

The main host defenses against gonococci are antibodies (IgA and IgG), complement, and neutrophils. Antibody-mediated opsonization and killing within phagocytes occur, but repeated gonococcal infections are common primarily as a result of antigenic changes of pili and the outer membrane proteins.

Gonococci infect primarily the mucosal surfaces, e.g., the urethra and vagina, but dissemination occurs. Certain strains of gonococci cause disseminated infections more frequently than others. The most important feature of

these strains is their resistance to being killed by antibodies and complement. The mechanism of this "serum resistance" is uncertain, but the presence of a porin protein (porin A) in the cell wall, which inactivates the C3b component of complement, appears to play an important role.

The occurrence of a disseminated infection is a function not only of the strain of gonococcus but also of the effectiveness of the host defenses. Persons with a deficiency of the late-acting complement components (C6–C9) are at risk for disseminated infections, as are women during menses and pregnancy. Disseminated infections usually arise from asymptomatic infections, indicating that local inflammation may deter dissemination.

Clinical Findings:

Gonococci cause both localized infections, usually in the genital tract, and disseminated infections with seeding of various organs. Gonococci reach these organs via the bloodstream (gonococcal bacteremia).

Gonorrhea in men is characterized primarily by urethritis accompanied by dysuria and a purulent discharge. Epididymitis can occur.

In women, infection is located primarily in the endocervix, causing a purulent vaginal discharge and intermenstrual bleeding (cervicitis). The most frequent complication in women is an ascending infection of the uterine tubes (**salpingitis, PID**), which can result in **sterility** or ectopic pregnancy as a result of scarring of the tubes.

Disseminated gonococcal infections (DGI) commonly manifest as arthritis, tenosynovitis, or pustules in the skin. Disseminated infection is the most common cause of septic arthritis in sexually active adults. The clinical diagnosis of DGI is often difficult to confirm using laboratory tests because the organism is not cultured in more than 50% of cases.

Other infected sites include the anorectal area, throat, and eyes. Anorectal infections occur chiefly in women and homosexual men. They are frequently asymptomatic, but a bloody or purulent discharge (proctitis) can occur. In the throat, pharyngitis occurs, but many patients are asymptomatic. In newborn infants, purulent conjunctivitis (ophthalmia neonatorum) is the result of gonococcal infection acquired from the mother during passage through the birth canal. The incidence of gonococcal ophthalmia has declined greatly in recent years because of the widespread use of prophylactic erythromycin eye ointment (or silver nitrate) applied shortly after birth. Gonococcal conjunctivitis also occurs in adults as a result of the transfer of organisms from the genitals to the eye.

Other sexually transmitted infections, e.g., syphilis and nongonococcal urethritis caused by *Chlamydia trachomatis,* can coexist with gonorrhea; therefore, appropriate diagnostic and therapeutic measures must be taken.

Laboratory Diagnosis

The diagnosis of localized infections depends on Gram staining and culture of the discharge. In **men,** the finding of gram-negative diplococci **within PMNs** in a urethral discharge specimen is sufficient for diagnosis. In **women,** the use of the Gram stain alone can be difficult to interpret; therefore, cultures should be done. Gram stains on cervical specimens can be falsely positive because of the presence of gram-negative diplococci in the normal flora and can be falsely negative because of the inability to see small numbers of gonococci when using the oil immersion lens. Cultures must also be used in diagnosing suspected pharyngitis or anorectal infections.

Specimens from mucosal sites, such as the urethra and cervix, are cultured on Thayer-Martin medium, which is a chocolate agar containing antibiotics (vancomycin, colistin, trimethoprim, and nystatin) to suppress the normal flora. The finding of an oxidase-positive colony composed of gram-negative diplococci is sufficient to identify the isolate as a member of the genus *Neisseria.* Specific identification of the gonococcus can be made either by its fermentation of glucose (but not maltose) or by fluorescent-antibody staining. Note that specimens from sterile sites, such as blood or joint fluid, can be cultured on chocolate agar without antibiotics because there is no competing normal flora.

Two rapid tests that detect the presence of gonococcal nucleic acids in patient specimens are widely used as a screening test. These tests are highly sensitive and specific. In one type of test the gonococcal nucleic acids are amplified (amplification tests), and in the other type they are not amplified. The amplification tests can be used on urine samples, obviating the need for more invasive collection techniques. Note that serologic tests to determine the presence of antibody to gonococci in the patient's serum are *not* useful for diagnosis.

* When late complement deficiency occurs (C6 – C9) then disseminated Nesseria gonorrhea and Nesseria meningitides infection occurs.

(Ref: LANGE Review-15th)

Q. *Neisseria gonorrhoeae* is transmitted through *(BSMMU –Residency – MD, MS, Basic – March' 15)*

a) sexual contact
b) blood transfusion
c) birth canal
d) placenta
e) aerosolization

Ans. a) T b) F c) T d) F e) F

Q. Followings are applicable for N. gonorrhoeae: *(BSMMU – MD/MS – January, 2010)*

a) can penetrate the intact skin F
b) fastidious bacteria T
c) many antigenic diversity T
d) Vaccine can not be produced because of difficult in isolation of bacteria T
e) Usually cause bateraemia F

Q. Complication of gonorrhoea in: (BSMMU – MD – January, 2010)

a) prostatitis T
b) charcot joint F
c) arthritis T
d) alopecia F
e) stricture urethra T

HELP LINK:

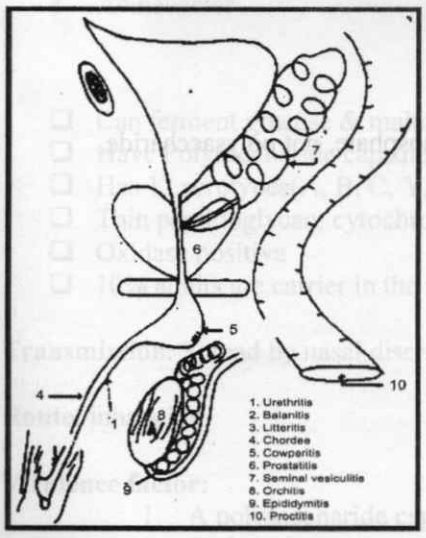


Fig: Lesions in gonococcal infection (male)

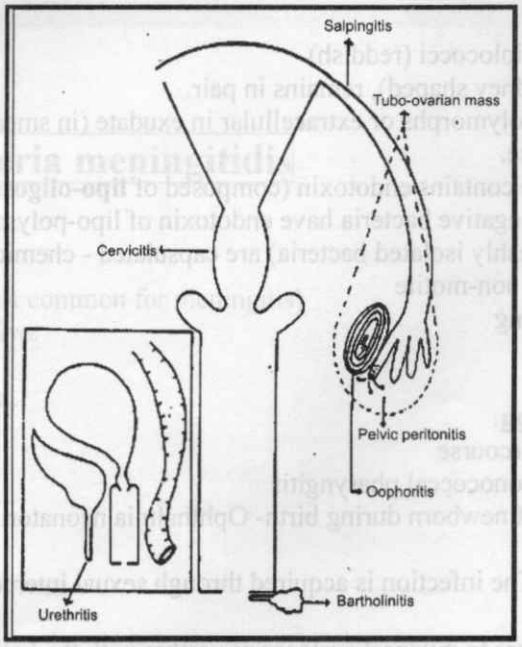


Fig: Lesions in gonococcal infection (female)

■ **Lesions occurred in gonorrhoea**:

A. In males	B. In females	C. New- born infants	D. Other lesions in both the sexes
1. Acute urethritis 2. Balanitis 3. Chordae 4. Litteritis 5. Cowperitis 6. Prostatitis 7. Seminal vesiculitis 8. Orchitis 9. Epididymitis 10. Proctitis 11. Urethral stricture(finally)	1.Endocervicitis 2.Urethritis 3.Bartholinitis 4.Salpingitis 5.Oophoritis 6.Vulvovaginitis (children only) 7.Proctitis 8.Pelvic peritonitis 9.Cystitis	Purulent conjunctivitis or ophthalmia neonatorum.	1.Septicaemia 2.Ulcerative endocarditis 3. Arthritis dermatitis-tenosynovitis syndrome 4.Spondylitis deformans 5.Iritis 6.Perihepatitis

(Ref: M.R. Chowdhury-5th, P-204-205)

Q. N. gonorrhoeae - (BSMMU – MS - January, 2009)

a) can infect the eyes in the neonates	T
b) may cause arthritis	T
c) infection may be symptomless	T
d) is diagnosed by complete blood count	F
e) can cross the placenta	F

Q. Following are applicable for *N. gonorrhea*: (BSMMU - M. Phil, Diploma, July-05)

A. gram negative diplococci	T
B. transmitted through sexual contact	T
C. causative agent of syphilis	F
D. can penetrate intact skin	F
E. blood contact is necessary for transmission	F

HELP LINK:

■ **Morphology**:

1. Gram negative diplococci (reddish)
2. Bean shaped (kidney shaped), remains in pair.
3. Intracellular in polymorphs or extracellular in exudate (in smear)
4. Pili on the surface.
5. Outer membrane contains endotoxin (composed of **lipo-oligosaccharide**).
   [Most of Gram negative bacteria have endotoxin of lipo-polysaccharide]
6. Some strains (freshly isolated bacteria) are capsulated - chemically polyphosphate, not polysaccharide.
7. Non-flagellated, non-motile
8. Non-spore forming
9. Non-capsulated

■ **Mode of infection**:

1. Sexual intercourse
2. Oral sex- gonococcal pharyngitis
3. Infection of newborn during birth- Ophthalmia neonatorum

■ **Pathogenesis**: The infection is acquired through sexual intercourse

↓

N. gonorrhoea adhere to mucosal surfaces of urethra with the help of pili.

↓

Penetration occurs and the organism enters into the subepithelial connective tissue.

↓

In this site, the organism exerts an acute inflammatory response with the accumulation of polymorphonuclear leucocytes. (Acute uretritis)

↓

In male → there is painful micturation with ***yellow creamy pus***→ During sexual intercourse, discharge goes to vagina & cervix → Cervicitis & urethritis →***mucopurulent urethral discharge*** with burning sensation during micturation → Gonorrhoea.

The infection may extend to the uterus, uterine tube that cause salphingitis with obliteration of uterine tube.

Sterility occurs in 20% female by gonococcal salphingitis.

Q. Gonorrhoea - (M. phil, Diploma (DMC) – 03,July)

a) is caused by treponema pallidum	F
b) the organism is a gram negative diplococcus	T
c) ophthalmia neonatarum is one of its consequences	T
d) affects mainly the ovaries and tubes	F
e) causes purulent vaginal discharge and dysuria.	T

Important for Exam.

❑ **Bacteria that never produce bacteremia**

- Corynebacterium
- Clostridium
- Shigella
- Vibrio

Causes of non gonococcal urethritis:

1. Chlamydia tracomatis
2. Ureaplasma urelyticum
3. Mycoplasma
4. HSV-2
5. CMV
6. Trichomonas vaginalis
7. Candida albicans
8. Acinebacter

Neisseria meningitidis

- ❑ Can ferment glucose & maltose
- ❑ Have Polysaccharide capsule.
- ❑ Has 13 serotypes(A, B, C, Y, W-135 most common for meningitis)
- ❑ Thin peptidoglycan, cytochrome C positive.
- ❑ Oxidase positive
- ❑ 10% adults are carrier in the nasopharynx.

Transmission: Spread by nasal discharge

Route: inhalation

Virulence factor:

1. A polysaccharide capsule
2. Endotoxin
3. IgA protease

Diseases:

1. Meningococcemia
2. Epidemic meningitis: Fever, neck rigidity, delirium, coma, hemorrhagic rash
3. Water house friderichsen syndrome

- 5% people become chronic carrier, carrier rate may be high 35% who live in military recruits, close family or dormitory.
- Bacteria go to brain by the olfactory nerve through the cribiform plate of ethmoid bone.

Water house friderichsen syndrome:

- Life threatening form of meningococcemia.
- Characterized by: High fever, shock, widespread purpura, DIC, thrombocytopenia, Adrenal insufficiency

Lab test: Chocolet agar 37c, environment is microaerophilic by candle jar in a 5% CO2 atmosphare.

CSF finding in meningitis:

	Normal	Sub araconoid hemorrhage	Bacterial meningitis	Viral meningitis	Tubercular meningitis
Pressure	50-250 mm of water	Increased	Normal/increased	Normal	Normal/increased
Colour	Clear	Blood-stained	Cloudy	Clear	Clear/cloudy
Red cell count ($\times 10^6$/L)	0-4	Raised	Normal	Normal	Normal
White cell count ($\times 10^6$/L)	0-4	Normal/slightly raised	1000-5000 polymorphs	10-2000 lymphocytes	50-5000 lymphocytes
Glucose	> 60% of blood level	Normal	Decreased	Normal	Decreased
Protein	< 0.45 g/L	Increased	Increased	Normal/increased	Increased

Corynebacterium diphtheriae

Q. Complications of diphtheria include *(BSMMU –Residency – MD, Basic science – March' 14)*

a) polyneuritis T
b) arthritis F
c) myocarditis T
d) bronchopneumonia F
e) nephritis F

HELP LINK:

Corynebacterium diphtheriae

Disease

C. diphtheriae causes diphtheria. Other *Corynebacterium* species (diphtheroids) are implicated in opportunistic infections.

Important Properties: Corynebacteria are gram-positive rods that appear **club-shaped** (wider at one end) and are arranged in palisades or in **V**- or **L**-shaped formations. The rods have a beaded appearance. The beads consist of granules of highly polymerized polyphosphate, a storage mechanism for high-energy phosphate bonds. The granules stain **metachromatically;** i.e., a dye that stains the rest of the cell blue will stain the granules red.

Transmission:

Humans are the only natural host of *C. diphtheriae.* Both toxigenic and nontoxigenic organisms reside in the upper respiratory tract and are transmitted by **airborne droplets.** The organism can also infect the skin at the site of a preexisting skin lesion. This occurs primarily in the tropics but can occur worldwide in indigent persons with poor skin hygiene.

Pathogenesis

Although exotoxin production is essential for pathogenesis, invasiveness is also necessary because the organism must first establish and maintain itself in the throat. Diphtheria toxin inhibits protein synthesis by **ADP-ribosylation of elongation factor 2** (EF-2). The toxin affects all eukaryotic cells regardless of tissue type but has no effect on the analogous factor in prokaryotic cells.

The toxin is a single polypeptide with two functional domains. One domain mediates binding of the toxin to glycoprotein receptors on the cell membrane. The other domain possesses enzymatic activity that cleaves nicotinamide from nicotinamide adenine dinucleotide (NAD) and transfers the remaining ADP-ribose to EF-2, thereby inactivating it. Other organisms whose exotoxins act by ADP-ribosylation.

The DNA that codes for diphtheria toxin is part of the genetic material of a temperate bacteriophage. During the lysogenic phase of viral growth, the DNA of this virus integrates into the bacterial chromosome and the toxin is synthesized. *C. diphtheriae* cells that are not lysogenized by this phage do not produce exotoxin and are nonpathogenic.

The host response to *C. diphtheriae* consists of:

1. Local inflammation in the throat, with a fibrinous exudate that forms the tough, adherent, gray **pseudomembrane** characteristic of the disease
2. Antibody that can neutralize exotoxin activity by blocking the interaction of fragment B with the receptors, thereby preventing entry into the cell. The immune status of a person can be assessed by Schick's test. The test is performed by intradermal injection of 0.1 mL of purified standardized toxin. If the patient has no antitoxin, the toxin will cause inflammation at the site 4–7 days later. If no inflammation occurs, antitoxin is present and the patient is immune. The test is rarely performed in the United States except under special epidemiologic circumstances.

Clinical Findings:

Although diphtheria is rare in the United States, physicians should be aware of its most prominent sign, the thick, gray, adherent **pseudomembrane** over the tonsils and throat. The other aspects are nonspecific: fever, sore throat, and cervical adenopathy. There are three prominent complications:

1. Extension of the membrane into the larynx and trachea, causing airway obstruction
2. Myocarditis accompanied by arrhythmias and circulatory collapse
3. Nerve weakness or paralysis, especially of the cranial nerves. Paralysis of the muscles of the soft palate and pharynx can lead to regurgitation of fluids through the nose. Peripheral neuritis affecting the muscles of the extremities also occurs.

Cutaneous diphtheria causes ulcerating skin lesions covered by a gray membrane. These lesions are often indolent and often do not invade surrounding tissue. Systemic symptoms rarely occur. In the United States, cutaneous diphtheria occurs primarily in the indigent.

Laboratory Diagnosis:

Laboratory diagnosis involves both isolating the organism and demonstrating toxin production. It should be emphasized that the decision to treat with antitoxin is a clinical one and cannot wait for the laboratory results. A throat swab should be cultured on Löffler's medium, a **tellurite plate,** and a blood agar plate. The tellurite plate contains a tellurium salt that is reduced to elemental tellurium within the organism. The typical gray-black color of tellurium in the colony is a telltale diagnostic criterion. If *C. diphtheriae* is recovered from the cultures, either animal inoculation or an antibody-based gel diffusion precipitin test is performed to document toxin production. A PCR assay for the presence of the toxin gene in the organism isolated from the patient can also be used.

Smears of the throat swab should be stained with both Gram stain and methylene blue. Although the diagnosis of diphtheria cannot be made by examination of the smear, the finding of many tapered, pleomorphic gram-positive rods can be suggestive. The methylene blue stain is excellent for revealing the typical metachromatic granules.

(Ref: LANGE Review-14th)

Q. Metachromatic granules containing bacteria are- (BSMMU – MD/MS - 06Ja)

A. C. diptheriae	T
B. Pseudomonas	T
C. E. coli	F
P. Bacillus	F
B. Coxiella	F

HELP LINK:

Metachromatic granules containing bacteria
1. C. diphtheriae
2. M. tuberculosis
3. Yersinia pestis
4. Enterobacter aerogenes
5. Pseudomonas

Q. Following properties are applicable for C. diphtheriae: *(BSMMU – MD/MS – January, 2010)*

a) usually cause bacteraemia	F
b) only lysogenic bacteria produce exotoxin	T
c) Death of the patient often results from cardiac toxicity	T
d) Bacteria can be found in throat after vaccination	T
e) Capsule is a virulent factor	F

LISTERIA MONOCYTOGENES

LISTERIA MONOCYTOGENES:

Monocytogenes is a small gram- positive rod arranged in V-or L-shaped formations similar to corynebacteria. The organism exhibits an unusual **tumbling** movement that distinguishes it from the corynebacteria, which are non-motile. Colonies on a blood agar plate produce a narrow zone of beta-hemolysis that resembles the hemolysis of some streptococci.

Listeria grows well at cold temperatures, so storage of contaminated food in the refrigerator can increase the risk of gastroenteritis. This paradoxical growth in the cold called "cold enhancement."

Pathogenesis:

Listeria infections occur primarily in two clinical settings:

(i) in the fetus or newborn as a result of transmission across the placenta or during delivery; and

(ii) in pregnant women and immunosuppressed adults, especially renal transplant patients. (Note that pregnant women have reduced cell-mediated immunity during i.e third trimester.)

The organism is distributed worldwide in animals, plants, and soil. From these reservoirs, it is transmitted to humans primarily by ingestion of unpasteurized milk products, undercooked meat, and raw vegetables. Contact with domestic farm animals and their also an important source. In the United States, listeriosis is primarily a food-borne disease associated with eating unpasteurized cheese and delicatessen meals.

The pathogenesis of Listeria depends on the organism's ability to invade and survive within cells. Invasion of cells is mediated by internalin made by Listeria and E-cadherin on the surface of human cells. The ability of Listeria to pass the placenta, enter the meninges, and invade the gastrointestinal tract depends on the interaction of internalin and E-cadherin on those tissues.

Upon entering the cell, the organism produces listeriolysin, which allows it to escape from the phagosome into the cytoplasm, thereby escaping destruction in the phagosome. Because Listeria preferentially grows intracellularly, cell- mediated immunity is a more important host defense than humoral immunity. Suppression of cell-mediated immunity predisposes to Listeria infections.

L. monocytogenes can move from cell to cell by means of actin rockets, a filament of actin that contracts and propels the bacteria through the membrane of one human cell and into another.

Clinical findings:

Infection during pregnancy can cause abortion, premature delivery, or sepsis during the peripartum period. Newborns infected at the time of delivery can have acute meningitis 1-4 weeks later. The bacteria reach the meninges via the bloodstream (bacteremia). The infected mother either is asymptomatic or has an infiuenza like illness. L. monocytogenes infections in immuno-compromised adults can be either sepsis or meningitis.

Gastroenteritis caused by L. monocytogenes is characterized by watery diarrhea, fever, headache, myalgias, and abdominal cramps hut little vomiting. Outbreaks are usually caused by contaminated dairy products, but undercooked meats such as chicken and hot dogs have also been involved.

Laboratory diagnosis:

Laboratory diagnosis is made primarily by Gram stain and culture, the appearance of gram-positive rods resembling diphtheroids and the formation of 'small, gray colonies with a narrow zone of beta-hemolysis on a blood agar plate suggest the presence of Listeria. The isolation of Listeria is confirmed by the presence of motile organisms, which differentiate them from the non-motile corynebacteria. Identification of the organism as *L. monocytogenes* is made by sugar fermentation tests. **(Ref: LANGE Review-14th)**

Question Bank

Q. *Listeria monocytogenes* *(BSMMU –Residency - MD/MS, Basic science, Paediatrics – March' 19)*

a) causes meningoencephalitis
b) causes intrauterine fetal death
c) grows at 4^0C temperature
d) does not grow on MacConkey's agar media
e) non-motile at 25°C

Ans. a) T b) T c) T
d) T (Gram negative bacteria grow in Mac conkeys agar media)
e) F(37 degree)

Help link:

- ❑ Gram positive, Non spore forming
- ❑ Facultative aerobic, Motile,
- ❑ Moves from cell to cell by actin rocket (become non motile at 37'c)
- ❑ Grow intracellularly, V or L shaped
- ❑ Produce β haemolysis in blood agar.
- ❑ **Transmission:**
  - Cross placenta
  - Transmit during delivery
  - Immunocompetent pt.
- ❑ Transmitted to human mainly through ingestion of unpasturised milk, undercooked meat, raw vegetable.
- ❑ Cold enhancement- grow in cold temp (die in cold temp- Neisseria)
- ❑ It's a zoonotic disease
- ❑ Contact with domestic animal is also a source.
- ❑ **Toxin:**
  - ❑ Lysterosin-prevent phagocytosis
- ❑ Cold enhancement- grow in cold temp
- ❑ **Diseases:**
  - Meningitis, Sepsis in new born, pregnant and immunosuppressed adults
  - Abortion, Premature delivery, Flu like illness
  - chorioamnionitis, febrile gastroenteritis, Cutaneous listeriosis, infective endocarditis

Q. *Listeria monocytogenes* *(BSMMU – Residency – MD, MS, Basic science – March' 16)*

a) causes meningoencephalitis	T
b) is responsible for intrauterine foetal death	T
c) can grow at 22^0C	T
d) grow on MacConkey's agar medium	F
e) is non motile at 25^0C	F

Q. *Listeria monocytogens*: *(BSMMU – Residency – MD/MS – March'13)*

a) Are gram positive T
b) Produces beta hemolysis on blood agar media T
c) are non-motile F (because non-motile in 37^0C)
d) can causes neonatal infections T
e) produces exotoxin T

Q. *Listeria monocytogens* are: *(BSMMU – M. Phil, Diploma (Non-Residency)–11Ju, DMC & others – MD/MS – 11Ju)*

a) gram negative and spore forming organisms F
b) facultative aerobic F
c) responsible for zoonotic diseases T
d) oxidase positive F
e) not microacrophilic T

Anaerobic bacteria

Q. Anaerobic bacteria are *(BSMMU –Residency - MD/MS, Basic science – March' 14)*

a) pseudomonas F
b) propionibacterium T
c) acinetobacter F
d) clostridium T
e) bacteroides T

HELP LINK:

Definition: Anaerobic bacteria are those bacteria which can't grow in presence of O_2 and oxygen is toxic for them and they can not use oxygen for their growth and metabolism. They obtain energy from from fermentation reaction.

Bacteria	Metabolic pathway from which energy obtain
Strict aerobe	Oxidative phosphorylation
Strict anaerobe (e.g. Cl. Tetani)	Fermentation
Facultative anaerobe	Both oxidative phosphorylation and fermentation

■ **Classification of anaerobic bacteria:**

	Bacilli	Cocci
1. Gram +ve	Spore forming: • Clostridium Non-spore forming: • Eubacterium • Bifidobacterium • Propionibacterium • Actinomyces • Lactobacillus	• Peptostreptococcus • Peptococci
2. Gram – ve	• Bacteroids • Fusobacterium •Prevotella melaninogenica	• Veillonella.

Why anaerobic bacteria can not grow in presence of oxygen:

The bacteria which can not grow in presence of O_2 are anaerobic bacteria. eg. Clostridium tetani.They can not grow in presence of O_2. Because, use of O_2 generates 2 toxic molecules:

i. H_2O_2 ii. Superoxide (O_2^-) free radical.

Bacteria require 2 enzymes to neutralize these toxic molecules:

i. $2O_2^- + 2H^+ \xrightarrow{\text{Superoxide dismutase}} H_2O_2 + O_2$
ii. $2H_2O_2 \xrightarrow{\text{Catalase}} 2H_2O_2 + O_2$

Anaerobic bacteria lack either superoxide dismutase or catalase or both. So, the toxic molecules (O_2^-, H_2O_2) accumulate in the bacteria, inhibit their growth or kill them rapidly.

Q. Anaerobic bacteria cannot grow in presence of oxygen because: *(BSMMU.– MD/MS – January, 2010)*
a) lack of metabolic activity F
b) lack of super oxide dismutase T
c) lack of catalase T
d) lack of oxidase F
e) high content of oxygen F

Q. Following organisms are anaerobic: (BSMMU - M. Phil, Diploma, July-09)
a) Clostradium tetani T
b) Clostradium Welchii T
c) Salmonella F
d) Pseudomonas F
e) E. coli F

Q. Anaerobic bacteria are: (DMC - M. Phil, Diploma, July.'06)
a) clostridium species T
b) bacteroids T
c) enterococci F
d) fusobacterium T
e) veillonella T

Q. Followings are anaerobic bacteria - (BSMMU- MS-04Ja)
a) Bacillus subtilis F
b) Clostridium perfringens T
c) Haemophilus influenzae F
d) Bordetella pertusis F
e) Peptostreptoccus T

Clostridium

Q. Followings are applicable for Clostridium: *(BSMMU – MD/MS – January, 2010)*
a) *Cl. botulinum* is capsulated F
b) *Cl. botulinum* is motile T
c) *Cl. perfrigens* is motile F
d) *Cl. perfringens* is capsulated T
e) *Cl. perfringens* remain as normal flora of the gut T

HELP LINK:

■ **Morphological features of Clostridium**:

- Gram positive bacilli.
- Spore forming
- Obligate anaerobes
- Motile - Motility is by peritrichous flagellae.
- Most are saprophytes.
- Natural habitat: soil, water (as sproes can survive for many years), decomposing plant, gut of animal & human (normal commensal)
- They do not germinate and growth does not proceed normally unless a suitable low redox potential exist.
- Biochemically active: Saccharolytic & proteolytic.
- Produce exotoxins.

Important Features of Pathogenesis by *Clostridium* Species

Organism	Disease	Transmission/Predisposing Factor	Action of Toxin	Prevention
C. tetani	Tetanus	Spores in soil enter wound	Blocks release of inhibitory transmitters, e.g., glycine	Toxoid vaccine
C. botulinum	Botulism	Exotoxin in food is ingested	Blocks release of acetylcholine	Proper canning; cook food
C. perfringens	1. Gas gangrene	Spores in soil enter wound	Lecithinase	Debride wounds
	2. Food poisoning	Exotoxin in food is ingested	Superantigen	Cook food
C. difficile	Pseudomembranous colitis	Antibiotics suppress normal flora	Cytotoxin damages colon mucosa	Appropriate use of antibiotics

■ **Classification of Clostridiae:**

A. ***Pathogens***:

- Cl. Tetani *(tetanus)*
- Cl. Botulinum *(food poisoning)*
- Cl. Perfringens *(food poisoning,gas gangrene)*
- Cl. Difficile *(pseudomembranous colitis)*
- Cl. Histolyticum *(gas gangrene)*
- Cl. Septicum *(gas gangrene)*
- Cl. Novyi *(gas gangrene)*

B. ***Non-pathogenic***: • Cl. sporogenes

■ **Medically important Clostridium species:**

Organisms	Diseases
1. *Clostridium tetani*	Tetanus
2. *Clostridium botulinum*	Botulism
3. *Clostridium perfringens* (Old name- C wel chii	Gas gangrene/cutaneous myonecrosis Food poisoning
4. *Clostridium difficile* (difficult to destroy)	Pseudomembranous colitis
5. *Clostridium septicum*	Sepsis

Clostridium tetani

Properties of *Clostridium tetani*:

- ❑ Gram positive
- ❑ Spore forming
- ❑ Anaerobic
- ❑ Motile/ Flagella
- ❑ Spore- terminal spore having tannis racket appearance.
- ❑ Present in soil.
- ❑ Saccharolytic & Proteolytic.

Transmission: Contaminated wound.

Toxin: a) Tetanoplasmin (causes tetanus) b) Tetanolysin

Pathogenesis:

1. Retrograde transmission to CNS
2. Binds with Ganglioside receptor (anterior horn)
3. Block inhibitory neurotransmitter – GLYCIN
4. Prevents inhibition of UMN on LMN.
5. I.P. Two days to several weeks

Clinical feature:

- Dysphagia
- severe neck pain
- Lock jaw (trismus): Usually painless (Ref. Davidson. 1210)
- Opisthotonus
- Risus sardoricus
- Spastic spasm

Immunization: Active passive immunization.

Question Bank

Q. Regarding Tetanus (FCPS – Medicine – 19Ja)

a) Caused by Strict anaerobic Gram (-) spore bearing organism.
b) Toxin affects anterior horn cell.
c) Tetnus toxin is heat stable endotoxin
d) Tetanus Prevents release of GABA toxin
e) metronidazole is of no use.

Ans. a) T b) T c) F d) F e) T **(Ref. Davidson-23rd)**

Q. Characteristic features of tetanus include *(BSMMU – Non-Residency – MD, MS, Basic science, Dentistry – July' 16)*

a) incubation period of 2-3 days F
b) local muscular spasm precedes the onset of trismus F
c) convulsion associated with loss of consciousness F
d) non tender abdominal rigidity F
e) jaw spasm is painless T **(Ref: Davidson)**

HELP LINK:

- Toxin of Cl. tetani causes increased muscle tone, exaggerated muscular response, hyper-excitability of voluntary Muscles.
- Cl. Botulinim can cause bulbar paralysis and death may ensue as a result respiratory paralysis or cardiac arrest.
- C. Jejuni is associated with Guillain Barre syndrome.
- C. diphtheriae may cause peripheral neuopathy.
- Poliovirus infection can cause aseptic meningitis; may results in LMN paralysis.

Q. Clostridium tetani – (MD/MS (DMC)-04Ja)

a) Is pathogenic by virtue of an endotoxin. F
b) Is a Gram-negative organism. F
c) Can form spores. T
d) Is sensitive to tetracycline. F
e) Is highly resistant to antiseptics. T

Help link:

■ **Morphological features:**

- Gram positive bacteria
- Motile (by peritrichous flagellae)
- Terminal spore (drum stick appearance)
- Non-capsulated (In most cases)
- Ferment carbohydrate (Saccharolytic)

- Protelytic (mild)
- Release exotoxin: •Tetanospasmin •Tetanolysin
  [Exotoxin: it is protein in nature. Endotoxin- lipopolysaccharide]

■ **Mode of infection**:

1. ***Trauma***: Major and important cause of tetanus.
2. ***Puerperal tetanus***: The raw surface of the uterus after removal of the placenta is a favourable site for the germination of tetanus spore.
3. ***Tetanus neonatorum***: Due to septic cutting of the umbilical stump/cord by un-sterilized instrument or due to application of mud, cow dung to the cut end of umbilical stump.
4. ***Otogenic***: It is more common in children due to introduction of foreign body. such as pencil, matches, leads into the ear.
5. ***Idiopathic***: There is no definite cause. Suspected causes are -
   i. Micro-trauma
   ii. Absorption of tetanus toxin from the intestinal tract (normal flora)
   iii. Inhalation of tetanus spores in dust, contaminated by animal or human faeces.

Pathogenesis of tetanus:

Tetanus occurs when a deep punctured wound is contaminated by *Cl. tetani* in un-immunized individual

↓

The clinical manifestations of the disease are due to the potent neurotoxin (exotoxin) - **tetanospasmin**. This exotoxin is released by disintegration of dead bacteria.

↓

The neurotoxin is absorbed by the motor nerve endings.

↓

Neurotoxin travels in the peripheral motor nerve (retrograde axonal transmission)

↓

Neurotoxin reaches the anterior horn cells of spinal cord.

↓

Neurotoxin binds to gangliosides of spinal cord.

↓

Acts at synaptic junction

↓

Inhibits release of glycin from the pre-synaptic neuron which is an inhibitory neurotransmitter.

↓

Prevents inhibition of upper motor neuron (UMN) on the LMN.

↓

Exaggerated action of LMN on the muscles.

↓

Generalized muscle rigidity & spasm.

■ **Clinical features**: After incubation period: 6 - 10 days-

i. Lock jaw (trismus) due to masseter muscle spasm.
ii. Risus sardonicus (Devil's smile) due to spasm of facial muscle.
iii. Opisthotonus: Due to marked trunk muscle spasm.

Q. The following infective agent are associated with flaccid paralysis: - (BSMMU – MD/MS – 08Ja)

a) *Clostridium tetani* F
b) *Clostridium botulinum* T
c) *Campylobacter jejuni* T
d) *Corynebacterium diphtheriae* T
e) polio virus T

Clostridium perfrigens

Q. *Clostridium perfrigens* are - (BSMMU - M. Phil, Diploma, July-05)

A. anaeorbic spore bearing bacteria T
B. produces endotoxin F
C. produces gas gangrene in human T
D. produces food poisoning in human T
E. normal flora of human GI tract T

HELP LINK:

■ **Morphological features**:

1. Gram positive bacilli.
2. Anaerobic spore bearing bacteria
3. Capsulated.
4. Non-motile (All the clostridium are motile except C. perfringens)
5. Produce exotoxin.
6. Two types of spores:
   i. Heat stable spores → Food poisoning.
   ii. Heat labile spores → Gas gangrene.
7. Normal flora of GI tract & vagina

Diseases: Gas gangrene, Food poisoning

Q. The causative organisms for gas gangrene: (MD/MS (DMC)-05Ja)

a) Clostridium perfringens T
b) Clostridium botulinum F
c) Clostridium septicum T
d) Clostridium tetani F
e) Clostridium oedematiens T

Help link:

■ **Organisms causing gas gangrene:**

Clostridia that are associated with gas gangrene are:

1. *Clostridium perfringens type A*
2. *Clostridium novyi type A*
3. *Clostridium septicum* (It causes septicemia who have malignancy like leukaemia)
4. *Clostridium histolyticum*
5. *Clostridium sporogenes*
7. *Clostridium sordellii*
8. *Clostridium oedematicus.*

[*C. penfringens* type C- causes enteritis]

Q. Gas gangrene is caused most commonly by - (MD/MS (DMC)-04/03Ja; M. phil, Diploma (DMC) – 05/03Ju)

a) *Clostridium welchii* T *(most common cause)*
b) *Clostridium tetani* F
c) *Clostridium oedematiens* T
d) *Clostridium septicum* T
e) *Mycobacterium fortuitum* F

HELP LINK

- Cl. Tetani *(tetanus)*
- Cl. Botulinum *(food poisoning)*
- Cl. Perfringens *(food poisoning, gas gangrene)*
- Cl. Difficile *(pseudomembranous colitis)*
- Cl. Histolyticum *(gas gangrene)*

- Cl. Septicum *(gas gangrene)*
- Cl. Novyi *(gas gangrene)*

Clostridium botulinum

- **Transmission**: Toxin is produced within canned food & ingested preformed toxin.
- **Toxin**: Toxin is heat labile & preformed, Block the release of acetylcholine
- **C/F**:
  - Descending type of Flaccid Paralysis.
  - Diplopia, dysphagia,
  - respiratory muscle paralysis
- **Prevention**: Proper canning & cooked food.
- **Risk of food poisoning**:
  - Alkaline vegetables,
  - green beans, peppers, mushrooms,
  - smoked fish
- **Use of botox:**
  - Removal of wrinkles of face
  - Achalasia cardia
  - Cong pelvic tilt
  - Paralysis of the fascial muscle
  - Blinking frequently
  - Treatment of certain spasmodic muscle disorder
    - Torticolis
    - Writers cramp
    - Blepherospasm

Food poisoning

Q. Bacteria associated with food poisoning are *(BSMMU – Residency – MD, MS, Basic science, Dentistry – March' 16)*

a) *Pseudomonas aeruginosa* F
b) *Staphylococcus epidermidis* F
c) *Clostridium perfringens* T
d) *Bacillus anthracis* F
e) *Salmonella typhi murium* T

Help link:

Bacterial Diseases Transmitted by Foods.			
Bacterium	**Typical Food**	**Main Reservoir**	**Disease**
I. Diarrheal diseases			
Gram-positive cocci			
Staphylococcus aureus	Custard-filled pastries; potato, egg, or tuna fish salad	Humans	Food poisoning, especially vomiting
Gram-positive rods			
Bacillus cereus	Reheated rice	Soil	Diarrhea
Clostridium perfringens	Cooked meat, stew, and gravy	Soil, animals, or humans	Diarrhea
Listeria monocytogenes	Unpasteurized milk products	Soil, animals, or plants	Diarrhea
Gram-negative rods			
Escherichia coli	Various foods and water	Humans	Diarrhea
E. coli O157:H7 strain	Undercooked meat	Cattle	Hemorrhagic colitis
Salmonella enteritidis	Poultry, meats, and eggs	Domestic animals, especially poultry	Diarrhea

Salmonella typhi	Various foods	Humans	Typhoid fever
Shigella species	Various foods and water	Humans	Diarrhea (dysentery)
Vibrio cholerae	Various foods, e.g., seafood, and water	Humans	Diarrhea
Vibrio parahaemolyticus	Seafood	Warm salt water	Diarrhea
Campylobacter jejuni	Various foods	Domestic animals	Diarrhea
Yersinia enterocolitica	Various foods	Domestic animals	Diarrhea
II. Nondiarrheal diseases			
Gram-positive rods			
Clostridium botulinum	Improperly canned vegetables and smoked fish	Soil	Botulism
Listeria monocytogenes	Unpasteurized milk products	Cows	Sepsis in neonate or mother
Gram-negative rods			
Vibrio vulnificus	Seafood	Warm salt water	Sepsis
Brucella species	Meat and milk	Domestic animals	Brucellosis
Francisella tularensis	Meat	Rabbits	Tularemia
Mycobacteria			
Mycobacterium bovis	Milk	Cows	Intestinal tuberculosis

Q. Bacteria associated with food poisoning are *(BSMMU – Non-Residency – MD, MS, Basic science, Dentistry – July' 15)*

a) *Pseudomonas aeruginosa* F
b) *Staphylococcus aureus* T
c) *Clostridium perfringens* T
d) *Bacillus anthracis* F
e) Proteus spp. F

Q. Bacterial agents of food poisonings are *(BSMMU – Non-Residency - MD/MS, Basic science – 13Ju)*

a) *Staphylococcus aureus* T
b) *Bacillus cereus* T
c) *Clostridium botulinum* T
d) *Kiebsiella spp.* F
e) *Vibrio cholera* T

Q. Following microorganisms are transmitted through milk: *(BSMMU – MD/MS – January, 2010)*

a) *Salmonella paratyphi* T
b) *Bacilus cereus* F
c) *Mycobacterium bovis* T
d) *Vibrio cholerae* T
e) *E. coli* T

Q. Bacteria associated with food poisoning: (BSMMU - M. Phil, Diploma, July-08)

a) Pseudomonas aeruginosa F
b) Staphylococcus aureus T
c) Clostridium perfringens T
d) Bacillus anthraces F
e) Salmonella typhimurium T

HELP LINK:

Bacteria associated with food poisoning:

1. *Staphylococcus aureus*
2. *Bacillus cereus*
3. *Clostridium perfringens type A*

4. *E. coli*
5. *Salmonella typhi*
6. *Campylobacter*
7. *Vibrio parahaemolyticus*

Q. Toxin mediated food poisoning causes by following organisms: (MD/MS (DMC)-03Ja)

a) E. coli 0157
b) Staph aureas
c) Salmonella
d) Basillus anthracis
e) Clostridium perfringens

Ans.
a) F (it is infection type food poisoning)
b) T
c) F (it is infection type food poisoning)
d) F (Bacillus cereus is a toxin type organism food poisoning)
e) T (It's incubation period 8-16 hours)

Help link:

■ **Definition**: Food poisoning is defined as an acute gastro-enteritis manifested by vomiting, diarrhoea, or both within 48 hours of taking food, in persons (more than one) who have taken that food.

■ **Causative agents**:

	Pathogenesis	Examples
A. **Microbial agents**		
i. **Toxin type** (always produced by preformed toxin)	Bacteria grows in food substance where they produce exotoxin and when this exotoxin is ingested along with food they produce gastro-enteritis.	• *Staphylococcus aureus.* • *Bacillus cercus.* • *Clostridium botulinum* • *Vibrio cholerae.* • *Clostridium perfringens type A.*
ii. **Infection type**	Bacteria along with food substance where they produce gastro-enteritis.	• *Escherichia coli* • *Salmonella typhi murium.* • *Campylobacter jejuni* • *Vibrio parahaemolyticus.*
B. **Non-microbial agents**		•Some chemicals •Some vegetable poisoning.

Clostridium difficile

Q. The strain of clostridia sometimes cause a antibiotic induced psedomembranous colitis: (MD/MS (DMC)-01Ja)

A. Clostridium bifermenta F
B. Clostridium difficile T
C. Clostridium sporogenes F
D. Clostridium sordellii F
E. Clostridium septicum F

HELP LINK:

Transmission: Feco-oral route
Most common csuse of nosocromial diarrhoea

Toxin:

-Exotoxin A
-Exotoxin B

■ **Pseudomembranous colitis**: It is caused by *Clostridium difficile* associated with antibiotics.

■ **Pathogenesis**:

Antibiotics suppress drug sensitive normal flora

↓

C. difficile multiplies and produce exotoxin A and B that glycosylates (add glucose to) a G-protein

↓

Depolymerization of the actin resulting in cytoskeletal integrity loss, apoptosis and death of the enterocytes

↓

Diarrhoea associated with pseudornembrane on the colonic mucosa.

↓

Pseudomembranous colitis

■ **Antibiotics responsible**:

1. Clindamycin
2. Ampicillin
3. Second & third generation Cephalosporins.

■ **Clinical findings**:

1. Cl. Difficile causes diarrhea associated with pseudomemnbranes (yellow-white plaques) on the colonic mucosa. Pseudomembranes are visualized by sigmoidoscopy.
2. Fever and abdominal cramping
3. Toxic megacolon can occur

■ **Diagnosis**:

1. History of diarrhea after antibiotic therapy
2. The presence of exotoxin in a filtrate of patient's stool specimen is tested by 2 ways-
   - ELISA
   - Cytotoxicity test

In cytotoxicity test, human cells in culture are exposed to the exotoxin in the stool filtrate and the death of the cells is observed.

■ **Treatment**:

1. Discontinuing the given antibiotic.
2. Maintaining fluid and electrolyte balance.
3. Oral antibiotic therapy – Metronidazole.

Bacillus anthracis

Q. Following are applicable for Bacillus. (BSMMU – MS - January, 2010)

a) Bacillus cereus cause toxin type of food poisoning T
b) Bacillus subtilis is used as quality control of sterilization T
c) Bacillus subtilis can be used to produce antibiotics, bacitracin T
d) Spore is the important virulence factor for Bacillus anthracis T
e) Toxin of Bacillus anthracis is produced by lysogenic bacteria F (B. cereus)

HELP LINK:

Important Features of Pathogenesis by *Bacillus* Species:

Organism	Disease	Transmission/Predisposing Factor	Action of Toxin	Prevention
B. anthracis	Anthrax	1. Cutaneous anthrax: spores in soil enter wound 2. Pulmonary anthrax: spores are inhaled into lung	Exotoxin has three components: Protective antigen binds to cells; edema factor is an adenylate cyclase; lethal factor is a protease that inhibits cell growth	Vaccine contains protective antigen as the immunogen
B. cereus	Food poisoning	Spores germinate in reheated rice, then bacteria produce exotoxins, which are ingested	Two exotoxins (enterotoxins): 1. Similar to cholera toxin, it increases cyclic AMP 2. Similar to staphylococcal enterotoxin, it is a superantigen	No vaccine

Q. Following are manifestations of anthrax- (BSMMU – MD/MS - 02Ja)

a) Malignant pustule T
b) Fatal gastroenteritis T
c) Heart block F
d) Pancreatitis F
e) Haemorrhagic broncho pneumonia T

Help link:

ANTHRAX: There are three recognised forms of infection with *Bacillus anthracis*:

- cutaneous anthrax
- gastrointestinal anthrax
- inhalational (pulmonary) anthrax.

The ease of production of B. anthracis spores makes this infection a candidate for biological warfare or bioterrorism.

■ **Cutaneous anthrax**: This skin lesion is associated with occupational exposure to anthrax spores during processing of hides and bone products, or with bioterrorism. It accounts for the vast majority of clinical cases. Animal infection is a serious problem in Africa, India, Pakistan and the Middle East. Spores are inoculated into exposed skin. A single lesion develops as an irritable papule on an oedematous haemorrhagic base. This progresses to a depressed black eschar. Despite extensive oedema, pain is infrequent.

■ **Gastrointestinal anthrax**: This is associated with the ingestion of meat products that have been contaminated or incompletely cooked. The caecum is the seat of the infection, which produces nausea, vomiting, anorexia and fever, followed in 2—3 days by severe abdominal pain and bloody diarrhoea. Toxaemia and death can develop rapidly thereafter.

■ **Inhalational anthrax**: This form of the disease is extremely rare unless associated with bioterrorism. Without rapid and aggressive therapy at the onset of symptoms, the mortality is greater than 90%. Fever, dyspnoea, cough, headache and symptoms of septicaemia develop 3—14 days following exposure. Typically, there is little on the chest X-ray other than widening of the mediastinum and pleural effusions.

Management:

B. anthracis can be cultured from lesional skin swabs. Skin lesions are readily curable with early antibiotic therapy. Treatment is with ciprofloxacin 500 mg daily until penicillin susceptibility is confirmed; the regimen can then be changed to benzylpenicillin 600 000 units i.m. 6-hourly or phenoxymethylpenicillin 500 mg 6-hourly. Aggressive fluid resuscitation and the addition of an aminoglycoside may improve the outlook. Ventilatory assistance will be required in inhalational disease. Prophylaxis with ciprofloxacin (500 mg 12-hourly) is recommended for anyone at high risk of exposure to biological warfare. **(Ref: Davidson-22nd)**

Mycobacterium

Q. Bacteria included in Mycobacterium tuberculosis complex are *(BSMMU – Residency - **Dentistry** - March' 17)*

a) Mycobacteriuin africanum
b) Mycohacterium leprae
c) Mycobacterium tuberculosis
d) Mvcobacterium avium intercellulare
e) Mycobacterium scrofulacium

Ans. a) T b)F c)T d) F e) F

Help link:

Mycobacterium tuberculosis complex is the term used currently, which includes four species that can cause tuberculosis in humans and other mammals. These are:

- ***Mycobacterium tuberculosis***, the human type

- ***Mycobacterium bovis***, bovine type
- ***Mycobacteriuin africanum***, a species intermediate between human and bovine type and causing human tuberculosis mostly in tropical Africa, and
- ***Mycobacteriuin microti***, another species which is pathogenic for goats and other small animals but does not cause any human infections.

Medically Important Mycobacteria:

Species	Growth on Bacteriologic Media	Preferred Temperature in vivo (°C)	Source or Mode of Transmission
M. tuberculosis	Slow (weeks)	37	Respiratory droplets
M. bovis	Slow (weeks)	37	Milk from infected animals
M. leprae	None	32	Prolonged close contact
Atypical mycobacteria[1]	Slow (weeks)	37	Soil and water
M. kansasii			
M. marinum	Slow (weeks)	32	Water
M. avium-intracellulare complex	Slow (weeks)	37	Soil and water
M. fortuitum-chelonei complex	Rapid (days)	37	Soil and water

(Ref: LANGE Review-14th, P-184)

Mycobacterium tuberculosis

Properties:

- Aerobic, slowly growing acid fast bacilli.
- Acid fast due to high lipid in cell wall (Mycolic acid)
- Doubling time 18 hours.
- Transmission: air droplet.
- They have no toxins, enzymes (catalase, peroxidase)
- Collected sputum with 2%NaOH for destroying unwanted bacteria, human cell and mucous
- Resistant to dehydration.
- In immunosuppressed patients (AIDS) - granuloma may form without caseous necrosis.
- **Classification:**
  a) **Non pathogenic**:
     - M. phlei (found on grass), M. butyricum (found on butter)

  b) **Pathogenic:**
     - Obligate pathogen: M. TB, M. leprae, M. ulcerans
     - Opportunistic pathogen/ atypical mycobacteria

Virulence:

- Produce exported repetitive Protein that prevents phagosome to fuse with lysosome that's why lysosomal degredative enzyme can't destroy M tuberculosis.
- Cord facror (trehalose dimycolate) - virulence factor

Lab dx:

- Lowenstain jensen media 6- 8wks
- Liquid BACTEC media 2-3 wks
- Gamma interferon assay test (Quanti feron)

Biochemical test:

- Positive in:
  - Niacin test
  - Catalase
  - Amidase

- Nitrate reduction test
- Neutral red test
- Negative in:
  - Arylsulfate test

Q. Regarding *Mycobacterium tuberculosis* *(BSMMU –Residency - MD/MS, Basic science, Paediatrics – March' 19)*
a) doubling time is 18 days
b) produce exotoxin
c) niacin test is positive
d) obligate aerobe
e) cord factor is a virulence factor

Ans. a) F (18 hours) b) F (no exotoxins are produced) c) T d) T e) T

Q. Virulence factor of Mycobacterium tuberculosis are *(BSMMU – Diploma – Dentistry-July' 16)*
a) cord factor
b) lipase
c) glycolipid
d) catalase
e) sulphate

Ans. a) T b) F c) F d) F e) F

Q. Regarding *mycobacterium tuberculosis* *(BSMMU –Residency – MD, MS, Basic Science – March' 15)*
a) obligate intracellular bacteria
b) infection rate in our community is nearly 70%
c) BCG vaccination prevent the disease
d) cord factor is a virulence factor
e) tuberculin skin test is diagnostic

Ans. a) T b) F c) F d) T e) F **(Ref. Apurbo sankar-6th, P-13)**

Help link:
M. tuberculosis is an **obligate aerobe**; this explains its predilection for causing disease in highly oxygenated tissues such as the upper lobe of the lung and the kidney. The acid-fast property of *M. tuberculosis* (and other mycobacteria) is attributed to long-chain (C**78**–C**90**) fatty acids called **mycolic acids** in the cell wall.

Cord factor (trehalose dimycolate) is correlated with virulence of the organism. Virulent strains grow in a characteristic "serpentine" cordlike pattern, whereas avirulent strains do not.

BCG vaccine can be used to induce partial resistance to tuberculosis. The vaccine contains a strain of live, attenuated *M. bovis* called bacillus Calmette-Guerin. The vaccine is effective in preventing the appearance of tuberculosis as a clinical disease, especially in children, although it does not prevent infection by *M. tuberculosis*. However, a major problem with the vaccine is its variable effectiveness, which can range from 0% to 70%. It is used primarily in areas of the world where the incidence of the disease is high. It is *not* usually used in the United States because of its variable effectiveness and because the incidence of the disease is low enough that it is not cost-effective.

Q. M. tuberculosis has the following character (BSMMU - MD - 11Ja)

a) obligate aerobe	T
b) is a photochromogen	F
c) cell wall has high lipid content	T
d) do not produce any toxin and enzyme	F
e) is easily stained by gram stain	F

HELP LINK:
MTB produces enzyme catalase & peroxidase but no toxin.

Q. Mycobacterium tuberculosis identified by following stains: (BSMMU - M. Phil, Diploma, July-09)

a) Gram stain F
b) H & E stain F
c) Acid fast stain T
d) Zeihl Nelsen stain T
e) PAS stain F

Q. Following statements are applicable to mycobacterium tuberculosis- (BSMMU–MD/MS-05Ja)

A. is member of mycobacterium tuberculosis complex
B. is strict aerobe
C. is a Gram negative bacilli
D. generation time is 18-20 minutes
E. vaccination prevent mililiary tuberculosis

Ans.
a) T
b) T *(obligate aerobe)*
c) F *(they are acid fast bacilli)*d) F *(18 hours)*
e) T

Atypical mycobacteria

Atypical mycobacteria:

- **Slow grower** (grow on culture >7 days): M. kansasii, M. Scrofulaceum, M. avium intracellulariae.
  - Photochromogens, scrotochromogens, Non chromogens
- **Rapid grower** (<7 days): M. fortuitum
- **Characteristics:**
  - Infect diseased lung with cong deformity, cystic fibrosis.
  - No direct human to human spread
  - Resistant to standard anti-TB drugs
  - They are low virulent

Differences between M. tuberculosis and atypical mycobacterium:

Traits	Typical mycobacterium	Atypical mycobacterium
1. Morphology	Rod shaped with beaded appearance	Long filamentous and stained uniformity
2. Acid fastness	More acid fast	Less acid fast
3. Alcohol fastness	Alcohol fast	Not
4. Pigment	No pigment production	Some produce pigment, some not
5. Culture	Dry heaped buff color colony	Smooth, soften & regular colony
6. Tuberculin test	Strongly positive	Weakly positive
7. Sensitivity to anti-TB drugs	Sensitive	Less sensitive/ resistant
8. Niacin test	Positive	Negative except M. simiae.

Acid fast bacteria

Q. Following are acid fast bacteria (BSMMU - MD - January - 11)

a) Atypical mycobacteria T
b) Nocardia T
c) Actinomyces F
d) Corynebacteria F
e) Aspergillus F

Help link:

Acid fast organisms:

1. Mycobacteria:
   - *Mycobacterium tuberculosis*
   - *Mycobacterium bovis*

- *Mycobacterium lepraes*
- *Mycobacterium kansasii*

2. Nocardia asyeroids.

Q. The acid fast staining characteristics of mycobacteria appears to be due to: (MD/MS (DMC)-01Ja)

A. N-acetylmuramic acid	F
B. N- Glycolylmuramic acid.	F
C. Lipopolysaccharide.	F
D. Mycolic acid.	T
E. Lipid A.	F

HELP LINK:

■Reason for acid fastness of M. tuberculosis:

Mycobacteria are acid fast. This means when they are stained Ziehl-Neelsen staining, they take up the color of primary stain (hot fuming carbol fuchsin) and they resist decolorization by upto 20% H_2SO_4.

The causes of acid fastness are-

1. The cell wall contains huge amount of mycolic fatty acid.(lipid)
2. Thick cell wall due to high content of lipid & waxes.
3. The cell wall has a very well Physical integrity.
4. Lipid binds with the stain very strongly. As a result decolorization is very difficult. (Lipid barrier principle)

[Lipid barrier principle: The lipid cell wall is very difficult to stain. But once stained, it is very difficult to decolorize.]

Cell wall of mycobacteria constitute 60% of cell weight. In the cell wall, there is special lipid mycolic acid which are long chain fatty acid anchored to arabinogalacton layer of cell wall via chemical bonds. This mycolic acid holds the primary stain and because of its long chain it does not allow decolorization by upto 20% H_2SO_4 in M. TB. In case of M. leprae because of its short chain, it resist 5% H_2SO_4.

■Non-mycobacterial acid fast bacteria: Nocardia asteroids (causes nocardiasis)

Primary tuberculosis

Q. Primary tuberculosis may occur in *(BSMMU – Residency - **Dentistry** - March' 17)*

a) kidneys
b) tonsils
c) gastro-intestinal tract
d) thoracic spine
e) epididymitis

Ans. a)F b) T c)T d)F e)F

HELP LINK:

List the primary sites of TB: Lung, Intestine, Skin, Tonsil.

Q. Primary tuberculosis may occur in: (BSMMU - M. Phil, Diploma, July-08)

a) kidneys	F
b) tonsils	T
c) gastro-intestinal tract	T
d) thoracic spine	F
e) epididymis	F

Mantoux test/ Tuberculin test

Q. Causes of false negative tuberculin test are *(BSMMU –Residency - Paediatrics – March' 19)*
a) Severe malnutrition
b) Prolonged steroid intake
c) Milliary tuberculosis
d) tubercular plural effusion
e) Atypical mycobacterial infection

Ans. a) T b) T c) T d) F e) F

HELP LINK:

Mantoux test/ Tuberculin test: It is an intra-dermal skin test depends on delayed type of hypersensitivity reaction in which intra-dermal injection of mycobacterial antigen is given and the immune responses against the antigen reveals whether the patient has been exposed to mycobacterial antigen or not.
It is a screening test of TB which can help in diagnosis of TB with other tests.

■ **Reagents**:
1. Old tuberculin- crude extract of mycobacterium. But it may produce serious complication. So, it is not used.
2. PPD (purified protein derivatives) – purified specific Ag extracted from mycobacterial cell wall. 5 TU (tuberculine unit)- 0.1 ml – now it is used.
3. International unit: 0.00002 mg of PPD

■ **Procedure**: 5 tuberculin unit of PPD contained in 0.1 ml NS is injected intradermally on the flexor surface of the forearm. The subject is observed for about half an hour for any immediate hypersensitivity reaction and advised to report after 72 hours for final reading.

■ **Result & interpretation**: after 72 hours

Induration	Reaction	Interpretation
≥ 10 mm in diameter	Positive reaction	1. Past infection or disease (TB) 2. Present infection or disease (TB) 3. BCG vaccination
< 6 mm	Negative reaction	No infection by M. tuberculosis
6 – 9 mm	Doubtful reaction	• Infection by atypical mycobacteria • Faulty technique
>20 mm	Strongly positive	
False positive: It means skin test is positive, but the pt. has no TB.		Infection by atypical mycobacterium.
False negative: It means skin test negative but the pt. has TB.		1. Overwhelming TB/ Recent TB infection (less than 8-10 weeks)/ Immunological compromise 2. Miliary TB 3. Infectious mononucleosis 4. Sarcoidosis 5. Measles 6. Brucellosis (undulant fever/ Malta fever) 7. Scarlet fever 8. Hodgkin's disease 9. Leprosy 10. Malnutrition 11. Immunosuppressive drugs/ corticosteroid therapry/ steroid use 12. Before 6 month age. 13. Live virus vaccine 14. Before 4 weeks of infection.

(Ref. Textbook of Microbiology by Subash chandra+ Apurba Sankar +Robbins-9th +Wikipedia)

- In case of doubtful reaction, patient is asked to come after 6 weeks or again test with 10 TU.
- Tuberculin test does not diagnose TB but help diagnosis.

■ **Importance of tuberculin test**:

1. It becomes positive in active infection, past infection of TB and post BCG vaccination cases. So it is difficult to diagnose an active TB case by tuberculin test alone. However it has been observed that in cases of active infection, the diameter of induration is more than 20 mm (Diameter more than 10 mm is considered as positive Tuberculin test)
2. It gives a clue in diagnosis of extra-pulmonary TB.
3. It has an important role in diagnosis of active TB among children below 5 yrs who are not vaccinated before. (As adult are exposed)

Q. False negative tuberculin test is found in *(BSMMU – Non-Residency – **MD** – July' 18)*

a) steroid therapy
b) infection with non-tubercular mycobacterial infection
c) recent measles infection
d) HIV infection
e) disseminated tuberculosis

Ans. a) T b) F c) T d) T e) T

Q. The causes of false negative Mantoux test are *(BSMMU – Non-Residency – **MD, MS, Basic science, Dentistry** – July' 16)*

a) severe tuberculosis T
b) recent infection T
c) BCG vaccination F
d) adrenal tuberculosis F
e) newborn T

Q. A false-negative reaction to the tuberculin test may occur in the following circumstances *(BSMMU – Residency – **MD, MS, Basic Science** – March' 15)*

a) cyclosporine therapy
b) malignant lymphoma
c) viral infections
d) active tuberculosis
e) Previous BCG vaccination

Ans. a) T b) T c) T d) F e) F

Q. Positive tuberculin test indicates that the individual: *(BSMMU – M. Phil, Diploma (Non-Residency)–11Ju, DMC & others – MD/MS – 11Ju)*

a) carries viable mycobacteria in some tissues F
b) has been suffering from active disease F
c) is immune to tuberculosis F
d) is infectious to other persons F
e) is at risk of developing disease from reactivation T

Q. The Mantoux test *(BSMMU – Residency - **MD/MS, Basic science** – March' 14)*

a) is positive in all patients with tuberculosis
b) involves injecting PPD intradermally
c) is more sensitive than the microscopy
d) becomes positive within 3 weeks of acquiring tuberculosis
e) involves the CD4 cells

Ans. a) F b) T c) F d) F e) T

Q. Montoux test depressed in – (M. Phil, Diploma (DMC) - 07July)

a) influenza	F
b) measles	T
c) sarcoidosis	T
d) leprosy	T
e) ulcerative colitis	F

HELP LINK: depressed means false negative.

Leprosy

■ **Leprosy**: It is a chronic infectious disease primarily involving the peripheral nerves and secondarily skin, nasal mucosa, caused by a bacteria *Mycobacterium leprae*.

- Hansen of Norway discovered M. leprae in 1873. So, leprosy is called **Hansen's sisease**.
- Robert Koch discovered M. TB in 1882.

Cardinal features of leprosy:

- Skin lesions, typically anaesthetic at tuberculoid end of spectrum.
- Thickened peripheral nerves.
- Acid-fast bacilli on skin smears or biopsy.

■ **Charateristics of M. leprae**:

1. Intracellular, aerobic, acid-fast
2. Not grow in artificial culture media
3. It grows in mouse food pad or in the armadillo
4. Leprosy mainly affects the skin, mucous membrane and peripheral nerves.
5. Optimim temperature for growth is 30^0C lower than the body temperature. So, grows preferentially in skin & superficial nerves.
6. Mode of transmission:
   - Prolonged contact with patient of lepromatous leprosy
   - Inhalation of droplet nuclei.
7. Incubation period: 3 – 5 years or more
8. Clinical features:
   - Hypopigmented patches
   - Partial or total loss of cutaneous sensation
   - Presence of thickened nerves

Classification of leprosy:

A. **Ridley & Jopling's classification**:

1. Tuberculoid leprosy (TT)
2. Borderline tuberculoid (BT)
3. Borderline leprosy (BB)
4. Borderline lepromatous (BL)
5. Lepromatous leprosy (LL)
6. Pure neural leprosy **(Ref: Davidson-23rd)**

B. WHO classification:

1. Paucibacillary leprosy
2. Multibacillary leprosy

■ **Pathogenesis of leprosy**: The organism replicates intracellularly, typically within skin histiocytes, endothelial cells and the Schawmn cells of nerves.

1. **In tuberculoid leprosy**, cell mediated immune (CMI) response to the organism limits its growth. Very few acid fast bacilli are seen and granulomas containing giant cells form.

2. **In lepromatous leprosy**, the cell mediated response to the organism is poor, the skin and mucous membrane lesions contain large numbers of organism, foamy histiocytes rather than granulomas are found and lepramin skin test is negative.

Lepra reaction

Q. Lepra reaction type I is characterized by *(BSMMU – Residency - **MD** - March' 17)*
a) cell-mediated hypersensitivity
b) tender skin nodules
c) tender nerves
d) orchitis
e) lymphadenitis
Ans. a) T b) F c) T (ref: Davidson-22nd, P-349) d)F e)F

Help link:
Lepra reaction:
Lepra reactions are events superimposed on the cardinal features. Or,
These may be defined as the episodes of inflammation in preexisting lesions of leprosy.

Types: Two types —
1) Type-I reaction (Reversal)
2) Type-2 reaction (Erythema nodusum leprosum, ENL)

11.47 Reactions in leprosy

	Lepra reaction type 1 (reversal)	Lepra reaction type 2 (erythema nodosum leprosum)
Mechanism	Cell-mediated hypersensitivity	Immune complexes
Clinical features	Painful tender nerves, loss of function Swollen skin lesions New skin lesions	Tender papules and nodules; may ulcerate Painful tender nerves, loss of function Iritis, orchitis, myositis, lymphadenitis Fever, oedema
Management	Prednisolone 40 mg, reducing over 3–6 months[1]	Moderate: prednisolone 40 mg daily Severe: thalidomide[2] or prednisolone 40–80 mg daily, reducing over 1–6 months; local if eye involved[3]

[1]Indicated for any new impairment of nerve or eye function. [2]Contraindicated in women who may become pregnant. [3]1% hydrocortisone drops or ointment and 1% atropine drops.

(Ref. Davidson-23rd, P-268)

Q. Type 1 lepra reaction: *(BSMMU – Residency – MD – March'13)*
a) Produces constitutional symptoms
b) Occurs at the site of existing lesions
c) Is associated with alteration in cell mediated immunity
d) Has multi system involvement
e) Produces nerve damage

Ans : a) F b) T c) T d) F e) T

Lepromatous & tuberculoid leprosy

Q. Characteristic(s) of tuberculoid leprosy is (are) *(BSMMU –Residency - MD – March' 19)*

a) multibacillary lesions
b) central healing in the skin lesions
c) marked loss of sensation at early stage
d) loss of sweating in the affected site
e) symmetrical skin lesions

Ans. a) F b) T c) T d) T e) F

(Ref: Davidson 23rd, P-268)

Help link:

i 11.46 Clinical characteristics of the polar forms of leprosy

Clinical and tissue-specific features	Lepromatous	Tuberculoid
Skin and nerves		
Number and distribution	Widely disseminated	One or a few sites, asymmetrical
Skin lesions		
Definition:		
Clarity of margin	Poor	Good
Elevation of margin	Never	Common
Colour:		
Dark skin	Slight hypopigmentation	Marked hypopigmentation
Light skin	Slight erythema	Coppery or red
Surface	Smooth, shiny	Dry, scaly
Central healing	None	Common
Sweat and hair growth	Impaired late	Impaired early
Loss of sensation	Late	Early and marked
Nerve enlargement and damage	Late	Early and marked
Bacilli (bacterial index)	Many (5 or 6+)	Absent (0)
Natural history	Progressive	Self-healing
Other tissues	Upper respiratory mucosa, eye, testes, bones, muscle	None
Reactions	Immune complexes (type 2)	Cell-mediated (type 1)

(Ref: Davidson-23rd, P-268)

Sometime this reaction is the first clinical manifestation of the leprosy, most of the pt. will suffer type 2 lepra reaction during the course of disease. This is common in any form of lepromatous leprosy and borderline lepromatous patients.Type 1 reaction is common in borderline tuberculoid present.

Q. In tuberculoid leprosy *(BSMMU – Non-Residency – **MD** – July' 18)*
a) lesions are asymmetrical
b) lesions are numerous
c) there is failure of T-helper cell activation
d) there is early and marked nerve damage
e) erythema nodosum leprosum can occur
Ans. a) T b) F c) F d) T e) F

Q. Ocular findings in leprosy are *(BSMMU –Residency – **MS** – March' 15)*
a) raised intraocular pressure
b) cataract
c) anterior uveitis
d) blepharospasm
e) reduced corneal sensation
Ans. a) T b) T c) T d) T e) F

HELP LINK:

Ocular manifestations of leprosy:
- Madarosis (loss of eyelash), subconjunctival fibrosis
- punctate epithelial keratopathy
- posterior subcapsular cataract
- corneal hypesthesia, lagophthalmos
- corneal pannus, Entropion, anterior uveitis
- prominent or beaded corneal nerves
- Iridocyclitis, focal avascular keratitis
- Scleritis, interstitial keratitis, iris pearls
- ocular clofazimine crystals, blepherospasm

Q. Tuberculoid leprosy *(BSMMU –Residency – **MD, Basic science** – March' 14)*
a) contain scanty bacilli
b) causes shiny and smooth lesion
c) leads to early and marked loss of sensation
d) does not produce granuloma
e) causes leonine facies Ans. a) T b) F c) T d) F e) F

Q. Lepromatous leprosy: *(BSMMU – M. Phil, Diploma (Non-Residency)–March-2012, DMC & others – **MD** – March-2012)*
a) is less infectious than tuberculoid type
b) may have leonine fades
c) is characterized by well formed granuloma
d) lesions contain scanty bacilli
e) may have erythema nodosum leprosum reaction

Ans. a) F b) T c) F d) F e) T

HELP LINK: Regarding Leprosy:
- Incubation period is 2-5 yrs in tubcrculoid & 8-12 yrs in lepromalous cases
- CNS is not involved at all
- facial nerve involvement causes impairment of eye closure
- Damage to 5th nerve causes anaesthesia of cornea & conjunctiva

(Ref: Davidson's Medicine-22nd)

Leprometous leprosy is associated with:
- Leonine fades
- Sweating loss
- Gloves & stocking neupathy
- Nasal callapse
- Testicular atrophy
- Azoospermia
- Gynaecomasria

(Ref: Davidson's Medicine-22nd)

Q. The following cardinal features are found in Tuberculoid Leprosy - (DMC – MD/ MS - 10Ja)

a. hyperpigmented patch F
b. anhidrosis T
c. alopecia T
d. hyperesthesia F
e. spinal cord involvement F

Q. Following are true about leprosy – (BSMMU – MD/MS - January, 2009)

a) it can cause facial nerve palsy T
b) it is caused by Acid Fast Bacilli T
c) tuberculoid type occur in patient with poor cellular immunity F
d) more bacilli are found in lesion of lepromatous leprosy T
e) granuloma is a feature of tuberculoid leprosy T

Q. Features suggestive of lepromatous leprosy are: (BSMMU - MD - 06Ja)

A. marked hypopigmentation
B. central healing
C. skin lesions are never elevated
D. nerve involvement is usually early
E. high bacillary index

Ans.

a) F *(Slight hypopigmentation)*
b) F *(No central healing in lepromatous leprosy, it is common in tuberculoid leprosy)*
c) T d) F *(late)* e) T *(5 or 6 + bacilli)*

Enterobacteriaceae

- **Common characteristics:**
  - Gram negative bacilli
  - Non sporing
  - Some are motile: E. coli, Salmonella, Proteus, enterobacter, citrobacter
  - Some are non motile: Shigella, Klebsiella
  - Grow basal culture(Mac conkey, nutrient agar) media, do not need enriched media
  - Either facultative anaerobic or aerobic
  - Ferment glucose, produce acid with or without production of gas.
  - Some can ferment lactose (memmo: KEEC-L): Klebsiella, E. coli, Enterobacter, Citrobacter.
  - Some are non lactose fermenter: Shigella (except shigella sonni), Salmonella, Proteus
  - **Late Lactose fermentar**: Shigella sonni, vibrio, providencia.
  - Oxidase Negative
  - Reduce Nitrate to Nitrites
  - All r catalase positive
  - Non capsulated EXCEPT Klebsiella
- ❑ Pseudomonas is not a enterobacteriaceae.
- ❑ **Classify enterobactericeae on the basis of infection:**
  - **Strict intestinal pathogen**: Shigella
  - **Extraintestinal pathogen**:
    - Klebsiella, Proteus, Citrobacter, Enterobacter
  - **Mixed (intestinal+ extra-intestinal):**
    - E. coli, Salmonella

Escherichia coli

Virulence:

1. Pilli
2. Capsule
3. Exotoxin (Heat labile & Heat stable)

Diarrhoeagenic stain:

1. Enterotoxigenic E. coli (ETEC)- Travelar's diarrhoea, Acute watery diarrhoea in children
2. Enteropathogenic E. coli (EPEC)- Infantile diarrhoea
3. Enteroadhesive E. coli (EAEC)- Persistant diarrhoea.
4. Enteroinvasive E coli (EIEC): causes diarrhoea
5. Enterohaemorrhagic E coli (EHEC)/ Verotoxin/Shiga like toxin E. coli (VTEC)-Diarrhoea, Bloody diarrhoea, Haemolytic uremic syndrome(VTEC O157: H7)

Diseases:

1. UTI, Diarrhoea, Dysentry
2. Wound infection ,Pneumonia
3. Septicemia ,Biliary tract infection
4. Meningitis, DIC
5. HUS:
   - Microangiopathic haemolytic Anaemia,
   - Thrombocytopenia,
   - Acte renal failure
   - Caused by O157:H7 strain of E coli

Bacteria causing UTI:

- **Bacteria:**
  - E coli
  - Proteus
  - Pseudomonas
  - Sterptococci
  - Staphylociccus epidermidis
  - Stap saprophyticus
- **Virus:**
  - Adeno virus
- **Fungus:**
  - Candida albicans
- **Parasites:**
  - Schistosoma haematobium,
  - W. banccrofti
- **Why UTI is more common in female:**
  - Short urethra
  - Proximity to vagina and anus
  - Absence of bactericidal prostatic secretion
  - Sexual intercourse

Klebsiella

- ❑ Frequent found in large intestine, also soil & water.
- ❑ Have anti phagocytic capsule.
- ❑ Diseases:
  - Pneumonia (Current jelly sputum)
  - UTI
  - Atrophic rhinitis.

Gram Negative Rods Related to Respiratory Tract

- Haemophylus
- Bordetella
- Legionella

Atypical Pneumonia:

1. Legionella
2. Mycoplasma
3. Chlamydial psitacosis
4. Q fever
5. Viral influenza.

Salmonalla

Properties of Salmonella:

- Gram negative rods.
- Produce H_2S.
- Have polysaccharide capsule.
- Flagella- Present.
- Survival & growth of organism within phagosome in phagocytic cells are striking feature of the diseases.
- **Diseases:**
  - Enterocolitis-self limiting
  - Enteric fever.
  - Septicemia.
  - Osteomyelitis.

Typhoid fever/ Enteric fever

Q. In typhoid fever - (MD/MS (DMC)-09Ja)

a. septicaemia occurs at the end of incubation period F
b. rose spots appear in 2nd week of illness T
c. bronchitis is uncommon T
d. mesenteric adenitis occurs F
e. organism can often be found in urine T

HELP LINK:

■ **Aetiology**: Enteric fever is caused by infection with:

Salmonella typhi
Salmonella para typhi A
Salmonella paratyphi B

The incubation period is 10-14 days.

■ **Pathogenesis**:

■ **Incubation**: 10-14 days (complain- fever- gradually rise, headache)

Small intestine → Attach of epithelial surface → submucosa → phagocytosed → Resist intracellular killing → multiply within cell → Mesenteric lymph nodes → blood stream (bacteremia) → cleared off by phagocytic cells of liver, spleen, bone, lymph nodes → After about 10 days macrophages are necrosed → bacilli pass to blood again & cause 2ndary bacteremia (heavier) → Onset of illness (14 days) → Endotoxins are liberated → Pyrexia & other signs → localization of bacilli in gall bladder → liver, spleen → Intestine → Intestinal inflammation (Pyer's patches) → Ulcer → perforation.

■ ***Clinical feature***:

A. **First week**:

- Fever- insidious onset.
- Temperature rises in step ladder pattern for 4-5 days associated with malaise with ↑headache.
- Headache and drowsiness.
- Myalgia
- Bradycardia
- Constipation (may be diarrhoea and vomiting)

B. End of first week:

- Rose spots on trunk.
- Splenomegaly
- Cough
- Abdominal distension
- Diarrhoea.

C. **End of second week**:

- Delirium
- Complications
- Coma and death (if untreated)

■ **Investigation**:

1. Blood count: Leucopenia with relative lymphocytosis.
2. Blood culture: Diagnostic in 1st week.
3. Widal test: Positive in 2nd week.
4. Stool & urine culture: Positive in 3rd week.

Q. Recognized complication of typhoid fever include: (MD/MS (DMC) - M. Phil, Diploma, July-06)

a) osteomyelitis T
b) endocarditis T
c) pneumonia. T
d) meningitis T
e) thrombocytosis F

HELP LINK:

Complication of Enteric fever	
GIT	Intestinal haemorrhage (1-10%), Intestinal perforation (0.5-3%)
Liver & Gall bladder	Overt hepatitis, cholecystitis
Pancreas	Pancreatitis
Lungs	Pneumonia, bronchitis
Meninges	Meningitis
CNS	Raised ICP, cerebral thrombosis, acute cerebellar ataxia, chorea, aphasia, deafness, psychosis, transverse myelitis, peripheral and optic neuritis
Heart	Toxic myocarditis, endocarditis, cardiogenic shock
Bones	Osteomyelitis, septic arthritis, severe bone marrow necrosis
Renal	Pyelonephritis, nephrotic syndrome

Others	Orchitis, parotitis, supporative lymphadenitis.

Q. Recognized complication of typhoid fever include: (MD/MS (DMC)-05Ja)

a. Osteomyelitis T
b. Endocarditis T
c. Pneumonia T
d. Meningitis T
e. Throbocytopenia F

HELP LINK:

■ **Complications:**

1. Bowel: Perforation, haemorrhage.
2. Arthritis, osteomyelitis.
3. Meningitis
4. Cholecystitis.
5. Myocarditis
6. Nephritis.
7. Septicaemia
8. Pneumonia
9. Abscess formation in different internal organs.

Q. Salmonella typhi- (BSMMU-MD/MS-05Ja)

A. causes septicaemia
B. is a late lactose fermenting bacilli
C. gives rise to positive Widal test in the 2nd week
D. are non-motile organism.
E. produces ureas

Ans.
a) T b) F *(It is a non-lactose fermenting)*
c) T
d) F *(Are usually motile. Shigella are non-motile)*
e) F *(Produces H_2S)*

Q. Complications of typhoid fever include: (BSMMU-05Ja)

A. Generalized pruritus F
B. Meningitis T
C. Endocarditis T *(causes myocarditis)*
D. Osteomyelitis T
E. Peptic ulcer F

Q. Recognised complications of typhoid fever, include - (M. phil, Diploma (DMC) – 03,July)

a) cholecystitis T
b) meningitis T
c) endocarditis T
d) Stricture urethra F
e) pneumonia T

Q. The following drugs are effective in enteric fever: (MD/MS (DMC)-03Ja)

a) Ciprofloxacin T
b) Co-trimoxazole T
c) Chloramphenicol T
d) Streptomycin F
e) Tetracycline F

HELP LINK:

■ **Treatment**:
Ciprofloxacin 500 mg 12 hourly for 14 days. Or, Cotrimoxazole 960 mg 12 hourly for 14 days
Or, Amoxycillin 750 mg 6 hourly for 14 days. Or, Chloramphenicol 500 mg 6 hourly for 14 days.
Or, Ceftriaxone 1-2 gm IV 12 hourly for 14 days.
A chronic carrier is treated by Ciprofloxacin for 4 wks. Cholecystectomy may necessary.

Q. How will you treat a case of multi drug resistant enteric fever?
Ans.
Multi drug resistant (MDR) S. typhi are usually resistant to chloramphenical, ampicillin, trimethoprim, sulfonamides and tetracycline. Thus the fluoroquinolone remain the drug of choice (e.g. ciprofloxacin 500 mg 12 hourly).
Extended-spectrum cephalosporins, ceftriaxone and cefotaxime, are useful alternatives.
Azithromycin (500 mg once daily) has been shown to be an alternative where fluoroquinolone resistance is present.

Treatment should be continued for 14 days. Pyrexia may persist for up to 5 days after the start of antibiotic therapy.

(Ref: Davidson-22nd)

Shigella

Q. ***Shigella dysenteriae* type 1** *(BSMMU – Residency – MD, MS, Basic science – March' 16)*
a) produce heat stable exotoxin F
b) invades gut mucosa T
c) gives positive Sereny's test F
d) produce neurotoxin homologous to tetanus toxin F
e) causes haemolytic uremic syndrome T

Help link:
Properties of Shigella:
- Non motile (due to lack of 'H' antigen)
- Gram negative bacilli
- Cause diseases only in human.
- Don't produce H_2S
- Classified on the basis of 'O' antigen
  - **Group A:** Shigella dysenteriae O1(called shigella shiga), 12 serotype, most dangerous bcoz it causes renal failure and HUS(hemolytic uraemic syndrome)
  - **Group B:** Shigella flexneri, 6 serotype
  - **Group C:** Shigella boydii, 18 serotype
  - **Group D:** Shigella sonnii, (lactose fermenter)
- **Infective dose:** 10-100 bacilli
- **Shiga toxin has 3 property:** Enterotoxic, Cytotoxic, Neurotoxic
- Shiga toxin may encoded by Lysogenic bacteriophage.
- Shiga infection remain confined to the mucosa, does not invade submucosa, no septicaemia or bacteremia
- Sometimes shiga toxin is absorbed in the blood, go to brain produces S/S of meningism without inflammation of meningitis by neurotoxic property of shiga toxin.

Vibrio cholerae

Criteria of V. cholerae:

- Curved, coma shaped, single polar flagellae.
- Gram negative.
- Oxidase positive.
- Clinical infection- enteric in nature. From sporadic diarrhoea to epidemic/Pandemic cholera.
- Natural habitat- water.
- Grow best at - pH 7.0. Well tolerated pH 9.5. Extremely sensitive pH 6.0 or less.
- Antigenic structures -'O' & 'H' Ag
- V. cholerae 0139 causes cholera

- **Classification:**
  - **Non toxigenic**: V. cholerae O1 or atypcal V. cholerae O1.
  - Non O1 (O2- O139)
  - V. cholerae O1(Toxigenic)
    - Classic and eltor(each biotype divided into inaba, ogaba, and Hikojima)
- V. Cholerae O139 is the major pathogen, also called Bengal strain(1992) of V. cholerae.
- **Organisms having biotype:**
  - V. cholerae, Corynebacterium,
  - Yersinia pestris
- Diseases run a self limiting course in up to 7 day.
- Who are at risk: Has little stomach acid, Taking PPI or antacid, Gastrectomy
- Mortality rate without treatment 40%
- Antibiotic (Tetracyclin) shorten the symptom & reduce the excretion of organism.
- **Lab dx:**
  - **Stool**: Rice watery, fishy smell, no blood.
  - **Microscopy**: No RBC, Plenty of mucous
  - **Hanging drop preparation of stool**: Motile bacteria, fish in stream.
  - **Dark ground microscopy**: Motile as shooting star in night sky.
  - **Immobilization test**: Bed side confirmatory test. No motility by antisera.
- There is no vaccination, bcoz vaccine protects against bacteria but not the toxin, so we need antitoxin immunity.
- Vibrio causes epidemic and pandemic cholerae: O1 and O139
- **What the transport media:**
  a) Carry blair media
  b) alkaline peptone water

Question Bank

Q. Following are the properties of *Vibrio cholerae* – (BSMMU – MD/MS - January, 2009)

a) produces exotoxin	T
b) best grow at slight acidic pH	T
c) oxidase negative	F
d) comma shaped bacilli	T
e) have peritrichous flagella	F

HELP LINK:

■ **Determinants of pathogenecity**:

1. Enterotoxin 2.Adherence factor Ag
3. Motility 4. Chemotaxis
5. Extracellular enzyme 'protease'.

■ Incubation period: 1-4 days

■ Infective dose: $10^8 - 10^{10}$ organisms
■ Mode of transmission: contaminated food & drinks.

■ **Transmission**:
Infection spreads via the stools or vomit of symptomatic patients or of the much larger number of subclinical cases. It survives for up to 2 weeks in fresh water and 8 weeks in salt water. Transmission is normally through infected drinking water, shellfish and food contaminated by flies, or on the hands of carriers.

■ **Pathogenesis of cholera:** Contaminated food & water with *Vibrio cholerae*
↓
Ingestion of contaminated food & water (containing at least 10^8 *Vibrio cholerae*)
↓
The organism passes through the acid barrier of the stomach and multiply in the alkaline media of small intestine.
↓
Vibrio cholera is not an invasive organism and it does not enter to the blood stream and remains in the intestinal epithelium by the adhesive factors.
↓
There they multiply and produce enterotoxin, mucinase and endotoxin. The mucinase attach the mucous membrane and makes the epithelial cell more vulnerable to the action of enterotoxin or cholera toxin or choleragen.
↓
V. cholerae release enterotoxin or Cholera toxin which has 2 subunit: A (active) & B (binding).
B Subunit binds to the ganglioside receptor of the brush border of living epithelium.
A Subunit enters the cells.
↓
Persistent stimulation of adenyl cyclase enzyme.
↓
Overproduction of cAMP
↓
↑ secretion of water & electrolytes (Cl^- ions) in the lumen (due to Na dependant Cl secretion & prevention of NaCl absorption)
↓
Results in massive watery diarrhea without inflammatory cells.
(Secretion of isotonic fluid with HCO_3^- level twice than plasma & K^+ conc. 4-8 times that of plasma. → Fluid loss may be upto 1 litre.)

Effects:
- Extreme fluid & electrolytes loss (Rice watery stool) (with epithelial cells, mucous & vibrio)
- Mascular cramps
- Severe dehydration
- Acidosis, Haematocrit & blood urea ↑, hypokalaemia
- If not corrected dehydration → it becomes fatal. Death may occur due to dehydration & electrolyte imbalance.
- Renal failure, cardiac failure

■ **Clinical features:**
Severe diarrhoea without pain or colic begins suddenly and is succeeded by vomiting. Following the evacuation of normal gut faecal contents, typical rice-water' material is passed consisting of clear fluid with flecks of mucus. Classical cholera produces enormous loss of fluid and electrolytes, leading to intense dehydration with muscular cramps. Shock and oliguria develop but mental clarity remains. Death from acute circulatory failure may occur rapidly unless fluid and electrolytes are replaced. Improvement is rapid with proper treatment.

The majority of infections, however, cause mild illness with slight diarrhoea. Occasionally, a very intense illness, 'cholera sicca', occurs, with loss of fluid into dilated bowel, killing the patient before typical gastrointestinal symptoms appear. The disease is more dangerous in children.

Diagnosis:
Clinical diagnosis is easy during an epidemic. Otherwise the diagnosis should be confirmed bacteriologically. Stool dark field microscopy shows the typical 'shooting star' motility of V. cholerae. Rectal swab or stool cultures allow identification.

Prevention:
1. Strict personal hygiene is vital and drinking water should come from a clean piped supply or be boiled. Flies must be denied access to food.
2. Parenteral vaccination with a killed suspension of *V. cholerae* may provide limited protection.
3. Oral vaccines containing killed *V. cholerae* and the B subunit of cholera toxin are available but are of limited efficacy.
4. In epidemics public education and control of water sources and population movement are vital.
5. Mass single-dose vaccination and treatment with tetracycline are valuable.
6. Disinfection of discharges and soiled clothing, and scrupulous hand-washing by medical attendants reduce the danger of spread.

(Ref: Davidson-22nd + LANGE REVIEW-14th)

Q. *Vibrio cholerae*: (MD/MS (DMC)-05Ja)
- a) Is a comma shaped gram negative bacterium — T
- b) Is an invasive organism — F
- c) Can cause a torrential watery diarrhea — T
- d) Can cause hypovolaemic shock — T
- e) Produces a powerful exotoxin — T

Q. The newest sero type of *V. cholerae* is: (MD/MS (DMC)-02Ja, BSMMU-02J, PG-96J)
- A. V. cholerae non O1 — F
- B. V. cholerae — F
- C. V. cholerae O139 — T
- D. V. cholerae O11 — F
- E. None of the above — F

Helicobacter pylori

Q. *Helicobacter Pylori* can be detected by *(BSMMU – Non-Residency – MD, MS, Basic science, Dentistry – July' 16)*
- a) H_2 breath test — F (urea breath test)
- b) rapid urease test — T
- c) blood culture — F
- d) endoscopy of upper GIT — F
- e) urea breath test — T

Help link:
Bacteria associated with peptic ulcer disease is *Helicobacter pylori.*

■ **Properties:**
1. It is a curved, spiral shaped Gram-negative rod that appear either comma or S-shaped.
2. It has multiple flagella at one pole and is actively motile.
3. Microaerophilic (i.e.- requires less O_2 concentration for survival)
4. Oxidase positive, catalase positive.
5. Grows at Skirrow's media.
6. Urease enzyme production.

(Ref: LANGE Review-14th, P-162)

■ **Special characteristics of *H. pylori*:**
1. *H. pylori* grow best at pH 6-7 and rapidly inactivated or killed by an acid pH within the gastric lumen.
2. Gastric mucosa is relatively impermeable to acid and has a strong buffering capacity on the luminal site (pH 1-2) while the epithelial site pH is 7.4. *H. pylori* is found deep in the mucous layer near the epithelial surface where physiological pH is present.

3. *H. pylori* produce a protease that modifies the gastric mucosa and further reduces the acid to diffuse into mucosa.
4. *H. pylori* produce a potent urease which converts urea to produce ammonia and cause further buffering of acid.
5. *H. pylori* is actively motile even within the mucosa and finds its way to the epithelial surface.

■ **Diseases**:
1. Antral gastritis
2. Duodenal (peptic) ulcer disease
3. Gastric ulcer
4. Gastric carcinoma.

■ **Pathogenesis**: H. pylori attaches to the mucous secreting cells of the gastric mucosa.

↓

Production of large amounts of ammonia from urea by the organism's urease, coupled with an inflammatory response

↓

This leads to damage to the mucosa.

↓

Loss of protective mucus coating predisposes to gastritis and peptic ulcer.

The ammonia also neutralizes stomach acid allowing the organisms to survive.

Ammonia also invites other inflammatory products (e.g. cells, cytokines) resulting in increasing inflammatory response.

(Ref: LANGE Review-14th, P-162)

■ **Lab. Diagnosis**: Diagnosis is based on demonstration of causative organism by microscopic examination and isolation & identification by bacteriological techniques. Serologicaltests are also helpful.

1. ***Specimen***: Gastric biopsy, Blood for serum antibodies.
2. ***Microscopic examination***:
   Gram staining: Gram-negative
   Giemsa staining
3. ***Isolation and identification from culture***: Culture is done in Skirrow's media at 42°C in micro-aerophilic environment.
4. ***Biochemical test***: **Rapid urease test**. Radiolabeled urea is ingested. If the organsm is present, radiolabeled CO_2 is evolved and the radioactivity is detected in the breath.
5. ***Serological test***: Detection of antibody

(Ref: LANGE Review-14th, P-162)

Non-invasive tests for detection of H. pylori:
- Urea breath test
- H. pylori antigen test in the stool
- Serum IgG antibodies

Invasive tests for H. pylori (antral biopsy)
- Culture
- Histology
- Rapid urease tests

Campylobacter jejuni

Properties:
- ❑ Curved, S shaped.
- ❑ Gram negative.
- ❑ Micro aerophilic, 5% O2 & 10% CO2.
- ❑ **Diseases:**

1. Enterocolitis.
2. Bloody diarrhoea,
3. Foul smelling diarrhoea.
4. Bacteremia
5. Autoimmune diseases-
   - GBS,
   - Reiter's syndrome,
   - Reactive arthritis.

Haemophylus

It is a blood loving organism. H. influenzae is not the causative agent of influenza. It was first discovered in a influenza pandemic when it is present as a secondary bacterial invader.

■ **Species of Haemophylus**:

Haemophylus influenza
Haemophylus parainfluenza
Haemophylus aegypticus
Haemophylus ducreyi
Haemophylus haemolyticus
Haemophylus parahaemolyticus

- *Haemophylus influenza* is pathogenic
- *Haemophylus aegypticus* is responsible for acute bacterial conjunctivitis
- *Haemophylus ducreyi* is responsible for chancroid

Q. The following infections are caused by H. influenzae: (MD/MS (DMC)-04Ja)

a) Meningitis in children	T
b) Epiglottitis	T
c) Pneumonia	T
d) Diarrhoea	F
e) Causes otitis media	T

Help link:

■ **Important properties**:

1. It is a small gram-negative rods (coccobacillus) with polysaccharide capsule.
2. Non-sporing, non-flagellated & non-motile.
3. They produce exotoxin (no endotoxin).
4. Produce IgA protease.
5. They are six serotypes. **Type b** causes most of the severe, invasive disease such as meningitis & sepsis.
6. They grow in the media containing V & X factors. *(Factor V is heat labile- Nicotinamide adenine dinucleotide, Factor X is heat stable – heme)*
7. It is the normal flora of the upper respiratory tract.

(Ref: LANGE Review-14th, P-171)

■ **Pathogenesis**: It enters into the body through upper respiratory tract. (Droplet infection) resulting in either asymptomatic colonization or infections such as otitis media, sinusitis or pneumonia. Then it produces IgA protease that degrades secretory IgA, thus facilitating attachment to the respiratory mucosa. Then the organism can enter blood stream (bacteremia) and spread to meninges.

■ **Disease caused by it**:

1. Meningitis in young children (6 months to 6 years).
2. Upper respiratory tract infections (otitis media, sinusitis, epiglottitis) & sepsis in children.
3. Pneumonia in adults.

PSEUDOMONAS

Q. ***Pseudomonas aeruginosa*** *(BSMMU – Residency - **MD, MS, Basic Science, Dentistry** - March' 17)*
a) is facultative anaerobe that grows on blood agar media
b) common source of it includes hospital respiratory equipment
c) cause pneumonia in mechanically ventilated patients
d) is susceptible to ticarcillin and piperacillin
e) is catalase positive and oxidase negative
Ans. a) F b)T c) T d)T e)F

Q. The following statements are about Pseudomonas aeruginosa: *(BSMMU – M. Phil, Diploma (Non-Residency)–12Ju, DMC & others – MD/MS – 12Ju)*

a) typically susceptible to penicillin G	F
b) frequently cause burn infection	T
c) readily grown in anaerobic culture	F
d) commonly present in moist environments in hospital	T
e) produce a greenish pigment	T

HELP LINK:

Important Properties:

• Pseudomonas are gram-negative rods that resemble the members of the Enterobacteriaceae but differ in that they are strict aerobes; ie, they derive their energy only by oxidation of sugars rather than by fermentation. Because they do not ferment glucose, they are called non-fermenters, in contrast to the members of the Enterobacteriaceae, which do ferment glucose. Oxidation involves electron transport by cytochrome c; ie, they are oxidase-positive.

• Pseudomonas are able to grow in water containing only traces of nutrients, eg, tap water, and this favors their persistence in the hospital environment. **P. aeruginosa** and **P. cepacia** have a remarkable ability to with-stand disinfectants; this accounts in part for their role in hospital-acquired infections. They have been found growing in hexachlorophene-containing solutions, in antiseptics, and in detergents.

• **P. aeruginosa** produces two pigments usual in clinical and laboratory diagnosis:

1. **Pyocyanin,** which can **color the pus in a wound blue**.
2. Pyoverdin (fluorescein), a yellow-green pigment that fluoresces under ultraviolet light, a properly that can be used in the early detection of skin infection in burn patients.

In the laboratory, these **pigments diffuse into the agar, imparting a blue-green color** that is useful in identification. **P. aeruginosa** is the only species of **Pseudomnnas** that synthesizes pyocyanin. Strains of P. aeruginosa isolated from cystic fibrosis patients have a prominent slime layer (glycocalyx), which gives their colonies a very mucoid appearance. The slime layer mediates adherence of the organism to mucous membranes of the respiratory tract and prevents antibody from binding to the organism.

Pathogenesis & Epidemiology:

• **P. aeruginosa** is found chiefly in soil and water, although approximately 10% of people carry it in the normal flora of the colon. It is found on the skin in moist areas and can colonize the upper respiratory tract of hospitalized patients. Its ability to grow in simple aqueous solutions has resulted in contamination of respiratory therapy and anesthesia equipment, intravenous fluids, and even distilled water.

• **P. aeruginosa** is primarily an opportunistic pathogen that causes infections in hospitalized patients, eg, those with extensive burns, in whom the skin host defenses are destroyed; in those with chronic respiratory disease (eg, cystic fibrosis), in whom the normal clearance mechanisms are impaired; in those who are immunosuppressed; in those with neutrophil counts of less than 500/μL; and in those with indwelling catheters. It causes 10-20% of hospital-acquired infections and, in many hospitals, is the most common cause of gram-negative nosocomial pneumonia.

• Pathogenesis is based on multiple virulence factors: endotoxin, exotoxins, and enzymes. Its endotoxin, like that of other gram-negative bacteria, causes the symptoms of sepsis and septic shock. The best known of the exotoxins is exotoxin A, which causes tissue necrosis. It inhibits eukaryotic protein synthesis by the same mechanism as diphtheria exotoxin, namely, ADP-ribosylation of elongation factor 2. It also produces enzymes, such as clastase

and proteases, which are histotoxic and facilitate invasion of the organism into the bloodstream. Pyocyanin damages the cilia and mucosal cells of the respiratory tract.

• Strains of **P. aeruginosa** that have a "type III secretion system" are significantly more virulent than those that do not. This secretion system transfers the exotoxin from the bacterium directly into the adjacent human cell, which allows the toxin to avoid neutralizing antibody. Type III secretion systems are mediated by transport pumps in the bacterial cell membrane. Of the four exoenzymes known to be transported by this secretion system, Exo S is the one most clearly associated with virulence. Exo S has several modes of action, the most important of which is ADP-ribosylation of a Ras protein, leading to damage to the cytoskeleton.

Clinical Findings:

P. aeruginosa can cause infections virtually anywhere in the body, but urinary tract infections, pneumonia (especially in cystic fibrosis patients), and wound infections (especial burns) predominate. From these sites, the organism can enter the blood, causing sepsis. The bacteria can spread to the skin, where they cause black, necrotic lesions called **ecthyma gangrenosum**. Patients with P. aeruginosa sepsis have a mortality rate of greater than 50%. It is an important muse of endocarditis in intravenous drug users.

Severe external otitis (malignant otitis externa) and other skin lesions (eg, folliculitis) occur in users of swimming pools and hot tubs in which the chlorination is inadequate. **P. aeruginosa** is the most common cause of osteochondritis of the foot in those who sustain puncture wounds through the soles of gym shoes. Corneal infections caused by P. aeruginosa are seen in contact lens users.

Laboratory Diagnosis:

P. aeruginosa grows as non-lactose-fermenting (colorless) colonies on MacConkey's or EMB agar. It is oxidase-positive. A typical metallic sheen of the growth on TSI agar,-coupled with the blue-green pigment on ordinary nutrient agar and a fruity aroma, is sufficient to make a presumptive diagnosis. The diagnosis is confirmed by biochemical reactions. Identification for epidemiologic purposes is done by bactcriophage or pyocing typing.

Treatment:

Because P. aeruginosa is resistant to many antibiotics, treatment must be tailored to the sensitivity of each isolate and monitored frequently; resistant strains can emerge during therapy. The treatment of choice is an anti-pseudomonal penicillin, eg, ticarcillin or piperacillin, plus an aminoglycosidc, eg, gentamicin or amikacin. The drug of choice for infections caused by B. cepacia and S. maltophilia is trimethoprim- sulfamethoxazole.

(Ref: LANGE Review-14th, P-165-166)

Rickettsia

Q. Followings are characteristics of Rickettsia: *(BSMMU – M. Phil, Diploma (Non-Residency)–11Ju, DMC & others – MD/MS – 11Ju)*

a) obligate intracellular parasite	T
b) small rod or cocci	T
c) lack cell wall	F
d) transmitted by vector	T
e) best treated with sulfonamide	F

HELP LINK:

ESSENTIAL FEATURES OF RICKETTSIAL INFECTIONS:

Disease	Reservoir	Vector	Primary complex[1]	Rash	Gangrene	Target organs	Mortality
SPOTTED FEVER GROUP							
Rocky Mountain spotted fever	Rodents, dogs, ticks	*Ixodes* tick	Often	Morbilliform Haemorrhagic	Often	Bronchi, myocardium, brain, skin	2-12%[2]
Other tick- borne typhus	Rodents, dogs, ticks	*Ixodes* tick	Usual	Maculo-papular	-	Skin, meninges	Rare[3]
TYPHUS GROUP							
Scrub typhus	Rodents	*Trombicula* mite	Often	Maculo-papular	Unusual	Bronchi, myocardium, brain, skin	Rare[3]
Epidemic typhus	Humans	Louse	-	Morbilliform Haemorrhagic	Often	Brain, skin, bronchi, myocardium	Up to 40%
Endemic typhus	Rats	Flea	-	Slight	-	-	Rare[3]

[1]Eschar at bite site and local lymphadenopathy.
[2]Highest in adult males.
[3]Except in infants, older people and the debilitated.

Investigation of rickettsial infection:
Routine blood investigations are unhelpful. Diagnosis is made on clinical grounds and response to treatment. Differential diagnoses include malaria, typhoid, meningococcal sepsis and leptospirosis.

(Ref: LANGE Review-14th)

CHLAMYDIAMA

Q. Chlamydia trachomatis infection in human has following characteristics: (BSMMU – MS - January, 2010)

a) involves genital tract T
b) involves lungs in children T
c) responses to antibiotics T
d) needs antiviral drugs for treatment F
e) carrier state in human T

HELP LINK:
Chlamydiae produce confusion with virus, because they have similarities with virus, such as-It is small obligate intracellular parasite, i.e it can not live outside the living cell like viruses. Because they have lack of ability to produce sufficient energy to grow independently.

But now, it is considered as bacteria. Because-

1. It has cell wall.[cell wall contains atypical peptidoglycans due to lack of muramic acid] – resemble those of Gram negative bacteria.
2. Multiply by binary fission similar to bacteria.
3. It contains both DNA & RNA, similar to bacteria.
4. Sensitive to antibiotic
5. They have a replicative cycle different from other bacteria.

■ **Developmental cycle**:

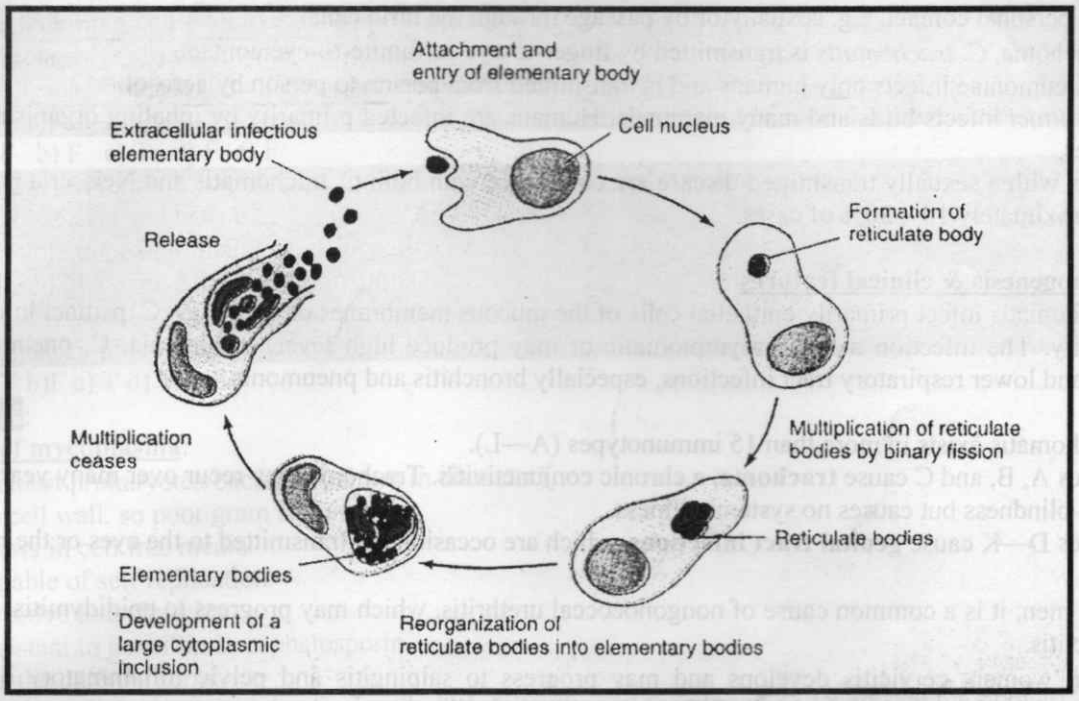


Fig: Life cycle of Chlamydia.

(Ref: LANGE Review-14th)

The cycle begins when the extracellular, metabolically inert, 'spore like' elementary body enters an epithelial cell

↓

The elementary body changes into a larger, metabolically active **reticulate body.**

↓

It divides many times by binary fission.

↓

The daughter reticulate bodies change into elementary bodies and are released from the epithelial cell.

↓

These elementary bodies again infect a new epithelial cell and thus the cycle repeats.

[Within cells, the site of replication appears as an inclusion body, which can be stained and visualized microscopically, consists of many daughter reticulate and elementary bodies. These inclusions are useful in the identification of these organisms in the clinical laboratory.]

Diseases caused by *chlamydia trachomatis*:

Species	Diseases
1. C. trachomatis	• Ocular: Trachoma, inclusion conjunctivitis • Genital: Non-gonococcal urethritis, Lymphogranuloma venereum • Respiratory: Pneumonia
2. C. pneumoniae	• Atypical Pneumonia
3. C. psittaci	• Psittacosis (pneumonia)

■ **Transmission**:

1. *C. trachomatis* infects only humans and is transmitted by
- close personal contact, e.g. sexually or by passage through the birth canal.
- In trachoma, *C. trachomatis* is transmitted by finger-to-eye or fomite-to-eye contact.

2. C. pneumoniae infects only humans and is transmitted from person to person by aerosol.
3. *C. psittaci* infects birds and many mammals. Humans are infected primarily by inhaling organisms in dry bird feces.

Patients with a sexually transmitted disease are coinfected with both C. trachomatis and Neisseria gonorrhoeae in approximately 10—30% of cases.

■ **Pathogenesis & clinical features**:

C. trachomatis infect primarily epithelial cells of the mucous membranes or the lungs. C. psittaci infects the lungs primarily. The infection may be asymptomatic or may produce high fever, pneumonia. C. pneumoniae causes upper and lower respiratory tract infections, especially bronchitis and pneumonia.

C. trachomatis exists in more than 15 immunotypes (A—L).

1. Types A, B, and C cause **trachoma**, a chronic conjunctivitis. Trachoma may recur over many years and may lead to blindness but causes no systemic illness.
2. Types D—K cause **genital tract infections**, which are occasionally transmitted to the eyes or the respiratory tract.
   - In men, it is a common cause of nongonococcal urethritis, which may progress to epididymitis, prostatitis, or proctitis.
   - In women, cervicitis develops and may progress to salpingitis and pelvic inflammatory disease (PID). Repeated episodes olsalpingitis or PID can result in infertility or ectopic pregnancy
3. Infants born to infected mothers often develop mucopurulent eye infections (neonatal inclusion conjunctivitis) 7—12 days after delivery, and some develop chlamydial pneumonitis 2—12 weeks after birth.
4. **Chlamydial conjunctivitis** also occurs in adults as a resuit of the transfer of organisms from the genitals to the eye. Patients with genital tract infections caused by C. trachomatis have a high incidence of **Reiter's syndrome**, which is characterized by urethritis, arthritis, and uveitis. Reiter's -syndrome is an autoimmune disease caused by antibodies formed against C. trachornatis cross-reacting with antigens on the cells of the urethra, joints, and uveal tract.
5. C. trachomatis L1 –L3 immunotypes cause **lymphogranuloma venereum**, a sexually transmitted disease with lesions on genitalia and in lymph nodes.

Q. Following diseases are caused by Chlamydia - (DMC – MD/ MS - January, 2010)

a. yellow fever	F
b. lymphogranuloma venereum	T
c. mumps	F
d. psittacosis	T
e. herpes simplex	F

Q. Chlamydia trachomatis infection in human has following characteristics- (BSMMU – MD/MS - 07Ja)

a. Involves genital tract	T
b. Involves lungs in children	T
c. Response to antibiotics is good	T
d. Antiviral drugs are needed for treatment	F
e. Carrier state in human	T

MYCOPLASMA

Q. Bacteria lacking a cell wall are *(BSMMU – Diploma - **Dentistry** – July' 18)*
a) treponema b) chlamydia
c) mycoplasma d) legionella
e) mycobacteria
Ans. a) F b) F c) T d) F e) F

Q. *Mycoplasma pneumonia* is *(BSMMU –Residency – **MD, MS, Basic Science** – March' 18)*
a) a small bacteria and has no cell wall
b) susceptible to penicillin and cephalosporin
c) diagnosed by positive cold agglutination test
d) a causative agent of atypical pneumonia
e) an obligatory intracellular bacteria
Ans. a) T b)F c) T d) T e) F

HELP LINK:

■ **Critrias of mycoplasma**:
1. Smallest prokaryotes/bacteria (0.3 μm in diameter)
2. No cell wall, so poor gram staining.
3. Grows in cell free media.
4. Capable of self replication
5. Sensitive to antibiotics
6. Resistant to pencillin & cephalosporin.
7. It is the parental form.
8. It is the only bacteria which contains cholesterol in the cell membrane. (3 layers cell membrane)
9. They grow very slowly (at least 1 week) and has a characteristic "fried egg" shape.
10. About 150 species, 15 are identified in human.
11. Found as normal flora in mucosa of genito-urinary tract.
12. Many healthy individuals carry the organisms in oral cavity: *M. hominis, M. salivarium*

Pathogenesis of Mycoplasma:
Mycoplasma attach to the ciliated or non-ciliated host cell by the mucosal cell sialoglycoconjugates and sulfated glycolipids. Then following events may occur-
- Direct cytotoxicity through generation of hydrogen peroxide & superoxide free radicals
- Cytolysis mediated by antigen-antibody reaction
- Cytolysis mediated by chemotaxis & action of mononuclear cells
- By competition for & depletion of nutrients

■ **Diseases caused by Mycoplasma**:

Species	Diseases
1. M. pneumoniae	Atypical pneumonia
2. M. hominis	PID, non-gonococcal urethritis
3. M. genitalium	Non-gonococcal urethritis
4. Ureaplasma urealyticum	Non-gonococcal arthritis Lung disease in low birth wt. infants.

Mycoplasma pneumoniae
■ **Transmission**: by respiratory droplet.
■ **Disease**: Atypical pneumonia
■ **Clinical features**: non-productive cough, sore throat, fever, headache.
■ **Diagnosis**: Diagnosis must be done clinically.
Special media: at least 1 week for colonies
Serology: Cold-haem agglutination test
Complement fixation test
■ **Treatment**: Penicillin and cephalosporin has no value, because the organism has not cell wall.

Q. Mycoplasma: *(BSMMU - M. Phil, Diploma –10Ju)*

a) can be grown on routine laboratory media F
b) have cell wall F
c) are resistant to β-lactum drugs T
d) are not found as commensal F
e) susceptible to erythromycin T

Spirochetes

- **Leptospira**: Leptospirosis
- ***Borrelia burgdorferi***: Lyme disease
- ***Borrelia recurrentis***: Relapsing fever
- ***Treponema pallidum***: Syphilis
- **Property:**
  - Thin, flexible, spiral rod(corkscrew shaped),
  - Motile(axial filament), Can not seen by light microscopy,
- **Seen by :**
  - Darkfield microscopy,
  - Immunoflurescence,
  - Silver impregnation test
- Most are anaerobes

Q. Leptospirosis: *(BSMMU - M. Phil, Diploma – July '10)*

a) may be acquired from cattle T
b) is diagnosed by blood culture T
c) vaccination prevent leptospirosis F
d) is self limiting disease T
e) ICT for detecting antibody are available F

HELP LINK:

Leptospira can enter their human hosts through intact skin or mucous membranes, but entry is facilitated by cuts and abrasions. Prolonged immersion in water will also favour invasion. After a relatively brief bacteraemia, invading leptospires are distributed throughout the body, in human the main organ affected are the kidneys, liver, meninges and brain.

Treponema pallidum

- **Mode of transmission**: Abrations of skin and mucous membrane, Sexual route, Blood transfusion, transplacental
- **Stages:**

❑ **Primary** (2-10 wks or 9-90 days):
  - Chancre, painless lymphadenopathy

❑ **Secondary** (1-3 months):
  - Maculopapular rash on palm and sole(non itchy),
  - Condyloma lata, Generalized lymphadenopathy, Snail track mouth ulcer,

❑ **Tertiary stage** (after many years):
  - Skin and bone gumma, CNS(paresis of insane, tabes dorsalis, Argyll –Robertson pupil
  - CVS: Aortitis, aneurysm of ascending aorta, aortic regurgitation.

❑ **Stigmata of syphilis:**
  - Hutchinsons incissiors teeth, Mulberry molars,
  - High arched palate, Maxillary hypoplasia, Saddle nose,
  - Corneal scarBossing of frontal and parietal bone

- **False positive VDRL:**
  - Leprosy, HBV,
  - Infectious mononucleosis,
  - Autoimmune disease.

Advantage of VDRL or RPR over TPHA:

- Can differentiate old and new infection,
- Treatment response can be monitored,
- Less expensive and easy to perform.

Others

Q. Airborne transmitted infections are *(BSMMU – Non-Residency – **Dentistry** – July' 19)*

a) influenza
b) typhoid fever
c) tuberculosis
d) measles
e) poliomyelitis

Ans. a) T b) F c) T d) T e) F

Help link:

✓ Airborne droplet nuclei (≤ 5 mm size) or dust particles that remain suspended in the air for long time and can travel longer distance:

✓ This is more efficient mode than droplet transmission.

- *Legionella*, *Mycobacterium tuberculosis*, measles and varicella viruses

(Ref: Textbook of Microbiology and Immunology-6th, P-531)

Airborne transmission by:

✓ Droplet nuclei-
- TB, Influenza, Chickenpox, Measles, Q fever

✓ Dust borne:(Common in Hospital acquired infection)
- Coccidiodomycosis, Streptococcal and staphylococcal infection,
- Pneumonia, TB, Q fever, Psittacosis.

(Ref: Park Preventive medicine-23rd, P-9)

✓ Others: Aspergillosis, Brucellosis, Inhalational anthrax, Meningococcal infection

Q. Exanthema is seen in the following disease: (DMC - M. Phil, Diploma, July-'07)

a) rubeola	T
b) meningococcal infections	F
c) rickettsial infection	T
d) secondary syphilis	F
e) multiple sclerosis	F

Help link:

An exanthema:

- An exanthem or exanthema is a widespread rash in children.
- **Cause:**
  - Toxins, drugs,
  - Autoimmune disease.
  - Rubeola
  - Measles
  - German Measles
  - Erythema infectiosum,
  - Varicella zoster virus (chickenpox or shingles)
  - Mumps
  - Rhinovirus (the common cold)
  - Viral haemorrhagic fever .
  - Tick-borne diseases like Rocky Mountain spotted fever

IMPORTANT MCQ OF BACTERIOLOGY

[Ref: Smiddy]

Q. The following diseases are the result of arthropod borne blood Infections:

a) cholera
b) trypanosomiasis
c) tetanus
d) malaria
e) hydatid disease

Ans.

a) **False** Cholera is a water-borne infection, transmission taking place by the faecal-oral route.

b) **True** Trypanosomiasis is transmitted by the tsetse fly. *T. gambiense* is transmitted mainly by intra-human cycles whereas *T. rhodesiense* is a zoonosis.

c) **False** Tetanus is due to the Gram positive *Clostridium tetani*, which is found in the soil often in spore form. Following injury the spore contaminates the wound and develops into the vegetative toxin producing form only if conditions are anaerobic.

d) **True** Malaria is transmitted by Inc anopheles mosquito. The disease is caused by one of four species of Plasmodium: *Plasmodium vivax, malariae, ovale* or *falciparum*. The latter is the most important.

e) **False** Hydatid disease is caused by the tapeworms. *Echinococcus granulosus* and *muitilocularis*. The natural cycle is from dog to sheep and man is infected only by accident.

Q. Streptococcus faecalis:

a) Is a common inhabitant of the gastro-intestinal tract
b) grows in long chains
c) flourishes in bile-salt lactose media
d) is concerned in the aetiology of periodontal disease
e) is an opportunistic rather than a true pathogen

Ans.

a) **True** *Streptococcus faecalis* is almost as numerous in the faeces of man as the bacteroides, bifidobacteria and enterobacteriaceae.

b) **False** This organism occurs in pairs looking like spectacles or at the most, in short chains.

c) **True** *Streptococcus faecails* grows on MacConkey's medium and other bile-salt lactose media to produce very small pink colonies. Normally no change occurs on a blood agar plate although a variant exists which causes a clear zone of haemolysis without producing a soluble haemolysin.

d) **True** The superficial dental plaques which form in the angle around the crown of the tooth just above the margin of the gum are inhabited by *Streptococcus mutans, mitis* and *faecalis*. When the mouth is not kept clean, this marginal plaque grows down into the gingival crevice and induces a change in the bacterial flora to one dominated by anaerobic Gram-negative cocci, bacilli, vibrios and spirochaetes. The toxins and enzymes produced by these various organisms accompanied by the immune response to their antigens damages the periodontal tissues causing the development of gingivitis and pyorrhoea.

e) **True** *Streptococcus faecalis* is an opportunistic pathogen. Unlike a true pathogen it can only produce a pathological lesion in the presence of a lowered tissue resistance or abnormal environmental conditions.

Q. Pseudomembranous enterolitis is caused by the following organisms:(FCPS–Sur–09Ja, BSMMU-MD-10Ja)

a) *Clostridium sporogenes*
b) *Clostridium difficile*
c) *Streptococcus faecalis*
d) Penicillin resistant staphylococci
e) *Pseudomonas aeruginosa*

Ans.

a) **False** *Clostridium sporogenes* is one of the causative organisms of gas gangrene. It plays no part in the development of enterocolitis.

b) **True** *Clostridium dificile* plays recently been identified as the causal agent of antibiotic associated colitis. The organism is resistant to both lincomycin and clindamycin and exerts its noxious effect through the production of cytopathic toxin. The organism is sensitive to vancomycin and metronidazole.

c) **False** *Streptococcus faecalis* plays no part in the development of pseudomembranous enterocolitis. This organism is an opportunistic pathogen and can only produce a pathological lesion when tissue resistance is lowered.

d) **True** Penicillin resistant sphylococci are believed to play a part in the development of one type of pseudomembranous enterocolitis. This type of enterocolitis as particularly common in the past, when broad spectrum antibiotics were over prolonged periods in an attempt to reduce post-operative wound infection.

e) **False** *Pseudomonas aeruginosa* plays no part in the development of pseudomembranous enterocolitis. This organism is of considerable importance, however in burns when the burnt surface tends to be colonised by this organism producing the characteristic greenish pus.

Q. The major pathogens in post operative chest infections are:

a) *Haemophilus influenzae*
b) *Streptococcus pyogenes*
c) *Mycobacterium tuberculosis*
d) *Staphylococcus aureus*
e) *Streptococcus pnemoniae*

Ans.

A) **True** This organism is one of the most important pathogens concerned in the development of post operative chest infections particularly in patients in whom pulmonary collapse occurs. This organism is sensitive to the cephalosporin group of antibiotics.

b) **False** This organism plays no part in the development of postoperative pulmonary infection. It is, however, an important pathogen causing acute tonsillitis, impetigo, wound infections, otitis media, scarlet and rheumatic fever.

c) **False** *Mycobacterium tuberculosis*, although a cause of severe chronic pulmonary infection, plays no part in the development of post operative chest infection.

d) **True** *Staphylococcus aureus* may be of importance in post operative chest infections but only in the presence of a staphylococcal septicaemia. Typically it causes multiple small abscesses to develop within the lungs.

e) **True** *Streptococcus pnumoniae* is the chief pathogenic invader of the lungs, normally producing lobar pneumonia. Since post operative pulmonary infection is normally limited to areas involved in collapse the classical picture does not develop. It should also be noted that the majority of pathogenic bacteria chlamydia, rickettsia, viruses and fungi are potential causes of post operative chest infection although all are uncommon.

Q. General factors predisposing to wound infection include:

a) uncontrolled diabetes
b) hypogammagiobulinaemia
c) low platelet count
d) agranulocytopenia
e) eosinophilia

Ans.

a) **True** The defective carbohydrate metabolism of diabetes results in a diminished supply of energy for the polymorphonuclear leucocytes. thus diminishng their phagocytic potential.

b) **True** Because all antibodies are gammaglobulins it follows that hypogammaglobulinaemia is associated with a failure of antibody formation and hence a reduction of one of the important factors concerned in resistance to infection.

c) **True** This statement is true only because severe thrombocytopenia predisposes to the development of a wound haematoma, a common precursor of wound inlection.

d) **True** In agranulocytosis the polymorphonuclear leucocytes suddenly disappear from the blood. Since these cells are a major factor in the defence against pathogenic micro-organisms, agranulocytosis leads to a greatly increased susceptibility to infection which may be rapidly fatal. In about one third of all cases no cause can be found and in the remainder the chief causes include a number of drugs including phenylbutazone, PAS, phenothiazines and thouracil.

e) **False** Although the eosinophil leucocyte does migrate into inflamed areas they play little part in the body's defences against bacterial infection. They are more conspicuous in hypersensitivity reactions and infestation with various kinds of worms.

Q. The following bacteria are commonly found in infected wounds following colonic operations:

a) *Escherichia coli*
b) *Neisseria meningitidis*
c) *Streptococcus pyogenes*
d) *Streptococcus faecalis*
e) *Bacteroides fragilis*

Ans.

a) **True** *Escherichia coli* belongs to a group of bacteria known as the Enterobacteriaceae, many members of which are responsible for wound infections. Other than *E. coli* these include *Klebsiella aerogenes* and *Proteus mirabilis*.

b) **False** *Neisseria meningitidis* is a coccal organism, normally a commensal in the nasopharynx which plays no part in wound infection but is, of course, the causal organism of acute meningococcal meningitis.

c) **True** A microaerophilic streptococcus may be involved in wound infection following colonic operations. If combined with other organisms such as *Proteus mirabilis* or *Staphylococcus aureus* a progressive synergistic gangrene may develop often referred to as Melaney's synergistic gangrene. This type of gangrene is particularly common in obese patients, black necrotic sloughs developing on the abdominal wall.

d) **True** *Streptococcus faecalis* is a commensal of the large intestine and may be involved in any wound infection following colonic surgery.

e) **True** The part played by *Bacteroides fragilis* has only recently been appreciated since it was common clinical practice to culture all wound swabs taken from infected wounds under aerobic conditions. Since *Bact. fragilis* is a strict anaerobe its presence in wound infections was, therefore, unrecognised.

Q. The incidence of postoperative infection can be reduced by the use of the following measures:

a) the use of negative pressure ventilation in the operating theatre
b) the use of filtered air in the operating theatre, pore size 10 μm
c) showering by the surgeon and all attendants prior to embarking upon the operation
d) the administration of prophylactic antibiotics
e) disinfection of the patient's skin prior to operation

Ans.

a) **False** The most commonly used system of theatre ventilation is a positive pressure (plenum) system. Although there are various methods by which this can be achieved the downward displacement method is the most popular. In this type of system filtered air is introduced into the theatre from ports in the ceiling and air is extracted from floor level.

b) **False** This is too large. The most commonly used filters have pores of approximately 5 μm in diameter. Pores smaller than this are unnecessary since the organisms are never solitary but are usually to be found on dust particles. One problem encountered with a smaller pore size is the difficulty of maintaining the filters which rapidly become blocked.

c) **False** Showering is not a practice which is to be recommended since it removes the oil from the surface skin to which organisms normally adhere. The result is that any movement by the surgeon or attendants will be attended by a shower of organisms.

d) **True** Prophylactic antibiotics have been shown to be effective in reducing the incidence of post operative wound infection in a variety of potentially infective conditions such as acute appendicitis, acute

cholecystitis and colonic operations. At the present time, clindamycin or metronidazole are being used with increasing frequency.

e) **True** Disinfection of the patient's skin prior to surgery is regarded as an essential pre-requisite of aseptic surgery. This may be carried out by a variety of materials. At present the iodophors or chlorhexidine are commonly used for this purpose.

Q. Renal tract infection is caused by a variety of bacteria including:

a) *Streptococcus pyogenes*
b) *Klebsiella pneumoniae*
c) *Streptococcus faecalis*
d) *Staphylococcus aureus*
e) *Escherichia coli*

Ans.

a) **False** This organism is associated with the development of progressive glomerulonephrits. In this latter situation fluorescent microscopy reveals a granular deposition of IgG and complement in the walls of the glomerular capillaries.

b) **True** Otherwise known as *Freidlander's bacillus* this organism is most commonly found in mixed infections and in the presence of structural deformities of the urinary tract.

c) **True** This organism is a particularly common offender in women, in whom it may be introduced into the renal tract by catheterization causing both cystitis and pyelonephritis.

d) **True** Both *Staphylococcus albus* (Coag -ve) and *Staphylococcus aureus* (Coag +ve) can cause pyelonephritis, the former more commonly than the latter. The Coagulase +ve organism is only occasionally found in structurally abnormal urinary tracts.

e) **True** This organism is the commonest cause of acute and chronic urinary tract infection.

Q. Staphylococci pathogenic to man:

a) produce a capsular polysaccharide
b) grow in irregular clusters in culture
c) produce coagulase
d) are resistant to penicillin
d) all produce an enterotoxin

Ans.

a) **False** Capsular polysaccharide is associated with the pathogenic forms of pneumococci. The presence of a capsule produces the smooth variant, loss of the capsule an avirulent rough form.

b) **True** The growth of the staphylococci is irregular thus producing irregular clusters.

c) **True** The ability to produce coagulase, an enzyme which clots citrated plasma in vitro, differentiates the pathogenic forms of staphylococci from the nonpathogenic.

d) **False** Pathogenic staphylococci are not necessarily resistant to penicillin although most strains associated with epidemic and endemic disease in hospitals in fact are resistant. Resistance to this, or any other antibiotics, affects the treatment of an infection but not the initial pathogenicity of the organisms.

e) **False** Only some strains of staphylococci produce an enterotoxin. Food containing such organisms acts as a culture medium and when ingested the toxin gives rise to giddiness, vomiting and diarrhea. This is often severe but recovery usually occurs within a day or two.

Q. The common pathogenic pyogenic organisms affecting man include:

a) *Staphylococcus aureus*
b) *Clostridium tetani*
c) *Staphylococcus albus*
d) bacteroides
e) *Pseudomonas aeruginosa*

Ans.

a) **True** The pathogenic varieties of this Gram-positive organism are particularly associated with:
(a) The development of localized infections such as boils, carbuncles and abscesses.
(b) Spreading infections of the skin such as impetigo.
(c) Septicaemia followed by the formation of pyogenic abscesses, osteomyelitis or endocarditis.

b) **False** *Clostridium tetani* is not a pyogenic organism. It causes its pathogenic effects by an exotoxin which diffuses up the peripheral or cranial motor nerves to reach the spinal cord or brain where it interferes with the normal inhibitory control of the lower motor neurons by the higher centres.

c) **False** *Staphylococcus albus* is a commensal and rarely pathogenic; it is extremely common on the skin.

d) **True** Bacteroides which are nonsporing anaerobic organisms are the commonest organisms present in the intestines. The are frequently associated in pyogenic infections with other organisms such as the anaerobic cocci. They are a particularly important cause of pus formation in surgical wounds following colo-rectal surgery and with intra-abdominal septic complications. Sometimes carried in the blood, they may cause brain abscesses and septicaemia.

e) **True** Normally present in small numbers in the gastro-intestinal tract these organisms can cause severe infections in burn patients. The pus produced possesses a characteristic greenish colour. These organisms are also responsible for some urinary tract infections and may invade the blood stream to produce a septicaemia.

DIARRHOEA

■ **Common causes of diarrhoea:**

A. ***Non invasive/*** Acute watery diarrhoea (lasting for hours or days)	
1. Bacterial	• V. cholerae* • Enterotoxigenic E. coli* • Enteropathogenic E. coli* • Enterotoxin of staph. aureus • Enterotoxin of bacillus cereus • Enterotoxin of C. perfringens type A
2. Viral	• Rota virus* • Norwalk virus • Entero virus
B. ***Invasive*** *(visible blood in stool i.e. dysentery)*	
1. Bacterial	• Shigella species • Enterohemorrhagic E. coli • Entero-invasive E. coli • Salmonella typhi • Vibrio parahaemolyticus • Escherichia enterocolitica. • Campylobater • Clostridium defficilli
2. Parasitic	• E. histolytica. • Giardia intestinalis • Cryptosporidium.
C. **Persistent diarrhoea** *(lasts for 14 days or more)*	
All above organism esp.	• Entero adhesive E. coil • Shigella • Cryptosporidium

Q. Microorganisms that cause bloody diarrhea are *(BSMMU –Residency – **MD, MS, Basic Science** – March' 18)*

a) *Shigella dysenteriae*
b) enterotoxigenic *Escherichia coli*
c) enterohemorrhagic *Escherichia coli*
d) *Giardia lamblia*
e) Rota virus

Ans. a) T b)F c) T d) F e) F

Q. Bacteria causing invasive diarrhoea includes *(BSMMU – Non-Residency – **MD, MS, Basic science – July' 16)***

a) Enterotoxigenic Escherichia coli F
b) Shigella dysenteriae T
c) Campylobacter jejuni T
d) Vibrio cholerae F
e) Yersinia enteroclitica T

Q. Organisms cause bloody diarrhea are *(BSMMU – Residency – **MD, Basic science** – March' 16)*

a) *Campylobacter spp.* T
b) *Bacillus spp.* F
c) *Clostridium difficile* T
d) *Giardia spp.* F
e) non typhoid salmonella T

HELP LINK:

Causes of bloody diarrhea	
Infections	**Non-Infectious**
• Camphylobacter spp.	• Diverticular disease
• Shigella dysentery	• Rectal or colonic malignancy
• Non-typhoidal salmonella	• Inflammatory bowel disease
• Entero-invasive E. coli (EIEC)	• Bleeding haemorrhoids
• Enterohaemorrhagic E coli (EHEC or VTEC)	• Anal fissure
• Clostridium difficile	• Ischaemic colitis
• Vibrio parahaemolyticus	• Intussusception
• Entamoeba histolytica (amoebic dysentery)	

Q. Causes of secretory diarrhea include *(BSMMU –Residency - **MD** – March' 14)*

a) cholera
b) lactase deficiency
c) shigellosis
d) vasoactive intestinal polypeptide induced
e) hyperthyroidism

Ans. a) T b) F c) F d) T e) F

Q. Bloody diarrhoea occur in the following diseases: *(BSMMU – Residency – MD – March'13)*

a) Ulcerative colitis
b) Tropical sprue
c) Crohn's disease
d) Coeliac disease
e) Irritable bowel syndrome

Ans : a) T b) F c) T d) F e) F

Q. Following are the causative agents of invasive diarrhoea: *(BSMMU – M. Phil, Diploma (Non-Residency)– March-2012, DMC & others – MD/MS – March-2012)*

a) Giardia lamblia F
b) Salmonella enteritidis T
c) Entamoeba histolytica T
d) Rota virus F
e) Vibrio cholerae F

Q. Micro-organisms causing non-inflammatory diarrhea *(BSMMU – MD/MS (Residency) – January, 2011)*

a) enteropathogenic Escherichia Coli
b) shigella
c) Entamoeba histolytica
d) Vibrio cholerae
e) rota virus

Ans.

a) **True** (Attachment, enterocyte effacement, no invasion)
b) **False** (Invasion, translocation, lymphoid inflammation, dissemenation)
c) **False** (Causes inflammation & tissue necrosis)
d) **True** (Enterotoxin mediated, no invasion)
e) **True**

Q. Causes of bloody diarrhoea include: (BSMMU – MD - January, 2009)

a) Campylobacter spp. T
b) Bacillus. cereus F
c) Clostridium difficile T
d) Non-typhoidal salmonellae T
e) Rotavirus F

Q. Bloody diarrhea is caused by - (MD/MS (DMC)-09Ja)

a. *Campylobacter jejuni* T
b. *Staphylococcal aureus* F
c. *Salmonella typhi* T
d. *Giardia lamblia* F
e. *Brucella abortus* F

Q. Non-inflammatory diarrhea is caused by: (BSMMU – MD-January, 2008)

a) entero-pathogenic Escherichia Coli T
b) shigella F
c) Entamoeba histolytica F
d) Vibrio cholerae T
e) rota virus T

Q. Following organisms may produce diarrhea - (BSMMU - M. Phil, Diploma, July-06)

a) Staphylococcus aureus
b) Bacillus cereus
c) Proteus species
d) Acinetobacter
e) Salmonella typhi

Ans.

a) **True** (*S. aureus* produce enterotoxin which causes food poisoning characterized by prominent vomiting and watery, nonbloody diarrhea.)

b) **True** (*B. cereus* causes 'chinese restaurant syndrome' which is characterized by rapid onset of vomiting with hours of food consumption. Fried rice or freshly made vanilla sauces are frequent sources. The organism grows and produces enterotoxin during storage; 1-4 hours after ingestion, brisk vomiting and some diarrhoea occur, with rapid resolution within 24 hours.)

c) **False** (This organism primarily causes urinary tract infections both community and hospital acquired.)

d) **False** (Acinetobacter species are gram negative coccobacillary rods found commonly in soil and water, but they can be part of the normal flora sepsis, pneumonia and urinary tract infections are the most frequent menifestations.)

e) **True** (Salmonella typhi may cause both diarrhoea and constipation. Diarrhoea is more common in children. Severe diarrhoea has been described in HIV patients with typhoid)

Q. The following viruses are associated with gastroenteritis - (BSMMU - M. Phil, Diploma, July-06)

a) Astroviruses T
b) Norwalk-like viruses T
c) Calcivirus T
d) Adenoviruses T
e) Parvovirus F

HELP LINK:

■ Astroviruses cause watery diarrhoea, especially in children. Most adults have antibodies against astroviruses, suggesting that infection occurs commonly.

■ Norwalk virus is one of the most common causes of viral gastroenteritis in adults worldwide. It is named for an outbreak of gastro-enteritis in a school ink Norwalk, Ohio, in 1969.

■ There are two human pathogens in the calcivirus family: Norwalk virus and hepatitis E virus.

■ Adenoviruses cause a variety of upper and lower respiratory tract diseases such as pharyngitis, conjunctivitis, common cold and pneumonia. Keratoconjucntivits, hemorrhagic cystitis, and gastro-enteritis also occur.

■ Parvovirus B19 is associated with four main clinical presentations:

1. Erythema infectiosum
2. Aplastic anaemia
3. Fetal infections
4. Arthritis
5. Chronic B19 infection.

Q. Causes of bloody diarrhea: (MD/MS (DMC)-05Ja)

a) Campylobacter spp. T
b) Bacillus cereus F
c) Clostridium perfringens F
d) Diverticular diseases T
e) Clostreidium difficile T

Q. Biochemical changes in diarrhea: (MD/MS (DMC)-05Ja)

a) Hypokalaemia T
b) Respiratory acidosis F
c) Hypocalcaemic tetany T
d) Azotaemia T
e) Hypo or hypernatraemia T

Help link:

■ **Biochemical changes in diarrhea:**

1. Shock
2. Hypo or hypernatraemia
3. Hypolalaemia, hypocalcaemia (tetany)
4. Hypoglycaemia
5. Metabolic acidosis
6. Convulsion
7. ARF, HUS, Azotaemia

Q. Chronic diarrhoea is a recognized cause of: (MD/MS (DMC)-04Ja)

a) Sodium depletion T
b) Magnesium deficiency T
c) Water intoxication F
d) Potassium depletion T
e) Metabolic alkalosis F

Q. Common symptoms and signs of amoebic dysentery: (MD/MS (DMC)-02Ja)

A. Fever F
B. Passage of blood and mucous with stool T
C. Tenesmus. T
D. Dehydration. F
E. Oliguria. F

Q. Recognized complications of acute diarrhoea are: (BSMMU-MD/MS-00Ja)

A. Hyponatremia. T
B. Hypernatremia. F
C. Metabolic alkalosis. F
D. Acute renal failure. T
E. Hemolytic uremic syndrome. T

Transmitted Diseases

Organisms transmitted by blood

Q. Organism(s) transmitted by blood is (are) *(BSMMU –Residency - MD – March' 19)*
a) *Leishmania donovani*
b) *Wuchereria bancrofti*
c) *Plasmodium falciparum*
d) *Treponema pallidum*
e) *Mycobacterium avium intracellulare*
Ans. a) T b) T (microfilaria) c) T d) T e) F

Help link: Parasites are transmitted by blood:
- Plasmodium
- Babesia
- Toxoplasma
- Trypanosoma
- Leishmania

Microorganisms transmitted by blood -
- Virus:
  - Hepatits virus-
    - HAV, HBV, HCV,
  - HIV
  - Human parvo virus B 19
  - EBV, CMV, HHV-8, HTLV-1,2, Westnile virus
- Prions proteins
- Bacteria:
  - Treponema pallidum
  - Brucelllosis, Lyme disease(Borrelia burgdorferi), Yersinia enterocolitica, salmonella
  - Staphylococcus, pseudomonas, Serratia, Rickettsia, Coxiella burnettii,
- Parasites:
  - Malaria, Trypanosoma cruzi,
  - Toxoplasma gondii, Babesia microti,
  - Leishmania donovani

(Ref: Hoffbrand hematology)

Q. Organisms transmitted through blood transfusion are *(BSMMU – Non-Residency – MD, MS, Basic science, Dentistry – July' 15)*
a) Pseudomonas spp. T
b) *Salmonella typhi* T
c) *Trypanosoma cruzi* T
d) *Toxoplasma gondii* T
e) *Leishmania donovani* T

HELP LINK:
Microorganisms trasmitted by transmitted:
Virus:
✓ Hepatits virus- HAV, HBV, HCV, HIV, Human parvo virus B 19, EBV, CMV, HHV-8, HTLV-1,2, Westnile virus, Prions proteins
Bacteria:
✓ Treponema pallidum , Brucelllosis, Lyme disease(Borrelia burgdorferi), Yersinia enterocolitica, salmonella, Staphylococcus, pseudomona, Serratia, Rickettsia, Coxiella burnettii,
Parasites: Malaria, Trypanosoma cruzi, Toxoplasma gondii, Babesia microti, Leishmania donovani

(Ref: Hoffbrand hematology)Q. Diseases transmitted by blood include: (MD/MS (DMC)-04Ja)

a) Hepatitis A	T (Ref: LANGE Review-14th)
b) Malaria	T
c) Typhoid fever	F
d) Chaga's disease	T
e) Poliomyelitis	F

Airborne transmission

Q. Airborne transmission occurs in *(BSMMU –Residency – **MD, MS, Basic Science** – March' 18)*

a) aspergillosis
b) brucellosis
c) poliomyelitis
d) Pulmonary anthrax
e) meningococcal meningitis

Ans. a) T b) T c) F d) T e) T

Help Link:

Airborne transmission by:

Droplet nuclei-

- TB, Influenza, Chickenpox, Measles, Q fever

Dust borne: (Common in Hospital acquired infection)

- Coccidiodomycosis, Streptococcal and staphylococcal infection,
- Pneumonia, TB, Q fever, Psittacosis.

(Ref: Park-23rd, P- 98)

Others: Aspergillosis, Brucellosis, Inhalational antrax, Meningococcal infection

Vertical transmission of some important pathogens

Mode of transmission	Pathogen	Disease in fetus or neonate
Transplacental	*Treponema pallidum*	Congenital syphilis
	Listeria monocytogenes	Neonatal sepsis and meningitis
	Cytomegalovirus	Congenital abnormalities
	Parvovirus 819	Hydrops fetalis
	Toxoplasma gondli	Toxoplasmosis
Within birth canal/ at time of birth	*Streptococcus agalactiac (group B streptococcus)*	Neonatal sepsis and meningitis
	Escherichia coli	Neonatal sepsis and meningitis
	Chlamydia trachomatis	Conjunctivitis or pneumonia
	Neisseria gonorrhoeae	Conjunctivitis
	Herpes simplex type-2	Skin, CNS, or disseminated infection (sepsis)
	Hepatitis B virus	Hepatitis B
	Human immunodeficiency virus	Asymptomatic infection
	Candida albicans	Thrush
Breast milk	*Staphylococcus aureus*	Oral or skin infections
	Cytomegalovirus	Asymptomatic infection
	Human T-cell leukemia virus	Asymptomatic infection

(Ref: LANGE review-14th, P-34)

Q. Parasites that transmit through placenta are *(BSMMU –Residency - MD/MS, Basic science, Paediatrics, Dentistry – March' 19)*

a) Plasmodium falciparum
b) Toxoplasma gondii
c) Wuchereria bancrofti
d) Trypanosoma cruzi
e) Leishmania donovani

Ans. a) T b) T c) F d) T e) T

Help Link: Congenital infection / Placenta transmission: Toxoplasma, malaria, American trypanosomiasis, Kala-a-zar (rarely)

Q. Perinatal infection through breast feeding occurs with *(BSMMU – Non-Residency – MS, Basic science – July' 18)*

a) Cytomegalo virus
b) Human T cell lymphotropic virus
c) Hepatitis C virus
d) Parvovirus
e) HIV

Ans. a) T b) T c) F d) F e) T

Help link:

TABLE 32–2 Viruses That Commonly Cause Perinatal Infection

Type of Transmission	Virus
Transplacental[1]	Cytomegalovirus Parvovirus B19 virus Rubella virus
At time of birth[2]	Hepatitis B virus Hepatitis C virus Herpes simplex virus type 2 Human immunodeficiency virus[3] Human papillomavirus
Breast feeding	Cytomegalovirus Human T-cell lymphotropic virus

Also: HIV and Staphylococcus aureus

(Ref: LANGE-15th, P-34)

Q. Perinatal infections that occur through breast feeding are *(BSMMU –Residency – MD, MS, Basic Science – March' 18)*

a) cytomegalovirus
b) human T cell lymphotrophic virus
c) hepatitis C virus
d) paramyxovirus
e) Human Immunodeficiency Virus (HIV)

Ans. a) T b) T c) F d) F e) T

(Ref: LANGE-15th, P-34)

Q. Congenital infections caused by microorganisms are *(BSMMU – Residency - MD, MS, Basic Science, Dentistry - March' 17)*

a) *Streptococcus agalactiae*
b) *Cytomegalovirus*
c) *Treponema pallidum*
d) *Influenzae A virus*
e) *Toxoplasma gondii*

Ans. a) F b) T c) T d)F e)T

Help link:

Congenital infection (transmission from placenta to fetus): They often lead to defects in fetal development or even death.

Examples TORCH syndrome:

- ✓ Toxoplasmosis
- ✓ Other infections (congenital syphilis, hepatitis B, Coxsackievirus, Epstein-Barr virus, varicellazoster virus, Plasmodium falciparum and human parvovirus)
- ✓ Rubella
- ✓ Cytomegalovirus (CMV)
- ✓ Herpes simplex virus

(Ref: Apurbo sankar-6th, P-519)

Q. Viruses transmitted through breast milk are *(BSMMU – Residency - **MD, MS, Basic Science** - March' 17)*

a) CMV
b) Rubella
c) HCV
d) HTLV
e) Parvo virus B 19

Ans. a) T b)F c) F d)T e) F

Q. Organisms causing transplacental transmission are *(BSMMU–Residency– **MD, MS, Basic science** – March' 16)*

a) *Neisseria meningitides* F
b) *Treponema pollidum* T
c) Pollio virus F
d) *Listeria monocytogens* T
e) *Toxoplasma gondii* T

Help link:

Transplacental/ Vertical	At the time of birth	Breast milk
• Treponema pallidum	• Strept. agalacti	• Staph. Aureus
• Staphylococcal infection	• E. coli	• Human T cell leukaemia virus
• Pseudomonas infection.	• C. trachomatis	• CMV, HIV
• Listeria monocytogens	• N. gonorrhoea	
• Toxoplasma gondii	• HIV, HPV	
• Malaria	• HBV, HCV, HSV type-II	
• Rubella	• Candida albicans	
• Cytomegalovirus (CMV)		
• Epstein-Barr virus		
• Herpes simplex		
• HIV		
• Hepatitis B (rare)		
• Parvovirus B19		

Q. Viruses transmitted by the vertical route are *(BSMMU – Residency – **MD, MS, Basic science, Dentistry** – March' 16; M. Phil, Diploma (Non-Residency)–March-2012, DMC & others – MD/MS – March-2012)*

a) Influenzae A virus F
b) Rabies virus F
c) Cytomegalovirus T
d) Rotavirus F
e) Rubella virus T

(Ref: LANGE-15th, P-34)

Q. Oral route is the main portal of entry for following viruses *(BSMMU–Residency–MD, MS, Basic – March' 15)*
a) Japanese B enchephalitis virus
b) rubella virus
c) hepatitis A virus
d) hepatitis C virus
e) polio virus

Ans. a) F b) F c) T d) F e) T

Help link:

Portal of entry	virus
Respiratory tract	Influenza virus Respiratory syncytial virus Epstein-Barr virus Mumps,Measles,Rubella etc
Gastrointestinal tract (faeco-oral)	Hepatitis A virus Polio virus Rota virus
Skin	Rabies virus Dengue virus Human Papilloma virus
Genital tract	Human Papilloma virus Hepatitis B virus HIV Herpes simplex virus type 2
Blood	Hepatitis B Hepatitis C Hepatitis D HIV Cytomegalo virus
Transplacental	Cytomegalovirus Rubella

(Ref: LANGE-15th, P-34)

Q. Respiratory tract is the main portal of entry for the following viruses *(BSMMU –Non-Residency – MD/MS, Basic science – July' 14)*
a) corona virus
b) rubella virus
c) measles virus
d) papilloma virus
e) yellow fever virus

Ans. a) T b) T c) T d) F e) F **(Ref: LANGE-15th, P-34)**

Q. Congenital infection can be caused by the *(BSMMU –Residency - MD/MS, Basic science – March' 14)*
a) cytomegalovirus
b) treponema pallidum
c) toxoplasma gondii
d) streptococcus pneumonia
e) influenza A virus

Ans. a) T b) T c) T d) F e) F

Q. Congenital viral infection can occur by following viruses: *(BSMMU – M. Phil, Diploma (Non-Residency)–11Ju, DMC & others – MD/MS –11Ju)*

a) Cytomegalovirus T
b) Parvo virus T
c) Rota virus F
d) Rabies virus F
e) Rubella virus T

HELP LINK:

Congenital anomalies are associated with the infection with the following organisms:

- Toxoplasmosis.
- Syphilis
- Herpes simplex virus
- Varicella zoster virus
- Rubella virus
- HIV
- CMV

Q. Following viruses are able to initiate infections through skin abrasions *(BSMMU – MD/MS (Residency) – January, 2011)*

a) parvovirus F
b) papilloma virus T
c) herpes virus T
d) corona virus F
e) pox virus F

Q. Virus that commonly causes perinatal infections: *(BSMMU - M. Phil, Diploma – July '10)*

a) Parvovirus B19 virus T
b) Human papilloma virus T
c) Yellow fever virus F
d) Enterovirus F
e) Hepatitis B virus T

(Ref: LANGE-15th, P-34)

Q. Following viruses spread via blood stream associated with lymphocytes: *(BSMMU - M. Phil, Diploma – July '10)*

a) Epstein-barr virus T
b) Rubella virus T
c) Poliovirus F
d) Toga virus F
e) Cytomegalovirus T

Q. Following are the example of virus that enter through skin abrasion: *(BSMMU - M. Phil, Diploma – July '10)*

a) Papilloma virus T
b) Adenovirus F
c) Herpes virus T
d) Corona virus F
e) Parvo virus F

(Ref: LANGE-15th, P-34)

Q. Vertical transmission of infection may occur in - (DMC – MD/ MS - January, 2010)

a. Rubella virus T
b. Influenza A virus F
c. Rabies virus F
d. Cytomegalovirus T
e. Polio virus F

(Ref: LANGE-15th, P-34)

Q. Organisms can cross placenta are - (MD/MS (DMC)-09Ja)

a. Hepatitis B virus T
b. *Treponema pallidum* T
c. *Toxoplasma gondi* T
d. *Neisseria gonorrhoe* F
e. *Leishmania infantum* F

Q. Agents which can cause congenital anomaly in foetus are - (BSMMU – MD - 07Ja)

a. Toxoplasma T
b. CMV T
c. Rubella virus T
d. Dengue virus F
e. Adenovirus F

Q. The following viruses can pass through the placenta: (M. Phil, Diploma-06July)

a) HIV T
b) HBV T
c) Rubella virus T
d) cytomegalovirus T
e) hepatitis-C virus T

HELP LINK:

Transplacental transmission:

- Rubella
- Cytomegalovirus (CMV) infection
- HIV infection
- Hepatitis B
- Parvovirus B19
- Toxoplasmosis
- Syphilis
- Malaria
- *Listeria monocytogens*

Q. Transplacental infection of fetus are caused by- (BSMMU - M. Phil, Diploma, July-06)

a) Toxoplasmosis T
b) Listeriosis T
c) Measles F
d) Syphilis T
c) Herpes simplex type II T

Q. Vertical transmission occurs in: (DMC - M. Phil, Diploma, July-'05)

a) *Treponema pallidum* T
b) Hepatitis-B T
c) Tuberculosis F
d) Chicken pox virus F
e) Rubella virus T

Q. Mosquitoes transmit the following diseases- (BSMMU – MD - 06/02Ja, MD/MS (DMC)-02Ja)

A. schistosomiasis
B. leishmaniasis
C. dengue
D. yellow fever
E. malaria

Ans.

A. **False** (The mosquito plays no part in the life cycle of the schistosoma, the intermediate host of this parasite is a snail found in fresh water.)

B. **False** (Leishmaniasis is protozoal disease transmitted by the bite of the sandfly, Phiebotomus papatasi. The condition is endemic throught the Middle East, South Asia, Africa and Latin Ameica. The infective agent is slender, flagellated parasite which is introduced into the host together with the sandfly saliva. It is

then phagocytosed by the mononuclear cells and transformed into a round amastigote which divides in the phagolysosomes of the macrophages, rupturing the cells nd infecting others. The extent of the spread of the amastigotes is determined by the species of Leishmania. Thus the cutaneous form is caused by several varieties including L. major and braziliensis whereas visceral leishmaniasis is caused by L. donovani in the New world.)

C. **True** (Dengue fever is a severe but usually short lived febrile illness which is caused by a toga virus transmitted by the mosquito Aedes aegypti).

D. **True** (Yellow fever is also caused by a toga virus transmitted by Aedes aegypti. Both the virus of dengue fever and yellow fever belong to the group collectively known as arthropod borne virus, hence the generic name arbovirus.)

E. **True** (Malaria is protozoal disease transmitted by the female anopheles mosquito. The various protozoal species are Plasmodium vivax, falciparum, maiariae and ovale. The most severe form of malaria is caused by P1. Falciparum which causes both malaria and blackwater fever. The latter is so named because of the haemoglobinuria whiëh follows the severe intrvascular haemolysis.) **(Ref: Smiddy)**

HELP LINK:

Mosquitoes	Diseases transmitted
a. Female anopheles	Malaria, Filaria
b. Female culex	Bancorftian filariasis, Japanese encephalitis, West fever, Viral arthritis
c. Female aedes	Yellow fever, Dengue fever, Dengue haemorrhagic fever.
d. Mansonoides	Malayan filariasis.

Q. Following organisms cause water borne diseases: (MD/MS (DMC)-04Ja)

a) Salmonella typhi T
b) Brucella abortus F
c) Aeromonus hydrophilia T
d) Haemophylus influenzae F
e) Ankylostoma duodenalae F

HELP LINK:

■ **Water born diseases**:

1. ***Viruses***: HAV, HEV, poliomyelitis, Rota virus diarrhoea in infants.
2. ***Bacterial***: Typhoid & paratyphoid fever, cholera, Bacillary dysentery, E. coli diarrhoea.
3. ***Protozoal***: Amoebiasis, Giardiasis
4. ***Helminthic***: Hydatid disease, Roundworm, threadworm.
5. ***Leptospiral***: Weil's disease

Q. Virus which may affect the fetus in utero: (MD/MS (DMC)-04Ja)

a) rubella T
b) polio F
c) varicella T
d) herpes T
e) toxoplasma. T

HELP LINK:

Organisms which may affect the fetus in utero:

TORCH:

- Toxoplasma

- Rubella
- Cytomegalovirus
- Herpes simplex, HIV, HBV

Others:

- Varicella
- HIV
- Hepatitis B

N.B. N. gonorrhea causes perinatal infection like opthalmia neonatorum.

Q. Diseases usually spread via the faecal oral route include - (M. phil, Diploma (MD/MS (DMC)) – 03,July)

a) poliomyelitis	T
b) cholera	T
c) hepatitis-E (non—A, non—B hepatitis)	T
d) hepatitis-B	F
a) salmonellosis	T

Q. Transplacental transmitted diseases are: (MD/MS (DMC)-03Ja)

a) AIDS	T
b) Rubellla	T
c) Mumps	F
d) Malaria	T
e) Gonorrhoea	F

Q. Materno-fetal transmission may occur with - (BSMMU-MS-01Ja)

a) HIV	T
b) Herpes zoster virus	T
c) Hepatitis B virus	T
d) Adenovirus	F
e) Rubella virus	T

Q. The following organization are transmitted by transplacental route- (BSMMU-Sur-01Ja)

a) Hepatitis C virus	F
b) Treponema pallidum	T
c) Cytomegalo virus	T
d) Neisseria gonorrhoeae	F
e) Toxoplasma gondii	T

Q. Microorganism crossing placenta is (are): (BSMMU-MS-01Ja)

a. Treponema pellidum	T
b. Neisseria gonorrhoea	F
c. Hepatitis B virus	T
d. HIV	T
e. Cytomegalo virus	T

Transmission from animal to human

Bacteria	Viruses	Parasites
Bovine tuberculosis	Rabies	Leishmanaisis
Bubonic plague	JE	Babesiosis
Q fever	Monkey pox	Toxoplasmosis
Brucellosis	Yellow fever	Taeniasis
Bacillus anthrax	Cow pox	Hydatid disease
Salmonella food poisoning	Fungus	Trichinellosis
Leptospirosis	Microsporum canis	Schistosomiasis
	Trichophyton verrucosum	Trypanosomiasis

(Ref: Apurbo sankar-6th, P-529 + LANGE-15th, P-245)

Q. Viruses transmitted from animals to humans are *(BSMMU –Residency – **MD, MS, Basic Science, Dentistry** – March' 18)*
a) Rabies virus
b) Polioviruses
c) Hepres viruses
d) Hantaviruses
e) Nipah virus

Ans. a) T b) F c) F d) T e) T

HELP LINK:

Viruses are transmitted from animals to humans:

- Rabies virus
- Hantavirus
- Yellow fever virus
- Dengue virus
- Necephalitis viruses
- SARS corona virus
- Avian influenza virus (HSN)

Q. Viruses transmitted from animals to humans are *(BSMMU –Residency - **MS, Basic science** – March' 14)*

a)	rabies virus	T
b)	polioviruses	F
c)	CMV	F
d)	hanta viruses	T
e)	lassa fever virus	F

(Ref. LANGE-15th, P-245)

Q. The following viruses are transmitted from animals to humans: *(BSMMU - M. Phil, Diploma – July '10)*

a) Rabies virus	T
b) Polio viruses	F
c) Herpes virus	F
ci) Hantaviruses	T
e) Nipah virus	T

Help link: Bats are mammals

(Ref. LANGE-15th, P-245)

CLINICAL MICROBIOLOGY

Bacteremia

Q. Bacteremia is caused by *(BSMMU – Diploma - **Dentistry** – July' 18)*
a) Corynebacterium diphtheriae
b) Staphylococcus aureus
c) Pseudomonas
d) KJebsiella
e) Shigella flexneri

Ans. a) F b) T c) T d) T e) F (rarely causes septicaemia except in malnourised children)

Help link:

■ **Important Pathogens causing Bacteraemia**:

Gram (+ve) Bacteria	Gram (-ve) Bacteria
Staphylococcus aureus	Salmonella
Streptococcus pyogens	Brucella
Streptococcus viridans	Haemophilus influenzae
Streptococcus pneumoniae	Escherichia coli (22%)
Enterococci	Pseudomonas aeruginosa
Anaerobic streptococci	Proteus
Clostridium perfringens	Bacteroids
	Neisseria meningitides
	Yersinia pestis
	Klebsiella pneumoniae

Bacteria that rarely produce bacteremia

1. Corynebacterium
2. Clostridium
3. Shigella
4. Vibrio

(Ref: Davidson-23rd, P-227)

Blood culture

Q. Blood culture may be positive in the following conditions *(BSMMU –Residency – **MS, Basic Science, Dentistry** – March' 18)*
a) bacillary dysentery
b) memingococcal meningitis
c) primary syphilis
d) enteric fever
e) rheumatic fever

Ans. a) F b) T c) F d) T e) F

Help link:

Following are the microorganisms causing septicaemia and bacteraemia:

Bacteria:

- Echcrichia coli (22%)
- Streptococcits pnenmoniae (17%)
- Staphylococcus aureus (14%)
- Klebsiella sp. (7%)
- Proteous sp. (5%)
- Haemophylus influenzae (4%)
- Salmonella sp. (4%)
- Streptococcus pyogenes (4%)

- Pseudomonas aeruginosa (3%)
- Group B Streptococci (2%)
- Str. viridans (2%)
- Staph. epidermidis
- Enterococci
- Enterobacter aerogenes
- Citrobacter sp..
- Helicobacter sp.
- Bacterbides sp.
- Fusobacterium sp.
- Anaerobic cocci-peptococci and peptostreptococci
- Neisseria meningitidis
- Legionella sp.
- Brucella sp.
- Bacillus sp.
- Rickettsia sp.
- coxiella sp.
- Leptospira sp.
- Borrelia sp.
- Yersinia sp.
- Streptococcus group C and G

Fungi:

- Candida albicans
- Crypiococcus neoformans
- Mucorsp.
- Aspergillus sp.
- Histoplasma capsulatum
- Coccidioides immitis
- Blastomyces dermatitidis

Indication of blood culture;FAN method-(Factors Antibiotic Neutralizing method)

1. Enteric fever , Brucellosis , Pneumonia, Meningitis
2. Osteomyelitis , Plague , Puerperal sepsis , PUO
3. Infective endocarditis , Bacterimia , Septicemia
4. Pyemia , Pyelonephritis , Cholangitis , Peritonitis

Q. Following are common contaminants in blood culture *(BSMMU – MD/MS (Residency) – January, 2011)*

a) Coagulase negative Staphylococcus F
b) Bacillus subtilis T
c) Candida albicans T
d) S. aureus T
e) Pseudomonas spp. T

Q. Blood culture is usually positive in case of: (BSMMU – MD/MS - January, 2008)

a) Listeria monocytogens infection T
b) rheumatic fever F
c) brucellosis T
d) leptospirosis T
e) pneumonia T

HELP LINK:

■ **Indications of blood culture**:

1. Enteric fever
2. Infective endocarditis
3. Meningitis
4. PUO (Pyrexia of unknown origin)
5. Bacteraemia
6. Septicaemia
7. Pyaemia
8. Pneumonia
9. Brucellosis
10. Pyelonephritis
11. Osteomyelitis
12. Plague
13. Cholangitis
14. Peritonitis
15. Abscess

Q. Blood cultures are usually positive in cases of: (BSMMU-Sur-01Ja)

a) Meningococcal meninigitis T
b) Bacillary dysentery F
c) Primary syphilis F
d) Typhoid fever T
e) Rheumatic fever F

Urine Exam.

Q. Pyuria with a negative urine culture found in infection caused by *(BSMMU – Residency - MD, MS, Basic Science - March' 17)*

a) *Neisseria gonorrhoeae*
b) *Staphylococcus saprophyticus*
c) *Chlamydia trachomatis*
d) *Ureaplasma urealyticum*
e) *Pseudomonas aeruginosa*

Ans. a) T b) F c) T (fastidious) d) T e)F

Help Link:

Sterile pyuria:

✓is urine which contains white blood cells while appearing sterile by standard culturing techniques.
✓It is often caused by sexually transmitted infections, such as gonorrhea, or viruses which will not grow in bacterial cultures.
✓ also associated with certain disease processes, such as Kawasaki disease and genitourinary tuberculosis.

Q. Pyuria without significant bacteruria are present in *(BSMMU –Residency – MD, MS, Basic Science – March' 15)*

a) renal tuberculosis
b) early urinary tract infection
c) leptospirosis
d) patient under antibiotic treatment
e) diabetes mellitus

Ans. a) T b) F c) F d) T e) F

Help link:

The causes of sterile pyuria include:

- a treated urinary tract infection (UTI) within 2 weeks of treatment/ inadequately treated (UTI)

- UTI with fastidious culture requirement
- renal stones
- prostatitis
- chlamydia urethritis
- renal papillary necrosis (e.g. from analgesic excess)
- tubulo-interstitial nephritis
- genitourinary tuberculosis (always consider - do 3 early morning urines)
- interstitial cystitis
- urinary tract neoplasm
- polycystic kidney

Q. Specific gravity of urine more accurate with: *(BSMMU-MS-10Ja)*

a) reagent strip
b) refractometer
c) urinometer
d) colorimeter
e) fallen drop

Ans. a) T b) T c) T d) F e) F

Help link:

Specific gravity of urine:

- Also called relative mass density
- **Normal**: 1.003- 1.030, depends on state of hydration
- In normal urine it depends on urea and sodium
- **Importance:**
  - measure of conc. ability of kidney
  - to get about idea about tubular function
  - Is affected by proteinuria and glycosuria
- **Increased in:** DM, Nephrotic syn. Fever dehydration
- **Decreased in:** Diabetes insipidus, CRF, Compulsive water drinking
- **Methods:**
  - Urinometer method,
  - refractometer,
  - reagent strip method

(Ref: Clinical pathology of Kawthalkar; P-06)

Q. Causes of sterile pyuria include- (BSMMU – MS - January, 2007)

a) Tuberculosis T
b) Anaerobic infection F
c) Pseudomonus infection F
d) Chlamydia infection T
e) Proteus infection F

Stool Examination

Q. Stool R/E with plenty of pus cells, RBC and macrophages are suggestive of *(BSMMU –Residency - MD/MS, Basic science – March' 14)*

a) amoebic dysentery F
b) allergic gastroenteritis F
c) cholera F
d) bacillary dysentery T
e) viral gastroenteritis F

Help link:

Traits	Amoebic dysentery	Bacillary dysentery
Macroscopic		
1.Number	6-8 motions a day	Over 10 motions a day
2.Amount	Relatively copious	Small
3.Odour	Offensive	Odorless
4.Colour	Dark red	Bright red
5.Nature	Blood & mucus with faeces	Blood and mucus: no faeces
6.Reaction	Acidic	Alkaline
7.Consistency	Not adherent to container	Adherent to the bottom of the container
Microscopic		
1.RBC	In clumps: reddish-yellowish in color	Discrete or in rouleax: bright red in color.
2.Pus cells	Scantly	Numerous
3.Macrophages	Very few	Large and numerous; many of them contain RBC
4.Eosinophils	Present	Scare
5.Pyknotic bodies	Very common	Nil
6.Ghost cells	Nil	Numerous
7.Parasite	Trophozoites of E. histolytica	Nil
8.Bacteria	Nil	Many motile bacteria
9.C.L. crystals	Present	Nil

Allergic gastroenteritis: Eosinophilic features
Viral gastroenteritis:
Causative virus: Rotavirus, Norovirus
Clinical features:

- watery diarrhea
- nausea and vomiting
- headache, muscle aches, joint aches
- fever, chills
- sweating, clammu skin
- abdominal cramps and pain
- loss of appetite
- weight loss

Q. Stool OBT method more sensitive with: *(BSMMU-MS-10Ja)*

a) benzidine T
b) guiac T
c) immunological T
d) orthotoluidine T
e) hemo-porphyrene F

Help Link:
Test for occult blood in stool
Methods:

- Peroxidase like activity of Hb
  - Benzidine, orthotolidine, aminophenazone, guaiac
- Immunochemical test
- Radioisotope tests

(Clinical pathology, Kawthalkar, P-117)

Meningitis

Q. Bacteria causing meningitis are: (BSMMU – MS - January, 2008)

a) N. gonorrhoeae F
b) Streptococcus pneumoniae T
c) E. coli T *(It causes neonatal meningitis)*
d) H. influenzae T
e) Chlamydia F

Help link:

■ **Causes of meningitis:**

26.76 Bacterial causes of meningitis

Age of onset	Common	Less common
Neonate	Gram-negative bacilli (*Escherichia coli, Proteus*) Group B streptococci	*Listeria monocytogenes*
Pre-school child	*Haemophilus influenzae* *Neisseria meningitidis* *Streptococcus pneumoniae*	*Mycobacterium tuberculosis*
Older child and adult	*Neisseria meningitidis* *Streptococcus pneumoniae*	*Listeria monocytogenes* *Mycobacterium tuberculosis* *Staphylococcus aureus* (skull fracture) *Haemophilus influenzae*

26.75 Causes of meningitis

Infective

Bacteria (see Box 26.76)

Viruses
- Enteroviruses (echo, Coxsackie, polio)
- Mumps
- Influenza
- Herpes simplex
- Varicella zoster
- Epstein–Barr
- HIV
- Lymphocytic choriomeningitis
- Mollaret's meningitis (herpes simplex virus type 2)

Protozoa and parasites
- Cysticerci
- Amoeba

Fungi
- *Cryptococcus neoformans*
- *Candida*
- *Histoplasma*
- *Blastomyces*
- *Coccidioides*
- *Sporothrix*

Non-infective ('sterile')

Malignant disease
- Breast cancer
- Bronchial cancer
- Leukaemia
- Lymphoma

Inflammatory disease (may be recurrent)
- Sarcoidosis
- SLE
- Behçet's disease

(Ref: Davidson-23rd)

Q. CSF findings in tuberculous meningitis are: (BSMMU – MS - January, 2008)

a) moderate number of polymorphs F
b) cloudy appearance T
c) raised protein T
d) tubercular fibrin clot formation F
e) raised glucose F

HELP LINK:

■ **Typical CSF changes in meningitis:**

26.5 How to interpret CSF results

	Normal	Subarachnoid haemorrhage	Acute bacterial meningitis	Viral meningitis	Tuberculous meningitis	Multiple sclerosis
Pressure	50–250 mm of water	Increased	Normal/ increased	Normal	Normal/increased	Normal
Colour	Clear	Blood-stained Xanthochromic	Cloudy	Clear	Clear/cloudy	Clear
Red cell count ($\times 10^6$/L)	0–4	Raised	Normal	Normal	Normal	Normal
White cell count ($\times 10^6$/L)	0–4	Normal/slightly raised	1000–5000 polymorphs	10–2000 lymphocytes	50–5000 lymphocytes	0–50 lymphocytes
Glucose	> 50–60% of blood level	Normal	Decreased	Normal	Decreased	Normal
Protein	< 0.45 g/L	Increased	Increased	Normal/ increased	Increased	Normal/ increased
Microbiology	Sterile	Sterile	Organisms on Gram stain and/or culture	Sterile/virus detected	Ziehl–Nielson/auramine stain or tuberculosis culture positive	Sterile
Oligoclonal bands	Negative	Negative	Can be positive	Can be positive	Can be positive	Often positive

Sexually Transmitted Infections (STI)

Sexually transmitted infections (STIs) are a group of contagious conditions whose principal mode of transmission is by intimate sexual activity involving the moist mucous membranes of the penis, vulva, vagina, cervix, anus, rectum, mouth and pharynx, along with their adjacent skin surfaces.

(Ref: Davidson-23rd)

Table 8-3 Classification of Important Sexually Transmitted Diseases

Pathogens	Disease or Syndrome and Population Principally Affected		
	Males	Females	Both
Viruses			
Herpes simplex virus			Primary and recurrent herpes, neonatal herpes
Hepatitis B virus			Hepatitis
Human papillomavirus	Cancer of penis (some cases)	Cervical dysplasia and cancer, vulvar cancer	Condyloma acuminatum
Human immunodeficiency virus			Acquired immunodeficiency syndrome
Chlamydiae			
Chlamydia trachomatis	Urethritis, epididymitis, proctitis	Urethral syndrome, cervicitis, bartholinitis, salpingitis and sequelae	Lymphogranuloma venereum
Mycoplasmas			
Ureaplasma urealyticum	Urethritis		
Bacteria			
Neisseria gonorrhoeae	Epididymitis, prostatitis, urethral stricture	Cervicitis, endometritis, bartholinitis, salpingitis, and sequelae (infertility, ectopic pregnancy, recurrent salpingitis)	Urethritis, proctitis, pharyngitis, disseminated gonococcal infection
Treponema pallidum			Syphilis
Haemophilus ducreyi			Chancroid
Klebsiella granulomatis			Granuloma inguinale (donovanosis)
Protozoa			
Trichomonas vaginalis	Urethritis, balanitis	Vaginitis	

Following are the STDS:

1. **Bacterial**:
- Gonorrhoea *(N. gonorrhoea)*
- Syphilis *(T. pallidum)*
- Chancroid *(H. ducreyi)*
- Lymphogranuloma venereum *(Chlamydia trachomatis)*
- Granuloma inguinale *(Calymmatobacterium granulomatis)*

2. **Viral**:
    - AIDS *(HIV)*
    - Hepatitis B, C.
    - Genital herpes *(Herpes simplex)*
    - Genital warts, anal warts *(HPV)*
    - Genital moluscum contagiosum *(Moluscum contagiosum)*

3. **Fungal**: • Candidiasis (moniliasis) – by *C. albicans*

4. **Protozoal**:
    - Trichomoniasis *(T. vaginalis)* • Giardiasis *(G. lamblia)*

5. **Ectoporarasite**:
   - Scabis *(Sarcoptes scabei)*
   - Peticulosis pubis. *(Pthysis pubis)*

■ **Veneral diseases**: Veneral diseases are those sexually transmitted diseases that must be transmitted sexually namely-

1. Gonorrhoea
2. Syphilis
3. Chancroid
4. Granuloma inguinale
5. Lymphogranuloma venereum.

Q. Women having multiple sex partners are more prone to develop: *(BSMMU – M. Phil, Diploma (Non-Residency)– March-2012, DMC & others – **MD** – March-2012)*
a) cervical cancer
b) acquired immune deficiency syndrome
c) endometrial carcinoma
d) breast cancer
e) autoimmune haemolytic anenmia
Ans. a) T b) T c) F d) F e) F

HELP LINK:

Sexually transmitted disease: Clinical features and diagnosis:

Agent	Clinical features	Diagnosis
Chlamydia trachomatis	Cervical ectopy and friability. Mucoid cervical discharge with leukocyte count. Dysuria (in men may not be accompanied by discharge) Pelvic tenderness in women. Pharyngitis, rectal irritation/ tenderness.	Chlamydia inclusion bodies identified though cell culture or rapid test such as fluorosent antibody staining or spectrometric evaluation.
Neisseria gonorrhoeae	Similar clinical features as with Chlamydial infection. Infection in men more likely to include purulent urethral discharge.	Positive culture for gonorrhea. Gram-negative diplococci in male urethral discharge.
Human immunodeficiency virus (HIV)	Different from adult presentation: lower male to female ratio. More prevalent in black/ Hispanic urban youth. Higher percentage of heterosexual transmission.	Specific blood assay for HIV virus.
Mycoplasma (ureaplasm)	Similar characteristics to chalmydial infection.	Culture (non-gonococcal urethritis)
Treponema pallidum, (syphilis)	Stage of disease: Primary (10-14 days): chancre, regional lymphadenopathy. Secondary (2-6 months): generalized malaise, lymphadenopathy, and skin changes/ alopecia. Late (2-10 years): central nervous system changes, cardiovascular changes, and musculoskeletal involvement.	Dark field examination or direct fluorescent antibody tests of lesion Serologic tests: Nontreponemal Treponemal
Haemophilus ducreyi, (chancroid),	Painful genital ulcer. Tender inguinal lymphadenopathy	Culture Clinical picture
Herpes simplex virus (HSV)	Vesicles/ ulcers on external genitalia, in vagina, on cervix, and around rectal area. Tender inguinal lymphadenopathy. Dysuria Dyspareunia	Viral culture Tzanck test
Condyloma acuminatum Molluscum contagiosum	Single or group of painless warts Small papule with umbilical centres	Clinical appearance Potassium hydroxide smear of contents. Biopsy
Trichomonas vaginalis	Presence of flagellate protozoan. Malodorous yellow-green vaginal discharge.	Microscopic identification of organism.

Phthirus pubis (pediculosis pubis, crab lice)	Pruritus in pubic hair. Tan egg cases in pubic hair.	Crab lice or egg cases in pubic hair.

Q. Lympho granuloma venerium is caused by : (MD/MS (DMC)-05Ja)

a) Cytomegalovirus F
b) Toxoplasma gondii F
c) Human papilloma virus F
d) Chlamydia tracomatis T
e) Herpes simplex virus F

HELP LINK:

Lymphogranuloma venereum.

Causative organism: *Chlamydia trachomatis* types L1, 2, 3

Incubation period: 3-30 days

Clinical features:

1. **Genital lesion**: Small, transient, painless ulcer, vesicle, papule; often unnoticed
2. **Lymph nodes**: Tender, usually unilateral, matted, adherent, multilocular, suppurative bubo; inguinal/femoral nodes involved; there may be late sequelae

Investigation: Serological tests for L1-3 serotypes; swab from ulcer or bubo pus for *Chlamydia*

Treatment: Doxycycline 12-hourly orally for 21 days *or* Erythromycin 500 mg 6-hourly orally

■ **Chlamydia tracomatis causes**:

1. Trachoma
2. Inclusion conjunctivitis
3. LGV
4. Non-gonococcal urethritis
5. Cervicitis
6. Salpingitis
7. RTI

Q. Causative organisms of sexually transmitted diseases (STD) are : (MD/MS (DMC)-02Ja)

A. Treponema pallidum T
B. Neisseria gonorrhoeae T
C. Chlamydia trachomatis T
D. Hemophilus ducreyi T
E. Mycobacterium tuberculosis F

HELP LINK: see before

Chancroid

■ **Causative organism**: *Haemophilus ducreyi*

■ **Incubation period**: 3 - 10 days

■ **Clinical Features**:

1. **Genital lesion** - single or multiple painful ulcers with ragged undermined edges.
2. **Lymph nodes** - tender, usually unilateral, matted, adherent, uniocular, suppurative bubo; inguinal nodes involved in about 50%.

■ **Investigation**: Microscopy & culture of scrapings from ulcer or pus from bubo.

■ **Treatment**:

Azithromycin 1 gm orally once *Or,*
Ceftriaxone 250 mg IM once *Or,*
Ciprofloxacin 500 mg 12 hourly orally for 3 days *Or,*
Erythromycin 500 mg 6 hourly for 7 days

(Ref: Davidson-23rd)

Difference between primary syphillis and chancroid:

Traits	Primary syphilis (chancre)	Chancroid
1. Causative agent	*Treponema pallidum*	*Haemophylus ducreyi*
2. Pain in ulcer	Painless	Painful
3. Edge of ulcer	Punched out	Ragged, undermined
4. Draining lymph nodes	Painless	Painful
5. Response to penicillin	Penicillin is the drug of choice	Not the drug of choice

Q. Sexually transmitted diseases are caused by- (BSMMU – MD/MS - 02Ja)

a) Hepatitis C virus T
b) Epstein Burr virus F
c) Human papilloma virus T
d) Hepatitis B virus T
e) Cytomegato virus T

GENITAL ULCER

Q. Causes of genital ulcer include *(BSMMU – Non-Residency – MD – July' 17)*

a) *Treponema pallidum*
b) *Neisseria gonnorhoea*
c) *Trichomonus vaginalis*
d) *Hemophilus ducreyi*
e) Behcet's disease

Ans. a) T b) F c) F d) T e) T

Help link:

■ **Causes of Genital ulcer:**

Associated with infection
• Primary syphilis (chancre)
• Secondary syphilis
• Gumma
• Herpes simplex virus
• Varicella zoster virus
• Erosive balanitis
• Chancroid
• Lymphogranuloma venereum
• Granuloma inguinale
• Scabies
Others
• Circinate balanitis (Reiter's syndrome)
• Steven-Johnson syndrome
• Behcet's syndrome
• Erythroplasia of Queyrat (Intraepidermal carcinoma)
• Squamous cell carcinoma

(Ref: Davidson-21st, P-413)

Q. Ulcerative lesions of the genitelia are caused by *(BSMMU –Residency – MD, MS, Basic Science – March' 15)*

a) *Neisseria gonorrhoeae*
b) *Haemophilus ducreyi*
c) *Treponema pallidum*
d) HIV
e) *Chalymmatobacterium granulomatis*

Ans. a) F b) T c) T d) F e) T

Help Link:

Table 7.1.9: Comparison of STDs producing genital ulcer

Feature	Syphilis	Herpes	Chancroid	LGV	Donovanosis
Incubation period	9–90 days	2–7 days	1–14 days	3 days–6 weeks	1–4 weeks (up to 6 months)
Genital ulcer	Painless, indurated, single	Multiple, painful	Painful, soft Single or multiple	Painful, soft	Painless
Lymphadenopathy	Painless, hard, moderate swelling (no bubo)	Absence or moderate swelling (no bubo)	Painful, soft, marked swelling leads to *bubo formation*	Painless	Absent (*pseudo bubo* may be present due to subcutaneous swelling)

Q. Microbes responsible for genital ulcerative lession include *(BSMMU –Residency - MD/MS, Basic science – March' 14)*

a) trichomonas vaginalis
b) H. ducreyi
c) herpes simplex virus type-2
d) treponema pallidum
e) chlamydia trachomatis

Ans. a) F b) T c) T d) T e) T

Q. Causes of genital ulcers include: *(BSMMU – M. Phil, Diploma – 11Ju, DMC & others – MD – 11Ju)*

a) syphilis T
b) gonorrhoea F
c) chancroid T
d) granuloma inguinale T
e) Trichomoniasis F

Q. Painful genital ulcers are due to : (MD/MS (DMC)-05Ja)

a) Lymphogranuloma venereum F
b) Syphilis F
c) Herpes simplex T
d) Chancroid T
e) Bachet's disease T

Help link:

■ **Painful genital ulcers:**

Common	Uncommon
1. Herpes simplex	1. 2ndary syphilis
2. Erosive balanitis	2. Scabies
3. Trauma with 2ndary infection	3. Reiter's disease
4. Chancroid	4. Stevens Johnson syndrome
	5. Bechet's disease

Q. Chancres is the feature of following diseases: (MD/MS (DMC)-03Ja)

a) Toxocariasis F
b) Syphilis T
c) Typhus T
d) Anthrax T
e) Schistosomiasis F

HELP LINK:

Causes of chancre:
1. Syphilis
2. Typhus
3. Anthrax
4. Trypanosomiasis
5. Rat bite fever

Q. Ulceration of the vulva occur in the following conditions: (MD/MS (DMC)-03Ja)

a) Gonorrhoea F
b) Chancroid T
c) Syphilis T
d) Candidiasis F
e) Bechet's syndrome. T

HELP LINK:

Behcet's syndrome is classically characterized as a triad of symptoms that include recurring crops of mouth ulcers (aphthous ulcers), genital ulcers, and inflammation of a specialized area around the pupil of the eye (the uvea). The inflammation of the area of the eye that is around the pupil is called uveitis. Behcet's syndrome is also sometimes referred to as Behcet's disease.

SYPHILIS

Syphilis

Syphilis is caused by infection, through abrasions in the skin or mucous membranes, with the spirochaete Treponema pallidum. In adults the infection is usually sexually acquired; however, transmission by kissing, blood transfusion and percutaneous injury has been reported. Transplacental infection of the fetus can occur.

The natural history of untreated syphilis is variable. Infection may remain latent throughout, or clinical features may develop at any time.

Causative agent: *Treponema pallidum.*

■ **Classification of syphilis**:

Stage	Acquired	Congenital
Early	• Primary • Secondary • Latent	Clinical & latent
Late	• Latent • Benign tertiary • Cardiovascular • Neurosyphilis	• Clinical & latent

(Ref: Davidson-23rd, P-337)

Natural course of untreated syphilis:

Exposure
↓ Incubation period (9-90 days)
Primary lesion (Chancre)
↓ within 2-6 weeks
Heal
↓ after 6-8 weeks of chancre
Secondary syphilis
↓
Heal
↓
Early latent

↓

Late latent (33%)

↓

Tertiary syphilis

(Ref: Davidson-23rd, P-337)

■ **Sources**: Serum, saliva, blood, cervical & vaginal secretion, lesion of skin & mucus mem.

■ **Transmission**:

1. Sexual intercourse
2. Indirect sexual contact (kissing, unusual sexual act)
3. Blood transfusion or injection
4. Transplacental.

In short

■ **Primary**: Hard chancere

■ **Secondary C/F**:

1. Condylomata lata
2. Patchy alopecia
3. Maculopapular/ scaly/ popular rash on palm & sole.
4. Low grade fever, malaise, anorexia, wt. Loss, headache, myalgia, generalized lymphadenopathy.

Uncommon:

1. CNS- meningitis
2. Eye- ant. & post. Uveitis
3. Visceral lesion- hypotrophis gastritis, nephritis, hepatitis, proctitis
4. Bone – arthritis, periostitis

■ **Tertiary**:

1. Neurosyphilis- meningovascular, tabes dorsalis, general paresis
2. Aortitis- Aneurism, aortic regurgitation
3. Gummas- Hepar labotum, skin, bones, others.

Primary Syphilis

■ **Features of acquired primary syphilis**:

History: H/O exposure usually 14-28 days back with a range of 9-90 days. (incubation period)

Clinical feature:

- The **primary lesion (chancre)**: develops at the site of infection, usually in the genitalia. A dull red macule develops, becomes papular & then erodes to form an indurated ulcer (chancre).
- The draining inguinal lymph nodes: moderately enlarged, mobile, discrete, rubbery.
- The chancre and the lymph nodes are both painless & non-tender, unless there is concurrent or secondary infection. (Without treatment, the chancre will resolve within 2-6 weeks to leave a thin atrophic scar.)
- Chancres may develop on the vaginal wall and on the cervix.
- Extra-genital chancres are found in about 10% of patients, affecting sites such as finger, lip, tongue, tonsil, nipple, anus or rectum. Anal chancres often resemble fissures and may be painful.

(Ref: Davidson-23rd, P-337)

Investigations:

a. ***M/E***: Tissue fluid expressed from chancre and then

- Dark ground illumination test.
- Immunoflurescent test.

b. ***Serology***:

i. Non-specific/Lipoidal Ag test:

- VDRL test
- RPR test

ii. Specific:

- TPHA (Treponema pallidum haemagglutination test)
- FTA-abs (Flurescent treponemal antigen absorbent test)
- ELISA (Treponemal enzyme linked immune sorbent assay)
- CFT.

■ **Treatment**:

1. Procain benzylpenicillin G – 6 lack unit IM daily for 10 days *(17 days if neurological involvement)*

or,

Benzathine penicillin G – 2.4 milion unit IM once a week for 2 wks.

2. ***In case of penicillin allergy***:

Doxycycline – 100 mg orally 12 hourly for 14 days

Or,

Erythromycin 500 mg orally 6 hourly for 14 days

3. All pts must be follow up to ensure cure, partner notification.

Question Bank

Q. Following are the features of primary chancre in syphilis *(BSMMU – Residency - **Basic science** – March' 14)*

a) very painful
b) indurated on palpation
c) bleeds on touch
d) coronal sulcus is the common site
e) associated with painful unilateral inguinal lymphadenopathy

Ans. a) F b) T c) F d) T (prepuce or corona) e) F

(Ref. P. chakraborti-3rd, P-440)

Q. Primary syphilis has the following characteristics: *(BSMMU– MD/MS – January, 2010)*

a) spirochaete. may be demonstrated in chancre. T
b) spirochaete is limited to the primary site T
c) forms multiple indolent ulcers F
d) dark ground microscopic examination is positive T
e) initial lesion appears 10 to 60 days after contact. T

Q. Primary syphilis has the following characteristics: (BSMMU - M. Phil, Diploma, July-07, MD/MS-07Ja)

a) spirochaete may be demonstrated in chancre T
b) spirochaete is limited to the primary site T
c) multiple indulent ulcers F
d) dark ground examination is positive T
e) initial lesion appear 10 to 60 days after contact T

Q. Primary chancre is manifested by- (BSMMU – MD/MS - 03Ja)

a) Kissing lesions T
b) Painless ulcer T
c) Bleeding easily to touch F
d) Firm induration T
e) Incubation period 3 to 10 days F

Secondary syphilis

■ **Clinical features**:

1. This occurs 6-8 weeks after the development of the chancre when treponemes disseminate to produce multisystem disease.
2. **Constitutional features** such as mild fever, malaise and headache are common.
3. **Maculopapular rash:** Over 75% of patients present with a rash on the trunk and limbs that may later involve the palms and soles; this is initially macular but evolves to maculo-papular or papular forms, which are generalised.symmetrical and non-irritable. Scales may form on the papules later. Without treatment, the rash may last for up to 12 weeks.
4. **Condylomata lata** (papules coalescing to plaques) may develop in warm, moist sites such as vulva or perianal area.
5. **Generalised non-tender lymphadenopathy** is present over 50% cases. Nodes are moderately enlarged, mobile, discrete, rubbery, painless & non-tender. Epi-trochlear lymph node- surest sign.
6. **Mucosal lesions**, known as mucous patches, may affect the genitalia, mouth, pharynx or larynx and are essentially modified papules, which become eroded. Rarely, confluence produces characteristics '**Snail track ulcer**' in the mouth.
7. **Other features**: meningitis, cranial nerve palsies, anterior or posterior uveitis, hepatitis, gastritis, glomerulonephritis, periostitis.

(Ref: Davidson-23rd, P-338)

The differential diagnosis of secondary syphilis can be extensive, but in the context of a suspected STI, primary HIV infection is the most important alternative condition to consider.

The clinical manifestations of secondary syphilis will resolve 2-3 weeks without treatment but relapse may occur, usually within the first year of infection. Thereafter, the disease enters the phase of latency.

Question Bank

Q. Features of secondary syphilis include: *(BSMMU – Residency – MD – March'13)*

a) Generalized lymphadenopathy
b) Aortitis
c) Snail track ulcers
d) Interstitial keratitis
e) Condylomata lata

Ans : a) T b) F c) T d) F e) T

Q. Characteristic features of secondary syphilis are- (BSMMU – MD - January, 2008)

a) Itchy rash	F
b) severe prostration	F
c) painless lymphadenopathy	T
d) mucosal erosions	T
e) interstitial keratitis	F

Q. Features of secondary syphilis- (BSMMU - M. Phil, Diploma, July-06)

a. Condyloma acunimata	F
b. Oral mucous patch	T
c. Weakly positive VDRL	F
d. Lichenoid papules	F
e. Patchy hyperpigmentation	T

Q. Skin lesions in secondary syphilis include: (MD/MS (DMC)-05Ja)

a) Patchy alopecia	T
b) Condylomata acuminate	F
c) Hypopigmented anaesthetic lesion	F
d) Erythroderma	T
e) Scaling rash on soles	T

Q. Skin eruption in secondary syphilis is characteristically: (BSMMU – MD/MS – 00Ja)

A. Pleomorphic T
B. Symmetrical T
C. Generalized T
D. Vesicular F
E. Itchy F

Latent syphilis

Latent syphilis: No lesion, only serological evidence

This phase is characterised by the presence of positive syphilis serology or the diagnostic cerebrospinal fluid (CSF) abnormalities of neurosyphilis in an untreated patient with no evidence of clinical disease. It is divided into early latency (within 2 years of infection), when syphilis may be transmitted sexually, and late latency, when the patient is no longer sexually infectious. Transmission of syphilis from a pregnant woman to her fetus, and rarely by blood transfusion, is possible for several years following infection.

Late syphilis

Late latent syphilis

This may persist for many years or for life. Without treatment over 60% of patients might be expected to suffer little or no ill health. Coincidental prescription of antibiotics for other illnesses such as respiratory tract or skin infections may treat latent syphilis serendipitously.

Benign tertiary syphilis

- This may develop between 3 and 10 years after infection but is now rarely seen in the UK.
- Skin, mucous membranes, bone, muscle or viscera can be involved. The characteristic feature is a chronic granulomatous lesion called a **gumma**, which may be single or multiple. Healing with scar formation may impair the function of the structure affected. Skin lesions may take the form of nodules or ulcers whilst subcutaneous lesions may ulcerate with a gummy discharge. Healing occurs slowly with the formation of characteristic tissue paper scars. Mucosal lesions may occur in the mouth, pharynx, larynx or nasal septum, appearing as punched-out ulcers. Of particular importance is gummatous involvement of the tongue, healing of which may lead to leucoplakia with the attendant risk of malignant change. Gummas of the tibia, skull, clavicle and sternum have been described, as has involvement of the brain, spinal cord, liver, testis and, rarely, other organs. Resolution of active disease should follow treatment, though some tissue damage may be permanent. Paroxysmal cold haemoglobinuria may be seen.

Cardiovascular syphilis

This may present many years after initial infection. Aortitis which may involve the aortic valve and/or the coronary ostia is the key feature. Clinical features include **aortic incompetence, angina and aortic aneurysm**. The condition typically affects the ascending aorta and sometimes the aortic arch; aneurysm of the descending aorta is rare. Treatment with penicillin will not correct anatomical damage and surgical intervention may be required.

Neurosyphilis

This may also take years to develop. Asymptomatic infection is associated with CSF abnormalities in the absence of clinical signs. **Meningovascular disease, tabes dorsalis or general paralysis of the insane** characterises the symptomatic forms. Neurosyphilis and cardiovascular syphilis may coexist and are sometimes referred to as quaternary syphilis.

Q. Asymptomatic neuro-syphilis is associated with the following: *(BSMMU – M. Phil, Diploma (Non-Residency)–March-2012, DMC & others – MD/MS – March-2012)*

a) the absence of clinical manifestation T
b) positive CSF VDRL T
c) normal CSF cell count F
d) negative treponemal serologic tests F
e) positive treponemal serologic tests T

HELP LINK:
INVESTIGATIONS IN ADULT CASES

• **T. pallidum** may be identified in serum collected from chancres, or from moist or eroded lesions in secondary syphilis using a dark-field microscope, a direct fluorescent antibody test or PCR.

• The serological tests for syphilis are listed. Many centres use treponemal enzyme immunoassays (EIAs) for IgG and IgM antibodies to screen for syphilis. EIA for anti-treponemal IgM becomes positive at approximately 2 weeks, whilst non-treponemal tests become positive about 4 weeks after primary syphilis. All positive results in asymptomatic patients must be confirmed by repeat tests.

• Biological false positive reactions occur occasionally; these are most commonly seen with Venereal Diseases Research Laboratory (VDRL) or rapid plasma reagin (RPR) tests (when treponemal tests will be negative). Acute false positive reactions may be associated with infections such as infectious mononucleosis, chickenpox and malaria, and may also occur in pregnancy. Chronic false positive reactions may be associated with autoimmune diseases. False negative results for non-treponemal tests may be found in secondary syphilis because extremely high antibody levels can prevent the formation of the antibody- antigen lattice necessary for the visualisation of the flocculation reaction (the prozone phenomenon).

• In benign tertiary and cardiovascular syphilis, examination of CSF should be considered because asymptomatic neurological disease may coexist. The CSF should also be examined in patients with clinical signs of neurosyphilis and in both early and late congenital syphilis. Chest X-ray, ECG and echocardiogram are useful in the investigation of cardiovascular syphilis. Biopsy may be required to diagnose gumma.

• Endemic treponematoses such as yaws, endemic (non-venereal) syphilis (bejel) and pinta are caused by treponemes morphologically indistinguishable from T. pallidum that cannot be differentiated by serological tests. A VDRL or RPR test may help to elucidate the correct diagnosis because adults with late yaws usually have low titres.

CONGENITAL SYPHILIS

Congenital syphilis is rare where antenatal serological screening is practised. Antisyphilitic treatment in pregnancy treats the fetus, if infected, as well as the mother.

Treponemal infection may give rise to a variety of outcomes after 4 months of gestation when the fetus becomes immunocompetent:

1. Miscarriage or still birth, premature or at term
2. Birth of a syphilitic baby (a very sick baby with hepatosplenomegaly, bullous rash and perhaps pneumonia)
3. Birth of a baby who develops signs of early congenital syphilis during the first few weeks of life.
4. Birth of a baby with latent infection who either remains well or develops congenital syphilis/stigmata later in life.

(Ref: Davidson-23rd, P-338)

■ **Clinical features:**

Early congenital syphilis (neonatal period)
• Maculo-papular rash • Condyloma lata • Mucous patches • Fissures around moth, nose & anus • Rhinitis with nasal discharge (snuffles) • Hepatosplenomegaly • Osteochondritis/ periostitis • Generalized lymphadenopathy • Choroiditis • Meningitis • Anaemia/ thrombocytopenia
Late congenital syphilis
• Benign tertian syphilis • Periostitis • Paroxysmal cold haemoglobinuria • Neurosyphilis

• 8th nerve deafness
• Interstitial keratitis
• Clutton's joints *(painless effusion into knee joint)*
Stigmata
• Hutchison's incisors *(anterior-posterior thivkening with notch or narrowed cutting edge)*
• Mulberry molars *(imperfectly formed cusps/ deficient dental enamel)*
• High arched palate
• Maxillary hypoplasia
• Saddle nose *(following snuffles)*
• Rhagades *(radiating scars around mouth, nose & anus following rash)*
• Salt and pepper scars on retina *(from choroiditis)*
• Corneal scars *(from interstitial keratitis)*
• Sabre tibia *(from periostitis)*
• Bossing of frontal & parietal bones *(healed periosteal nodes)*

(Ref: Davidson-23rd)

■ **Treatment**:

A. ***Early congenital syphilis***:

Benzylpenicillin – 50,000 U/ kg IV 12 hourly for the first 7 days of life then 50,000 U/ kg IV 8 hourly for 3 days

Or,

Procaine Benzylpenicillin G – 50,000 U/ kg IM daily for 10 days

B. ***Late congenital syphilis***:

- Dose depends on weight & age of child.
- Adult regimen for age 15.

(Ref: Davidson-[illegible])

INVESTIGATIONS IN ADULT CASES

Q. Specific antibody tests for syphilis are *(BSMMU – Non-Residency – MD – July' 17)*

a) TPHA
b) TPPA
c) FTA-ABS
d) VDRL
e) RPR

Ans. a) T b)T c) T d) F e) F

Help link:

T pallidum may be identified in serum collected from chancres, or from moist or eroded lesions in secondary syphilis using a dark-field microscope, a direct fluorescent antibody test or PCR.

The serological tests for syphilis are listed in Box. Many centres use treponemal enzyme immunoassays (EIAs) for IgG and 1gM antibodies to screen tbr syphilis. EIA for antitreponemal 1gM becomes positive at approximately 2 weeks, whilst non-treponemal tests become positive about 4 weeks after primary syphilis. All positive results in asymptomatic patients must be confirmed by repeat tests.

SEROLOGICAL TESTS FOR SYPHILIS
Non-treponemal (non-specific) tests
• Venereal Diseases Research Laboratory (VDRL) test
• Rapid plasma reagirt (RPR) test
Treponemal (specific) antibody tests
• Treponemal antigen-based enzyme immunoassay (El/f) for IgG and IgM
• T pallidum haemagglutination assay (TPHA)
• T pallidum particle agglutination assay (TPPA)
• Fluorescent treponemal antibody-absorbed (FTA-ABS) Test

Biological false positive reactions occur occasionally; these are most commonly seen with Venereal Diseases Research Laboratory (VDRL) or rapid plasma reagin (RPR) tests (when treponemal tests will be negative). Acute false positive reactions may be associated with infections such as infectious mononucleosis, chickenpox and malaria, and may also occur in pregnancy. Chronic false positive reactions may be associated with autoimmune diseases. False negative results for non-treponemal tests may be found in secondary syphilis because extremely high antibody levels can prevent the formation of the antibody—antigen lattice necessary for the visualisation of the flocculation reaction (the prozone phenomenon).

In benign tertiary and cardiovascular syphilis, examination of CSF should be considered because asymptomatic neurological disease may coexist. The CSF should also be examined in patients with clinical signs of neurosyphilis and in both early and late congenital syphilis. Chest X-ray. ECG and echocardiogram are useful in the investigation of cardiovascular syphilis. Biopsy may be required to diagnose gumma.

Endemic treponematoses such as yaws, endemic (non-venereal) syphilis (bejel) and pinta are caused by treponemes morphologically indistinguishable from T pallidum that cannot be differentiated by serological tests. A VDRL or RPR test may help to elucidate the correct diagnosis because adults with late yaws usually have low titres.

Q. Tests used for the diagnosis of syphilis are *(BSMMU – Residency - **Dentistry** - March' 17)*
a) RPR test
b) RA test
c) CRP test
d) TPHA test
e) VDRL test
Ans. a) T b) F c) F d) T e)T

Treponema pallidum

Q. Treponema pallidum - (BSMMU - M. Phil, Diploma, July-07)

A. Is bacteria	T
B. Is parasite	F
C. Is resistant to penicilline	F
D. Grows in tissue culture	F
F. Can produce latent infection	T

HELP LINK:

■ **Morphology of Spirochetes**:

1. Thin walled, flexible, spiral rods.
2. Long (4-30 mm), motile with axial filaments (other bacteria are motile with flagella).
3. Very thin, visible oniy by dark ground microscopy, silver impregnation technique, or immunofluorescence.
4. Pathogenic strains cannot be cultured.
5. Do not take Gram's stain. Borreliae are large, accept Giemsa & other blood stain and can be seen under light microscope.

(Ref: LANGE Review-14th)

■ **Special properties/ Morphology of T. pallidum**:

1. Slender, filamentous (6-14 micro meter x 0.2)
2. Culture: not possible in artificial media.
3. Actively motile.
4. As it is very thin cannot be seen by light microscopy.
   -Seen by 'Dark field microscopy'
   -Gram staining not possible.
   - Stained by silver impregnation

Q. The following statements regarding syphilis is correct (M. phil, Diploma (DMC) – 03Ju)

a) VDRL test is a specific test F
b) TPHA is a nonspecific test F
c) VDRL test has prognostic Value and the test result may become negative 6-24 months after effective treatment. T
d) Treponema pallidum can be cultured in Mac Conkey's agar media F
e) the causative agent is N. gonorrhoea F

HELP LINK:
Mac Conkey's agar media for culture of enterobacteriaceae

VDRL test

■ **VDRL test**: This is the non-neoplastic test which is used to diagnose syphilis. Here non-specific Ab is detected by cardiolipin Ag. Cardiolipin is extracted from beaf heart & the 'C' particle is coated to cadiolipin. These Ag is then mixed with the pt's serum. The test is reactive when the agglutination occurs. Such reactive test is done by serial dilution of serum to detect the titre of reagin Ab.

■ **Advantage**:
1. The outcome of treatment can only be assessed by VDRL test. After successful treatment of syphilis, the titre of VDRL test will fall down & will become non-reactive over a period of time. To become non-reactive, VDRL test takes about 6 - 18 months.
2. The test can be used as screening test.
3. The test is comperatively cheaper than TPHA.

■ **Disadvantage**: Some false positive & false negative results may be found in VDRL test.
1. ***False positive***:
   - Pregnancy
   - Viral hepatitis/ Hepatitis B virus infection
   - Autoimmune disease, Collagen diseases(rheumatoid arthritis, SLE,PAN)/ Antiphospholipid antibody/Lupus anticoagulant
   - Tropical pulmonary eosinophilia
   - Leprosy
   - Infectious mononucleosis/ glandular fever
   - Relapsing fever/Lyme disease
   - Kala- azar, Malaria
   - Measles, Mumps, Chicken pox
   - Small pox vaccination
   - Tuberculosis
   - Mycoplasma pneumoniae/ Atypical pneumonia
   - IV drug abusers
   - Following vaccination
   - HIV
2. ***False negative***: Late & tertiary syphilis. (due to prozone phenomenon from using undilated serum)

Q. VDRL may be false positive in *(BSMMU –Residency - MD – March' 19)*

a) anti-phospholipid antibody syndrome
b) tuberculoid leprosy
c) measles
d) Henoch-Schönlein purpura
e) tuberculosis

Ans. a) T b) F (lepromatous leprosy) c) T d) F e) T

Q. VDRL test may be reactive in *(BSMMU –Residency - **MD/MS, Basic science, Paediatrics, Dentistry** – March' 19)*
a) syphilis
b) systemic lupus erythromatosus
c) chancroid
d) yaws
e) lepromatous leprosy
Ans. a) T b) T c) F d) T e) T

Help link:
Yaws is a tropical infection of the skin, bones and joints caused by the spirochetebacterium Treponema pallidum pertenue

Q. False positive VDRL test may occur in *(BSMMU –Residency – **Dentistry** – March' 18)*
a) amebiasis
b) tuberculosis
c) malaria
d) leprosy
e) measles
Ans. a) F b) T c) T d) T (lepromatous leprosy) e) T

Q. False positive reaction of VDRL is found in *(BSMMU – Residency - **MD** - March' 17)*
a) leprosy
b) gonorrhea
c) systemic lupus erythematosus
d) granuloma inguinale
e) pregnancy
Ans. a)T b) F c)T d) F e)T

Q. VDRL test may be reactive in *(BSMMU – Non-Residency – **MD, MS, Basic science, Dentistry** – July' 15)*

a) syphilis	T
b) systemic lupus erythematosus	T
c) chancroid	F
d) yaws	T
e) lepromatous leprosy	T

Q. VDRL test may be reactive in *(BSMMU – Non-Residency - **MD** – 13Ju)*

a) secondary syphilis	T
b) chancroid	F
c) tinea nigra	F
d) systemic lupus erythematosus	T
e) lepromatous leprosy	T

Q. VDRL test may be reactive in the following diseases: (BSMMU – MD-January, 2009)

a) Syphilis	T
b) Systemic lupus erythematosus	T
c) Chancroid	F
d) Yaws	F
e) Lepromatous leprosy	T

Q. VDRL is reactive in the following diseases: (BSMMU - M. Phil, Diploma, July-08)

a) syphilis	T
b) gonorrhea	F
c) collagen diseases	T
d) lymphoganuloma venorum	F
e) urinary tract infection	F

Q. Biological false positive reaction of VDRL is found in - (BSMMU – MD/MS - 07Ja)

a) Leprosy T
b) Gonorrhoea F
c) Disseminated lupus erythematosus T
d) Granuloma inguinale F
e) Pregnancy T

Q. Biological false positive reactions of VDRL occurs in following conditions- (BSMMU – MD - 03/02Ja)

a) Leprosy T
b) Gonorrhea F
c) DLE T
d) Haemolytic F
e) Thyroiditis F

Q. Biological falls positive reactions of VDRL occur in-(BSMMU-Med/Sur-01Ja)

a) Leprosy T
b) Typhoid F
c) Atypical pneumonia T
d) Yellow fever F
e) Malaria T

Human Immunodeficiency Virus (HIV)

HIV means human immunodeficiency virus which is a single stranded, enveloped RNA virus ausing AIDS.

■ **Diseases caused by HIV**:

1. Acquired immuno-deficiency syndrome (AIDS)
2. AIDS related complex (ARC).

■ **Properties of HIV**:

1. Single stranded, enveloped RNA virus.
2. Member of retrovirus family.
3. Contains reverse transcriptase enzyme.
4. Not oncogenic.
5. Several important surface antigens:
   - Glycoprotein-120: initiates viral infection by binding to host CD 4+ molecules.
   - Glycoprotein-41

■ **Viruses which cause AIDS**:

1. Human immuno deficiency virus type - 1
2. Human immuno deficiency virus type – 2

■ **Incubation period**: 6 months - 6 years or more.

■ **Differences between HIV-1 & HIV-2**:

Features	HIV - 1	HIV - 2
1. Distribution	More common in America & Europe	West Africa
2. Incubation period	Short	Long
3. Infection	Highly infectious	Less
4. Predominate opportunistic infection	Pneumocystic pneumonia	Cryptosporidiosis Persistent diarrhoea
5. Tumor	Kaposi's sarcoma is more common	Not common

■HIV-1 is of 2 types:
1. M type- in Bangladesh.
2. O type

■**Important antigens of HIV**:
1. Envelop Ag:
   - gp-120
   - gp-41
   - Enzyme antigen: P 53
2. Nucleocapsid core protein:
   - P-24
   - P-17

■**Important genes of HIV**:
1. **Envelope gene**: The envelope gene encodes gp-160, a precursor glycoprotein that is cleaved to form 2 envelope (surface) glycoproteins- gp 120 & gp 41.
2. **Pol gene**: The gene encodes- reverse transcriptase, integrase & protease.
3. **Gag gene**: The gene encodes the internal core protein- P24.
4. **Tat gene**: The tat gene encodes

i. A protein that enhances viral & cellular gene transcription.
ii. The tat gene also reduces the synthesis of class I MHC proteins, thereby reducing the ability of cytotoxic T cells to kill HIV infected cells.

■**Interaction between HIV & CD4+ T-cell/ Viral replication**:
Binding of the virus GP-120 (envelope protein) to the CD4 receptor on the T cell surface
↓
The virus gp-41 protein then mediates fusion of the viral envelope with the cell membrane
↓
The virion enters the cell
↓
Uncoating
↓
Transcription of viral RNA into double stranded DNA by RNA dependent DNA polymerase (reverse transcriptase) ↓
This viral DNA integrates with host cell DNA by integrase
↓
Transcription of viral mRNA from pro-viral DNA by RNA polymerase
↓
Translation of mRNA into several large polypeptide/proteins
↓
This large proteins are then cleaved by the virus-encoded protease to form the viral proteins, such as reverse transcriptase, the core proteins & envelope gps.
↓
Assembling in the cytoplasm
↓
They are released from the cell by budding.

Name the human cells infected by HIV:
1. CD4 + T cells (Helper T cells)
2. Certain monocytes & macrophages which contain CD4 molecules on their surface. CD4 acts as a high affinity receptor for gp-120 molecule of HIV.

Question Bank

Q. HIV infection is associated with *(BSMMU – Non-Residency - MD – July' 19)*
a) reduction in the number of B cells
b) hypergammaglobulinemia
c) increased tuberculin skin test reactivity
d) cytokine abnormalities
e) Autoimmunity

Ans. a) F b) T c) F (MT is false negative) d) T e) F

(Ref: P. Chakroborti-3rd, P-640)

Help link:
Major immunological abnormality in HIV infection

- Lymphopenia:
  - In HIV CD4:CD8 ratio reversed(Normal CD4:CD8; 2:1
- Decreased T cell function:
  - Decreased delayed type hypersensitivity on skin test
  - Susceptibility to opportunistic infection
  - Susceptibility to neoplasm
- Altered T cell function:
  - Decreased IL-2, TNF gamma production
  - Decreased specific cytotoxic response by T cell and NK cells
- Polyclonal B cell activation:
  - Hypergammaglobulinaemia
- Altered functions of monocytes and macrophage:
  - Decreased chemotaxis and phagocytosis
  - Diminished class II antigen expression
  - Diminished capacity of antigen presentation to T cells
  - Increased spontaneous secretion of IL-1, IL-6, TNF

(Ref: P. Chakroborti-3rd, P-640)

Q. During the period of clinical latency in HIV infection *(BSMMU –Residency – MD, MS, Basic Science – March' 18)*
a) virus is not detectable in the blood
b) neutralizing antibodies are not elicited
c) CD4 cell counts remain unchanged
d) virus is present in lymphoid organs
e) virus can be transmitted to others

Ans. a) T b) F(Anti p24 and anti Gp 120 are found in latent stage) c) F d) T e) T

Help Link:

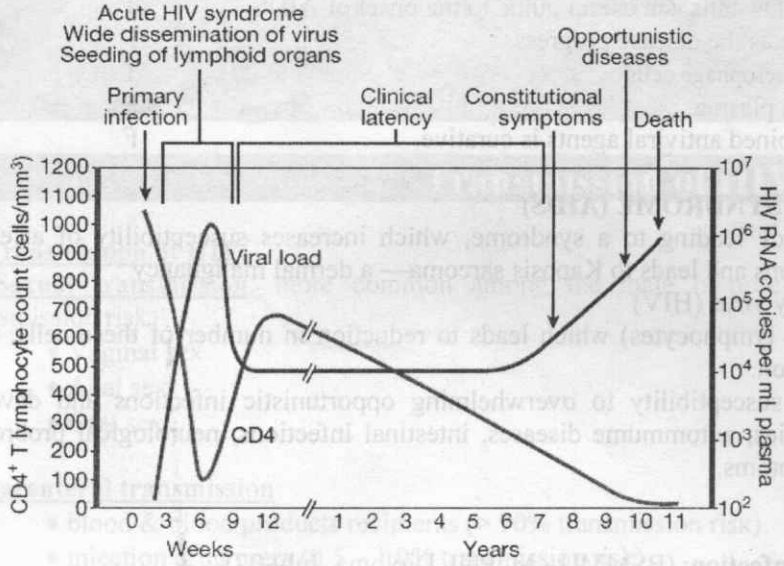


Fig. 14.3 Virological and immunological progression of untreated HIV infection.

(Ref: Davidson-20th, P-394)

Q. HIV *(BSMMU –Residency – **Dentistry** – March' 18)*
a) is a single-stranded RNA
b) gains entry into cells with CD4 cell-surface receptor molecules
c) core protein p24 can be used to monitor progression of AIDS
d) can be passed from mother to fetus
e) causes a drop in the CD4/CD8 ratio

Ans. a) T b) T c) T d) T e) T

Help Link:

CD4 helper T cell, Macrophage, Monocytes have CD4 proteins on their surfaces that can be infected by HIV.

(Ref: Lange-14th, P-378)

Core protein P24: The sensitivity of the test improves with clinical progression of disease showing 4% positivity in asymptomatic patients, 56% in AIDS related complex patients and 70% in AIDS patients

Q. During acute stage of HIV infection *(BSMMU – Residency – **MD, MS, Basic science** – March' 16)*

a) patient is asymptomatic	F
b) genome is integrated into the DNA of CD4+ T cells	T
c) high turnover of CD4+ T cells	T
d) viral load has direct bearing on the prognosis	T
e) virus is not transmissible to others	F

Q. Human immunodeficiency virus infects *(BSMMU –Residency – **MD, MS, Basic Science** – March' 15)*
a) CD4 + T lymphocytes
b) CD8 + T lymphocytes
c) macrophage
d) monocytes
e) neutrophil

Ans. a) T b) F c) T d) T e) F

Q. In patients with AIDS: *(BSMMU - M. Phil, Diploma – July '10)*

a) More than 85% develop pneumonia caused by P carinii.	T
b) Histoplasmosis is the most common fungal infection	F
c) Kaposi sarcoma is the most common neoplasm	T
d) Opportunistic infections account for the majority of death	T
e) HPV-associated cervical dysplasia is ten times more common in females	T

Q. In HIV infection: (BSMMU - M. Phil, Diploma, July'09)

a) Monitoring of the number of CD4 cells is a useful guide to the onset of AIDS T
b) Numbers of CD8 cells increase as the disease progress F
c) The virus is found in monocyte macrophage cells T
d) The HIV virus is not present in plasma F
e) Prolonged.treatment with combined antiviral agents is curative. F

HELP LINK:

ACQUIRED IMMUNODEFICIENCY SYNDROME (AIDS)

- AIDS is an acquired immunodeficiency leading to a syndrome, which increases susceptibility of affected individuals to various microbial infections and leads to Kaposis sarcoma— a dermal malignancy
- It is caused by human immunodeficiency virus (HIV)
- The HIV attacks T-helper cells (CD-4 lymphocytes) which leads to reduction in number of these cells, thus causing loss of immunological protection.
- Infected individuals show increased susceptibility to overwhelming opportunistic infections and develop Kaposis sarcoma and other malignancies, autommume diseases, intestinal infections, neurological probrems, lymphadenopathy and many other symptoms.

Q. In human immunodeficiency virus infection: (BSMMU - M. Phil, Diploma, July-07)

a) median time to progression to AIDS is 5 years T
b) T helper cells are specially susceptible T
c) infected cells carry the CD5 molecule F
d) the incubation period for HIV 1 is twice as long as for HIV 2 F
e) Herpes simplex is a common infection. F

Q. Human immunodeficiency virus (HIV) (BSMMU - M. Phil, Diploma, July-05)

A. contains reverse transcriptase enzyme T
B. infect dendritic cells T
C. cause rapid decline in CD8 cell count F *(CD4 cell count)*
D. is associated with body cavity lymphoma T
E. genome is detected by western blotting T

Q. The virus associated with HIV is - (BSMMU - M. Phil, Diploma, July-04)

A. a obligatory intracellular virus T
B. common in hemophiliacs than in normal individuals F
C. transmitted from mother to infant T
D. related to the visna virus which infects sheep T
E. a single genetic form F

HELP LINK:

- All viruses infecting man are obligate intracellular organisms multiplying within the living cell.
- Normally HIV infection is not more common in haemophiliacs than in normal individuals, but outbreaks have occurred in this group of people due to them receiving contaminated blood products.
- Mother to infant infection can be transmitted either via the placental blood, during delivery or by ingestion of infected breast milk.
- There are two genetically different but related forms of HIV, HIV_1 and HIV_2. HIV_1 is common in Central Africa, whereas HIV_2 is common in West Africa.

Q. AIDS is caused by- (MD/MS (DMC)-04Ja)

a) A human retrovirus T
b) Kills B lymphocytes F
c) Lymphocyte stem cells F
d) Monocytes/ Macrophages T
e) CD+ T lymphocytes T

Q. HIV is - (M. Phil, Diploma (DMC) – 03,July)
a) a retrovirus T
b) dependant on reverse transcriptase for its replication T
c) causes hypertension F
d) related to T cell leukemia T
e) associated with reduced production of IgG2 T

Transmission of HIV

■ **Transmission of HIV**:

1. **Sexual transmission**: more common among the male homosexuals than heterosexuals. (0.2 – 0.5% transmission risk)
   - Vaginal sex
   - Anal sex
   - Oral sex

2. **Parenteral transmission**:
   - blood & blood products recipients (> 90% transmission risk)
   - injection drug users (0.5 – 1.0% transmission risk)
   - those experiencing occupational injury
   - Contaminated needles, syringes & surgical instruments

3. **Vertical transmission**: (From mother to baby)
   - transplacental & during delivery (15-40%% transmission risk)
   - breast feeding.

Question Bank

Q. Mode of transmission of HIV are *(BSMMU – Residency - **MD** - March' 17)*
a) kidney transplantation
b) mosquito bite
c) breast milk
d) anal intercourse
e) direct non-sexual contact
Ans. a) T b) F c) T d)T e)F

Q. Modes of transmission of HIV are: (BSMMU - M. Phil, Diploma, July-07)
a) sexual T
b) oral F
c) perinatal T
d) parenteral T
e) physical contact F

Q. HIV is transmitted through: (M. Phil, Diploma (DMC)-05July)
a) Parenteral route T
b) Fecal oral route F
c) Droplet infection F
d) Breast milk T
e) Sexual contact T

Q. Modes of transmission of HIV are- (BSMMU – MD/MS - 05Ja)

A. Kidney donation T
B. Droplet spread F
C. Breast milk T
D. Anal intercourse T
E. Direct non-sexual contact F

Q. Transmission of HIV takes place - (BSMMU - M. Phil, Diploma, July-04)

A. Through sexual route T
B. Through respiratory route F
C. Through blood transfusion T
D. Through transplacental route T
E. Through utensil F

Q. Transmission of HIV occurs via - (MD/MS (DMC)-04Ja)

a) Fecal oral route F
b) Sexual T
c) Breast milk T
d) Droplet infection F
e) Parenteral T

Q. Transmission of HIV occur- (BSMMU-MS-02Ja)

a) By parenteral inoculation T
b) By casual personal contact in the household F
c) During delivery from an infected mother T
d) After birth by ingestion of breast milk T
e) By insect bites F

Q. AIDS is transmitted by: (MD/MS (DMC)-01Ja)

A. Sexual contact T
B. Coughing F
C. Sneezing F
D. Utensils F
E. Syringe and needle T

AIDS

Q. Oral manifestations of HIV infection are *(BSMMU –Residency – **MS, Basic Science** – March' 15)*

a) oral candidiasis
b) hairy leukoplakia
c) recurrent apthous ulcer
d) lichen planus
e) gingivitis

Ans. a) T b) T c) F d) F e) T (by HSV-1)

(Ref. LANGE Review-15th, P-385)

HELP LINK:

■ **AIDS**: It is a fatal illness caused by a retrovirus known as human immuno-deficiency virus which breaks down the body's immune system, leaving the victim vulnerable of life-threatening infections, neurological disorders or unusual malignancies. Actually, AIDS refers only to the last stage of HIV infection characterized by

- CMI suppression
- Opportunistic infection
- Secondary neoplasms.

Only 5-10% of HIV infected persons develop AIDS.

■ **Pathogenesis**: After entering the blood stream, the HIV infects CD4+ T cells. HIV replicates within the CD4+ T cells and causes destruction of CD4+ T cells by 2 mechanisms-

1. Lysis of the infected CD4+ T cells.
2. The infected CD4+ T cells adhere together to form multinucleated giant cells which are non-functioning.

So, due to decrease number of CD4+ T cells, there occurs suppression of both cell mediated immunity (CMI) and humoral immunity. But the suppression of CMI is more marked. Due to immune suppression, opportunistic microbial infection occurs which ultimately lead to death.

HIV also infects the brain, monocytes, macrophages- producing MNGC and significant symptoms, eg. dementia, neuropathy etc.

■ **Immunodeficiency in HIV infection**:

- HIV binds with the CD4 receptor in the CD4+ T-cell
- The virion enters the cell and shut down the protein synthesis of T-cell
- Virus infected CD4+ T-cell is destroyed by cytotoxic T-cells
- Loss of function of CD4+ T-cell hampers the T-cell dependent activation of macrophage, cytotoxic cells, natural killer cells & B-lymphocyte.

Thus both humoral & cell mediated immunity is affected by HIV leading to immunodeficiency.

■ **Clinical diagnosis**:

A. ***Major sings***:

1. Wt loss ≥10% of body wt.
2. Chronic diarrhoea for more than 1 month.
3. Prolonged fever for more than 1 month.

B. ***Minor signs***:

1. Persistent cough for > 1 month.
2. Generalized pruritic dermatitis.
3. H/O herpes zoster.
4. Oropharyngeal candidiasis.
5. Chronic progressive or disseminated herpes simplex infection.
6. Generalized lymphadenopathy.

As lest 2 major signs & 1 minor sign is diagnostic.

■ **Clinical classification of HIV infection**:

Group-1: Early stage (within 15 days of infection). Here infectious mononucleosis like symptom, fever, malaise, sore-throat, encephalitis or meningitis.
Group-2: No symptom but seropositive after 2 months of infection. Ab can be detected.
Group-3: Persistent generalized lymphadenopathy. History of more than 3 months.
Group-4: AIDS related condition. Various diseases as complication.
Group-5: AIDS (extremely severe AIDS related complex)

■ **C/F of extremely severe AIDS related complex**:

1. Persistent diarrhoea > 1 month.
2. Loss of weight > 10%
3. Fatigue, malaise, night sweat
4. Oral thrush.

■ **Stages in the course of HIV infection**: C/F of HIV infection have been classified in 4 broad categories-

A. ***Initial infection***:

- No symptom for 5 years
- Mild illness (fever, sore throat, rash)

B. ***Asymptomatic carrier stage***:

- No overt sign of disease except persistant generalized lymphadenopathy.

C. ***AIDS related complex***: (ARC)

- Pt. who has a decreased number of T helper lymphocyte are considered to have ARC.
- Clinical signs- unexplained diarrhea, fatigue, malaise, loss of body wt., fever, night sweat, oral thrush.

D. ***End stage of HIV infection***:

- Opportunistic infection
- Malignancy

Q. HIV virus: *(BSMMU – M. Phil, Diploma – 11Ju, DMC & others – MD – 11Ju)*

a) mainly of two types, HIV-I & HIV-II T
b) HIV-I produces severe infection than HIV-II T
c) HIV-I is confined to West Africa F
d) ELISA is the confirmatory test F
e) Western blot is the screening test F

Q. Presenting features of HIV infection –(BSMMU – MD - 08Ja)

a. Hairy leukoplakia T
b. Atypical pneumonia T
c. Thrombocytopenia purpura T
d. Pulmonary TB T
e. Hyperglycaemia F

HELP LINK:

AIDS defining disease:

- Oesophageal candidiasis
- Cryptococcal meningitis
- Chronic cryptosporidial diarrhoea
- Cerebral toxoplasmosis
- CMV retinitis or colitis
- Chronic mucocutaneous herpes simplex
- Disseminated *Mycobacterium avium intracellulare*
- Pulmonary or extrapulmonary tuberculosis
- *Pneumocystis carinii* (*jirovecii*) pneumonia
- Progressive multifocal leucoencephalopathy
- Recurrent non-typhi *Salmonella* septicaemia
- Extrapulmonary coccidioidomycosis
- Invasive cervical cancer
- Extrapulmonary histoplasmosis
- Kaposi's sarcoma
- Non-Hodgkin lymphoma
- Primary cerebral lymphoma
- HIV-associated wasting
- HIV-associated dementia

HIV symptomatic diseases

- Oral hairy leucoplakia
- Recurrent oropharyngeal candidiasis
- Recurrent vaginal candidiasis
- Severe pelvic inflammatory disease
- Bacillary angiomatosis
- Cervical dysplsia
- Idiopathic thrombocytopenic purpura
- Weight loss *
- Chronic diarrhea*
- Herpes zoster
- Peripheral neuropathy
- Low grade fever/ night sweats*

* But not AIDS-defining

(Ref: Davidson-23rd)

Q. Common AIDS defining conditions are- (BSMMU – MD/MS - 06Ja)

A. oral candidiasis
B. cryptococcal meningitis
C. Hodgkin's lymphoma
D. Pulmonary tuberculosis
E. progressive.multifocal leucoencephalopàthy

Ans.

a) T b) T c) F **(Ref: Davidson-23rd)**
d) T
e) T *(PMFL is a fatal demyelinating disease caused by the JC papovavirus that was first described in non-HIV immunocompromising states. It occurs in approximately 2- 3% of AIDS patients at very low CD4 counts)*

Opportunistic infection in AIDS patients

Opportunistic infection in AIDS patients:

1. Bacterial	• M. tuberculosis *(pulmonary or extrapulmonary)* • Atypical tuberculosis *(M. avium intracellulare disseminated or extrapulmonary)* • Salmonella infection *(disseminated)* • Nocardia asteroids infection *(pneumonia, meningitis, disseminated)*
2. Protozoal	• Cryptosporidiosis (causes diarrhoea) • Toxoplasma infection in brain *(pneumonia or CNS infection)* • Pneumocystis carinii infection *(pneumonia or disseminated infection)* • Isospora belli infection *(enteritis)*
3. Viral	• Herpex simplex *(localized or disseminated)* • Cytomegalo virus *(causes disseminated infection - pulmonary, intestinal, retinitis, or CNS infections)* • Vericella zoster virus *(localized or disseminated)* • Epstein barr virus • Progressive multifocal leukoencephalopathy
4. Fungal	• Candidiasis (esophageal, tracheal, or pulmonary) • Cryptococcosis (CNS infection) • Histoplasmosis (disseminated) • Preamocystic cariric infection • Coccidioidosis (disseminated)
5.Neoplasm	• Kaposi's sarcoma • Burkitt's lymphoma • B cell Non-Hodgkin lymphoma • Anogenital (vulval/ vaginal, anal, penile) and in situ cervical (CIN III) cancer) • Primary lymphoma of the brain • Invasive cancer of uterine cervix
6.Nematode	• Strongiloid infection other than intestine.

■ **Common HIV related Pulmonary diseases**:

1. Peumocystis carinii
2. Mycobacterium tuberculosis
3. Mycobacterium avium intracellulare
4. Pulmonary kaposis sarcoma
5. Community acquired pneumonia
6. Cryptococcus neoformans

TABLE 45–2 Common Opportunistic Infections in AIDS Patients

Site of Infection	Disease or Symptom	Causative Organism
Lung	1. Pneumonia 2. Tuberculosis	*Pneumocystis jiroveci*, cytomegalovirus *Mycobacterium tuberculosis*
Mouth	1. Thrush 2. Hairy leukoplakia 3. Ulcers	*Candida albicans* Epstein–Barr virus Herpes simplex virus-1, *Histoplasma capsulatum*
Esophagus	1. Thrush 2. Esophagitis	*C. albicans* Cytomegalovirus, herpes simplex virus-1
Intestinal tract	Diarrhea	*Salmonella* species, *Shigella* species, cytomegalovirus, *Cryptosporidium parvum*, *Giardia lamblia*
Central nervous system	1. Meningitis 2. Brain abscess 3. Progressive multifocal leukoencephalopathy	*Cryptococcus neoformans* *Toxoplasma gondii* JC virus
Eye	Retinitis	Cytomegalovirus
Skin	1. Kaposi's sarcoma 2. Zoster 3. Subcutaneous nodules	Human herpesvirus 8 Varicella-zoster virus *C. neoformans*
Reticuloendothelial system	Lymphadenopathy or splenomegaly	*Mycobacterium avium* complex, Epstein–Barr virus

Question Bank

Q. The following infections are common in immuno-deficient patients *(BSMMU-Non-Residency-**Paediatrics**-july'19)*

a) Pneumocystis jirovecii
b) diphtheria
c) poliomyelitis
d) cytomegalovirus
e) Candida albicans

Ans. a) T b) F c) F d) T e) T

(Ref: LANGE-15th, P-372)

Q. Protozoa causing diarrhea in AIDS patients are *(BSMMU –Residency - **MD/MS, Basic science, Paediatrics, Dentistry** – March' 19)*

a) *Toxoplasma gondii*
b) *Cryptosporidium parvum*
c) *Giardia lamblia*
d) *Cryptococcus neoformans*
e) *Blastomyces hominis*

Ans. a) F b) T c) T d) F(fungus) e) F (Fungus)

Q. Common bacterial infections in AIDs patients include*(BSMMU–Residency–**MD, MS, Basic Science**–March' 15)*

a) *Candida albincans*
b) *Staphylococcus aureus*
c) *Strpetococcus pneumoniae*
d) *Haemophilus influenzae*
e) *Mycobacterium tuberculosis*

Ans. a) F b) F c) F d) T e) T

Q. Complication of AIDs are -*(BSMMU –Residency – **MS, Basic Science** – March' 15)*
a) infertility
b) pathological fracture
c) tuberculosis
d) Kaposi's sarcoma
e) lymphoma Ans. a) F b) F c) T d) T e) T

Q. Neoplasms found in patients with HIV infection are *(BSMMU –Residency - **MD/ Basic science** – March' 14)*
a) Kaposi sarcoma
b) Hodgkin lymphoma
c) bronchogenic carcinoma
d) primary lymphoma of the brain
e) invasive squamous cell carcinoma of uterine cervix

Ans. a) T b) T c) F d) T e) T

Q. Neoplasms found in patients with HIV infections are: *(BSMMU – Residency – MD/MS – March'13)*
a) Breast carcinoma
b) Kaposi sarcoma
c) Lung cancer
d) Non Hodgkin lymphoma
e) Invasive cancer of uterine cervix

Ans : a) F b) T c) F d) T e) T

Q. Opportunistic infection in AIDS are: *(BSMMU – M. Phil, Diploma (Non-Residency)–March-2012, DMC & others – MD/MS – March-2012)*

a) Candida	T
b) Poliomyelitis	F
c) Pneumocystis carinii	T
d) Diphtheria	F
e) Tuberculosis	T

Q. The following organisms are opportunistic pathogens: (BSMMU - M. Phil, Diploma, July'09)

a) Salmonella typhi	T
b) Mycobacterium tuberculosis	T
c) Candida albican	T
d) Coagulase negative staph (CNS)	F
e) S. pneumoniae	F

Q. Opportunistic infections which may occur in AIDS are- (BSMMU –MD- January, 2008)

a) pneumocytosis	T
b) HCV hepatitis	F
c) HBV hepatitis	F
d) toxoplasmosis	T
e) cryptococcosis	T

Q. Opportunistic infections in AIDS- (BSMMU – MD/MS - 08Ja)

a) Are a major cause of death	T
b) Are not caused by viruses	F
c) Are common when CD4 cells are extremely low	T
d) Commonly involves invasive candidiasis	T
e) Can be of multiple type at the same time	T

Q. AIDS patients commonly develop the following type of cancers - (BSMMU - M. Phil, Diploma, July-06)

a) Burkitt's lymphoma T
b) Anogenital cancer T
c) Nasopharyngeal carcinoma F
d) Squamous cell carcinoma F
e) Kapasis sarcoma T

Q. The following infection are common in AIDS patients - (BSMMU - M. Phil, Diploma, July-04)

A. Diphtheria F
B. Poliomyelitis F
C. Tuberculosis T
D. Pneumocystic carinii T
E. Candida albicans T

Q. Which of the following organisms would be least likely a patient with AIDS: (MD/MS (DMC)-04Ja)

a) Cytomegalovirus F
b) Cryptococcus neoformans F
c) Pneumocystis carinii F
d) Pseudomonas aeruginosa T
e) Mycobacterium avium intracellulare F

Q. AIDS Patients commonly develop the following of tumours- (BSMMU – MD/MS - 02Ja)

a) Burkitt's lymphoma T
b) Anorectal cancers T
c) Nasopharyngeal carcinoma F
d) Sqmamous cell carcinoma F
e) Caposi's sarcoma T

Investigations for HIV/AIDS

■ **Investigations for HIV/AIDS**:

a) **Laboratory confirmation**:

- Serology using commercial ELISA screening test
- Western blot
- Nucleic acid amplification test (PCR)

b) **Baseline investigations**:

For all: • CD4 count
- Viral load
- Hepatitis B status
- Hepatitis C antibody
- HIV resistance test
- Hepatitis A IgG antibody
- Toxoplasma and cytomegalovirus IgG antibody
- Treponema serology
- HLA-B* 5701 screen for hypersensitivity to abacavir
- Lipid profile and urinalysis
- Cervical smear in women
- STI screen

Special situation:
- Chest X-ray
- HCV-RNA

- Cryptococcal antigen
- CMV-PCR
- Dilated fundoscopy

Nice to know:

■ When screening test is positive, it doesn't mean that it is HIV until confirmatory test is positive.
■ In ELISA, two Ag are used.
■ In western blot 5 Ag are used. If 3 Ag are positive then HIV is confirmatory.
■ **Window period in HIV infection**:

Window period is the time between the exposure of a patient to HIV & production of Antibody. It is about 3-4 weeks.

Importance:

- Screening Test becomes negative during this period. This is a dangerous period of HIV infection, because HIV can be transmitted to others during this period.
- Detected by identifying viral p24 antigen or viral RNA by PCR method.

Question Bank

Q. The initial screening test for acquired immunodeficiency syndrome is: (DMC - M. Phil, Diploma, Juty-'05, MD/MS - 02J; MD/MS (DMC)-02Ja)

a) Enzyme linked immunosorbent assay for HIV infection T
b) Western blot F
c) Polymerase chain reaction F
d) Reverse transcriptase assay F
e) Direct agglutination test F

Q. The routine screening test for diagnosis of HIV infection in adults is: (BSMMU – MD - 00Ja)

A. PCR (Polymerase chain reaction) F
B. Western blot F
C. ELISA (Enzyme linked immunosorbent Assay) T
D. Direct viral culture from blood lymphocytes. F
E. All of the above. F

Treatment & Prevention of AIDS

■ **Treatment of AIDS**: At present there is no curative Rx of vaccine for AIDS. So prevention is the best policy.

1. Preventive measures (as stated below)
2. Antiretroviral treatment: Drugs -
   - Zidovudine
   - Didanosine
   - Zalcitabine .
3. Specific prophylaxis: Until more effective antiviral therapy, becomes available, the main aim of existing therapies will be to treat the manifestations of AIDS.
4. Primary health care: • Mother & child health care Family planning and education.

ANTI RETROVIRAL DRUGS	
Nucleoside reverse transcriptase inhibitors(NRTIs)	
Zalcitabine(ddC)	Zidovudine(ZDV)
Didanosine(ddl)	Stavudine(d4T)
Lamivudine(3TC)	Abacavir
	Emitricitabine(FTC)
Non-nucleoside reverse transcriptase inhibitors(NNRTIs)	
Nevirapine	Delavirdine
Efavirenz	
Protease inhibitors(PIs)	
Indinavir	Fosamprenavir

Ritonavir	Saquinavir
Nelfinavir	Amprenavir
Lopinavir	Tipranavir
Atazanavir	
Others	
Tenofovir	Enfuvirtide(T-20)

■ **Preventive measures of AIDS**:

A. ***Sexual***:

1. Comprehensive school sex education programmes in schools
2. Public awareness campaigns for HIV
3. Easily accessible/ discreet testing centers.
4. Safe sex practices:
   - Avoidance of penetrative intercourse
   - Delaying sexual debut
   - Condom use
   - Fewer sexual partners
5. Targeting safe sex methods to high-risk groups
6. Control of sexually transmitted infections
7. Effective treatment of HIV-infected individuals
8. Post-sexual prophylaxis

B. ***Parenteral***:

1. Blood product transmission:
   - Donor questionnaire
   - Routine screening of donated blood
   - Blood substitute use
2. Injection drug use:
   - Education (safe practice/ support service/ unprotected sex)
   - Needle/ syringe exchange
   - Avoidance of high-risk situations ('shooting galleries')
   - Sharing and support for methadone maintenance programmes

C. ***Perinatal***:

1. Routine 'opt-out' antenatal HIV antibody testing
2. Preconception family planning if HIV-seropositive.
3. Measures to reduce vertical transmission:
   - Highly active antiretroviral therapy treatment during pregnancy
   - Perinatal antiretroviral prophylaxis
   - Zidovudine to neonate
   - Avoidance of breastfeeding

D. ***Occupational***:

1. Education/ training:
   - Universal precautions
   - Needlestick avoidance
2. Post-exposure prophylaxis

(Ref: Davidson-23rd)

Counseling of person incidentally found to be HIV positive. Counseling HIV –infected patients can present great challenges to physicians. Many HIV –infected persons enter the physician–patient relationship with significant emotional distress and numerous complicating circumstances. These complicating circumstances can include issues of fundamental mistrust ,sexual orientation and sexuality, the need for risk reduction, substance abuse, societal discrimination and increasing poverty .The physician must enter this relationship prepared to address these issues with knowledge and compassion and with out becoming judgemental about their content. A crucial component involved in counseling HIV-infected persons is education concerning HIV disease, its

transmission and its potential treatments. This process should continue for the duration of the physician-patient relationship; given the extensive knowledge base of many persons with HIV infection, there may be a mutual exchange of important information. The best medical interventions will not succeed unless HIV-infected persons have been counseled carefully regarding their potential benefits, costs and acquisition. A well informed patient can be a strong ally in tackling difficult therapeutic decisions, and many therapeutic decisions are currently not straight forward, such as the optimal time to initiate ART. A well informed patient will be more compliant with prescribed medications and may recognize better the early manifestations of HIV-related clinical complications and potential drug toxicities. Finally, a well informed patient can guide constructively decisions regarding advance directives for his or her care if HIV disease progress.

Q. Which of the following antiviral drugs act by inhibiting HIV protease: *(BSMMU – Residency – MD/MS – March'13)*

a) Acyclovir
b) Ritonavir
c) Oseltamivir
d) Saquinavir
e) Indinavir

Ans : a) F b) T c) F d) T e) T

Help link:

Protease inhibitors (PIs)

The first PI developed was saquinavir followed by indinavir, ritonavir, lopinavir and tipranavir; more recently, atazanavir, fosamprenavir and darunavir have become available. Currently used PIs should always be boosted by low-dose ritonavir, which is a potent inhibitor of liver metabolism. This increases drug exposure, thereby prolonging the PI's half-life, allowing reduction in pill burden and dosing frequency and so optimising adherence. It also limits the development of resistance. PIs prevent post-translational cleavage of polypeptides into functional virus proteins. When they are given with two NRTIs, the combination controls viral replication in plasma and tissues, and allows reconstitution of the immune system.

Early and late side-effects are common. PI use has been linked with fat accumulation which is characterised by central adiposity and localised collections (buffalo hump, peripheral lipomatosis, and breast enlargement in women). In addition, their use may be associated with hyperlipidaemia (mainly total cholesterol and triglyceride), and abnormal glucose tolerance; this is less marked for atazanavir and darunavir. An increased risk of myocardial infarction has been linked to certain PIs that is not explained by dyslipidaemia. Individual PI side-effects include diarrhoea (lopinavir), renal stones (indinavir), hyperbilirubinaemia (atazanavir) and rash (fosamprenavir and darunavir).

PIs are metabolised by the P450 cytochrome system (mainly the CYP3A4 isoenzyme), giving rise to the potential for multiple drug interactions. Commonly used drugs that interact with PIs (in particular ritonavir) are rifampicin, midazolam and simvastatin. Monitoring plasma levels and dose adjustments may be necessary to optimise the antiviral effect and reduce toxicity.

ANTI RETROVIRAL DRUGS	
Nucleoside reverse transcriptase inhibitors(NRTIs)	
Zalcitabine(ddC)	Zidovudine(ZDV)
Didanosine(ddl)	Stavudine(d4T)
Lamivudine(3TC)	Abacavir
	Emitricitabine(FTC)
Non-nucleoside reverse transcriptase inhibitors(NNRTIs)	
Nevirapine	Delavirdine
Efavirenz	
Protease inhibitors(PIs)	
Indinavir	Fosamprenavir
Ritonavir	Saquinavir
Nelfinavir	Amprenavir

Lopinavir	Tipranavir
Atazanavir	
Others	
Tenofovir	Enfuvirtide(T-20)

IMPORTANT MCQ OF STI

[Ref: Smiddy]

Q. The following diseases are caused by chlamydia: (FCPS – Surgery – 08Ja)

a) yellow fever
b) lymphogranuloma venereum
c) mumps
d) psittacosis
e) herpes simplex

Ans.

a) **False** Yellow fever is caused by an arthropod borne RNA virus of the togavirus group. It is transmitted by the mosquito, Aedes aegypti.

b) **True** Lymphogranuloma venereum is caused by a subgroup A chlamydia which is closely related to the chlamydia causing trachoma. The Frei test for LGV is a delayed hypersensitivity skin test.

c) **False** Mumps is caused by a paramyxovirus. Typically a bilateral parotitis occurs but in addition there is a high incidence of involvement of central nervous system and occasionally orchitis. Paramyxoviruses are large filamentous double stranded RNA viruses (150 to 20 nm in size)

d) **True** Psittacosis is a febrile disease chiefly involving the respiratory tract, caused by a subgroup B chiamydia. It is acquired by inhaling infected aerosols or dust from birds, usually of domestic origin.

e) **False** Herpes viruses are double stranded DNA viruses which produce acidophilic intranuclear inclusion bodies. The herpes viruses have the peculiar property of remaining latent for many months or years and then being reactivated by a variety of stimuli, including UV light and febrile illnesses. The herpes group also includes varicellalzoster, the Epstein—Barr virus and cytomegalovirus.

Q. Acquired syphilis of the cardiovascular system may involve the following lesions:

a) myocardial gummata
b) aortitis
c) aortic regurgitation
d) abdominal aortic aneurysm
e) stenosis of the coronary ostia

Ans.

a) **True** Gummata are ubiquitous, occurring in any tissue of the body. A second type of myocardial lesion has been described in which only fibrosis occurs. There is, however, doubt as to whether this represents a specific form of syphilitic involvement.

b) **True** The distinctive features of syphilitic aortitis, which is often accompanied by atherosclerosis, are as follows:

(a) Bluish grey or porcelain-grey intimal plaques
(b) Wrinkling and puckering of the inner aspect of the aorta with a tendency to form radial or parallel grooves, the latter in the long axis of the aorta
(c) Sharp transverse demarcation of the aortic lesions ending at the origins of the vessels of the neck, at the level of the diaphragm or at the origin ot the renal arteries
(d) Localization of the most extensive lesions to the ascending aorta above the sinuses of Valsalva.

c) **True** Syphilis produces endarteritis of the vasa vasorum with resulting ischaemia of the aorticwatl. This causes destruction of the medial elastic leading to weakening of the wall of the aorta and loss of its elasticity. Since the disease chiefly affects the root of the aorta, the aortic ring widens separating the aortic cusps thus causing aortic regurgitation.

d) **False** Abdominal aortic aneurysms are most commonly due to atherosclerosis. Syphilitic aneurysms chiefly occur in the root and ascending parts of the aorta.

e) **True** The ostia of the coronary arteries are usually involved in either inflammatory or fibrotic changes which results in narrowing leading to angina pectoris.

Q. The virus associated with HIV is:

a) an obligate intracellular virus
b) a commoner infection in haemophiliacs than in normal individuals
c) transmitted from mother to infant
d) related to the visna virus which infects sheep
e) a single genetic form

Ans.

a) **True** This is the significant difference between bacterial and viral infections. All viruses infecting man are obligate intracellular organisms multiplying within the living cell.

b) **False** Normally HIV infection is not more common in haemophiliacs than in normal individuals, but outbreaks have occurred in this group of people due to them receiving contaminated blood products.

c) **True** Mother to infant infection can be transmitted either via the placental blood, during delivery or by ingestion of infected breast milk.

d) **True** HIV is a retrovirus belonging to the lentovirus family; included within this group is the visna virus of sheep.

e) **False** There are two genetically different but related forms of HIV, HIV1 and HIV2. HIV1 is common in Central Africa. whereas HIV2 is common in West Africa.

Q. AIDS encephalopathy is:

a) an infrequent feature of the disease
b) mainly affects the grey matter
c) associated with rarefaction and vacuolation
d) associated with mental retardation in children
e) caused by CD4+ T-cell deficiency

Ans.

a) **False** About 40% of AIDS patients have neurological symptoms and 80% have pathological changes in the CNS at autopsy, changes which are due to the direct or indirect effects of the virus, opportunistic infection and primary CNS lymphoma.

b) **False** The white matter and basal ganglia are chiefly affected.

c) **True** Rarefaction and vacuolation are associated with the destruction of myelin sheaths and disruption of some axons. Infiltration with macrophages and multinucleate cells may be found.

d) **True** Almost half of the infants and children infected with HIV develop an encephatopathy which leads to mental retardation and motor dysfunction.

e) **False** These changes are thought to be the direct result ot viral infection and unrelated to a defect in cell-mediated immunity.

Q. Kaposi sarcoma is:

a) not as common as non-Hodgkins lymphoma in patients suffering from AIDS
b) different in the sporadic form from that occurring in AIDS
c) histologically idenlical in both the sporadic and AIDS-related forms
d) not associated with transplantation
e) related to haemangiosarcoma

Ans.

a) **False** Non-Hodgkin's lymphoma is less common in the end stage of AIDS than is Kaposi saicom. Approxmately 3% of AIDS patients devolop lymphoma whereas one third develop a Kaposi sarcoma.

b) **True** Sporadic Kaposi sarcoma occurs especially in Ashkenazi Jews, forming red nodule principally on the lower extremities, whereas AIDS-related Kaposi sarcoma has no such specific site. disseminating widely.

c) **True** The two types. sporadic and AIDS-related, cannot be distinguished histologically.
d) **False** High doses of immune suppressive drugs in transplant patients may be followed by the development of Kappsi sarcoma.
e) **False** Haemangiosarcoma are rare tumours which may be associated with exposure to arsenical pesticides and polyvinyl chloride which is widely used in the plastic industry.

Q. HIV infection is associated with:

a) a reducon in the number of B cells
b) hypergarnmaglobulinaemia
c) increased tuberculin skin test reactivity
d) cytokine abnormaliites
e) autoimmunity

Ans.

a) **False** There is profound depletion of CD4+ T lymphocytes. B-lymphocyte function may only be affected in that it may depend on T helper cell function.
b) **True** There is a polyclonal hypergammaglobulinaemia resulting from non-specific stimulation of B cells.
c) **False** Delayed hypersensitivity is reduced or absent due to depletion of Tcells.
d) **True** There is reduced production of cytokines produced by CD4+ T cells, Such as IL-2 and gamma-interferon.
e) **False** There is no evidence that HIV infection predisposes to autoimmunity.

Q. Which of the following statements regarding HIV infection is true:

a) infection with HIV is followed by a short incubation period and by a rapidly progressive illness ending in a fatal outcome
b) it is associated with the formation of giant cells
c) the virus expresses specific trophism for the haemopoetic and nervous systems
d) the risk of infection by blood transfusion has been completely eliminated
e) the virus is surrounded by a lipid membrane

Ans.

a) **False** Characteristically all retroviral infections are followed by a long incubation period and a slowly progressive fatal outcome.
b) **True** The fusion of infected and uninfected cells leads to the formation of giant cells which usriafly die within a few hours.
c) **True** The retroviruses exhibit marked trophism for the haemopoetic and the nervous systems.
d) **False** Even with present day screening a very slight risk of infection remains, since a recently infected individual may be antibody negative at the time of giving blood.
e) **True** The virion is spherical and contains an efectron dense core surrounded by a lipid envelope derived from the host cell.

Q. Infection with HIV can cause:

a) an illness resembling.acute glandular fever
b) persistent generalized lymphadenopathy
c) neurological complications
d) monoclonal B-cell activation
e) antibody formation within 7 days of exposure to infection

Ans.

a) **True** An illness resembling acute glandular fever occurs is some 10—20% of patients within a few weeks of infection and precedes seroconversion.
b) **True** Persistent generalized lymphadenopathy occurs after a prolonged asymptomatic latent period and is followed by AIDS or ARC, (AIDS-related complex) in which lymphadenopathy. diarrhoea, night sweats, candidiasis and weight.oss occur. Haematological examination reveals atypical lymphocytes and an increased number of CD8+ T cells.

c) **True** These include acute aseptic meningitis, encephalopathy, myelopathy and neuropathy. Clinically, 70% of AIDS patients become demented.

d) **False** In the later stages of infection, polyclonat B-cell activation occurs with an associated rise in the serum iinmunoglobulins, possibly due to direct activation of the B cells by the virus.

e) **False** Antibody of HIV usually appears 3 weeks to 3 months after exposure and thereafter is detectable throughout ·the life of the patient. The antibodies are typically directed against the envelope glycoproteins.

Q. HIV is: (FCPS-Surgery-13/09Ja)

a) a retrovirus
b) dependent on reverse transcriptase for its replication
c) causes a monoclonal hyperglobulininaemia
d) associated with the production of excessive amounts of IgG2
e) related to T-cell lukaemia

Ans.

a) **True** The human immunodeficiency virus, which is an enveloped RNA virus, has the capacity-to make a DNA copy of itself through its characteristic enzyme, reverse transcriptase.

b) **True** This enzyme reverses the normal process of gene replication and enables HIV to establish a latency similar to the DNA viruses, thus establishing a long term infection.

c) **False** AIDS is associated with a polyclonal hypergammaglobulinaemia which results from the non-specific stimulation of B cells, predominantly causing the production of excessive amounts of IgG1, IgG3, IgA, IgD, IgE and in children, IgM.

d) **False** Once AIDS has developed, the production of lgG2 is reduced. This is of particular importance in the defence against capsulated bacteria; this, together with a failure of B-cell response, accounts for the Susceptibility of patients to bacterial infections.

e) **True** Adult T-cell leukaemia has been shown to arise from infection with T-cell leukaemia virus Type 1 (NTLV1), a virus which causes unrestrained T-cell proliferation.

MYCOLOGY

Property of fungus:

- It is eukaryotic, unicellular or multicellular saprophytic parasitic microbes.
- Got chitin on their cell wall and ergosterol in their cell membrane
- Chitin: polysaccharide composed of long chains of NAGA(N- acytyl glutamic acid)
- Fungus can not be destroyed by penicillin, polymyxin, polyein.

Structural classification of fungi

- Mould: filamentous network of multicellular fungus. Individual filament is known as mycelium (another name hyphae), eg: dermatophytes causes septate hyphae (dermatophytosis). Hyphae grows by tip elongation and by branching.
- Yeast: single cell, round or convex, grows by asexual budding. e.g: *C. neoformans* (causes meningitis)
- Yeast like fungus: daughter cells do not separate from parents. e.g: *C. albicans*
- Dimorphic fungus: two morphological character in two temperature, in 37 degree- yeast (body temp), in 25 degree- mould (environmental temp.)

Dimorphic fungi

Q. Dimorphic fungi causing human infections are *(BSMMU – Non-Residency – MD, MS, Paediatrics, Basic Science – July' 19)*

a) *Blastomyces dermatitis*
b) *Histoplasma capsulatum*
c) *Sporothrix chenckii*
d) *Cryptococcus neoformans*
e) *Aspergillus fumigatus*

Ans. a) T b) T c) T d) F e) F

(Ref: P. Chakroborti-3rd, P-678)

HELP LINK:

Dimorphic fungi either grow as moulds or as yeasts depending upon the environments of growth. Usually they grow as moulds in culture media at 22^{0}C and in soil (saprophytic phase). On the other hand, they grow as yeasts in culture media at 37^{0}C and in the body of the animal host (parasitic phase). Coccidioides immitis is however an exception which is mycelial in culture both at 22^{0}C and at 37^{0}C. In the body of the host it grows as yeast.

Examples of pathogenic dimorphic fungi are as under:

1. *Sporothrix schenckii*
2. *Histoplasma capsulatum*
3. *Coccidioides imrnitis*
4. *Bastomyces dermatitidis*
5. *Rhinosporidiurn seeberi*

The general properties of the dimorphic fungi are enumerated below:

1. Dimorphic.
2. Most live in soil.
3. Not communicable from man to man.
4. General mode of infection is by inhalation except in case of *Sporothrix schenckii*, which requires traumatic implantation.
5. For diagnosis, identification of the. causative agents is important. Serological findings are uncertain.
6. Dimorphic fungi are generally slow growers.

Q. Dimorphic fungi are - *(BSMMU – Non-Residency – MD, MS, Basic Science & Dentistry – July' 17)*
a) *Candida albicans*
b) *Histoplasma capsulatum*
c) *Cryptococcus neoformans*
d) *Blastomyces dermatidis*
e) *Melassezia furfur*
Ans. a) F b) T c) F d) T e) F

Q. Medically important dimorphic fungi are *(BSMMU – Residency - **MD, MS, Basic Science** - March' 17)*
a) *Histoplasma capsulatum*
b) *Blastomyces dermatitidis*
c) *Sporothrix schenckii*
d) *Candida albicans*
e) *Cryptococcus neoformans*
Ans. a)T b) T c) T d) F e)F

Q. Following are dimorphic fungus: (BSMMU – MD – January, 2010)

a) Malassegia furfur	F
b) Cryptococcous neoformans	F
c) Blastomyces spp.	T
d) Histoplasma capsulatum	T
e) Coccidiodes imitis	T

CLINICAL CLASSIFICATION OF FUNGUS:

■ **Clinical classification of fungus**: based on the anatomical sites involved.

1. **Superficial fungal agents**: These fungi remain only on the superficial layer of skin i.e stratum corneum of the epidermis. But they do not involve keratin layer. They are lipophilic and live on the lipid of our sebaseous secretion.

Keratin is a protein of skin & skin appendages (hair, nail)

Superficial fungal agents	Superficial mycoses
Malassezia furfur	Pityriasis versicolor / Tinea versicolor
Piedriaea hortae	Black piedra
Exophiala werneckii	Tinea nigra
Trichosporon beigelli.	White piedra

2. **Cutaneous fungal agents**: Fungi invade stratum corneum of skin. They liberate enzyme that digest keratin and use them as their nutrition.

Cutaneous fungal agents	Cutaneous mycoses
Dermatophytes	Dermatophytosis/Tinea worm/Ring worm
Candida species	Cutaneous candidiasis

■ **Classification of dermatophytes**: 3 Genera:

Microsporum	Trichophyton	Epidermophyton
M. canis	*T. rubrum* (BD)	*E. floccosum* (BD)
M. gypseum	*T. mentagrophytes* (BD)	
M. audounii	*T. tonsurans*	
	T. schoenleinii.	

[BD=Bangladesh. they are found more in BD]

3. **Subcutaneous fungal agents**: They invade subcutaneous tissue.

Subcutaneous fungal agents	Subcutaneous mycoses
Sporothrix schenkii.	Sporotrichosis
Phialophora verrucosa	Chromomycosis
Madurella mycetomatis [Bacterial agent –Actinomycetes]	Mycetoma / madura foot
Rhynosporidium sceberi	Rhynosporidiosis

4. **Systemic\Deep fungal agents**: These fungi invades various internal organs of the body after being carried there by blood.

A. ***Primary fungal Agents***: These fungi infect healthy individuals.

Primary fungal agents	Primary mycoses
Histoplasma capsulatum	Histoplasmosis
Blastomyces dermatitidis	Blastomycosis
Coccidioido immitis	Coccidioidomycosis
Paracoccidioido brasiliensis	Paracoccidioidomycosis

B. ***Opportunistic fungal agents***: These fungi infect immunocompromized patients.

Opportunistic fungal agents	Diseases
Cryptococcus neoformans	Cryptococcosis
Candida albicans	Systemic candidiasis
Mucor species: Penicillium	Mucor mycosis
Aspergillus	Aspergillosis
Pneumocystis carini (now called jerovecii)	Pneumonia
Sporothrix schenckii	Local subcutaneous infection at the site of entry by accidental injury, osteoarticular and pulmonary lesion.

Question Bank

Q. Cutaneous fungi are *(BSMMU –Residency - **MD/MS, Basic science, Paediatrics** – March' 19)*

a) *Trichophyton rubrum*
b) *Epidermophyton flocosum*
c) *Microsporum species*
d) *Aspergillus species*
e) *Mucor species*

a) T b) T c) T d) F (opportunistic) e) F Opportunistic mycosis)

Help Link:

Cutaneous mycosis:

✓Not only skin but also hair, nail. Can produce keratinase, as keratin as their food.

Dermatophytes(causes ring worm/ tinea/ dermatophytosis) –
trichophyton- infect skin, nail, hair
Epidermophyton- infect skin, nail but not hair,
microsporum- infect skin, hair but not nail.

Candidiasis.

Q. Fungi associated with opportunistic mycosis are *(BSMMU –Residency - **Dentistry** – March' 19)*

a) aspergilus
b) *Malassezia furfur*
c) *Cryptococcus neoformans*
d) trichophyton
e) mucor and rhizopus

Ans. a) T b) F (superficial mycosis) c) T d) F (cutaneous) e) T

Q. Opportunistic fungi are *(BSMMU – Diploma - **Dentistry** – July' 18)*
a) Pneurnocystic carinli
b) Rhinosporidium spp.
c) Cryptococcus neoformans
d) Aspergillus fumigatus
e) Histoplasma capsulatum Ans. a) T b) F c) T d) T e) F

Q. Subcutaneous fungal infections are *(BSMMU –Residency – **MD, MS, Basic Science** – March' 18)*
a) *Malassezia furfur*
b) *Sporothrix schenckii*
c) *Rhinosporidium spp.*
d) *Trichophyton spp.*
e) *Aspergillus spp.*
Ans. a) F b) T c) T d)F e) F

Q. Fungi that cause opportunistic mycoses are *(BSMMU –Residency – **MD, MS, Basic Science** – March' 18)*
a) *Aspergillus fumigatus*
b) *Cryptococcus neoformans*
c) *Pneumocystis jeroveci*
d) *Histoplasma capsulatum*
e) *Sporothrix schenkii*
Ans. a) T b) T c) T d) F e) F

Q. Opportunistic fungi are *(BSMMU – Residency - **MD, MS, Basic Science, Dentistry** - March' 17)*
a) *Candida albicans*
b) *Cryptococcus neoformans*
c) *Histoplasma capsulatum*
d) *Trichophyton rubrum*
e) *Pneumocystis jirovecii*
Ans. a) T b) T c) F d) F e)T

Q. Subcutaneous mycosis are *(BSMMU – Residency – **MD, MS, Basic science, Dentistry** – March' 16)*
a) sporotrichosis T
b) candidiasis F
c) chromomycosis T
d) dermatophytosis F
e) mycetoma T

Q. Fungi causing opportunistic mycoses are *(BSMMU – Residency – **MD, MS, Basic science** – March' 16)*
a) *Histoplasma capsulatum* F
b) *Cryptococcus neoformans* T
c) *Pneumocystis jirovecii* T
d) *Blastomyces dermatitides* F
e) Mucor spp. T

Q. Fungus causing systemic mycoses include *(BSMMU –Residency - **MD/MS, Basic science** – March' 14)*
a) paracoccidioides brasiliensis
b) aspergillus fumigatus
c) candida albicans
d) histoplasma capsulatum
e) blastomyces dermatitidis
Ans. a) T b) T c) T d) T e) T

Q. The opportunistic fungi are *(BSMMU –Residency - **MD/MS, Basic science** – March' 14)*
a) candida albicans
b) cryptococcus neoformans
c) histoplasma capsulatum
d) trichophyton rubrum
e) pneumocystis jiroveci
Ans. a) T b) T c) F d) F e) T

Q. Systemic deep fungal infections are caused by - (BSMMU – MD/MS (Residency)-11Ja)

a. *Blastomyces dermatidis* T
b. *Malassezia furfur* F
c. *Histoplasma capsulatum* T
d. *Coccidioides immitis* T
e. *Microsporum audouinii* F

Q. The following causes systemic mycosis - (MD/MS (DMC)-09Ja)

a. *Aspergilus spp* T
b. *Histoplasma capsulalum* T
c. *Microsporum spp* F (dermatophytes – cutaneous fungal agent)
d. *Cryptococcus neoformans* T
e. *Coccidiodes immitis* T

Cryptococcus neoformans

Q. ***Cryptococcus neoformans*** *(BSMMU – Residency – MD, MS, Basic science – March' 16)*

a) forms hyphae F
b) has polysaccharide capsule T
c) is dimorphic F
d) cause infection through inhalation T
e) is associated with infection in immunocompromised person T

Help link:

Cryptococcus neoformans is not a dimorphic fungus.
It is capsulated.

- **Types**: 2 types:
  1. Var neoformans
  2. Var gattii
- **Disease caused by it**: Cryptococcosis
- **Pathogenesis**: They grow commonly in soil containing faeces of pigeon. Man gets infection by inhalation.In most of the cases, pulmonary infection is asymptomatic & dissolves spontaneously but in immunocompromized individuals, they may disseminate to meninges where they produce cryptococcal meningitis.Moreover, they may settle to skin, eye, prostate.

Mycetoma

Q. Causative agents of eumycotic mycetoma ate: *(BSMMU – M. Phil, Diploma (Non-Residency)–March-2012, DMC & others – MD/MS – March-2012)*

a) Madurella spp T
b) Nocardia F
c) Fusarium spp T
d) Sporothrix schenckii F
e) Acremonium spp T

HELP LINK: Mycetoma is a general term which indicates characteristic lesions due to infection by fungi or bacteria. In typical mycetoma there are grains or granules which are discharged from the lesions. These are visible to the naked eye, may be variously coloured. They are generally soft but may be hard. There are three principal varieties of mycetomas eg.- • Actinomycosis • Nocardiosis • Maduromycosis

DERMATOPHYTES

Q. Following are dermatophytes: (BSMMU – MD/MS (Residency) – January, 2011, 10)

a) *Trichophyton mentagrophytes* T
b) *Sporothrix schenkii* F
c) *Microsporum canis* T
d) *Epidermophyton floccosum* T
e) *Malassegia furfur* F

HELP LINK:

■ **Definition**: Dermatophytes are the fungi which infect only superficial keratinized structures (skin, hair & nail).

■ **Classification of dermatophytes**: 3 Genera:

Microsporum	Trichophyton	Epidermophyton
M. canis	*T. rubrum* (BD)	*E. floccosum* (BD)
M. gypseum	*T. mentagrophytes* (BD)	
M. audounii	*T. tonsurans*	
	T. schoenleinii.	

[BD=Bangladesh. they are found more in BD]

Q. The followings are the dermatophytes- (MD/MS (DMC)-08Ja)

a) Microsporum T
b) Candida albicans F
c) Tricophyrton T
d) Tinea nigra F
e) Epidermophyton T

Q. The following are the dermatophytes: (DMC - M. Phil, Diploma, July-07)

a) Microsporum T
b) Canida albicans F
c) Tricophyton T
d) Tinea nigra F
e) Epidermophyton T

HELP LINK: The most important dermatophytes are classified in three genera: Epidermo-phyton, Trichophyton, and Microsporum.

Onycomycosis

Q. Onycomycosis is caused by: (BSMMU – MD/MS - January, 2008)

a) Trichophyton rnentagrophytes T
b) Mucor mycosis F
c) Epidermophyton floccosum T
d) Microsporum gypseum F
e) Candida albicans T

HELP LINK:

■ **Onychomycosis / Tinea unguium**:

- Site of lesion: nail
- Nails become thickened or crumbling distally; discolored; lusterless. Usually associated with tinea pedis.
- Fungi responsible: T. rubrum, T. metagrophytes, E. floccosum & C. albicans. **(Ref: LANGE-14th)**

Candida albicans

Q. Regarding C. albicans *(BSMMU –Residency - **Dentistry** – March' 19)*

a) it exists as yeast on mucosal surfaces but forms pseudohyphae when it invades tissue
b) antibody-mediated immunity is a more important host defense than cell-mediate immunity
c) it is the most Common fungal infection encountered in general dental practice
d) it produces germ tubes in serum at 37°C
e) a positive skin test can be used to confirm the diagnosis

Ans. a) T b) F (CMI is most important as it is intracellular) c) T d) T e) F

Help Link:

Morphology of *C. albicans*:

- ✓ Ovoid spherical yeasts with a single bud.
- ✓ Normal flora of mucous membrane of the GIT, genitourinary and respiratory tract.
- ✓ Produces pseudohyphae in culture and tissue
- ✓ In HIV: disseminate to lung, heart, brain, eye (endophthalmitis)

✓ Both CMI and humoural immunity confer protection but CMI is more.

Identification:

✓ **Germ tube:** a rapid method, produce within 2 hours when incubate 37 degree. this phenomenon is known as Renold - Braud phenomenon.

✓ **Chlamydospore** produced only in albicans on cornmeal gagr at 25 degree C.

✓ **Serological test** not useful

✓ **Skin test:** delayed hypersensitivity skin test, is an indicator of functions of the CMI

✓ positive in immunocompetent adults indicates intact CMI.

(Ref. Subash chandra Parija-2nd, P-610)

Q. Candida infection has a recognized association with *(BSMMU – Residency - **Dentistry** - March' 17)*

a) chronic renal disease
b) antibiotic treatment
c) oral contraceptives
d) menopause
e) cervical dysplasia

Ans. a) F b)T c) T d) F e) F

Q. Causative agents of oral thrush are *(BSMMU – Non-Residency - **MD/MS, Basic science** – 13Ju)*

a) *Actinomyces israelii*
b) *Actinomyces naeslundii*
c) *Candida albicans*
d) *Streptococcus mutants*
e) *Bacteroides gingivalis*

Ans. a) F b) F c) T d) F e) F

Help link: Candidiasis (thrush): Superficial candidiasis is caused by *Candida* spp., mainly *C. albicans*. Manifestations include oropharyngeal and vaginal candidiasis ('thrush'), intertrigo and chronic paronychia. Superficial candidiasis often follows antibiotic therapy. Intertrigo is characterized by inflammation in skin folds with surrounding 'satellite lesions'. Chronic paronychia is associated with frequent wetting of the hands. Superficial candidiasis is treated mainly with topical azoles, oral azoles being reserved for refractory or recurrent disease. Severe oropharyngeal and oesophageal candidiasis is a consequence of CD4+ T lymphocyte depletion/dysfunction, as in HIV infection. Recurrent vaginal or penile candidiasis may be a manifestation of diabetes mellitus. Rarely, mutations in the autoimmune regulator gene, *AIRE*, cause a syndrome of chronic mucocutaneous candidiasis **. (Ref: Davidson-23rd -381)**

Q. Causative agents in oral thrush- (MD/MS (DMC)-07Ja)

a) Actinomyees Israeli	F
b) Actinomyees naeslundii	F
c) Candida albicans	T
d) Streptococcus mutans	F
e) Bacteriodes gingivalis.	F

Others

Q. Fungal agents causing keratitis are: *(BSMMU – M. Phil, Diploma (Non-Residency)–March-2012, DMC & others – MD/MS – March-2012)*

a) Cryptococcus neoformans
b) Paracoccidioides brasiliensis
c) Aspergillus niger
d) Penicillium spp
e) Fusarium spp

Ans. a) F b) F c) T d) F e) T

IMMUNOLOGY

Immunization

Classification of immunity:

- Immunity
  - Innate immunity
  - Acquired immunity
    - Active immunity
      - Natural immunity
      - Artificial immunity
    - Passive immunity
      - Natural immunity
      - Artificial immunity

■ **Components or factors involved in innate immunity**:

1. Mechanical barriers/ Barrier to infectious agent	• Intactness of the skin and mucous membrane. • Muco-ciliary apparatus of upper respiratory tract. • Normal flora of different anatomical sites
2. Soluble factors	• Lysozymes of tears & saliva. • Acid pH of stomach & vagina. • Complements • Interferon α & β. • Fatty acid in skin
3. Cellular components	• Macrophage • Neutrophil • NK cells (natural killer cells)
4. Genetic factors	Individuals with deficiency of glucose 6-phosphate dehydrogenase are resistant to P. falciparum.

Innate immunity: Innate immunity protect us from hostile environment by the following factors:

A. **Factors that limit entry of micro-organisms into the body**:

Factors	Mode of action
1. Keratin layer of intact skin	Acts as mechanical barrier
2. Lysozymes of saliva & other secretions (e,g.tear)	Degrade peptydoglycans in bacterial cell wall.
3. Respiratory cilia	Elevate mucous-containing trapped organisms
4. Low pH of stomach acid & vagina; Fatty acid of skin	Retards growth of microbes
5. Surface phagocytes (e,g. alveolar macrophages)	Ingest & destroy microbes
6. Defensins (cationic peptides)	Create pores in microbial membrane
7. Normal flora of throat, colon & vagina	Occupy receptors which prevents colonization by pathogens.

B. **Factors that limit growth of microbes within the body**:

Factors	Mode of action
1. Neutrophils	Ingest & destroy microbes
2. Macrophages & dendritic cells	Ingest & destroy microbes and present Ag to helper T cell.
3. Natural killer cells	Kill virus-infected cells
4. Interferons	Inhibit viral replication
5. Complement	C3b is an opsonin; membrane attack complex creates holes in bacterial membranes
6. Transferrin & lactoferrin	Sequester iron required for bacterial growth
7. Fever	Elevated temperature retards bacterial growth
8. Inflammatory response	Limits spread of microbes
9. APOBEC3G (apolipoprotein B RNA-editing enzyme)	Causes hypermaturation in retroviral DNA and mRNA.

(Ref: Lange Review-15th)

C. **Genetic factors**:

1. Individuals with deficiency of glucose 6 phosphate dehydrogenase are resistant to P. falciparum.
2. Patients with sickle cell anaemia are also resistant to P. falciparum infection.

■ **Acquired immunity**: Acquired immunity is that type of immunity which develops after the exposure of an antigen & is not present by birth.

A. **Active immunity**: It is that type of acquired immunity, where immuno-competent cells of body participate actively. It is 2 types.

1. ***Natural immunity***: Active immunity which develops after clinical & sub-clinical infections, is called natural active immunity. eg. measles, small pox, mumps, rubella, tetanus. etc.
2. ***Artificial immunity***: The immunity which develops after vaccination. eg. DPT.

B. **Passive immunity**: It is that type of acquired immunity where the preformed Ab is introduced into a host to produce a specific immunity. It is of 2 types.

1. ***Natural immunity***: Here the Ab (IgG) from mother passes to the foetus through placental circulation. This Ab offers immunity for 6 month after birth. The secretory IgA is secreted in breast milk which offers local immunity in GIT in breast-feed baby.

2. ***Artificial immunity***: Here the preformed Ab is transferred to host from another human/animal where they offer a specific immunity. eg. ATS (anti-tetanus serum), ADS (anti-diphtheria serum), TIG , Human Ig against hepatitis B virus.

Innate immunity	Acquired/ adaptive immunity
1. It is present by birth	It develops after the exposure of an antigen.
2. Non-specific	Specific
3. No memory cell is produced	Memory cell is produced in active immunity
4. First line of defense	Second line of defense.
5. Secondary immune response occurs	Secondary immune response occurs in active immunity
6. Present in both vetebrate & invertebrate animals	Present in only vetebrate animals.
7. Cells- Macrophage, neutrophil, NK cells	Macrophage, B- cell, T- cell, neutrophil, NK cells, basophil, mast cell & platelets.
8. Soluble components- Lysozyme, acid pH of stomach & vagina, fatty acid of skin, complement & interferon α & β.	Ig, complements, cytokines, inflammatory mediators.

Active immunity	Passive immunity
1. It is that type of acquired immunity, where immuno-competent cells of body participate actively.	It is that type of acquired immunity where the preformed Ab is introduced into a host to produce a specific immunity.
2. Action starts slowly	Rapid
3. It gives long time even life long immunity	Shorter
4. Memory cell is produced	Not
5. Secondary immune response occurs	Not

Question Bank

Q. Components of the innate immune system are *(BSMMU – Non-Residency – **MD, MS, Paediatrics, Basic Science, Dentistry** – July' 19)*

a) lectin pathway of complement activation
b) natural killer cells
c) CD8 T-cells
d) B-cells
e) Macrophages

Ans. a) T b) T c) F (Acquired immunity) d) F(Acquired immunity) e) T

(Ref: Review of Microbiology by Apurbo Sankar-6th, P-52)

Q. Parts of the innate immune system are *(BSMMU – Diploma - **Dentistry** – July' 18)*

a) lectin pathway of complement activation
b) natural killer cells
c) CD8 cells
d) B cells
e) macrophages

Ans. a) T b) T c) F d) F e) T

Q. Passive immunization is given in *(BSMMU – Non-Residency – **MS, Basic science** – July' 18)*

a) enteric fever
b) diphtheria
c) rabies
d) botulism
e) cholera

Ans. a) F b) T c) T d) T e) F

Help Link:

FDA approved products for passive immunization and immunotherapy:

1) Botulism, CMV
2) Diphtheria, Rabies virus
3) HAV, HBV, VZV
4) Measles , Tetanus
5) Vaccinia against small pox

Q. Tissue fluids that act in innate immunity are *(BSMMU –Residency – **MD, MS, Basic Science** – March' 18)*

a) gastric acid
b) mucus
c) pleural fluid
d) tear
e) saliva

Ans. a) T b) T c) F d) T e) T

Q. Active immunity is induced by - *(BSMMU – Non-Residency – MD, MS, Basic Science & Dentistry – July' 17)*
a) placental transfer of antibody
b) contracting specific infection
c) viral infection
d) conjugate vaccination
e) injection of monoclonal antibody
Ans. a) F b) T c)T d) T e) F

Help link:

Active immunity:

- **Natural:** Exposure to the infectious agents, subclinical infection, eg: chicken pox
- **Artificial:** Vaccine, toxoid

Q. Immunity *(BSMMU – Residency - **Dentistry** - March' 17)*
a) helps in invasion by bacteria.
b) is responsible for transplantation reaction.
c) helps in hemostasis
d) cause damage to body tissue in some diseases
e) produces generalised weakness
Ans. a) F b) T c) F d) T e)F

Q. Characteristics of innate immunity are *(BSMMU – Residency - **MD, MS, Basic Science, Dentistry** - March' 17)*
a) rapid onset of action
b) long lasting immunity
c) first and second line of body defenses
d) acute phase proteins play important role
e) immune response is specific
Ans. a) T b) F c) T d) T e)F

Q. Active immunity achieved by *(BSMMU – Residency - **Dentistry** - March' 17)*
a) vaccine
b) immunoglobulin
c) toxoid
d) bacterial product
e) subclinical infection
Ans. a) T b)F c) T d) F e)T

Q. Components of innate immunity are *(BSMMU–Residency - **MD, MS, Basic Science, Dentistry** - March' 17)*
a) dendritic cells
b) mast cells
c) B lymphocytes
d) fibroblasts
e) natural killer cells
Ans. a) T b) T c) F d) F e)T

(Ref: Apurbo sankar-6th, P-51)

Q. Active immunity is produced by *(BSMMU – Diploma – Dentistry-July' 16)*
a) antitoxin
b) toxoid
c) immunoglobulin' s
d) live attenuated organisms
e) anti-serum
Ans. a) F b) T c) F d) T e) F

Q. Acquired immunity has following, characteristics *(BSMMU – MD/MS (Residency) – January, 2011)*

a) antigen specific	T
b) has memory	T
c) primary and secondary immune response	T
d) only T and B cell are involved	F
e) is independent of innate immunity	F

HELP LINK: see before +

Table: Differences between the innate and adaptive immune resonse systems:

Innate (non-specific system)	Adaptive (acquired system)
Components Anatomical and physiological barriers. Inflammatory response with leakage of antibacterial serum proteins (acute phase proteins) and phagocytic cells Phagocytosis by neutroptiils and macrophages Complements system.	**Components** 1. Cell mediated response effected by T cell. 2. Humoral immune response effected by B cell.
Properties 1. **Rapid**: responds within minutes to infection 2. No antigenic specificity, i.e. the same molecules and cells respond to a range of pathogens 3. No memory i.e. the response after repeated exposure 4. Performed or rapidly formed components.	**Properties** 1. **Slow**: response over days to weeks 2. Antigenic specificity i.e. each cell is programmed genetically to response to a single antigen 3. Immunological memory, i.e. on repeated, exposure the response is faster stronger and qualitatively different. 4. Diversty: ability to recognize and respond to a vast number of different antigens. 5. Self/ non-self recognition i.e. lack of response (tolerance) to self antigens but response to foreign antigens.

(Ref: Basic MRCP)

Q. Acquired immunity has following characteristics:*(BSMMU–MD/MS(Residency)–10 Ja)*

a) Antigen specific	T
b) Is independent of innate immunity	F
c) Only T and B cells are involved	F
d) Has memory	T
e) Primary and secondary response are not same	T

HELP LINK:

Acquired immunity:

This refers to acquired resistance to infections which an individual acquires during the course of his/her life. It is immunity specific for a particular disease, hence it is also known specific immunity.

It is of two types:

1. **Active immunity**—induced by infection or vaccination
2. **Passive immunity** - conferred by transfer of antibodies or lymphocytes from an actively immunized individual

Q. Innate immunity posses following features: (BSMMU – MD – January, 2010)

a) Present prior to exposure microbe	T
b) Plasma cells are the component of innate immunity	F
c) Posses both short and long term memory	F
d) Does not improve after exposure to GIT	T
e) Kills invading organisms and active acquired immune response	T

Q. The indicator of immune deficiency state includes: (BSMMU – MD – January, 2010)

a) more than 4 respiratory tract infections per year in an adult T
b) obesity F
c) infections with unusual organisms T
d) infections at unusual sites T
e) secondary hypertension F

Q. Examples of active immunization are: (DMC – M. Phil, Diploma July, 2008)

A. Small pox vaccination. T
B. Tetanus toxoid administration. T
C. Transplacental antibody transfer. F
D. BCG vaccination. T
E. Antitoxin therapy in diphtheria. F (passive immunization)

Q. Passive immunity is conferred by: (BSMMU - M. Phil, Diploma, July-08)

a) precipitated toxoid F
b) formalized toxoid F
c) antitoxic serum T
d) convalescent serum F
e) live vaccine F

Q. Followings are cell derived factors that participate in non-specific immune response: (BSMMU - M. Phil, Diploma, July-09)

a) Complement T
b) Interferon T
c) C-reactive protein F
d) Tumour necrosis fador (TNF) T
e) Lactic acid F

Q. Innate immunity is mediated by: (M. Phil, Diploma (DMC) (DMC)-07July)

a) physiological barrier T
b) lysozyme of tear T
c) T lymphocytes F
d) Eosinophils F
e) lymphokines F

Cells of immune system

■ **Components of immune system**:

	Examples
1.Cellular components/ Immuno-competent cells	♦ Macrophage ♦ B-lymphocyte ♦ T-lymphocyte ♦ NK cell / Natural killer cell ♦ Neutrophil ♦ Eosinophil ♦ Basophil ♦ Mast cell ♦ Platelet
2. Soluble components	♦ Ig / antibody ♦ Complements ♦ Cytokines

■ **Distribution of immuno-competent cells**: The cells are distributed throughout the body but predominantly in the lympho-reticular organs.

Q. Cells that play a role in innate immunity are *(BSMMU –Residency - **MD/MS, Basic science, Paediatrics, Dentistry** – March' 19)*
a) dendritic cells
b) CD4+ T lymphocytes
c) neutrophils
d) basophils
e) mast cells
Ans. a) T b) F c) T d) F e) T

Help Link:
Cells of innate immunity: NK cells, Macrophage, Neutrophils, Dendritic cells, Mast cells

	Innate immunity	Acquired immunity
Humoral immunity	Neutrophil Complement	B cell Plasma cell
Cell mediated immunity	Macrophage NK cell	Helper T cells Cytotoxic cells

(Ref: LANGE-14th, P-490)

Q. Cellular components of innate immunity includes *(BSMMU –Residency - **Dentistry** – March' 19)*
a) helper T cell
b) folicular dendritic cell
c) macrophage
d) natural killer cell
e) B cell
Ans. a) F b) T c) T d) T e) F
Help link: Cells of innate immunity: NK cells, Macrophage, Neutrophils, Dendritic cells, Mast cells

Q. Antibody producing cells are *(BSMMU –Residency - **Dentistry** – March' 19)*
a) B cells
b) T cells
c) macrophages
d) plasma cells
e) eosinophils
Ans. a) T b) F c) F d) T e) F

Q. Cell mediated immunity is the main host defense against *(BSMMU –Residency – **MD, MS, Basic Science** – March' 18)*
a) *Klebsiella spp.*
b) *Pneumocystis jiroveci*
c) *Mycobacterium tuberculosis*
d) *Candida albicans*
e) *Streptococcus pyogenes*
Ans. a) F b) T c) T d) T e) F

Q. Cell mediated immunity involves the following mechanisms *(BSMMU – Residency - **Dentistry** - March' 17)*
a) IgG
b) T lumphocytes
c) eosinophils
d) complement
e) macrophages
Ans. a) F b) T c) F d) F e)T

Q. Antibody attacks foreign invader by *(BSMMU – Residency - **Dentistry** - March' 17)*

a) toxins
b) lysis
c) chemotaxis
d) clotting
e) precipitation

Ans. a) F b)T c) F d) F e)F

Q. Components of CMI include *(BSMMU –Residency - **MD/MS, Basic science** – March' 14)*

a)	CD4 lymphocyte	T
b)	memory T cell	T
c)	platelet	F
d)	basophil	F
e)	macrophage	T

Q. The following components are associated with cell mediated immunity: *(BSMMU – Residency – MD/MS – March'13)*

a) IgG
b) T-lymphocytes
c) Eosinophils
d) Complements
e) Macrophage

Ans : a) F b) T c) F d) F e) T

Q. In the immune system of the body *(BSMMU – MD/MS (Residency) – January, 2011)*

a) germinal centres are absent from the speen.	T
b) germinal centres produce lymphocytes.	T
c) the neutrophils are phagocytic cells.	T
d) the antigen presenting cells include the Langerhans' cells of skin.	T
e) the T-cells mature both in the central and peripheral lymphoid tissues.	F (mature in thymus)

HELP LINK:

The immune system comprises structures and cells that are distributed throughout the body; their principal function is to protect the body from invasion and damage by microorganisms and foreign substances. Cells of the immune system have the ability to distinguish "self" (the organism's own macromolecules) from "nonseif" (foreign substances) and to coordinate the destruction or inactivation of foreign substances (eg, individual molecules), parts of microorganisms, or even cancer cells that originate in the body. On occasion, the immune system reacts against normal body tissues, causing autoimmune diseases. The immune system includes both individual structured (eg, lymph nodes, spleen) and free cells (eg, lymphocytes, granulocytes, and cells of the mononuclear phagocyte system that are present in the blood, lymph, and connective tissues) that participate in immune responses. Another important component of the immune system is the antigen-presenting cells, found not only in the lymphoid tissues but also in other organs, such as the 'skin (which is heavily exposed to foreign antigens). The cells of the immune) system communicate with each other and with cells of other systems through signaling proteins known as **cytokines**.

Q. Cell mediated immune processes are of great importance in the control of the following infections: *(BSMMU – M. Phil, Diploma (Non-Residency) – 11Ju, DMC & others – MD – 11Ju)*

a) pneumonia
b) diphtheria
c) tuberculosis
d) candidia
e) mumps

Ans.

a) **False** Cell-mediateci immunity plays no part in the host's defences against pneumococcal infections. These organisms are opsonised and killed by humoral antibody, and complement The specificity of the antibody is directed against the 'specific soluble substance', the pnumococcal polysaccharide Antibodies against these soluble antigen were used prior to the introduction of antibiotics for immunotherapeutic purposes with some success.

b) **False** Cell-mediated immunity is not involved in diphtheritic infections. *Corynebacterium diphtheriae* is harmful because it produces an exotoxin which particularly damages the myocardium and peripheral nerves. This toxin may be inactivated before it is fixed in the tissues by an antitoxin which can be prepared in the horse. The use of this antitoxin carries the risk of anaphylaxis or serum sickness and, therefore active immunization with toxoid is preferable

c) **True** Host resistance to mycobacteria is dependent on cell-mediated immune processes. The mycobacteria are facultative intracellular parasites and are found mainly within macrophages. If cell-mediated immunity fails dissemination of the disease occurs and frequently a negative delayed hypersensitivity test is found as in miliary tuberculosis.

d) **True** A failure of cell-mediated immunity is frequently associated with mucocutaneous or diffuse candidiasis. Thus diffuse candidiasis may occur in Hodgkin's disease and non-Hodgkin's lymphomas and in the primary T-cell deficiencies of childhood associated with a specific failure of T-cell response to candida antigens. Transfer factor has been successfully used to treat muco cutaneous candidiasis by specifically increasing the T-cell response to Candida albicans.

e) **True** Mumps is caused by a paramyxovirus. Previous infection with mumps virus is associated with a positive delayed hypersensitivity skin reaction. Mumps antigen is one of the standard skin test reagent used to diagnose a general non-specific loss of cell-mediated immunity in adults with conditions such as non-Hodgkih's lymphomas, Hodgkin's disease and sarcoidosis.

Q. Component of cell mediated immunity includes: *(BSMMU - M. Phil, Diploma – July '10)*

a) neutrophil F
b) T helper cell T
c) cytotoxic T cell T
d) eosinophil F
e) macrophage T

Q. Following are the components of cell mediated immunity - (DMC – MD/ MS - January, 2010)

a. mast cells F
b. neutrophil F
c. macrophage T
d. T-lymphocytes T
e. N-K cell T

Q. Component of cell mediated immunity include: (BSMMU – MD/MS – January, 2010)

a) Helper T cell T
b) Cytotoxic T cell T
c) Neutrophil F
d) Eosinophil F
e) Macrophage T

Q. Innate immunity is maintained by: (MD/MS (DMC) – 06Ja)

a. T cells F
b. B cells F
c. Polymorpho nuclear leukocytes T (neutrophils)
d. Macrophage T
e. NK cell T

Q. Cell mediated immunity involves the followings- (BSMMU – MD/MS - 06Ja)

A. Ig-G
B. T lymphocytes
C. Eosinophils
D. Complements
E. Macrophages

Ans.
a) F *(It provides humoral immunity)* b) T
c) F d) F *(It provides humoral immunity)*
e) T *(Macrophages & NK cells are the Cells of cell mediated immunity)*

Q. Cell mediated immunity involve the following cells: (MD/MS (DMC)-01Ja,00Ju)

A. IgG. F
B. T lymphocytes T
C. Eosinophils F
D. Complement F
E. Macrophages T

HELP LINK: See before

T cell

Q. Principal cytokines produced by T_H2 cells are *(BSMMU –Residency - **Dentistry** – March' 19)*

a) IL-4
b) IL-17
c) IL-5
d) IL-10
e) IFN-β

Ans. a) T b) T c) T d) T e) F (Produced by Fibroblast)

Help Link:

Sources of Cytokines:

Cytokines of Innate immunity:

- ✓ IL-1: Monocytes, macrophage, Endothelial cells, epithelial cells,
- ✓ TNF- alpha: Macrophage
- ✓ IL-12: Macrophage, Dendritic cells,
- ✓ IL-6: Macrophage, Endothelial cells
- ✓ Interferon-alpha: Macrophage
- ✓ Interferon Beta: Fibroblast

Cytokines of adaptive immunity:

- ✓ IL-2: T -cells
- ✓ IL-4: TH-2 cells, Mast cells
- ✓ IL-5: TH-2 cells
- ✓ TGF-beta: T-cells, Macrophage
- ✓ Interferon- gamma: TH-1 cells, CD8 cells, NK cells

➢ IL-17 -producing $CD4^+$ T cells into either Th1 or Th2 subsets.
➢ IL- 10 : T (TH-2 subset) and B lymphocytes.

(Ref. Prof Akram immunology-5th, P-125)

Q. Sources of interferon gamma are *(BSMMU –Residency - **Dentistry** – March' 19)*

a) NK cells
b) macrophages
c) T lymphocytes
d) dendritic cells
e) platelets

Ans. a) T b) F c) T(Th1 cells and some CD8 cells) d) F e) F

Help Link: Interferon- gamma: TH-1 cells, CD8 cells, NK cells

(Ref: Prof Akram immunology-5th, P-125)

Q. T cell functions are assessed by *(BSMMU – Residency - **MD, MS, Basic Science** - March' 17)*

a) complement fixation test (CFT)
b) precipitation test
c) skin testing
d) agglutination test
e) lymphocyte proliferation assay

Ans. a) F b) F c) T (e.g. delayed type hypersensitivity) d) F
e) T (lymphocyte function assessed by mixed lymphocytic reaction (MLR) with responder lymphocyte)

Q. Cytotoxic T-cells are involved in the following functions: *(BSMMU – M. Phil, Diploma (Non-Residency)– March-2012, DMC & others – MD/MS – March-2012)*

a) lysis of viral infected cells T
b) antibody production F
c) graft rejection T
d) tumour destruction T
e) antigen presentation F

HELP LINK:

Cytotoxic (Tc) T-cells (CDS Cells)

•These cells are responsible for killing of specific target cells whose surface antigens can be recoganized by them, e.g. virally infected host cells, tumour cells and allogenic graft cells in transplanted tissues
• They possess membrane glycoprotein CD8 receptors on their surface
• They cause destruction of target cells by releasing lymphotoxins, and perform.

Q. T cells have following characteristics: *(BSMMU – MD/MS (Residency) – January, 2011)*

a) are produced in Bone marrow in adult T
b) mature in thymus and bone marrow F (only thymus)
c) are of two types CD4+ and CD8+ T
d) produce antibody F
e) takes part in ADCC T

HELP LINK:

Table: Comparison of T Cells and B Cells.

Feature	T Cells	B Cells
Antigen receptors on surface	Yes	Yes
Antigen receptor recognizes only processed peptides in association with MHC protein	Yes	No
Antigen receptor recognizes whole, unprocessed proteins and has no requirement for presentation by MHC protein	No	Yes
IgM on surface	No	Yes
CD3 proteins on surface	Yes	No
Clonal expansion after contact with specific antigen	Yes	Yes
Immunoglobulin synthesis	No	Yes

Regulator of antibody synthesis	Yes	No
IL-2, IL-4, IL-5, and gamma interferon synthesis	Yes	No
Effector of cell-mediated immunity	Yes	No
Maturation in thymus	Yes	No
Maturation in bursa or its equivalent	No	Yes

Q. Followings are the cell surface proteins that play an important role in immune response: (BSMMU – MD – January, 2010)

a) CD28 in helper T cells T
b) CD8 in cytotoxic T cells T
c) B7 in macrophages T
d) Class II MHC in B cells T
e) TCR in helper T cells not in cytotoxic T cells F

HELP LINK:

Cell surface proteins that play an important role in the immune cells:

Type of cells	Surface proteins
Helper T-cells	CD4, TCR, CD28
Cytotoxic T-cells	CD8, TCR
B-cells	IgM, B7
Macrophages	Class II MHC
Natural killer cells	Receptors for class I MHC
All cells other than mature red cells	Class I MHC

(Ref: LANGE Review-15th)

Q. Main functions of helper T cells: (BSMMU – MD – January, 2010)

a) Activate CD8 cells via IL-2 T
b) Activate B cells via IL-2 F (through IL-4, IL-5)
c) Secret IL-2 T
d) Activate natural killer cells F (activate CD8)
e) Activate macrophages through gamma IFN T (IFN-α)

HELP LINK:

Main Functions of Helper T Cells.

Main Functions	Cytokine That Mediates That Function
Activates the antigen-specific helper T cell to produce a clone of these cells	IL-2
Activates cytotoxic T cells	IL-2
Activates B cells	IL-4 and IL-5
Activates macrophages	Gamma interferon

(Ref: Lange Review-15th)

Q. Cytotoxic T cells are involved following functions: (BSMMU – MD/MS - January, 2008)

a) graft rejection T
b) antigen presentation F
c) lysis of virus infected cells T
d) antibody formation F
e) tumour destruction T

HELP LINK:

■ **Functions of T-cell**:

a) **CD4+ T-Cell / Helper T-cell**:

1. Activated CD4+ T-cell produce interleukins (IL-2 to IL-6) which causes activation, proliferation & differentiation of B-cell into plasma cells & memory cells. Plasma cells then produce Ig & memory cells participate in 2ndary immune response. So, helper T-cells participate in humoral immunity.
2. IL-2 produced by activated helper T-cell activates CD8+ cytoxic T-cell which then participate in cellular immunity. So, CD4+ T-cell participate in cellular immunity.
3. CD4+ T-cell produces lymphokines which activates macrophages & active macrophages then destroy the ingested microbes by intracellular killing mechanism. So, CD+4 T-cell participate in cellular immunity.
4. Lymphokines produced by CD4+ T-cell produce delayed type hypersensitivity i.e type 4 hypersensitivity.

b) **CD8+ T-cell**:

1. CD8+ suppressor T-cell regulates the immunological reaction by suppressing the action of activated CD4+ T-cell.
2. CD8+ cytotoxic T-cell can destroy the virus infected cells, tumor cells & allograft cells by extracellular killing mechanism.

Q. T cell function can be assessed by: (M. Phil, Diploma (DMC)-07July)

a) complement fixation test F
b) polyacrylamide gel electrophores F
c) skin testing T
d) agglutination tests F
e) lymphocyte proliferation T

HELP LINK:

The principal tests for T -lymphocyte deficiencies are

1. Total lymphocyte count and
2. quantitation of lymphocyte subpopulations by flow cytometry.

Serum immunoglobulins should also be quantified. Functional tests of T-cell activation and proliferation and/ or an HIV test may be indicated.

Patients with suspected T-cell immune deficiencies should receive antipneumocystis and antifungal prophylaxis, and require aggressive management of specific infections. Immunoglobulin replacement may be indicated if disease is associated with defective antibody production. Stem cell transplantation may be appropriate in bare lymphocyte syndromes, and thymic transplantation has been used for DiGeorge syndrome.

Lymphocyte proliferation can be assessed in HLA tissue typing before organ transplantation and lymphocyte are mixed together to see DNA structure.

Q. T cell function can be evaluated by: (BSMMU - M. Phil, Diploma, July-07)

a) complement fixation test F
b) mitogen induced in vitro lymphocyte proliferation T
c) skin testing T
d) mixed lymphocyte reaction (MLR) T
e) agglutination test F

Q. After release into blood stream the T-lymphocytes are colonized in: (MD/MS (DMC) – 06Ja)

a) Spleen T
b) Bone marrow F
c) Lymphatic follicles T
d) Liver F
e) Lymph node T

Q. Following are applicable for T lymphocytes –(BSMMU – MD - 02Ja)

a) Constitute 70— 80% of total peripheral lymphocytes T
b) Have receptors for EB virus F
c) CD_4 cells have regulatory effects on B lymphocytes T
d) Can recognize unprocessed antigen F
e) Can recognize antigen in association with class 1 MHC molecules T

Q. CD4 + lymphocytes- (BSMMU – MD - 01Ja)

a) Are cytotoxic for orally infected cells	F
b) Are restricted in antigen recognition by MHC class II molecules	T
c) Released cytokines in response to antigen stimulation.	T
d) Are major target cell for infection with HIV	T
e) Are involved in delayed type hypersensitivity.	T

Help link: In HIV CD4 : CD4 ratio is altered. Normal ration CD4: CD8 = 4 : 1

B cell

Q. Characteristics of memory B cell: (BSMMU - MS –10Ja)

a) produced by polysaccharide antigen stimulation	F
b) have surface immunoglobulin receptor	T (IgM monomer)
c) cytokines are involved in their production	T
d) response to antigen within 7-10 days	F (3-5 days)
e) produced only IgM	F (IgG)

Help link: Memory B cells are produced due to stimulation of protein antigen.

Q. Following are applicable for B- lymphocytes— (BSMMU - M. Phil, Diploma, July-05)

a) constitute about 70% of lymphocyte profile
b) has surface immunoglobulin receptor
c) recognize the antigen is association with MHC class II molecule
d) has receptor for complement
e) acts as antigen presenting cell

Ans.

a) F (15-20%) b) (IgM, IgD) c) F (Recognition is a function of CD4T lymphocyte) d) F e) T

HELP LINK:

■ **Origin**: Stem cells of bone marrow.

■ **Maturation**: B-cell matures in bursa fabricius, a lympho-epithelial organ in birds. In human, B-cell matures in micro-environment of bone marrow.

■ **Nomenclature**: B-cell matures in bursa fabricius in birds. From this name, the cells are nomanclated as B- cell lymphocyte.

■ **Receptors of B-cells**:

1. Ag receptors of B-cell are Ig which are mainly monomeric IgM & IgD.
2. B-cell has got receptors for Fc fragment of IgG & receptor for Epstein-barr virus.

■ **Functions of B-cells**:

1. B-cell is transformed into plasma cell to produce Ig.
2. B-cell is differentiated to memory cell which participate in secondary immune response.
3. B-cell also act as antigen presenting cell (APC).

(Ref: LANGE Review-15th)

■ **Differences between B-cell & T-cell:**

Traits	B- cell	T-cell
1. Origin	Stem cell of bone marrow.	Stem cell of bone marrow
2. Maturation	Micro-environment of bone marrow	Thymus.
3. Ag receptors	IgM, IgD, EBV	T cell receptors, Sheep RBC
4. Presence of IgM on surface	Present	Absent
5. CD Molecule	CD14, CD20, CD22	CD3 For all T-cells, CD4 for CD_4 + T-cells, (66%) CD8 for CD8+ T-cells.(33%)
6. Production of Ig	B-cell after differentiation into plasma cell produce Ig	Can't
7. Humoral immunity	Participate in humoral immunity	CD4+ T-cell participate in humoral immunity but not CD8+ T-cell
8. Cellular immunity	Can't participate in cellular immunity	Both CD4+ T-cell & CD8+ T-cell participate in cell mediated immunity.
9. Function as APC	Can act as antigen presenting cell.	Can't act.
10. % in blood	20-35%	65-80%
11. Presence of sheep RBC receptor on cell	Yes	No

Q. Following statements are applicable for B cells- (BSMMU – MD/MS - 02Ja)

a) Produce humoral immunity T
b) Do not require any help from T cells. F
c) Large surface immunoglobulin F
d) About 75% of total circulating lymphocytes F
e) Produce IgM in primary immune response. T

Mononuclear phagocytic system

Q. Function of macrophages are *(BSMMU – Non-Residency – **Dentistry** – July' 19)*

a) activation of B cells
b) produce antibodies
c) cytokine production
d) antigen presentation
e) phagocytosis

Ans. a) F b) F c) T d) T e) T

(Ref. LANGE-14th, P-514)

Q. Cells belonging to the mononuclear phagocytic system are *(BSMMU –Residency - **Dentistry** – March' 19)*

a) macrophages
b) mast cells
c) epithelioid cells
d) fibroblasts
e) Kupffer cells

Ans. a) T b) F c) F d) F e) T

Help Link:

In the gut	Intestinal macrophages
In the lung	Alveolar macrophages
In connective tissues	Histocytes
In the liver	Kupffer cells
In the kidney	Mesangial cells
In the brain	Microglial cells
In bone	Osteoclasts

Q. Cells of monocyte-macrophage system include *(BSMMU –Residency – MD, MS, Basic Science, Dentistry – March' 18)*
a) Kupffer's cell
b) histiocyte
c) microglia
d) mesengial cell
e) neutrophil
Ans. a) T b) T c) T d) T e) F

Q. The cells of mononuclear phagocytic system originates from – (MD/MS (DMC) – January, 2008)
a) spleen F
b) thymus F
c) liver F
d) bone marrow T
e) lymph node F

Help link:

Mononuclear phagocytic system:

- Older name: Reticuloendothelial system or macrophage system
- Origin of cells: Bone marrow
- Location of cells: Reticular connective tissue
- **Primary cells**: Monocytes and macrophage
- The cells may accumulate in the following organs:
  - Spleen(largest unit), lymph node, different tissue like lung, brain, bone

Q. Regarding mast cells - (BSMMU - M. Phil, Diploma, July-05)
a) they are found mostly near the small blood vessels T (also connective tissue)
b) have surface receptor for IgE T
c) they liberate histamine T
d) mostly formed in the spleen F
e) have large cytoplasmic vacuoles F

Help link:

Functions of mast cells:

- Found mostly near the small blood vessels
- Basophils and mast cells have receptors on the cell surface for the Fc portion of IgE.
- When cross-linked by antigen, release of histamine, and enzymes, such as peroxidases and hydrolases and causes inflammation and severe immediate hypersensitivity reactions such as systemic anaphylaxis.
- play role in innate response to bacteria and viruses.
- The surface contain Toll-like receptors that recognize bacteria and viruses.

- Major role in rheumatoid arthritis, where produce both inflammatory cytokines and enzymes that degrade the cartilage in the joints.

Q. Macrophages: (DMC - MD/MS - 02Ja)

a) Are derived from blood monocytes.	T
b) Can multiply	F
c) Fuse to form multinucleate giant cells.	T
d) Live longer than neutrophils.	T
e) Produce immunoglobulins	F

HELP LINK:

Macrophage:

■ **Origin**: Stem cells of bone marrow.

■ **Nomenclature**: They are synthesized as monocytes & when they are in circulation, they are called blood monocytes. These monocytes when become fixed with different organs, they are called macrophages.

■ **Distribution of macrophages**:

- ♦ Skin- Langerhan's cell.
- ♦ Interstitial tissue- Histiocyte.
- ♦ Brain - Microglia
- ♦ Lungs - Alveolar macrophage
- ♦ Liver - Kuffer's cells
- ♦ Spleen- •Splenic macrophage •Red pulp macrophages
- ♦ Kidney - Messangial cells.
- ♦ Lymph node - Resident macrophage.

■ **Functions of macrophages**:

1. ***Phagocytosis***:
   a. Macrophages can phagocytose Ag directly & can destroy intracellularly by formation of phagolysosome. This group of macrophages are called '**professional macrophage / phagocytic macrophage**'.
   b. Another group of macrophages have receptors on their surfaces for Fc portion of IgG. So, they can phagocytose the opsonized Ag by IgG. [Opsonized = Coating of Ag by Ab]
   c. These macrophages have got receptors for C3b also. They can phagocytose C3b coated Ag.
2. ***Antigen presentation***: Antigen presenting macrophages are called APC. They engulf the Ag which are processed, fragmented & expressed on the cell surface along with MHC class I Ag or MHC class II Ag.
   - When the Ag is expressed along with class II Ag, they are recognized by CD4 + T-cells.
   - When the Ag are expressed along with class I Ag, they are recognized by CD8+ T-cell.
3. ***Release of cytokines***:
   i. During the process of Ag presentation, APC secretes IL-I which activates the CD4+ T-cell.
   ii. TNF-α (Tumor necrotinize factor- α) takes part in inflammation.

(Ref: Lange-26th)

Lymphoid organ

Q. Primary lymphoid organs are- (MD/MS (DMC)-05Ja)

A. Bone marrow	T
B. Lymph nodes	F
C. Thymus	T
D. Spleen	F
E. Peyer's patches	F

HELP LINK:

Immune system is composed of lympho-reticular organs.

1. Primary/ Central lymphoid organs:	2. Peripheral lymphoid organs:
♦Bone marrow ♦Thymus	♦Spleen ♦Lymph node ♦MALT (Mucosa associated lymphoid tissue): eg. Peyer's patches.

Antigen presenting cells

Q. Antigen presenting cells are *(BSMMU –Residency – Dentistry – March' 18)*
a) dendritic cell
b) macrophage
c) T lymphocyte
d) B lymphocyte
e) NK cell
Ans. a) T b) T c) F d) T e) F

Q. Antigen presenting cells are *(BSMMU – Non-Residency – MD, MS, Basic science – July' 16)*

a) dendritic cell	T
b) macrophage	T
c) T cell	F
d) B cell	T
e) natural killer cell	F

HELP LINK:

■ **Definition**: The immunocompetent cells which receive, process & present antigen to helper T cell, are called antigen presenting cells. Or,

Any cell, bearing surface class II MHC antigens, involved in processing and presentation of antigen to Helper T-cells or CD4+ T-cells, are called antigen-presenting cells (APCs).

■ **List of antigen presenting cells:**

1. ***Phagocytic cells***:
   - Monocytes
   - Macrophages*
   - Kupffer cells
   - Dendritic cell* (Professional APC) & follicular dendritic cell etc.
2. ***Lymphocyte***: Activated B-lymphocyte*.
3. ***Non-phagocytic constitutive presenters***: Langerhans cells
4. ***Facultative presenters***:
   - Astrocytes
   - Endothelium
   - Fibroblasts.

Q. Professional antigen presenting cells are *(BSMMU – Residency – MD, MS, Basic science, Dentistry – March' 16)*

a) B lymphocyte	T
b) natural killer cell	F
c) macrophage	T
d) neutrophil	F
e) dendritic cell	T

Q. Professional antigen presenting cells are *(BSMMU – Non-Residency – MD/MS, Basic science – July' 14, 13; Residency – MD/MS – March'13)*
a) dendritic cells
b) fibroblasts
c) pancreatic cells
d) B cells
e) macrophages

Ans. a) T b) F c) F d) T e) T

Q. Followings are professional antigen presenting cells *(BSMMU – MD/MS (Residency) – January, 2011)*

a) dentritic cell	T
b) fibroblast	F
c) B cell	T
d) pancreatic beta cells	F
e) macrophage	T

Q. Antigen presenting cells are: (BSMMU - M. Phil, Diploma, July-07)

a) Macrophage	T
b) Eosinophil	F
c) Kupffer's cells	T
d) Basophil	F
e) B lymphocyte	T

HELP LINK:

■ Antigen presenting cells:
- Macrophage
- Monocytes
- Kupffers cells
- Microglial cells
- Skin Langerhans cell
- Dendritic cell

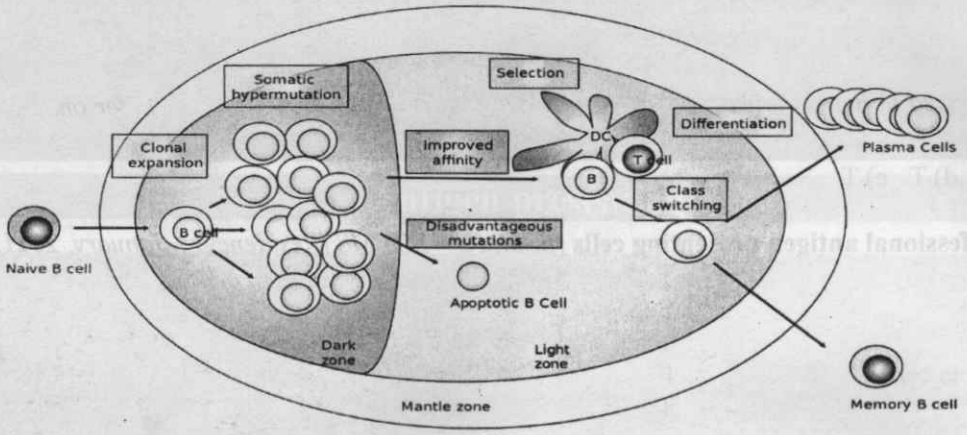
Q. Antigen presenting cells are: (MD/MS (DMC)-03Ja)

a) Kupffers cells	T
b) Plasma cells	F
c) T cells	F
d) Microglial cells	T
e) Macrophage	T

Natural killer cell

Q. Natural killer cells have the ability to destroy *(BSMMU –Residency - MD/MS, Basic science, Paediatrics, Dentistry – March' 19)*
a) irreversibly stressed cells
b) germinal center cells
c) virus infected cells
d) senescent epithelial cells
e) cancer cells

a) T (they have the ability to recognize stressed cells in the absence of antibodies and MHC, allowing for a much faster immune reaction) b) F c) T d) F e) T



(Ref: Wikipedia)

Fig: Germinal center of L.N

Others

Q. Immune component that reacts with Fc receptor are *(BSMMU – Non-Residency - MD/MS, Basic science – 13Ju)*

a) Macrophages T
b) NK cells T
c) B cells T
d) immunoglobulin E F
e) C3a F

Major Histocompatibility Complex (MHC)

■ **Definition**: The cluster of genes located in the short arm of chrosomose 6 is called MHC.

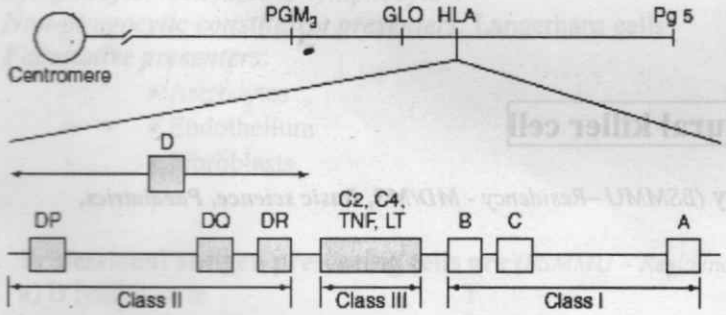


Fig. The human leukocyte antigen (HLA)–gene complex. A, B, and C are class I loci. DP, DQ, and DR are class II loci. C2 and C4 are complement loci. TNF = tumor necrosis factor; LT = lymphotoxin. PGM3, GLO, and Pg5 are adjacent, unrelated genes.

■ **MHC Antigen/MHC molecules/HLA (Human leukocyte Ag)**:

- Products of genes of MHC = MHC antigen/MHC molecule/HLA.
- Products of genes A,B,C = MHC class I Ag.
- Products of genes DP, DQ, DR = MHC Class II Ag.

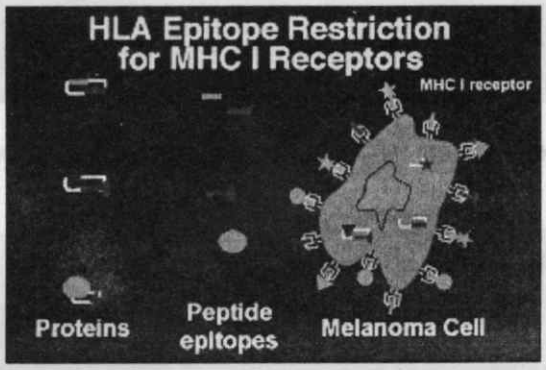
- In between MHC class I genes & MHC class II genes, there is another clusters of genes, which is known as MHC class III Ag, which includes complements, C_4, TNF (Tumour necrotizing factor) and LT.

Expression: MHC class I & class II Ags are expressed on the cell surface. MHC class III Ags are soluble Ag & secreted in circulation.

[These Ags were 1st detected in human leukocyte and nomenclatured as human leukocyte Ag. Later on, these Ags were detected in other cells also. So, the HLA becomes misnomer, but traditionally the term is still in used.]

■ **Distribution of MHC Ag**:

1. MHC class I Ag are present in all nucleated cells and platelets. So, they are present in all immuno-competent cells as well as other nucleated cell.
2. MHC class II Ag are present in monocyte, macrophage, B-cell & active helper T-cell (CD4+).
3. MHC class III Ag are soluble Ag, secreted in circulation. Not expressed on the cell surface.



■ **Biological importance/functions of MHC**:

1. ***Antigen recognition***:
   - CD4 + T cell can recognize Ag when it is presented along with class II MHC molecules.
   - CD8 + cytotoxic T cell can recognize Ag when it is presented along with class I MHC molecules.
   - The proteins which are endogenously synthesized are usually presented along with MHC class I Ag.eg. viral proteins.
   - The tumour markers are usually presented with class I Ag and are recognized by CD8+ cytotoxic T cell & destroy them by extracellular killing mechanism.
   - The exogenous proteins which are taken up by the Ag presenting cell while it is processed, fragmented & presented on the APC along with MHC class II Ag.

3. ***Importance in transplantation***: MHC Ags are allo-antigen i.e. they are different in different individuals of same species. eg, the MHC Ag of kidney cells of one individual is different from MHC Ag of kidney cells of other individuals. So it has got a very important role in organ transplantation like blood grouping, HLA typing & matching. It is necessary for successful organ transplantation.If HLA is not well matched, the immuno-competent cells of recipient will recognize the HLA antigens of donar tissues or cells as foreign. So, there will be immunological reaction resulting rejection of transplanted tissues.

3. ***Association with diseases***: Many diseases have got a reaction with HLA genes. eg. there is 80% possibility in developing of ankylosing spondilytis in a person who possesses HLA allele.

Comparison between class-I and class-II MHC proteins:

Feature	Class I MHC Proteins	Class II MHC Proteins
1. Present antigen to CD4-positive cell	No	Yes
2.Present antigen to CD8-positive cells	Yes	No
3.Found on surface of all nucleated cells	Yes	No
4.Found on surface of "professional" antigen-presenting cells, such as dendritic cells, macrophages, and B cells	Yes[1]	Yes
5.Encoded by genes in the HLA locus	Yes	Yes
6.Expression of genes is codominant	Yes	Yes
7.Multiple alleles at each gene locus	Yes	Yes
8.Composed of two peptides encoded in the HLA locus	No	Yes
9.Composed of one peptide encoded in the HLA locus and a β_2-microglobulin	Yes	No

(Ref: Lange Review-15th)

Question Bank

Q. Human leukocyte antigens are *(BSMMU –Residency - MD/MS, Basic science, Paediatrics, Dentistry – March' 19)*
a) intracellular glycoprotein
b) encoded by MHC gene
c) present on the cell surface of almost all nucleated cell
d) play major role in causing infection
e) play a critical role in antigen presentation
Ans. a) F (surface glycoprotein) b) T c) T (MHC -1 present in all nucleated cells including platelets except RBC) d) F e) T (MHC -1 presents antigen)

Q. MHC restriction is experienced by *(BSMMU – Residency – MD, MS, Basic science, Dentistry – March' 16)*

a) helper T lymphocytes	T
b) B-lymphocytes	F
c) macrophages	F
d) lymphokine activated killer cell (LAK)	F
e) NK cell	F

Q. MHC class II molecules are expressed on *(BSMMU – Residency – MD, MS, Basic science, Dentistry – March' 16)*

a) dendritic cell	T
b) fibroblast	F
c) macrophage	T
d) platelet	F
e) red blood cell	F

Q. Regarding MHC molecules *(BSMMU –Residency – MD, MS, Basic – March' 15)*
a) they are cell surface glycoprotein
b) MHC I molecules present only on antigen presenting cells surface
c) play critical role in self and nonself recognition
d) highest level of MHC molecules are expressed on hepatocytes
e) MHC genes are located on short arm of chromosome 6
Ans. a) T b) F c) T d) F e) T

Q. MHC class I molecules *(BSMMU –Residency – MD, MS, Basic Science – March' 15)*
a) are only expressed on professional antigen presenting cells
b) are highly polymorphic
c) associated preferentially with pathogen derived peptides
d) associated with β-microglobulin
e) accommodate peptides in an open-ended peptide binding groove
Ans. a) F b) T c) F d) T e) T

Q. Class II MHC protein *(BSMMU –Residency – MD, MS, Basic Science – March' 15)*
a) found on the surface of both T cell and B cells
b) have high degree of polymorphism
c) involved in the presentation of antigen by macrophage
d) have binding sites for CD4 proteins
e) composed of one polypeptide chain
Ans. a) F (B cell bcoz it is a APC) b) T c) T d) T e) F

(Ref: LANGE-15th, P-531)

Q. Diseases associated with HLA are *(BSMMU – Non-Residency - MD/MS, Basic science – 13Ju)*

a) familial poliposis coli	F
b) insulin dependent diabetes	T (HLA DR3 and DR4)
c) cushings disease	F
d) tuberculosis	F
e) ankylosing spondylitis	T (HLA B27)

Q. The major histocompatibility complex (MHC) in man: (BSMMU – MD – January, 2010)

a) is situated on chromosome 6	T
b) the genes are grouped into class I and class II	F (also class III)
c) is involved in antigen presentation	T
d) has positive association with renal failure	F
e) is tested on a serum sample.	F

Q. MHC class-I molecules- (BSMMU-MS-04Ja)

a) Are encoded in HLA A,B & C genes	T
b) Present only in antigen presenting cells	F
c) Presence antigen to CD8+ cells	T
d) Are Involved in cytolytic killing of target cells by 'T' helper cell	F (CD8 cell)
e) Involed in recognition and rejection of allograft	T

Q. The majority of HLA antibodies are: (MD/MS (DMC)-01Ja)

A. IgA.	F
B. IgD.	F
C. IgE.	F
D. IgG	T
E. IgM.	F

ANTIGEN

Q. Following are the determinants of antigenicity of a good antigen: *(BSMMU – M. Phil, Diploma (Non-Residency)–March-2012, DMC & others – MD/MS – March-2012)*

a) low molecular weight	F
b) foreignness	T
c) chemically complex	T
d) lipid in nature	F (protein)
e) structural-rigidity	T

HELP LINK:

■ **Criteria of good immunogen/Ag:**

1. **Foreignness**: To be a good immunogen, a substance must be foreign to the host or foreign to the immunological system. e.g. When rabit serum is introduced into a rabit, it does not produce Ab, but when introduced into a guineapig produces Ab.
2. **Molecular weight**: The greater the molecular wt. of a substance, the greater the immunogenicity. Molecular weight > 10,000 are more immunogenic.
3. **Chemical structural complexity**:
   - Chemically complex substances are more immunogenic.
   - Chemical complexity is provided by ring structures or side chains.
   - Protein substances are more immunogenic because they contain ring structures or side chains.
4. **Rigidity**:
   - Within a certain limit, greater the rigidity, greater the immunogenicity of a substance.
   - Rigidity is provided by coiling and folding.
   - DNA is not immunogenic due to hypercoiling. But it becomes immunogenic when it is decoilled.
5. **Suitable host**: A substance which is immunogenic in one host is less immunogenic or no immunogenic in another host.
6. **Route of administration**: Some substances when introduced orally, they produce allergic response, but when they are introduced parenterally, they do not so. e.g. insulin.
7. **Dosage**: Upto a certain limit, when the dose is increased, immune response is also increased, but a minimum dose of Ag is required below which immune response is not achieved.

(Ref: LANGE Review-15th)

Immunoglobulins

■ **Classification of Ig**: On the basis of amino acid sequence in the constant region of heavy chain the Ig are divided into 5 classes.

- IgG contains γ chain
- IgA contains α chain
- IgM contains μ chain
- IgE contains ε chain
- IgD contains δ chain

■ **Subclass of Ig**:

- IgG contains 4 sub-classes: IgG_1, IgG_2, IgG_3, IgG_4
- IgA contains 2 sub-classes: IgA_1, IgA_2
- IgM, IgE, IgD do not have subclasses.

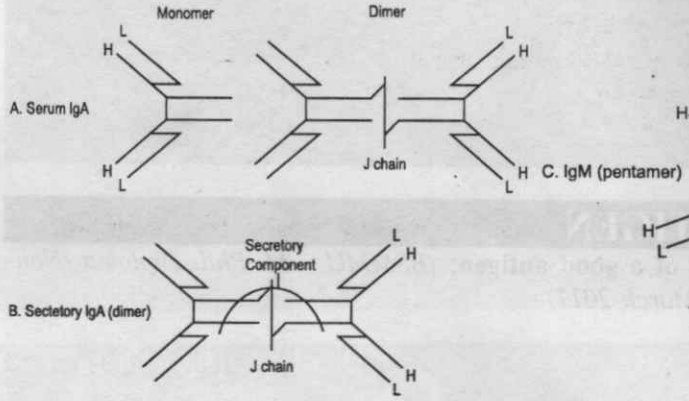


Fig: Structure of IgA

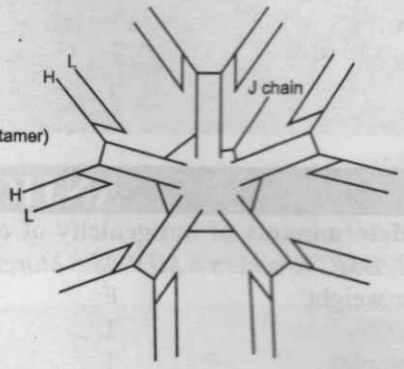


Fig: Structure of IgM

■ **Important properties of Ig**:

Traits	IgG	IgA	IgM	IgD	IgE
A. Physical properties					
1. Molecular wt.	1,50,000	1.7- 4 lacks	9 lacks	1,80,000	1,90,000
2. Subclasses	4	2	-	-	-
3. Basic structural unit	Monomer	Monomer (A_1) or Dimer (A_2)	Pentamer or monomer	Monomer	Monomer
4.Serum conc.(mg/dl)	1000	200	120	3	0.05
5.Serum half life	23 days	6 days	5 days	2-8 days	1-5 days
6. Percentage of total Ig in serum	75%	15%	9%	0.2%	0.004%
B. Biological Properties	**IgG**	**IgA**	**IgM**	**IgD**	**IgE**
1. Transplacental passage	Yes	-	-	-	-
2. Antiviral activity	Yes	IgA_2	-	-	-
3. Complement fixation	Yes.	-	Yes	-	-
4. Opsonization	Yes	-	-	-	Yes
5. Binding with phagocytic cells	Yes	-	-	-	Yes
6. Bindings with mast cell & basophil (allergic activity)	-	-	-	-	Yes

(Ref: Lange Review-15th)

IgG:
- IgG is produced in **2ndary** immune response.
- These Ig are present abundantly both in intra-vascularly & extra-vascularly.
- IgG can cross the placenta except IgG_2. Because, syncytotrophoblast cells of placenta have receptors for Fc portion of IgG.
- Fc portion contains receptors for macrophage, NK cells, neutrophil, C1, syncytotrophoblast.
- They are not involved in allergic reaction.
- They are not found in body secretion.
- They do not contain J chain.
- They take part in opsonization/ opsonic adherence.
- They are found as Ag receptor on B cell.
- IgG takes part Ab dependent cellular cytotoxicity (ADCC).
- They constitute 20% of plasma protein.
- IgG takes part in activation of classical complement pathway except IgG_4.
- IgG takes part in toxin nutralization--antitetanus toxin, antideptheria toxin, snake venom.
- IgG immobilizes motile bacteria and thus promotes phagocytosis.

IgA:
- IgA_1 (93%)- present in circulation.
- IgA_2 (7%)- also known as secretory IgA and is secreted in breast milk & other body fluids. IgA_2 binds with bacteria & viruses and prevent their attachment to the mucosal cells.
- Aggregated IgA activate alternative pathway.
- It has J chain.
- Takes part in agglutination reaction.

IgM:
- It is produced in **primary** immune response.
- Since IgM is pentamer, they act as potent complement activators & agglutinators. Activates classic compliment pathway.
- Fc portion contains receptors for C1.
- It has two forms: Monomer lies on B lymphocyte. Pentamer present in serum.
- This is an important antibody against virus and bacteria.
- It is produced during 5th month of intrauterine life. So, it provides humoral immunity.
- As it is the main Ig in primary immune response diagnosis of IgM in the lab indicates acute infection.
- Does not take part in allergic reaction.
- Does not found in body secretion.
- It causes indirect opsonization (immune adherence).
- It contains J chain.
- It can neutralize toxin but poorly.

IgD:
- Present on the B-cell surface and act as Ag receptor.
- Their function in circulation is still unknown.

IgE:
- They are mainly responsible for anaphylactic reaction (type I hypersensitivity)
- IgE also provides defense against parasitic infection.
- Have receptors for basophil, mast cells, eosinophil.
- Measuring IgE level in serum is a diagnostic tool for helminthic infection.
- Takes part in allergic response.

■ **Functions of Ig as a whole**:

1. Neutralization of toxins.
2. Neutralization of viruses.
3. Immobilzation of motile bacteria and enhance phagocytosis.
4. Opsonization by which enhances phagocytosis.
5. Activation of complements:
   - Immune complex containing IgG & IgM activates the complements by chemical pathway.
   - Aggregated IgA can activate the complements by alternative pathway.(The subclass IgG_4 cannot activate complemetns)
6. Immune adherence: is a function of IgM when microbe become bound within IgM complement is activated resulting in generation of C_{3b} which binds with constant region of IgM. Phagocytes carry receptor for C_{3b}. So they are phagocytosed. this is called immunoadherence.
7. IgM & IgD are present on the surface of B lymphocyte and they act as antigen presenting cell (APC).
8. Type 1 hypersensitivity is the function of IgE.
9. Immunity against helminthic parasite is function of IgE.
10. Immunity at mucosal level provided by IgA.

■ **Biological functions of Fc portion of Ig**:

1. Some phagocytic cells have receptors for Fc portion of Ig. So, they can bind with the opsonized particles which facilitate phagocytosis as well as extracellular killing mechanism. e, g. Eosinophil have receptors for Fc portion of IgE which facilitate the extracelullar killing mechanism of helminths coated with IgE.
2. Basophils & mast cells have receptors for Fc portion of IgE which facilitate degranulation of basophil & mast cell in type I hypersensitivity.
3. Placental cells (syncytotrophoblast cells) have receptors for Fc portion of IgG which facilitate their passage from maternal to foetal circulation.
4. Fc portion of IgG & IgM have receptors for C_1 which facilitate the activation of complement by classical pathway.

■ **Variants of Ig**: There are 3 variants of Ig.

1. **Iso - type**: The 5 classes of Ig are present in all the individuals of some species. They are called iso-type variants. They are present in constant region. e.g. IgG_1, IgG_2, IgG_3, IgG_4 are isotypes of IgG.
2. **Allo-type**: Allo-type variants of Ig occur due to alternate expression of allele. So, they are different in different individuals of same species. Present in variable region. e.g. the γ H chain contains an allotype called Gm.
3. **Idio-type**: Are the variation of amino acid sequence in the hypervariable region of an Ig. So, they are different in a single class of Ig.

Question Bank

Q. IgE is produced by *(BSMMU – Non-Residency – Dentistry – July' 19)*

a) eosinophil
b) monocyte
c) macrophage
d) plasma cell
e) B lymphocyte

Ans. a) F b) F c) F d) T e) T

(Ref. LANGE-15th, P-518)

Q. In case of immunoglobulin *(BSMMU – Residency – MD, MS, Basic Science – March' 18)*

a) Fab portion of IgG binds with antigen
b) J chain is present in IgA
c) IgM is bivalent antibody
d) IgG crosses placenta
e) IgE binds with eosinophil

Ans. a) T b) T c) F d) T e) T

Q. Secretary IgA *(BSMMU –Residency – **Dentistry** – March' 18)*
a) is responsible for mucosal immunity
b) is found in the plasma
c) is assembled in the lymph nodes
d) is transferred across placenta to the foetus
e) inhibits bacterial adhesion to mucosal membrane
Ans. a) T b) F(serum) c) T d) F e) T

Q. IgE binds with *(BSMMU – Residency - **MD, MS, Basic Science, Dentistry** - March' 17)*
a) eosinophil
b) basophil
c) mast cell
d) macrophage
e) endothelial cell
Ans. a) T b) T c) Td) F e)F

Q. The following statements regarding immunoglobulins are true: *(BSMMU – Residency – MD/MS – March'13)*
a) Majority immunoglobulins are γ globulin
b) Differentiated by heavy chain
c) IgA cross the placenta
d) IgE is found in old infection
e) IgE is responsible for atopic hypersensitivity
Ans : a) T (75%) b) T c) F d) F e) T (Type I hypersensitivity)

Q. True statements about IgM are: *(BSMMU – Residency – MD/MS – March'13)*
a) Participate in type II hypersensitivity
b) Participate in type III hypersensitivity
c) Can cross placenta
d) Activate complement system
e) Major Ig of secondary immune response
Ans : a) T b) T c) F d) T e) F (IgG)

Q. Fetal IgA at birth is derived from: *(BSMMU – M. Phil, Diploma (Non-Residency)–11Ju, DMC & others – MD/MS – 11Ju)*

a) mother through placenta	F (breast milk)
b) maternal HPV infection	F
c) synthesis by himself	T
d) maternal diet	F
e) maternal ascending infection	F

Q. Following are applicable for IgG: *(BSMMU - M. Phil, Diploma – 10Ju, 08Ju, 07Ju, 05Ju)*

a) lower concentration in serum among immunoglobulin	F
b) present on virgin B cell surface	F
c) short half life among immunoglobulin	F
d) produced in secondary immune response	T
e) highest concentration in serum among immunoglobulin	T

Q. Following are applicable for IgG: (BSMMU – MD/MS –10Ja, 09Ja,08Ja,07Ja)
a) Highest concentration in serum among immunoglobulin
b) Found mainly in secretion
c) Binds to mast cells
d) Produced in secondary immune responses
e) Longest half life among immunoglobulin

Ans.
a) T
b) F (IgA is found mainly in secretions)
c) F (IgE binds to mast cell)
d) T (Produced in secondary immune response)
e) T
f) binds antigen firmly than any other immunoglobulin T

Q. The followings are applicable for IgM: (BSMMU - MS –10Ja)
a) Only IgM is present on virgin B cell F
b) IgM on B cell surface is monomeric T
c) Can fix complement more efficiently than IgG T
d) plasma cell has surface immunoglobulin IgM T
e) only IgM is produced by T independent antigen stimulation F

Q. Regarding IgE antibodies: (BSMMU - M. Phil, Diploma, July-09)
a) Can pass the placenta F
b) Can passively sensitize the skin F
c) Can fix complement F
d) Present in high concentration in blood F
e) Plays a major role in allergy T

Q. The followings are applicable for IgM: (BSMMU - M. Phil, Diploma, 09Ju, 06Ju; MD/MS-06Ja)
a) First immunoglobulin (Ig) appeared on B cell surface T
b) Principal Ig in secondary immune response F
c) Remain monomeric form on B cell surface T
d) Highest concentration in serum F
e) Can fix complement T

Q. Antibody of secondary immune responses are: (BSMMU - M. Phil, Diploma, July-09)
a) IgG T
b) IgM F
c) IgA F
d) IgD F
e) IgE F

Q. Reaginic antibodies: (BSMMU – M. Phil, Diploma, July-08)
a) can pass the placenta F
b) can passively sensitize the skin T
c) can fix complement F
d) present in high cortcentration in blood F
e) plays a major role in allergy T

Q. Secretory IgA antibody- (MD/MS (DMC) – January, 2008)
a) is responsible for type I hypersensitivity F
b) activates complement by classical pathway F (aggregated IgA activate alternate pathway)
c) is found in the saliva T
d) confers immunity on mucosal surface T
e) appears as a dimmer at the site of action T (IgM is pentamer)

Q. The following antibodies can cross placenta: (M. Phil, Diploma (DMC) (DMC)-05July)

a) IgG T (only Ig that has Fc receptor on placenta)
b) IgA F
c) IgD F
d) IgM F
e) IgE F

Q. Bence - Jones proteins are- (BSMMU – M. Phil, Diploma July, 2005)

A. The heavy chain of immunoglobulins
B. Found in urine in multiple myeloma
C. Associated with a monoclonal gammopathy
D. Found in urine of W. macroglobinaemia
E. Precipitated by boiling

Ans.

A. **False** (Bence-Jones proteins are light chains not associated with the heavy chains which form normal inimunoglobulines. They are secreted by the abnormal plasma cells in the condition known as multiple myeloma and pass from the plasma into the urine.)

B. **True** (Bence-Jones proteins are only found in the urine in multiple myeloma.They are necessary finding for the diagnosis of this disease. Additional diagnostic features of the disease are the presence of osteolytic deposits in the bones and abnormal plasma cells found on sternal marrow biopsy.)

C. **True** (A monoclonal gammopathy together with the presence of an 'M' protein is a necessary feature of multiple myeloma but both are found in other conditions such as old age or following a massive immune response. hi the latter conditions they are not associated with Bence-Jones proteins.)

D. **False** (An excess of monclonal 1gM is found Waldenstrom's macroglobulinaemia in which, because of the excessive amounts of IgM, the plasmapheresis. Only occasionally does a Bence-Jones proteinuria occur. The clinical features include weakness, fatigue, malaise and anorexia, congestive heart failure, neurological symptoms such as vertigo and nystagmus and occasionally spontaneous haemorrhages from mucosal surface. Lymphadenopathy and hepatosplenomegally are common.)-

E. **False** (Bence—Jones proteins precipitate at 80°C but return into solution on boiling. Other proteins in the urine are precipitated by boiling.) **(Ref: Smiddy)**

Q. Following statements are applicable to IgG: (BSMMU – MD/MS - 05Ja)

A. first Ig produced by B lymphocytes
B. Present on virgin B cell surface
C. Occurs in highest concentration is serum among Igs
D. Crosses the placenta,
E. Present in secretions

Ans.

a) F (IgM is produced first) b) F c) T
d) T
e) F (Only IgA is found in secretions)

Q. Immunoglobulins are found in: (MD/MS (DMC)-01Ja)

A. Secretions. T
B. T-lymphocytes. F
C. Red cells. F
D. Platelets F
E. Plasma. T

Help link: RBC, platelet normally does not contain immunoglobulin. But when autoimmune reaction - then found.

Complements

Complements are the plasma proteins which remain inactive, but when activated a series of reaction occur and the products of the reaction can complement or augment the effect of other components of the immune system.

■ **Sources**:

- Liver cell (Mainly)
- Macrophage (Mainly)
- Fibroblast

Components of complement: Approximately 22 in numbers. Among these 9 are major complements and are designated as C_1 - C_9.

- C1, C2, C3, C4, C5, C6, C7, C8 C9
- Others- factor – B, D, H, L, protein S, properdin, C1 inhibitor, C4 binding protein etc.

■ **Nomenclature**: There are nomenclated as C_1, C_2, C_3 & so on according to the mode of invention & not according to their position in complement activation.

■ **Important criteria**:

1. They are heat-labile & become inactivated at 56^0C for half an hour.
2. Many of the complements are pro-enzymes & becomes active enzyme during the process of complement activation.
3. When activated many of the complements are converted into fragment a & fragment b.

- Fragment a is the smaller part and goes out of the reaction.
- Fragment b is the larger part and remains in the reaction.

■ **Activation of complement**: Complements are activated by -

- Classical pathway.
- Alternative pathway.
- Lectin/ Mannan binding lectin pathway.

■ **Classical pathway**:

The immune complex containing IgG & IgM activates the complements in the classical pathway. They are known as activators of classical pathway.

- C1 binds with the receptors present in Fc fragment of Ig in the immune complex. The immune complex then activate the C1 and convert it into active C1 enzyme.
- C1 then convert C4 into C4a & C4b. C4a goes out ot the reaction & C4b remains in the reaction.
- C1 then convert C2 into C2a & C2b. C2a goes out of the reaction. C2b remains in reaction. And the complex remain in the reaction is C4bC2b.
- C4bC2b is an active enzyme and is called C3 convertase in classical pathway. They convert C3 into C3a and C3b. C3a goes out of the reaction & C3b remains in reaction. And the complex remain in the reaction is C4bC2bC3b.
- C4bC2bC3b is an active enzyme and is called C5 convertase in classical pathway. This enzyme convert C5 into C5a & C5b. C5a goes out of the reaction & C5b remains in the reaction.
- C5 & C7 then bind with C5b to produce C5b67 complex. C5b67 is capable of binding with the target cell membrane.
- Then C8 & C9 bind with C5b67 to produce C5b6789 complex. C9 in the complex produces minor hole on the cell membrane through which the ECF enters the cell resulting in cell lysis. C5b6789 is called **'membrane attack complex '** (MAC)

■ **Alternative pathway**:

It is activated mainly in innate immunity. However, activation may also occur in acquired immunity by aggregated IgA. The activators of alternative pathway includes-

- Lipopolysaccharide of gram negative bacteria
- Teichoid acid of gram positive bacteria
- Fungal cell wall
- Viral envelop
- Cobra venom and
- Aggregated IgA.

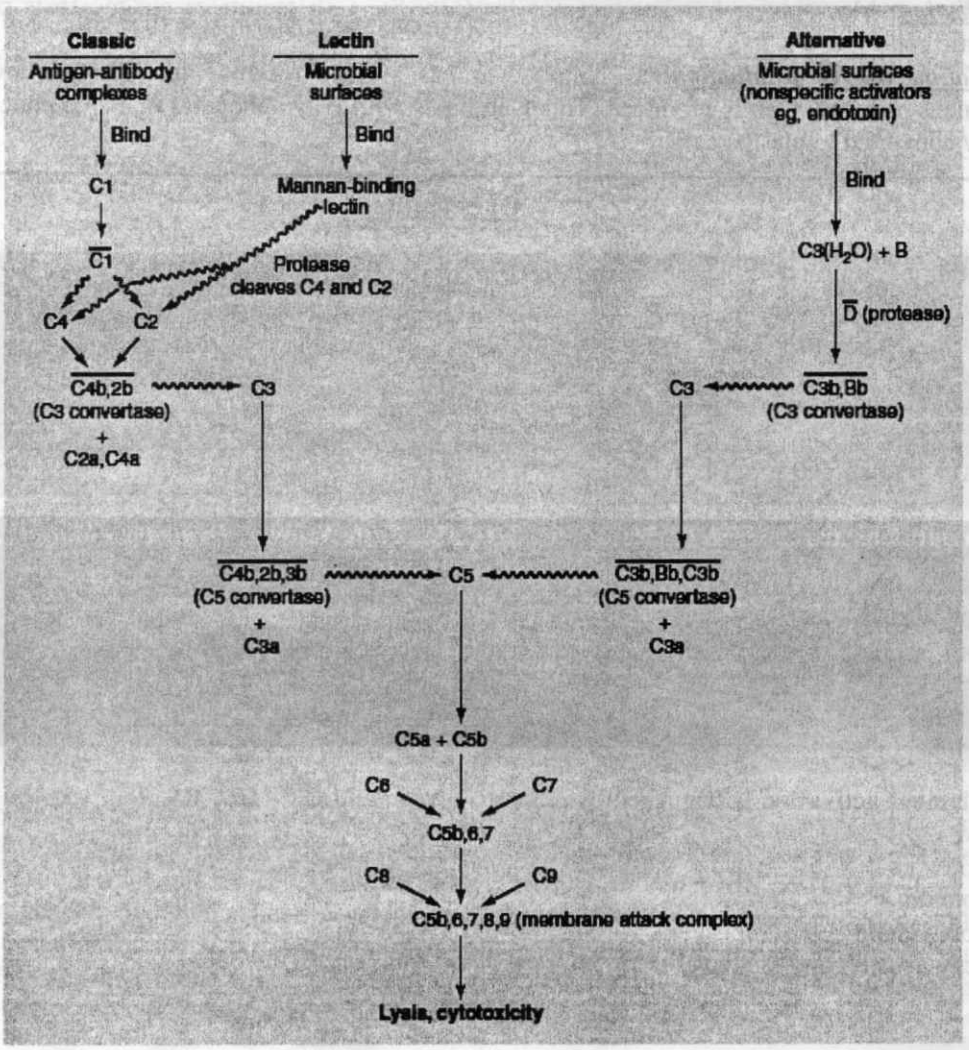
These activators in presence of factor D & Mg^{++} convert directly a small portion of C3 into C3a & C3b. C3a goes out of the reaction and C3b remains in the reaction.

The activators again in presence of factor D & Mg^{++} convert factor B into Ba & Bb. Ba goes out of reaction & Bb remains in the reaction. The complex remain in the reaction is C3bBb.

C3bBb is an active enzyme and is called C3 convertase in alternative pathway. This enzyme convert C3 into C3a & C3b. C3a goes out of reaction. C3b remains in reaction. The complex remain in the reaction is C3bBbC3b.

C3bBbC3b is an active enzyme and is called C5 convertase in alternative pathway. This enzyme then convert C5 into C5a & C5b. The rest of the reaction in alternative pathway are same as classical pathway.

(Ref: Lange Review-15th + Robbins-9th)



Characteristic features of lectin pathway:

- Lectins are proteins
- Bind to specific carbohydrate targets
- It activates complements bind to mannose residues on glycoproteins or carbohydrates on the surface of microbes
- Human cell normally have sialic acids covering the sugar, recognized by MBL and not a target for binding.
- Does not depends on antibody for its activation

■ **Biological functions of complement**:

1. ***Generation of anaphylatoxin***: (DU-97S): C3a, C4a, C5a are called anaphylatoxin. They cause degranulation of the basophil & mast cell resulting the release of various vaso-active mediators that produce sign symptoms of anaphylaxis (type 1 hypersensitivity).
2. ***Chemotaxis***: C5a is the chemotactic factor. It acts on neutrophil and monocyte and causes
   * ↑ Stickiness to endothelial cell
   * ↑ migration
   * ↑ release of lysosomal content
   * ↑ release of toxic O_2 metabolites.
3. ***Cytolysis***: The membrane attack complex (C5b6789) produced in complement pathway activation causes cell lysis like RBC, enveloped virus, gm -ve bacteria, malarial parasite, trypanosome.
4. ***Opsonization***: Macrophage has got receptor for C3b. So, C3b facilitates phagocytosis of a cellular Ag by phagocytic cell.
5. ***Stimulation of Ab production***: B lymphocyte has surface receptor for C3b. Following activation of complement pathway, C3b is produced. This C3b binds with B lymphocytes & B lymphocyte is stimulated to produce/ converted to plasma cell.

Question Bank

Q. Activation of complement can be induced by *(BSMMU –Residency – **MD, MS, Basic Science** – March' 18)*
a) IgD
b) IgG
c) IgM
d) IgA
e) IgE
Ans. a) F b) T c) T d) F e) F

Q. Anaphylatoxins are *(BSMMU – Residency - **MD, MS, Basic Science, Dentistry** - March' 17)*
a) C3a
b) C5a
c) C4a
d) C3b
e) C5b
Ans. a) T b)T c)T d) F e)F

Q. Complement activation is triggered by *(BSMMU – Non-Residency – **MD, MS, Basic science, Dentistry – July' 16)***

a) IgM	T
b) IgG	T
c) exotoxin	F
d) cobra venom	T
e) decay-accelerating factor (DAF)	F

Q. Complement component C3b *(BSMMU – Non-Residency – MD, MS, Basic science – July' 16)*
a) directly kill bacteria F
b) is an anaphylatoxin F
c) is chemotactic F
d) opsonizes bacteria T
e) is derived from C3 T

Q. Products of activated complement components are *(BSMMU – DIPLOMA – DENTISTRY-July' 16)*
a) C3b
b) C3a
c) C4a
d) C2b
e) C2a
Ans. a) T b) T c) T d) F e) F

Q. Deference between classic and alternate pathway includes *(BSMMU –Residency – MD, MS, Basic Science – March' 15)*
a) the alternate pathway needs C_1 activation
b) the classic pathway needs antibody
c) the classic pathway does not need C_5
d) the alternate pathway needs C_5
e) the classic pathway needs factor B and D
Ans. a) F b) T c) F d) T e) F (alternate pathway)

Q. Biologically active complement components are *(BSMMU –Residency – MD, MS, Basic Science – March' 15)*
a) C3a
b) C3b
c) C4a
d) C4b
e) C5b
Ans. a) T b) T c) T d) T (major opsonin) e) T

Q. Regarding complements *(BSMMU –Residency – MD, MS, Basic Science – March' 15)*
a) C5a regarded as central molecule
b) deficiency of C1 inhibitor results in angioedema
c) activation leads to production of anphylatoxins
d) have no role in opsonization
e) deficiency is associated with many congenital disease
Ans. a) F b) T c) T d) F e) T

Q. Complement activation takes place: (BSMMU – MD – January, 2010)
a) in the presence of endotoxin
b) as part of the tuberculin reaction
c) by more than one pathway
d) in anaphylaxis
e) by antigen IgA interaction

Ans.
a) **True** Gram-negative organisms possess an outer coat composed of molecular complexes containing protein, lipid and carbohydrate. Death of the organism, liberates these complexes in the form of endotoxins which are thermolabile at 100^0C. When large amounts of endotoxin are liberated by death of the microorganism, endotoxic shock develops which is a response in part mediated by complement. Large quantities of C3a and C5a (anaphylotoxins) are produced, which results in the activation of PML, basophils and mast cells which stimulate intravascular clotting associated with embolisation into the pulmonary microcirculation, producing the clinical syndrome known as 'shock lung'.

b) **False** The tuberculin reaction does not involve the complement system. It is a delayed hypersensitivity reaction in which the pharmacological mediators are lymphokines.

c) **True** Complement activation resembles the mechanism involved in the clotting of blood, in that it is a cascade reaction which can be activated either by classical or alternative pathways. In all, the complement system consists of some 20 serum proteins, the majority being acute phase proteins, each component reacting
with another. In the classical pathway the system is atwated by antibodies, IgM, IgG1, IgG2 or IgG3 bound to the surface of a pathogen, whereas in. the alternative pathway, the microorgagism itself spontaneously activates the complement system by means of its activator surface.

d) **False** Anaphylaxis is an antigen-specific immune reaction mediated by mast cells liberating vasoactive materials. This mechanism must not be confused with the action of anaphylotoxins which are complement peptides C3a and C5a. Anaphylotoxins when injected, cause an anaphylactic reaction by causing mast cell degranulation.

e) **False** Although aggregated IgA can activate the alternative pathway under experimental conditions, it is considered that antigen IgA interaction does not normally work through the classical complement cascade.

(Ref: Smiddy)

Q. Role of complement component in acute inflammation: (BSMMU – MD/MS – January, 2010)

a) C3a increases vascular permeability	T
b) C4a produces endothelial damage	F
c) Neutrophils are attracted by C5a.	T
d) C3b helps in phagocytosis	T
e) C5 activates kinin system	F

Q. Complement action takes place - (DMC – MD/ MS - January, 2010)

a. in presence of endotoxin	T
b. as a part of tuberculin reaction	F
c. through more than two pathways	T
d. during anaphylactic reaction	F
e. in antigen and IgA interaction	T

Q. Complement C3 (DMC – MD/ MS - January, 2010)

a. is produced by the macrophages	F (liver)
b. is produced by the liver	T
c. is activated by the alternative pathway	T
d. inhibits neutrophil function	F
e. causes leucopenia	F

Q. The result of complement activation is: (BSMMU - M. Phil, Diploma, July-09)

a) Chemotaxis of WBC	T
b) Activation of phagocytic cell	T
c) Type-I hypersensitivity	F
d) Cytolysis of target cell	T
e) Mast cell degranulation	T (due to anaphylaxis)

Q. The followings are the sources of complement: (M. Phil, Diploma (DMC) (DMC)-07July)

a) liver	T
b) intestine	T
c) macrophage	T
d) plasma cell	F
e) kidney	F

HELP LINK:

Complements	Site of synthesis
C1	Intestinal epithelium
C2 & C4	Macrophage
C5 & C8	Spleen
C3, C6 & C9	Liver

Q. Role of complement components in acute inflammation is/are- (BSMMU – MD/MS - 07Ja)

a) C3a increases vascular permeability T
b) C4a produces endothelial damage F
c) Neutrophils are attracted by C5a T
d) C3b helps in phagocytosis T
e) C5 activates kinin system F

Q. The followings are the sources of complement: (MD/MS (DMC) – 06Ja)

a. Liver T
b. Intestine T
c. Macrophage T
d. Plasma cells F
e. Kidney F

Q. Mode of actions of complements are: (M. Phil, Diploma (DMC) (DMC)-05July)

a) agglutination T
b) Lysis T
c) phagocytosis T
d) enzyme activation F
e) opsonization T

Q. Complement is required - (BIRDEM-04)

a) In IgG mediated anaphylaxis F
b) In killing by NK cells F
c) In development of glomerulonephritis caused by antigen-antibody complexes T
d) In haemagglutination reaction T
e) In antibody dependent cell mediated cytotoxicity (ADCC) T

Q. Lectins are: (MD/MS (DMC)-01Ja)

A. Antibodies. F
B. Plant extracts. F
C. Enzymes F
D. Bacterial metabolites. F
E. Antigens F

Nice to know:

Deficiency of the complement components	Diseases
C1	SLE, increased susceptibility to pyogenic bacterial infections ,Nephritis
C4,C2	SLE, other autoimmune disease
C3	Recurrent bacterial infections , Chronic glomerulonephritis
C5	Recurrent pyogenic bacterial infections with Neisseria (both gonorrhoea and meningococcal) ,SLE
C6	Recurrent infections with Neisseria (both gonorrhoea and meningococcal), Raynaud's phenomenon
C7	Recurrent infections with Neisseria(both gonorrhoea and

	meningococcal), Raynauds phenomenon Glomerulonephritis
C8	Recurrent infections with Neisseria (both gonorrhoea and meningococcal) , Raynauds phenomenon, SLE
C1 esterase	Hereditary angioneurotic oedema
Properdin	Severe meningococcal infections
C3 convertage can be inhibited by	Decay accelerating factors(DAF)
Paroxysmal nocturnal hemoglobinuria	By complement breakdown(DAF) of RBC

Opsonins

Q. Components in blood are opsonins *(BSMMU –Residency - MD/MS, Basic science – March' 14)*

a) Antibody T
b) C3b T
c) C3a F
d) IL-2 F
e) GM-CSF F

Help link:

Opsonin: Opsonins are naturally occurring factors in serum. Most micro-organisms are recognized when they are coated by opsonins which bind to specific receptors on the leukocytes. This is called opsonization.

Opsonins	Corresponding receptors on leukocytes
1. Fc fragment of IgG (major opsonin)	FcγR
2. C3b (Opsonic fragment of C3)	CR 1, 2, 3 (Complement receptors1, 2 & 3)
3. Collectins [carbohydrate binding proteins (lectins) of plasma]	C1q

Immune Response

Immune response: Immune response means any defensive reaction to foreign material by the immune system.

Types of immune response:

1. Primary immune response
2. Secondary immune response

Primary immune response: It is the immune response which develops after the 1st exposure of Ag to the immune system.

Secondary immune response: It is the immune response which develops after the subsequent exposure of an Ag to the immune system.

Differences:

Traits	Primary Immune Response	Secondary Immune Response
1. Definition	It occurs in 1st exposure of Ag.	It occurs after subsequent exposure of an Ag.
2. Onset of action	Slow	Quick
3. Lag period	Longer	Very short
4. Memory cells	Memory cells are produced in primary immune response	Memory cells participate in secondary immune response.
5. Types of Ig	IgM	IgG
6. Ab titre	Low	High
7. Duration of immune response	Short	Longer

Question Bank

Q. Memory cells are present in case of *(BSMMU –Residency – **MD, MS, Basic Science, Dentistry** – March' 18)*

a) eosinophil
b) B lymphocyte
c) T lymphocyte
d) mast cell
e) macrophage

Ans. a) F b) T c) T d) F e) F

Q. Following are the statements about primary immune response: *(BSMMU – M. Phil, Diploma (Non-Residency)–March-2012, DMC & others – MD/MS – March-2012)*

a) responding B-cell is memory B-cell F
b) IgG predominates F
c) time of peak response generally 7-10 days T
d) antibody affinity is lower T
e) antibody affinity is higher F

HELP LINK:

Table: Comparison between Primary and Secondary immune response:

Features	Primary response	Secondary response
Latent period (Lag phase)	Long	Short
Rate of antibody production	Low	High
Peak antibody titer	Low	High
Persistence of Ab liter	Short	Long
Affinity of Ab	Low	High
Memory cells	Absent	Present
Cross reactive antibody	Low	High
Predominant Ig class	IgM	IgG
Dose of antigen	Large	Small

Q. In primary immune response- (BSMMU – MD/MS - 05Ja)

A. IgG and IgA appear first
B. occurs 7 to 10 days of infection
C. more specific than secondary immune response
D. memory cells are produced
E. antibody level persists longer

Ans.

a) F (IgM appears first)
b) T
c) F (Non-Specific)
d) F (produced in secondary response)
e) F (longer in secondary response)

Hypersensitivity

■ **Definition**: Hypersensitivity may be defined as inappropriate, altered & exaggerated immune response of the body or tissue to an Ag to which the body has been exposed before & the whole process leads to gross tissue damage.

■ **Classification of hypersensitivity**:
- Type I - Anaphylactic reaction
- Type II – Antibody dependant cytotoxic hypersensitivity
- Type III - Immune complex mediated hypersensitivity.
- Type IV - Cell mediated or delayed type hypersensitivity.
- Type V - Stimulatory type hypersensitivity.

[Type IV- Cell mediated hypersensitivity. The rest of types - Ab mediated hypersensitivity]

TYPE I HYPERSENSITIVITY/ ANAPHYLAXIS

■ **Anaphylaxis**: It may be defined as rapidly developing immunological reaction occuring within minutes after the combination of Ag with IgE present on the mast cell or basophil in an individual who is pre-sensitized to that Ag.

■ **Mechanism of type I hypersensitivity**:
An allergen enters into the body 1st time → It binds with specific B cell → Humoral immune response → Transformation of B cell into plasma cells & produce IgE → IgE binds with mast cell & basophil.

■ In 2ndary exposure, Allergen binds with IgE on the mast cell & basophil → Degranulation of mast cells & basophils → Release of primary mediators (Histamine, Eosinophil & neutrophil chemotactic factor,proteases)
and
Another stimulatory signals activate enzyme phospholipase. The active enzyme phospholipase then breaks down the membrane phospholipid into platelet activating factor & arachidonic acid. The metabolism of arachidonic acid by cyclo-oxygenase pathway releases PG & by lypo-oxygenase pathway releases leukotriens.
↓
Secondary mediators (platelet activating factor, PG, leukotriens)
↓
These primary & secondary mediators mediators causes hypersensitivity reaction.
- Vasodilatation
- ↑vascular permeability
- Contraction of smooth muscles)

■ **Example of type I hypersensitivity**:

	Examples
1.**Local anaphylaxis**:	• Urticaria (hives), Eczema (atopic dermatitis) • Angioedema • Conjunctivitis • Atopic diseases. e.g. asthma, hay fever and allergic rhinitis • Allergic gastroenteropathy
2. **Systemic anaphylaxis**:	• Penicillin hypersensitivity • ATS hypersensitivity • Anaphylactic shock, e.g. bee & wasp venom

■ Useful test- specific IgE test and skin prick testing (with caution)

Mediators released in anaphylactic reaction:

1. **Preformed mediators**: Histamine, serotonin, eosinophil chemotactic factors.
   - these mediators are released within minutes
2. **Newly synthesized**: platelet activating factor, Prostaglandin, leukotriens
   - released after 6 hours.

Clinical features & management of anaphylaxis:

Anaphylaxis is an immediate hypersensitivity response triggered by IgE mediated mas cell degranulation.

Causes:

Food: peanut, shell fish
Insects stings – bee venom
Drugs: penicillin, anaesthetic agents etc
Animal danders
Environmental agents - Grass & flower pollen, House dust

Clinical features:

- Generalized pruritus, erythema, urticaria
- Laryngeal oedema, angioedema of lips & mucous membrane
- Hypotension and shock
- Bronchial obstruction (Dyspnoea, bronchospasm)
- Crampy abdominal pain, nausea, diarrhorea
- Sweating, flushing
- Cardiac arrhythmia
- Impaired consciousness
- Death

Fig: Anaphylaxis

Diagnosis: on the basis of history & clinical features mainly. Some inv. may help.

Investigations:

- **Patch test**/ Skin test – nonsensitive (pt. may be previously sensitized) – Done in BD
  Strip containing Ag is applied on skin. Like micropore (hilsha ilish, mite)
  ↓
  Attachment site – reaction (wheel)
- **ELISA**
- **RAST** (Radio allergen – sobrent test): Specific IgE test.
- Supervised exposure to allergen (Challenge test) e.g. bronchial provocation test, nasal challenge, food challenge
- Serum **mast cell tryptase concentration test** – confirmatory. After allergic reaction, tryptase level. increase dramatically within 1-2 hrs & remaining upto 24 hrs. very useful in anaphylactic event.
- **Skin Prick test**: not done. Because, AIDS infection can occur. Disadvantage: anaphylaxis may occur.
- **Non-specific marker**: serum IgE level, serum eosinophil level.

Management:

- Prevent further contact with allergen
- Ensure airway patency
- Oxygenation
- I/M Epinephrine (Adrenalin) – promptly
  1 : 1000 dilution, 0.3 – 1.0 ml
  Repeat at 5 – 10 min (if initial response is inadequate)
- Antihistamine – directly oppose the effects of mast cell activation (IM or slow IV)
- Corticosteroid – Hydrocortisone 200 mg IV (prevents rebound symptoms in severely affected patients)

- Treatment of shock by IV fluid, O_2 inhalation, inj. Epinephrine, inj. Dopamine
- Treatment of laryngeal oedema by tracheostomy
- Others –
  Nebulization
  Other symptomatics

TYPE II HYPERSENSITIVITY

It is mediated by Ab which is directed towards Ag present on the cell surface resulting in cellular damage or cellular dysfunction.

Basic characteristics:
- Immunoglobilin involved – IgG & IgM
- Antibody mediated cytotoxic hypersensitivity
- Antigen present on cell surface

■ **Mechanism**: After combination of Ab with Ag present on the cell surface, produce either of the following immunological reactions.
1. Complement dependant cellular cytotoxicity
2. Ab dependant cellular cytotoxicity
3. Ab dependant cellular dysfunction

1. **Complement dependant cellular cytotoxicity (CDCC)**: The Ab-Ag complex on the cell surface activate complements to produce membrane attack complex (MAC) which causes lysis of the cell.

Ag on the cell surface + Ab
↓
Ab binds with Ag to form Ag-Ab complex on the cell surface
↓
Activation of complements
↓
Produce membrane attack complex (MAC) – (C5b6789)
↓
Causes lysis of the cell.
↓
Clinical features

Examples:
- Incompatible blood transfusion.
- Erythroblastosis foetalis
- Pernicious anaemia
- Auto-immune haemolytic anaemia
- Auto-immune thrombocytopenia.
- Auto-immune thyroiditis
- Rheumatic fever.
- Goodpastaur's syndrome.

2. **Antibody dependent cellular cytotoxicity (ADCC)**: One group of NK cells (and also monocytes, neutrophils, eosinophils) possess receptors for Fc fragment of IgG. These group of NK cells bind with the opsonized cells & destroy them by extracellular killing mechanism. This is known as ADCC.

Examples:
- Graft rejection
- Lysis of parasites
- Lysis of tumor cells

3. **Antibody dependent cellular dysfunction**: Ab after binding with Ag, present on the cell instead of cellular cytotoxicity, they cause inhibition of cell function

Examples: Myesthenia gravis. *(Here Auto-antibodies are produced against the Ach receptors. Subsequently the auto-Ab bind with the receptors & interfere Ach attachment with the receptors resulting in inhibition of cell containing receptors for Ach.)*

- Pemphigus vulgaris
- Graves disease (hyperthyroidism)

Other Examples of type II hypersensitivity:

1. Vasculitis
2. Bullous pemphigoid
3. Myxodema & thyrotoxicosis

Useful test: Coomb's test

■ **Examples of antibody-mediated diseases (Type II Hypersensitivity)**:

Disease	Target Antigen	Mechanisms of disease	Clinic pathologic Manifestations
Autoimmune hemolytic anemia	Erythrocyte membrane proteins (Rh blood group antigens, I antigen)	Opsonization and phagocytosis of erythrocytes	Hemolysis, anemia
Autoimmune Thrombocytopenic purpura	Platelet membrane proteins (gpIIb:IIIa intergrin)	Opsonization and phagocytosis of platelets	Bleeding
Pemphigus vulgaris	Proteins in intercellular junctions of epidermal cells (epidermal cadherin)	Antibody-mediated activation of proteases, disruption of intercellular adhesions	Skin vesicles (bullae)
Vasculitis caused by ANCA	Neutrophil granule proteins, presumably released from activated neutrophils	Neutrophil degranulation and inflammation	Vasculitis
Goodpasture syndrome	Noncollagenous protein in basement membranes of kidney glomeruli and lung alveoli	Complement and Fc receptor-mediated inflammation	Nephritis, lung hemorrhage
Acute rheumatic fever	Streptococcal cell wall antigen; antibody cross-reacts with myocardial antigen	Inflammation, macrophage activation	Myocarditis, Arthritis

TYPE -III HYPERSENSITIVITY

It is mediated by immune complex and the tissue damage is mainly due to activation of complements & platelets.

Basic characteristics:

- Immunoglobilin involved – IgG & IgM
- Immune complex mediated hypersensitivity
- Antigen present in cerculation

■ **Mechanism**:

Ag in circulation
↓
Ab binds with Ag in circulation
↓

Immune complex is produced in circulation.
↓
Immune complex then activate complements to produce C3a, C4a & C5a. These are toxin.
↓
They degranulate the circulating basophils.
↓
Thereby releasing histamine, vasoactive amines tryptamine (5HT).
↓
Vasoctive amines cause dilatation of vessels and ↑ vascular permeability.
↓
Retraction of endothelial cells.
↓
Gaping are produced in the endothelial lining
↓
Immune complexes become deposited in these gaping. (specially in the organs e.g. kidney, blood vessels (where filtration occurs), joints (synovial membrane))
↓
The deposited immune complexes continue the activation of complements to produce C5a which is a chemotactic factor.
↓
C5a attracts the neutrophils at site of reaction
↓
The accumulated neutrophils then attempt to phagocytose the deposited complexes & release proteases. This mechanism is known as '**Frustated phagocytosis**'.
↓
Proteases cause tissue damage.

The deposited immune complex also activates platelets.
↓
The activated platelets produce microthrombi.
↓
Microthrombi produce ischemia which causes further tissue damage.

[Q. In every individual immune complex is produced but immure complex mediated disease occurs in small numbers. Why?
Ans. Genetic factor plays an important role in immune complex mediated diseases.]

■ **Examples of type III hypersensitivity**:

Arthus reaction: localized reaction (Ab excess)
Allergic alveolitis
Farmer's lungs (actinomycetes induced)
Cheese worker's lung
Wood worker's lung
Wheat-miller's lung
erythema nodosum laprosum.

Serum sickness: generalized reaction (Ag excess)
SLE (Systemic lupus erythematosus)
Rheumatoid arthritis, Reactive arthritis
AGN (Acute glumerulonephritis)
Infective endocarditis, polyarteritis nodosa

Others: Syphilis, Quartan malaria, Shistosomiasis

■ **Types of type III hypersensitivity**: According to conc. of Ag & Ab in immune complex:
1. Arthus reaction: Ab is excess in immune complex.
2. Serum sickness: Ag is excess in immune complex.

■ **Differences:**

Arthus reaction	Serum Sickness
1. In immune complex, Ab conc. is more	Ag conc. is more.
2. It develops after multiple exposure of Ag	It develops in single exposure of Ag.
3. Usually localized.	Always generalized.
4. Occurs within 4-8 hours after entrance of an Ag	Occurs after 8-12 days in a single exposure of Ag.
5. Example: Farmer's lung	Delayed complication of ATS & ADS.

TYPE IV HYPERSENSITIVITY

Basic characteristics:
- Delayed or cell mediated immune response.
- Onset is slow after 24 hours
- Peaks within 48 – 72 hours
- Phages :
  1. Sensitization phase – after 1st exposure
  2. Effector phase – after subsequent exposure

■ **Mechanism**: It usually develops against the intracellular microbes & also by repeated exposure of inorganic substances like chromium, nickle, talc, hair dye & cosmetics in the skin.

1st exposure of Ag
↓
A portion of Ag is taken up by APC & expressed on the cell surface of APC which is recognized by CD4+ helper T cell.
↓
Differentiation of helper T cell (by IL-12 by APC)
↓
Th 1 cells enter in the circulation and remain in the memory T cell pool – for long periods (years)

On subsequent exposure,

Memory T cell recognizes the Ag with class II MHC presented by APC
↓
Memory T cell becomes activated (by IL-12, liberated by macrophage)
↓
Produces cytokines (IL-3, GMCSF)
↓
Stimulates bone marrow to produce monocytes
↓
Monocytes become macrophages
↓
Produces lymphokines macrophage activating factor (MAF) - INF-γ, TNF-β
↓
Activates the macrophages.
↓
Due to persistent Ag, the activated helper T cell in many cases continue to release MAF.

↓

Due to continuous presence of MAF, many of the macrophages are transformed into epithelioid cell. These cells then fuse to form giant cell.

There also occurs proliferation of fibroblasts & release of collagen leading to fibrosis. In many occasion there also occurs caseous necrosis.

On the other hand, CD8+ cytotoxic T cells destroy the cells where Ag is presented with MHC class I Ag. Tissue damage in case of type IV hypersensitivity is more marked by cytotoxic T cell rather than CD4+ helper T cell.

Examples:

1. Tuberculin test → In TB.
2. Lepromin test → in leprosy.
3. Granulomatous lesion produced in TB, leprosy, leishmaniasis, histoplasmosis.
4. Eczema (Contact dermatitis)→ occurs due to repeated contact of inorganic substances.

Other examples:

1. DM type I
2. Multiple sclerosis
3. GBS, peripheral neuropathy
4. Graft rejection, GVHD
5. Tumor immunity.

■ **Variants**: According to onset of reaction & involvement of immuno-component cell, type IV hypersensitivity is of 3 types: a) Contact type b) Tuberculin type c) Granulomatous type.

■ **Differences**:

Traits	Contact	Tuberculin	Granulomatous
1. Ag	Inorganic subs.	PPD (Purified protein derivatives) Lepromin Ag	Intracellular microbes (TB, M. leprosy, LD)
2. Onset	48 - 72 hrs	48- 72 hrs	3 - 4 weeks
3. Clinical appearance	Hard	Induration	Hard
4. Histological appearance	Lymphocytes & macrophages (Mainly)	•Lymphocytes, •Monocytes •Macrophages.	•Epithelial cells, •Giant cells, •Macrophages, •Lymphocytes, •Fibroblast.

TYPE V HYPERSENSITIVITY:

(Stimulating type hypersensitivity)

■ **Definition**: It is mediated by Ab which when binds with the Ag on the cell surface, stimulates the cellular function. eg, Grave's disease.

■ **Mechanism**: Auto-antibodies are produced against the receptors for TSH (thyroid stimulating hormone) present in the thyroid follicular cell. This Ab binds with the TSH receptor and stimulates the follicular cell like a hormone. So thyroid hormones are produced in excess and result in thyrotoxicosis or hyperthyroidism.

■ Grave's disease is an auto-immune disease and is mediated by type V hypersensitivity.

Nice to know

Skin testing:

- ***Type I*** (prick test): An urticarial weal & flare develops within 20 minutes and resolves within 2 hours.
- **Type II** (intradermal injection) An ill-defined weal develops over several hours, is maximal at 5-7 hours and resolves within 24 hours.
- **Type III** (intradermal or patch test: delayed hypersensitivity) An indurated area develops within 2-4 days and resolves over several days.

Different types of hypersensitivity reactions in skin conditions		
Skin disease	**Hypersensitivity type**	**Mechanisms involved**
Urticaria	I	IgE, mast cells, histamine
Bullous diseases	II	Autoantibody to skin components, complement
Vasculitis	III	Immune complexes, PMN, complement
Allergic contact dermatitis	IV	T cells, cytokines

Question Bank

Q. Type IV hypersensitivity mediated reactions are *(BSMMU – Non-Residency – **MD, MS, Paediatrics, Basic Science, Dentistry** – July' 19)*

a) granulomatous inilammation
b) positive tuberculin test
c) anaphylactoid reaction
d) transfusion reactions
e) contact dermatitis

Ans. a) T b) T c) F (Type I) d) F (Type II) e) T

(Ref. LANGE-15th, P-558)

Q. Anaphylaxis *(BSMMU –Residency - **Basic science** – March' 19)*

a) develops 24 hour after the initial stimulation
b) causes a wheal and flare responses
c) is produced by IgA antibody
d) eosinophilia is an association
e) causes degranulation of basophils and mast cells

Ans. a) F b) T c) F d) T e) T

(Ref: Smiddy)

Q. Antibodies mediating type-II hypersensitivity are *(BSMMU – Non-Residency – **MS, Basic science** – July' 18)*

a) IgE
b) IgG
c) IgM
d) IgA
e) IgD

Ans. a) F b) T c) T d) F e) F

Q. Preformed mediators of immediate hypersensitivity are *(BSMMU –Residency – **MD, MS, Basic Science, Dentistry** – March' 18)*

a) vasoactive amines
b) leukotrienes
c) proteoglycans
d) prostaglandin D
e) platelet activating factor

Ans. a) T b) F c) F d) F e) F

Help Link:

Preformed mediators: Vasoactive amines (Histamin, Serotonin, Eosinophil chemotactic factor of anaphylaxis, Neutrophil chemotactic factor of anaphylaxis, Proteases (tryptase, chymase).

Q. Clinical manifestations of anaphylaxis are *(BSMMU –Residency – **MS, Basic Science, Dentistry** – March' 18)*
a) bradycardia
b) bronchospasm
c) hypotension
d) fever
e) urticaria
Ans. a) F b) T c) T d) F e) T

Q. Delayed type of hypersensitivity is seen in - *(BSMMU – Non-Residency – MD, MS, Basic Science & Dentistry – July' 17)*
a) contact dermatitis
b) penicillin allergy
c) arthus reaction
d) positive tuberculin skin test
e) acute allograft rejection
Ans. a) T b) F c) F d) T e) T

Help link:

Effector mechanisms in allograft rejection: A variety of effector mechanisms participate in allograft rejection:

- The most common are cell-mediated reactions involving delayed-type hypersensitivity and cytotoxic T lymphocyte (CTL)-mediated cytotoxicity.
- Less common mechanisms are antibody plus complement lysis and destruction by antibody-dependent cell-mediated cytotoxicity (ADCC).

Acute rejection is predomintly mediated by T lymphocytes. CD4 helper T cells are believed to play the key role in acute rejection of the graft by release of IL-2, IL-4.

(Ref: Textbook of microbiology by Subash chnadra Parija page 163)

Q. Type IV hypersensitivity reactions are *(BSMMU – Residency - **MD, MS, Basic Science, Dentistry** - March' 17)*
a) granulomatous hypersensitivity
b) tuberculin hypersensitivity
c) transfusion reaction hypersensitivity
d) contact hypersensitivity
e) anaphylactoid reaction
Ans. a) T b) T c) F d) T e)F

Q. Examples of delayed type hypersensitivity are *(BSMMU – Residency - **MD, MS, Basic Science, Dentistry** - March' 17)*
a) systemic lupus erythematosus
b) Grave's disease
c) rheumatoid arthritis
d) contact dermatitis
e) bronchial asthma
Ans. a) F b)F c) F d) T e)F

Q. Anaphylactic reaction involves *(BSMMU – Residency - **Dentistry** - March' 17)*
a) Langhan's giant cell
b) histamine
c) macrophage
d) mast cell
e) IgE

Ans. a) F b) T c) F d) T e) T

Q. Diseases caused by type II hypersensitivity reaction are *(BSMMU – Residency – MD – March' 16)*
a) farmer's lung F
b) Grave's disease T
c) serum sickness F
d) systemic lupus erythemetosus F
e) Good Pasture's disease T

Q. Type III hypersensitivity reactions are *(BSMMU – Residency – MD, MS, Basic science – March' 16)*
a) blood transfusion reaction F
b) serum sickness T
c) rheumatoid arthritis T
d) erythroblastosis foetalis F
e) systemic anaphylaxis F

Q. Immunologically mediated diseases are *(BSMMU – Non-Residency – MD, MS, Basic science – July' 15)*
a) Parkinson's disease F
b) myasthenia gravis T
c) Duchenne muscular dystrophy F
d) Grave's disease T
e) multiple sclerosis T

Q. Products of mast cell degranulation are *(BSMMU – Non-Residency – MD, MS, Basic science – July' 15)*
a) leukotrienes T
b) Throboxane A_2 F
c) histamine T
d) serotonin T
e) eosinophilic chemotactic factor F(neutrophil and eosinophi)

Help link:
Mast cell mediators
✓ Histamine
✓ Proteases(Tryptase or chymase), acid hydrolases
✓ Proteiglycans(Heparin, Chondroitin sulphate)
✓ PG D2
✓ Leukotriens C4,D4, E4
✓ PAF

(Ref: Prof Akram-5th, P-182)

Q. Diseases mediated by type-III hypersensitivity *(BSMMU –Residency – MD, MS, Basic Science – March' 15)*
a) rheumatic fever
b) systemic lupus erythometosus
c) Hashimoto's thyroiditis
d) rheumatoid arthritis
e) Grave's disease

Ans. a) F b) T c) F d) T e) F

Q. Diseases mediated by type-II hypersensitivity are *(BSMMU – Non-Residency – MD/MS, Basic science – July' 14)*
a) autoimmune haemolytic anaemia
b) rheumatoid arthritis
c) acute glomerulonephritis
d) acute rheumatic fever
e) idiopathic thrombocytopenic purpura

Ans. a) T b) F c) F d) T e) T

Q. Diseases mediated by type-II hypersensitivity are *(BSMMU –Residency - MD/MS, Basic science – March' 14)*

a) rheumatoid arthritis F
b) ABO incompatibility T
c) Grave's disease T
d) idiopathic thrombocytopenic purpura T
e) Systemic lupus erythematosus (SLE) F

Help link:
Type III mainly, partly type II particularly drug induced SLE(hydralazine)

(Ref: LANGE-15th, P-556)

Q. Urticaria *(BSMMU – Non-Residency - MD – 13Ju)*

a) is a type II hypersensitivity reaction
b) is characterized by spontaneous mast cell degranulation
c) occurs due to autoimmunity in 5% cases
d) may require appropriate challenge test
e) may be precipitated by aspirin

Ans. a) F b) T c) F d) T e) T

Q. Allergic reaction includes: *(BSMMU – Residency – MD/MS – March'13)*

a) Hay fever
b) Asthma
c) Raynauds diseases
d) Herpes zoster
e) Urticaria

Ans : a) T b) T c) F d) F e) T

Q. Following diseases are mediated by type II hypersensitivity: *(BSMMU – Residency – MD/MS – March'13)*

a) Autoimmune haemolytic anaemia
b) Erythroblastosis foetalis
c) Serum sickness
d) Bronchial asthma
e) Acute rheumatic fever

Ans : a) T b) T c) F d) F e) T

Q. Delayed type of hypersensitivity: *(BSMMU – M. Phil, Diploma (Non-Residency)–March-2012, DMC & others – MD/MS – March-2012)*

a) is a cell mediated type of hypersensitivity reaction
b) is encountered in contact dermatitis
c) is often called allergy
d) is characterized by IgE production
e) is cytokine mediated **Ans.** a) T b) T c) F d) F e) T

Q. Hypersensitivity reaction may have the following consequences *(BSMMU – MD/MS (Residency) – January, 2011)*

a) may be lost after some period T
b) may lead to chronic disease T
c) can be prevented by vaccination T
d) may produce oncogenesis after chronic phase F
e) may lead to immunosuppression T

Q. Type-III hypersensitivity reaction occurs in: *(BSMMU-M.phil-10Ju)*

a) Hashimotos thyroiditis F
b) Myasthenia Gravis F
c) Farmer's lung T
d) Sarcoidosis F
e) SLE T

Q. Following are the example of type II hypersensitivity: (BSMMU – MD – January, 2010)

a) Drug induced haemolytic anaemia T
b) Erythroblastosis foetalis T
c) Hay fever F
d) Acute glomerulonephritis (AGN) F
e) Serum sickness F

Q. Following are the examples of type-Ill hypersensitivity reaction: (BSMMU - M. Phil, Diploma, July-08)

a) serum sickness T
b) SLE T
c) myasthaenia graves F
d) multiple sclerosis F
e) rheumatoid arthritis T

Q. Following diseases are the example of type II hypersensitivity- (BSMMU – MD/MS - January, 2008)

a. Drug induced hemolytic anaemia T
b. Erythroblastosis foetalis T
c. Hay fever F
d. Acute glomerulonephritis F
e. Serum sickness F

Q. Type I hypersensitivity reaction found in: (BSMMU - M. Phil, Diploma, July-07)

a) hay fever T
b) koch's phenomenon F
c) genetic defect F
d) anaphylactic shock T
e) contact dermatitis F

Q. Following diseases are the example of type II hypersensitivity- (BSMMU – MD/MS -07Ja)

a. Drug induced hemolytic anaemia T
b. Erythroblastosis foetalis T
c. Hay fever F
d. Acute glomerulonephritis F
e. Serum sickness F

Q. Allergic reaction includes- (BSMMU - M. Phil, Diploma, July-06)

a) Hay fever T
b) Asthma T
c) Raynaud's disease F
d) Herpes zoster F
e) Urticaria T

Q. Immune complex disease associated with - (BSMMU - M. Phil, Diploma, July-06)

a) Autoimmunity
b) Skin graft rejection
c) Pigeon fancier's lung
d) Granulomatous inflammation
e) Arthus reaction

Ans.

a) **True** (In both organ specific and non-organ specific autoimmune disease, the clinical presentation is due to failure of the affected individual or animal to deal with the immune complexes formed by the interaction of antigen and antibody. In the human, immune complexes are normally recognised by the mononuclear phagocyte system, particularly in the liver by the Kupffer cells having been transported

there bound by CR1 receptors to erythrocytes. If such a process is overwhelmed by the excessive production of complexes, an autoimmune disease follows, e.g. Hashimoto's disease)

b) **False** (Immune complexes play no part in graft rejection which is a T-cell mediated response, T-cells recognising donor-derived peptides in association with the MHC antigens expressed on the graft)

c) **True** (The basic pathology of Pigeon Fancier's disease is one of an alveolitis in which destruction of the alveoli with associated consolidation occurs due to locally formed immune complexes. The disease follows repeated exposure to pigeon antigens, the antibody induced by such exposure being primarily IgG rather than IgE. When antigen enters the lungs by inhaiation, local immune complexes are formed leading to parenchymal destruction)

d) **False** (Granulomatous inflammation like tuberculosis, coccidiodomycosis are examples of cell mediated hypersensitivity reaction)

e) **True** (Arthus reaction and serum sickness are the classical examples of immune complex hypersensitivity reaction)

(Ref: Smiddy)

Q. Following are example of type-II hypersensitivity - (BSMMU - M. Phil, Diploma, July-05)

A. Rh incompatibility	T
B. ABO incompatibility	T
C. rheumatoid arthritis	F
D. glomerulonephritis	F
E. indiopathic thrombocytopenic purpura	T

Q. Following are examples of type-II hypersensitivity: (BSMMU – MD/MS - 05Ja)

A. serum sickness	F
B. Rh. Incompatibility	T
C. Drug induced haemolytic anaemia	T
D. Arthus reaction	F
E. Bronchial asthma	F

Q. The following are the examples of immune complex diseases: (MD/MS (DMC)-04Ja)

a) sytemic lupus erythematosus	T
b) auto-immune haemolytic anaemia	F
c) erythroblastosis foetalis	F
d) acute glomerulonephritis	T
e) contact dermatitis.	F

Q. The following statements are applicable for anaphylaxis - (BSMMU-MS-04Ja)

a) Develop 24 hours after initial stimulus	F
b) Causes eosinophilia	T
c) Is produced by IgA antibody	F (IgE)
d) Is produced due to degranulation of mast cells and basophils	T
e) Causes urticarial eruptions	T

Q. Anaphylaxis: (MD/MS (DMC)-04Ja)

a) Develops 24 hours after initial stimulus.
b) Causes a wheal and flare response.
c) It is produced by IgA antibody.
d) Causes eosinophilia.
e) Causes degranulation of basophils & mast cell.

Ans.

A. **False** Anaphylaxis is an antigen specific immune response classified as a Type I, immediate hypersensitivity reaction. The response is mediated by the specific triggering of IgE sensitised mast cells by an allergen. As a result mast cells become degranulated, leading to either loca' or generalized effects caused by the liberation of vasoactive amines, of which, in man histamine is the chief effector. Normally exposure to the allergen is followed by a response within minutes.

B. **True** If a skin prick test is used to detect Type I hypersensitivity, an immediate weal and flare response follows the injection of the allergen into the skin. The test results in an erythematous and oedematous response vary in severity according to the amount of allergen injected and demonstrates that IgE is bound to the skin mast cells.

C. **False** IgA plays no part in anaphylaxis. IgA is present in human serum in which it forms approximately one fifth of the immunoglobulin pool. It is also present in seiomucoiis secretions such as saliva and the secretions of the tracheo-bronchial mucosa.

D. **True** Eosinophils are attracted by products released from T cells, mast cells and basophils known as the eosinophil chemotactic factor of anaphylaxis (ECF-A). These cells release histamine and aryl sulphatase, the latter inactivating the slow reactive substance (SRS-A) of anaphylaxis. However, one of their chief functions is to combat worms and protozoal infections. When a helminth infection of the bowel occurs, T cells recruit eosinophils by means of the Eosinophil Stimulation Promotor (ESP). The eosinophils then adhere to the worm and degranulate, breaking the integument of the worms allowing access to further eosinophils into the body of the worm itself.

E. **True** Degranulation of basophil and mast cells follows the interaction between an antigen and IgE. These granules contain heparin and it is this which stains metachromatically with toluidine blue. The histamine which these cells contain, is formed from histidine by the action of the enzyme histidine decarboxylase; but in addition to histamine, 5-hydroxy tryptamine (serotonin), the slow reacting substance (SFRS) of anaphylaxis and basophil derived kallikrein may be released. The latter cleaves the plasma euglobulin kininogen to kinins. The release of these various pharmacologically active agents causes the various local and general manifestations of anaphylaxis.

(Ref: Smiddy)

Q. The drug of choice of anaphylactic shock is: (MD/MS (DMC)-04Ja)

a) Corticosteroids	T
b) Adrenaline	T
c) Nor-adrenaline	F
d) Dopamine	F
e) Isoprenaline	F

HELP LINK:

Adrenaline causes ↑ cAMP production →↓ mediator release.
But when ↑ cGMP → ↑ mediator release.

■ **Clinical features of Anaphylactic shock**:

- Bronchospasm
- Laryngeal spasm
- Breathlessness
- Cyanosis
- Hypotension
- Nausea, vomiting, diarrhoea.

■ **Management of a case of anaphylactic shock**:

A. **General measures**:

1. The drug (e.g. Penicillin) is to be discontinued.
2. Pt. should be kept in supine position with leg elevated for 30^0 or wearing anti-shock trousers.
3. Airway is cleared & High flow O_2 inhalation, endotracheal intubation is done where necessary.
4. Monitor BP.

B. **Specific measures**:

1. Inj. Adrenaline 0.5 mg (i.e. 0.5 ml of 1:1000) [0.5 to 1 ml] is to be administered intramuscularly or subcutaneously. It is repeated every 3 minutes depending on severity & extent of shock. If response is poor, then (1,50,000) IV 1 ml – 3 min.
2. Inj. Hydrocortisone hemisuccinate is to be given 100-250 mg, intravenously, followed by oral Prednisolone when pt. can take drug by mouth. Prednisolone is given 5 mg 6 hourly.
3. Inj. Promethazine (anti-histamine) 10 mg is given intravenously.
4. IV fluid is given to combat circulatory failure.
5. Aminophyllin or other bronchodilators in aerosal or nebulizer form may be given according to need.

Q. Regarding Type III hypersensitivity reaction (BSMMU – MD/MS - 02Ja)

a) It may occur in iso-immune blood transfusion. F
b) Are due to formation of immune complexes T
c) Produce effect by activation of complement T
d) Brief exposure to antigens is sufficient to produce this reaction. F
e) Always produce Systemic effect. F

Q. Following immunological phenomenon are: (MD/MS (DMC)-01Ja)

A. Transfusion reaction is a type III reaction F
B. Myasthenia Gravis is a type II reaction T
C. Extrinsic allergic alveolitis is a type II reaction F
D. Urticaria is a type III reaction. F
E. Montoux test is a type IV reaction. T

Q. Examples of type II hypersensitivity disorders are- (BSMMU – MD/MS - 01Ja)

a) Goodpasture syndrome T
b) Bullous pemphigoid T
c) Autoimmune haemolytic anaemia T
d) Serum sickness F
e) SLE F

Q. Type I hyper-sensitivity (BSMMU-Med/Sur-01Ja)

a) Is mediated by IgE. T
b) Is dependent on serum IgE level T
c) Can occur on 1st exposure F
d) Involves mast cells T
e) Can be blocked by antihistamin T

Immunodeficiency

Immunodeficiency:

- Clinical conditions due to abnormality in the development and functions of the immune system.
- Can occur in any of the four major components of the immune system:
  - B cells (antibody)
  - T cells,
  - complement, and
  - phagocytes.
- Either congenital or acquired
- Recurrent or opportunistic infections are commonly seen.
- Recurrent infections with pyogenic bacteria (e.g., staphylococci) indicate a B-cell deficiency,
- Whereas recurrent infections with certain fungi, viruses, or protozoa indicate a T-cell deficiency.

Primary immunodeficiency:

- Rare: in about half the children affected no defect is ever found, and then it usually in the phagocytic cells.
- Primary B-cell deficiency is very rare, and of T cells even more so.
- Respiratory system is the most common site of infection. The pattern of infection depends on the type of defect.

1. **B cell deficiency**	• X-linked Agammaglobinaemia (**Bruton's Agammaglobinaemia**) • Selective immunoglobulin deficiency (IgA)
2. **T cell deficiency**	• Di George syndrome/ Thymic aplasia • Chronic mucocutaneous candidiasis • Hyper IgM syndrome • IL-12 receptor deficiency
3. **Combined T & B cell deficiency**	• Severe combined immuno deficiency diseases • Wiskott Aldrich syndrome • Ataxia telangiectasia
4. **Complement deficiency disorders**	• Hereditary angio-oedema • Recurrent infection: staph. aureus, NM,NG. • Autoimmune disease-SLE • Paroxismal nocturnal haemoglobinaemia
5. **Phagocytic deficiency disorders**	• Chronic granulomatous disease • Chediak Higashi • Job's syndrome (Hyper IgE) • Leucocyte adhesion deficiency • Cyclic neutropenia • Myeloperoxide deficiency • IF-γ receptor deficiency

Acquired immunodeficiency:

1. **B cell deficiency**	• Common variable hypogammaglobinaemia • Malnutrition
2. **T cell deficiency**	• Acquired immunodeficiency syndrome • Measles
3. **Complement deficiency disorders**	• Liver failure • Malnutrition
4. **Phagocytic deficiencies**	• Neutropenia • Chronic Fatigue syndrome (Chronic Fatigue Immune Dysfunction syndrome)

(Ref: LANGE Review-15th, P-578-582)

Secondary immunodeficiency:

- Most immunodeficiency in adults is secondary to other conditions.
- Infection is usually with opportunistic pathogens, such as pneumocystis, CMV or yeasts.

CAUSES OF SECONDARY IMMUNE DEFICIENCY
Physiological immune deficiency
• Ageing • Prematurity • Pregnancy
Infection
• Human immunodeficiency virus • Mycobacterial infection • Measles
Iatrogenic
• Immunosuppressive therapy • Stem cell transplantation • Antineoplastic agents

• Radiation injury
• Corticosteroids
Malignancy
• B-cell malignancies including leukaemia, lymphoma and myeloma
• Solid tumours
•Thymoma
Biochemical and nutritional disorders
• Malnutrition
• Diabetes mellitus
• Renal insufficiency/ dialysis
• Specific mineral deficiencies, e.g. iron, zinc
Other conditions
• Burns
• Asplenia/ hyposplenism

(Ref: Davidson-20th, P-75)

Question Bank

Q. Immunodeficient disease states are *(BSMMU –Residency - MD/MS, Basic science, Paediatrics – March' 19)*
a) chronic granulomatous disease
b) idiopathic thrombocytopenic purpura
c) hereditary angioedema
d) chronic mucocutaneous candidiasis
e) IgA nephropathy
Ans. a) T b) F c) T d) T e) F

(Ref: Subash chandra Parija-2nd, P-143)

Q. B cell immunodeficiency states are *(BSMMU – Residency - MD, MS, Basic Science - March' 17)*
a) X link agammaglobulinemia
b) DiGeorge syndrome
c) hyper IgM syndrome
d) selective IgA deficiency
e) hereditary angiooedema
Ans. a) T b) F (T cell) c) T d)T e) F (complement deficiency)

(Ref: Subash chandra Parija-2nd, P-143)

Q. Acquired immunodeficiency syndrome is caused by viral infection of *(BSMMU – Residency - MD, MS, Basic Science, Dentistry - March' 17)*
a) B cell
b) cytotoxic T cell
c) helper T cell
d) membrane of lymphnode
e) platelet
Ans. a) F b) F c) T d) F e)F

Q. Conditions associated with T cell immunodeficiency are *(BSMMU – Non-Residency – MD, MS, Basic science, Dentistry – July' 16)*
a) Hodgkin's disease
b) Tay-Sach's disease
c) Wiscott-Aldrich syndrome
d) Down's syndrome
e) Di George syndrome
Ans.a) F b) F (It is lysosomal storage deficiency)

c) F (combined B cel and T cell) d) F (Triosomy 21)
e) T (or Thymic aplasia)

Help link: SCID – includes combined immunodeficiency, Wiskott-Aldrich, Ataxic telangiectasia.

Q. Infections common in immunodeficient patients are: *(BSMMU – M. Phil, Diploma (Non-Residency) – DMC & others – MD – 11Ju)*

a) pneumocystis carinii	T
b) diphtheria	F
c) poliomyelitis	F
d) cytomegalovirus	T
e) candida albicans	T

Q. The followings are the example of T cell defect: (DMC – M. Phil, Diploma July, 2008)

A. AIDS	T
B. Bruton disease	F (B cell)
C. Di George syndrome	T
D. Ataxia telangiectasia	T
E. Chronic granulomatous disease (CGD)	F

(Ref. LANGE Review-15th, P-573)

Q. The following conditions may lead to secondary immunodeficiency disease- (MD/MS (DMC)-08Ja)

a) malnutrition	T
b) IgA deficiency	F
c) cancer	T
d) HIV infection	T
e) Wiskott-Aldrich syndrome	F

Q. Diseases associated with T-cell depletion are – (M. Phil, Diploma (DMC)-07July)

a) Hodgkin's disease	T
b) Tay-Sachs disease	F
c) Wiscott-Aldrich syndrome	T
d) Down's syndrome	F
e) Di-George syndrome	T

(Ref. LANGE Review-15th, P-573)

Q. The following conditions are associated with T cell immunodeficiency. (MD/MS (DMC)-05Ja)

a) Hodgkin's disease
b) Tay-Sachs disease
c) Wiskott-Aldrich syndrome
d) Down's syndrome
e) Di George syndrome

Ans.

a) **True** The pathological tissue in Hodgkin's disease permeates the T-lymphocyte areas of lymphoid tissue, the B lymphocytes and plasma cells remaining unaffected. Many of the tests of T lymphocyte function (Skin tests, mitogen induced lymphocyte transformation) become depressed as the disease progresses. Patients become susceptible to opportunistic infections with organisms normally controlled by T-lymphocyte function, including Pneumocystis carinii, cytomegalovirus, Candidà albicans and other fungal agents.

b) **False** Tay—Sachs disease is a lipid storage disease affecting the nervous system only. The ganglion cells are ballooned with ganglioside giving rise to amaurotic familial idiocy. These children typically have a cherry red spot in the macula.

c) **True** This is a sex linked recessive disease manifested in childhood in which there is delayed growth and thrombocytopenia, the platelets being both small in number and abnormal in structure. Such children develop severe eczema and pyogenic infections. The serum contains increased amounts of IgA and IgE, normal levels of IgG but T-cell function is defective and cell-mediated immunity becomes

progressively worse so that affected children become susceptible to viral, fungal and bacterial infections.

d) **False** Down's syndrome, once known as mongolism, is associated with trisomy of chromosome 21. This chromosomal abnormality gives rise to mental retardation as well as the characteristic physical features. Although there may be an increased incidence of leukaemias it is not associated with immunodeficiency.

e) **True** The Di George syndrome is due to a defect in development of the third and fourth branchial arches resulting in thynic aplasia and T-cetl immunodeficiency, together with an absence of the parathyroid glands which causes hypocalcaemjc tetany. **(Ref: Smiddy)**

Q. An immunodeficiency that result in increases susceptibility to viral and fungal infection is primary deficiency of: (MD/MS (DMC)-01Ja)

A. Macrophage. F
B. Neutrophil. F
C. B. Cell. F
D. T cell T
E. NK cell. F

Tolerance

Q. Central tolerance of the immune system takes place in *(BSMMU –Residency – **MD, MS, Basic Science** – March' 18)*

a) bone marrow
b) lymph nodes
c) spleen
d) tonsils
e) thymus

Ans. a) T b) F c) F d) F e) T

Help link:

Tolerance is immunological unresponsiveness to self antigen.

'non-self':

Antigens that are not present during the process of maturation, i.e., that are encountered first when the body is immunologically mature, are considered "**nonself**".

- They usually elicit an immunologic response.

N.B. Although both B cells and T cells participate in tolerance, it is **T-cell tolerance** that plays the primary role.

Self tolerance refers to lack of responsiveness of immune system to an individual's own antigen. In general, antigens that are present during embryonic life are considered as "**self**".

Types of tolerance:

T cell tolerance:

- Central tolerance (Site- thymus)
- Peripheral tolerance

B cell tolerance:

- Central tolerance *(Site-Bone marrow)*
- Peripheral tolerance

[Tolerance to self acquired within the thymus & bone marrow is called **central tolerance.** Tolerance acquired outside the thymus is called **peripheral tolerance.**]

Autoimmunity

AUTOIMMUNE DISEASES:

- The adult show tolerance to tissue antigens
- Present in fetal life and recognized as "self."
- In some cases, tolerance may be lost and immune reactions to host antigens may develop autoimmune diseases.
- Activation of self-reactive helper (CD4) T cells.
- Th-1 or Th-2 cells can induce either cell-mediated or antibody-mediated autoimmune reactions, respectively.
- Most autoimmune diseases are antibody-mediated.

Factors of Autoimmune Disease

Factors	Example
1. Genetic	Ankylosing spondylitis is 100 times more likely to occur in people who carry HLA-B27, a class I gene,
2.Hormonal	Approximately 90% of all autoimmune diseases occur in women.
3. Environmental	Pharyngitis caused by Streptococcus pyogenes predisposes to rheumatic fever.

Mechanism / hypothesis of Autoimmune diseases:

Mechanism	Explanation and Example
Molecular Mimicry	Various bacteria and viruses are implicated as the source of cross-reacting antigens that trigger the activation of autore-active T cells or B cells. Example- 1. Reiter's syndrome occurs following infections with Shigella ,Chlamydia 2. Guillain-Barré syndrome occurs following infections with Campylobacter
Alteration of Normal Proteins	(Drugs can bind to normal proteins and make them immunogenic) Example- Procainamide-induced systemic lupus erythematosus .
Release of Sequestered Antigens	Certain tissues (e.g., sperm, central nervous system, and the lens and uveal tract of the eye) are sequestered so that their antigens are not exposed to the immune system. These are known as immunologically privileged sites. aspermatogenesis, encephalitis, or endophthalmitis, respectively. Intracellular antigens, such as DNA, histones, and mitochondrial enzymes, are normally sequestered from the immune system. However, bacterial or viral infection may damage cells and cause the release of these sequestered antigens, which then elicit an immune response.
Epitope Spreading	Epitope spreading means the new exposure of sequestered autoantigens as a result of damage to cells caused by viral infection.
Failure of Regulatory T Cells	Regulatory T cells (Tr) suppress the proinflammatory . Example- SLE

Q. Autoimmune disease are *(BSMMU – Residency – **MD, MS, Basic science, Dentistry** – March' 16)*

a) Paget's disease F
b) rheumatoid arthritis T
c) type I insulin-dependent diabetes mellitus T
d) multiple sclerosis T
e) amyloidosis F

HELP LINK:

■ **Types of auto-immune diseases:**

Autoimmune diseases	
Diseases	**Autoantibody present against**
Organ specific	
Graves' disease	TSH receptor
Myasthenia gravis	Acetylcholine receptor
Lambert-Eaton myasthenia	Calcium channel receptor
Pernicious anaemia	Gastric parietal cells, intrinsic factor
Goodpasture's syndrome	Basement membrane of kidney & lung
AGN	Glomerular basement membrane
Autoimmune haemolylic anaemia (AIHA)	Red blood cell membrane
Autoimmune thrombocytopenic purpura	Platelet membrane
Autoimmune orchitis	
Autoimmune (chronic active) hepatitis	
Primary biliary cirrhosis	Mitochondria
Coeliac disease	Enterocytes
Autoimmune colitis	
Insulin dependant DM	Islet cells
Insulin resistant DM	Insulin receptor
Hashimoto's thyroiditis	Thyrogiobulin, thyroid peroxidase
Addison's disease	Adrenal cortex
Primary antiphospholipid antibody syndrome	Anticardiolipin (antiphospholipid)
Premature Ovarian failure	Corpus luteum, interstitial cells
Pemphigus	Desmoglein in tight junctions of skin
Pemphigoid	Basement membrane
Allergic encephalomyelitis & multiple sclerosis	Reaction to myelin protein causes demyelination of brain neurons
Non-organ-specific	
SLE	Nuclear antigens. e.g. ANA, anti-double stranded DNA,smooth muscle Ag and IgG. Lupus anticoagulation (up to 40% of patients)
Rheumatoid arthritis	IgG (rheumatoid factor)
Rheumatic fever	Heart & joint tissue
Reiter syndrome	
Sjogren syndrome	
Guillian Barre syndrome	Myelin protein
Wegner's granulomatosis	Cytoplasmic enzymes of neutrophils
Inflammatory myopathies	
Polyarteritis nodosa (vasculitis)	ANCA
Drug-induced lupus	Histone
Systemic sclerosis (Scleroderma) (CREST variant)	Centromere
Mixed connective tissue disorder	Extractable nuclear antigens

*About 90% of all autoimmune diseases occur in women.

Q. HLA allele-B27 is associated with following inflammatory disease *(BSMMU –Residency – MD, MS, Basic Science – March' 15)*

a) ankylosing spondylitis
b) rheumatoid arthritis
c) chronic active hepatitis
d) post gonococcal arthritis
e) acute anterior uveitis

Ans. a) T b) F c) F d) T e) T

Help link:

HLA allele-B27 is associated with following inflammatory disease:

Ankylosing spondilytis
Reiter's syndrome/
Postgonococcal arthritis
Psoriatic arthritis
Acute anterior uveitis

Q. The organ-specific autoimmune diseases are: *(BSMMU – M. Phil, Diploma (Non-Residency)–March-2012, DMC & others – MD/MS – March-2012)*

a) rheumatoid arthritis F
b) autoimmune haemolytic anaemia T
c) scleroderma F
d) myasthenia gravis T
e) systemic lupus erythematosus F

Q. The following are autoimmune diseases - (MD/MS (DMC) – January, 2010)

a. Myasthenia Gravis T
b. GBS T
c. multiple sclerosis T
d. motor neuron disease F
e. paraneoplastic syndrome F

HELP LINK:

Important Autoimmune Diseases.

Type of Immune Response	Autoimmune Disease	Target of the Immune Response
Antibody to receptors	Myasthenia gravis	Acetylcholine receptor
	Graves' disease	TSH[1] receptor
	Insulin-resistant diabetes	Insulin receptor
	Lambert-Eaton myasthenia	Calcium channel receptor
Antibody to cell components other than receptors	Systemic lupus erythematosus	dsDNA, histones
	Rheumatoid arthritis[2]	IgG in joints
	Rheumatic fever	Heart and joint tissue
	Hemolytic anemia	RBC membrane
	Idiopathic thrombocytopenic purpura	Platelet membranes
	Goodpasture's syndrome	Basement membrane of kidney and lung
	Pernicious anemia	Intrinsic factor and parietal cells
	Hashimoto's thyroiditis[2]	Thyroglobulin
	Insulin-dependent diabetes mellitus[2]	Islet cells
	Addison's disease	Adrenal cortex
	Acute glomerulonephritis	Glomerular basement membrane
	Periarteritis nodosa	Small and medium-sized arteries
	Guillain-Barré syndrome	Myelin protein

	Wegener's granulomatosis	Cytoplasmic enzymes of neutrophils
	Pemphigus	Desmoglein in tight junctions of skin
	IgA nephropathy	Glomerulus
Cell-mediated	Allergic encephalomyelitis and multiple sclerosis	Reaction to myelin protein causes demyelination of brain neurons
	Celiac disease	Enterocytes

MICROBIAL INFECTIONS ASSOCIATED WITH AUTOIMMUNE DISEASES	
Microbe	**Autoimmune Disease**
1. Bacteria	
Streptococcus pyogenes	Rheumatic fever
Campylobacter jejuni	Guillain-Barre syndrome
Escherichia coli	Primary biliary cirrhosis
Chlamydia trachomatis	Reiter's syndrome
Shigella species	Reiter's syndrome
Yersinia enterocolitica	Grave's syndrome
Borrelia burgdorferi	Lyme arthritis
2. Viruses	
Hepatitis B virus	Multiple sclerosis
Hepatitis C virus	Mixed cryoglobulinemia
Measles virus	Allergic encephalitis
Coxsackievirus B3	Myocarditis
Coxsackievirus B4	Type 1 diabetes mellitus
Cytomegalovirus	Scleroderma
Human T-cell leukemia virus	HTLV-associated myelopathy

(Ref: LANGE Review-15th)

Q. Following are the organ specific autoimmune diseases - (MD/MS (DMC)-09Ja)

a. Sjogren's syndrome T
b. Hashimoto's thyroiditis T
c. Grave's disease T
d. acute glomerulonephritis T
e. pernicious anaemia T

Q. The following diseases are immunologically mediated: (BSMMU – MD/MS - January, 2009)

a) Parkinson's disease F
b) Myasthenia gravis T
.c) Duchenne muscular dystrophy F
d) Familial periodic paralysis F
e) Multiple sclerosis T

Q. The followings are autoimmune disease: (M. Phil, Diploma (DMC)-05July)

a) Hashimoto's thyroiditis T
b) Thyrotoxicosis T
c) SLE T
d) Systemic sclerosis T
e) Atherosclerosis F

Q. The following diseases are immunologically mediated - (BSMMU - M. Phil, Diploma, July-05)

A. myasthenia gravis
B. Duchenne muscular dystrophy
C. familial periodic paralyis
D. multiple sclerosis
E. Parkinson's disease

Ans.
a) T *(Ab is formed against Acetylcholine receptor)*
b) F *(X linked disorder)*
c) F
d) T *(HLA associated)*
e) F *(Cause is unknown, genetic influence, environmental toxin may be associated)*

Q. Autoimmune diseases include: (MD/MS (DMC)-05Ja)

a) Nasal polyp F
b) Systemic lupus erythomatosus T
c) Pernicious anaemia T
d) Hashimoto's thyroiditis T
e) Bell's palsy. F

HELP LINK:

Systemic	Organ specific
1. RA	1.Hashimoto's thyroiditis
2. SLE	2.Autoimmune haemolytic anaemia
3. Reiter's syndrome	3.Autoimmune pernicious anaemia
4. Inflammatory myopathies	4.Multiple sclerosis
5. Systemic sclerosis (scleroderma)	5.Autoimmune aortitis
6. PAN	6.Good pastaur syndrome
7. AGN	7.Autoimmune thromocytopenia
8. GBS	8.Insulin dependant DM
9. RF	9.Insulin resistant DM
10. Addison's disease	10. gears disease
11. Wegner's granulomatosa	11. Myasthenia gravis
12. Pemphigus	12. Lambert eaton myasthenia
	13. Primary biliary cirrhosis
	14. Autoimmune (chronic active) hepatitis
	15. Ulcerative colitis

Q. HLA association and susceptibility to autoimmune diseases- (MD/MS (DMC)-03Ja)

A. Myasthenia gravis – DR3 T
B. SLE – DR3 T
C. Ankylosing spondylitis – B27 T
D. NIDDM – DR4 F (DR2)
E. Rheumatoid arthritis – DR4 T

HELP LINK:

Association of HLA with diseases	
Disease	**HLA allele**
Haemochromatosis	A3
Bechet's disease	B5
Ankylosing spondilytis Reiter's syndrome/ Postgonococcal arthritis Psoriatic arthritis Acute anterior uveitis	B27

Multiple sclerosis Pernicious anaemia Narcolepsy Juvenile onset DM	DR2
Chronic active hepatitis Dermatitis herpetiformis Coeliac disease Primary Sjogren syndrome Primary biliary cirrhosis Grave's disease Hashimoto's thyroiditis Addison's disease SLE, Myasthenia gravis	DR3
Type I DM	DR3 &/ DR4
Rheumatoid arthritis	DR4
Pernicious anaemia	DR5
Coeliac disease	DR7

Q. Basic mechanisms responsible for the development of autoimmune disease are- (BSMMU – MD - 02Ja)

a) Activation of autoreactive T cells T
b) Apoptosis of autoreactive T cells F (mechanism of tolerance)
c) Polyclonal activation of B cells T
d) Loss of suppressor – T cell activity T
e) Immune suppression by chemotherapy. F

Transplantation

Q. Hyperacute rejection of grafts *(BSMMU –Residency - MD/MS, Basic science, Paediatrics – March' 19)*

a) occurs within 2-4 days after transplantation
b) is a cell-mediated response
c) can be minimized by matching blood groups of donor and recipient
d) never occurs in autografts
e) may be reversed by cyclosporine

Ans. a) F b) F c) T d) T e) F

(Ref: Prof Akram's immunology-5th, P-163)

Help link:

Graft rejection: It is the condition in which recipients immune system recognize the graft as being foreign & attack it.

Classification: On the basis of time of rejection, graft rejections are catagorized into-

Topics	Hyper –acute rejection	Acute rejection	Chronic rejection
Mediated by	Occurs due to preformed Ab against the transplanted MHC Ag	By cell mediated immune response	By both humoral and cell mediated immune response
Time	With in minutes	After days-months (Usually 10 to 14 days)	After months-years
causes	Preform antibody source 1.Previous blood transfusion, 2.multiparous lady 3.Ab against minor ag	Due to insufficient immunosuppression before graft	Atherosclerosis Minor antigenic variation Side effects of immunosuppressive drugs
Fate	Ischaemic damage and failure of transplant.	May be preventable with proper immunosuppressive therapy	Progress to end stage organ damage

1. Hyper-acute rejection: Immediately after transplantation, the transplanted organ become pale/ while due to vascular occlusion, so called white graft.
- It occurs within minutes. Surgeon can see on operation table.
- Occurs due to preformed Ab against the transplanted MHC Ag.
- Complement mediated lysis occur
- Source of preformed antibody -
  - Previous blood transfusion (Ab against MHC I & II)
  - Ab against minor Ag (normal plasma protein)
  - Multiparous lady (Ab against MHC molecule)
  - Fate – ischaemic damage & failure of transplant

2. Acute rejection:
- Have cell mediated immune response predominate over the humoral immune response.
- Occurs after Days – months (usually 10-14 days)
- Both cytotoxic & helper T cell responsible
- Due to insufficient immunosuppression before graft
- May be preventable with proper immunosuppressive therapy.

3. Chronic rejection:
- By both humoral & cell mediated immune response
- After months – years (although it is accepted initially)
- Causes –
  - Atherosclerosis
  - Minor antigenic variation
  - Side effects of immunosuppressive drugs
- It is difficult to prevent
- If rejected then re-transplantation

Q. Hyperacute rejection of grafts *(BSMMU – Residency – **MD, MS, Basic science, Dentistry** – March' 16)*

a) occurs within 2-4 days of transplantation	F
b) associated with T-cell mediated reaction	F
c) may be minimized by matching blood group	T
d) occurs in autograft	F
e) mediated by preformed antibodies	T

Q. Acute graft rejection following transplantation is *(BSMMU –Residency – **MS, Basic Science, Dentistry** – March' 16)*

a) antibody mediated	T
b) cell mediated	T
c) T-cell dependent	T
d) irreversible	F
e) seen after first six months	F

Q. In acute rejection of solid organ transplant graft damage is *(BSMMU –Residency – **MD, MS, Basic Science** – March' 15)*

a) due to pre-formed antibody
b) caused by recognition of donor peptides by cytotoxic T-cell
c) caused by release of macrophage cytokines such as IL-I & TNF-a
d) caused by helper T-cells
e) caused by transplant atherosclerosis

Ans. a) F (hyper acute) b) T c) T d) T e) F (mechanism of chronic rejection)

Q. The following grafts are rejected *(BSMMU –Residency – MS, Basic science – March' 14)*
a) autograft
b) iso graft
c) allo graft
d) xeno graft
e) corneal graft

Ans.

a) **False** Transplantation of an individual's own tissue to another site, e.g. the covering of a full thickness burn with skin from an unburnt area, is not rejected.

b) **False** Transplantation of tissues between genetically identical members of the same species, e.g. kidney transplants between monozygotic twins or skin grafts between mice of the same inbred strain, are not rejected.

c) **True** Transplantation between genetically non-identical members of the same species, e.g. a cadaveric renal transplant or a skin graft between mice of different inbred strains are rejected.

d) **True** Transplantation of tissues between members of different species are rejected.

e) **False** The cornna is in an immunologically privileged site.

Q. Immuno-suppression for transplantation may be induced by: *(BSMMU – M. Phil, Diploma (Non-Residency)–March-2012, DMC & others – MD/MS – March-2012)*

a) lymphoid irradiation	T
b) cyclosporin A	T
c) interferon α	F
d) plasmapheresis	F
e) antilymphocytic serum	T

HELP LINK: To reduce the chance of rejection of transplanted tissue, immunosuppressive measures, eg. cyclosporine, tacrolimus (FK506, Prograf), sirolimus (rapamycin, Rapamune), corticosteroids, azathioprine, monoclonal antibodies, and radiation, are used. Cyclosporine prevents the activation of T lymphocytes by inhibiting the synthesis of IL-2 and IL-2 receptor. It does so by inhibiting calcineurin, a protein (a serine phosphatase) involved in the activation of transcription of the genes for IL-2 and the IL-2 receptor. Cyclosporine is well-tolerated and is remarkably successful in preventing the rejection of transplants, Cyclosporine and tacrolimus have the same mode of action; tacrolimus is more immunosuppressive but causes more side effects, Rapamycin also inhibits signal transduction but at a site different from that of cyclosporine and tacrolimus.

Corticosteroids act primarily by inhibiting cytokine (eg.- IL-1 and tumor necrosis factor) production, by macrophages and by lysing certain types of T cells. Corticosteroids inhibit cytokine production by blocking transcription factors, such as NFκB and AP-1, which prevents the mRNA for these cytokines from being synthesized. Azathioprine is an inhibitor of DNA synthesis and blocks the growth of T cells. Mycophenolate mofetil also inhibits DNA synthesis and has fewer side effects than azathioprine.

Monoclonal antibodies are used in immunosuppressive regimens, both to prevent rejection and to treat rejection episodes. Muromonab (OKT3) is a monoclonal antibody against CDS, and basiliximab and daclizumab are monoclonal antibodies against the IL-2 receptor. Describes these monoclonal antibodies as well as others in clinical use.

Unfortunately, immunosuppression greatly enhances the recipient's susceptibility to opportunistic infections and neoplasms. For example, some patients undergoing treatment for multiple sclerosis with the monoclonal antibody, natalizumab, developed progressive multifocal leukoencephalopathy. The incidence of cancer is imeased as much as 100-fold in transplant recipients. Immunosuppressive drugs, eg.- cyclosporine, also reduce GVH reactions.

Note that although these drugs suppress the allograft reaction, tolerance to the graft tissue does not ensue. Therefore, most patients must take these drugs during their entire lives.

HLA matching

Q. HLA matching is not required in transplant of *(BSMMU – Non-Residency – **MD, MS, Basic science** – July' 18)*
a) cornea
b) bone
c) kidney
d) bone marrow
e) liver

Ans. a) T b) F c) F d) F e) F

Help Link:
Immunologically privileged sites:
1. Anterior chamber of the eye
2. Cornea
3. Uterus-placenta and foetus
4. Testis
5. Brain-CNS
6. Cartilage

Q. HLA matching is required in following organ transplantation *(BSMMU – Non-Residency – **MD, MS, Basic science** – July' 15)*
a) cornea F
b) bone T
c) kidney T
d) bone marrow T
e) liver T

Tumor immunity

Tumor immunity: Study of tumor Ag and immunological reaction of host. Or,
It refers to the capacity of host's immune system to recognize, destroy & eliminate tumor cells.Or,
When normal cell is transformed into malignant cell, they produce some new proteins which are recognized by the immunocompetent cells as foreign & destroy the malignant cells by immune response. This is known as **tumor immunity.**

Q. Cells implicated in tumour immunity are *(BSMMU – Non-Residency – **MD/MS, Basic science** – July' 14)*
a) natural killer cell
b) neutrophil
c) macrophage
d) cytotoxic T cell
e) eosinophil

Ans. a) T b) F c) T d) T e) F

Immune surveillance

Q. Tumors escape body's immune surveillance by *(BSMMU –Residency – **MD, MS, Basic Science** – March' 18)*
a) selective overgrowth of antigen negative variants
b) inhibition of regulatory T cells
c) inactivation of immuno regulatory pathways
d) reduced expression of MHC molecules
e) secretion of immune suppressive factors by tumor cells

Ans. a) T b) F (Induction) c) F (Activation) d) T e) T

Help link:

Immune surveillance:

Definition: Protective process against cancer development: the body mechanism that detects early cancers and destroys them before they can grow to dangerous size.

Mechanism:

1. **Cytotoxic T- lymphocyte mediated:** Recognizes the tumor antigen and produce cell mediated cytotoxicity.
2. **Natural Killer cell mediated:** NK cells are capable of destroying tumor cell without prior sensitization
3. **Macrophage mediated**: Activated macrophage shows selective cytotoxicity against tumor cells
4. **Humoral mechanism:** These may participate in tumor cell destruction by-
   -Activation of complements
   -Induction of Ab-dependent cellular cytotoxicity by NK cells.

(Ref: Robbin's Basic pathology-9th, P-313)

Q. Immunosurvellance system against cancer cell *(BSMMU – Diploma – Dentistry-July' 16)*

a) NK cell
b) B lymphocyte
c) eosinophil
d) neutrophil
e) cytotoxic T cell

Ans. a) T b) F c) F d) F e) T

Help Link: Cytotoxic T cells, NK cell, Macrophage

(Ref: Robbins-9th, P-312)

Others

Q. The following conditions are associated with a polyclonal gammopathy: *(BSMMU – M. Phil, Diploma (Non-Residency)–March-2012, DMC & others – MD/MS – March-2012)*

a) Waldenström's macroglobulaemia
b) rheumatoid arthritis
c) Down's syndrome
d) Wiskott—Aldrich syndrome
e) post-streptococcal glomerulonephritis

Ans.

a) **False** Waldenström's macroglobulinaemia usually presents between the sixth and seventh decade with a group of non-specific symptoms such as fatigue, weakness and weight loss, although in 50% of patients a lymphadenopathy, hepatomegaly and splenomegaly are present. Pathologically the bone marrow is diffusely infiltrated with lymphocytes and plasma cells which synthesize a monoclonal IgM immunoglobulin leading to a macroglobulinaemia which causes a greatly increased viscosity of the blood.

b) **True** Rheumatoid arthritis is a chronic inflammatory disorder which may affect many tissues. Its most obvious and usual presentation is the occurrence of joint disease in which a proliferative synovitis results in destruction of the articular cartilage and ultimately in severe cases ankylosis of the affected joints. Approximately 80% of patients suffering from the disease develop autoantibodies to the Fc portion of the autologous IgG and IgM.

c) **False** There is no evidence of increased inrnunoglobulin synthesis in Down's syndrome which is a genetic defect associated with three instead of the normal pair of number 21 chromosomes.

d) **False** The Wiskott—Aldrich syndrome is a condition in which atopic eczema, thrombocytopenia and an increased susceptibility to infection in infants occurs. It is a sex linked recessive condition accompanied by a defect in antibody production, low levels of IgM and detective T-cell function.

e) **True** Acute post-streptococcal glomerulonephritis occurs most frequently in children between 6 and 10 years of age. It is caused by certain strains of Group A beta-haemolytic streptococci, chiefly types 12, 4 and 1. A latent period of some four weeks occurs after the streptococcal infection, usually of the throat or skin during which antibodies and immune complexes are formed, the latter being deposited

in the mesangium and the basement membrane of the glomeruli at which points immunofluorescent microscopy shows granular deposits of IgG, IgM and C3.

Polyclonal gammopathy is found in:
- Sjogren's syndrome
- Sarcoidosis

(Ref Davidson's Medicine, 21st Edi, P-1040)

Monoclonal gammapathy is found in:
- Multiple myeloma
- Lymphoma
- Amyloidosis
- Rheumatoid arthritis
- Polymyalgia rheumatica
- HIV
- Solid tumour

(Ref: Davidson's Medicine, 21st Edi, P-1040)

Causes / disorders associated with paraproteinaemia:
- Multiple myeloma.
- Waldenstrom's macroglobulinaemia.
- Chronic lymphatic leukaemia.
- Non-Hodgkin's lymphoma.
- Benign monoclonal gammopathy
- Heavy chain disease.
- Primary amyloidosis.

Q. Graft versus host disease: *(FCPS – Surgery -09Ja. BSMMU-M.phil-10Ju)*
a) may follow bone marrow transplants
b) may follow blood transfusion
c) occurs in Hodgkin's disease
d) can be suppressed by tetracyclines
e) can be suppressedty cyclophosphamide

Ans.

a) **True** Bone marrow transplants are used as a therapeutic measure in patients suffering from the combined immunodeficiency syndrome or whose immune response has.been destroyed by irradiation or cytotoxic drugs. If the marrow transplant is not HLA matched the donor T lymphocytes will react against host tissues. Signs that this is occurring include the development of erythroderma, exfoliative dermatitis, splenomegaly and wasting. Death ultimately occurs if the reaction cannot be controlled by immunosuppressive agents such as cyclosporin A.

b) **True** In patients suffering from a severe depression of their immunological systems a blood transfusion may provoke a graft versus host reaction due to the T cells which are contained in the dgnor blood. This can be avoided by irradiating the blood prior to transfusion in order to destroy T-cell function.

c) **False** Graft versus host disease could only occur in a patient with Hodgkin's disease if that patient was rendered completely immunodeficient ly irradiation or cytotoxic therapy and then received a transfusion of unirradiated blood.

d) **False** Tetracyclines will only suppress the intercurrent infection that occurs as the graft versus host reaction becomes severe and then only if the bacteria causing the infection are sensitive to this antibiotic. This is not usually the case since the common agents of infections in this disease are fungi and viruses, all of which are insensitive to the tetracyclines.

e) **True** Temporary suppression ot the graft versus host reaction can be achieved by the use of cyclophsphamide because this drug is a nitrogen mustard derivative cytotoxic to dividing lymphocytes. It is, however, an extremely toxic compound which may cause hair loss resulting in alopecia, destruction of the bladder mucosa causing haematuria and increasing susceptibility to fungal infection.

(Ref: Smiddy)

Q. Non-specific host defenses against viral infection are: (BSMMU – MD/MS - January, 2009)

a) Natural killer cells (NK cells) T
b) IgM T
c) Interferons T
d) Anti-viral drugs F
e) IgG T

Q. Examples of agglutination reactions are- (BSMMU – MD - 01Ja)

a) VDRL test T
b) Widal test T
c) Elek's test F
d) Well –felix test T
e) Paul-Bunnel test F

IMPORTANT MCQ OF IMMUNOLOGY

[Ref: Smiddy]

Q. Following substances normally act as antigens, i.e. stimulate antibody production, when administered to humans:

a) dextrans with a molecular weight below 150 000
b) bovine insulin
c) extracts of Primula
d) human thyroglobulin
e) Rh.D. antigen

Ans.

a) **True** Dextrans are polysaccharides produced by the fermentation of sucrose by certain strains of Leuconostoc mesenteroides. They can be used in the emergency treatment of stiock due to a falling blood volume, acting by maintaining the colloid osmotic pressure of plasma. They have no oxygen carrying capacity, contain no plasma proteins or blood clotting factors. Occasionally severe anaphylactic reactions an occur during their administration.

b) **True** Insulin antibodies are produced in any diabetic patient treated with non-purified insulin for more than 30 days, in some patients high enough to impair insulin action. Conventional insulins may be separated into: component a, comprising material of high molecular weight, component b comprising pro-insulin, intermediates, a diner and component c comprising insulin, arginine insulin, the ethyl ester of insulin and desamidoinsulin. It is generally agreed that beef insulin is more antigenic than pork insulin. 'Human' insulin produced by recombinant DNA technology can be produced which is totally nonantigenic.

c) **False** Extracts of the Primula have a molecular weight of only 210. They act, however, as haptens binding to the body's own protein through covalent linkages causing them to behave as antigens. This is a common cause of contact sensitivity in gardeners.

d) **False** Normally the body does not react against its own thyroglobulin. However, in Hashimoto's thyroiditis autoimmune antibodies make their appearance in the circulation which are directed against thyroglobulin.

e) **True** Immunisation with Rhesus antigens occurs in:
(a) Rh negative individuals transfused with Rh +ve blood
(b) In some Rh - ve mothers following a pregnancy in which the fetus is Rh +ve

Q. The following statements are true or false:

a) IgA is produced at mucous surfaces
b) IgM has a molecular weight of 1,50,000
c) IgE is the anaphylactic antibody
d) antibody specificity depends on the constant regions of the F(ab) fragment
e) immunoglobulin synthesis is dependent on thymic integrity in neonatal life

Ans.

a) **True** IgA is a very important immunological immunoglobulin frequently secreted as a dimer, Sig A (a compound formed by the combination of two simpler molecules). IgA antibodies are found in secretions covering mucosal surfaces of the stomach and bronchi and in the secretions of the nose, mouth and tears partly bound to high moleular weight mucous.

b) **False** IgM has a molecular weight of 9,70,000. The molecule has a pentameric structure in which each individual heavy chain has a molecular weight of approximately 65,000. The greater part of IgM is within the vascular system and is most frequently seen in the immune response to antigenically complex infectious organisms, e.g. S. typhi.

c) **True** IgE is the antibody involved in all anaphylactic reactions, binding to the surface of mast cells. An immediate hypersensitivity reaction occurs following the interaction of an antigen (the allergen) with the specific IgE antibody which is predominantly bound to tissue mast cells and circulating basophils. The ensuing reaction results in the mast cells becoming degranulated with the release of mediators producing a variety of effects, e.g. asthma, eczema, hay fever or anaphylaxis, (Type I Hypersensitivity).

d) **False** Antibody specificity towards antigen depends on the variable sequence of aminoacids in the adjoining heavy and light chains of the F(ab) fragment of the immunoglobulin molecule.

e) **False** Immunoglobulins are secreted by plasma cells of the B-lymphocyte line, cells which are not under thymic control. In birds the site of B-lymphocyte maturation is the Bursa of Fabricus, hence the term B-lymphocyte. This is a ymphoepithelial organ found at the junction of the hind gut and the cloaca. The bursa is colonised by sinall numbers of stem cells in a few days du/ing early .embryonic development and these cells then proliferate and differentiate to form B lymphocytes in the bursal follicles. An equivalent organ has not been identified in mammals, but it has been shown that in neonatal thymectomised mice or chidren with thymic atresia that alnough they are unable to produce T lymphocytes, they are still able to produce immunoglobulins.

Q. Bence Jones proteins are - (BSMMU–MD - 06Ja)

A. The heavy chain of immunoglobulins
B. Found in urine in multiple myeloma
C. Associated with a monoclonal gammopathy
D. Found in urine of W. macroglobinaemia
E. Precipitated by boiling.

Ans.

A. **False** Bence Jones proteins are light chains not associated with the heavy chains which form normal immunoglobulins. They are secreted by the abnormal plasma cells in the condition known as multiple myeloma and pass from the plasma into the urine

B. **True** Bence Jones proteins are only found in the urine in multiple myeloma. They are necessary finding for the diagnosis of this disease. Additional diagnostic features of the disease are the presence of osteolytic deposits in the bones and abnormal plasma cells found on sternal marrow biopsy

C. **True** A monoclonal gammopathy together with the presence of an 'M' protein is a necessary feature of multiple myeloma but both are found in other conditions such as old age or following a massive immune response. In the latter conditions they are not associated with Bence Jones proteins

D. **False** An excess of monoclonal IgM is found Waldenstrom's macroglobulinaemia in which, because of the excessive amounts of IgM, the plasmapheresis. Only occasionally does a Bence Jones proteinuria occurs. The clinical features include weakness, fatigue, malaise and anorexia, congestive heart failure, neurological symptoms such as vertigo and nystagmus and occasionally spontaneous haemorrhages from mucosal surface. Lymphadenopathy and hepatosplenomegaly are common.

E. **False** Bence Jones proteins precipitate at 80^0 C but return into solution on boiling. Other proteins in the urine are precipitated by boiling

Q. T lymphocytes:
a) are immunoglobulin secreting cells
b) are found in the paracortical area of lymph nodes
c) are involved in contact dermatitis
d) are not involved in protection against tuberculosis
e) secrete lymphokines
Ans.
a) **False** T lymphocytes do not produce or secrete immunoglobulins. They carry antibody-like receptor groups on their surface which specifically react with antigen. These are related to antigen reactive sites on the immunoglobulins as they have the same idiotypes. Anti-idiotypic antibodies produced against immunoglobulin idiotypes react with T lymphocytes responding to the same antigen.
b) **True** The paracortical areas of the lymph nodes lie between the true cortex and the corticomedullary junction which is the site of the post-capillary venules with their high walled endothelium. These areas become depleted of lymphocytes of neonatally thymectomised mice and in children born with thymic atresia and because of this the paracortical areas are sometimes known as the thymus dependent areas.
c) **True** Contact dermatitis in man is most commonly caused by haptens, molecules too small of themselves to act as antigens, but which conjugated with protein provoke a Type IV hypersensitivity reaction. Common agents are metals, nickel and dichromate and simple organic compounds such as dinitrochlorobenzene. The process of sensitisation takes between 10-14 days and the reaction once initiated begins to wane after 48—72 hours. Sensitisation takes place as the hapten-protein conjugate is taken up by the Langerhan cells of the suprabasal epidermis. These cells act as antigen presenting cells and appear in the paracortical areas of the draining lymph nodes in which the T cells are situated. A set of CD4+ lymphocytes transformed into 'memory' CD4 T cells and then activated CD4 T cells release interferons (INFY) which induce changes in the surface keratinocytes and the endothelial cells of the dermal capillaries, resulting in the liberation of cytokines and the development of an eczematous reaction in the skin.
d) **False** Mycobacteria such as *M. tuberculosis* and *M. leprae* are facultative intracellular parasites which tend to reside within macrophages. Host resistance to *M. tuberculosis* is produced by a reaction between specifically sensitised T lymphocytes and mycobacterial antigen. These cells then secrete lymphokines which activate the macrophages causing increased activity of the hexose monophosphate shunt and the intracellular formation of bactericidal superoxides.
e) **True** Both T and B lymphocytes will when activated by either specific antigens or mitogenic lectins (carbohydrate binding proteins stimulating cell division) such as phytohaemagglutrnln and Concavalin A produce lymphokines; this being the generic term for molecules other than antibodies which are involved in signalling between cells. Such activation can be demonstrated by the development of activation markers which are either an increased expression of existing cell molecules or the de novo appearance of others and by structural changes in the cells which can be seen by both light and electron microscopy.

Q. The major histocompatibility complex (MHC) in man: (FCPS – Surgery – 08Ja,04Ja)
a) is situated on Chromosome 6
b) has three loci controlling five groups of histocompatibility antigens
c) i involved in the expression of immune response (lr) genes
d) Shows a positive association with Hodgkin's disease rfiultiple sclerosis and ankylosing Spondylitis
e) is tested for by the laboratory on a serum sample
Ans.
a) **True** The major histocompatrbility ompfex Consists of four foci Situated on chromosome 6 in man. These control four groups of histocompatihil,ty antigens HLA-A, B, C and D. The A and B group of

antigens are serologically determined and the D locus antigens are mainly determined by mixed lymphocyte reaction,

b) **False** Four loci control four groups of histocompatibility antigens, One antigen in each group is inherited from the father and one from the mother HLA-D (related) antigens are found mainly on B lymphocytes and these are coded for either by HLA-D or a very closely linked locus. Recently D related antigens have been discovered serologically and are referred to as HLA-DR.

c) **True** HLA-D and HLA-DR are Considered to be equivalent to the I region of the MHC in the mouse, (Ir) genes coded in this area which are autosomal dominant and inherited in a strictly Mendelian fashion are responsible for the immune response to a number of antigens.

d) **True** Hodgkin's disease shows positive association with A1 and B8, multiple sclerosis with A3, B7 and DW2 and ankylosing spondylitis with B8.

e) **False** HLA antigens are identified by the use of loucocyte suspensions. The term HLA is an abbreviation of the words human leucocyte antigens. Unclotted blood is needed by the laboratory.

Q. Macrophages:

a) are not involved in the recognition of antigens.
b) do not secrete lysosomal antibodies.
c) carry receptors on their surface.
d) are involved in the tuberculin reaction
e) play an important role in graft rejection

Ans.

a) **False** Macrophages are important in antigen recognition, immune response genes being expressed by macrophages as well as lymphocytes. The macrophages process antigen which frequently results in the production of a more immunogenic material.

b) **False** Following the engulfment of the bacterial cell by the pseudopodia of the macrophage, the bacillus lies in a phagosome. The engulfing macrophage then secretes into the phagosome reactive oxygen intermediates (ROls), which are toxic to some bacteria and in addition granules and lysosomes fuse with the phagosome pouring into it enzymes which digest the bacterium. Whilst macrophages remain active in the resting state, their function can be enhanced by exposure to lymphokines derived from T cells.

c) **True** Macrophages have three distinct forms of receptor:
(1) Fc receptors for lgG with the highest affinity for FcyRL (CD64).
(2) CD14 which is a specific receptor for the lipopolysaccharide capsule of Gram-negative bacteria.
(3) Complement receptors
In addition they have receptors for cytokines which produced by the T cell explains their enhanced activity.

d) **True** The tuberculin reaction is an example of type IV hypersensitivity in which followlhg the intradermal injection of tuberculin into an already sensitised individual a skin reaction occurs. In this response, a cellular infiltrate cnsisting chiefly of CD4+ and CD8+ cells infiltrates the dermis disrupting the, collagen bundles. Some 12 hours after the challenge, macrophages begin to accumulate around the dermal vessels, these cells forrriing the chief antigen-presenting cells stimulating the lymphocytes.

e) **False** The important cell in relation to graft rejection is the T lymphocyte. In the absence of these cells, as for example in a mouse in which the thymus has been removed in the neonatal period prior to the release of mature T cells into the periphery, rejection does not occur. Neither B lymphocytes or macrophages play a significant role in primary rejection. Most important in rejection is the action cit lymphokines especially IL-2 which is required for the activation of T cytotoxic cells.

Q. Autoimmunity:

a) occurs because of a breakdown in the ability of the body to distinguish betweenselt and non-self.
b) is a rare cause of infertility in the male
c) is not involved in the development of pernicious anaemia
d) is important in the pathogenesis of lupus erythematosus
e) does not result in immune complex disease

Ans.

a) **True** The development of certain human diseases such as Hashimoto's disease of the thyroid is due to a breakdown of the self-recognition mechanisms. The ability to recognise 'self' antigens is determined by the state of maturity of the lymphocyte at the time it encounters the antigen, not as was once thought by the age of the individual, The latter concept arose because it had been shown that if an individual was exposed to a foreign antigen prior to birth, his or her ability to recognise that antigen continued throughout life: However, it is now believed that it is the state of maturity of the lymphocyte and not the individual which is important. When the body is unable to distinguish self' and 'non-self, an autoimmune response occurs which results in. the development 'autoantibodies'. Whilst Hashimoto's disease is an organ specific disease, in that only the thyroid gland is affected, there are a range of conditions in which nearly all tissues in the body are affected.

b) **True** Rarely infertility in the male is due to the development of antibodies to sperm. As a result the sperms are rendered immobile either by fusing tail to tail or head to head.

c) **False** Pernicious anaemia is an autoimmune condition. Normally vitamin B12 is absorbed by the intestine only after it has become associated with the intrinsic factor which is a protein. In PA, the plasma cells in the gastric mucosa secrete an antibody acting against IF, The resulting lack of vitamin B12 results in the development of pernicious (Addisonian) anaemia which is characterized by the appearance of megaloblastic cells in the peripheral blood. Like many autoimmune conditions, it is commoner in females than in males and frequently runs in families.

d) **True** Whereas Hashimoto's disease is an example of an organ specific disease, the autoantibodies being directed solely at the thyroid cells themselves, systemic lupus erythematosus is an example of a non-specific autoimmune disease, in which the autoantibodies are directed against the majority if not all the tissue cells of the body, almost specifically against the cell nucleus.

e) **True** Immune complexes are the result of an antigen reacting with antibody. Usually removed by the reticulo endothelial system in some patients in whom the system is detective or overwhelmed, the complexes are deposited in the tissues, e.g. the kidney, joints or skin.

Q. The germinal centres of lymph nodes:

a) participate in cell-mediated immunity

b) contain macrophages and plasma cells

c) after producing B cells discharge these via the subcapsular (marginal) sinus into the general circulation

d) enlarge in chronic infectious diseases

e) are absent in humans suffering from congenital thymic aplasia

Ans.

a) **False** Cells concerned with cell mediated immunity are not produced in the germinal centres. The germinal centres are concerned with the maturation of B lymphocytes into lymphocyte memory cells and the antibody forming cells. These cells are chiefly concerned with humoral antibody production and develop within the primary nodules in response to antigenic stimulation.

b) **True** In addition to proliferating B lymphocytes occasional plasma cells of B lymphocyte origin can be found. In addition macrophages can be seen which contain tangible bodies. These are deeply staining nuclear debris derived from disintegrating cells.

c) **False** Lymphocytes enter the lymph node via the afferent lymphatics which give access to the marginal sinus, but cells can only leave the node via the efferent lymphatic at the hilum of the node.

d) **True** In chronic infections lymph node enlargement is common because the nodes respond to a number of antigens. In such an enlarged node a characteristic feature is the number of large germinal centres scattered throughout the lymphoid tissue.

e) **False** In humans suffering from the rare condition known as the Di George anomaly, organs derived from the third and fourth pharyngeal pouches fail to develop. As a result there is a T-cell deficiency. In addition a variety of facial deformities occur, the eyes are wideset. the ears low and the philtrum of the upper lip is shortened. Because of possible failure of the parathyroid glands to develop, the affected neonate may suffer tetany.

Q. Lymphokines, soluble factors released from primed lymphocytes in contact with an antigen are important in:

a) anaphylaxis
b) immune complex disease
c) macrophage activation
d) graft rejection
e) the involvement of the activation of natural killer cells

Ans.

a) **False** The chief manifestations of anaphylaxis are caused by the degranulation of mast cells with the liberation of a variety of material such as histamine, platelet activating factors, tryptase and kininogens, together with materials causing smooth muscle spasm such as the leukotrienes and prostaglandins.

b) **False** Immune complex disease is also known as Type IV hypersensitivity. Examples include rheumatoid arthritis and glomerulonephritis.concentration of IgA isotype falls, thus reducing the ability of the gut wall to repel bacterial invaders.

c) **False** The Di George syndrome is not associated with this condition is due to a defect in the third and fourth branchial arches during embryonic development, It is not, however, genetically controlled. Thymic dysplasia occurs accompanied by an absence of the Parathyroid glands. Humoral antibodies are, therefore, normal in concentration but cell-mediated Immunity is defective.

d) **False** Autoimmune thyroiditis is associated with an increase in the gamma globulin levels due to the appearance of a variety of antibodies in the circulation. These react against thyroglobulin, the cytoplasmic components of the thyroid and in approximately 6% of patients, the gastric parietal cells.

e) **True** Secondary hypogammaglobulinaemia occurs in Hodgkin's disease, lymphosarcoma, chronic lymphatic leukaemia and turnours of the thyrnus. Low leves of IgG may also be found in multiple myelomatosis because the neoplastic plasma cells are producing abnormal immunoglobulins.

Q. Active immunity can be produced by an appropriate vaccine in the following diseases:

a) pneumococcal pneumonia
b) plague
c) chicken pox
d) poliomyelitis
e) typhoid

Ans.

a) **True** Pneumococcal vaccine is a sterile preparation of polysaccharide capsular antigen from 14 serotypes of *Streptococcus pneumoniae*. The commercial vaccine contains 50 μg of polysaccharide from each of the 14 serotypes in 0.5 ml. It should be given to all patients in whom a splenectomy has been performed, since following this operation patients are especially liable to overwhelming pneumococcal septicaemia.

b) **True** Plague vaccine is made by producing a sterile suspension of formaldehyde-killed *Yersinia pestis*. One ml of the vaccine contains 3000 million bacteria.

c) **False** No suitable vaccine has been prepared which will protect against the pox virus. This is not so for other viral infections, the incidence of measles; mumps and rubella have all been reduced by using vaccines containing live strains of these viruses. Each vaccine contains a variable number of attenuated organisms which are usually cultured on live chick embryo cells.

d) **True** Live attenuated polio virus which can be administered by mouth is now the most commonly used method in the Western World to control this disease. It stimulates the production of antibodies which can be found in the circulation and also produces local resistance in the intestinal tissues by the activation of the MALT system. In the UK, the trivalent oral vaccine is given; the first dose at three months of age, the second at 6-8 months and a third dose some 4-6 months later.

e) **True** The vaccine most commonly used consists of a mixture of cultures of *Salmonella typhi* and *Salmonella paratyphi A, B* and *C* killed by heating at about 60^0C and preserved in 0.5% phenol.

Q. The Arthus reaction:
a) is associated with marked emigration of polymorphonuclear leucocytes into the affected tissues.
b) the relative concentration of antigen and antibody is of no importance in this reaction.
c) is a delayed hypersensitivity reaction
d) is associated with vascular damage
e) is similar to the Schwartzmann reaction

Ans.

a) **True** One of the major features of the Arthus reaction is the marked polymorphonuclear infiltration which occurs at the height of the reaction. This is in contrast to the infiltration of mononuclear cells accompanying Type IV hypersensitivity reactions such as the tuberculin reaction.
The PML infiltration is the result of complement activation along either the classical or alternative pathways. In the absence of complement, PML are not attracted to the site. The Arthus reaction reaches a peak in between 4-10 hours following the injection of antigen, after which the PML are replaced by mononuclear cells.

b) **False** The relative concentrations of antigen and antibody is of great importance in the Arthus reaction.

c) **False** The Arthus reaction is not cell-mediated. It is an example of a Type III hypersensitivity reaction. The reaction reaches a peak between 4-10 hours after the injection of the antigen as compared to the tuberculin reaction, in which the response is maximal between 24-48 hours.

d) **True** One of the histological features of the Arthus reaction is the damage to the walls of small blood vessels caused by the liberation of lysosomal enzymes from the polymorphonuclear leucocyles.

e) **False** There is no similarity between these two reactions. The Schwartzrnann reaction is provoked by the injection of bacterial polysaccharides of the Gram-negative organism, i.e. endotoxin. Schwartzmann himself described how, after the injection of Gram-negative organisms into the skin of a rabbit followed by a second injection given intravenously, haemorrhagic necrosis occurred at the site of the intradermal injection. This is the local reaction. If however the first dose is given intravenously, followed some hours later by a second dose, a systematic reaction occurs in which necrosis of the pancreas, pituitary, adrenals and gut occurs, accompanied by diffuse intravascular coagulation. A sublethal second dose provokes a biphasic fever which after repeated injections is abolished, although the primary pyrogenic effect remains.

Q. Immune complex disease is associated with – (FCPS – Surgery - 09Ja,08Ju)
a. Autoimmunity
b. Skin graft rejection
c. Pigeon facier's lung.
d. meningococcal infection
e. talc granuloma

Ans.

a) **True** In both organ specific and non-organ specific autoimmune disease, the clinical presentation is due to failure of the affected individual or animal to deal with the immune complexes formed by the interaction of antigen and antibody. In the human, immune complexes are normally recognised by the mononuclear phagocyte system, particularly in the liver by the Kupffer cells having been transported there bound by CR1 receptors to erythrocytes. If such a process is overwhelmed by the excessive production of complexes, an autoimmune disease follows, e.g. Hashimoto's disease.

b) **False** Immune complexes play no part in graft rejection which is a T-cell mediated response, T cells recognizing donor-derived peptides in association with the MHC antigend expressed on the graft.

c) **True** The basic pathology of Pigeon Fancier's disease is one of an alveolitis in which destruction of the alveoli with associated consolidation occurs due to locally formed immune complexes. The disease follows repeated exposure to pigeon antigens, the antibody induced by such exposure being primarily IgG rather than IgE. When antigen enters the lungs by inhalation, local immune complexes are formed leading to parenchymal destruction.

d) **True** Meningococcal infections may be associated with certain sigmata of immune complex disease, such as cutaneous vasculitis, arthritis and episcleritis.

e) **False** Talc induces a foreign body granuloma, a non-immunological granuloma, of a tuberculous granuloma, distinguished by the absence of lymphocytes. Characteristically the lesion is composed of scattered groups of multi-nucleated giant cells, some of which contain the foreign material together with a few macrophages.

Q. The third component of complement is:
a) a factor in phagocytosis
b) an anaphylatoxin
c) chemotactic
d) a migration inhibition factor
e) an interferon
Ans.

a) **True** Complement C3 gives rise to three prnducts, C3b' (* denotes that this derivation is unstable, interacting chiefly with water and also proteins and sugars), C3c and C3d which are known as opsonic fragments. The fragments coat the target cells, i.e. bacteria bound by the opsonic receptor itos on the activated phagocytic cells, thus enabling these cots to phaqocytose the offending organism.

b) **True** An anaphylatoxin is a substance which causes the degranulation of basophils and mast cells with the result that histamine and leukotriene-mediated smooth muscle contraction occurs. Anaphylatoxin activity is present in both the C3a and C5a fractions and an assay of thctir activity in this regard can be made by observing the contraction of plain muscle in a Schultz—Dale bath. A, further effect of anaphylatoxin is to increase vascular permeability accounting for the development of oedema in acute inflammation.

c) **True** C3a and C5a are chemotactic to polymorphonucler leucoytes. This explains the intense polymorphonuclear infiltration which occurs in the Arthus reaction.

d) **False** MIF is a group of peptides released by the activation of T lymphocytes which inhibit macrophage migration.

e) **False** Interferons are composed of three protein groups IFNα, IFNβ and IFNγ, all of which have an antiviral activity. In addition to this, both IFNα and IFNβ inhibit cell growth and have a possible clinical application in the treatment of some rare malignancies such as renal cell carcinoma and hairy cell leukaemia.Maximal antiviral activity is shown by IFNα which is produced by leucoytes in response to viruses or nucleic acids.

Q. Anaphylaxis:
a) develops 24 hours after the initial stimulus
b) causes a weal and flare response
c) is produced by IgA antibody
d) causes eosinophilia
e) causes degranulation of basophilis and mast cells
Ans.

a) **False** Anaphylaxis is an antigen specific immune response classified as a Type I, immediate hypersensitivity reaction. The response is mediated by the specific triggenng of IgE sensitised mast cells by an allergen. As a result mast cells become degranulated, leading to either local or generalized effects caused by the liberation of vasoactive amines, of which, in man histamine is the chief effector. Normally exposure to the allergen is followed by a response within minutes.

b) **True** If a skin prick test is used to detect Type I hypersensitivity, an immediate weal and flare response follows the injection of the allergen into the skin. The test results in an erythematous and oedematous response vary in severity according to the amount of allergen injected and demonstrates that gE is bound to the skin mast cells.

c) **False** IgA plays no part in anaphylaxis. IgA is present in human serum in which it forms approximately one fifth of the immunoglobulin pool. It is also present in seromucois secretions such as saliva and the secretions of the tracheobronchial mucosa.

d) **True** Eosinophil are attracted by products released from T cells, mast cells and basophils known as the eosinophil chemotactic factor of anaphylaxis (ECF-A). These cells release histamine and aryl

sulphatase, the latter inactivating the slow reactive substance (SRS-A) of anaphylaxis. However, one of their chief functions is to combat worms and protozoal infections. When a helminth infection of the bowel occurs, T cells recruit eosinophils by means of the Eosinophil Stimulation Promotor (ESP) The eosinophils then adhere to the worm and degranulate, breaking the integument of the worms allowing access to further eosinophils into the body of the worm itself.

e) **True** Degranulation of basophil and mast cells follows the interaction etween an antigen and IgE. These granules contain heparin and it is this which stains metachromatically with toluidine blue. The histamine which these cells contain, is formed from histidine by the action of the enzyme histidine decarboxylase; but in addition io histamine, 5-hydroxy tryptamine (serotonin), the slow reacting substance (SPS) of anaphylaxis and basophil derived kallikrein may be released. The latter cleaves the plasma euglobulin kininogen to kinins. The release of these various pharmacologically active agents causes the various local and general manifestations of anaphytaxis.

Q. Complement activation takes place: (BSMMU – MD – January, 2010)

a) in the presence of endotoxin
b) as part of the tuberculin reaction
c) by more than one pathway
d) in anaphylaxis
e) by antigen IgA interaction

Ans.

a) **True** Gram-negative organisms possess an outer coat composed of molecular complexes containing protein, lipid and carbohydrate. Death of the organism, liberates these complexes in the form of endotoxins which are thermolabile at 100^0C. When large amounts of endotoxin are liberated by death of the microorganism, endotoxic shock develops which is a response in part mediated by complement. Large quantities of C3a and C5a (anaphylotoxins) are produced, which results in the activation of PML, basophils and mast cells which stimulate intravascular clotting associated with embolisation into the pulmonary microcirculation, producing the clinical syndrome known as 'shock lung'.

b) **False** The tuberculin reaction does not involve the complement system. It is a delayed hypersensitivity reaction in which the pharmacological mediators are lymphokines.

c) **True** Complement activation resembles the mechanism involved in the clotting of blood, in that it is a cascade reaction which can be activated either by classical or alternative pathways. In all, the complement system consists of some 20 serum proteins, the majority being acute phase proteins, each component reacting with another. In the classical pathway the system is atwated by antibodies, IgM, IgG1, IgG2 or IgG3 bound to the surface of a pathogen, whereas in. the alternative pathway, the microorgagism itself spontaneously activates the complement system by means of its activator surface.

d) **False** Anaphylaxis is an antigen-specific immune reaction mediated by mast cells liberating vasoactive materials. This mechanism must not be confused with the action of anaphylotoxins which are complement peptides C3a and C5a. Anaphylotoxins when injected, cause an anaphylactic reaction by causing mast cell degranulation.

e) **False** Although aggregated IgA can activate the alternative pathway under experimental conditions, it is considered that antigen IgA interaction does not normally work through the classical complement cascade.

Q. The production of antibody is essential to host resistance in the following infections:

a) leprosy
b) Streptococcus pneumoniae
c) variola
d) tetanus
e) malaria

Ans.

a) **False** Host resistance to infection with Mycobacterium leprae is cell mediated. Three main types of this disease are recognised: tuberculoid, lepromatous and dimorphous or borderline. In tuberculoid

leprosy, well defined patches of hypopigmentation of the skin develop, biopsy of which shows an intense lymphocytic and epithelioid infiltration but no microorganisms. In the lepromatous type occurring in patients having a negible resistance to the bacillus, the skin lesions are extremely varied and biopsy shows the presence of numerous bacilli, foamy macrophages and few lymphocytes. Borderline leprosy has the characteristics of both types of lesion. A well known test for leprosy which is of limited value is the lepromin test, in which a cell free filtrate prepared from a ground up excised lepromatous nodule is injected intradermally. The test is of value in following the progress of a patient with borderline disease, because if the initial test is negative and it then becomes positive, it indicates the development of cellular immunity and a swing towards a tuberculoid form of the disease.

b) **True** A sterile preparation of polysaccharide capsular antigen from 14 serotypes of *Str. pneumoniae* is now available. These serotypes are considered to be the cause of 80% of all pneumococcal infections. Vaccination by this material is considered mandatory in children in whom a splenectomy has been performed, such children been especially prone to overwhelming infection by this organism.

c) **True** Vaccination against variola (small pox) is normally given by applying one dose of a living avirulent vaccine into the skin in the second year of life, complications been least in this age group. The agent used to produce active immunity is a living related virus, known as vaccinia. The vaccine consists of lymph obtained from vesicular lesions produced on the skin of calves or sheep by inoculating the scarified skin with the virus.

d) **True** Active immunization against tetanus is achieved by the injection of antigens in the form of tetanus vaccine or the more potent Adsorbed Tetanus Vaccine, this latter consisting of toxoid, a formaldehyde treated product of a growth of *Cl. tetani* which is adsorbed on aluminium hydroxide. A high degree of protection develops of approximately five years duration. Normally three doses are given; 0.5 ml stat, 6-12 weeks later a second dose and a third dose some 6-12 months later still.

e) **False** Resistance to malarial infection is dependent of TCD4+ and CD8+ T cells. In malarial infection, an increase in the number of circulating monocytes occurs, together with gross enlargement of the spleen due to an accumulation of macrophages. CD8+ cells destroy infected hepatocytes and also secrete IFNγ which inhibits the multiplication of the Plasmodium within these cells. Recently a number of antigens of *Plasmodium falciparum* have been cloned which may in future lead to an effective vaccine.

Q. Serum sickness:

a) can be caused by an injection of diphtheria antitoxin
b) is common following immunization against tetanus
c) can follow an infection of penicillin
d) is mediated by immune complexes
e) may involve IgE

Ans.

a) **True** Diphtheria antitoxin contains antibodies obtained from the serum or plasma of horses which have been immunized against diphtheria toxin or toxoid. It neutralises circulating toxin but does not affect the pathological changes already induced by the toxin. The cause of the reaction is the formation of antibodies to the horse protein. If the individual has not been previously sensitised, an acute generalized reaction occurs within 7—10 days of the injection, which is chnically characterized by the development of skin rashes, fever, joint pains and frequently swelling of the regional lymph nodes. Both the severity and the duration of the reaction vary greatly. Serum sickness is an example of Type III hypersensitivity.

b) **False** Immunization against tetanus is performed by the use of tetanus toxoid. This is a formalised preparation of tetanus toxin which is immunogenic but seldom allergenic, except in persops who ap already known to suffer from allergic diseases such as asthma and infantile eczema. If there is such a history, a test case of 0.2 ml of serum should be injected subcutaneously. If no general reaction occurs over a 30 minute period, the main dose may be given intramuscularly.

c) **True** Allergic reactions to penicillin are relatively common. The hypersensitivity is the result of penicilloyl residues from the degradation of penicillin. Prolonged treatment with benzyl penicillin can result in

renal failure, biopsy showing tubular damage and an interstitial accumulation of mononuclear cells and eosinophils.

d) **True** Serum sickness is an immune complex disease, an example of Type III hypersensitivity which develops in three stages; first the formation of complexes in the circulation, second the deposition of the complexes in various tissues and third an inflammatory reaction provoked by such deposition, due to the activation of complement and the formation of biologically active fragments.

e) **True** It is possible that IgE may play a part in Type III hypersensitivity. Induced by the antigen, the IgE antibody may bind to mast cells arid platelet activating factors; these mediators then separate the endothelial cells, thus allowing the complexes to enter the vessel wall and then the tissues. Within the tissues, the complexes initiate an acute inflammatory reaction accounting for the joint and renal complications. By immunofluorescent microscopy, the complexes can be seen as granular lumpy deposits of immunoglobulin and complement and, by electron microscopy, as dense deposits along the glomerular basement membrane.

Q. Anaphylactic reactions commonly follow the administration of the following drugs:

a) penicillin
b) azathioprine
c) procaine
d) α-methyldopa
e) corticosteroicis

Ans.

a) **True** Penicillin is an important cause of anaphylaetic reactions. The penicilloyl degradation product acts as an hapten binding onto body protein, inducing the formation of IgE antibodies.

b) **False** Azathioprine is an immune suppressive and antineoplastic agent with a similar action to 6-mercaptopunine to which it is slowly converted in the body. This agent is an analogue of natural purines. After conversion active nucleotides including thioinosinic acid, it inteferes with nucleic acid synthesis. Azathioprine is chiefly used as an immunosuppressant but it is also used to control certain immune complex diseases, lupus erythematosus, rheumatoid arthritis and chronic active hepatitis. Azathioprine is an antimetabolite which combines with the same enzymes as physiologically occurring cellular metabolites, but prevents the metabolic process.

c) **True** Procaine can act as a hapten binding to protein to become an antigen.

d) **False** α-methyldopa is an antihypertensive agent classified as an enzyme inhibitor which probably acts centrally. It is now rarely used because of its numerous side effects. In 0.3% of patients to whom methyldopa is administered, an allergic reaction occurs due to the production of autoantibodies similar to warm-reactive antibodies frequently found against Rhesus system antigens. These result in a positive direct Coombs Test.

e) **False** The chief side effects of corticosteroids results from disturbances of electrolyte balance, glucogeneogenesis, their adverse action on tissue repair and wound healing and the inhibitory effect on the secretion of corticotrophins by the anterior pituitary resulting in adrenal atrophy. They have no direct imjnunological effect but, by depressing the activity of PML and reducing the number of circulating lymphocytes, impair the response to acute infections.

Q. An autoimmune haemolytic anaemia:

a) does not occur in systemic lupus erythematosus
b) does not show Rhesus specificity
c) is associated with a negative Coombs test
d) may be caused by drug therapy
e) is not associated with leucopenia

Ans.

a) **False** Systemic lupus erythematosus is characterized by the development of a large variety of autoantibodies which affect nearly every organ of the body; most are antinuclear. Haematological changes are the commonest clinical manifestation of this condition, of greater frequency than

involvement of the joints or skin. Not only are the red cells damaged by autoantibodies, but also by trauma to the red cells in areas of necrotising arteritis and arteriolitis.

b) **False** In 30% of patients suffering from a haemolytic anaemia due to 'warm autoantibodies', the specificity of some of these is directed to one or more of the Rhesus antibodies, commonly anti-c or anti-e.

c) **False** The major diagnostic criteria of an autoimmune haemolytic anaemia is the positive Coombs test. This test is designed to show the presence of adsorbed antibodies on the surface of red cells. It can be carried out in two ways; either using the patient's own red cells (the direct test) or normal red cells previousiy mixed with the patient's serum (the indirect test). Anti-human globulin is added to the red cell suspension and causes agglutination when the incomplete antibody is present on the surface.

d) **True** Drugs which may be associated with an autoimmune haemolytic anaemia include para-aminosalicylic acid, phenacetin, quinidine, quinine, chlorpromazine, penicillin and α-methyldopa.

e) **False** Among the various haematological abnormalities seen in autoimmune haemolytic anaemia, is a leucopenia of less than 4.0 x 10/ L, a lymphopenia of less than 1.5 x 10/ L and a thrombocytopenia of less than 100 x 10/ L.

Q. The following are, or contain, autoantibodies:

a) cryoglobulins
b) rheumatoid factor
c) migration inhibitory factor
d) antinuclear factor
e) transfer factor

Ans.

a) **True** Cryoglobulins are immune complexes formed by the reaction between immunoglobulins and anti-immunoglobulin antibodies. Characteristically they precipitate after overnight storage in the refrigerator or when serum is cooled below 37^0C. Cryoglobulins are present in the plasma in a wide range of chronic infections and autoimmune diseases, including systemic lupus erythematosus.

b) **True** Rheumatoid factor is an IgM anti-immunoglobulin antibody with specificity directed against the Gm groups on the Fc portion of immunoglobulin molecules. It can be detected by the agglutination of latex particles coated with immunoglobulin or by the agglutination of sheep erythrocytes that have reacted with specific rabbit immunoglobulin (Rose—Waaler test). This factor is found in the sera of pafte?s with rheumatoid arthritis and is valuable in distinguishing this ctlase from the polyarthritis associated with psoriasis. It may also occur, however, in the sera of patients suffering from chronic infections or chronic autoimmune disese.

c) **False** The migration inhibitory factor is a lymphokine produced by the action of an antigen or mitogen on T lymphocytes. It inhibits the migration from capillary tubes, in vitro, of macrophages obtained from a peritoneal exudate or leucocytes from the human buffy coat from capillary tubes in vitro. .

d) **True** The antinuclear factor is an autoantibody directed against DNA and nucleoproteins. It is present in the sera of patients suffering from systemic lupus erythematosu. It may also occur in the sera of patients suffering from chronic infectious diseases such as leprosy and in connective tissue diseases such as Sjogren's syndrome.

e) **False** Transfer factor is an extract of human buffy coat leucocytes that can transfer tuberculin sensitivity and othef delayed hypersensitivity reactions.

Q. Antiglobulins may be involved in the:

a) Wassermann reaction
b) Coombs test
c) fluorescent antibody test
d) rheumatoid factor test
e) Casoni test

Ans.

a) **False** The Wasserrnann reaction is a complement fixation test in which the antigen is cardiolipin derived from ox heart with which the antibody. probably an autoantibody developing in syphilis, reacts. The

indicator system used consists of sheep erythrocytes and rabbit (or horse) anti-sheep erythrocyte antibody.

b) **True** The direct Cooms test is an agglutination reaction in which erythrocytes coated with antibody are agglutinated by an antiglohulin reagent. The direct oombs test indicates that sensitised erythrocytes are already present in the circulation as occurs in some haernolytic anaomias. In the indirect test the red cells are sensitised in the laboratory by antibody before exposure to the antiglobulin eagent. This is a very sensitive test for non-agglutinating rhesus antibodies in a patient's serum.

c) **True** In the direct fluorescent antibody test fluoroscein may be linked to an antiglobulin through an isothiocyariate linkage. This is then used to detect the presence of bound immunoglobulin fixed in the tissue. Antinuclear factor and other autoantibodies, such as antimitochondrial or antimicrosomal antibodies can be detected by this means.

d) **True** Rheumatoid factor is an IgM anti-immunoglobulin molecule that binds to the Gm groups on the Fc portion of the immunoglobutin molecules. It may be detected by the latex agglutination test or Rose - Waaler test. The highest concentrations are found in rheumatoid arthritis.

e) **False** The Casoni test is used for the diagnosis of hydatid disease, the causal agent of which is the Echinococcus granulosus. In a patient suffering from hydatid disease a local anaphylactic reaction occurs within 15 minutes of the injection of hydatid antigen into the skin with the development of a flare followed by a weal.

Q. Cell-mediated immunity involves the following mechanisms:

a) IgG
b) T lymphocytes
c) eosinophils
d) complement
e) macrophages

Ans.

a) **False** IgG is an immunoglobulin produced by B lymphocytes. Immunoglobulins are the soluble form of B-cell antigen receptors. IgG plays no part in cell-mediated immunity.

b) **True** T lymphocytes are the chief cell concerned in cell-mediated immunity. Lymphocytes developing in the foetal liver and bone marrow develop into T cells in the thymus, due to chemotactic signals emitted from the thymic rudiment. Stem cells reaching the thymus differentiate into thymocytes, which are then able to recognise antigens belonging to the major histocompatibility complex. These antigens are presented to the T cells by a variety of antigen presenting cells.

c) **False** Eosinophils are granulocytes in which the bibbed nucleus stains blue with Leishman stain and the cytoplasmic granules red. They comprise between 2—5% of the blood leucocytes in non-allergic individuals. They play no part in cell-mediated immunity. but are especially important in the body's defence against worm infections.

d) **False** Complement is an enzymatic system of about 20 serum proteins activated by antigen-antibody reactions: several of the components are acute phase proteins and their chief function is the overall control of inflammation. The system is activated either by the so-called classical pathway or by the alternative pathway.

e) **True** Macrophages are concerned with antigen processing and presentation and are the important non-specific effector cell involved in cell-mediated immunity.

Q. The following tests are based upon a delayed hypersensitivity reaction:

a) Schick test
b) Wassermann reaction
c) Frei test
d) Leishmanin test
e) Prausnittz-Kustner reaction

Ans.

a) **False** The Schick test is used to determine an individuals Susceptibility to nfection by Corynebacterium diphtheriae, the causative organism of diphtheria which, prior to the Second World War, was the

commonest cause of death in children between the ages of 8-10 years in the Western World, To perform the Schick test 0.2 ml of fluid containing a measured dose of diphtheria exotoxin is injected intradermally. A positive red reaction reaching its maximum intensity within 4-7 days signifies a lack of immunity and hence vulnerability to infection. A negative test conversely signifies the presence of antitoxin in the circulation.

b) **False** This is a complement fixation reaction used to detect infection with the *Treponema pallidum*, the causative agent of syphilis. In all stages of the disease, immunoglobulins belonging to the IgG and IgM class increase in the serum. To perform the test, antibody i.e. the patient's serum is mixed with complement and antigen and after incubation an indicator system consisting of antibody coated, sheep red cells is added. If complement has been taker' up during the incubation stage by the antibody/antigen complex lysis of the added red cells does not occur. Thus a positive CFT is indicated by an absence of lysis. In the Wassormann reaction, the test system consists of the patient's serum in the presence of guinea pig complement.

c) **True** The Frei test is a delayed hypersensitivity reaction used in the diagnosis of *L. venereum* which is caused by a specific strain of *Chlamydia trachomatis* resulting in inflammation of the inguinal and rectal lymph nodes and at the site of the initial infection, a granubomatous ulcer. the causative organism is larger than a virus particle but smaller than a bacterium. The Frei test is performed by the intradermal injection of a heat killed suspension of Chlamydia initially grown on chick yolk sacs. A positive test consists of the development of a swelling at least 7 mm in diameter, reaching a maximum in four days. The test becomes positive 7—40 days after the iniial infection.

d) **True** The Leishmanin test. Leishmaniasis is an infection of mammals by a protozoa of the genus Leishmania with an intracellular stage in the mammalian host and an extracellular flagellate stage in the sand fly. Four species are recognised which cannot be distinguished morphologically. The Leishmanin test indicates the presence of delayed hypersensitivity. A 0.2 ml suspension of promastigotes containing 8 x 10^6 organisms in 0.5% formal saline is injected intradermally. The reaction is read between 48-72 hours later. When positive, an indurated nodule some 5 mm in diameter develops. If the infection is by L. donovani, the Leishmanin test is of no use in diagnosis because the test does not become positive until after recovery from the disease.

e) **False** The Prausnittz—Kustner reaction, first described by these two investigators, is an example of Type I hypersensitivity. Kustner was allergic to fish and the injection of his sertjrn into the skin of Praus, led to an immediate weal and flare reaction, when fresh antigen wa. Subsequently injected into the skin of the serisitised site. It was lat Shown that the reaction depended on the formation of IgE immunoglobulin produced by B cells, after an allergen had been presented by antigen presenting cells. it requires cooperation between B cells and T cells and the response is ca used by the triggering of IgE sensitised mast cells by the allergen.

Q. The followings are the chief characteristics of delayed hypersensitivity reactions.

a) the developm of a leucocyte infiltration
b) the reaction has reached its maximum intensity at 4 hours
c) an individual can be passively sensitised with serum
d) it is associated with T lymphocyte function
e) complement activation is an essential factor

Ans.

a) **False** Polymorphonuclear leucocytes are not involved in any delayed hypersensitivity reactions The chief cell involved in delayed hypersensitivity is the lymphocyte with the later appearance of the macrophage in the granulomatous type of delayed hypersensitivity epithelioid cells, Possibly derived from activated macrophages and giant cells are found.

b) **False** The characteristic feature of alt delayed hypersensitivity reactions is that they take more than 12 hours to develop. Even rapidly developing contact dermatitis takes 2-4 days to develop after the application of the offending allergen; this after a period of sensitisation which may require some 14 days.

c) **False** Because delayed hypersensitivity reactions are not antibody mediated, passive sensitisation cannot be transferred from one animal to another by serum. In experimental models, however, it can be transferred by sensitised T cells which can be obtained from peripheral blood, lymph nodes or spleen.

d) **True** Delayed hypersensitivity follows an interaction between specifically sensitised T lymphocytes and the antigens, In contact hypersensitivity the hapten forms hapten carrying complex in the epidermis Langerans cells then carry the complex via the lymphatics to the paracortical region of the regional lymph nodes, where interdigitating cells then present the complex to the CD4+ T Cells.

e) **False** Complement is not involved in the mechanism of delayed hypersensitivity. The equivalent non-specific mediators are the lymphokines. Lymphokine is the generic term for molecules other than antibodies derived from lymphocytes, which are involved in signalling between cells of the immune system.

Q. Maximum changes occur in the following skin reactions within 24 to 48 hours:

a) Schwartzmann reaction
b) Arthus reaction
c) tuberculin reaction
d) contact patch test
e) skin allograft rejection

Ans.

a) **False** The Schwartzmann reaction is a haemorrhagic reaction in the skin or tissues which reaches its maximun within 4 hours. The local Schwartzmann reaction is elicited in the following manner: an intradermal injection of endotoxin or related polysaccharide is administered followed 24 hours later by an intravenous injection. A generalized reaction involving particularly the lungs and kidneys can be produced if both closes of endotoxn are administered intravenously. It is considered by many investigators that this haemorrhagic reaction underlies similar phenomena observed in bacterial infections such as meningococcal infections in which haemorrhagic destruction of the adrenal glands results in the development of the Waterhouse—Friderickson syndrome.

b) **False** The Arthus reaction which is the result of union between antigen and free antibody with the subsequent activation of complement reaches a maximum between 4 and 8 hours. The reaction is chiefly associated with accumulation of polymorphonuctear leucocytes arid the aggregation of platètels. Macroscopically the reaction is oedematous and haemorrhagic due to local vasculitis.

c) **True** A positive tuberculin reaction occurs following the intradermal injection of tuberculin a lipo-protein antigen derived from the tubercle bacillus, into a sensitised individual, i.e. an individual already suffering from a tuberculous infection. Following the injection of tuberculin, T cells migrate from the capillaries disrupting the collagen bundles of the epidermis, the reaction reaching a peak after some 48 hours although macrophages, the main antigen presenting cells begin to accumulate around the dermal vessels after approximately 12 hours and increase in density over the ensuing 2-3 days. Unlike contact sensitivity the epidermis does not become oedemtous.

d) **True** Contact sensitivity was first noticed by Josef Jadassohn in 1886. It is induced by haptens all of which have at least two features in common; a low molecular mass thus allowing the sensitising agent to diffuse through the skin and an ability to conjugate with the aminoacid side chains of normal body proteins, thus becoming immunogenic and Provoking a Type IV hypersensitivity reaction.Common agents are metals, nickel and dichromate and simple organic compounds such as Dinitrochlorobenzene. The process of sensitisation takes between 10-14 days and the reaction once initiated begins to wane after 48—72 hours.Sensitisation takes place as the hapten protein conjugate is taken up by the Langerhans cells of the suprabasal epidermis. These cells act as antigen presenting cells, and appear in the paracortical areas of the draining lymph nodes in which the T cells are situated. A set of CD4+ lymphocytes are transformed into 'memory' CD4 T cells and then activated CD4 T cells release interferons (INFY) which induce changes in the surface keratinocyte and the endothelial cells f the dermal capillaries resulting in the liberation of cytokines and the development of an eczematous reaction in the skin.

e) **False** Although the rejection of a skin graft is also a T-cell mediated immune phenomenon approximately 10 days are required for rejection in homo sapiens. This is because on primary graft application, it is necessary for the graft to heal and establish a blood supply from the host after which the primary immune response develops. This has a latent period of at least 5 days.

Q. Cell mediated immune processes are of great importance in the control of the following infections:
a) pneumonia
b) diphtheria
c) tuberculosis
d) candidia
e) mumps
Ans.

a) **False** Cell-mediateci immunity plays no part in the host's defences against pneumococcal infections. These organisms are opsonised and killed by humoral antibody, and complement The specificity of the antibody is directed against the 'specific soluble substance', the pnumococcal polysaccharide Antibodies against these soluble antigen were used prior to the introduction of antibiotics for immunotherapeutic purposes with some success.

b) **False** Cell-mediated immunity is not involved in diphtheritic infections. *Corynebacterium diphtheriae* is harmful because it produces an exotoxin which particularly damages the myocardium and peripheral nerves. This toxin may be inactivated before it is fixed in the tissues by an antitoxin which can be prepared in the horse. The use of this antitoxin carries the risk of anaphylaxis or serum sickness and, therefore active immunization with toxoid is preferable

c) **True** Host resistance to mycobacteria is dependent on cell-mediated immune processes. The mycobacteria are facultative intracellular parasites and are found mainly within macrophages. If cell-mediated immunity fails dissemination of the disease occurs and frequently a negative delayed hypersensitivity test is found as in miliary tuberculosis.

d) **True** A failure of cell-mediated immunity is frequently associated with mucocutaneous or diffuse candidiasis. Thus diffuse candidiasis may occur in Hodgkin's disease and non-Hodgkin's lymphomas and in the primary T-cell deficiencies of childhood associated with a specific failure of T-cell response to candida antigens. Transfer factor has been successfully used to treat muco cutaneous candidiasis by specifically increasing the T-cell response to Candida albicans.

e) **True** Mumps is caused by a paramyxovirus. Previous infection with mumps virus is associated with a positive delayed hypersensitivity skin reaction. Mumps antigen is one of the standard skin test reagent used to diagnose a general non-specific loss of cell-mediated immunity in adults with conditions such as non-Hodgkih's lymphomas, Hodgkin's disease and sarcoidosis.

Q. The following microorganisms are obligate or falcultative intracellular parasites:
a) Mycobacterium tuberculosis
b) Clostridium welchii
c) Corynebacterium diphtheriae
d) Leishmania tropic
e) herpes simplex
Ans.

a) **True** M. tuberculosis may be found within macrophages or other cells of the mononuclear phagocyte series in the centre of a typical epithelioid cell granuloma. *Myco. tuberculosis* requires active cell-mediated immune processes for its elimination.

b) **False** *Cl. welchii*, one of the organisms involved in gas gangrene, is an-anaerobic spore bearing organism. The clostridia produce tissue damage by means of exotoxins which are proteolytic and saccharolytic enzymes. In addition the organism produces hyaluronidase which breaks down tissue barriers, thus ehabling the organisms to spread through the connective tissue planes. Protection from the clostridial group of organisms may be obtained by the use of an anti gas gangrene serum.

c) **False** *C. diphtheriae* is an aerobic bacillus usually found extracellularly. Its effects are produced by an exotoxin affecting the myocardium and peripheral nerves which can be neutralized by a specific antitoxin.

d) **True** The amastigote form of *L. tropica*, the causative organism of oriental sore, is generally found within macrophages in a granuloma lying within the dermis. In this form the organisms are referred to as 'Leishman-Donovan' bodies.

e) **True** Herpes simplex is caused by a virus of the herpes virus group. This group also includes varicella/zoster, the Epstein—Barr virus and cytomegalovirus. Herpes infections are recurrent with long latent periods. Prior to the &ruption the virus remains latent in the cells of the posterior root ganglia.

Q. The following tests may be used to assess host resistance in mycobacterial infections:
a) skin test
b) complement fixation
c) lymphocyte transformation test
d) radioimmunoassay
e) leucocyte migration inhibition test
Ans.

a) **True** The classical way of assessing whether a patient has had previous contact with the *Mycobactorium tuberculosis* and hence has developed some resistance by means of cell-mediated immunity to the diease is by the tuberculin test. A positive test is indicated by the development over 18 to 48 hours of an inflammatory indurated response in the skin into which tuberculin has been injected. This test is negative during the early stages of infection and in rapidly progressive forms of the disease, e.g. miliary tuberculosis. Similarly the lepromin test conducted with a suspension of *Mycobacterium leprae* is positive in tuberculoid leprosy but is negative in lepromatous leprosy in which the tissues team with organisms.

b) **False** Complement fixation tests are basically used to assess antibody production and since host resistance to mycobacterial infections is cell-mediated these tests play no part in estimating such resistance. Complement fixation tests are used in the diagnosis of viral infections and some bacterial infections such as gonorrhoea and syphilis.

c) **True** In this test the patient's lymphocytes are incubated with a mitogen such as phytohaemagglutinin or an antigen to which they have been primed for some 3 to 5 days. If positive the cells become transformed into large blast cells which readily incorporate H-thymidine. This test is used as an in vitro correlate of delayed hypersensitivity and as such frequently correlates well with resistance to infection in conditions in which T cells are important in host protection.

d) **False** Radioimmunoassay is used to measure specific IgE antibodies to allergens such as pollens. In the RAST (radioallergosorbent test). It can also be used to measure the concentration of hormones such as insulin in the blood if a specific antiserum is available.

e) **True** Buffy coat leucocytes can, under normal circumstances, if cultured overnight, be induced to grow out of the ends of capillary tubes in a fan-like manner. In the presence of antigen and specifically sensitised T lymphocytes, however, migration is inhibited by lymphokine. Such migration inhibition correlates with delayed hypersensitivity and host resistance in mycobacterial infections.

Q. The following cells play an important role in skin allograft rejection- (FCPS – Sur-07Ja)
a) Polymorphonuclear leucocytes b) Macrophage
c) Mast cell d) B lymphocyte
e) T lymphocyte
Ans.

a) **False** Polymorphonuclear leucocytes play no part in skin allograft rejection. These cells play their major role in acute inflammatory reactions and immunological reactions mediated by immune complex deposition, such as the Arthus reaction.

b) **True** Skin allograft rejection is a T-cell mediated event in which lymphokine is released. The latter is the generic name given to soluble factors released by primed lymphocytes after contact with a specific antigen. These substances are chemotactic for macrophages and cause the activation of macrophage enzymes. Macrophages form the major cellular component of the mononuclear infiltrate which develops around a skin allograft prior to rejection.

c) **False** These cells play no part in skin allograft rejection. They are of particular importance, however, in anaphytactic reactions when degranulation results in the liberation of the vasoactive amines,

histamine, serotonin, SRS-A and kallikrien. Degranutation is initiated by the interaction between antigen and IgE antibody on the cell membrane.

d) **False** The B lymphocytes are the precursors of plasma cells which produce immunoglobulins. The latter are not considered to play a major role in skin graft rejection. B lymphocytes, which are not so mobile as T lymphocytes, are found chiefly in collections in central lymphoid tissues, i.e. the spleen and lymph nodes, particularly in the lymph follicles, germinal centres and at the cortico-medullary junction.

e) **True** Skin allograft rejection is a cell-mediated event caused by the reaction of specifically sensitised T lymphocytes with antigen. The T lymphocytes are part of the mobile pool of long-lived lymphocytes which may be found circulating through the tissues and in the lymph. They migrate into the tissues particularly through post-capillary venules. The production of lymphokine by reaction with antigen brings the next most important cell, the macrophage into the area of activity.

Q. The following substances are lymphokines:

a) properdin
b) migration inhibitory factor
c) macrophage chemotactic factor
d) Factor B
e) interferon

Ans.

a) **False** Properdin as a globulin found in normal serum. It is part of the complement alternative pathway to C3 conversion by-passing C1, C4 and C2. It is activated by bacterial endotoxins and polysaccharicjes such as zymosan which is obtained from yeast nd insulin. Mg^{++} but not Ca^{++} ions are necessary for the activation of the alternative pathway.

b) **True** The migration inhibitory factor (MIF), a glycoprotein with a molecular weight of approximately 40,000, was the first of the various substances now known under the generic title of lymphokines to be discovered. It is assayed by its ability to inhibit the migration of mácrophages obtained from the peritoneal exudate of the guinea-pig from capillary tubes in vitro.

c) **True** Macrophage chemotactic factor is another lymphokine. It is distinguished from the polymorph chemotactic factor by its molecular weight. It is assayed by its ability to attract macrophages onto a millipore membrane ma closed Boyden chamber.

d) **False** Factor B is an important component in the alternative pathway of complement activation. It is also referred to as C3 proactivator.

e) **True** Interferons are a family of substances, molecular weight approximately 30,000, produced by cells infected with a virus or by synthetic inducers such as polyinosinic and polycytidylic acid (poly I:C). They can also be produced by T lymphocytes activated by antigen or mitogen and as such are included in lists of lymphokines. When taken up by other cells interferon inhibits the replication of virus within them.

Q. Graft versus host disease: (FCPS – Surgery -09Ja, BSMMU-M.phil-10Ju)

a) may follow bone marrow transplants
b) may follow blood transfusion
c) occurs in Hodgkin's disease
d) can be suppressed by tetracyclines
e) can be suppressedty cyclophosphamide

Ans.

a) **True** Bone marrow transplants are used as a therapeutic measure in patients suffering from the combined immunodeficiency syndrome or whose immune response has.been destroyed by irradiation or cytotoxic drugs. If the marrow transplant is not HLA matched the donor T lymphocytes will react against host tissues. Signs that this is occurring include the development of erythroderma, exfoliative dermatitis, splenomegaly and wasting. Death ultimately occurs if the reaction cannot be controlled by immunosuppressive agents such as cyclosporin A.

b) **True** In patients suffering from a severe depression of their immunological systems a blood transfusion may provoke a graft versus host reaction due to the T cells which are contained in the dgnor blood. This can be avoided by irradiating the blood prior to transfusion in order to destroy T-cell function.

c) **False** Graft versus host disease could only occur in a patient with Hodgkin's disease if that patient was rendered completely immunodeficient ly irradiation or cytotoxic therapy and then received a transfusion of unirradiated blood.

d) **False** Tetracyclines will only suppress the intercurrent infection that occurs as the graft versus host reaction becomes severe and then only if the bacteria causing the infection are sensitive to this antibiotic. This is not usually the case since the common agents of infections in this disease are fungi and viruses, all of which are insensitive to the tetracyclines.

e) **True** Temporary suppression ot the graft versus host reaction can be achieved by the use of cyclophsphamide because this drug is a nitrogen mustard derivative cytotoxic to dividing lymphocytes. It is, however, an extremely toxic compound which may cause hair loss resulting in alopecia, destruction of the bladder mucosa causing haematuria and increasing susceptibility to fungal infection.

Q. The following can cause immunological unresponsiveness:

a) immunological tolerance
b) immunological enhancement
c) Freund's adjuvant
d) T lymphocytes
e) antigen-antibody complexes

Ans.

a) **True.** Immunological tolernce is the term given to the specific immunological unresponsiveness caused by the elimination or depletion of a specific clone of immunologically competent cells. This may be the result of exposure to high concentrations of antigen, particularly in late fetal or early. neonatal life which is the period of Immunological immaturity. This phenomenon is mainly applicable to allograft rejection.

b) **True** Immunological enhancement paradoxically does not refer to the enhancement of the immune response but to enhancement of tumour growth. This is caused by the stimulation by the tumour of a blocking antibody which combines with the antigenic sites on the surface of the tumour cells. This results in a markedly decreased stimulation of cellmediated immunity against the tumour and also prevents the Sensitised T cells reacting with tumour antigens to kill the tumour cells.

c) **False** Freund's adjuvant is a water in oil emulsion with or without added mycobacteria. The addition of antigen to this mixture promotes both increased antibody formation and delayed hypersensitivity.

d) **True** A special subpopulation of T lymphocytes may act as suppressor cells diminishing the immune response. In mice these cells can be distinguished by the presence of surface antiens. (Ly. antigens) from the effector cells of delayed hypersensitivity and helper cells required both in vitro and in vivo for antibody formation.

e) **True** The presence of soluble antigen-antibody complexes formed between soluble tumour antigens and antibody in the circulation can suppress the cell-mediated immune response against tumours and lead to enhanced turnour growth.

Q. The following infections are common in Immunodeficient patients:

a) *Pneumocystis carinii*
b) diphtheria
c) poliomyelitis
d) cytomegalovirus
e) Candida albicans

Ans.

a) **True** *Pneumocystis carinii* is a protozoan related to the plasmodia and toxoplasma. It is ubiquitous in the upper respiratory tract but causes chronic pneumonia in patients who have become immunodeficient

whether due to malnutrition, the administration of cytotoxic drugs in the treatment of Hodgkin's disease or primary T-lymphocyte deficiency.

b) **False** There isno evidence that an increase in infection by *Corynebacterium diphthenae* occurs in immunodeficient subjects.

c) **False** There is no evidence of an increase in infection with poliovirus occurring in immunodeficient subjects.

d) **True** Cytomegalovirus is a herpes virus causing cytomegalic inclusion disease. Although infection with this virus is commonly associated with the newborn it is also an important opportunistic infection occurring in immunodeficient patients. The virus affects any tissues and intracellular inclusion bodies are found particularly in the bronchial epithelium.

e) **True** Mucocutaneous candidiasis is a particular complication of immunodeticiency regardless of the cause. It is generally associated with other evidence ot depressed T-lymphocyte function, negative candidin skin test, depressed lymphocyte transformation test and absent leucocyte migration inhibition test with candida antigens. Other non-specific tests of T-lymphocyte function may also be depressed.

Q. The following conditions are associated with T-cell immunodeficiency:

a). Hodgkin's disease
b). Tay—Sachs disease
c). Wiskott—Aldrich syndrome
d). Down's syndrome .
e). Di George syndrome

Ans.

a) **True** The pathological tissue in Hodgkin's disease permeates the T-lymphocyte areas of lymphoid tissue, the B lymphocytes and plasma cells remaining unaffected. Many of the tests of T lymphocyte function (Skin tests, mitogen induced lymphocyte transformation) become depressed as the disease progresses. Patients become susceptible to opportunistic infections with organisms normally controlled by T-lymphocyte function, including Pneumocystis carinii, cytomegalovirus, Candidà albicans and other fungal agents.

b) **False** Tay—Sachs disease is a lipid storage disease affecting the nervous system only. The ganglion cells are ballooned with ganglioside giving rise to amaurotic familial idiocy. These children typically have a cherry red spot in the macula.

c) **True** This is a sex linked recessive disease manifested in childhood in which there is delayed growth and thrombocytopenia, the platelets being both small in number and abnormal in structure. Such children develop severe eczema and pyogenic infections. The serum contains increased amounts of IgA and IgE, normal levels of IgG but T-cell function is defective and cell-mediated immunity becomes progressively worse so that affected children become susceptible to viral, fungal and bacterial infections.

d) **False** Down's syndrome, once known as mongolism, is associated with trisomy of chromosome 21. This chromosomal abnormality gives rise to mental retardation as well as the characteristic physical features. Although there may be an increased incidence of leukaemias it is not associated with immunodeficiency.

e) **True** The Di George syndrome is due to a defect in development of the third and fourth branchial arches resulting in thynic aplasia and T-cetl immunodeficiency, together with an absence of the parathyroid glands which causes hypocalcaemic tetany.

Q. A non-specific depression of the tuberculin reaction occurs in:

a) influenza
b) measles
c) sarcoidosis
d) leprosy
e) ulcerative colitis

Ans.

a) **False** Infection with the influenza virus does not lead to non-specific depression of cell-mediated immunity.

b) **True** The depression of tuberculin reactivity in measles was first described by Von Pirquet in 1908 and it was eventually established that this was the result of Infection of the T-lymphocytes wth the virus. The disease is frequently accompanied by a lymphopenia. The lymphocyte transformation and leucocyte migration inhibition responses to tuberculin and candida antigens are lost.

c) **True** Certain parameters of T-lymphocyte function are depressed in sarcoidosis including the tuberculin reaction and ability to cause sensitisation with 2,4 dinitrochlorobenzene (DNCB). In addition, the lymphocyte transformation response in the presence of phytohaemagglutinin (PHA) may be depressed.

d) **True** A non-specific depression of tuberculin reactivity and the ability to be sensitised with DNCB occurs in over 50% patients with lepromatous leprosy but only occasionally in tuberculoid leprosy. However, there is no generalized decline in T-lymphocyte function which apart from the specific loss of cell-mediated immunity against Mycobacteriumleprae is otherwise normal.

e) **False** There is no evidence of even a partial loss of T-lymphocyte function in ulcerative colitis and tuberculin reactivity remains therefore within normal limits.

Q. Haptoglobins

a) bind to the body's own proteins to make them immunogenic
b) are immunogobulins
c) bind to free haemoglobin
d) are controlled by genetic factors
e) can bind rheumatoid factor

Ans.

a) **True** Haptens are simple chemical groupings that are too small to be immunogenic, but can interact with antibody. They can bind to proteins generally by covalent linkages to become immunogenic.

b) **False** Haptoglobins are a globulin giycoproteins with a molecular weight not exceeding 1000. They carry only one or two antigenic determinants.

c) **True** Haptoglobins bind to free haemoglobin.

d) **True** Three types of haptoglobin can be distinguished by the use of electrophoresis. Each type is determined by the interaction of two co-dominant somatic genes Hp1 and Hp2.

e) **False** Haptoglobins play no part in the rheumatoid factor. The latter is an autoantibody directed against the Gm antigens on the heavy chain of IgG molecules. Gm antigens form allotypes of immunoglobulin molecules. This characteristic of IgG molecules is determined by a dominant autosomal gene.

Q. The chief effector cells involved in the rejection of a renal allograft are:

a) CD4+ T cells
b) CD8+ T cells
c) passenger leucocytes
d) platelets
e) B lymphocytes

Ans.

a) **True** The importance of hese cells is shown by the finding that 'nude' mice and rats which have a congenital lack of CD4+ T cells require no immunosuppression.

b) **True** These cells cause lysis of the renal parenchymal cells.

c) **True** Passenger leucocytes (dendritic cells) act in the initial phase of sensitisation without which rejection would not be initiated. They are present in the graft and carry high concentrations of donor MHC molecules recognised by the recipient's CD4+ cells.

d) **False** Platelets play no part in the rejection process.

e) **False** B cells play no part in the effector phase of rejection.

Q. Acute graft versus host disease following bone marrow transplantation is followed by damage to:
a) the skin
b) the gut
c) the brain
d) the liver
e) the endocrine glands
Ans.
a) **True** AGVHD is characterized by dermatitis. The skin eruption takes the form of pruritic macular areas on the palms and soles with rttoniliform lesions of the extremities, trunk and face.
b) **True** In the gastrointestinal tract, crypt cell necrosis with marked lymphocytic infiltration occurs. The diagnosis can be made by rectal biopsy.
c) **False** The brain is never involved.
d) **True** Damage to the liver occurs between 10-50 days after the transplantation. It is dominated by a direct attack of the donor lymphocytes on the hepatocytes and the bile duct epithelium, producing a hepoatitic picture.
e) **False** The endocrine glands do not appear to be damaged.

Q. Immunosuppression can be achieved by:
a) cyclosporine
b) rapamycin
c) monoclonal antibodies
d) poor renal function
e) blood transfusion prior to surgery
Ans.
a) **True** The introduction of cyclosporine produced a great advance in transplant surgery. Cyclosporine is a fungal macrolide which affects the production of lymphokines by the T cells.
b) **True** Rapamycin is another lungal derivative which bauses immunosuppression by interfering with the action of IL-α.
c) **True** Various monoclonal antibodies have been produced which act in different ways e.g. Anti CD3 acts on mature T cells, Anti CD4 acts on T helper cells and Anti CD25 acts on activated T cells.
d) **True** As renal function fails, so a non-specific atrophy of all lymphoid tissue occurs due to the development of uraemia.
e) **True** It has been shown that prior transfusion increases the percentage of graft survival. How this is achieved is possibly by the selective activation of Th cells or by the activation of T cells.

Q. The following grafts are rejected *(BSMMU –Residency – **MS, Basic science** – March' 14)*
a) autograft
b) iso graft
c) allo graft
d) xeno graft
e) corneal graft
Ans.
a) **False** Transplantation of an individual's own tissue to another site, e.g. the covering of a full thickness burn with skin from an unburnt area, is not rejected.
b) **False** Transplantation of tissues between genetically identical members of the same species, e.g. kidney transplants between monozygotic twins or skin grafts between mice of the same inbred strain, are not rejected.
c) **True** Transplantation between genetically non-identical members of the same species, e.g. a cadaveric renal transplant or a skin graft between mice of different inbred strains are rejected.
d) **True** Transplantation of tissues between members of different species are rejected.
e) **False** The cornna is in an immunologically privileged site.

Q. Chronic renal allograft rejection is a process:
a) affecting about 10—30% of long-surviving grafts
b) characterized by proliferative stenosis of the arteries
c) in which cellular infiltrates arid librinoid necrosis occurs
d) can be reversed by medical treatment
e) requires graft replacement
Ans.
a) **True** Approximately 10--30% of long-surviving grafts are finally rejected.
b) **True** Whereas acute rejection is charaôterized by cellular infiltration and fibrinoid necrosis, chronic rejection is characterized by proliferative stenosing lesions of arteries.
c) **False** Celfular infiltration does occur, but ills abnormal typically arterial obliteration which causes renal failure in chronic rejection.
d) **False** The process once begun cannot be reversed.
e) **True** Because medical treatment cannot affect the gradual stenosis of the renal arteries, the only treatment available is to remove the graft and possibly regraft later.

Q. Hyperacute rejection- (FCPS – Surgery - 08Ja,06Ju)
a) A condition associated with a Tcell mediated reaction
b) A condition recognised at operation
c) Associated with the Schwartzmann reaction
d) A condition mediated by performed antibodies
e) A condition seen in multiparous women
Ans.
a) **False** Hyperacute rejection occurs in the presence of preformed antidonor antibodies in the circulation of the recipient.
b) **True** In hyperacute rejection, the phenomenon occurs so rapidly that it s almost instantly recognised. In renal transplantation following the restitution of the vascular supply, the kidney instead of becoming pink and excreting urine becomes cyanosed, mottled and may excrete only a few drops of bloody urine.
c) **False** The histological changes resemble those of the Arthus reaction, in which immunofluorescent studies show that after the initial deposition of antigen (in the case of transplantation the donor organ), deposition of antibody (already preformed) and complement occurs in the arterioles and peritubular capillaries, followed by an intravascular clumping of platelets.
d) **True** The reaction is mediated by antibodies rather than T cells.
e) **True** Preformed donor antibodies may be present in a patient who has already received and rejected a homograft and they may also - present in multiparous women who develop anti-HLA antibodies against paternal antigens shed from the fetus; these may cause a hyperacute rejection to grafts taken from their husbands or children.

Q. The major histocompatibilty complex (MHC) in man- (FCPS – Surgery - January, 2008)
a) Is situated on chromosome 6
b) Has three loci controlling of five groups of histocompatibility antigens
c) Is involved in the expression of immune response (Ir) genes
d) Shows a positive association with multiple scle
e) Is tested for by the laboratory on a serum sample
Ans.
a) **True** The MCH complex is located on the short arm of chromosome 6.
b) **True** The genes have been grouped into three types, classes I. II and III.
c) **True** MHC proteins play a crucial role in antigen presentation to T-cell receptors. Class I and II products povoke strong allograft rejection and have antigen-presenting functions. Class III products are components of the complement system.

d) **True** Hodgkin's disease shows positive association with A1 and B8, multiple sclerosis with A3, 87 and DW2 and ankylosing spondylitis with 88.

e) **False** MHC antigens are identified by the use of ieucbcyte suspensions. The term HLA is an abbreviation of the words human leucocyte antigen. Unclotted blood is needed by the laboratory.

Q. The so-called 'Second Set' phenomenon:

a) occurs in an animal or human who has not previously rejected an allograft
b) occurs after a latent period of several days
c) depends on the graft antigenicity being recognised by the host T cells
d) can be demonstrated in both man and animals
e) can be delayed by prior irradiation of the graft

Ans.

a) **False** A 'Second Set' response only occurs in an animal or patient who has previously encountered an allograft.

b) **False** A Second Set' response in a sensitised individual occurs within 2—3 days and in a highly sensitised individual, the graft may never become vascularized.

c) **True** If the graft is unrecognised, as for example a graft placed in the anterior chamber of the eye, rejection will not occur.

d) **True** A free .allograft, e.g. skin, becomes vascularized in the same way as an isograft and retrains viable for between 2—3 weeks, but in a Second Set respone in a sensitised individual, graft rejection occurs within 2—3 days and the graft may never become vascutarized at all.

e) **True** Pretreatment of a graft by radiation reduces its immunogenicity, possibly by destroying highly immunogenic donor leucocytes of bone marrow origin.

Q. Rejection of liver transplants is associated with:

a) arterial lesions
b) cholestasis
c) opportunistic infection
d) autoimmune chronic active hepatitis
e) multiple sclerosis

Ans.

a) **True** Arterial lesions develop in which a significant feature is the intimal accumulation of foamy lipid laden macrophages.

b) **True** Canalicular cholestasis is present in chronic rejection, together with a destructive cholangitis and fibrotic changes in the protal tracts.

c) **False** Opportunistic infections are not associated with rejection but with immunosuppression.

c) **False** This appears to be inhibited by the immunosuppressive regime.

d) **False** There is no association between liver transplantation and neurological disease.

Q. Renal transplantation may be followed by:

a) infection
b) malignant neoplasia
c) amyloidosis
d) rheumatoid arthritis
e) psoriasis

Ans.

a) **True** However, it is not the transplant per se which predisposes to infection, but the suppression of immunity by the cocktail of immunosuppressive drugs.

b) **True** There is an increase in the incidence of squamous cell carcinoma of the skin and lymphoproliferatiVe disorders. Many of these latter are Epstein—Barr related.

c) **False** Amyloidosis does not follow transplantation; it is associated with chronic infections.

d) **False** Rheumatoid arthritis, an erosive arthropathy, is an autoimmufle disease, possibly related to a viral infection.

e) **False** Psoriasis is a skin disease of unknown aetiology. An increased incidence of the disease in certain HLA types suggests that genetic factors produce a predisposition to the development of the condition, but the basic cause has yet to be determined.

Q. Acute rejection of a renal aflograft involves:

a) cellular infiltration of the donor kidney
b) a humoral component
c) subacute vasculitis
d) polymorphónuClear infiltration of the graft
e) a fall in the serum creatinine

Ans.

a) **True** Acute rejection is accompanied by an extensive interstitial mononuclear infiltration of the kidney, consisting chiefly of medium and small-sized lymphocytes which immunoperoxidase staining reveals to be CD4+ andCD8+ lymphocytes.

b) **True** The humoral element of acute rejection is manifested by a necrotising vasculitis which leads to extensive glomerular necrosis and cortical arteriolar thrombosis.

c) **True** Subacute vasculitis is more common than necrotising vasculitis. The major finding is of a marked thickening of the renal arteries leading to luminal obstruction and a gradual failure of renal function.

d) **False** Polymorphonuclear leucocytes play no part in the rejection phenomenon.

e) **False** Evidence that rejection is occurring is shown by the rapid rise in the serum creatinine level.

Q. The following are referred to as 'Incomplete antibodies':

a) lgD anti-D
b) IgM anti-D
c) anti-A isohaemagglutinin
d) the Wassermann antibody
e) tetanus antitoxin

Ans.

a) **True** IgG anti-D antibodies will not agglutinate D-positive erythrocytes in a saline solution alone. They require a polloid solution such as 30% bovine albumin or alternatively they can be detected by the use of the indirect Coombs test.

b) **False** IgM anti-D antibodies will agglutinate D-positive erythrocytes in saline alone and they are, therefore, referred to as 'complete' antibodies. The terms 'complete' and 'incomplete' are used by haematologists to describe blood group antibodies only. The terms do not mean that structural deficiencies are present in the immunoglobulin molecule. Differences in reaction are probably a function of. physical chemical forces.

c) **False** Anti-A isohaemagglutinin is an 1gM molecule and agglutinates blood group A erythrocytes directly in saline.

d) **False** The Wassermann antibody is an IgM antibody which is present in individuals suffering from syphilis and other chronic infectious diseases. It is directed against an antigen presentin cholesterollsed extracts of bovine heart muscle, and is detected by a complement fixation test.

e) **False** Tetanus antitoxin is demonstrated maifliy by toxin neutralisation assay in mice. It can also be titrated by passive haemagglutination assay in which tetanus toxoid is bound to a red cell carrier.

MNEMONICS

সূত্র = ১: Complements are synthesized by:

LIMPS

L = Liver (C_3, C_6, C_9)
I = Intestinal epithelium (C_1)
M = Macrophages (C_2, C_4)
P = Placenta
S = Spleen (C_5, C_8).

সূত্র = ২: Following cytokines in regulation of the immune response:

124 and 612

1 = Interleukin-1 (IL -1)
2 =Interleukin-2 (IL-2)
4 =Interleukin-4 (IL -4)
6 =Interleukin-6 (IL-6)
12 =Interleukin-12 (IL-12)

Cytokine	Source	Actions
IFN-α	*T cells and NK cells* Macrophages	*Antiviral activity Activates NK cells, CB8+ T cells and macrophages*
IFN-γ	T cells	Increases antimicrobial and antitumour activity of macrophages Determines cytokine production by T cells and macrophages
TNF-α	Macrophages	Pro-inflammatory Increases apoptosis and expression of cytokines and adhesion molecules Directly cytotoxic
IL-1	Macrophages and neutrophils	Acute phase reactant Stimulates neutrophil recruitment, fever, T cell and macrophage activaon, immunglobulin production
IL-2	CD+ T cells	Stimulates proliferation and differentiation of antigen specific T lymphocytes
IL-4	CD4+ T cells and mast cells	Stimulates maturation of B and T cells, and production of IgE antibody
IL-6	Monocytes and macrophages	Acute phase reatant Smuates maturation of B cells into plasma cells
IL-12	Monocytes and macrophages	Stimulates IFN-y and TNF-a release by T cells, activates natural killer (NK) cells

সূত্র = ৩: Coombs test is found positive in: SMALL CHAIR

S = SLE
M = Methyldopa therapy
A = Autoimmune haemolytic anaemia
L = Lymphoma
L = Leukaemia

C = Carcinoma
H = Haemolytic disease of newborn
A = Alloaritibodies (eg. HDN)
I = Idiopathic acquired heamolytic anaemia
R = Rhesus incompatibility.

সূত্র = ৪: The coombs test is used for detecting the following antibodies:

HCR

H = Haemolytic autoantibodies
C = Cold agglulinins
R = Rhesus antibodies.

VACCINE

Characteristic features of live attenuated vaccine:

- All live, killed and subunit vaccine induce active immunity.
- Pathogenicity has been attenuated
- Why live viral vaccines are preferable than killed vaccines/ advange?
  - (1) they induce a higher titer of antibody and hence longer-lasting protection;
  - (2) they induce a broader range of antibody (e.g., both IgA and IgG);
  - (3) they activate cytotoxic T cells, which kill virus-infected cells.
- Protection is greater and long lasting
- Multiplies in the host
- Three concern abot live vaccine/ disadvantage:
  - Revert to virulence, should not be given in immunocompromized and pregnant women
  - It is doble edge sword- excreted by the immunized people(oral live polio vaccine), virulent polio can revertant spreads to a susceptible persons.
  - Second virus may contaminate the vaccine during preparation.

❑ Influenza, measles, mumps, and yellow fever vaccines, are grown in chick embryos , should *not be given who has an* anaphylactic reaction to eggs

Characteristic features of killed vaccine

- **Advantage:**
  - cannot revert to virulence
  - they are more heat-stable
  - can be used more easily in tropical climates.
- **Disadvantage:**
  - Induce a shorter duration of protection
  - Are less protective, and induce fewer IgA antibodies
  - Usually given intramuscularly,
  - Do not stimulate a major IgA response.
  - Typically do not stimulate a cytotoxic T cell response

Subunit vaccine/ Recombinant DNA vaccine

1. Hepatitis B (Purified viral proteins)
2. Influenza
3. HPV
4. Bordetella pertusis
5. Bacillus anthracis

❑ The features are same as killed vaccines

❑ No viral replication occurs

Human normal Immunoglobulins(HNI)

- It induces passive immunity
- Administration of preformed antibody
- Naturally:
  1. IgG is transferred from the mother to the fetus across the placenta
  2. IgA is transferred through colostrum.

Immune globulin preparations available in:

- Rabies virus
- HAV, HBV, VZV
- Measles
- Vaccinia against small pox

Passive–active immunity:

- Administering both immune globulins and a viral vaccine.
- Provides both immediate as well as long-term protection.
- Example : Rabies, Tetanus, Hepatis B virus

Conjugate vaccine:

- the carrier peptide is attached to polysaccharide target antigen that presents to MHC molecule and T cell is activated.
- T cells stimulate a more vigorous immune response and more rapid and long-lasting immunologic memory is developed.
- e.g: Haemophylus influenza type B(HIB vaccine), Pneumococcal vaccine

Toxoid (Inactivated toxin)

1. Diphtheria
2. Tetanus Toxoid(TT)

Having both live and killed vaccine

1. Polio(salk and sabin)
2. Influenza
3. Typhoid

Viral vaccines		
Live attenuated vaccines	**Killed vaccines (Inactivated conjugated vaccine)**	**Toxoid (Inactivated toxin)**
Childhood immunization • Measles • Mumps • Rubella • **Polio (oral)** • BCG (for TB) • MMR	• H. influenza B • Pertusis • Meningococcal type A & C	• Diphtheria • Tetanus toxoid (TT)
Travel • Yellow fever • Typhoid*	• Hepatitis A • Typhoid • Cholera • Rabies • Japanese encephalitis	
Special risk groups • Influenza* • Chicken pox (varicella)	• **Polio (salk)** • Hepatitis B • Influenza • Meningococcal type A & C • Plague	
Others- • Rota virus • Adenovirus • Small pox		

Bacterial vaccines	
A. Capsular polysaccharides	• Streptococcus, pneumoniae • Neisseria meningitides • Haemophylus influenzae • Salmonella typhi
B. Toxoid	• Corynebacterium diphtheriae. • Clostridium tetani
C. Live organism	• Mycobacterium bovis (BCG) • Francisella tularensis • Salmonella
D. Killed organism	• Bordetella pertussis • Vibrio cholerae • Yersinia pestis • Rickettsia • Coxiella burnetti • Salmonella
E. Purified protein	• Bordetella pertussis • Bacillus anthracis
F. Recombinant surface protein	• Borrelia burdorferi

i 6.14 Guidelines for vaccination against infectious disease

- The principal contraindication to inactivated vaccines is an anaphylactic reaction to a previous dose or a vaccine component
- Live vaccines should not be given during an acute infection, to pregnant women or to the immunosuppressed, unless the immunosuppression is mild and the benefits outweigh the risks
- If two live vaccines are required, they should be given either simultaneously in opposite arms or 4 weeks apart
- Live vaccines should not be given for 3 months after an injection of human normal immunoglobulin (HNI)
- HNI should not be given for 2 weeks after a live vaccine
- Hay fever, asthma, eczema, sickle-cell disease, topical glucocorticoid therapy, antibiotic therapy, prematurity and chronic heart and lung diseases, including tuberculosis, are not contraindications to vaccination

(Ref: Davidson-23rd, P-16)

■ **Contraindications of immunization**:

1. Febrilc illness, inter-current infection.
2. Hypersensitivity to egg, protein contraindicates influenza vaccine; previous anaphylactic reaction to egg contraindicates influenza and yellow fever.

■ **Contraindications of live vaccine**:

1. Immunodeficiency
2. Immunosuppression.
3. High dose of cortiocosteroids
4. Malignancy, e.g. lymphorna, leukaemia, or Hodgkin's disease.
5. Pregnancy

Question Bank

Q. Live attenuated vaccines are available against *(BSMMU – Non-Residency – **MD, MS, Paediatrics, Basic Science, Dentistry** – July' 19)*

a) Rubella virus
b) Rabies virus
c) Measles virus
d) Yellow fever virus
e) Hepatitis B virus

Ans. a) T b) F (Killed) c) T d) T e) F (Killed)

Q. Vaccines used to prevent cancer are *(BSMMU –Residency - **MD/MS, Paediatrics, Dentistry** – March' 19)*

a) HHV-8 vaccine
b) Polio vaccine
c) HBV vaccine
d) MCPV vaccine
e) HPV vaccine

Ans. a) F b) F c) T d) F e) T

Help Link:

HPV vaccine: Recombinant vaccine.

Recommendation:

- ✓ All boys and girls by the age 11-12 yrs as well as young men and women upto 26 yrs of age.
- ✓ Vaccine is recommended for boys bcoz they play major role in spread of HPV to women.

Protection:

- ✓ Vaccine gives nearly complete protection against high risk HPV(HPV 16,18 accounts about 70% of cervical cancer)
- ✓ Vaccine offers protection upto 10yrs

Q. Recombinant vaccines are available against *(BSMMU –Residency - **MD/MS, Basic science, Paediatrics, Dentistry** – March' 19)*

a) rabies
b) rota virus
c) hepatitis B virus
d) human papilloma virus
e) yellow fever

Ans.

a) T (Neural vaccine, Duck egg vaccine, Live attenuated chick embryo vaccine, Human diploid cell vaccine, Primary cell culture vaccine, Subunit vaccine/ Recombinant vaccine)
b) F (A rhesus-human reassotant rotavirus tetravalent vaccine (RRV-TV)
c) T d) T e) F (17 D strain of yellow fever vaccine)

Q. Vaccines are available against following bacteria *(BSMMU –Residency - **MD/MS, Basic science, Paediatrics, Dentistry** – March' 19)*

a) *Haemophilus influenza* type-B
b) *Listeria monocytogenes*
c) *Streptococcus pneumonia*
d) *Staphylococcus aureus*
e) *Streptococcus pyogenes*

Ans. a) T b) F c) T d) F e) F

Q. Live vaccines are used to protect against *(BSMMU –Residency - **Paediatrics** – March' 19)*
a) Measles
b) Rota virus
c) Chicken pox
d) Rabies
e) Hepatitis A
Ans. a) T b) T c) T d) F (killed) e) F (killed)

Q. Live attenuated vaccines are available against the following viruses *(BSMMU –Residency – **MD, MS, Basic Science** – March' 18)*
a) Rubella virus
b) Rabies virus
c) Yellow fever virus
d) Varicella-Zoster virus
e) Hepatitis B virus
Ans. a) T b) F c) T d) T e) F

Q. Live vaccine/s is/are *(BSMMU –Residency – **MD, Basic Science** – March' 18)*
a) MMR
b) BCG
c) DPT
d) vaccine for meningococcus
e) vaccine for rotavirus
Ans. a) T b) T c) F d) F e) T

Q. The following vaccines contain live attenuated virus *(BSMMU–Residency- **MD, Basic Science** - March' 17)*
a) measles
b) hepatitis A
c) rubella
d) hemophillus influenzae-type B
e) oral polio
Ans. a) T b) F c) T d) F e) T

Q. Live attenuated vaccines are *(BSMMU – Non-Residency – **MD, MS, Basic science – July' 16)***

a) BCG vaccine	T
b) salks vaccine	F
c) rubella vaccine	T
d) meningococcal vaccine	F
e) hepatitis B vaccine	F

Q. Viral vaccines prepared using recombinant DNA technology are *(BSMMU – Non-Residency – **MD, MS, Basic science – July' 16)***

a) hepatits A virus	F
b) hepatits B virus	T
c) human rota vurus	F
d) human papilloma virus	T
e) varicella-zoster virus	F

Help link:

Recombinant DNA vaccine

1. Hepatitis B (Purified viral proteins)
2. Influenza
3. HPV
4. Bordetella pertusis
5. Bacillus anthracis

6. Lyme disease
7. Cholera toxin B
8. Rabies

Q. Live attenuated vaccines are *(BSMMU – Non-Residency – MS, Dentistry – July' 16)*
a) oral polio vaccine T
b) BCG T
c) Cholera F
d) Influenza T
e) Hepatitis B vaccine F

Q. Liver attenuated viral vaccines are *(BSMMU – Residency – MD, MS, Basic science, Dentistry – March' 16)*
a) Rubella virus T
b) rabies virus F
c) Yellow fever virus T
d) Varicella-Zoster virus T
e) Hepatitis B virus F

Q. Live attenuated vaccines are given in the prevention of *(BSMMU –Residency – MS – March' 16)*
a) influenza T
b) measles T
c) mumps T
d) pulmonary tuberculosis T
e) rubella T

Q. Live vaccines are used in immunization against *(BSMMU – Non-Residency – MD, MS, Basic science – July' 15)*
a) diphtheria F
b) poliomyelitis T (oral polio)
c) tetanus F
d) tuberculosis T
e) typhoid fever T

Q. Vaccine preventable viral diseases are *(BSMMU – Non-Residency – MD, MS, Basic science, Dentistry – July' 15)*
a) hepatits C infection F
b) hepatits D infection F
c) rubella virus infection T
d) ebola virus F
e) yellow fever virus T

Q. Live attenuated vaccines are *(BSMMU – Non-Residency – MD, Basic science – July' 15)*
a) MMR T
b) oral polio T
c) BCG T
d) Rib F
e) DPT F

Q. Regarding viral vaccine *(BSMMU –Residency – MD, MS, Basic – March' 15)*
a) HPV vaccine is live attenuated
b) HBV vaccine is recombinant DNA type
c) Yellow fever vaccine is a subunit vaccine
d) Varicella vaccine is a live vaccine
e) Rubella vaccine is a conjugate vaccine.

Ans. a) F b) T c) F (17 D strain of yellow fever vaccine)
d) T (chicken pox) e) F

Q. Live vaccines include *(BSMMU –Residency – MD – March' 15)*
a) oral polio vaccine
b) tetanus vaccine
c) diphtheria vaccine
d) BCG vaccine
e) measles rotavirus
Ans. a) T b) F c) F d) T e) T

Q. Live attenuated vaccines are *(BSMMU – Non-Residency – MD/MS, Basic science – July' 14)*
a) Sabin vaccine for polio
b) influenza vaccine
c) cholera vaccine
d) varicella vaccine
e) rota virus vaccine
Ans. a) T b) T c) F d) T e) T

Q. Following types of vaccines can be used in immunocompromized child *(BSMMU –Residency – MD, Basic science – March' 14)*

a)	live attenuated vaccine	F
b)	recombinant viral protein antigen	T
c)	Toxoid	T
d)	killed whole bacterial cell suspension	T
e)	BCG vaccine	F

Help Link: Live attenuated vaccine should not be given to immunocompromised individulas or pregnancy.

Q. Live attenuated vaccines are available against the following viruses *(BSMMU – Non-Residency - MD/MS, Basic science – 13Ju)*

a)	influenzae A virus	T
b)	hepatits B virus	F
c)	rubella virus	T
d)	yellow fever virus	T
e)	Varicella-Zoster virus	T

Q. Live attenuated vaccines are followings: *(BSMMU – Residency – MD/MS – March'13)*
a) BCG
b) TAB
c) OPV
d) MMR
e) Hib
Ans : a) T b) F c) T d) T e) F

Q. Vaccine preventable viral infections are: *(BSMMU – M. Phil, Diploma (Non-Residency)–March-2012, DMC & others – MD/MS – March-2012)*

a) Hepatitis D virus	F
b) Rubella virus	T
c) Hepatitis E virus	F
d) Hepatitis A virus	T
e) Herpes simplex virus	F

HELP LINK:

Table: Current viral vaccines:

Usage	Vaccine	Live virus, killed virus, or subunit of virus
Common	Measles	Live
	Mumps	Live
	Rubella	Live
	Varicella (chickenpox)	Live
	Polio	Live and killed
	Influenza	Live and killed (purified subunits)
	Hepatitis A	Killed
	Hepatitis B	Subunit
	Rabies	Killed
Special situations	Yellow fever	Live
	Japanese encephalitis	Killed
	Adenovirus	Live
	Smallpox	Live

Q. Live attenuated vaccines are available against the following viruses *(BSMMU – MD/MS (Residency) – January, 2011)*

a) rubella virus T
b) rabies virus F
c) yellow fever virus T
d) vericella zoster virus T
e) hepatitis B virus F

Q. The followings are subunit vaccine produced by recombinant DNA technique: *(BSMMU – M. Phil, Diploma (Non-Residency)–11Ju, DMC & others – MD/MS – 11Ju)*

a) Hepatitis vaccine F
b) Hepatitis-B vaccine T
c) Oral Polio vaccine F
d) Human Papilloma virus vaccine T
e) Human Rotavirus vaccine F

Q. Attenuated live organisms are used to immunize against: *(BSMMU – M. Phil, Diploma – 11Ju, DMC & others – MD – 11Ju)*

a) haemophilus influenza type b F
b) measles T
c) oral polio T
d) whooping cough F
e) tuberculosis T

Q. A vaccine: *(BSMMU - M. Phil, Diploma – July '10)*

a) Contains one or more antigens
b) Produces active immunity
c) Contains one or more antibodies
d) Stimulates polymorphonuclear leucocyte activity
e) Can be administered orally

Ans.

a) **True** The aim of vaccine production is to alter a pathogen in such a way that it becomes harmless to the recipient but retains its antigenicity. Vaccines may be produced from bacteria or viruses and the organisms may be alive, attenuated or dead.

b) **True** Active immunity is produced following the administration of a vaccine by the stimulation of antibody production by the plasma cells which are themselves derived from B lymphocytes.

c) **False** Vaccines contain antigens. Immunisation against diphtheria toxin may be produced with toxin—antitoxin floccules (TAF).

d) **False** A vaccine has no effect on polymorphonuclear leucocyte activity.

e) **True** Vaccines may be administered in a number of ways. The most common Orally administered vaccine is the poliomyelitis vaccine introduced by Sabin which consists of living attenuated strains which have undergone mutation after passage
through monkey-kidney cell cultures. The disadvantages associated with this type
of vaccine are that the virus may not enter the cells of the intestinal tract and, therefore, no immunity develops and secondly, that the virus may undergo mutation in the alimentary tract reverting to a more virulent type which may then infect others. **(Ref: Smiddy)**

Q. Followings are vaccine preventable viral disease: *(BSMMU - M. Phil, Diploma – July '10)*

a) Mumps T
b) Hepatitis C F
c) HIV F
d) Hepatitis A T
e) Human papilloma virus infection T

Q. Vaccine exist for the following bacteria: (BSMMU – MD – January, 2010)

a) Haemophilius infiuenzae type B T
b) Listeria monocytogens F
c) Streptococcus pneumoniae T
d) Staphylococcus aureus F
e) Streptococcus pyogenes F

Q. Subunit vaccine produced by recombinant DNA technique are: (BSMMU – MS - January, 2010)

a) hepatitis A vaccine F
b) hepatitis B vaccine T
c) oral polio vaccine F
d) human papilloma virus vaccine T
e) human rotavirus vaccine F

Help link: List of subunit vaccine – HBV, injectable influenza, Hemophyllus influenza (Hib), pertusis, pneumococcal, meningococcal, HPV.

Q. Following are the examples of killed vaccines - (MD/MS (DMC) – January, 2010)

a. OPV F
b. BCG F
c. Rabies T
d. Measles F
e. Hepatitis B T

Q. The triple vaccine for prevention for viral infections includes protection against: (BSMMU - M. Phil, Diploma, July-09)

a) Rabies virus F
b) Polio virus F
c) Hepatitis virus F
d) Mumps virus T
e) Rubella virus T

Help Link: Measles, mupms, Rubella

Q. Following are live vaccine: (BSMMU - M. Phil, Diploma, July-08)

a) Tetanus F
b) Hepatitis B F
c) Measles T
d) Mumps T
e) Rubella T

Q. Following are live attenuated vaccine: (BSMMU – MD/MS - January, 2008)

a) HBV vaccine F
b) HAV vaccine F
c) BCG vaccine T
d) Oral polio vaccine T
e) Measles vaccine T

Q. Live attenuated vaccine is/ are: (M. Phil, Diploma-07July)

a) BCG T
b) Pertusis F
c) rabies F
d) yellow fever T
e) measles T

Q. Live attenuated vaccines include - (BSMMU – MD - 07Ja)

a. Tetanus F
b. BCG T
c. Typhoid T
d. Haemophylus influenza B F
e. Measles T

Q.The following are live vaccines:(BSMMU–MD-06Ja)

A. DPT F
B. BCG T
C. Measles T
D. Cholera F
F. mumps T

Q. Human normal immunoglobulin is used for prophylaxis against: (M. Phil, Diploma-05July)

a) Varicella F
b) Viral hepatitis A T
c) Measles T
d) Rubella F
e) Viral hepatitis type-B T

Q. A live vaccine should not be given: (M. Phil, Diploma-05July)

a) To patient with chronic heart disease F
b) In early pregnancy T
c) During an acute febrile illness T
d) With another live vaccine T
e) During corticosteroid therapy T

Q. Tripple vaccine protects against- (MD/MS (DMC)-05Ja)

a) Mumps virus T
b) Measles virus T
c) Polio virus F
d) Hepatitis virus F
e) Rubella virus T

Q. Live attenuated vaccines are: (MD/MS (DMC)-05Ja)

a) Cholera F
b) Yellow fever T
c) Pertusis F
d) Mumps T
e) Japanese encephalitis F

Q. Regarding vaccines- (BIRDEM-04)

a) Oral polio vaccine is live attenuated virus T
b) BCG is killed Mycobacterium tuberculosis bacilli F
c) Tetanus toxoid is heat stable vaccine T (all killed vaccines are heat stable)
d) Measles vaccine is given at the age of 1 month F
e) Vaccine for Hepatitis B contains killed virus. T

Q. Most children should have received the following vaccines before entry into Primary school: - (MD/MS (DMC)-03Ja)

a) Measles, mumps and rubella T
b) Influenza T
c) Diphtheria, tetanus and pertusis T
d) Polio T
e) Small pox T

Q. Live vaccines are used in immunization against : (MD/MS (DMC)-02J)

A. Diphtheria F
B. Poliomyelitis T
C. Tetanus F
D. Tuberculosis T
E. Typhoid fever T

Nice to know

শিশুদের নিয়মিত টিকাদান সময়সূচি

রোগের নাম	টিকার নাম	টিকার ডোজ	ডোজের সংখ্যা	ডোজের মধ্যে ন্যূনতম বিরতি	টিকা দেয়ার সঠিক সময়	টিকাদানের স্থান	টিকার প্রয়োগ পথ
যক্ষ্মা	বিসিজি	০.০৫ এম এল	১	-	জন্মের পর থেকে	বাম বাহুর উপরের অংশে	চামড়ার মধ্যে
ডিফথেরিয়া, হুপিংকাশি, ধনুষ্টংকার, হেপাটাইটিস-বি, হিমোফাইলাস ইনফ্লুয়েঞ্জা-বি	পেন্টাভ্যালেন্ট টিকা (ডিপিটি, হেপাটাইটিস-বি, হিব)	০.৫ এম এল	৩	৪ সপ্তাহ	৬ সপ্তাহ ১০ সপ্তাহ ১৪ সপ্তাহ	বাম উরুর মধ্যভাগের বহিরাংশে	মাংসপেশী
নিউমোকক্কাল নিউমোনিয়া	পিসিভি টিকা	০.৫ এম এল	৩	৪ সপ্তাহ	৬ সপ্তাহ ১০ সপ্তাহ ১৪ সপ্তাহ	ডান উরুর মধ্যভাগের বহিরাংশে	মাংসপেশী
পোলিওমাইলাইটিস	বিওপিভি	২ ফোঁটা	৩	৪ সপ্তাহ	৬ সপ্তাহ ১০ সপ্তাহ ১৪ সপ্তাহ	মুখে	মুখে
	আইপিভি (ফ্রাকশনাল)	০.১ এম এল	২	৮ সপ্তাহ	৬ সপ্তাহ ১৪ সপ্তাহ	ডান বাহুর উপরের অংশে	চামড়ার মধ্যে
হাম ও রুবেলা	এমআর টিকা	০.৫ এম এল	২	-	৯ মাস ও ১৫ মাস বয়স পূর্ণ হলে	ডান উরুর মধ্যভাগের বহিরাংশে	চামড়ার নীচে

১৫-৪৯ বছর বয়সের মহিলাদের টিকাদান সময়সূচি

রোগের নাম	টিকার নাম	টিকার ডোজ	ডোজের সংখ্যা	টিকা শুরু করার সঠিক সময়	টিকাদানের স্থান	টিকার প্রয়োগ পথ
ধনুষ্টংকার	টিটি (টিটেনাস টক্সয়েড)	০.৫ এম এল	টিটি-১	১৫ বছর বয়স হলেই যথাশীঘ্র	বাহুর উপরের অংশে	মাংশপেশী
			টিটি-২	টিটি-১ পাওয়ার কমপক্ষে ২৮ দিন পর		
			টিটি-৩	টিটি-২ পাওয়ার কমপক্ষে ৬ মাস পর		
			টিটি-৪	টিটি-৩ পাওয়ার কমপক্ষে ১ বৎসর পর		
			টিটি-৫	টিটি-৪ পাওয়ার কমপক্ষে ১ বৎসর পর		

(Ref. DGHS website)

Herd immunity/ community immunity

- Unimmunized people is protected
- Vaccine can prevent transmission of the virus and prevent disease
- Eg: oral polio/ sabin vaccine induces intestinal IgA that prevents replication of virus in the intestine

VIROLOGY

General property of virus:

- Viruses has either DNA or RNA (but not both) covered by a protective protein coat.
- It replicates within cells, because they cannot generate energy or synthesize proteins.
- It is called obligate intracellular parasites **because** they cannot synthesize sufficient energy to replicate independently.
- Viruses range in size from that of large proteins (~20 nm) to that of the smallest cells (~300 nm).
- Most viruses appear as spheres or rods in the electron microscope.
- All viruses have a protein coat called a capsid that covers the genome.
- In some viruses, the capsid is the outer surface, but in other viruses, the capsid is covered with a lipoprotein envelope that becomes the outer surface.
- The structure composed of the nucleic acid genome and the capsid proteins is called the nucleocapsid.
- Some viral nucleocapsids have spherical (icosahedral) symmetry, whereas others have helical symmetry.
- All human viruses that have a helical(hollow coil) nucleocapsid are enveloped (i.e., there are no naked helical viruses that infect humans).
- Viruses that have an icosahedral nucleocapsid can be either enveloped or naked.
- Culture is normally not possible ,except polio virus, cultured in cell free media.
- Antibiotic resistant.
- Interferon sensitive.
- Not divided by binary fission.
- DNA and RNA genomes can be either single stranded or double stranded.
- All viruses have one copy of their genome (haploid) except retroviruses ,which have two copies of RNA genome (diploid).
- Transcriptase/polymerase: it is enzyme necessary for transcription.
- DNA viruses take the enzyme from our body (only DNA dependent RNA polymerase enzyme)
- Matrix protein mediates the interaction between the viral nucleocapsid proteins and the envelop proteins.
- Some viruses have one serotype, others have multiple serotypes.

Enveloped viruses: more sensitive to heat, drying, detergents, and lipid solvents such as alcohol and ether. Transmitted by direct contact or sexual contact.

- e.g: HIV, HSV and HBV, HCV.

Naked nucleocapsid viruses: All viruses transmitted by the fecal–oral route (have to survive in the environment) do not have an envelope;

- eg: HAV, polio, Coxsackie, echovirus, Norwalk virus, and rotavirus

Atypical virus like agents:

- Defective viruses: Composed of viral nucleic acid and proteins but can not replicate without a helper virus, eg: HDV
- Pseudovirions: Contains host cell DNA instead of viral DNA.
- **Viroids**: Solely composed of single circular RNA without capsid or envelop.
- **Prions**: Infectious particle composed solely of proteins.

Question Bank

Q. Preferred sites for establishment of persistent viral infection are *(BSMMU –Residency - **MD/MS, Basic science, Paediatrics** – March' 19)*
a) neuron
b) muscle
c) liver
d) RBC
e) lymphocyte
Ans. a) T b) F c) T d) T e) T (eg: EBV causes persistent infection in B lymphocytes)

Help Link:

Persistent viral infection:

✓ In most viral infections, the virus does not remain in the body for a significant period after clinical recovery.
✓ in certain instances, the virus persists for long periods either intact or in the form of a subviral component (e.g., the genome).

The mechanisms that may play a role in the persistence of viruses include
(1) integration of a DNA provirus into host cell DNA, as occurs with retroviruses;
(2) immune tolerance, because neutralizing antibodies are not formed;
(3) formation of virus–antibody complexes, which remain infectious;
(4) location within an immunologically sheltered "sanctuary" (e.g., the brain);
(5) rapid antigenic variation;
(6) spread from cell to cell without an extracellular phase, so that virus is not exposed to antibody; and
(7) immunosuppression, as in acquired immunodeficiency syndrome (AIDS).

Q. Presence of inclusion bodies may be associated with following viruses *(BSMMU –Residency - **MD/MS, Basic science, Paediatrics** – March' 19)*
a) Measles virus
b) Rota virus
c) Corona virus
d) Rabies virus
e) Cytomegalovirus
Ans. a) T b) T c) F d) T e) T

Help Link:

Inclusion body

They are the aggregates of virions or viral proteins and other products of viral replication by which they can be demonstrated in virus infected cells under the light microscope.

Intracytoplasmic inclusion bodies	Intranuclear inclusion bodies
Negri bodies–seen in Rabies virus Paschen body–seen in Variola virus Guarnieri bodies–seen in Vaccinia virus Bollinger bodies–seen in Fowl pox virus Molluscum bodies–seen in Molluscum contagiosum virus Perinuclear cytoplasmic body- seen in Reovirus	A) Cowdry type A inclusions • Torres body–seen in Yellow fever • Lipschultz body–seen in Herpes simplex B) Cowdry type B inclusions–seen in Poliovirus (non specific, may be illusory type)
Intracytoplasmic and intranuclear inclusion bodies: Seen in Measles and Cytomegalovirus (Owl's eye appearance)	

(Ref. Textbook of Microbiology by Apurbo sankar sasry)

Q. Human are the only natural host for the following viruses *(BSMMU – Non-Residency – MD, MS, Basic science – July' 16)*

a) rabies virus F
b) measles virus T
c) dengue virus F
d) rubella virus T
e) ebola virus F

Q. Followings viruses have an outer glycoprotein envelope *(BSMMU – Non-Residency - MD/MS, Basic science – 13Ju)*

a) hepatitis E virus F
b) measles virus T
c) ebola virus T
d) human papilloma virus F
e) adeno virus F

Q. Human are the only natural host for followings viruses: *(BSMMU – Residency – MD/MS – March'13)*

a) Rabies
b) Rota virus
c) Measles virus
d) Rubella virus
e) Hepatitis B virus

Ans: a) F b) F c) T d) T e) T

Help link:

Humans are the only natural host for HBV. There is no animal reservoir.

Q. Following are the statements regarding viruses: *(BSMMU – M. Phil, Diploma (Non-Residency)–March-2012, DMC & others – MD/MS – March-2012)*

a) viruses may produce cytopathic changes in cell culture
b) virus infected cells may be transformed
c) all viruses are sensitive to antiviral agents
d) some viruses may have a lipid envelope
e) naked viruses are destroyed by lipid solvents

Ans. a) T b) T c) F d) T e) F

HELP LINK:

The followings are correct:

- The genome of some viruses is **DNA,** whereas the genome of others is **RNA.** These DNA and RNA genomes can be either single-stranded or double-stranded.
- Some RNA viruses, such as influenza virus and rotavirus, have a segmented genome, ie. the genome is in several pieces,
- All viruses have one copy of their genome (haploid) excent retroviruses, which have two copies (diploid).
- Viral surface proteins mediate attachment to host cell receptors. This interaction determines the host specificity and organ specificity of the virus.
- The surface proteins are the targets of antibody, ie. antibody bound to these surface proteins prevents the virus from attaching to the cell receptor. This "neutralizes" (inhibits) viral replication.
- Viruses also have internal proteins, some of which are DNA or RNA polymerases.
- The matrix protein mediates the interaction between the viral nucleocapsid proteins and the envelope proteins.
- Some viruses produce antigenic variants of their surface proteins that allow the viruses to evade our host defenses. Antibody against one antigenic variant (serotype) will not neutralize a different serotype. Some viruses have one serotype; others have multiple serotypes.
- The viral **envelope** consists of a membrane that contains lipid derived from the host cell and proteins encoded by the virus. Typically, the envelope is acquired as the virus exits from the cell in a process called **budding**.

- Viruses with an envelope are less stable, ie. they are more easily inactivated, than naked viruses (those without an envelope). In general, enveloped viruses are transmitted by direct contact via blood and body fluids, whereas naked viruses can survive longer in the environment and can be transmitted by indirect means such as the fecal-oral route.

Q. The following are examples of viral genome detection (molecular methods): *(BSMMU – M. Phil, Diploma (Non-Residency)–March-2012, DMC & others – MD/MS – March-2012)*

a) Southern blot T
b) Western blot F
c) RIBA (Recombinant immunoblot assay) F
d) Branched DNA T
e) Polymerase chain reaction (PCR) T

Help Link:

✓ Genotypic methods include plasmid profile analysis, restriction endonuclease analysis of chromosomal DNA with Southern blotting, PCR, and nucleotide sequence analysis.
✓ **Western blot** detects specific proteins (antibodies) in a sample containing mixture of antibodies each targeted against different antigens of same microbe:
✓ **Brancehed DNA**: HIV RNA can be detected

Q. The following statements regarding viruses are true: *(BSMMU – M. Phil, Diploma (Non-Residency)–11Ju, DMC & others – MD/MS – 11Ju)*

a) viruses may produce cytopathic changes in cell culture T
b) virus infected cells may be transformed T
c) all viruses are sensitive to antiviral agents F
d) some viruses may have a lipid envelope T
e) naked viruses are destroyed by lipid solvents F

Q. The following statements are true for viruses *(BSMMU – MD/MS (Residency) – January, 2011)*

a) contain both DNA and RNA F
b) may have an envelope T
c) have their own metabolism F
d) may contain a cell wall F
è) may contain enzymes for replication T

HELP LINK:

Traits	Bacteria	Viruses	Fungi	Protozoa
Cells	Yes	No	Yes	Yes
Approximate diameter(μm)	1-5	.02-.2	3-10(yeast)	15-25(trophozoite)
Nucleic acid	Both DNA and RNA	Either DNA or RNA	Both DNA and RNA	Both DNA and RNA
Type of nucleus	Prokaryotic	None	Eukaryotic	Eukaryotic
Ribosomes	70s	Absent	80S	80S
Mitochondria	Absent	Absent	Present	Present
Nature of outer surface	Rigid wall containing peptidoglycan	Protein capsid and lipoprotein envelope	Rigid wall containing chitin	Flexible membrane.
Motility	Some	None	None	Most
Method of replication	Binary fission	Not binary fission	Budding or mitosis	Mitosis

(Ref: LANGE REVIEW-15th)

Q. Nonspecific host defenses against viral infection are : *(BSMMU – MD/MS (Residency) – January, 2011)*

a) IgG F
b) IgM F
c) interferon T
d) natural killer cells T
e) antiviral drugs F

HELP LINK:

Host defenses against viruses fall into two major categories:

- **nonspecific**, of which the most important are interferons and natural killer cells.
- **specific**, including both humoral and cell-mediated immunity.
- Interferons are an early, first-line defense, whereas humoral immunity and cell-mediated immunity are effective only later because it takes several days to induce an immune response.

(Ref. LANGE Review-15th, P-53-54)

Q. Following characteristics are attributed to a virus: (BSMMU - M. Phil, Diploma, July-08)

a) obligatory intracellular organism T
b) possesses a rigid cell wall F
c) viruses have either DNA or RNA T
d) viruses can synthesize protein F
e) some viruse can cause cancer T

HELP LINK:

■ **Differences between bacteria & viruses:**

Traits	Virus	Bacteria
1. Size	20 - 300 nm	More than 300 nm
2. Nucleic acid	Either DNA or RNA	Both DNA and RNA
3. Cell wall	Absent	Present
4. Ribosome	Absent	Present
5. Metabolic enzyme	Absent	Present
6. Ordinary culture media	Normally not possible, except polio virus which is cultured in cell free media.	Possible
7. Capsule	Lipoprotein	Lipo-polysaccharide
8. Antibiotic	Resistant	Sensitive
9. Interferon	Sensitive	Resistant

Q. Following statements are applicable for a virus- (BSMMU – MD/MS - 06Ja)

a) Obligatory intracellular organism T
b) Smallest intracellular organism T
c) Does not have ribosome T
d) Contains both RNA and DNA F
e) Does not have cell wall T

HELP LINK:

■ **General properties of a virus:**

1. Smallest obligatory intracellular parasite.
2. Having one type nucleic acid either RNA or DNA.
3. No cell wall
4. No ribosome, no mitochondria
5. Having no metabolic enzyme
6. Culture is normally not possible, except polio virus which is cultured in cell free media.
7. Capsule- Lipoprotein
8. Antibiotic resistant.
9. Interferon sensitive

Q. Antibiotics do not act against virus because- (BSMMU - MS-01Ja)

a) Viruses do not have cell wall T
b) Viruses produce enzymes which destroy antibiotics. F
c) Virus do not have ribosome. T
d) Virus do not have receptor for antibiotics T
e) Antibiotics cannot penetrate viral envelope. T

Q. These are the unique characteristics of viruses - (BSMMU-MS-01Ja)

a) Contain either RNA or DNA T
b) Ribosome is present in a virus. F
c) Cell wall is present in a virus F
d) A virus maintain cell tropism T
e) A virus divides by binary fission F

Prions

Prions;

• Prions are infectious particles that are composed solely of protein; ie, they contain no detectable nucleic acid. They are implicated as the cause of certain "slow" diseases called transmissible spongiform encephalopathies, which include such diseases as Creutzfeldt-Jakob disease in humans and scrapie in sheep. Because neither DNA nor RNA has been detected in prions, they are dearly different from viruses. Furthermore, electron microscopy reveals filaments rather than virus particles. Prions are much more resistant to inactivation by ultraviolet light and heat than are viruses. They arc remarkably resistant to formaldehyde and nucleases. However, they are inactivated by hypochlorite, NaOH, and autoclaving. Hypochlorite is used to sterilize surgical instruments and other medical supplies that cannot be autoclaved.

• Prions are composed of a single glycoprotein with a molecular weight of 27,000-30,000. With scrapie prions as the model, it was found that this protein is encoded by a single cellular gene. This gene is found in equal numbers in the cells of both infected and uninfected animals. Furthermore, the amount of prion protein mRNA is the same in uninfected as in infected cells. In view of these findings, posttranslational modifications of the prion protein are hypothesized to be the important distinction between the protein found in infected and uninfected cells.

• These is evidence that a change in the conformation from the normal alpha- helical form (known as PrP, or prion protein cellular) to the abnormal beta- pleated sheet form (known as PrP, or prion protein scrapie) is the important modification. The abnormal form then recruits additional normal forms to change their configuration, and the number of abnormal pathogenic particles increases Although prions are composed only of proteins, specific cellular RNAs enhance the conversion of the normal alpha-helical form to the pathologic beta-pleated sheet form.

• The function of the normal prion protein is unclear. There is some evidence that it is one of the signal transduction proteins in neurons and that it is a copper-binding protein. "Knockout" mice in which the gene encoding the prion protein is inactive appear normal. The prion protein in normal cells is protease-sensitive, whereas the prion protein in infected cells is protease resistant, probably because of the change in conformation.

Question Bank

Q. Prions are infectious partical that are *(BSMMU –Residency - **MS, Basic science** – March' 14)*

a) Composed of only protein T
b) only nuclic acid F
c) both nuclic acid and protein F
d) cause infection of CNS T
e) infect only animal F

Q. Slow viral diseases are *(BSMMU–Residency – **MD, MS, Basic** – March' 15; Non-Residency–July-2012, DMC & others – MD/MS – July-2012)*

a) AIDs
b) Creutzfeldt-Jacob disease virus
c) subacute sclerosing panencephalitis (SSPE)
d) Rabies
e) progressive multifocal leucoencephalopathy (PML)

Ans. a) T b) T c) T d) F e) T

Help link:

Table: Important features of slow viral diseases caused by prions:

Disease	Pathogenesis	Important feature
Kuru	Transmissible/ infectious	Caused by ingesting or handling brain tissue. Occurred in New Guinea tribes people
Creutzfeldt-Jakob disease	i. Transmissible/ infectious	Iatrogenic transmission by corneal transplant, brain, electrodes, and growth hormone
	ii. Hereditary/ genetic	Mutation in germ cells
	iii. Sporadic	No relationship to any known cause; possible new mutation in somatic cells; most common form
Variant creatzfeldt-Jakob disease	Transmissible/ infectious	Probably acquired by eating meat or nervous tissue from animals with "mad cow' disease
Gerstmann-Straussler-Scheinker syndrome	Hereditary/ genetic	Mutation in germ cells
Fatal familial insomnia	Hereditary/ genetic	Mutation in germ cells

Table: Important features of slow viral diseases caused by conventional viruses:

Disease	Virus	Virus Family	Important Characteristic
Progressive multifocal leukoencephalopathy	JC virus	Papovavirus	Infection widespread; disease only in immunocompromised
Subacute sclerosing panencephalitis	Measles virus	Paramyxovirus	Disease in young children with defective virus in brain
Acquired immunodeficiency syndrome (AIDS)	Human immunodeficiency virus (HIV)	Retrovirus	HIV infects CD4-positive cells, eg. brain macrophages

Q. Prion is an infectious particle that: (BSMMU – MS - January, 2010)

a) is composed of a single molecule of circular DNA F
b) is encoded by the host chromosome DNA F
c) can be inactivated by ultraviolet light F
d) causes transmissIble spongiform encephalitis T
e) causes a number of transmissible plant diseases F

Virus causing infection/ diseases

Q. Multinucleated giant cell associated viruses are *(BSMMU – Non-Residency – MD, MS, Paediatrics, Basic Science – July' 19)*

a) Coxsackie virus
b) Adenovirus
c) Reovirus
d) Varicella-zoster virus
e) Herpes simplex virus

Ans. a) F b) F c) F d) T e) T

(Ref. LANGE-15th, P-282)

Help Link: Orthomyxovirus like influenza A, B, C, Rubella , Rabies does not produce giant cells

Multinucleated giant cell associated viruses:

a) Herpes simplex virus(1 ,2)
b) Varicella zoster virus
c) Parainfluenza HIV
d) Cytomegalo virus

e) Measles (Paramyoxi virus)
f) Mumps
g) Respiratory syncytial virus

Q. Viruses having animal reservoir are *(BSMMU – Non-Residency – **MS, Basic science** – July' 18)*
a) Yellow fever virus
b) Dengue virus
c) Hepatitis E virus
d) Western encephalitis virus
e) Rubella virus

Ans. a) T b) T c) F (reservoir is unknown but may be animal) **[Ref. Robins-9th, P-835]** d) T e) F

Help link:

Virus	Animal Reservoir	Mode of Transmission	Disease
Rabies virus	In United States, skunks, raccoons, and bats; in developing countries, dogs	Usually bite of infected animal; also aerosol of bat saliva	Rabies
Hantavirus[1]	Deer mice	Aerosol of dried excreta	Hantavirus pulmonary syndrome (pneumonia)
Yellow fever virus	Monkeys	Bite of *Aedes* mosquito	Yellow fever
Dengue virus	Monkeys	Bite of *Aedes* mosquito	Dengue
Encephalitis viruses[2]	Wild birds (e.g., sparrows)	Bite of various mosquitoes	Encephalitis
SARS[3] coronavirus	Civet cat	Aerosol droplets	SARS
Avian influenza virus (H5N1)	Chickens and other fowl	Aerosol droplets, guano	Influenza

(Ref: LANGE-15th, P-245)

Q. Organisms associated with congenital anomaly are *(BSMMU – Non-Residency – **MS, Basic Science** – July' 19)*
a) Toxoplasma gondi
b) HIV
c) Rubella virus
d) HPV
e) Treponema pallidum

Ans. a) T b) T (Causes Microcephaly, Ref: MR Molla Paedi) c) T d) F e) T

(Ref: Langman Embryology-14th, P-132 + Robbins-9th, P-454)

Q. Congenital anomalies in the fetus can be caused by - *(BSMMU – Non-Residency – MD, MS, Basic Science & Dentistry – July' 17)*
a) Poliovirus
b) Cytomegalovirus
c) Zika virus
d) Rubella virus
e) Adenovirus

Ans. a) F b) T c) T d) T e) F

Help link: Teratogens causing congenital malformations:

Infectious agents:

- **Rubella virus** - Cataracts, glaucoma, heart defects, deafness, teeth, microphthalmia (not macrophthalmia)
- **Cytomegalovirus** - Microcephaly, blindness, mental retardation, fetal death.
- **Herpes simplex virus** - Microphthalmia, microcephaly, retinal dysplasia
- **Varicella virus** - Limb hypoplasia, mental retardation, muscle atrophy
- **HIV** - Microcephaly, growth retardation
- **Toxoplasmosis** – Hydrocephalus, cerebral calcifications, microphthalmia
- **Syphilis** – Mental retardation, deafness

Physical agents

- **X-rays** - Microcephaly, spina bifida, cleft palate, limb defects
- **Hyperthermia** – Anencephaly

Chemical agents

- **Thalidomide** - Limb defects, heart malformations
- **Aminopterin** - Anencephaly, hydrocephaly, cleft lip and palate
- **Diphenylhydantoin (phenytoin)** - Fetal hydantoin syndrome: facial defects, mental retardation
- **Valproic acid** - Neural tube defects, heart, craniofacial, and limb anomalies.
- **Trimethadione** - Cleft palate, heart defects, urogenital and skeletal abnormalities
- **Lithium** - Heart malformations
- **Amphetamines** - Cleft lip and palate, heart defects
- **Warfarin** - Chondrodysplasia, microcephaly
- **ACE inhibitors** - Growth retardation, fetal death
- **Cocaine** - Growth retardation, microcephaly, behavioral abnormalities, gastroschisis
- **Alcohol** - Fetal alcohol syndrome, short palpebral fissures, maxilary hypoplasia, heart defects, mental retardation
- **Isotretinoin (Vitamin-A)** - embryopathy: small, abnormally shaped ears, mandibular hypoplasia, cleft palate, heart defects.
- **Organic mercury** - Neurological symptoms similar to those of cerebral pals; **Lead** - Growth retardation, neurological disorders

Hormones:

- **Androgenic agents (ethisterone, norethisterone)** - Masculinization of female genitalia: fused labia, clitoral hypertrophy
- **Diethylstilbestrol** (DES) - Malformation of the uterus, uterine tubes, and upper vagina; vaginal cancer; malformed testes
- **Maternal diabetes** - Variety of malformations; heart and neural tube defects most common

(Ref: Langmans)

Q. Viruses associated with vesicular rash are *(BSMMU – Non-Residency – MD, MS, Basic science – July' 16)*

a) Rubella virus F
b) Measles virus F
c) Parvo virus F
d) Herpes simplex virus T
e) Varicella zoster virus T

Help link:

11.24 Rash in tropical travellers/residents

Maculopapular rash

- Dengue
- HIV-1
- Typhoid
- *Spirillum minus*
- Rickettsial infections
- Measles

Petechial or purpuric rash

- Viral haemorrhagic fevers
- Yellow fever
- Meningococcal sepsis
- Leptospirosis
- Rickettsial spotted fevers
- Malaria

Vesicular rash

- Monkeypox
- Insect bites
- Rickettsial pox

Urticarial rash

- Katayama fever (schistosomiasis)
- *Toxocara* spp.
- *Strongyloides stercoralis*
- Fascioliasis

Ulcers

- Leishmaniasis
- *Mycobacterium ulcerans* (Buruli ulcer)
- Dracunculosis
- Anthrax
- Rickettsial eschar
- Tropical ulcer (*Fusobacterium ulcerans* and *Treponema vincentii*)
- Ecthyma (staphylococci, streptococci)

Papules

- Scabies
- Insect bites
- Prickly heat
- Ringworm
- Onchocerciasis

Nodules or plaques

- Leprosy
- Chromoblastomycosis
- Dimorphic fungi
- Trypanosomiasis
- Onchocerciasis
- Myiasis (larvae of tumbu fly or botfly)
- Tungiasis (*Tunga penetrans*)

Migratory linear rash

- Cutaneous larva migrans (CLM; dog hookworms)
- *Strongyloides stercoralis* (larva currens, more rapid than CLM)

Migratory papules/nodules

- *Loa loa*
- Gnathostomiasis
- Schistosomiasis

Thickened skin

- Mycetoma (actinomycetoma/ eumycetoma)
- Elephantiasis (filariasis)

(Ref: Davidson-23rd, P-234)

Q. Preferred sites for establishment of persistent viral infection are *(BSMMU – Non-Residency – MD, MS, Basic science – July' 16)*

a) neuron T
b) muscle F
c) liver T
d) RBC T
e) neutrophil F

Q. Viruses those have an animal reservoir are *(BSMMU –Residency–MD, MS, Basic science, Dentistry–March' 16)*

a) Hepatitis virus F
b) Rabies virus T
c) Varicella-Zoster virus F
d) Measles virus F
e) Yellow fever virus T

(Ref: LANGE-15th, P-245)

Q. Following viruses could establish a latent infection *(BSMMU – Residency – MD, MS,Basic science–March' 16)*

a) Adenovirus T
b) Parvovirus T
c) Coxakie virus group B F
d) Cytomegalovirus T
e) Epstein Barr Virus T

Help link:

Latent infection: All herpes family including adenovirus and parvo virus, HTLV-1, HIV, CMV, EBV, HBV.

Virus causing latent infection:

Name of the virus	Primary infection	Latent in
HSV-1	infect eye and face	Thoracic and trigeminal sensory ganglia
HSV-2	infects genitalia	Lumber and sacral sensory ganglia
Variecella zoster - forms painful vesicles or shingles. first time as varicella (chicken pox) than after latent period as zoster(shingles)	face and trunk	Thoracic and trigeminal sensory ganglia

Q. Viruses associated with gastroenteritis are *(BSMMU.– Residency – MD, MS, Basic science – March' 16)*

a) Measles virus F
b) Norwalk like virus T
c) Corona virus F
d) Adenovirus T
e) Rota virus T

Help link:

Various type important virus:

Virus causing Diarrhoea	Rota virus Nor-walk virus Calci virus Astro virus Adeno virus
Giant cell forminig virus	Herpes simplex virus(1 ,2) Varicella zoster virus HIV Cytomegalo virus Measles(Paramyoxi virus) Respiratory syncytial virus
Mosquito borne viral diseases	Dengue Yellow fever West nile fever Viral arthritis Jananese encephalitis

Q. Conditions likely to be caused by adenovirus are *(BSMMU –Residency – MD, MS, Basic – March' 15)*
a) glomerulonephritis
b) encephalitis
c) conjunctivitis
d) pharyngitis
e) pneumonia
Ans. a) F b) F c) T d) T e) T

Help Link:
Adenovirus causes:
a) Upper and lower respirator tract disease, pharyngitis,
b) conjunctivitis(pink eyes),
c) common cold, Pneumonia, Keratoconjunctivitis, Hemorrhagic cystitis,
d) Gastroenteritis,
e) Some adenoviris can cause sarcoma in rodents

(Ref. LANGE Review-15th, P-308)

Q. Viruses those have animal reservoir *(BSMMU –Residency – MD, MS, Basic – March' 15)*
a) Rabies virus
b) Adeno virus
c) Epstein Barr virus
d) Yellow fever virus
e) SARS corona virus
Ans. a) T b) F c) F d) T e) T

(Ref: LANGE-15th, P-245)

Q. Viruses that produce generalized infections *(BSMMU –Residency – MD, MS, Basic Science – March' 15)*
a) Rhino virus
b) Varicella virus
c) Rubella virus
d) Rota virus
e) Respiratory syncytial virus
Ans. a) F b) T c) F d) F e) T

Help Link:
Rhinovirus, Corona virus, adenovirus, enterovirus, parainfluenza, influenza causes infection of the upper respiratory passage including common cold syndrome.

Q. The following viruses are associated with vesicular rash *(BSMMU – Non-Residency – MD/MS, Basic science – July' 14)*
a) rubella virus
b) measles virus
c) parvovirus
d) herpes simplex virus type-I
e) varicella zoster virus
Ans. a) F b) F c) F d) T e) T

Help Link: Vesicular rash:
Rickettsial Pox and African tick Typhus
Varicella zoster, Herpes simples

Q. The following viruses have segmented genome *(BSMMU – Non-Residency – MD/MS, Basic science – July' 14)*
a) rota virus
b) HIV
c) orbi virus
d) orthomyxovirus
e) paramyxovirus
Ans. a) T b) T c) F d) T e) F

Help Link: All the RNA viruses have one copy of single stranded unsegmented RNA except:

a) Reo viruses (the only double stranded RNA virus)
b) Retroviruses including HIV (possess 2 copies of SS RNA)

Segmented RNA Viruses (code-BIRA)

a) Bunya virus (3 segments)
b) Influenza virus (8 segments),
c) Rotavirus (11 segments),
d) Arenavirus (2 segments) e.g. LCM i.e. lymphocytic choriomeningitis virus
(Ref: P. Chakraborti-1st, P-511+ Apubo sankar-6th, P-298)

Help Link:

Example of Orthomyxovirus: Influenza A, B, C

Paramyxovirus:

- Parainfuenza virus, Respiratory syncytial virus,
- Newcastle disease virus, Mumps, Rubeola(measles) virus

Q. Inclusion body can form in following viral infection *(BSMMU –Residency - MS, Basic science – March' 14)*

a) Rubella F
b) Cytomegalo virus T
c) Pox virus T
d) Measles T
e) Hepatitis A F

Help link:

New Inclusion bodies: During the growth of virus particles inside the cells, certain abnormal bodies are formed which cafl be visualized by light microscope. These are known as inclusion bodies. In many instances they are colonies of viral particles. They may be intranuclear or intra-cytoplasmic or both and constitute a diagnostic feature in many viral infections. They may vary from I to 30 jin in size. Following are the few examples of the types of inclusion bodies in viral diseases.

Inclusion body can form in following viral infection:

a) Intracytoplasmic eosinophilic -

- Negri bodies in Rabies
- Guarnieri bodies in small pox
- Henderson-Peterson bodies in Molluscum contagiosum

b) Intranuclear acidophilic -

- Cowdry type A in Herpes simplex virus and Varicella zoster virus.
- Torres bodies in Yellow fever.
- Cowdry type B in Polio

c) Intranuclear basophilic -

- Cowdry type B in Adenovirus
- Owl eyes in cytomegalovirus

d) Both Intranuclear & intracytoplasmic -

- Warthin finkeldey bodies in Measles.

Q. The following viruses are associated with respiratory infections *(BSMMU –Residency – MS, Basic science – March' 14)*

a) rota viruses F
b) adeno viruses T
c) influenza viruses T
d) HTLV-1 F
e) RSV T

Help Link: Rhinovirus, Corona virus, adenovirus, enterovirus, parainfluenza, influenza causes infection of the upper respiratory passage including common cold syndrome.

Q. Foetal abnormalities may occurs if pregnant mother becomes infected with: *(BSMMU – Residency – MD/MS – March'13)*

a) Hepatitis A virus
b) Cytomegalovirus
c) Treponema pallidum
d) Toxoplasma gondii
e) Gardenella vaginalis

Ans: a) F b) T c) T d) T e) F

Help Link: TORCH infection

Q. Inclusion bodies may be produced by following viral Infections *(BSMMU – MD/MS (Residency) – January, 2011)*

a) pox virus T
b) hepatitis C virus F
c) rabies virus T
d) dengue virus F
e) herpes virus T

Q. Following viruses have segmental genome *(BSMMU – MD/MS (Residency) – January, 2011)*

a) rota virus T
b) parainfluenza virus F
c) orthomyxo virus T
d) colti virus F
e) rabies virus F

Q. Viruses belonging to this family are likely to establish latent infections: (BSMMU - M. Phil, Diploma, July-09)

a) Filoviridae F
b) Caliciviridae F
c) Herpesviridae T
d) Adenoviridae T
e) Poxviridae F

Help link:

Caliciviridae – example of Norwalk virus

Q. Virus produce disease by: (BSMMU - M. Phil, Diploma, July-07)

a) cytopathic effect in infected cells T
b) malignant transformation T
c) immune response to virus infected cells T
d) production of exotoxin that activates adenylate cyclase F
e) production of endotoxin causes decrease in protein synthesis F

Q. Viruses which invade central nervous system include- (BIRDEM-04)

a) Polio virus T
b) Measles virus T
c) Varicella zoster virus T
d) Herpes simplex virus T
e) Rabies virus T

Help link:

Neurotropic Virus (CNS invader)

- Polio virus
- Herpes virus
- Varicella zoster
- Measles
- Rabies virus

Chronic carrier state

Q. A chronic carrier state may occur in the following viral infections *(BSMMU –Residency - **MD/MS, Basic science, Paediatrics, Dentistry** – March' 19)*

a) Rubella
b) HBV
c) Chikungunya
d) HCV
e) Influenza

a) F b) T c) F d) T e) F

Help link:

Chronic carrier infections caused by

1. Hepatitis B virus
2. Hepatitis C virus
3. Neonatal rubella virus
4. Cytomegalo virus
5. Hanta virus

Q. A chronic carrier state may occur in *(BSMMU – Non-Residency – **MD, MS, Basic science, Dentistry** – July' 15)*

a) hantavirus infection	T
b) hepatitis A virus infection	F
c) hepatitis B virus infection	T
d) hepatitis C virus infection	T
e) small pox infection	F

Replication of virus

Replication of virus:

- **DNA viruses:** Replicate in the nucleus and use the host cell DNA-dependent RNA polymerase to synthesize their mRNA except poxviruses that replicate in the cytoplasm and carry own polymerase.
- **Most RNA viruses**: Replicate in the cytoplasm except retroviruses, influenza viruses and hepatitis delta virus.

Q. RNA polymerase play role in *(BSMMU – Residency - **Dentistry** - March' 17)*

a) DNA replication
b) separation of DNA strand
c) RNA formation
d) DNA synthesis
e) base pairing

Ans. a) F b)F c) T d) F e)F

Q. The groups of viruses contains an RNA dependent DNA polymerase as a component of virion are: (MD/MS (DMC)-01Ja)

a) Adenovirus	F
b) Orthomyxovirus	F
c) Rhabdovirus	F
d) Reovirus	F
e) Retrovirus	T

Ans. a) F b) F c) F d) F e) T

HELP LINK:

■ **Transcriptase / polymerase**: Enzyme necessary for transcription. DNA viruses take the enzyme from our body (only DNA dependent RNA polymerase enzyme)

Four types of enzyme:

1. DNA DNA dependent DNA polymerase DNA. (virus)

2. DNA $\xrightarrow{\text{DNA dependent RNA polymerase}}$ RNA (Host cell)
3. RNA $\xrightarrow{\text{RNA dependent RNA polymerase}}$ RNA (virus)
4. RNA $\xrightarrow{\text{RNA dependent DNA polymerase}}$ DNA (virus) or, reverse transcriptase.

DNA & RNA Viruses

DNA Viruses: PHHAPP	RNA Viruses
1. Pox virus (small pox/ variola): • Small pox virus • Alastrim virus • Vaccinia virus • Molluscum contagiosum (STD) 2. Herpes virus: • HSV-1,2 (STD) • HSV-3 (varicella virus) • HSV-4 (Epstein Barr virus) • HSV-5 (Cytomegalo virus) • HSV-6,7 • HSV-8 (kaposi's sarcoma herpes virus) 3. Hepadna virus (Hepatitis B virus) 4. Adeno virus 5. Papova virus: • Papilloma (STD) • Polyoma • Vacuolating 6. Parvo virus (B19) - Single stranded. 1-3 = enveloped	1. Myxo virus: • Orthomyxovirus (influenza) • Paramyxovirus: - Para-influenza - Mumps - Measles - Respiratory syncytial virus - Newcastle disease virus 2. Rhabdo virus-rabies 3. Toga virus 4. Retro virus (HTLV, HIV) 5. Corona virus 6. Picorona virus (HAV) 7. Arena virus 8. Reo virus - double str.- reo, Rota, orbi, colti. 9. Astro virus 10. Flavi virus (HCV, Dengue virus) 11. Calici virus- •Norwalk virus •Sapporo virus •HEV •Marine •Rabbit haemorrhagic disease virus 1 – 5 = enveloped *[All enveloped virus are ether sensitive except pox virus]*

Question Bank

Q. Following are RNA virus *(BSMMU –Residency - **Basic science** – March' 19)*
a) Adenovirus
b) Rotavirus
c) Hepatitis B virus
d) Coxsackie virus
e) Hepatitis A virus
Ans. a) F (DNA) b) T c) F (DNA) d) T e) T

Q. Enveloped viruses are *(BSMMU – Non-Residency – **MS, Basic science** – July' 18)*
a) Picorna virus
b) Hepadna virus
c) Orthomyxovirus
d) Retrovirus
e) Adenovirus
Ans. a) F b) T c) T d) T e) F **(Ref: LANGE-15th, P-239)**

Q. DNA viruses are *(BSMMU – Non-Residency – MD, MS, Basic science – July' 15)*

a) herpes viruses T
b) orthomyxo viruses F
c) entero viruses F
d) hepadna viruses T
e) parvo viruses T

Ans. a) T b) F c) F d) T e) T

(Ref. LANGE Review-15th, P-238)

Q. Non enveloped viruses are *(BSMMU –Residency – MD, MS, Basic – March' 15)*

a) Papilloma virus
b) Herpes virus
c) Polio virus
d) Rota virus
e) Corona virus

Ans. a) T b) F c) T d) T e) F

(Ref. LANGE Review-15th, P-238)

Q. Enveloped DNA viruses are *(BSMMU –Residency - MS, Basic science – March' 14)*

a) polio virus
b) hepatitis B virus
c) herpes simplex virus
d) dengue virus
e) adeno virus

Ans. a) F b) T c) T d) F e) F

Help link:

Classification of DNA Viruses:

Virus Family	Envelope Present	Capsid Symmetry	Particle Size (nm)	DNA MW ($x10^6$)	DNA Structure[1]	Medically Important Viruses
Parvovirus	No	Icosahedral	22	2	SS, linear	B19 virus
Papovavirus	No	Icosahedral	55	3–5	DS, circular, supercoiled	Papillomavirus
Adenovirus	No	Icosahedral	75	23	DS, linear	Adenovirus
Hepadnavirus	Yes	Icosahedral	42	1.5	DS, incomplete circular	Hepatitis B virus
Herpesvirus	Yes	Icosahedral	100[2]	100–150	DS, linear	Herpes simplex virus, varicella-zoster virus, cytomegalovirus, Epstein-Barr virus
Poxvirus	Yes	Complex	250 x 400	125–185	DS, linear	Smallpox virus, vaccinia virus

[1]SS, single-stranded; DS, double-stranded.
[2]The herpesvirus nucleocapsid is 100 nm, but the envelope varies in size. The entire virus can be as large as 200 nm in diameter.

Q. Virus contains double stranded genome in following virus: *(BSMMU – Residency – MD/MS – March'13)*

a) Parvo virus
b) Adeno virus
c) Pox virus
d) Rabies virus
e) Reo virus

Ans : a) F b) T c) T d) F e) T

HELP LINK:

COMPARISON OF DNA and RNA VIRUSES

In general:

• All DNA viruses are double stranded except parvovirus and naked (except for herpes virus, poxvirus and hapadna virus).

• All RNA viruses are single-stranded (except reovirus) and enveloped (except for picornavirus and reovirus).

Q. Viruses having segmented genome are: (BSMMU – MS - January, 2010)

a) human rotavirus (HRV)
b) rhabdovirus
c) human immunodeficiency virus (HIV)
d) influenza virus
e) parainfluenza virus Ans. a) T b) F c) T d) T e) F

HELP LINK:

Classification of RNA Viruses:

Virus Family	Envelope Present	Capsid Symmetry	Particle Size (nm)	RNA MW ($x10^6$)	RNA Structure[1]	Medically Important Viruses
Picornavirus	No	Icosahedral	28	2.5	SS linear, nonsegmented, positive polarity	Poliovirus, rhinovirus, hepatitis A virus
Calicivirus	No	Icosahedral	38	2.7	SS linear, nonsegmented, positive polarity	Norwalk virus, hepatitis E virus
Reovirus	No	Icosahedral	75	15	DS linear, 10 segments	Rotavirus
Flavivirus	Yes	Icosahedral	45	4	SS linear, nonsegmented, positive polarity	Yellow fever virus, dengue virus, West Nile virus, hepatitis C virus
Togavirus	Yes	Icosahedral	60	4	SS linear, nonsegmented, positive polarity	Rubella virus
Retrovirus	Yes	Icosahedral	100	7[2]	SS linear, 2 identical strands (diploid), positive polarity	HIV, human T-cell leukemia virus
Orthomyxovirus	Yes	Helical	80–120	4	SS linear, 8 segments, negative polarity	Influenza virus
Paramyxovirus	Yes	Helical	150	6	SS linear, nonsegmented, negative polarity	Measles virus, mumps virus, respiratory syncytial virus
Rhabdovirus	Yes	Helical	75 x 180	4	SS linear, nonsegmented, negative polarity	Rabies virus

[1]SS, single-stranded; DS, double-stranded.
[2]Retrovirus RNA contains 2 identical molecules of MW 3.5 x 10^6.
[3]Particles are 80 nm wide but can be thousands of nanometers long.
[4]The nucleocapsid appears spherical but its symmetry is unknown.

Virus Family	Envelope Present	Capsid Symmetry	Particle Size (nm)	RNA MW ($x10^6$)	RNA Structure[1]	Medically Important Viruses
Filovirus	Yes	Helical	803	4	SS linear, nonsegmented, negative polarity	Ebola virus, Marburg virus
Coronavirus	Yes	Helical	100	10	SS linear, nonsegmented, positive polarity	Coronavirus
Arenavirus	Yes	Helical	80–130	5	SS circular, 2 segments with cohesive ends, negative polarity	Lymphocytic choriomeningitis virus
Bunyavirus	Yes	Helical	100	5	SS circular, 3 segments with cohesive ends, negative polarity	California encephalitis virus, hantavirus
Deltavirus	Yes	Uncertain4	37	0.5	SS circular, closed circle, negative polarity	Hepatitis delta virus

[All enveloped virus are ether sensitive except pox virus]

Q. DNA viruses are: (M. Phil, Diploma (DMC) -06July)

a) hepatltis-B virus T
b) hepatitis-C virus F
c) hepatitis-D virus F
d) human immunodeficiency virus F
e) adenovirus T

Q. The following are DNA viruses - (BSMMU - M. Phil, Diploma, July-06)

a) Influenza A virus F
b) Rubella virus F
c) Hepatitis B virus T
d) CMV T
e) Parvovirus T

Q. Following are the DNA viruses: (DMC - M. Phil, Diploma, July-'05)

a) HIV virus F
b) Hepatitis-B virus T
c) Polio virus F
d) Parvo virus T
e) Adeno virus T

Q. Reverse transcriptase enzyme is present in: (BSMMU - M. Phil, Diploma, July-05)

A. cytomegalo virus F
B. human papilloma virus F
C. hepatitis-B virus F
D. Epstein Bar virus F
E. human immunodeficiency virus T *(and also HTLV)*

Q. Following viruses possess a genome of single stranded RNA that is infectious when purified- (BSMMU – MD/MS - 05Ja)

A. Rotavirus F
B. Poliovirus T
C. Coxsackivrus T
D. Retrovirus T
E. Hepatitis A virus T

Q. Nucleic acid may be present in the viruses in the form of- (BSMMU – MD/MS - 05Ja)

A. Single stranded RNA T
B. Double stranded RNA T
C. Double stranded DNA T
D. DNA with reverse transcriptase enzyme T
E. DNA always with complete strands F

Q. Following in diseases caused by viruses: (MD/MS (DMC)-03Ja)

a) Molluscum contagiosum T
b) Toxic epidermal necrolysis F
c) Condylomata acuminata T
d) Herpes zoster T
e) Verruca vulgaris T*(caused by Human Papilloma virus)*

HELP LINK:

■ **Molluscum contagiosum** is a member of poxvirus family causing small, pink, papular, wattlike benign tumours of the skin or mucous membrane.

■ **Verruca vulgaris**: A rough surface protruding only slightly from the skin and are surrounded by a horny collar called plantar warts or verruca caused by Human papilloma virus.

■ **Toxic epidermal necrolysis** is a severe form of wide spread blistering that can occur at any age often due to drugs.

■ **Condylomata acuminata**: Skin & planter warts are caused primarily by HPV-I through HPV-4 whereas genital warts or condylomata acuminata are caused primarily by HPV-6 and HPV-11.

Q. Following are examples of DNA viruses- (BSMMU - MS-01Ja)
a) Herpes simplex virus.
b) Papilloma virus
c) Influenza virus
d) Enteroviruses
e) Epstein Barr virus.
Ans. a) T b) T c) F d) F e) T

Oncogenic organisms

■ **Oncogenic viruses**: These are the cancer causing viruses.

Oncogenic viruses with causing neoplasms

	Virus	Neoplasm
DNA oncogenic viruses	• Human papillomavirus HPV (1, 2, 4 & 7) HPV – 6 HPV – 16, 18	 Benign squamous papilloma/ viral warts Condyloma acunimatum of genitalia/ Verrucae vulgaris Carcinoma cervix, anogenital region, head & neck (arising in tonsillar mucosa). Penis, vvulva, vagina
	HHS - 8	Kaposi sarcoma (In AIDS patient)
	• Epstein Barr virus	• Burkitt's lymphoma • Nasopharyngeal cancer • B-cell lymphoma in immunosuppressed patients especially those with AIDS. • Some forms of Hodgkin disease. • Oral hairy leucoplakia (AIDS pt)
	• Hepatitis B virus	Hepatocellular carcinoma
	Merkel cell polyoma virus	Merkel cell carcinoma
RNA oncogenic virus	Hepatitis C Virus	Hepatocellular Carcinoma
	Human T-cell leukaemia virus type-1	T cell leukaemia
	Human T cell leukaemia virus type-II	leukaemia

■ ***Oncogenic Bacteria***: Helicobacter pylori. It causes-
1. Gastric carcinoma
2. Gastric lymphoma (MALToma)

Oncogenic parasite:
Schistosoma haematobium
Clorchis sinensis
Opisthorchis sinensis

Question Bank

Q. Oncogenic viruses that cause infection in the oral cavity are *(BSMMU – Non-Residency – **Dentistry** – July' 19)*

a) Human papillomavirus
b) Cytomegalovirus
c) Herpes simplex virus type-1
d) Epstein Barr virus
e) Human T-cell leukemia virus type-1

Ans. a) T b) F (Not oncogenic) c) F (Not oncogenic) d) T e) F

Q. Cancers of infective origin are *(BSMMU – Non-Residency - **MS** – July' 19)*

a) ovarian carcinoma
b) Kaposi's sarcoma
c) thyroid carcinoma
d) cervical carcinoma
e) Burkitt's lymphoma

Ans. a) F b) T (Human Herpes Virus -8) c) F d) T (HPV) e) T (EBV)

Q. Viruses implicated in the causation of human cancer are *(BSMMU –Residency - **MD/MS, Basic science, Paediatrics** – March' 19)*

a) Cytomegalovirus
b) Human papillomavirus
c) Epstein-Barr virus
d) Varicella-Zoster virus
e) Herpes simplex type 2 virus

Ans. a) F b) T c) T d) F e) F

Q. Oncogenic DNA viruses are *(BSMMU – Residency - **MD, MS, Basic Science, Dentistry** - March' 17)*

a) Human papilloma virus
b) Epstein-Barr virus
c) Human T-cell leukaemia virus type I
d) Hepatitis C virus
e) Cytomegalovirus

Ans. a) T b) T c)F d) F e)F

Q. Viruses associated with human cancer are *(BSMMU – Residency - **MD, MS, Basic Science, Dentistry** - March' 17)*

a) Smallpox virus
b) Epstein Barr virus
c) Hepatitis C virus
d) Adenoviruses
e) Human papilloma virus

Ans. a) F b) T c)T d) F e)T

Q. Oncogenic viruses are *(BSMMU – Non-Residency – **MD, MS, Basic science, Dentistry** – July' 15)*

a) human papillomavirus	T
b) cytomegalo virus	F
c) adenovirus	F
d) hepatitis C virus	T
e) herpes simplex virus	F

Q. Oncogenic viruses are *(BSMMU – Non-Residency - **MD/MS, Basic science** – 13Ju)*

a)	human papilloma virus	T
b)	adeno virus	F
c)	paramyxovirus	F
d)	hepatitis B virus	T
e)	Epstein Barr virus	T

Q. The following viruses are associated with malignancy in human: *(BSMMU – M. Phil, Diploma (Non-Residency)–March-2012, DMC & others – MD/MS – March-2012)*

a) Epstein-Barr virus	T
b) Cytomegalovirus	F
c) Hepatitis B virus	T
d) Human immunodeficiency virus	T
e) Coxsackievirus	F

Q. Oncogenic microbial agents include: *(BSMMU –M. Phil, Diploma (Non-Residency)–11Ju, DMC & others – MD/MS – 11Ju)*

a) Hepatitis-C virus.	T
b) Hepatitis-E virus.	F
b) Epstein —Barr virus.	T
c) Nipah virus.	F
e) Helicobacter pylon.	T

Q. Oncogenic viruses are - (DMC – MD/ MS - January, 2010)

a. Hepatitis A virus	F
b. Hepatitis B virus	T
c. Rubella virus	F
d. Human Papilloma virus	T
e. Epstein-Barr virus	T

Q. The following organisms have oncogenic properties in human: (BSMMU - M. Phil, Diploma, July-09)

a) Rabies virus	F
b) Hepatitis B virus	T
c) Schistosoma hematobium	T
d) Epstein barn virus	T
e) Helicobacter pylon	T

Q. Viruses that can cause cancer in human are – (MD/MS (DMC)-08Ja)

a) Epstein-Barr virus	T
b) Human papilloma virus	T
c) Hepatitis B virus	T
d) Hepatitis C virus	T
e) Congo-crimean virus	F

Q. Oncogenic viruses are- (BSMMU-MD/MS-06Ja)

A. Papilloma	T
B. Polyoma	F
C. Hepatitis A	F
D. Respiratory syncitial virus	F
E. Rhebdovirus	F

Q. The human oncognic DNA viruses are (M. Phil, Diploma (DMC) – 03Ju)
a) Human papilloma virus T
b) Hepatitis B virus T
c) HTLV-1 F
d) Epstein barr virus T
e) Kaposi sarcoma herpes virus T

Q. Oncogenic viruses are - (BSMMU – MD/MS - 01Ja)
A. Papilloma T
B. Polyoma F
C. Hepatitis A F
D. Respiratory syncitial virus F
E. Rhabdovirus F

Q. Viruses that can cause cancer in human are – (BSMMU – MD/MS - 00Ja)
a) Epstein-Barr virus T
b) Human papilloma virus T
c) Hepatitis B virus T
d) Hepatitis C virus T
e) Congo-crimean virus F

HELP LINK: See before

Antiviral Agents

Q. Commonly used antiviral agents are: (M. Phil, Diploma (DMC)-05July)
a) Acyclovir T
b) AZT T
c) Vancomycine F
d) Lamivudin T
e) Interferon T

HELP LINK:

■ **Anti-viral drugs**:

Action	Drug	Indication
1. Acting on early events (prevent uncoating)	Amantidine, Rimantidine	Influenza A virus
2. Inhibition of viral NA	Acyclovir	Herpes simplex 1 & 2 Vericella zoster
	Gancyclovir	CMV
3. Inhibitors of retro viruses	Azidothymidine/ Zidovudine/ Retrovir	HIV
4. Inhibition of viral protein synthesis	Interferon	HIV, hepatitis
	Methisazone	Pox virus
5. Inhibition of release of virus	Zanamedrine	Influenza A & B
6. Attachment preventing agent: These are neutralizing antibiotics	B virus antibody Rabies antibody	

Q. Viruses are not affected by antibiotics because - (BSMMU - M. Phil, Diploma, July-05)
A. viruses do not have receptor for antibiotics T
B. viruses do not synthesize protein F
C. viruses degrade the antibiotics by enzymatic action F
D. viruses do not have cell wall T
E. antibiotics cannot penetrate viral envelope T

Human papilloma virus

Q. Human papilloma virus is responsible for *(BSMMU –Residency - **MS, Basic science** – March' 19)*

a) cervical cancer
b) colonic cancer
c) genital wart
d) laryngeal cancer
e) thyroid cancer

Ans. a) T b) F c) T d) F e) F

Help Link:

HPV is responsible for:

1. Benign squamous papilloma/ Viral wart(1,2,4,7)/Condyloma accuminatum/Verrucae vulgaris
2. SCC of cervix, anogenital region, Head and neck(arising in tonsillar mucosa), penis, vulva, vagina- HPV 16, 18

Q. Human papilloma virus is most commonly associated with *(BSMMU –Residency – **MD, MS, Basic** – March' 15)*

a) anogenital cancers
b) breast cancers
c) cervical cancers
d) lung cancers
e) prostate cancer

Ans. a) T b) F c) T (mostly 16, 18 type) d) F e) F **(Ref. LANGE Review-15th, P-238)**

HELP LINK:

Diseases:

Human papillomavirus (HPV) causes papillomas, which are benign tumors of squamous cells, e.g., warts on the skin. Some HPV types, especially types 16 and 18, cause **carcinoma of the cervix and penis.**

Important Properties:

Papillomaviruses are nonenveloped viruses with double-stranded circular DNA and an icosahedral nucleocapsid. Two of the early genes, **E6** and **E7,** are implicated in carcinogenesis. They encode proteins that inactivate proteins encoded by tumor suppressor genes in human cells, e.g., the p53 gene and the retinoblastoma (RB) gene, respectively. Inactivation of the p53 and RB proteins is an important step in the process by which a normal cell becomes a cancer cell.

There are at least 100 types of papillomaviruses, classified primarily on the basis of DNA restriction fragment analysis. There is a pronounced **predilection of certain types to infect certain tissues.** For example, skin warts are caused primarily by HPV-1 through HPV-4, whereas genital warts are usually caused by HPV-6 and HPV-11. Approximately 30 types of HPV infect the genital tract.

Summary of Replicative Cycle:

Little is known of the specifics of viral replication, because the virus grows poorly, if at all, in cell culture. In human tissue, infectious virus particles are found in the terminally differentiated squamous cells rather than in the basal cells. In malignant cells, viral DNA is integrated into host cell DNA in the vicinity of cellular proto-oncogenes, and E6 and E7 are overexpressed. However, in latently infected, nonmalignant cells, the viral DNA is episomal and E6 and E7 are not overexpressed. This difference occurs because another early gene, E2, controls E6 and E7 expression. The E2 gene is functional when the viral DNA is episomal but is inactivated when it is integrated.

Transmission & Epidemiology: Papillomaviruses are transmitted primarily by skin-to-skin contact and by genital contact. Genital warts are among the **most common sexually transmitted diseases.** Skin warts are more common in children and young adults and tend to regress in older adults. HPV transmitted from an infected mother to the neonate during childbirth causes warts in the mouth and in the respiratory tract, especially on the larynx, of the infant. Many species of animals are infected with their own types of papillomaviruses, but these viruses are not an important source of human infection.

Pathogenesis & Immunity:
Papillomaviruses infect squamous epithelial cells and induce within those cells a characteristic cytoplasmic vacuole. These vacuolated cells, called **koilocytes,** are the hallmark of infection by these viruses. Most warts are benign and do not progress to malignancy. However, HPV infection is associated with carcinoma of the uterine cervix and penis. The proteins encoded by viral genes E6 and E7 interfere with the growth-inhibitory activity of the proteins encoded by the p53 and RB tumor suppressor genes and thereby contribute to oncogenesis by these viruses. The E6 and E7 proteins of HPV type 16 bind more strongly to p53 and RB proteins than the E6 and E7 proteins of HPV types not implicated in carcinomas, a finding that explains why type 16 causes carcinomas more frequently than the other types.
Both cell-mediated immunity and antibody are induced by viral infection and are involved in the spontaneous regression of warts. Immunosuppressed patients, e.g., AIDS patients, have more extensive warts, and women infected with HIV have a very high rate of carcinoma of the cervix.

Clinical Findings: Papillomas of various organs are the predominant finding. These papillomas are caused by specific HPV types. For example, skin and plantar warts are caused primarily by HPV-1 through HPV-4, whereas genital warts (**condylomata acuminata**) are caused primarily by HPV-6 and HPV-11. HPV-6 and HPV-11 also cause respiratory tract papillomas, especially laryngeal papillomas, in young children. Carcinoma of the uterine cervix, the penis, and the anus, as well as premalignant lesions called intraepithelial neoplasia, are associated with infection by HPV-16 and HPV-18. Occult premalignant lesions of the cervix and penis can be revealed by applying acetic acid to the tissue.

Laboratory Diagnosis: Infections are usually diagnosed clinically. The presence of koilocytes in the lesions indicates HPV infection. DNA hybridization tests to detect the presence of viral DNA are commercially available. Diagnostic tests based on detection of antibodies in a patient's serum or on isolation of the virus from a patient's tissue are not used.

Treatment & Prevention: The usual treatment for genital warts is podophyllin; alpha interferon is also effective and is better at preventing recurrences than are non-antiviral treatments. Liquid nitrogen is commonly used for skin warts. Plantar warts can be removed surgically or treated with salicylic acid topically. Cidofovir may be useful in the treatment of severe HPV infections.

A vaccine against four types of HPV was approved by the FDA in 2006. The vaccine, called Gardasil, contains the capsid proteins of types 6 and 11, which cause genital warts, and types 16 and 18, which are the two most common causes of cervical carcinoma. It is approved for use in females between the ages of 9 and 26 years. The role of cesarean section in preventing transmission of HPV from a mother with genital warts to her newborn is uncertain.

Q. Human papilloma virus causes following tumors *(BSMMU – Non-Residency – MD/MS, Basic science – July' 14)*
a) condyloma acuminata
b) hepatic carcinoma
c) cervical cancer
d) plantar wart
e) colorectal cancer

Ans. a) T b) F c) T d) T e) F

Help Link:
- **Disease:**
  1. HPV 1 and 4 (low risk): Skin wart(verucae vulgaris)
  2. HPV 6 and 11(low risk): Genital wart (condyloma acuminatum)
  3. HPV 16 and 18(high risk): Carcinoma of cervix, penis, anus, Head and neck area (arising in tonsillar mucosa), vulva, vagina, oropharynx,

Q. The following is correct for human papilloma virus (HPV): *(BSMMU – Residency – MD/MS – March'13)*
a) HPV is a non enveloped icosahedral, ds-DNA virus
b) Blood and blood products are an important mode of transmission of HPV
c) HPV induces the formation of koilocytes in the skin that are important diagnostic features of HPV infection
d) amantadine inhibits HPV replication by blocking DNA synthesis
e) Recombinant vaccine is available against HPV
Ans: a) T b) F c) T d) F e) T

Q. Human papillonam virus may cause cancer in the following sites: *(BSMMU – Residency – MD – March'13)*
a) Nasopharynx
b) Uterine cervix
c) Oropharynx
d) Urinary bladder
e) Liver Ans : a) T b) T c) F d) F e) F

Q. Human papilloma commonly associated conditions: (BSMMU – MS - January, 2010)
a) anogenital cancers T
b) breast cancers F
c) prostrate cancers F
d) lung cancers F
e) cervical cancers T

Q. Human papilloma virus infection of skin causes – (MD/MS (DMC)-08Ja)
a) Milker's nodule F
b) Verruca vulgaris T
c) Condyloma accuminata T
d) Buruli ulcer F
e) Molluscum contagiosum F

HELP LINK:

Important properties of human papilloma virus:
Virion: Icosahedral, 55 nm in diameter
Composition: DNA (10%), protein (90%)
Genome: Double-stranded DNA, circular MW 5 million, 8 kbp
Proteins: Two structural proteins; cellular histones condense DNA in virion
Envelop: None
Replication: Nucleus
Outstanding chatacteristics:
- stimulate cell DNA synthesis
- restricted host range and tissue tropism
- significant cause of human cancer, especially cervical cancer
- viral oncoproteins interact with cellular tumour suppressor proteins.

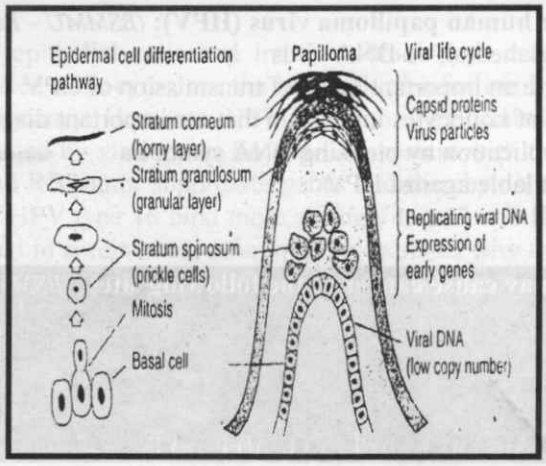


Fig: Schematic representation of a skin wart (papilloma)

Lesions caused by human papilloma virus:

1. Planter warts
2. Common warts
3. Flat warts
4. Hand warts of meat and animal handlers
5. Epidermodysplasia verruciformis
6. Anogenital condylomas
7. Laryngeal papillomas
8. Esophageal carcinoma
9. Oral focal epithelial hyperplasia
10. Intraepithelial neoplasias (genital, other mucosal sites)
11. Keratocanthoma

Q. Human papilloma virus infection of skin causes – (BSMMU – MD/MS - 00Ja)

a) Milker's nodule	F
b) Verruca vulgaris	T
c) Condyloma accuminata	T
d) Buruli ulcer	F
e) Molluscum contagiosum	F

Herpes viruses

Q. Herpes viruses: (BSMMU - M. Phil, Diploma, July-07)

a) are RNA viruses	F
b) include varicella zoster virus	T
c) include pox virus	F
d) include Epstein Barr virus	T
e) include cytomegalovirus	T

Help link:

❑ **Property of Herpes virus**

- All herpesviruses are structurally similar.
- Icosahedral core surrounded by a lipoprotein envelope
- Double-stranded DNA.
- The virion does not contain a polymerase.
- Replicate in the nucleus, form intranuclear inclusions,
- The only viruses that obtain envelope by budding from the nuclear membrane.

- Causes latent Infection.
- HSV 1, 2 , VZV cause a vesicular rash, both in primary infections and in reactivations. Primary infections are usually more severe than reactivations.

Q. Herpes simplex virus infection produce: (M. Phil, Diploma-07July)

a) post herpetic neuralgia	F
b) genital herpes	T
c) herpetic psychosis	T
d) eczema herpeticum	T
e) orolabial herpes	T

Help link:

11.29 Herpesvirus infections

Virus	Infection
Herpes simplex virus (HSV)	
HSV-1 (p. 247)	Herpes labialis ('cold sores') Stomatitis, pharyngitis Corneal ulceration Finger infections ('whitlows') Eczema herpeticum Encephalitis
HSV-2 (p. 247)	Genital ulceration and neonatal infection (acquired during vaginal delivery) Acute meningitis or transverse myelitis; rarely, encephalitis
Varicella zoster virus (VZV)	Chickenpox (varicella) Shingles (herpes zoster)
Cytomegalovirus (CMV) (p. 242)	Congenital infection Infectious mononucleosis (heterophile antibody-negative) Hepatitis Disease in immunocompromised patients: retinitis, encephalitis, pneumonitis, hepatitis, enteritis Fever with abnormalities in haematological parameters
Epstein–Barr virus (EBV) (p. 241)	Infectious mononucleosis Burkitt's and other lymphomas Nasopharyngeal carcinoma Oral hairy leucoplakia (AIDS patients) Other lymphomas, post-transplant lymphoproliferative disorder (p. 225)
Human herpesvirus 6 and 7 (HHV-6, HHV-7)	Exanthem subitum Disease in immunocompromised patients
Human herpesvirus 8 (HHV-8) (p. 248)	Kaposi's sarcoma, primary effusion lymphoma, multicentric Castleman's disease

(Ref: Davidson-23rd, P-238)

Q. Herpes simplex virus infection include: (DMC - M. Phil, Diploma-06July; MD/MS (DMC)-06Ja)

a) shingles F
b) recurrent genital ulcer T
c) meningitis T
d) paronychia T
e) acute gingivo-stomatitis T

Help link:

-Herpetic whitlow is an infection of thumb or finger mainly index finger.
-Paronychia is an infection of nail or nail bed.

Varicella Zoster Virus

Q. Herpes zoster *(BSMMU – Residency – MD, MS, Basic – March' 15)*

a) is caused by herpes simplex virus
b) occurs unilaterally
c) presents with painless blisters
d) leaves scarring
e) may be complicated with neuralgia

Ans. a) F b) T c) F d) T e) T

Help link:

- **Important Properties:**
  - Single serotype.
  - Humans are the natural hosts.
- **Transmission & Epidemiology:**
  - Respiratory droplets
  - direct contact with the lesions.
  - Varicella (chicken pox) is a highly contagious disease of childhood

❑ **Pathogenesis and immunity:**

- ➢ VZV infects the mucosa of the upper respiratory tract, and then spreads via the blood to the skin (vesicular rash)
- ➢ Multinucleated giant cells
- ➢ intranuclear inclusions are seen in the base of the lesions.
- ➢ Causes latent infection
- ➢ Immunity following varicella is lifelong:
- ➢ Zoster can occur despite this immunity to varicella.
- ➢ Zoster usually occurs only once.
- ➢ The frequency of zoster increases with advancing age,

❑ **Clinical feature**

Varicella

- ❖ I. P: 14 to 21 days,
- ❖ fever and malaise occur. A papulovesicular rash then appears in crops on the trunk and spreads to the head and extremities
- ❖ The rash evolves from papules to vesicles, pustules, and, finally, crusts. Itching (pruritus) is a prominent symptom,
- ❖ Varicella is mild in children but more severe in adults.
- ❖ Varicella pneumonia and encephalitis are the major rare complications, occurring more often in adults.
- ❖ Reye's syndrome: encephalopathy and liver degeneration, is associated with VZV and influenza B virus infection, especially in children given aspirin. Its pathogenesis is unknown.

❖ **Zoster:**

- ❖ Painful vesicles along the course of a sensory nerve of the head or trunk.
- ❖ The pain can last for weeks,

- Postzoster neuralgia (also known as postherpetic neuralgia) can be debilitating.
- In immunocompromised patients, life-threatening disseminated infections such as pneumonia can occur.

Epstein Barr Virus (EBV)

Q. Epstein-Barr Virus(EBV) is associated with *(BSMMU – Non-Residency – **Dentistry** – July' 19)*
a) infectious mononucleosis
b) immune deficiency
c) Burkitt's lymphoma
d) nasopharyngeal carcinoma
e) oral leukoplakia

Ans. a) T b) F c) T d) T e) T

(Ref: LANGE-15th, P-289 + Davidson-23rd, P-77)

Q. Epstein barr virus is associated with *(BSMMU – Diploma - **Dentistry** – July' 18)*
a) nasopharyngeal carcinoma
b) carcinoma of the lung
c) oropharyngeal carcinoma
d) laryngeal cancer
e) hypopharyngeal cancer

Ans. a) T b) F c) F d) F e) F **(Ref: Davidson-23rd, P-242)**

Q. Complications of Epstein-Barr virus are *(BSMMU – Residency - **MD** - March' 17)*
a) severe pharyngeal edema
b) hepatitis
c) transverse myelitis
d) thrombocytosis
e) granulocytosis

Ans. a) T b) T c) T d) F e) F

Help link:

11.33 Complications of Epstein–Barr virus infection

Common

- Severe pharyngeal oedema
- Antibiotic-induced rash (80–90% with ampicillin)
- Hepatitis (80%)
- Prolonged post-viral fatigue (10%)
- Jaundice (<10%)

Uncommon

Neurological

- Cranial nerve palsies
- Polyneuritis
- Transverse myelitis
- Meningoencephalitis

Haematological

- Haemolytic anaemia
- Thrombocytopenia

Renal

- Abnormalities on urinalysis
- Interstitial nephritis

Cardiac

- Myocarditis
- ECG abnormalities
- Pericarditis

Rare

- Ruptured spleen
- Respiratory obstruction
- Agranulocytosis
- X-linked lymphoproliferative syndrome

EBV-associated malignancy

- Nasopharyngeal carcinoma
- Burkitt's lymphoma
- Hodgkin lymphoma (certain subtypes only)
- Primary CNS lymphoma
- Lymphoproliferative disease in immunocompromised

(Ref: Davidson-23rd, P-242)

Q. Epstein-Barr virus is implicated in *(BSMMU – Residency - **Dentistry** - March' 17)*

a) Burkitt's lymphoma
b) B cell lymphoma
c) Kaposi's sarcoma
d) T-cell leukaemia
e) nasopharyngeal carcinoma

Ans. a)T b) T c)F d) F e)T

Q. The Epstein-Barr virus is associated with *(BSMMU – Non-Residency – **MD/MS, Basic science** – July' 14)*

a) glandular fever
b) Australia antigen
c) Burkitt's lymphoma
d) nasopharyngeal carcinoma
e) common cold

Ans. a) T b) F c) T d) T e) F

Q. Epstein-Barr virus causes *(BSMMU –Residency – **Dental surgery** – March' 14)*

a) infectious mononucleosis T
b Burkitt's lymphoma T
c) hairy leukoplakia T
d) Hech's disease F
e) oral condylomas F

Q. Epstein Barr Virus may cause *(BSMMU – Non-Residency - MD – 13Ju)*
a) leukemia F
b) lymphoma T
c) hepatocellular carcinoma F
d) nasopharyngeal carcinoma T
e) carcinoma of cervix F

Q. Epstein-Barr Virus (EBV) is associated with: *(BSMMU – MD/MS (Residency) – January, 2011)*
a) infectious mononucleosis T
b) Kaposis sarcoma F
c) Burkitts lymphoma T
d) nasopharyngeal carcinoma T
e) adult T-cell lymphoma F

Q. Epstein barr virus is associated with: *(BSMMU - M. Phil, Diploma – July '10)*
a) Infectious mononucleosis T
b) Burkitt's lymphoma T
c) Nasopharyngeal carcinoma T
d) Carcinoma of pancreas F
e) DIC F

Q. Epstein Barr virus infection causes: (BSMMU – MD/MS - January, 2009)
a) Latency in sacral ganglia F
b) Immortalization of B lymphocytes T (Latency in B lymphocyte)
c) Kaposi's sarcoma F
d) Infectious mononucleosis T
e) Heterophil antibody production T

Q. The Epstein Barr virus is associated with – (MD/MS (DMC)-08Ja)
a) nasopharyngeal carcinoma T
b) nasopharyngeal angiofibroma F
c) maxillary carcinoma F
d) glandular fever T
e) Burkitt's lymphoma T

Q. Diseases associated with EB virus infection are: (BSMMU - Basic Science:M. Phil, DIpoma,July-'07)
a) Burkitt's lymphoma T
b) Carcinoma of the cervix uteri F
c) Nasopharyngeal carcinoma T
d) T-cell lymphoma T (ref: Robbin's-9th, P-327)
e) Hepatocellular carcinoma F

Q. The Epstein Barr virus is associated with - (BSMMU - M. Phil, Diploma, July-06)
a) Glandular fever T
b) Burkitt's lymphoma T
c) Carcinoma cervix F
d) Nasopharyngeal carcinoma T
e) Mantle cell lymphoma F

Q. Epstein Barr virus causes- (BSMMU – MD - 06Ja)

A. Burkitts lymphoma T
B. nasopharyngeal carcinoma T
C. carcinoma of uterine cervix F
D. bronchogenic carcinoma F
E. prostatic carcinoma F

Q. Infectious mononucleosis- (MD/MS (DMC)-04Ja)

a) Is caused by Ebstein Barr virus T
b) Incubation period is from 4-7 weeks. T
c) Heterophil antibody forms T
d) Relative & absolute lymphocytosis occurs. T
e) Is common in old people F *(common in children, adolescent, early adults)*

HELP LINK:

INFECTIOUS MONONUCLEOSIS (IM)

- Infectious mononucleosis (IM) is a clinical syndrome characterised by pharyngitis, cervical lymphadenopathy, fever and lymphocytosis (known colloquially as glandular fever).
- It is most often caused by Epstein–Barr virus (EBV) but other infections can produce a similar clinical syndrome.
- EBV is a gamma herpesvirus. In developing countries, subclinical infection in childhood is virtually universal.
- In developed countries, primary infection may be delayed until adolescence or early adult life.
- Under these circumstances, about 50% of infections result in typical IM. The virus is usually acquired from asymptomatic excreters via saliva, either by droplet infection or environmental contamination in childhood, or by kissing among adolescents and adults.
- EBV is not highly contagious and isolation of cases is unnecessary.

Clinical features

- EBV infection has a prolonged but undetermined incubation period, followed in some cases by a prodrome of fever, headache and malaise.
- This is followed by IM with severe pharyngitis, which may include tonsillar exudates and non-tender anterior and posterior cervical lymphadenopathy.
- Palatal petechiae, periorbital oedema, splenomegaly, inguinal or axillary lymphadenopathy, and macular, petechial or erythema multiforme rashes may occur.
- In most cases, fever resolves over 2 weeks, and fatigue and other abnormalities settle over a further few weeks.
- Death is rare but can occur due to respiratory obstruction, haemorrhage from splenic rupture, thrombocytopenia or encephalitis.
- The diagnosis of EBV infection outside the usual age in adolescence and young adulthood is more challenging. In children under 10 years the illness is mild and short-lived, but in adults over 30 years of age it can be severe and prolonged.

In both groups, pharyngeal symptoms are often absent. EBV may present with jaundice, as a PUO or with a complication.

Long-term complications of EBV infection Lymphoma complicates EBV infection in immunocompromised hosts, and some forms of Hodgkin lymphoma are EBV-associated. The endemic form of Burkitt's lymphoma complicates EBV infection in areas of sub-Saharan Africa where *falciparum* malaria is endemic. Nasopharyngeal carcinoma is a geographically restricted tumour seen in China and Alaska that is associated with EBV infection. X-linked lymphoproliferative (Duncan's) syndrome is a familial lymphoproliferative disorder that follows primary EBV infection in boys without any other history of immunodeficiency;

Investigations

- Atypical lymphocytes are common in EBV infection but also occur in other causes of IM, acute retroviral syndrome with HIV infection, viral hepatitis, mumps and rubella.

- A 'heterophile' antibody is present during the acute illness and convalescence, which is detected by the Paul–Bunnell or 'Monospot' test. (A heterophile antibody is an antibody that has affinity for antigens other than the specific one, in this case animal immunoglobulins; the Paul–Bunnell and Monospot tests exploit this feature by detecting the ability of test serum to agglutinate sheep and horse red blood cells, respectively.).
- Sometimes antibody production is delayed, so an initially negative test should be repeated. However, many children and 10% of adolescents with IM do not produce heterophile antibody at any stage.
- Specific EBV serology confirms the diagnosis. Acute infection is characterised by IgM antibodies against the viral capsid, antibodies to EBV early antigen and the initial absence of antibodies to EBV nuclear antigen (anti-EBNA).
- Seroconversion of anti-EBNA at approximately 1 month after the initial illness may confirm the diagnosis in retrospect. CNS infections may be diagnosed by detection of viral DNA in CSF.

Management

- Treatment is largely symptomatic.
- If a throat culture yields a β-haemolytic streptococcus, penicillin should be given.
- Administration of **ampicillin or amoxicillin** in this condition commonly causes an itchy macular rash and should be avoided.
- When pharyngeal oedema is severe, a short course of **glucocorticoids**, e.g. prednisolone 30 mg daily for 5 days, may help.
- Current antiviral drugs are not active against EBV.

Return to work or school is governed by physical fitness rather than laboratory tests; contact sports should be avoided until splenomegaly has resolved because of the danger of splenic rupture. Unfortunately, about 10% of patients with IM suffer a chronic relapsing syndrome.

(Ref: Davidson-23rd, P-241-242)

Q. Epstein Barr virus may cause: (MD/MS (DMC)-02Ja)

A. Nasopharyngeal carcinoma T
B. Oral hairy cell leucoplakia in AIDS patients T
C. Burkitt,s lymphoma T
D. Hairy cell leukaemia F
E. Infectious mononucleosis T

Cytomegalovirus

Q. The following are true for Cytomegalovirus (CMV): *(BSMMU – MD/MS (Residency) –11 Ja)*

a) transmitted by the respiratory route.
b) an infectious mononucleosis-like syndrome may occur during primary infection.
c) may cause severe infection in immuno-compromised individuals
d) fetal and newborn infections may be severe
e) it is teratogenic.

Ans. a) T b) T c) T d) T e) T

HELP LINK:

Important Properties:

- It has a single serotype.
- Humans are the natural hosts;
- Animal CMV strains do not infect humans.
- Giant cells are formed, hence the name *cytomegalo.* The virus is called cytomegalovirus because the infection become enlarged in size.
- EBV latent within B lymphocyte.

Transmission:

1. From mother to baby-
   a. Transplacental
   b. From birth canal of infected mother during delivery of fetus.
   c. Breast milk

2. In children through saliva.
3. In adult through sexual contact
4. In all age group through blood transfusion and organ transplantation.

- **Pathogenesis & Immunity:**
  - Cytomegalic inclusion disease(in fetus): Multinucleated giant cells with prominent intranuclear inclusions
  - Infections of children and adults are usually asymptomatic, except in immunocompromised individuals.
  - Latent state primarily in monocytes and bone marrow progenitors and can be reactivated when cell-mediated immunity is decreased.
  - It can also persist in kidneys for years.
  - It causes an immunosuppressive effect by inhibiting T cells.

Clinical features: Cytomegalic inclusion disease of infants-
Congenital anomalies:
1. Intra-uterine growth retardation
2. Jaundice
3. Hepatosplenomegaly
4. Thrombocytopenia
5. Microcephaly
6. Retinitis

Primary cytomegalovirus infection of older children and adults is usually asymptomatic, but occasionally causes a spontaneous infectious mononucleosis syndrome. The disease is characterized by malaise, myalgia, protracted fever, liver function abnormalities and lymphocytosis.

Lab. Diagnosis:
1. Detection of replicating virus, not latent viral genome by PCR.
2. Isolation and identification of viruses in cell culture.
3. Microscopical examination of clinical specimen may detect multinucleated giant cell and prominent intra-nuclear inclusions.
4. Detection of viral IgM – current infection
   Detection of viral IgG – past infection
   Four fold rise of IgG in 2 serum samples – current infection

Diagnosis of CMV infection
1. Infection is sub clinical
2. Atypical lymphocytosis less prominent
3. Negative heterophil antibody
4. Abnormal liver function tests (↑ Alkaline phosphatase)
5. Presence of CMV-specific IgM antibody

❑ **Diseases:**
- **Cytomegalic inclusion disease (congenital):**
  - congenital abnormalities in neonates:
  - microcephaly, seizures, deafness, sensoneural hearing loss
  - jaundice, and purpura(blueberry muffin"),
  - Hepatosplenomegaly, mental retardation, intra cranial calcification
  - Infected infants excrete virus in urine for many years.
- **In immunocompetent adults:**
  - heterophil-negative mononucleosis
    - fever, sore throat, lethargy, maculopapular rash, hepatomegaly, abnormal lymphocytes in peripheral blood smears,

- **In immunocompromised patients:**
  - Those with renal and bone marrow transplants):
    - Pneumonitis, esophagitis, and hepatitis.
  - In AIDS pts: infects the intestinal tract and causes intractable colitis with diarrhea, CMV retinitis lead to blindness.`

❑ **Drugs to treat CMV:**
- Gancyclovir,
- Valgancyclovir,
- Foscarnet or cidofovir

Q. Cytomegalovirus infection: (BSMMU-06Ja)
A. is more common in immunocompromised host
B. may cause impaired renal function
C. may cause impaired hepatic function
D. is more common in patients of chronic renal failure
E. can effectively be treated with acyclovir *(Ref: Kumar & Clark)*

Ans.
a) T b) F c) T
d) T *(Common following solid organ transplantation)*
e) F *(Actualy it is a self limiting disease, If Rx is required, Aciclovir is not used, ganciclovir is used in immunocompromised host)*

Q. Cytomegalovirus causes: (MD/MS (DMC)-01Ja)

A. Burkit's lymphoma.	F
B. Mononucleosis.	T
C. Interstitial pneumonia.	T
D. Eczema herpeticum.	F
E. Keratoconjuntivitis.	F

MEASLES

Q. Measles virus infection *(BSMMU – Non-Residency – MD, MS, Paediatrics, Basic Science – July' 19)*
a) results in pneumonia
b) results in encephalitis
c) undergoes antigenic drift
d) responds to acyclovir
e) is prevented by vaccination

Ans. a) T b) T c) F d) F (Meascles has no antiviral therapy) e) T (Live attenuated vaccine)
(Ref: LANGE-15th, P-313)

HELP LINK:
MEASLES
- RNA and nucleocapsid of measles virus are those of a typical paramyxovirus.
- It has a single serotype, and the hemagglutinin is the antigen against which neutralizing antibody is directed.
- Humans are the natural host.
- Incubation period of 10 to 14 days,
- Multinucleated giant cells are formed
- Lifelong immunity occurs .
- Vaccine available

Transmission & Epidemiology:

- respiratory droplets
- malnourished children has much more serious disease
- Vitamin A supplementation greatly reduces the severity of measles.
- Deficient CMI (e.g., AIDS patients) have a severe, life threatening disease.

Clinical features:

- Incubation period of 14 days to onset of rash.
- fever, conjunctivitis (causing photophobia),
- running nose, and coughing occurs.
- Koplik's spots are bright red lesions with a white, central dot that are located on the buccal mucosa and are virtually diagnostic.
- maculopapular rash appears on the face and proceeds gradually down the body to the lower extremities, including the palms and soles
- The rash develops a brownish hue several days later.

Complication of measles:

- Giant cell pneumonia
- Secondary bacterial pneumonia
- Otitis media
- Diarrhoea, hypocalcaemia, hepatitis
- Cancrum oris
- Acute demyelinating encephalitis (mortality 10%)
- Subacute sclerosing panencephalitis (SSPE)
- In immunocompromised pt: Inclusion body encephalitis
- In pregnant women increased risk of still birth

❑ Fetal Infection is more severe than rubella
❑ Fetal death may occur
❑ cong malformation never occurs by measles **(Ref. P chakraborti-3rd, P-580)**

Q. Complication of measles are *(BSMMU –Residency - **Paediatrics** – March' 19)*
a) Otitis media
b) Diarrhea
c) Pancreatitis
d) Vit A deficiency
e) Deafness Ans. a) T b) T c) F d) T e) F

Q. Infection with the measles virus - *(BSMMU – Non-Residency – MD, MS, Basic Science & Dentistry – July' 17)*
a) can cause pneumonia
b) can cause encephalitis
c) undergo antigenic drift
d) can respond to acyclovir
e) causes infection immunity
Ans. a) T b) T c) F d) F (no antiviral therapy is available) e) T

Q. Infection with the Measles virus: *(BSMMU – M. Phil, Diploma (Non-Residency)–March-2012, DMC & others – MD/MS – March-2012, BSMMU – MD –11Ja)*

a) may result in pneumonia	T
b) may result in encephalitis	T
c) undergo antigenic drift	F
d) may respond to acyclovir	F
e) may be prevented by vaccination	T

Rubella (German measles)

Q. Congenital condition/s caused by rubella is/are (BSMMU –Residency – MD – March' 18)
a) pulmonary artery stenosis
b) tetralogy of Fallot
c) retinopathy
d) micro-ophthalmia
e) duodenal atresia
Ans. a) T b) T c) T d) T e) F

HELP LINK:

Rubella virus

Important characteristics:
- Member of the togavirus family.
- single-stranded RNA,
- I. P: 14-21 days
- an icosahedral nucleocapsid,
- a lipoprotein envelope.
- has no virion polymerase.
- Its surface spikes contain hemagglutinin.
- The virus has a single antigenic type.
- Antibody against hemagglutinin neutralizes infectivity.
- Humans are the natural host

Transmission & Epidemiology:
- respiratory droplets
- Transplacental.

Diseases:
1. Rubella or German measles (syndrome)
2. Congenital rubella syndrome

Pathogenesis & Immunity:
- Replication occurs in the nasopharynx and local lymph nodes then spreads via the blood to the internal organs and skin.
- The origin of the rash is unclear; it may be due to antigen/antibody–mediated vasculitis.
- Natural infection leads to lifelong immunity.
- Second cases of rubella do not occur;
- similar rashes are caused by Coxsackie viruses and echoviruses.
- Antibody crosses the placenta and protects the newborn.

Clinical features:
- Fever and malaise followed by a maculopapular rash starts on the face and progresses downward to involve the extremities
- Posterior auricular lymphadenopathy is characteristic.
- Also suboccipital lymphadenopathy is present
- Petechiae on the soft palate(Forchheimers sign)
- The rash typically lasts 3 days.
- When rubella occurs in adults women, polyarthritis caused by immune complexes often occurs

Rubella: It is a milder, shorter disease than measles. After an incubation period of 14-21 days, a brief prodromal period with fever and malaise is followed by a maculo-papular rash, which starts on the face and progresses downward to involve the extremities. Posterior auricular lymphadenopathy is characteristic. The rash typically

lasts 3 days. When rubella occurs in adults, especially women, polyarthritis caused by immune complexes often occurs.

■ **Congenital rubella syndrome**: A pregnant woman is infected with rubella virus in 1st trimester of gestation → Virus may pass to the foetus through placenta → teratogenesis: **(Congenital rubella syndrome)**

1. Heart - Patent ductal arteriosus, aortic stenosis, pulmonary stenosis.
2. Eye – Congenital cataract, glaucoma.
3. Ear – Congenital deafness.
4. GIT- Hepatospenomegaly.
5. Brain – mental retardation
6. Others- jaundice, anaemia.

■ It never occurs in adults.

Complication of rubella:

- Rubella encephalopathy about six days after the rash
- Arthritis in adult women
- Thrombocytopenia
- GBS

Lab. Diagnosis:

1. Detection of anti-rubella IgM in serum indicates recent infection.
2. Four fold rise of anti-rubella IgG in 4 fold rise in serum sample.
3. Isolation & identification of virus by tissue culture.

Prevention: By vaccination – MMR vaccine. It is a live, attenuated vaccine. It is given to unimmunized young adult women. If they are not pregnant, they will use contraception for next 3 months.

More information:

Congenital rubella syndrome: The significance of rubella virus is not as a cause of mild childhood disease but as a teratogen. When a nonimmune pregnant woman is infected during the first trimester, especially the first month, significant congenital malformations can occur as a result of maternal viremia and fetal infection. The increased rate of abnormalities during the early weeks of pregnancy is attributed to the very sensitive organ development that occurs at that time. The malformations are widespread and involve primarily the heart (e.g. patent ductus arteriosus), the eyes (e.g. cataracts) and the brain (e.g. deafness and mental retardation).

In addition, some children infected in utero can continue to excrete rubella virus for months following birth, which is a significant public health hazard because the virus can be transmitted to pregnant women. Some congenital shedders are asymptomatic and without malformations and hence can be diagnosed only if the virus is isolated. Congenitally infected infant also have significant IgM titers and persistent IgG titers long after maternal antibody has disappeared.

Q. Congenital abnormalities caused by rubella virus are *(BSMMU –Residency - MS, Basic science – March' 14)*

a) cataract T
b) patent ductus arteriosus T
c) macrophthalmia F
d) conductive deafness F (Sensorineural hearing deafness)
e) glucoma T

(Ref. LANGE Review-15th, P-314)

Q. Rubella virus *(BSMMU –Residency – MS, Basic science – March' 14)*

a) cause a vesicular rash
b) is teratogenic
c) causes congenital defects in eye, ear and heart
d) produces specific antibody in the cord blood which helps to diagnose congenital infection
e) persistence congenital rubella in infants does not poses a risk

Ans. a) F b) T c) T d) T e) F

Q. Congenital rubella results in: *(BSMMU - M. Phil, Diploma – July '10)*

a) deafness T
b) cataract T
c) glaucoma T
d) microcephaly T
e) phocomelia F

HELP LINK:

Congenital rubella syndrome is associated with the following abnormalities:

- Sensory neural deafness
- Thrombocytopenia
- Anaemia
- Retinopathy
- Septal defects & FDA
- Chromosomal abnormalities
- Osteopathy
- Oculopathy (cataract, cloudy cornea)
- Liver & spleen enlargement
- (Hepatosplenomegaly & Jaundice).

Q. Common manifestations of rubella embryopathy are - (DMC – MD/ MS - January, 2010)

a. growth retardation T
b. infantile autism T
c. diabetes mellitus T
d. hypothyroidism T
e. hearing loss T

HELP LINK:

Common manifestations of rubella embryopathy:

- Growth retardation, < 2500 gm at birth,microcephaly
- 35% congenital cataract, 90% hearing loss, 5% congetal glaucoma
- 10-20% active meningoencephalitis
- 30% cardiac defects (PDA, pulmonary artery stenosis, VSD)
- Other features: pneumonitis, hepatitis, purpura, infantile autism, diabetes or thyroid dysfunction, progreesive rubella encephalitis.

(ref: M. R. khan-3rd , P-630)

Q. Congenital rubella results in - (BSMMU - M. Phil, Diploma, July-04)

A. deafness T
B. cataract T
C. glaucoma T
D. macrocephaly F *(Microcephaly)*
E. phocomelia F

Q. The following are recognized features of Rubella: (BSMMU – MD/MS - 00Ja)

A. Koplik's sports F
B. Conjunctivitis F
C. Suboccipital lymph node enlargement T
D. Thrombocytopenia T
E. Rashes on the 5 day of illness F *(Coinciding with onset of illness)*

Rabies virus

- **Important Properties:**
  - rhabdovirus family.
  - single-stranded RNA enclosed within a bullet-shaped capsid surrounded by a lipoprotein envelope.
  - contains an RNA-dependent RNA polymerase.
  - Rabies virus has a single antigenic type.
  - The antigenicity resides in the envelope glycoprotein spikes.
  - Rabies virus has a broad host range

- **Transmission & Epidemiology:**
  - bite of a rabid animal that manifests aggressive,
  - biting behavior induced by the viral encephalitis.
  - The virus is in the saliva of the rabid animal
  - Rodents and rabbits do not transmit rabies
  - exposure to aerosols of bat secretions
  - transplants of corneas
- **Pathogenesis & Immunity:**
  - multiplies locally at the bite site, infects the sensory neurons, and moves by axonal transport to the CNS.
  - During transporation. It is sheltered from the immune system and multiplies and travel to salivary glands and other organs.
  - no viremic stage occurs .
  - encephalitis develops, with the death of neurons and demyelination.
  - Infected neurons contain an eosinophilic cytoplasmic inclusion called a Negri body, which is important in laboratory diagnosis of rabies
- **Disease:** Rabies/ Acute viral fulminating encephalitis.
- **Clinical Findings:**
  - I. P: 1-2 months, may upto 6 yrs(but may be less than 7 days). It is shorter when bites are sustained on the head rather than on the leg, because the virus has a shorter distance to travel to reach the CNS.
  - fever, anorexia, and changes in sensation at the bite site called paresthesias.
  - "furious" (encephalitic) or "dumb" (paralytic).
  - The furious form occurs in about 80% of cases.
  - In the furious form, agitation, delirium, seizures, and hydrophobia occur.
  - dumb form: symptoms do not occur. The spinal cord is primarily involved, and an ascending paralysis occurs.
  - Death almost invariably occurs following both forms, but may sustain with advent of life support.
  - Cause of death in rabies: Respiratory failure due to respiratory arrest produced by destruction of respiratory neurons

- ❑ **Street virus**: comes from dog
- ❑ **Fixed virus:** after changing

Street virus	Fixed virus
Freshly isolated from clinical specimen	Produced by serial brain to brain passage of the street virus in to the susceptible animal.
Multiply slowly	Multiply rapidly
I. P: Long and variable(21-60 days in dogs)	Short and relatively fixed.
Can multiply both in neuron and extraneuronal tissue	Only in neurons
Rapid production of intracytoplasmic eosinophilic inclusion body	Same but much difficulty

Prevention:

- The human diploid cell vaccine (HDCV) is preferred.
- In Bangladesh, Chick embryo vaccine (Rabipur) is used.
- rabies vaccine contains inactivated virus grown in human diploid cells. (Vaccine grown in monkey lung cells or chick embryo cells is also available.)
- duck embryo vaccine or various nerve tissue vaccines are available as well.It has low immunogenicity,
- nerve tissue vaccines can cause an allergic encephalomyelitis as a result of a cross-reaction with human myelin.
- There are preexposure and postexposure immunization.
- Preexposure vaccine: should be given in high-risk groups, dose on days 0, 7, and 21 or 28. Booster doses are given as needed to maintain an antibody titer of 1:5.
- **Post exposure vaccine:**
  - Used routinely, The long incubation period gives time to vaccine to induce protective immunity, both the vaccine and human rabies immune globulin (RIG, obtained from hyperimmunized persons) plus immediate cleaning of the wound.
  - When given:
    - (1) When all wild animal attacks
    - (2) whether animal is available to be observed to produce symptoms;
    - (3) whether rabies is endemic in the area.
- This is an example of passive–active immunization.
- Tetanus immunization should also be considered.
- Hospital personnel exposed to a patient with rabies need not be immunized unless a significant exposure has occurred (e.g., a traumatic wound to the health care worker).
- Five doses of HDCV are given (on days 0, 3, 7, 14, and 28),
- RIG is given only once with the first dose of HDCV (at a different site).
- HDCV and RIG are given at different sites to prevent neutralization of the virus in the vaccine by the antibody in the RIG.
- RIG is given into the bite site, and the remainder is given intramuscularly.
- **For animal:**
  - should observed for 10 days for symptoms development.
  - The brain of the animal should be examined by immunofluorescence.
  - The vaccine for immunization of dogs and cats consists of inactivated rabies virus.
  - The first immunization is usually given at 3 months of age, with booster doses given either annually or at 3-year intervals.

Laboratory Diagnosis

- **Sample:** Brain, Cornea, saliva, spinal fluid, Skin biopsy from back of the neck.
- **From animal:**
  - PCR: For brain tissue.
  - fluorescent antibody to rabies virus,
  - histologic staining of Negri bodies in the cytoplasm of hippocampal neurons
  - The virus can be isolated from the animal brain by growth in cell culture.
- **From human:**
  - PCR assay;
  - fluorescent antibody
  - staining of a biopsy specimen, usually taken from the skin of the neck at the hairline;
  - by isolation of the virus from saliva, spinal fluid, and brain tissue;
  - rise in titer of antibody to the virus.
  - Negri bodies can be demonstrated in corneal scrapings and in autopsy specimens of the brain.

Question Bank

Q. Post exposure prophylaxis Vaccination are recommended in *(BSMMU –Residency - MD/MS, Basic science, Paediatrics, Dentistry – March' 19; Residency – MD, MS, Basic Science – March' 18; Non-Residency – MD, MS, Basic Science & Dentistry – July' 17))*

a) Hepatitis A virus infection
b) Hepatitis B virus infection
c) Human Immunodeficiency virus infection
d) rubella
e) rabies

Ans. a) T b) T c) F d) F e) T

Help Link:

Commonly used post-exposure prophylaxia: Rabies, HAV, HBV, HCV, HIV, Tetanus

Post exposure prophylaxis by vaccine: Rabies, HAV, HBV, Tetanus

Q. Which of the following statements about rabies vaccines for human use is true? *(BSMMU –Residency - MS, Basic science – March' 14)*

a) contains live attenuated rabies virus
b) may cause allergic encephalitis when prepared from nerve tissue
c) duck embryo vaccine is highly antigenic and only a single dose is needed
d) contain multiple antigenic types of rabies virus
e) human diploid cell vaccine requires fewer doses

Ans. a) F b) T c) F
d) F (Rabies virus has a single antigenic type) e) T

HELP LINK: **Rabies immune globulin (RIG)** is used in the prevention of rabies in people who may have been exposed to the virus. It is administered by injecting as much RIG as possible into the tissue at the bite site and the remainder is given intramuscularly. The preparation contains a high titer of antibody made by hyperimmunizing human volunteers with rabies vaccine. RIG is obtained from humans to avoid hypersensitivity reactions. In addition to RIG, the vaccine containing killed rabies virus made in human diploid cells should be given. RIG and the vaccine should be given at different sites. This is an example of passive-active immunization.

Q. Following statements regarding human rabies vaccine are correct: *(BSMMU – Residency – MD/MS – March'13)*

a) Contains live attenuated rabies virus
b) Contains multiple antigenic types of rabies virus
c) May cause allergic encephalitis when prepared from nerve tissue
d) Duck embryo vaccine is highly antigenic and only a single dose is needed
e) Can be used for both pre and post exposure prophylaxis

Ans : a) F b) F c) T d) F e) T

Q. Following statements are applicable for Rabies virus infection: (BSMMU – MS - January, 2010)

a) all warm blooded animals including human are hosts for rabies virus T
b) the virus can be isolated from the blood of infected person F
c) a definitive pathogenic diagnosis can be based on the finding of 'Negri body' T
d) virus multiplies in muscle or connective tissue at the site of inoculation F
e) there are two antigenic types of Rabies virus F

Q. Fixed rabies virus is associated with: (BSMMU - M. Phil, Diploma, July-07)

a) long incubation period F
b) incubation period of 7 days T
c) exhaustive production of negri body T
d) production of antirabies vaccine T
e) exclusive neurotransmission T

Q. Wild rabies virus can grow in: (M. Phil, Diploma, July-08)
a) nerve cell
b) epithelial cell
c) fibroblast
d) Minimum Essential Medium (MEM)
e) stem cell
Ans. a) T b) T c) F d) F e) F

Congenital infection

Q. Microbial agents that may cause congenital infections are *(BSMMU – Non-Residency – **MD, MS, Paediatrics, Basic Science, Dentistry** – July' 19)*
a) Cytomegalovirus
b) Treponema pallidum
c) Toxoplasma gondii
d) Streptococcus agalactiae
e) Influenza A virus
Ans. a) T b) T c) T d) T e) F

(Ref: Davidson-23rd, P-235)

Q. Viruses that have teratogenic effects are *(BSMMU –Residency - **MD/MS, Basic science, Paediatrics** – March' 19)*
a) Rubella virus
b) Cytomegalovirus
c) Human papilloma virus
d) Parvovirus
e) Rhinovirus
Ans. a) T b) T c) F d) T e) F

(Ref. Lange-14th, P-34)

HELP LINK:

Table: Taratogens causing congenital malformations:

Teratogen	Congenital malformations
Infectious agents	
Rubella virus	Cataracts, glaucoma, heart defects, deafness, teeth.
Cytomegalovirus	Microcephaaly, blindness, mental retardation, fetal death
Herpes simplex virus	Microphthalmia, microcephaly, retinal dysplasia
Varicella virus	Limb hypoasia, mental retardation, muscle atropy
HIV	Microcealy, growth retardation
Toxoplasmosis	Hrocephalus, cerebral calcifications, microthalmia
Syphilis	Mental retardation, deafness
Physical agents	
X-rays	Microcephaly, spina bifida, cleft palate, limb defects
Hyperthermia	Anencephaly
Chemical agents	
Thalidomide	Limb defects, heart malformations
Aminopterin	Anencephaly, hrocephaly, cleft lip and palate
Diphenyihydantoin (phenytoin)	Fetal hydantoin syndrome: facial defects, mental retardation
Valproic acid	Neural tube defects, heart, craniofacial, and limb anomalies
Trimethadione	Cleft palate, heart defects, urogenital and skeletal abnormalities
Lithium	Heart malformations
Amphetamines	Cleft lip and palate, heart defects
Warfarin	Chondrodysplasia, microcephaly
ACE inhibitors	Growth retardation, fetal death

Cocaine	Growth retardation, microcephaly, behavioral abnormalities, gastroschisis
Alcohol	Fetal alcohol syndrome, short palpebral fissures, maxilary hypoplasia, heart defects, mental retardation
Isotretinoin (vitamin A)	Vitamin-A embryopathy: small, abnormally shaped ears, mandibular hypoplasia, cleft palate, heart defects.
Organic mercury	Neurological symptoms similar to those of cerebral palsy
Lead	Growth retardation, neurological disorders
Hormones	
Androgenic agents (ethisterone, norethisterone)	Masculinization of female genitalia: fused labia, clitoral hypertrophy
Diethylstilbestrol (DES)	Malformation of the uterus, uterine tubes, and upper vagina; vaginal cancer; malformed testes
Maternal diabetes	Variety of malformations; heart and neural tube defects most common

Q. Which of the following viruses responsible for congenital infection? (BSMMU - M. Phil, Diploma, July'09)

a) Epstein— Barr virus F
b) Cytomegalovirus T
c) Varicella zoster virus T
d) Herpes simplex virus T
e) Hepatitis B virus F

Q. Following viruses can cause congenital malformations - (MD/MS (DMC)-09Ja)

a. Epstein Barr virus F
b. Hepatitis B virus F
c. Rubella virus T
d. HIV T
e. Cytomegalo virus T

Q. Agents which can cause congenital anomaly in foetus are- (BSMMU – MS - January, 2007)

a. Toxoplasma T
b. CMV T
c. Rubella virus T
d. Dengue virus F
e. Adenovirus F

Q. Viruses causing congenital infection are: (M. Phil, Diploma (DMC)-05July)

a) Herpes simplex T
b) Rubelle virus T
c) Rabies viruses F
d) Hepatitis-B viruse T
e) Dengue viruses F

Others

Q. Viruses responsible for causing common cold are: (BSMMU – MS - January, 2010)

a) influenza virus T
b) parainfluenza virus T
c) adenovirus T
d) rhinovirus T
e) coronavirus T

HELP LINK:

Rhinovirus, Corona virus, adenovirus, enterovirus, parainfluenza, influenza causes infection of the upper respiratory passage including common cold syndrome.

Features of Viruses that Infect the Respiratory Tract.[1]						
Virus	Disease	Number of Serotypes	Lifelong Immunity to Disease	Vaccine Available	Viral Latency	Treatment
RNA viruses						
Influenza virus	Influenza	Many	No	+	–	Amantadine rimantidine, oseltamivir, zanamivir
Parainfluenza virus	Croup	Many	No	–	–	None
Respiratory syncytial virus	Bronchiolitis	One	Incomplete	–	–	Ribavirin
Rubella virus	Rubella	One	Yes	+	–	None
Measles virus	Measles	One	Yes	+	–	None
Mumps virus	Parotitis, meningitis	One	Yes	+	–	None
Rhinovirus	Common cold	Many	No	–	–	None
Coronavirus	Common cold, SARS[2]	Three	No	–	–	None
Coxsackievirus	Herpangina, pleurodynia, myocarditis	Many	No	–	–	None
DNA viruses						
Herpes simplex virus type 1	Gingivostomatitis	One	No	–	+	Acyclovir in immunodeficient patients
Epstein-Barr virus	Infectious mononucleosis	One	Yes	–	+	None
Varicella-zoster virus	Chickenpox, shingles	One	Yes[3]	–	+	Acyclovir in immunodeficient patients
s	Pharyngitis, pneumonia	Many	No	+[4]	+	None

[1]Influenza virus, parainfluenza virus, respiratory syncytial virus, rubella virus, measles virus, mumps virus, and coronavirus are enveloped RNA viruses and are described in this chapter. [2]SARS is severe acute respiratory syndrome.
[3]Lifelong immunity to varicella (chickenpox) but not to zoster (shingles).[4]For military recruits only.

a) labyrinthitis T
b) thyroiditis T
c) oropharyrgitis F
d) pancreatitis T
e) encephalitis T

HELP LINK: CNS involvement is the most common extrasalivary gland manifestation of mumps. Clinical meningitis occurs in 5% of all infected patients, and 30% of patients with CNS involvement have no evidence of parotid gland involvement. Epididymoorchitis develops in about one-third of patients who develop mumps after puberty. Bilateral testicular involvement results in sterility in only a small percentage of these patients. Pancreatitis, oophoritis, myocaditis, mastitis, hepatitis and polyarthritis may also occur.

Q. The following viruses can be inactivated by detergent: (BSMMU - M. Phil, Diploma, July-08)
a) human immunodeficiency virus T
b) hepatitis A virus F
c) hepatitis B virus T
d) poliomyelitis virus F
e) rabies virus T

Q. The following viruses cause vesicular rashes (MD/MS (DMC)-08Ja)
a) herpes simplex T
b) measles F
c) rubella F
d) Varicella-zoster T
e) Ebstein-Barr F

Q. Virus capable of causing anterior horn cell disease include: (M. Phil, Diploma (DMC)-07July)

a) varicella T
b) entero virus F
c) polio virus T
d) Epstein Barr virus F
e) herpes simplex virus T

Q. Post exposure vaccination is effective in viral diseases: (DMC - M. Phil, Diploma-05July)

a) Polio F
b) Measles F
c) Rabies T
d) Rubella F
e) Hepatitis B T

HELP LINK:

Measles: Standard human immune globulin is recommended for exposed infants and adults with normal immunocompetence (but with a contraindication to measles vaccine) and for immunocompromised patients exposed to measles (regardless of immunization status). Patients should be actively immunized 3 to 6 months after immunoglobulin administration.

Rubella: Efficacy is unreliable. Therefore, standard human immune globulin is recommended for administration only to antibody-negative pregnant women in the first trimester who have a documented rubella exposure and will not consider terminating the pregnancy.

Tetanus: Human tetanus immune globulin (TIG) has replaced equine tetanus antitoxin because of the risk of serum sickness with equine serum.

Rabies: Human rabies immune globulin (RIG) is preferred over equine rabies antiserum because of the risk of serum sickness with equine serum. RIG or antiserum is recommended for nonimmunized individuals with animal bites in whom rabies cannot be ruled out and with other exposures to known rapid animals.

Hepatitis A: Standard immune serum globulin is given in a single dose of 0.02 - 0.04 ml/ Kg of (for continuous exposure) in a dose up to 0.06 ml/ kg every 5 months. Postexposure treatment with hepatitis A immune globulin has not been studied.

Q. The incubation period is ten days or less in: (DMC - M. Phil, Diploma, July-05)

a) falciparum malaria F (10 – 15 days)
b) rubella F (15 – 20 days)
c) scarlet fever T (2 – 4 days)
d) chicken pox F (11 – 20 days)
e) measles F (6 – 19 days) **(Ref: Davidson-23rd)**

Q. Viruses which infect nervous system are - (BSMMU - M. Phil, Diploma, July-05)

A. dengue virus
B. polio virus
C. bunya virus
D. cytomegalo virus
E. varicella zoster virus

Ans.

a) F
b) T *(It has special propensity for anterior horn cells of spinal cord)*
c) T *(It causes encephalitis and Korean hemorrhagic fever)*
d) F
e) T *(It probably remain in the dorsal root ganglia following recovery from chicken pox)*

Q. The following viruses are likely to cause chronic or latent Infection: (BSMMU - M. Phil, Diploma, 04Ju)

A. Corona virus F
B. Herpes virus T
C. Hepatitis A virus F
D. Hepatitis B virus T
E. Adeno Virus T

A. **False** (No long term sequelae)
B. **True** (Herpes zoster or shingles may develop after a long time of development of chicken pox)
C. **False** (Never causes chronicity)
D. **True** (May cause chronic liver disease)
E. **True** (In addition to acute infection leading to death of the cells, adenoviruses cause a talent infection, particularly in the adenoid and tonsillar tissues of the throat.) **(REF: LANGE-12th)**

Q. Following micro-organism invade CNS via peripheral nerve - (BSMMU - M. Phil, Diploma, July-04)

A. Herpes simplex virus F
B. Varicella zoster virus F
C. Rabies virus T
D. Clostridium tetani T
E. Clostridium botulinum F

HELP LINK:

■ Rabies virus multiplies locally at the bite site, infects the sensory neurons and moves by axonal transport to the CNS.

■ Clostridium tetani produces an exotoxin. This toxin is produced at the wound site & this polypeptide toxin is carried intra axonally to the CNS where it binds to the ganglioside receptors & blocks release of inhibitory mediators e.g. glycine at spinal synapses.

Q. Viruses which invade central nervous system include- (BIRDEM-04)

a) Polio virus T
b) Measles virus T
c) Varicella zoster virus T
d) Herpes simplex virus T
e) Rabies virus T

HEPATITIS VIRUSES

Q. Infection with hepatitis E virus *(BSMMU –Residency - **MD/MS, Basic science, Paediatrics, Dentistry** – March' 19)*

a) occurs more often in developed countries
b) occurs in epidemic forms in developing countries
e) has a higher incidence rate in children
d) has a higher mortality rate in pregnant women
e) animal strains of HEV are common in western world

Ans. a) F b) T c) F(pregnant lady) d) T e) F (developing country)

Help Link:

Epidemiology of HEV:

- ✓ Occurs primarily in young to middle-aged adults.
- ✓ is a zoonotic disease with animal reservoirs, such as monkeys, cats, pigs, and dogs.
- ✓ Epidemics have been reported in Asia and the Indian subcontinent, most commonly seen in developing countries.
- ✓ Sporadic infection may also occur in travelers to these regions.
- ✓ Chronic HEV infection does occur in patients with AIDS and immunosuppressed transplant patients.
- ✓ Enterically transmitted non-A non-B hepatitis virus (NANBH), family Calciviridae, nonenveloped, similarities with HAV.

✓ causes an acute, self-limiting disease.
✓ The incubation period : 2 to 9 weeks (4 to 5 weeks, Accor. to Robbins) with an average of 35 days.

(Ref. Subash chandra parija 558+Robbins-9th)

Q. Severe infection with hepatitis E virus are seen in *(BSMMU – Residency - MD, MS, Basic Science - March' 17)*
a) children
b) adult
c) infants
d) pregnant women
e) both infant and children
Ans. a) F b)F c) F d)T e)F

Q. Hepatitis virus can be transmitted by blood transfusion are *(BSMMU – Non-Residency – MD, MS, Basic science, Dentistry – July' 16)*
a) hepatitis B virus T
b) hepatitis E virus F
c) hepatitis C virus T
d) hepatitis A Virus T
e) hepatitis D virus T

Help link:
d) HAV is rarely transmitted by blood

(Ref: LANGE-13th edition)

22.34 Features of the main hepatitis viruses

	Hepatitis A	Hepatitis B	Hepatitis C	Hepatitis D	Hepatitis E
Virus					
Group	Enterovirus	Hepadnavirus	Flavivirus	Incomplete virus	Calicivirus
Nucleic acid	RNA	DNA	RNA	RNA	RNA
Size (diameter)	27 nm	42 nm	30–38 nm	35 nm	27 nm
Incubation (weeks)	2–4	4–20	2–26	6–9	3–8
Spread*					
Faeces	Yes	No	No	No	Yes
Blood	Uncommon	Yes	Yes	Yes	No
Saliva	Yes	Yes	Yes	Unknown	Unknown
Sexual	Uncommon	Yes	Uncommon	Yes	Unknown
Vertical	No	Yes	Uncommon	Yes	No
Chronic infection	No	Yes	Yes	Yes	No (except immune-compromised)
Prevention					
Active	Vaccine	Vaccine	No	Prevented by hepatitis B vaccination	No
Passive	Immune serum globulin	Hyperimmune serum globulin	No		No

*All body fluids are potentially infectious, although some (e.g. urine) are less infectious than others.

(Ref: Davidson-23rd, P-872)

Q. Investigations should be done before hepatitis B vaccination includes *(BSMMU – Residency – MD, Basic Science – March' 16; MD – January, 2010)*
a) HBsAg T
b) anti-HBs F
c) HBeAg F
d) anti HBc T
e) HBV DNA F

Q. Markers usually present in a hepatitis B carrier with chronic active hepatitis are *(BSMMU – Non-Residency - MD/MS, Basic science – 13Ju)*

a) anti-HBs F
b) HBeAg T
c) anti-HBc IgM F
d) HBV-DNA T
e) HbsAg T

Q. Chronic hepatitis is caused by: (BSMMU – MD – January, 2010)

a) Hepatitis A virus F
b) Hepatitis B virus T
c) Hepatitis C virus T
d) Hepatitis D virus T
e) Hepatitis E virus F

Q. HBsAg is detectable in serum during- (BSMMU – January, 2007)

a) Acute hepatitis-B virus infection T
b) Window period of hepatitis-B virus infection F
c) Carrier state of hepatitis-B virus infection T
d) Late incubation period of hepatitis- B virus infection T
e) The presence of anti-HBs in serum F

Q. There may be possibility of carrier state in following hepatitis viruses: (BSMMU-M. Phil, Diploma, 07Ju)

a) A virus infection F
b) B virus infection T
c) C virus infection T
d) D virus infection T
e) E virus infection F

HELP LINK:

■ **Hepatitis viruses**:

A. **Classical hepatitis viruses**:

1. Hepatitis A virus (HAV)
2. Hepatitis B virus (HBV)
3. Hepatitis C virus (HCV)
4. Hepatitis D virus (HDV)
5. Hepatitis E virus (HEV)
6. Hepatitis G virus (HGV)

B. **Others**:

1. Epstein bar virus
2. Cytomegalo virus
3. Herpes simplex virus
4. Yellow fever virus
5. Rubella virus
6. Enterovirus

	HAV	HBV	HCV	HDV	HEV
Nucleic acid	RNA	DNA	RNA	RNA	RNA
Strandedness	Single stranded	Double stranded	Single stranded	Single stranded	Single stranded
Envelope	No	Yes	Yes	Yes	No
Family	Picorna	Hepadna	Flavi virus	Delta virus	Calici virus
Ag	HA Ag	HBs Ag HBc Ag Hbe Ag	-	HD Ag	-
Ab	AntiHAV	Anti-HBs Anti-HBc	Anti-HCV	Anti-HDV	Anti-HEV
Predominate mode of transmission	Faeco-oral	Parenteral	Parenteral	Parenteral	Faeco-oral
Incubation period	2-6 weeks	2-6 months	8 weeks		
Age groups	Children	All age	All age	All age	Adult
Common disease	Infectious hepatitis	Serum hepatitis	Post-transfusional hepatitis	Delta hepatitis	Infectious hepatitis
Complication	No, except Fulminant hepatitis in a few cases	Chronic hepatitis, Cirrhosis, HCC (5-10% of case)	Chronic hepatitis, Cirrhosis, HCC (30- 50% of case)	Unknown	Fulminant hepatitis in a few cases.
Chronic carrier	No	Yes	Yes	Yes	No
Oncogenic	-	+	+	?	-
Lab diagnosis	Anti HAV IgM	HBs Ag HBe Ag Anti-HBc IgM	Anti-HCV IgM	Anti-HDV IgM	Anti-HEV IgM
Vaccine available	Yes	Yes	No	No	No
Ig useful	Yes	Yes	No	No	No

Table: Glossary of hepatitis viruses and their serologic markers.

Abbreviation	Name and Description
HAV	Hepatitis A virus (enterovirus 72), a picorflavirus (nonenveloped RNA virus).
IgM HAV Ab	IgM antibody to HAV; best test to detect acute hepatitis A.
HBV	Hepatitis B virus, a hepadnavirus (enveloped, partially double-stranded DNA vifus); also known as Dane particle.
HBsAg	Antigen found on surface of HBV, also found on noninfectious particles in patient's blood; positive during acute disease; continued presence indicates carrier state.
HBsAb	Antibody to HBsAg; provides immunity to hepatitis B.
HBcAg	Antigen associated with core of HBV.
HBcAb	Antibody to HBcAg; positive during window phase. 1gM HBcAb is an indicator of recent disease.
HBeAg	A second, different antigenic determinant in the HBV core. Important indicator of transmissibility.
HBeAb	Antibody toe antigen; indicates low transmissibility.
Non-A, non-B	Hepatitis viruses that are neither HAV nor HBV.
HCV	Enveloped RNA virus; one of the non-A, non-B viruses.
HDV	Small RNA virus with HB5Ag envelope; defective virus that replicates only in HBV-infected cells.
HEV	Nonenveloped RNA virus; one of the non-A, non-B viruses.

(Ref: LANGE Review-14th)

Q. Viral hepatitis may be caused by: (M. Phil, Diploma (DMC) - 07July)

a) coxsackie virus F
b) cytomegalo virus T
c) EB virus T
d) herpes simplex virus T
e) polio virus F

Q. There may be possibility of carrier state - (BSMMU - M. Phil, Diploma, July-06)

a) Hepatitis A Virus F
b) Hepatitis B Virus T
c) Hepatitis C Virus T
d) Hepatitis D Virus T
e) Hepatitis F Virus F

Q. A proportion of patient develop carrier state after infection by- BSMMU - MS - 06Ja)

A. Hepatitis - A virus F
B. Hepatitis - B virus T
C. Hepatitis - C virus T
D. Hepatitis - D virus T
E. Hepatitis - B virus T

Q. The following micro-organisms may cause chronic hepatitis - (M. Phil, Diploma (DMC)-05July)

a) Leptospira F
b) Delta virus T
c) Hepatitis B virus T
d) Hepatitis C virus T
e) Hepatitis E virus F

HELP LINK: See before +

Table. Important properties of hepatitis viruses.

Virus	Genome	Replication Defective	DNA Polymerase in Virion	HBsAg in Envelop	Virus Family
HAV	ssRNA	No	No	No	Picornavirus
HBV	dsDNA[1]	No	Yes	Yes	Hepadnavirus
HCV	ssRNA	No	No	No	Flavivirus
HDV	ssRNA[2]	Yes	No	Yes	Deltavirus
HEV	ssRNA	No	No	No	Calicivirus

[1] Interrupted, circular dsDNA.
[2] Circular, negative-stranded ssRNA.

(Ref: LANGE Review-14th, P-272)

Virus	Mode of transmission	Chronic Carriers	Laboratory Test Usually Used for Diagnosis	Vaccine Available	Immune Globulins Useful
HAV	fecal—oral	No	IgM HAV	Yes	Yes
HBV	Blood, sexual[1]	Yes	HBsAg, HBsAb, IgM HBcAb	Yes	Yes
HCV	Blood, sexual, at birth	Yes	HCV Ab	No	No
HDV	Blood, sexual[1]	Yes	Ab to delta Ag	No	No
HEV	fecal-oral	No	None	No	No

[1]Sexual transmission seems likely but is poorly documented. **(Ref: LANGE Review-14th, P-272)**

Q. Viruses causing chronic hepatitis are: (DMC - MD/MS - 05Ja,BSMMU-00/97Ja)

A. Hepatitis Virus A. F
B. Hepatitis virus B T
C. Hepatitis virus C T
D. Hepatitis virus D T
E. Hepatitis virus E F

Q. Hepatitis may be produced by the following- (BSMMU - MD - 05Ja)

A. Salmonella typhi F
B. Dengue virus F
C. Rabies virus F
D. Cytomegalovirus T
E. Leptospira icterophaemorrhagica T *(Jaundice is deep & liver is enlarged)*

HELP LINK:

Causes of viral hepatitis	
• Hepatitis A virus (HAV)	• Non-A-E viral hepatitis
• Hepatitis B virus (HBV)	• Cytomegalovirus
• Hepatitis C virus (HCV)	• Epstein-Bar virus
• Hepatitis D virus (HDV)	• Herpes simplex virus
• Hepatitis E virus (HEV)	• Yellow lever virus

Q. The following statements regarding hepatitis viruses are correct (M. Phil, Diploma (DMC) – 03Ju)

a) HCV is transmitted by blood, during birth and by sexual intercourse T
b) both HCV & HDV can establish a chronic carrier state T
c) There is an effective vaccine against HCV F
d) alpha interferon eradicates chronic HCV carrier state F
e) both HCV and HDV are defective RNA viruses and require concurrent HBV infection to replicate. F

Q. Apart from the hepatitis viruses, which of the following viruses may also cause hepatitis? (BSMMU – MD/MS - 02Ja)

a) Rubella Virus T
b) Yellow fever virus T
c) Adenovirus F
d) Poliovirus F
c) Cytomegalovirus T

Q. Chronic hepatitis is causes by: (BSMMU – MD/MS - 00/97Ja,DMC-05Ja)

A. Hepatitis virus A. F
B. Hepatitis virus B T
C. Hepatitis virus C T
D. Hepatitis virus D T
E. Hepatitis virus E F

Hepatitis A virus

- is a typical enterovirus classified in the picornavirus family
- Single stranded RNA genome
- Non-enveloped icosahedral nucleocapsid
- Replicates in the cytoplasm of the cell.
- It is also known as enterovirus 72.
- It has one serotype,

❑ **Transmission & Epidemiology:**
- fecal–oral route.
- rarely transmitted via blood
- Humans are the reservoir for HAV.
- Virus appears in the feces roughly 2 weeks before the appearance of symptoms,
- Children are the most frequently infected
- Risk groups: summer camps, boarding schools. oysters grown in polluted water and eaten raw.
- level of viremia is low and chronic infection does not occur.

❑ The detection of IgM antibody is the most important test
❑ Active immunization,
❑ Passive immunization with immune serum globulin prior to infection or within 14 days after exposure can prevent or mitigate the disease

Hepatitis B

Properties of HBV:

- Hepadnavirus family.
- enveloped virion,
- partially double-stranded circular DNA genome
- surface antigen (HBsAg), important for laboratory diagnosis and immunization.
- Within the core is a DNA-dependent DNA polymerase.
- The genome contains four genes that encode five proteins; namely, the S gene
- encodes the surface antigen, the C gene encodes the core antigen and the e antigen, the P gene encodes the polymerase, and the X gene encodes the X protein (HBx).
- HBx is an activator of viral RNA transcription and may be involved in oncogenesis
  - it can inactivate the p53 tumor suppressor protein.

Transmission & Epidemiology:
- blood, during sexual intercourse, and perinatally from mother to newborn.
- HBV infection is especially prevalent in addicts who use intravenous drugs.
- HBV is found in semen and vaginal fluids,
- Transmission from mother to child during birth is another important natural route.
- Transplacental transmission is rare.
- No evidence of transmission breast feeding.

Pathogenesis & Immunity:
- HBV itself does not cause a cytopathic effect
- Antigen–antibody complexes cause some of the early symptoms (e.g., arthralgias, arthritis, and urticaria)
- Complications in chronic hepatitis:
  - glomerulonephritis, cryoglobulinemia, and vasculitis).
- 5% adult pts become chronic carriers
- 90% of infected newborns become chronic carriers and high risk for HCC.

- HCC occurs in chronic carriers(by HBx gene)
- HBV vaccine is the first vaccine to prevent a human cancer.
- Lifelong immunity occurs after the natural infection
- HBcAb is *not* protective because the core antigen is inside the virion and the antibody cannot interact with it.

Viral marker of HBV:

HBsAg (surface antigen)	meaning acute diseases More than 6 month= carrier .
Surface antibody: HBsAb(IgG)	means life long immunity, it may be –post infective ,after vaccination, passive immunity
HBcAg (core antigen)	found in liver not in blood.
HBc(IgM)	means active B infection. (both recent and in window period).Most reliable test for diagnosis.
HBeAg (e antigen)	meaning virus is now in replication mode and highly infectious .
HBeAb:	means recovery and low transmissibility

NB: Window phase: period between incubation period and prodomal phase , where surface antigen is disappear but still surface antibody is not developed.

Q. Serological markers of acute hepatitis B virus are *(BSMMU –Residency – Dentistry – March' 18)*

a) anti HBc IgM antibody
b) anti HBs antibody
c) anti HBe antibody
d) anti HBc IgG antibody
e) HBs antigen

Ans. a) T b) F c) F d) T e) T

Q. Chronic hepatitis B infection is characterized by: *(BSMMU – M. Phil, Diploma (Non-Residency)–12Ju, DMC & others – **MD** – 12Ju)*

a) HBsAg positive for less than 6 months
b) HBeAg either positive or negative
c) HBV DNA level less than 10,000 copies/ mL
d) histologically minimal hepatitis
e) SGPT level twice of normal limit

Ans. a) F b) T c) F d) F e) T

HELP LINK:

■ **Lab diagnosis of Hepatitis B**:

1. **Detection of Ag in serum**:
   - HBs Ag
   - HBe Ag
2. **Detection of Ab in serum**:
   - Anti HBc IgM
   - Anti HBs IgG
   - Anti HBe IgM

■ **Interpretation**:

1. Detection of HBs Ag is the indication of recent or chronic infection (if > 6 months) - carrier state.
2. Detection of HBe Ag is the indication of replication stage of viruses & the pt. is highly infectious.
3. Detection of Anti HBc IgM is the most reliable test for active hepatitis B infection (recent & in window period)
4. Detection of Anti HBs IgG indicates protective immunity against HBV infection (life long immunity)- Post infection / vaccination / passive immunity
5. Detection of Ante-HBe IgM indicates recovery & low transmissibility.

Serology: HBV contains several antigens to which infected persons can make immune responses; these antigens and their antibodies are important in identifying HBV infection.

In acute infection, the hepatitis B surface antigen (HBsAg) is a reliable marker of HBV infection, and a negative test for HBsAg makes HBV infection very unlikely but not impossible. HBsAg appears in the blood late in the incubation period and before the prodromal phase of acute type B hepatitis; it may be present for only a few days. disappearing even before jaundice has developed hut usually lasts for 3 - 4 weeks and can persist for up to 5 months.

Antibody to HBsAg (anti-HBs) usually appears after about 3 - 6 months and persists for many years or perhaps permanently. Anti-HBs implies either a previous infection, in which case anti-HBc is usually also present, or previous vaccination when anti-HBc is not present.

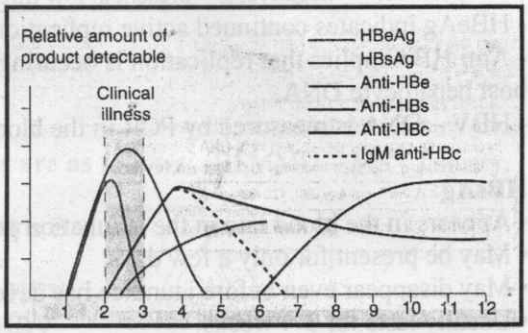


Fig: Serological responses to hepatitis B virus infection. HBsAg = Hepatitis B surface antigen; anti-HBs = antibody to HBsAg, HBeAg = Hepatitis B e surface antigen; anti-HBe = antibody to HBeAg, Anti-HBc = antibody to hepatitis B core antigen

The hepatitis B core antigen (HBcAg) is not found in the blood, but antibody to it (anti-HBc) appears early in the illness and rapidly reaches a high titre which then subsides gradually but persists. Anti-HBc is initially of IgM type with lgG antibody appearing later. Anti-HBc (IgM) can sometimes reveal an acute HBV infection when the HBsAg has disappeared and before anti-HBs has developed.

The hepatitis B e antigen (HBeAg) appears only transiently at the outset of the illness and is followed by the production of antibody (anti-HBe), The HBeAg reflects active replication of the virus in the liver. The persistence of HBsAg for longer than 6 months indicates chronic infection.

Chronic HBV infection is marked by the presence of HBsAg and anti-HBc (lgG) in the blood. Usually, HBeAg or anti-HBe is also present; HBeAg indicates continued active replication of the virus in liver while anti-HBe implies that replication is occurring at a much lower level or that HBV-DNA has become integrated into host hepatocyte DNA.

More information:

• HBV-DNA has become intergrated into host hepatocyte DNA

• PCR can show .HBV-DNA in the blood, implying that viral replication is occuring. This is rarely needed for diagnosis but can be useful in selecting for, and measuring response to therapy some rare mutant forms of the, virus cannot synthesize the 'e' antigen and HBV-DNA is necessary for their detection.

• The individuals are most infectious when markers of continuing viral replication such as HBe Ag, HBV-DNA or DNA polymerase are present in the blood and are least infectious when these are absent and only anti HBe is present.

• This marker does not indicate replication

Interpretation of main investigations used in the serological diagnosis of hepatitis B virus infection

Interpretation	HBsAg	Anti HBc		Anti-HBs
		IgM	IgG	
Incubation period	+	+	-	-
Acute hepatitis				
Early	+	+	-	-
Established	+	+	+	-
Established (occasional)	-	+	+	-
Convalescence				
(3-6 months)	-	±	+	+
(6-9 months)	-	-	+	-
Post-infection				
> 1 year	-	-	+	+
Uncertain	-	-	+	-

Chronic infection				
Usual	+	-	+	-
Occasional	-	-	+	-
Immunisation without infection	-	-	-	+
+ = positive; - = negative, ± = present at low titre or absent				

- HBeAg indicates continued active replication of the virus in the liver.
- Anti HBc implies that replication is occuring at a much lower level or HBV-DNA has become integrated into host hepatocyte DNA.
- HBV – DNA is measured by PCR in the blood. **(Ref: Davidson-23rd)**

HBsAg:
- Appears in the blood late in the incubation period & before the prodromal phase of acute type B hepatitis.
- May be present for only a few days.
- May disappear even before jaundice has developed.
- Usually lasts for 3-4 weeks.
- Can persist upto 5 months.
- When persists longer than 6 months, indicates chronic infection.

Anti HBs:
- Usually appears after about 3-6
- Persists for many years.
- May persist lifelong permanently.
- Implies a previous infection in whin case Anti-HBc is usually also present.
- Implies a previous vaccination in whit case Anti-NBc is not present.

HBcAg:
- Found in liver.
- Is not found in blood.
- Antibody to it (Anti HBc) appears ea in the illness and rapidly reaches a hi, titre which then subsides gradually b persists.

Anti-HBc:
- Has two types lgM & IgG.
- IgM type is found initiàlly.
- IgG type is found in later.
- IgM can sometimes reveal an acute HBV infection when the HBsAg has disappeared and before anti-HBs has developed.

HBeAg:
- Appears only transiently at the onset of the illness and is followed by the production of anti-HBe.
- Reflects active replication of the virus in the liver.

Markers may be found in chronic HBV infection:
- HBsAg
- Anti-HBc (IgG)
- HBeAg
- Anti-HBe

Q. HBSAg positive means: *(BSMMU – M. Phil,Diploma (Non-residency) – 11Ju, DMC & others – MD – 11Ju)*

a) hepatitis-B virus is present in the body T
b) patient is suffering from liver disease F
c) patient will develop chronic liver disease F
d) patient needs no vaccinator T
e) patient should take antiviral drugs T

Q. Raised titre of anti-HBs antibody: *(BSMMU - M. Phil, Diploma – July '10)*

a) Signifies previous hepatitis B infection T
b) Indicate active hepatitis B infection F
c) Occurs during the incubation period F
d) Is produced after hepatitis B vaccination T
e) Indicate immunity hepatitis B infection T

HELP LINK: see before +
Subclinical infection causes rising antibody titre in HBV.

Q. Interpretation of serological markers in patients with hepatitis are as follows: (BSMMU – MS - January, 2010)

a) HBsAg positive— indicate active replicating stage of hepatitis B virus F
b) anti HAV IgM positive— indicate past infection with HAV F
c) anti HCV positive— indicate current or past infection with HCV T
d) anti HBc (total) positive— indicate current infection with HBV F
e) anti HBe negative- indicate resolution of HBV infection F

Q. Antibody to hepatitis B surface antigen is indicative of: (DMC – M. Phil, Diploma July, 2008)

A. Recent hepatitis B infection. F
B. Immunity to hepatitis B infection. T
C. Need for hepatitis vaccine. F
D. Chronic active hepatitis. F
E. Acquired immune deficiency state. F

Q. The following markers are usually present in a hepatitis B carrier with chronic active hepatitis: (BSMMU – MD/MS - January, 2008)

a) HBeAg T
b) Anti-HBc IgG T
c) Anti-HBc IgM F
d) HBV-DNA T
e) HBsAg T

Q. The following serological findings are found in chronic Hepatitis B viral infection - (DMC - MD/MS - 09Ja)

a. HBsAg positive T
b. Anti HBcAg IgM positive F
c. Anti HBeAg positive T
d. Anti HBs positive F
e. HBeAg positive T

Q. Markers of hepatitis B virus replication are - (BSMMU – MD - 07Ja)

a. HBsAg F
b. HBeAg T
c. HBcAg F
d. HBV-DNA T
e. Anti-HBc IgM F

Q. Hepatitis B surface antigen: (DMC - M. Phil, Diploma-06July)

a) appears in serum during incubation period T
b) may be detected in saliva F
c) persists during acute illness T
d) is a marker of virus replication F
e) is usually absent during convalescence period T (in window period)

HELP LINK:

Table: Glossary of hepatitis viruses and their serologic markers – see before

Q. B viral Hepatitis (BSMMU - MD - 05Ja)

A. Is caused by a flavivirus F *(Hepadna virus; Hepatitis C virus is flavivirus)*
B. Is transmitted by blood transfusion T
C. Is transmitted by fecal oral route F
D. Becomes chronic more frequently in adults F
E. May be prevented by both active and passive immunization T

Hepatitis C Virus

Important Properties:

- Flavivirus family. enveloped , six genotypes
- Has no virion polymerase.
- Humans are the reservoir for HCV.
- Transmitted:
  - blood, mother to child during birth,
  - needle-stick injury, Sexual transmission is uncommon, and
  - there is no evidence for transmission across the placenta or during breast feeding.
- Infectious disease transmitted by immune globulins.
- It infects hepatocytes primarily
- chronic carriage of HCV is much higher than HBV
- strongly predisposes to HCC
- Alcoholism greatly enhances the rate of hepatocellular carcinoma in HCV-infected individuals.
- Chronic active hepatitis and cirrhosis occur in 10% patients.
- incubation period is 8 weeks.
- Cirrhosis resulting from chronic HCV infection is the most common indication for liver transplantation.
- **Complications:** Autoimmune reactions, including vasculitis, arthralgias, purpura, and membranoproliferative glomerulonephritis., essential mixed cryoglobulinemia.

Treatment:

- Combination of peginterferon and ribavirin significantly improved the duration of the suppression of viral replication of HCV genotype 1.

Question Bank

Q. Hepatitis C virus *(BSMMU –Residency – MD, Dental surgery – March' 14)*

a) is an RNA virus
b) mostly causes acute symptomatic infection
c) leads to chronicity in 80% of the cases
d) can be prevented by vaccination
e) can be transmitted by oro-fecal route

Ans. a) T b) F c) T d) F e) F

HELP LINK:

HEPATITIS C

• This is caused by an RNA flavivirus. Primates have .provided an animal model for infection as the virus has been difficult to grow in cell culture. Acute symptomatic infection with hepatitis C is rare. Most individuals will be unaware of when they became infected and are only identified when they develop chronic liver disease.

• Eighty per cent of individuals exposed to the virus will become chronically infected and late spontaneous viral clearance is rare.

• Hepatitis C is the cause of what used to be known as non-A, non-B hepatitis, a syndrome of acute hepatitis often with jaundice seen after a transfusion of blood or blood products. Following the identification of the virus in

1990, blood donors are now screened for infection in many parts of the world. New cases of post-transfusion hepatitis C no longer occur in the UK.

• Hepatitis C infection is usually now identified in asymptomatic individuals screened because they have risk factors for infection such as previous injection drug use or because they have incidentally been found to have abnormal liver blood tests. Although most individuals remain asymptomatic until progression to cirrhosis occurs, fatigue can complicate chronic infection and appears to be unrelated to the degree of liver damage.

Hepatitis-C is the most dangerous because:

- Most of the patients are unaware of when they become infected.
- The virus usually does not produce any acute symptomatic infection.
- 80% of infected patients develop chronicity & hepatocellular carcinoma.
- Spontaneous viral clearance is rare.
- Vaccines are not available.

Q. Hepatitis C virus: *(BSMMU - M. Phil, Diploma – July '10)*

a) Is a RNA virus	T
b) May be transmitted orally	F
c) Has a sero-prevalence rate of 60-90% in haemophilias	T
d) Rarely leads to chronic liver disease	F
e) May be treated effectively with high dose acyclovir	F

Influenza virus

- **Influenza A virus**: worldwide epidemics (pandemics)
- **Influenza B virus**: major outbreaks of influenza
- **Influenza C virus**: mild respiratory tract infections but does not cause outbreaks of influenza.
- **Pandemics occur:** when a variant of influenza A virus contains a new hemagglutinin with no preexisting antibodies in human.

Important properties of influenza virus:

- Segmented single-stranded RNA genome.
- Contains an RNA dependent RNA polymerase.
- The envelope is covered with two different types of spikes, a hemagglutinin and a neuraminidase.
- **Influenza A virus**: has 16 antigenic types of hemagglutinin (HA) and 9 antigenic types of neuraminidase (NA).
- Some cause disease in humans, but most of the types cause disease in birds, horses, and pigs.
- The function of the hemagglutinin is to bind to the cell surface receptor (neuraminic acid, sialic acid) to initiate infection of the cell.
- The hemagglutinin is also the target of neutralizing antibody.
- The neuraminidase cleaves neuraminic acid (sialic acid) to release progeny virus from the infected cell.
- The hemagglutinin functions at the beginning of infection, whereas the neuraminidase functions at the end.
- Neuraminidase also degrades the protective layer of mucus in the respiratory tract.
- This enhances the ability of the virus to gain access to the respiratory epithelial cells.

Immunization is not effective against influenza A virus due to antigenic changes in the haemagglutinin (HA) & neuraminidase (NA). There are 2 types of changes-

Antigenic shift- major change based on the reassortment of segments of the genome RNA. This change appears about every 10 or 11 yrs.

Anti-genic drift- minor change based on mutations(frame shift) in the genome RNA. This change appears about every year.
Thus the antigenicity of the virus is changed sufficiently → pre-existing immunity is no longer effective. The antigenicity of influenza B virus also changes but not as dramatically or as often, like influenza A virus.
[Reassortment means high frequency recombination of the different segments of genome RNA. The entire segments of RNA are changed, each one codes a single protein such as HA]

Group-specific and type-specific antigens:

1. The internal ribonucleoprotein is the group-specific antigen that distinguishes influenza A, B, and C viruses.
2. The hemagglutinin and the neuraminidase are the type-specific antigens located on the surface.

- Antibody against the hemagglutinin neutralizes the infectivity of the virus (and prevents disease),
- whereas antibody against the group-specific antigen (which is located internally) does not.
- Antibody against the neuraminidase does not neutralize infectivity but does reduce disease by decreasing the amount of virus released from the infected cell and thus reducing spread of the virus to adjacent cells.

Question Bank

Q. Influenza A virus *(BSMMU – Non-Residency – MD, MS, Paediatrics, Basic Science – July' 19)*
a) undergoes antigenic shift
b) can cause pandemics
c) are resistant to neuraminidase inhibitors
d) can respond to rimantidine
e) vaccination confers lifelong protection

Ans. a) T b) T c) F d) T e) F

(Ref: LANGE-15th, P-302)

Help link:

Transmission:
1. By respiratory droplets
2. By direct contact with the contaminated fomites.

Pathogenesis:
- The virus enter to the respiratory tract through inhalation. The virus then become attached with epithelial cell of upper respiratory tract by haemaglutinine. The viruses replicate in those cells and comeout by the budding of the cells.
- Neuraminidase of the virus degrades the mucous secretion and facilitate the transport to the lower respiratory tract.
- The infected cells eventually die and it results desquamation of the respiratory epithelial cells. This desquamation process lowers the local resistance of the respiratory tract and fascilitate the secondary bacterial infection.

(Ref: LANGE Review-14th, P-301)

Nice to know:
Antibiotics are used because to prevent secondary infection.

Clinical feature:
Fever, headache, cough, malaise, running nose, sore throat, muscle pain – flue like syndrome.

Laboratory diagnosis:
1. Serological test – 4 fold rise of antibody in two serum samples.
2. It is diagnosed mainly clinically.

Treatment of Influenza:

- ✓ Oseltamivir (Tamiflu) taken orally and zanamivir (Relenza) inhaled into the nose.
- ✓ peramivir (Rapivab) is administered intravenously
- ✓ They are members of **neuraminidase inhibitors**, effective against both influenza A and B viruses.
- ✓ Amantadine (Symmetrel) is approved for treatment and prevention of influenza A. 90% H3N2 strains are resistant to amantadine (and rimantadine).
- ✓ amantadine is effective only against influenza A, not influenza B.
- ✓ **Rimantadine** (Flumadine), a derivative of amantadine, can also be used for treatment and prevention of influenza A and has fewer side effects than amantadine.
- ✓ vaccine is preferred over these drugs in the prevention of influenza.

(Ref: LANGE-15th, P-302)

Prevention:

Every year booster dose with the present strain is essential. Because influenza virus undergo antigenic drift every year.

(Ref: LANGE Review-14th, P-301)

Q. Influenza A virus *(BSMMU – Non-Residency – MD/MS, Basic science – July' 14)*

a) may undergo antigenic shift and antigenic drift
b) may cause pandemic
c) respond to rimantidine
d) does not respond to neuraminidase inhibitors
e) vaccination confers lifelong protection

Ans. a) T b) T c) T d) F e) F

Q. Which of the following statements reflects the pathogenesis of influenza *(BSMMU –Residency – MS, Basic science – March' 14)*

a) the virus enters the host in airborn droplets
b) viraemia is common
c) the virus establishes persistent infection in the lung
d) pneumonia is associated with secondary bacterial infections
e) viral infection does not destroy cells in the respiratory tract

Ans. a) T b) F c) F d) T e) F

Help link:

Transmission & Epidemiology:

The virus is transmitted by **airborne respiratory droplets.** The ability of influenza A virus to cause epidemics is dependent on antigenic changes in the hemagglutinin and neuraminidase. As mentioned previously, influenza A virus undergoes both major antigenic shifts as well as minor antigenic drifts. Antigenic shift variants appear infrequently, whereas drift variants appear virtually every year. The last major antigenic shift that caused a pandemic in humans was in 1968 when H3N2 emerged. Epidemics and pandemics (worldwide epidemics) occur when the antigenicity of the virus has changed sufficiently that the preexisting immunity of many people is no longer effective. The antigenicity of influenza B virus undergoes antigenic drift but not antigenic shift. The antigenic changes exhibited by influenza B virus are less dramatic and less frequent than those of influenza A virus.

Influenza occurs primarily in the winter months, when this and bacterial pneumonia secondary to influenza cause a significant number of deaths, especially in older people. The morbidity of influenza in children younger than 2 years is also very high, second only to the morbidity in the elderly. In the southern hemisphere (e.g., in Australia and New Zealand), influenza occurs primarily in the winter months of June through August.

Pathogenesis & Immunity:

After the virus has been inhaled, the neuraminidase degrades the protective mucus layer, allowing the virus to gain access to the cells of the upper and lower respiratory tract. The infection is limited primarily to this area because the proteases that cleave the hemagglutinin are located in the respiratory tract. Despite systemic

symptoms, viremia rarely occurs. The systemic symptoms, such as severe myalgias, are due to cytokines circulating in the blood. There is necrosis of the superficial layers of the respiratory epithelium.Influenza virus pneumonia, which can complicate influenza, is interstitial in location.

Immunity depends mainly on secretory IgA in the respiratory tract. IgG is also produced but is less protective. Cytotoxic T cells also play a protective role.

Clinical Findings:

After an incubation period of 24 to 48 hours, fever, myalgias, headache, sore throat, and cough develop suddenly. Severe myalgias (muscle pains) coupled with respiratory tract symptoms are typical of influenza. Vomiting and diarrhea are rare. The symptoms usually resolve spontaneously in 4 to 7 days, but influenzal or bacterial pneumonia may complicate the course. One of the well-known complications of influenza is pneumonia caused by *Staphylococcus aureus*.

Reye's syndrome, characterized by encephalopathy and liver degeneration, is a rare, life-threatening complication in children following some viral infections, particularly influenza B and chickenpox. Aspirin given to reduce fever in viral infections has been implicated in the pathogenesis of Reye's syndrome.

Q. Antigenic variation of influenza viruses depend on following surface glycoproteins: (BSMMU – MD – January, 2010)

a) Matrix protein F
b) Neuraminidase T
c) RNA transcriptase F
d) Hemagglutinin T
e) Nucleocapsid protein F

Q. Following statement is applicable antigenic drift in influenza virus: (BSMMU – MS - 10Ja)

a) is exhibited only by influenza A virus F
b) predominantly affects the matrix protein T
c) results from minor antigenic changes T
d) results in new subtypes over time T
e) is due to frame shift mutations in viral genes T

Q. Antigenic variation of influenza viruses depend on following surface glycoproteins: (BSMMU – MD/MS - January, 2009)

a) Matrix protein F
b) Neuraminidase T
c) RNA transcriptase F
d) Hemagglutinin T
e) Nucleocapsid protein F

Dengue

The dengue flavivirus is a common cause of fever in and from the tropics. It is endemic in South-east Asia and India and is also seen in Africa; there have been recent large epidemics in the Caribbean and Americas. The principal vector is *Aedes aegypti*, which breeds in standing water; collections of water in containers and tyre dumps are a particular risk in large cities. *Aedes albopictus* is a vector in some South-east Asian countries. There are four serotypes of dengue virus, all producing a similar clinical syndrome; homotypic immunity is life-long but heterotypic immunity between serotypes lasts only a few months. The incubation period from being bitten by an infected mosquito is usually 2-7 days.

(Ref: Davidson-23rd)

■ **Important characteristics of dengue virus:**

1. It is a flavivirus.
2. It has 4 serotypes- 1, 2, 3, 4.
3. Incubation period : 2-7 days

4. Mode of transmission:
- Female ***Aedes agepti*** mosquito transmits the disease.
- Blood meal is necessary for ovulation.
- It requires infection by feeding on dengue sometime may be on monkey.
- No person to person transmission.

Dengue is a mosquito born infection which is caused by dengue virus.

■ **Host**: All races, ages & sexes are affected.
■ **Environment**:
- Aedes mosquito are domestic species.
- More urban than rural.
- Heavy rainfall, 80% humidity, 28% temperature are favourable condition.
- Explosive epidemics may occur in rainy season.

■ **Reservoir**: Patients are the reservoirs.
■ **Incubation period**: 2-7 days
■ **Mode of transmission**: The dengue virus enters into the body through the biting of the infected female ***Aedes agepti*** mosquito.

■ **Period of communicability**:
- Pts are usually infective for mosquito from day before onset of the 5th.day of disease.
- Mosquito become infective 8-11 days after the blood meal.
- Being infected from a dengue pt. the mosquito remains infected for life long.

■ **Manifestation of dengue**:
A. Asymptomatic
B. Symptomatic: 3 clinical forms
   1. Classical dengue fever
   2. Dengue hemorrhagic fever (DHF)
   3. Dengue shock syndrome (DSS)

Clinical forms of Dengue
1. Classical dengue fever
Produce influenza like symptoms which includes- • Fever – sudden rise of temperature *(acute onset, high continuous & lasting 2-7 days in most cases)* • Headache • Severe muscle pain, joint pain and retro-orbital pain. • Maculo-papular rash The pain is so severe, as it is called ***break bone fever***.
2. Dengue hemorrhagic fever (DHF)
- Present all symptoms of Classical dengue fever. - There is haemorrhagic manifestation (including positive tourniquet test) mainly occur in GIT. - Gum bleeding, epistaxis, intensified menstrual bleeding, & haematemesis and/ or malena.
3. Dengue shock syndrome (DSS)
Presented with bleeding manifestation and shock. *(manifested by rapid and weak pulse with narrowing of pulse (20 mm Hg) or hypotension with the presence of cold clammy skin & restlessness)*

Pathogenesis of dengue fever
Dengue infection by dengue virus
↓
Antibody is formed
↓

Formation of immune-complex & activation of complement
↓
Increased vascular permeability and thrombocytopenia

Pathogenesis of dengue hemorrhagic fever

■ In primary dengue, the platelet and PCV are usually normal.

■ In secondary dengue, the platelet count is decreased markedly which is responsible for haemorrhage.

There is also plasma leakage which leads to haemoconcentration. It may interfere the blood circulation in different organs.

■ When primary infection occurs – no antibody.

So immunocomplex is made.
↓
This complex cause complement activation producing C3a & C5a.
↓
C3a & C5a degranulate basophil
↓
Release of vaso-active amines
↓
They cause dilatation of vessels, leakage occurs and bleeding manifestation occur.

■ When secondary infection occurs – antibody is already produced.

So antibody binds with any strain of dengue
↓
Promotes infection of higher numbers of mononuclear cells
↓
Release of cytokines, vasoactive mediators and pro-coagulants
↓
Leads to disseminated intravascular coagulation (DIC) seen in Dengue haemorrhagic fever.

(Ref: Lecture + LANGE-24th)

The pathogenesis is unclear but pre-existing immunity to a dengue virus serotype, heterotypic to the one causing the current infection, predisposes to the syndrome. In vitro such heterotypic antibody causes enhanced virus entry and replication in monocytes; it is believed that enhancing antibody from previous dengue infection with a different serotype, or from acquired maternal antibody in infants, facilitates development of a very heavy viral load. Disseminated intravascular coagulation, complement activation and release of vasoactive mediators may contribute to the pathogenesis of the syndrome, possibly triggered by immunopathological mechanisms. Cytokine release is thought to be the cause of vascular damage at the site of post-capillary endothelial junctions. Even with good treatment the case fatality may be up to 10%. Adults rarely have classical dengue shock syndrome but may have a stormy and fatal course characterised by elevated liver enzymes, haemostatic abnormalities and gastrointestinal bleeding.

(Ref: Davidson-23rd)

Clinical features:

The disease varies in severity. The clinical features are listed below. Asymptomatic infections are common. The morbilliform rash characteristically blanches under pressure.

Clinical features of dengue fever:	
Prodrome	•2 days of malaise & headache
Acute onset	•Fever, backache, arthralgias, headache, generalized pains (Breakbone fever), pain on eye movement, lacrimation, anorexia, nausea, vomiting, relative bradycardia, prostration, lymphadenopathy.
Fever	•Continuous or 'Saddle back', with break on 4th or 5th days
Rash	•Transient macular in 1st 1-2 days.Maculopapular, scarletmorbilliform from day 3-5 on trunk, spreading centrifugally and spearing palm & soles
Convalescence	•Slow

Dengue haemorrhagic fever or dengue shock syndrome: This occurs mainly in children in south-east Asia.
Incubation period: 2-7 days

■ **Clinical feature**:

1. ***Prodromal***- (2 days)
   - Malaise, headache
2. ***Acute onset***:
   - Fever
   - Headache, backache, arthralgia,
   - Generalized pains ('break-bone fever')
   - Pain on eye movement, lacrimation
   - Anorexia, nausea, vomiting.
   - Depression
   - Relative bradycardia
   - Lymphadenopathy
   - Prostration
   - Scleral injection
3. **Fever**: continuous or 'saddle back' with break on 4 or 5th day and then recrudescence; usually lasts 7-8 days.
4. **Rash**: Initial flushing faint macular rash in first 1-2 days.

Maculopapular, scarlet morbiliform rash from days 3-5 on trunk, spreading centrifugally and sparing palms & soles, onset often with fever defervescence. May desquamate on resolution or give rise to petechiae on extensor surfaces.

5. **Convalescence**- slow.
6. **Complications**: minor bleeding from mucosal sites, hepatitis, cerebral haemorrhage or oedema, rhabdomyolysis
7. **Features of shock**- manifested by
   - Sweating on forehead
   - Rapid thready pulse
   - Hypotension
   - Shallow breathing
   - Cold clammy skin
   - Restlessness.
   - Oliguria

(Ref: Davidson-23rd, Lecture of DMC)

In mild forms there is thrombocytopenia and haemoconcentration. In the most severe form, after 3-4 days of fever, hypotension and circulatory failure develop with features of a capillary leak syndrome. Minor (petechiae, ecchymoses, epistaxis) or major (gastrointestinal bleeding) haemorrhagic signs may occur.

Investigations :

Diagnosis of dengue is easier in an endemic area when a patient has the characteristic symptoms and signs. However, mild cases may have a similar presentation to other viral infections. Leucopenia is usual and thrombocytopenia common. The diagnosis is confirmed by either a fourfold rise in IgG antibody titres, isolation of dengue virus from blood or detection of dengue virus genomic sequences by real-time PCR. Serological tests may detect cross-reacting antibodies from other flaviviruses, including yellow fever vaccine.

Management and prevention:

There is no specific treatment. The severe pains can be relieved by paracetamol. Aspirin should be avoided. Volume replacement, blood transfusions and management of shock are indicated in the capillary leak syndrome. Corticosteroids have not been shown to help. No existing antivirals are effective.

Breeding places of *Aedes* mosquitoes should be abolished and the adults destroyed by insecticides. There is as yet no vaccine and in any case a tetravalent vaccine would be needed to cover all four serotypes. Until the *Aedes* mosquito can be controlled or a cost-effective vaccine developed, the incidence of dengue can be expected to continue to escalate.

(Ref: Davidson-23rd)

Virus persists for long periods:

- integration of a DNA provirus into host cell DNA, eg: retroviruses;
- immune tolerance,
- formation of virus–antibody complexes, which remain infectious;
- location within an immunologically sheltered "sanctuary" (e.g., the brain);
- rapid antigenic variation;
- spread from cell to cell without an extracellular phase, so that virus is not exposed to antibody; and
- immunosuppression, as in acquired immunodeficiency syndrome (AIDS).

Five approaches to the diagnosis of viral diseases:

(1) Identification of the virus in cell culture: By cytopathic effect(cell size, shape and formation of multinucleated giant cells)

A definitive identification of the virus grown in cell culture is made by

- Complement fixation,
- Hemagglutination inhibition,
- Fluorescent antibody,
- Radioimmunoassay,
- Enzyme-linked immunosorbent assay (ELISA), and
- Immunoelectron microscopy

(1) Microscopic identification directly in the specimen,
(2) Serologic procedures to detect a rise in antibody titer or the presence of IgM antibody,
(3) Detection of viral antigens in blood or body fluids, and
(4) Detection of viral nucleic acids in blood or the patient's cells: By PCR.

Question Bank

Q. Clinical manifestations of hemorrhagic fever are: *(BSMMU - M. Phil, Diploma – July '10)*

a) Positive tourniquet test T
b) Spontaneous bleeding T
c) Normal pulse pressure F
d) Severe pleural effusion T
e) Hematocrit rise more than 20% T

HELP LINK: Dengue haemorrhagic fever or dengue shock syndrome: See before

Q. In dengue haemorrhagic fever following consequences usually occur. (DMC - M. Phil, Diploma, July-07)

a) capillary leakage T
b) fall in haematocrit T (National guideline of Dengue fever)
c) thrombocytopenia T
d) vasculitis F
e) narrow pulse pressure F (National guideline of Dengue fever)

Q. Evidence of plasma leakage in dengue haemorrhagic fever are: (MD/MS (DMC)-05Ja)

a) Increased haematocrit T
b) Narrow pulse pressure F
c) Shock F
d) Thrombocytopenia T
e) Haemorrhage T

Q. The vectors of dengue is (M. Phil, Diploma (DMC) – 03Ju)

a) Anopheles minimus F
b) Culex fatigans F
c) Aedes aegypti T
d) Mansonia indica F
e)Aedes albopictus T

HELP LINK:

Table: Periods of infectivity in childhood infectious diseases:

Diseases	Infectious period
Chickenpox	5 days before rash to 6 days after last crop
Diphtheria	2-3 weeks (shorter with antibiotic therapy)
Measles	From onset of prodromal symptoms to 4 days after onset of rash
Mumps	3 days before salivary swelling to 7 day after
Rubella	7 days before onset of rash to 4 days after
Scarlet fever	10-21 days after onset of rash (Shortened to 1 day by penicillin)
Whooping cough	7 days after exposure to 3 weeks after onset of symptoms (shortened to 7 days by antibiotics)

Q. Dengue- (BSMMU-Med/Sur-01Ja)

a) Is a febrile condition caused by flavi-virus infection. T
b) Has five serotypes F
c) Has the principal vector is Aedes aegypti T
d) Dengue shock syndrome is cause of repeated infection with different serotype T
e) DK in haemorrhagic dengue is due to immunological cause. T

Q. Dengue fever-(BSMMU-Med/Sur-01Ja)

a) Produce life long homotypic immunity T
b) May lead to DIC T
c) May be well managed by corticosteroid F
d) May be prevented by vaccines F
e) Is a flavivirus infection T

Nipah virus

Q. Nipah virus *(BSMMU –Residency - **MS, Basic science** – March' 14)*

a) is a member of orthomyxo viridae family
b) Is transmitted by contaminated date palm sap (date juice)
c) has 5% mortality rate
d) occurs through man to man transmission
e) vaccine is available

Ans. a) F b) T c) F (67 – 74%) d) T e) F

Help link:

Important properties:

- Nipah virus is a paramyxovirus.
- Causes encephalitis.
- Reservoir of virus: fruit bats of the genus pteropus.
- Contact with pigs are particularly at risk for encephalitis.

Transmission: human-to-human transmission occurs. by saliva or sputum and that is the likely mode of transmission.

Season: December to may.

C/F: Fever, Altered mental status, seizure, neurological deficit

Epidemiological linkage:

- Drinking raw date palm juice,
- close contact with Nipah pt,
- visiting in Nipah outbreak community within 3 weeks.

Treatment: There is no treatment, or vaccine for Nipah virus infections.

Avian influenza (H5N1)

Q. H5N1 virus: (BSMMU - M. Phil, Diploma, July-'07)

a) is transmitted from birds to animals T
b) is a DNA virus F
c) can be transmitted from the environment to human T
d) human to human transmission is common F
e) can be detected by reverse transcriptase polymerase chain reaction (PCR) T

HELP LINK:

The H5N1 strain that causes avian influenza, primarily in chickens, caused in aggressive form of human influenza with high mortality in Hong Kong. In the winter of 2003-2O04, an outbreakofavain influenza caused by H5N1 strain killed thousands of chickens in several Asian countries. Millions of chickens were killed in an effort to stop the spread of the disease. In this outbreak of H5N1 influenza, 122 people have been infected, of whom 62 have died, a 50% mortality rate (as of November 2005). The spread of the H5N1 strain from person to person occurs rarely but remains a major concern because it could increase dramatically if reassortment with the human-adapted strains occurs. In 2005, the H5N1 virus spread from Asia to Siberia and into eastern Europe, where it killed thousands of birds but has not caused human disease.

Disease caused by adenovirus:

- Lower respiratory tract disease
  1. Pharyngitis, conjunctivitis(pink eye)
  2. Common cold, pneumonia,
- Keratoconjunctivitis, hemorrhagic cystitis, gastroenteritis

❑ **Serotype:**
- measles virus: one serotype,
- Polioviruses: three serotypes
- Rhinoviruses: 100 serotypes

❑ **Superantigens producing virus:**
- Epstein–Barr virus
- Cytomegalovirus,
- Retrovirus mouse mammary tumor virus

❑ **Tegument:** regulatory proteins (transcription and translation factors that control either viral or cellular processes.) in the virion , located between the nucleocapsid and envelope.
- eg: herpes simplex virus and cytomegalovirus .

Ebola virus

Q. Ebola virus *(BSMMU – Non-Residency – MD, MS, Basic Science & Dentistry – July' 17)*

a) is transmitted by mosquitoes
b) is a filovirus
c) is antigenically related to lassa fever virus
d) is spread by contact with blood or other body fluids
e) causes infection but no disease in non-human primates

Ans. a) F b) T c) F d) T e) F

Help link:

- Is a filo virus family
- Transmission:
  - reuse of unsterilized needles
  - close personal contact, body fluids and places where the person has touched
- Cause a severe and often fatal hemorrhagic fever in humans and other mammals, known as Ebola virus disease (EVD).
- the cause of the 2013–2015 Ebola virus epidemic in West Africa,

- The natural reservoir of Ebola virus is believed to be bats, particularly fruit bats, and it is primarily transmitted between humans and from animals to humans through body fluids
- The EBOV genome is a single-stranded RNA approximately 19,000 nucleotides long.
- high mortality rate (up to 83-90%)
- is a zoonotic pathogen. Intermediary hosts have been reported to be "various species of fruit bats

Others

Q. Zika virus *(BSMMU-Non-Residency-**Paediatrics**-july'19)*
a) is a DNA virus
b) is transmitted by Aedes mosquitoes
c) is transmitted by mosquito bite during the night time
d) causes macrocephaly
e) is a trigger of Guillain-Barre syndrome

Ans. a) F (SSRNA) b) T c) F (Day time biter) d) F (Microcephaly) e) T

(Ref: Textbook of Microbiology by Apurbo Sonkar-6th, P-351)

Q. Virus sensitive to inactivation of lipid solvents and detergents are *(BSMMU –Residency – **Dentistry** – March' 18)*
a) hepatitis A virus
b) poliovirus
c) influenza virus
d) rabies virus
e) rotavirus

Ans. a) F b) F c) T d) T e) F

Q. Following viruses give life long immunity after recovery from natural intecion *(BSMMU –Residency - **MS, Basic science** – March' 14)*

a)	Rubella virus	T
b)	Hepatitis E virus	F
c)	Hepatitis B virus	T **(Ref. LANGE – 15th, P-346)**
d)	Influenza virus	F
e)	Measles	T

Help link: Also Chicken pox

Q. Rodent borne viruses are: (BSMMU – MD – January, 2010)

a)	Rabies virus	F
b)	Yellow fever virus	F
c)	Dengue virus	F
d)	Rota virus	F
e)	Corona virus	F

Help Link:
Rodent borne virus disease:
✓ Hanta virus, Seoul virus, African Lassa fever, Ebola and Marburg virus

(Ref. P. chakraborti-3rd, P-595)

Q. Human are the only natural hosts for following viruses: (BSMMU – MD – January, 2010)

a)	Rabies virus	F
b)	Measles virus	T
c)	Influenza virus	F
d)	Rota virus	F
e)	Rubella virus	T

Help Link: Humans are the natural host: EBV, Small pox, Measles, Mumps, Rubella, HBV, HSV, VZV, CMV, Parvo B19, RSV, Coxsachie, HAV, HCV, HDV

Q. Viruses that can infect immune system are – (DMC – MD/ MS - January, 2010)

a. Cytomegalovirus F
b. HIV T
c. Hepatitis B virus T
d. Human papilloma virus F
e. Measles virus T

Q. Human are the only natural hosts for following viruses (BSMMU – MD/MS - January, 2009)

a) Influenza virus F
b) Rota virus T
c) Rubella virus T
d) Rabies virus F
e) Measles virus T

Help link:

Natural host means long term host of a pathogen where host do not get the disease or carried as a subclinical infection or it may be asymptomatic.

Q. Bilateral parotid enlargement may occur in- (BSMMU – MD - 06Ja)

A. Mumps T
B. Sarcoidosis T
C. Von Willebrand disease F
D. Phenytoin therapy F
E. Cirrhosis F

HELP LINK:

Causes of salivary gland swelling
1. Infection:
• Mumps • Bacterial (post-operative)
2. Calculi
3. Tumours:
• Benign: pleomorphic adenoma (95% of cases) • Intermediate: mucoepidermoid tumour • Malignant: carcinoma
4. Sjogren's syndrome
5. Sarcoidosis

Q. Which of the following features of smallpox contributed to its eradication? (BSMMU – MD/MS - 02Ja)

a) It is a DNA virus F
b) It has one antigenic type F
c) Inapparent infection is rare T
d) Administration of live vaccine reliably induces immunity T
e) There is animal reservoir. F

Q. The following are human prior mediated diseases - (BSMMU – MD - 02Ja)

a) Acquired immunodeficiency syndrome F
b) Kuru T
c) Subacute selerosing panencephalitis F
d) Progressive multifocal leucocuccphalopathy F
e) Creutzfeildt- jakob disease T

IMPORTANT MCQ OF VIROLOGY

[Ref: Smiddy]

Q. The following are viral diseases:

a) cytomegalic inclusion disease
b) trachoma
c) dengue
d) primary atypical pneumonia
e) typhus

Ans.

a) **True** CMD is caused by a B group herpes virus which, infecting a normal individual, is asymptomatic or causes a mononucleosis-like infection. However, infection by this virus in the peonate or immunosuppressed individual causes serious consequences. In neonates, infection with CMV may cause a condition resembling erythroblastosis foetalis in which severe haemolytic anaemia occurs associted with purpura, hepatosplenomegaly, pneumonitis, deafness and extensive brain damage. In immunosuppressed individuals, the virus causes oesophagitis, colitis, pneumonitis, renal damage, chorioretinitis and meningoencephalitis. In patients already suffering from AIDS, CMV pneumonitis is nearly alwaysassociated with infection with *Pneumocytis carinii*. Cells infected with CMV are markedly enlarged containing large purple staining intranuclear inclusions surrounded by a clear halo.

b) **False** Trachoma is a chronic suppurative disease of the eye in which a follicular keratoconjunctivitis develops. It is caused by various subtypes of Chlamydia trachomatis and is one of the commonest causes of blindness in the world. It is transmitted by direct human contact or possibly by flies and is commonest in sandy regions and in nomads.

c) **True** Dengue is an acute painful febrile illness which is often haemorrhagic. It is produced by an RNA virus of the togavirus type. The virus is arthropod borne (Arbor) and transmitted by the mosquito *Aedes aegypti*. The dengue virus is related to that causing yellow fever.

d) **False** Primary atypical pneumonia is caused by the Mycoplasma pneumoniae which are 200 to 250 nm in diameter and among the smallest of bacteria. Patients with mycoplasmal pneumonia have autoantibodies against the I antigen carried on erythrocytes.

e) **False** Epidemic typhus which is transmitted by the louse, is caused by the *Rickettsia prowazeki*, obligate intracellular parasites that can be grown in tissue culture or egg. The rickettsiae are small organisms 300 to 700 nm in diameter. Other rickettsiae cause similar febrile illnesses and are either flea or tick borne. The chief snicroscopic changes in typhus are seen in the small blood vessels in which proliferation and swelling of the endothelium may cause narrowing. Surrounding the affected vessels is an inflammatory reaction chiefly composed of leucocytes. Thrombosis of affected vessels leads to gangrene of the skin and other areas.

Q. Encephalitis may be a complication of the following virus infections:

a) Epstein—Barr virus
b) measles virus
c) rubella virus
d) herpes virus
e) adenovirus

Ans.

a) **True** The Epstein—Barr virus is a gamma-group herpes virus normally causing fever, generalized lymph node enlargement, splenomegaly and the appearance in the blood of mononucleosis cells which are atypical activated T lymphocytes. In immune deficient states, infection with this virus causes lymphoma and Burkitt's lymphoma. In normal individuals meningoencephalitis may occur.

b) **True** Measles is caused by an RNA virus of the paramyxovirus family and is only rarely a cause of transnt encephalitis because most children develop a T cell-mediated immunity controlling the infection. In immunocompromised individuals however, a condition known as subacute sclerosing panencephalitis may occur caused possibly by a hypermutated 'defective' virus that cannot produce either matrix or

envelope proteins. The measles virus is spread by droplets and multiplies in the epithelial cells of the upper respiratory tract.

c) **True** A progressive encephalitis may occur in children with the congenital rubella syndrome. However its real importance is that it is teratogenic and may cause serious fetal damage. A female infected in the first sixteen weeks of pregnancy has a 1:4 chance of giving birth to a child with some congenital abnormality.

d) **True** Herpes simplex infection may be associated with meningoencephalitis, particularly in immunodepressed individuals.

e) **False** The adenoviruses chiefly affect the upper respiratory tract and occasionally cause gastroenteritis. They are not particularly associated with the development of encephalitis.

Q. Inclusion bodies are found in the following viral infections:

a) measles
b) yellow fever
c) rabies
d) hepatitis B
e) smallpox

Ans.

a) **True** In the hyperplastic lymphoid organs with follicular hyperplasia and large germinal centres, multinucleate giant cells can be found randomly arranged which contain eosinophilic cytoplasmic inclusion bodies. These cells, known as the Warthin—Finkeledy cells, can be found in the sputum and are pathognomonic of the disease.

b) **True** Yellow fever is caused by an arbovirus of the B group. The infection is transmitted by the mosquitoe, *Aedes aegypti*. Death is caused by acute hepatic necrosis. Within 72 hours of infection, examination of the liver shows an eosinophilic degeneration of the cytoplasm producing the Councilman bodies. Very occasionally spherical eosinphilic inclusion bodies develop in the nuclei of the affected liver cells called Torres bodies.

c) **True** Rabies is caused by rhabdoviruses. The pathognornonic histological feature of this disease is the development of acidophilic cytoplasmic inclusion bodies known as Negri bodies in the neurons, particularly in the pyramidal cells of the hippocampus and in the Purkinje cells in the cerebellum.

d) **False** Intracellular inclusion bodies are not found in infections due to the hepatitis B virus. However, actual HBV particles may be found in the serum by electron microscopy.

e) **True** Both small pox and vaccinia are associated with the development of spheroidal eosinophilic masses in the cytoplasm of the epidermal cells known as the Guanieri bodies.,Within them the elementary particles of the virus which contain DNA are elaborated.

Q. The following are DNA containing viruses:

a) rhinovirus
b) herpes virus
c) vaccinia
d) yellow fever
e) influenza

Ans.

a) **False** Rhinoviruses are upper respiratory tract vruses causing the common cold. They are a subgroup of the picornaviruses, a group which also includes the enteroviruses. Their habitat is the nose and they areamongst the smallest of all viruses infecting man.

b) **True** The herpes viruses cause herpes simplex, varicella/ zoster, cytomegalic inclusion disease and infectious mononucleosis. They are DNA viruses with a capsid of cubical symmetry possessing no outer envelope. Among the most interesting members of this group is the Epstein—Barr virus which is the cause of infectious mononucleosis and is also found in children suffering from Burkitt's lymphoma in Central Africa.

c) **True** Vaccinia is a large brick shaped DNA containing virus belonging to the group known as the poxviruses. Included in this group is also the virus responsible for smallpox.

d) **False** Yellow fever is caused by an RNA containing togavirus, most of which are arthropod borne, hence the collective name for the group, the ARBOR viruses.

e) **False** The Influenza virus is an RNA myxovirus. The capsid has a helical symmetry and an outer envelope. This group of viruses undergo frequent antigenic variations making it difficult to prepare effective vaccines. Epidemic influenza is caused by the subgroup Influenza A.

Q. The Epstein—Barr virus is associated with: (FCPS – Sur – 08Ju)

a) glandular fever
b) the Australia antigen
c) Burkitt's lymphoma
d) nasopharyngeal carcinoma
e) the common cold

Ans.

a) **True** The Epstein—barr virus (EBV) is a herpes virus. The peripheral lymphocytes in patients suffering from this disease can be shown to contain the virus. Furthermore, during the acute phase of the illness antibodies to EBV can be identified in the patient's serum. In addition individuals suffering from infectious mononucleosis also develop heterophile antibodies in the serum which are capable of agglutinating sheep erythrocytes; such antibodies are not absorbed by guinea-pig kidney but can be absorbed with ox erythrocytes, the basis of the Paul-Bunnell test.

b) **False** The Australia antigen is not associated with infection by the EBV. It is associated, however, with the hepatitis B virus and is the name originally given to Hepatitis B surface antigen (HBsAg) because this antigen was originally identified in the serum of an Australian aborigine.

c) **True** The EBV was first isolated from cultures of lymphoblasts in children suffering from Burkitt's lymphoma, a tumour affecting the jaws and facial region of children in Central Afirca. It is especially prevalent in malaria endemic areas possibly because chronic malarial infection reduces immunity to the virus. An unexplained finding is the relatively low titre of anti-EBV antibodies found in Burkitt's lymphoma.

d) **True** Nasopharyngeal carcinoma is associated with a high titre of antibodies to EBV.

e) **False** The common cold is associated with rhinoviruses, a subgroup of the picornaviruses.

Q. The hepatitis B virus:

a) is transmitted by the oral route
b) is transmitted by dogs
c) is common in renal dialysis units
d) is the cause of Burkitt's lymphoma
e) causes immune complex disease

Ans.

a) **True** Hepatitis B virus (HBV) is a DNA virus transmitted by the oral-faecal route, by aerosols or by syringe and needle. An HBV infection can be detected by identifying the antigen HBsAg in the serum of carriers.

b) **False** There does not appearto be an intermediate host. However, in the tropics a mosquito, vector has been suspected.

c) **True** Renal dialysis units are high risk areas for HBV infection as infection is common in people with chronic renal ilure. A number of renal units have been associated with a high mortality among doctors and nursing staff from HBV infection. Other groups in which HBV is common are workers in mental hospitals, drug addicts and homosexuals.

d) **False** Burkitt's tymphoma is associated with EB virus infection. HBV infection has, however, been associated with primary hepatoma particularly in the tropics.

e) **True** HBV infection may be associated with polyarteritis nodosa and arthritis. Immunoglobulin and complement have both been demonstrated in the walls of bfood vessels and immune complexes containing HBV have been demonstrated as aggregates in the serum of infected individuals by electron microscopy.

Q. Serum levels of HBsAg may be high in:

a. lepromatous leprosy
b. tuberculosis
c. Down's syndrome
d. heroin addicts
e. malignant melanoma

Ans.

a. **True** The titre of HBsAg antigen tends to be high in the inmates of institutions such as prisons and leprosaria. Since the majority of individuals suffering from lepromatous leprosy are found in leprosaria, it follows that a higher than normal incidence of HBsAg positivity occurs in these patients.

b. **False** Since the treatment of tuberculosis no longer requires long term residence in sanatoria an increased incidence of HBsAg positivity in this condition does not occur.

c. **True** A higher incidence of HBsAg than normal has been reported in Down's syndrome. The cause for this remains unknown and is particularly difficult to explain since these patients are not usually confined to institutions or particUlarly immunodeficient.

d. **True** Heroin addicts have a high incidence of HBsAg positivity because of their use of contaminated syringes and needles

e. **False** Patients suffering from neoplastic diseases do not appear to have an increased incidence of HBsAg positivity., They are, however, at risk if they require multiple transfusions or long stay residence in hospital.

Q. The following viral infections are controlled by cell-mediated ithmunity:

a) herpes simptex
b) cytomegalic inclusion disease
c) poliomyelitis
d) ECHO virus
e) vaccinia

Ans.

a) **True** The herpes simplex virus can cause severe generalized visceral disease in children born with a primary T-lymphocyte deficiency.

b) **True** This ubiquitous virus causes a'disseminated infection which particularly affects the upper respiratory tract of babies with T-lymphocyte deficiency, adults receiving immunosuppressive drugs and individuals in whom cell-mediated immunity has diminished due to the development of Hodgkin's disease.

c) **False** The polioviruses are classified as picornaviruses among which are the echoviruses and the rhinoviruses which cause upper respiratory tract infections. The polio virus causes a non-specific gastroenteritis and in approximately 1:100 of those infected secondarily invades the lower motor neurons to produce a flaccid paralysis. Natural protection from invasion is provided by the MALT system, mucous associated lymphoid tissue, of the gastrointestinal tract which by secreting a humoral immune response of the IgA isotype prevents invasion.

d) **False** The ECHO viruses are a subgroup of the picornaviruses, the name standing for 'enteric cytopathogenic human orphan'. This group is responsible for a variety of febrile illnesses including meningitis, respiratory infections, conjunctivitis and diarrhoea. As with the polioviruses it is believed that natural protection is dependent upon the production of an IgA antibody by the gastrointestinal tract.

e) **True** The 'reaction of immunity' to vaccinia virus is a delayed hypersensitivity reaction seen when the individual is vaccinated on the second or subsequent occasions. This reaction is T-lymphocyte mediated as is resistance to clinical infection. The presence of immunity is marked by the failure of the4viividual to develop a 'pock' at the vaccination site.

Q. Interferons:

a) are cytokines
b) can be produced in response to mitogens
c) are components of the complement system
d) are important in viral infections
e) are a dialysable fraction

Ans.

a) **True** The interferons are a group of proteins whose chief function is to regulate the immune system. Three groups have so far been recognized: IFN which is made up of a number of variants which are produced by leucocytes, IFNβ made by fibroblasts and IFN made by T cells.

b) **False** Mitogens such as phytohaemoglutinin and concanavalin A stimulate human and mouse T cells resulting in the increased expression of existing surface markers such as the adhesion molecules which allow increased interaction with other cells.

c) **False** The complement system is an entirely different group of proteins whose chief function is to protect an individual from bacterial infections by promoting lysis, opsonisation and chemotaxis.

d) **True** The interferons provide protection against viral infections by a number of different mechanisms; by the activation of killer cells with the ability to destroy virus infected targets and by direct inhibition of viral replication. The importance of the interferons has been demonstrated in vivo by treating mice with antibodies to murine interferons. Such mice are killed by a dose of virus several hundred times less than the untreated controls.

e) **False** The interferons do not pass through a dialysis membrane.

MNEMONICS

সূত্র = ১: DNA containing viruses: pH pH pA

Herpesviruses	Papovaviruses
Hepadnaviruses	Pox viruses
AdenoviwseS	Parvoviruses
All DNA viruses are double stranded except Parvoviruses.	

Comparison of DNA and RNA viruses in general.

• All DNA viruses are double stranded except parvovirus and naked (except for herpesvirus, poxvirus and hapadnavirus).

• All RNA viruses are single-stranded (except reovirus) and enveloped (except for picomavirus and reovirus).

সূত্র = ২: Epstein Barr virus associated diseases are: BONI (বনী)

B = Barkitt's lymphoma
O = Oral hairy leucoplakia (in AIDS patients)
N = Nasopharyngeal carcinoma.
I = Infectious mononucleosis.

সূত্র = ৩ : Congenital rubella syndrome is associated with the following abnormalities:

COOL STARS

C = Chromosomal abnormalities
O = Osteopathy
O = Oculopathy (cataract, cloudy cornea).
L = Liver & spleen enlargement
(Hepatosplenomegaly & Jaundice).

S = Sensory neural deafness
T = Thrombocytopenia
A = Anaemia
R = Retinopathy
S = Septal defects & PDA.

সূত্র = ৪: The followings are the live/ killed/ toxoids vaccines:

MY TB VIP

M — MMR, (Mumps, measles, Rubella)
Y — Yellow fever
T — Typhoid
B — BCG
V — Varicella
I —Influenza
P — Polio

To remember the name of Toxoid (inactivated toxin) try to remember w`wZ (DT)
D — Diphtheria
T — Tetanus
All other vaccines except **MY TB VIP and** দিতি are killed or inactivated or conjugated vaccines.

সূত্র = ৫: Both live and inactivated vaccines are available for: TIP

- Poliomyelitis
- Typhoid
- Influenza

সূত্র = ৬: Live vaccines are contraindicated in: AMI PC

A — Acute infection
M —Malignancy
I — Immunosuppression
P — Pregnancy
C — Corticosteroid (high dose)
NB: All other conditions except **AMI PC** are not contraindications of live vaccination.