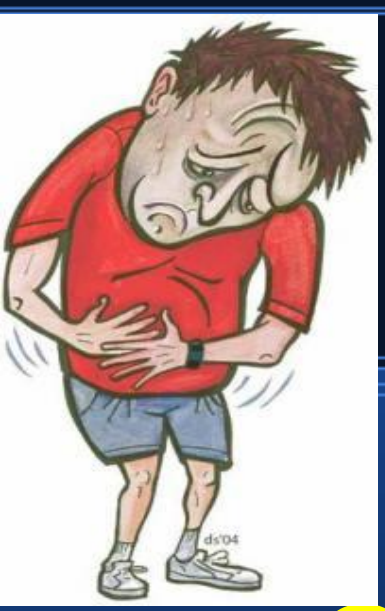


Gastro-intestinal infections

Clinical manifestations - according to the segment concerned of the digestive tract

- Acute gastritis - which affects the stomach and is evidenced by nausea, vomiting, pain in epigastrium.
- Acute gastroenteritis - which affects the stomach and small intestine include, clinical manifestations including further colicative abdominal pain and diarrhea
- Acute gastroenterocolitis -affects the stomach, small intestine and colon.
- Acute enterocolitis - affected the small intestine and colon.

ETIOLOGY

- Noninvasive acute enterocolitis pattern can be produced by Vibrio cholerae, enterotoxic E. coli, Enterobacter, Klebsiella, Clostridium perfringens, Bacillus cereus, Staphylococcus aureus, Citrobacter, Arizona and the following viruses: Rotavirusuri, Norwalk, Baltimore, Parvovirus, Minireovirus, Astrovirus, Adenovirus, Calicivirus, enteroviruses.
- Invasive acute enterocolitis pattern may be caused by Shigella, Salmonella, enteropathogen and enteroinvasive E. coli , Yersinia enterocolitica, Campylobacter jejuni, Vibrio parahemolyticus, B hemolytic streptococci group A and group D enterococci, Proteus, Piocianic
- Systemic enterocolitis may be caused by Enterobacteriaceae: Salmonella, E. coli, Yersinia enterocolitica, Campylobacter, Shigella, Klebsiella, Enterobacter, Yersinia, Proteus, Arizona, Citrobacter.

Epidemiology

Reservoir of infection can be the sick man / carriers or an animal

Almost all domestic and wild animals can eliminate Salmonella.

E. coli is found more frequently in cattle, and Vibrio cholerae in crustaceans and molluscs. Foods containing these animal products can cause illness (milk, milk products, especially duck eggs, meat products).

Route of transmission is fecal-oral.

Contamination may be direct (direct contact with patients or carriers of germs from dirty hands) or indirectly (contamination of various objects, food, water).

THE ORGANISMS DEFENCE

Age

infants - intestinal microbial flora is not fully developed and specific immunological factors in the intestinal tract are poor

Personal Hygiene

Enterocolitica outbreak depends on the number of seeds ingested---> necessary number of germs (100,000 - 100 million) to trigger disease. An exception is infection with Shigella, which can produce only 10 to 100 seeds.

Gastric juice acidity and other physical barriers

This barrier may be neutralized by antiacids, hypoacid gastritis, increased liquid ingestion (as happens in summer) . Another physical barrier is the integrity of gastrointestinal mucosa and biochemical composition of intestinal mucus

Intestinal motility

a) Inhibition of intestinal motility leads to inhibition of Na + and water absorption.

b) Intestinal stasis favors excessive development of bacteria.

Normal intestinal microflora

Loss of the normal intestinal flora, or changes in its balance, caused by antibiotics, often leads to its replacement by other pathogenic microbes that can cause developing severe infections. Endogenous intestinal flora has been shown to attach to receptors of intestinal mucosa and acting through a competitive mechanism preventing attachment of pathogens.

Local specific immunity

Disorders of humoral immunity, particularly in the production of Ig A, and cellular immunity, favor the onset of gastrointestinal infections

Protective factor in milk and serum

The mother's milk are a number of factors such as lactoferrin, lysozyme, phagocytes, acting bacteriostatic and bactericidal.

Microorganism's aggresion

- Enterotoxins are attached to specific receptors in the intestine ---> a massive loss of water and electrolytes in the faeces leading to isotonic dehydration and metabolic acidosis. Intestinal mucosa do not show inflammatory changes remain intact. Therefore stools are watery, no mucus, blood and leukocytes. Thus Vibrio cholerae produces enterotoxin secretion of water and electrolytes through activation of adenylcyclase increasing the intracellular cyclic ATP, which stimulates the secretion to the intestinal lumen Na, Cl, K, bicarbonate and water. The mechanism acts like thermolabile enterotoxin of E. coli. Thermostable enterotoxin of E. coli acts on guanyl cyclase with increasing concentrations of cyclic GMP, with similar effects . Some strains of Shigella, Salmonella, Clostridium perfringens, Klebsiella, Enterobacter, Citrobacter enterotoxin which can cause the exact mechanism of action is not elucidated causes *noninvasive enterocolitis--- prototype model is cholera*

- Cytotoxin products of different intestinal pathogens act mainly in the large intestine and are responsible for inflammation at this level. After penetrating the intestinal mucosa, germs multiply, have cytolytic effects and cytotoxins are released. The intestinal mucosa is an ulcerative colitis with pathological factors: mucus, blood, pus, white blood cells and destroyed epithelial cells . *-causes invasive enterocolitis-- prototype model is dysentery*

- There is a third pathogenic mechanism that is systemic mechanism. Bacilli reach the small intestine where they multiply penetrates the intestinal mucosa ----> in the blood causing a secondary metastatic sepsis and systemic toxicity. Systemic enterocolitis model is the typhoid infection

Microorganism's aggresion

Neurotoxins are usually ingested as preformed toxins in food, stimulates vagal receptors in the intestinal tract, which then transmittes/(or act directly) the excitation to the vomiting center. These neurotoxins are produced by Staphylococcus and Bacillus cereus. With short incubation period (30 minutes to 6 hours) and began with nausea and vomiting.

Endotoxin is a lipopolysaccharide (or LPS). Pyrogens are in the wall of all Gram negative. The lipid A(part of LPS) is responsible for biological properties of endotoxins. They are:

---- initial leukopenia as a result of margination of circulating leukocytes and leukocytosis by stimulating bone marrow.

---- thrombocytopenia

---- disseminated intravascular coagulation

---- complement activation by alternate pathway

---- damages of the vascular endothelium leading to release of histamine, kinin, serotonin

---- depress myocardial function by direct action

---- alters the metabolism of carbohydrates, fat, protein

----ACTH promotes the release site and growth hormone

----is responsible for generalized Shwartzman phenomenon

Shwartzman reaction, is a rare reaction of a body to endotoxins, which cause thrombosis in the affected tissue.

Clinical

- Dyspeptic digestive syndrome
  - manifested by loss of appetite by anorexia, nausea, vomiting,colicative diffuse abdominal pain tenesmus in small children can lead to prolapse of the anal mucosa, in dysentery you can feel the descending colon spastic, a sign called "colic rope" .
- Noninvasive diarrhea is watery, without mucus or blood,the microscopic examination shows no leukocytes, red blood cells, skin cells exfoliate. The stools are very numerous in cholera – can lose tens of liters of fluid per 24 hours , containing mucus with the appearance of white grain "rice soup"
- The invasive enterocolitic stools contains mucus, blood or pus, had a musty odor and microscopic examination shows the presence of white blood cells, red cells, epithelial cells. In dysentery stools are numerous, in small quantity and are emptied by faeces. Salmonellosis stool is green "mashed peas "appearance and in E. coli infection looks yellowish.
- Febrile syndrome
- Dehydration syndrome manifested as thirst, dry mucous membranes, sunken eyes with prominent nose, dry skin with reduced or persistent skin fold. Biological Ht is increased, leukocytosis

Clinical

- Shock Syndrome
  by adding a component of endotoxin shock due to Gram-negative bacilli endotoxins.
- Renal Syndrome
  -if the shock is prolonged acute renal failure may occur--oliguria, -with albuminuria, cilindruria and blood urea and creatinine are elevated.
- Disorders of ionic and acid-base balance
  - hypo-K + with muscular asthenia and cardiac rhythm disorders, hypo Na + with muscle pain, hypo Ca + + - muscle cramps and metabolic acidosis. If vomiting predominate metabolic alkalosis may occur by loss of Cl-.
- Syndrome of nervous intoxication
  Manifested by headache, meningism, drowsiness.

Laboratory

Blood : Serum ionogram and Astrup parameters, CBC, proteinemia, urea, creatinine, urinalysis.

Leukocytes in stool examination

Coprocultures establishing etiologic diagnosis-- at least 3 and collected before antibiotic administration.

Serological tests - determin bacterial serotype and highlights the enterotoxin.

Symptom	Minimal or no Dehydration (<3%)	Mild to Moderate (3%-9%)	Severe (>9%)
Mental Status	Alert	Normal, restless, irritable	Lethargic, unconscious
Thirst	Normal PO or refuses	Thirsty	Drinks poorly or unable
Heart Rate	Normal	Normal to increased	Tachycardia
Quality of pulses	Normal	Normal to decreased	Weak or impalpable
Breathing	Normal	Normal to fast	Deep
Eyes	Normal	Slightly sunken	Deeply sunken
Tears	Present	Decreased	Absent
Oral mucosa	Moist	Dry	Parched
Skin fold	Instant recoil	Recoil in < 2 sec	Recoil > 2sec
Capillary refill	Normal	Prolonged	Prolonged; minimal
Extremities	Warm	Cool	Cool, mottled, cyanotic
Urine output	Normal to decrease	Decreased	Minimal

Management of diahrrea

- Breastfed infants with acute diarrhea should be continued on breast milk without any need for interruption- Breast milk contains many substances that promote bowel growth and antagonize bacteria
- The BRAT diet (ie, bananas, rice, applesauce, toast) - is adequate during early convalescence, but, as the patient tolerates solid food, advance the diet to provide adequate protein and caloric intake
- Lactose ingestion- a very transient use of lactose-free formulas (5-6 days) can be considered.
- Oral or iv rehydration therapy
- Antimicrobial therapy is indicated for some bacterial gastroenteritis infections.

Assessment of degree of hydration

No dehydration

1) Age-approriate diet.
2) Replace ongoing losses with oral replacement solution (ORS).

Mild dehydration (< 5%)

1) Rehydrated with ORS (50 mL/kg) over 4 hours.
2) Replace ongoing losses with ORS.
3) Age-appropriate diet after rehydration.

Moderate dehydration (5% to 10%)

1) Rehydrated with ORS (100 mL/kg) over 4 hours.
2) Replace ongoing losses with ORS.
3) Age-appropriate diet after rehydration.

Severe dehydration (> 10%)

1) Intravenous resuscitation with normal saline or Ringer lactate (20 to 40 mL/kg for 1 hour.
2) Re-assess and repeat if necessary.
3) Begin oral replacement therapy (ORT) when patient is stable.
4) Replace ongoing losses with ORS.
5) Age-appropriate diet after rehydration.

	0 to 10 kg										10 to 20 kg										20kg and over									
	4 mls /kg /hr										2 mls /kg /hr										1 ml /kg /hr									
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
8 kg child:	4 x 8																													
15 kg child:	4 x 10								plus		2 x 5																			
28 kg child:	4 x 10								plus		2 x 10									plus	1 x 8									

Table 1. Antimicrobial agents used most frequently for the treatment of acute infectious diarrhea

Drug	Posology	Remarks
Ampicillin	50-100 mg/Kg/day in four doses if weight under 20 Kg; for children above 20 Kg 250-500 mg four times a day if weight above 20 Kg	Empirical use not recommended unless supported by up-to-date knowledge of local susceptibility patterns. Combinations with beta-lactamase inhibitors may be especially useful for treating outpatients.
TMP-SMX	10/50 mg/Kg/day in 2 doses	Empirical use not recommended unless supported by up-to-date knowledge of local susceptibility patterns.
Chloramphenicol	50-100 mg/Kg/day in 4 doses	Currently, has its use limited to typhoid fever. Widespread resistance may render it not suitable for empirical use in many areas. Caution with aplastic anemia.
Tetracycline	20-50 mg/Kg/day in 4 doses	Do not use in children younger than 8 yrs-old. High resistance rates in several areas.
Doxycycline	2-4 mg/Kg/day in 1-2 doses*	Do not use in children younger than 8 yrs-old, unless as a last resort for severe cholera. Tetracycline preferred for young children.
Nalidixic acid	55 mg/Kg/day in 4 doses	Still useful in many areas of the world, despite high resistance rates in others. Affordability is a major advantage.
Ciprofloxacin	20-30 mg/Kg/day in 2 doses	No empirical use in children except in some individual cases strongly suspected of being caused by *Shigella sp.* or typhoid *Salmonella* resistant to safer agents. The commonest drug used in adolescents with bloody Traveler's diarrhea.
Ceftriaxone	50-100 mg/Kg/day in 1-2 doses	Safe and effective, but expensive. Reserve for use in cases of evident dissemination of disease. Avoid use in infants younger than 1 year.
Cefixime	7.5-10 mg/Kg/day in 1-2 doses	Safe and effective, but expensive. Reasonable choice for treating outpatients.
Azithromycin	5-12 mg/Kg/day in a single dose	Safe and effective, but expensive. Reasonable choice for treating outpatients.
Metronidazole	20-40 mg/Kg/day in 3 doses	Drug of choice for antibiotic-associated diarrhea.
Rifamixin	600 mg/day in 3 doses**	Promising drug for empirical therapy due to low tendency for side effects and raising antimicrobial resistance

* Adult dosing (100 mg twice a day) may be used if weight above 45 Kg. **Adult dosing. No pediatric data.

Bacillary dysentery
Etiology

Dysenteric bacilli belong to the genus Shigella, the family Enterobacteriaceae.

They are immobile, unsporulated Gram-negative bacilli of the intestinal habitat. Genus Shigella is divided into 4 subgroups: A, B, C, D, each containing several serotypes.

- Subgroup A is the species of Shigella dysenteriae serotypes 10 (1 Shigella Shigae, 2 Shigella Schmitzii, 3.10 Large-Sachs).
- Subgroup B - Shigella flexneri, with 6 serotypes.
- Subgroup C - Shigella boydii, with 15 serotypes
- Subgroup D - Shigella sonne one serotype

Shiga invasion

- Shiga toxin (Stx) - true Shiga toxin is produced by Shigella dysenteriae.Shiga toxins act to inhibit protein synthesis within target cells
- All virulent strains of Shigella flexneri possess a plasmid that mediates its virulence properties. This so-called the invasion plasmid has been shown to encode the genes for several aspects of Shigella virulence, including

- Adhesins that are involved in the adherence of bacteria on the surface of target epithelial cells
- The production of invasion plasmid antigens (Ipa) that have a direct role in the Shigella invasion process

Bacillary dysentery Pathophysiology

- Bacilli ingested with food pass without difficulty gastric acid barrier, reach the large intestine where it multiplies. Colonic epithelial cell invasion --->spread infection from one cell to another, acting through pyrogens (possibly citotoxin or enterotoxin), causing epithelial cell damage and local nerve irritation (tenesmus).
- impaired intestinal motility and inhibition of intestinal secretion promotes the proliferation of dysenteric bacilli.
- the intestinal mucosa with areas of necrosis and ulceration predominently involved the sigmoid and rectum. When ulceration is not too large is healing without scars, but when is infected and extended ---->scar healing, fibrosis and even intestinal stenosis. Dezenteric bacilli enters the bloodstream only exceptionally.
- Immunity is serotype specific but appears to be protective.

Bacillary dysentery
Clinical

Incubation is 2-4 (1-7) days.
Onset is sudden, manifested by abdominal cramps, tenesmus, diarrheal watery stools, fever.

Dyspeptic digestive syndrome is characterized by typical small stool amounts (as a spoon) – sputum like -empty of faeces, composed of mucus, blood and pus, smelling musty, 20-50 stools / 24h.Typical appear tenesmus and intestinal cramps.
Febrile syndrome is versatile (can miss), manifested by fever 38-39 ° C.
Nervous syndrome occurs mainly in dysentery on Sh. dizenteriae - neurotoxin
Syndromes of dehydration, shock and renal failure are rare, because although the stools are very common in dysentery, their amount is small.

Bacillary dysentery
Lab Diagnosis

Coprocitogram

- Fecal leukocytes (confirming the presence of colitis)
- Fecal blood

Stool culture- positive in the first phase, the index of positivity decreased in convalescence.

Blood

- leukocytosis with neutrophilia
- changes in blood ionogram with hypo Na, K, Ca and Astrup parameters changes with metabolic acidosis.

Serological diagnosis is used only for epidemiological studies

Bacillary dysentery
Clinical forms

- After severity :
  - mild - as a ordinary enterocolitis
  - medium
  - severe caused mainly by Shigella dizenteriae, characterized by severe nervous symptoms, dehydration and shock
- After age appear:
  - infant forms (atypical with fetal evolution)
  - small child forms (with more frequent atypical manifestations)
  - adult forms
  - old forms (more frequent toxic form and severe evolution)
- After clinical status :
  - Typical forms
  - Atypical forms that simulate food or ordinary enterocolitis
  - Chronic dysentery occurs following an ignored/untreated/acute dysentery with elements of reactivity

Bacillary dysentery
Prognosis

treated correctly for both clinical and bacteriological cure ---- excellent

Dysentery untreated can develop into a slow recovery, but long convalescence and many recrudescent, or to a state of chronic carriers of dysenteric bacilli.

Another possible evolution is chronic, which may occur in 2-4% of cases.

Bacillary dysentery
Differential diagnosis

WITH the acute invasive enterocolitis caused by

- E. coli enteroinvasive Shiga toxin producing E Coli 0157:H7
- Salmonella
- Yersinia enterocolitica
- Campylobacter jejuni
- Paratifoid fevers,
- Entamoeba histolytica

WITH lower gastro-intestinal bleeding :ulcero-hemorrhagic colitis, rectal polyps, rectal cancer, mesenteric infarction, hemorrhoids, intestinal invagination.

Bacillary dysentery Complications

- Dehydration – most common
- chronic colitis, paresis and paresthesia ,sd. Fissinger-Leroy- Reiter (reactive arthritis)
- Other complications are the consequence of intestinal lesions of chronic colitis, anemia, malabsorbtion with avitaminosis occurring in dysentery in infants with chronic or long evolution of the disease.
- Cholestatic hepatitis
- Pneumonia
- S.dysenteriae serotype 1 – Shiga Toxin- produces hemolysis, anemia--> hemolytic uremic syndrome

Bacillary dysentery Treatment

- Proper rehydration and diet
- Because shigellosis is self-limiting, some authorities recommend withholding antibiotic therapy. However, even if not fatal, the untreated illness may cause chronic or recurrent diarrhea, this may lead to malnutrition The risk of continued shedding of organisms in stool increases the risk of transmission of further disease among contacts argues against withholding antimicrobial treatment.
- Antibiotic treatment
- effective for susceptible strains Ampicillin 50-100 mg/kg/d PO divided q4-6h and TMP-SMZ >40 kg: 160 mg/dose PO bid and children >2 months: 8-10 mg/kg/d PO divided bid for 5 d
- If ampicillin and TMP-SMZ resistant strain is isolated or if susceptibility is unknown, parenteral ceftriaxone sodium adult 2 g IV/IM, child 50-100 mg/kg/d IV/IM for 5 d , a fluoroquinolone (eg, ciprofloxacin, ofloxacin), or azithromycin dihydrate are the drugs of choice

Cholera

The word cholera is derived from a Greek term that means "flow of bile." Cholera is caused by Vibrio cholerae, the most feared epidemic diarrheal disease because of its severity. Dehydration and death can occur within hours of infection.

Cholera
History

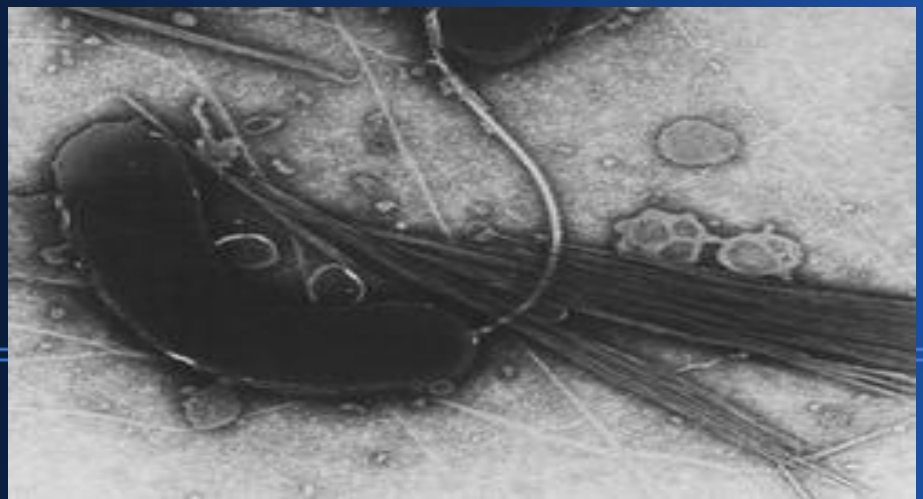
- The modern era has seen 7 cholera pandemics .

- Top 6 developed between 1817-1923 and were caused by VH (Vibrio cholerae) classic O1-serotype . They have evolved from Asian (Indian subcontinent), with further expansion in Europe and America

- 7th cholera pandemic is driven by the VH O1 biotype El Tor, a biotype which was originally isolated in Egypt (the early twentieth century) and was associated with sporadic cases until 1961.

Cholera
Etiology

- The organism is a comma-shaped, gram-negative aerobic bacillus whose size varies from 1-3 µm in length by 0.5-0.8 µm in diameter, belongs to genus Vibrio, the gamma subdivision of the Proteobacteria.
- Its antigenic structure consists of a flagellar H antigen and a somatic O antigen.
- The species *V. cholerae* can be sub-classified into 200 serogroups based on the O antigen of LPS (lipopolysaccharide).
- Only O1 and O139 strains - implicated in the cholera syndrome.



Cholera
Antigenic structure

- Vibrio cholerae serogroup O1, containing 13 antigenic factors, noted with the first 13 capital letters of the alphabet: A-M.
- V cholerae O1 is classified into 2 major biotypes: classic and El Tor. Currently, El Tor is the predominant cholera pathogen.
- Organisms in both biotypes are subdivided into serotypes according to the structure of the O antigen, as follows:
  - Serotype Inaba - O antigens A and C
  - Serotype Ogawa - O antigens A and B
  - Serotype Hikojima - O antigens A, B, and C

Cholera
Epidemiology

Habitat - Vibrions live in sea water or surface water. The diseases they produce appear on the sea coast, in summer-autumn seasons or in connection with the consumption of seefood. Seasonality is another characteristic of cholera. Epidemics tend to occur in warm seasons and in countries where there is more than 1 hot season / year.

Transmission- fecal-oral route. Owing to the relatively large infectious dose, transmission occurs almost exclusively via contaminated water or food.

Receptivity is general. Pregnant women are serious forms of disease-abortion or premature birth. Direct transmission through inter-human contact is possible.

Immunity from the disease is fairly effective and long lasting.

Sensitivity to antibiotics: Classical Vibrio cholerae is highly sensitive to Tetracycline, and is sensitive to Chloramphenicol, Ampicillin, Erythromycin, Neomycin, Furazolidone.

Cholera Pathogenesis

Low infectious dose is required :103 -106 organisms to produce disease.

V cholerae O1 and V cholerae O139 cause clinical disease by producing an enterotoxin - promotes the secretion of fluid and electrolytes into the lumen of the small intestine. The enterotoxin is a protein molecule composed of 5 B subunits and 2 A subunits. The B subunits are responsible for binding to a ganglioside (monosialosyl ganglioside, GM1) receptor located on the surface of the cells that line the intestinal mucosa.

The activation of the A1 subunit by adenylate cyclase is responsible for the net increase in cyclic adenosine monophosphate (cAMP). cAMP blocks the absorption of sodium and chloride by the microvilli and promotes the secretion of chloride and water by the crypt cells. The result is watery diarrhea with electrolyte concentrations isotonic to those of plasma.

Fluid loss originates in the duodenum and upper jejunum; the ileum is less affected. The colon is usually in a state of absorption because it is relatively insensitive to the toxin. However, the large volume of fluid produced in the upper intestine overwhelms the absorptive capacity of the lower bowel, resulting in severe diarrhea.The enterotoxin acts locally and does not invade the intestinal wall. As a result, few neutrophils are found in the stool.

Cholera
Clinical

After a 24- to 48-hour incubation period

- sudden onset of painless watery diarrhea that may quickly become voluminous and is often followed by vomiting. The diarrhea has a "rice water" appearance and a fishy odor. In patients with severe disease, the stool volume can exceed 250 mL/kg in the first 24 hours. Without replacement of fluids and electrolytes--> hypovolemic shock and death .

- accompanying abdominal cramps.

-Fever is typically absent. Full recovery is achieved within 5-8 days.

The amount of fluid loss and the corresponding clinical signs of cholera are as follows:

* With 3-5% loss of normal body weight - Excessive thirst

* With 5-8% loss of normal body weight - Postural hypotension, tachycardia, weakness, fatigue, and dry mucous membranes or dry mouth

* With greater than 10% loss of normal body weight - Oliguria; glassy or sunken eyes; sunken fontanelles in infants; weak, thready, or absent pulse; wrinkled "washerwoman" skin; somnolence; and coma

Cholera Lab studies

Hypovolemia

- Elevated hematocrit
- Neutrophil leukocytosis
- Elevated blood urea nitrogen and creatinine levels consistent with prerenal azotemia.
- Hypovolemia may cause hyperglycemia secondary to systemic release of epinephrine, glucagon, and cortisol.

- Diagnosis may be confirmed via identification of V cholerae in the stool. The organism may be detected directly with dark-field microscopy examination of a wet mount of fresh stool; chaotic motility is observed.
- Laboratory isolation requires a selective medium. V cholerae grows as a flat, yellow colony on thiosulfate-citrate-bile salts-sucrose agar or taurocholate-tellurite-gelatin agar.
- PCR has been used with a high degree of sensitivity and specificity.

Cholera
Differential diagnosis

- Food intoxication
- Severe infant diarrhea
- Clostridium enterocolitis after antibiotic therapy
- Enterocolitis with E. coli enteropathogens
- Diahorrea with hormonal disorder

Cholera
Complications and Prognosis

If a patient is adequately treated with fluid and electrolytes, complications are averted and the self-limited process resolves in a few days.

Potential complications include dehydration and volume loss that lead to acute tubular necrosis and renal failure. Hypovolemic shock and death ensue. Relapses are possible in convalescence.

The prognosis is severe cholera. Mortality in untreated cases is 50-80%, but may be decreased by early treatment, even below 1%.

Cholera
Treatment

The primary goal of therapy is to replenish fluid losses caused by diarrhea and vomiting

Rehydration is accomplished in 2 phases, rehydration and maintenance.

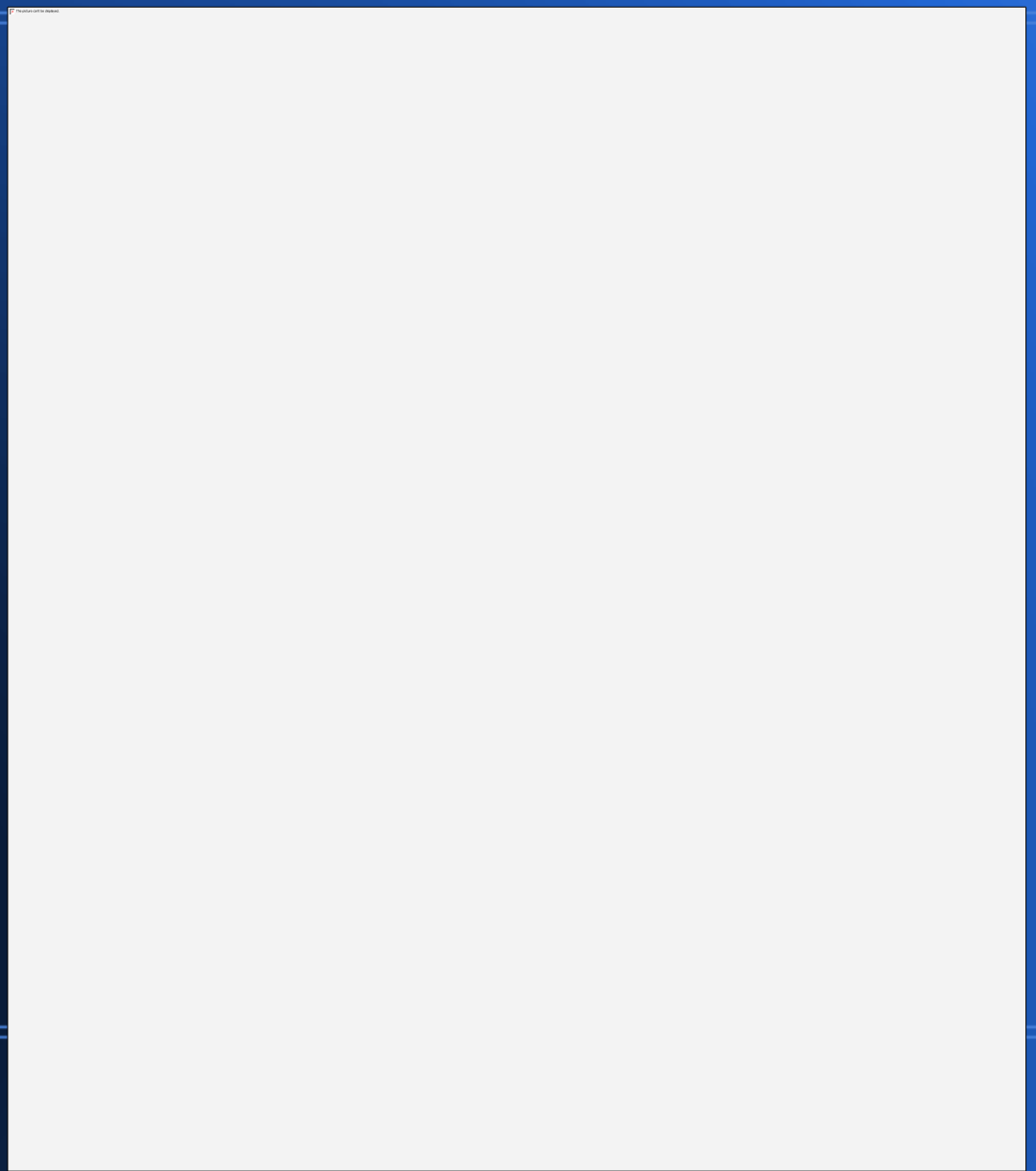
Treatment with an antibiotic to which the organism is susceptible diminishes the duration and volume of the fluid loss and hastens clearance of the organism from stool.

Pharmacotherapy plays a secondary role in the management of cholera.

Treatment of choice is Tetracycline 2 g / day for 3 days or Doxycycline 300 mg PO once

In areas of known tetracycline resistance, therapeutic options include Ciprofloxacin 250 mg PO qd for 3 d or 1 g once, Erythromycin 40 mg/kg PO divided tid for 3 d, Chloramphenicol.

FOOD poisoning



FOOD INTOXICATION (FOOD POISONING)

- **NO INFECTION** (no viable bacteria need to encounter the host)

- **toxin preformed** in the food as a result of bacterial contamination (soil or human)

correlation symptoms ------- food borne illness etiology (1)

1) Nausea and vomiting occurred in 30 min - 6 hours of food intake

Etiology:

Staphylococcus aureus

Bacillus cereus (release thermostable toxin). Short incubation period reflects the fact that these conditions are caused by enterotoxins preformed in food. Ingested with food they trigger the disease. Watery diarrhea occurs in a smaller percent. Disease duration is short, until 12 h

2) Abdominal cramps and diarrhea in 8-16 hours after ingestion of food

Etiology:

Clostridium perfringens (which release a thermolabile enterotoxin)

Bacillus cereus (which release a thermolabile enterotoxin)

nausea may occur, but vomiting and fever are rare. Toxinfection usually resolve in 24 hours.

3) Fever, abdominal cramps, invasive diarrhea in 16-48 hours after ingestion of the food.

Etiology:

Salmonella Shigella E Coli V. Parahaemolytious Campylobacter jejuni

Diarrhea is of invasive pattern with mucus, blood and leukocytes. Toxinfection may take up to a week and relapses may occur in untreated patients.

correlation symptoms ------- food borne illness etiology (2)

4) Colic, watery diarrhea 16-72 hours after ingestion of food

Etiology:

Enterotoxigenic E. coli, V. cholerae, V. parahaemolyticus, Sometimes, Salmonella, Shigella, Norwalk virus

Fever and vomiting are rare. It takes 3-4 days, except VH non-O1, which can take 2-12 days and 1-2 days Norwalk virus.

5) Fever, abdominal cramps 16-48 hours after ingestion of food

Etiology:

Yersinia enterocolitica (producing a thermostable toxin)

Abdominal cramps often mimic an acute appendicitis. Diarrhea is common. It takes 24 hours - 4 weeks.

6) Bloody diarrhea without fever in 72-120 hours after food intake

Etiology:

E. coli O157: H7 that produces a cytotoxin.

Originally diarrhea is watery, with blood and mucus and accompanied by abdominal cramps.

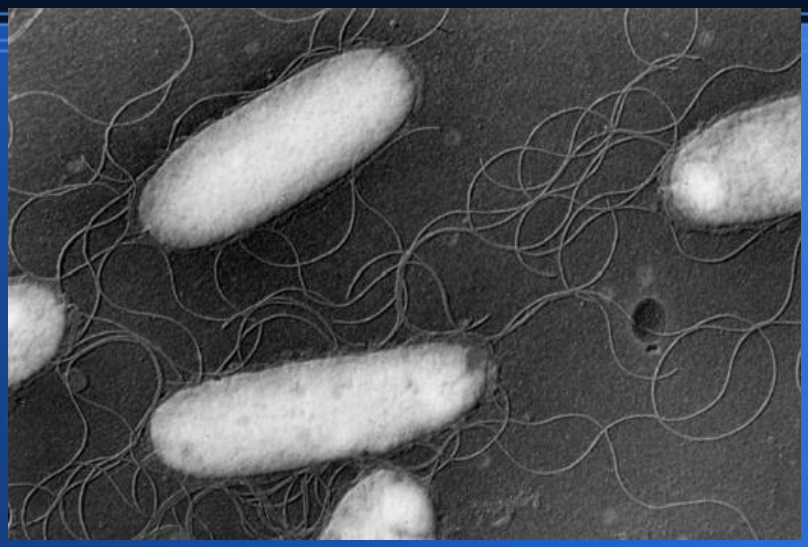
It takes 1-12 days.

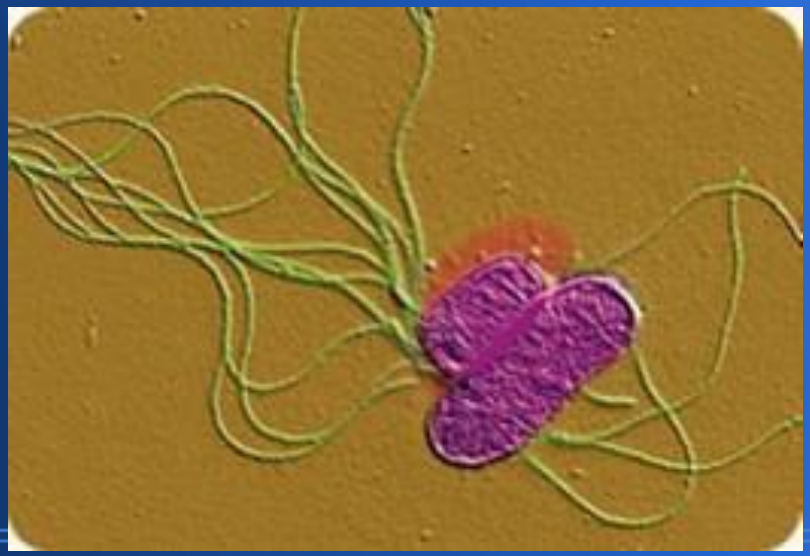
SALMONELLA

Salmonella is a rod-shaped, facultative anaerobe in the family Enterobacteriaceae

- Gram-negative
- Facultative anaerobes
  - Glucose-fermenting
- Straight, rod
- 2-3 µm in length
- Flagellated

- Many serovars
  - Typhi
  - Typhimurium
  - Enteriditis





Different types of Salmonella

Three clinical forms of salmonellosis

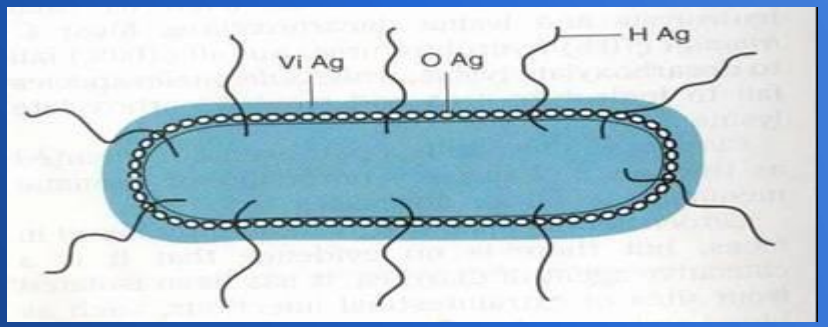
- Gastroenteritis (*S. typhimurium) Food poisoning*
- Septicemia (*S. enterica*)
- Enteric Fevers (i.e. *S. typhi* – Typhoid Fever)

Antigenic structure of Salmonella

Over 2000 strains are grouped into S. enterica.

- divided into six subgroups based on three surface antigens, O, H and Vi.

I - *enterica*
II - *salamae*
IIIa -*arizonae*
IIIb -*diarizonae*
IV - *houtenae*
V - *bongori*
VI - *indica*



Somatic or 0 Antigens contain long chain polysaccharides (LPS) comprises of heat stable polysaccharide commonly.

- ***Flagellar or H Antigens*** are strongly immunogenic and induces antibody formation rapidly and in high titers following infection or immunization
- Surface antigen - the Vi antigen. The Vi antigen occurs in only three Salmonella serovars: Typhi, Paratyphi C, and Dublin. Important for epidemiological reason: germ carriers

All strains that are pathogenic to humans are in species S. enterica, subgroup 1 (also called enterica).

Pathology and Pathogenesis of Salmonellosis

- Caused by

  S. typhi

  S.paratyphi

  A B C

The organisms penetrate ileal mucosa--> reach mesentric lymph nodes via lymphatics , multiply, invade blood stream via thoracic duct

In 7 – 10 days through blood stream infects:

Liver, Gall Bladder, Spleen, Kidney, Bone marrow.

After multiplication bacilli pass into blood causing secondary and heavier bactermia

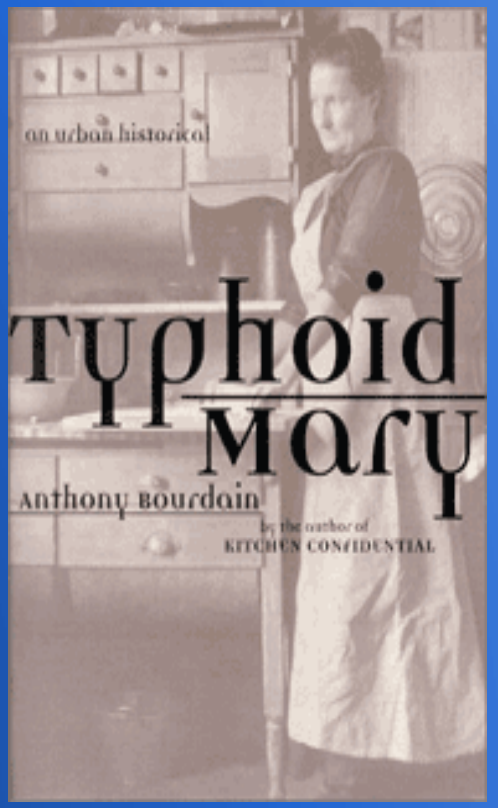
Virulence factors responsible for pathogenicity in enteric bacteria are often encode by plasmids, as in E Coli, Yersinia spp, and Shigella spp. Salmonella spp. The virulence plasmid of Salmonella is important for bacterial multiplication in the rethiculoendotelial system.

Typhoid fever
History

- "Typhoid Mary" Mallon was the first famous carrier of typhoid fever in the U.S.

- Some individuals have natural immunity to Salmonella. Known as "chronic carriers", they contract only mild or asymptomatic disease, but still carry the bacteria in their body for a long time. These cases serve as natural reservoir for the disease.

- One such case was Mary Mallon, who was hired as a cook at several private homes in the new York area in the early 1900's.



Salmonellosis - epidemiology

RESERVOIR

a) multiple animal reservoirs

b) mainly from poultry and eggs (80% cases from eggs)

c) fresh produce and exotic pets are also a source of contamination (> 90% of reptile stool contain *salmonella* bacterium); small turtles,lizards

TRANSMISSION - improperly prepared, previously contaminated food or water - contaminated eggs, medical products of animal origin (billiary salt, tisular extract of thyroid)

CRONIC CARRIER -excreted in feces up to 5 weeks

HIGH RISK -veterinarians, contaminated food consumers

RECEPTIVITY Everyone, especially: the elderly, infants, achlorhydia, immunocompromised patients

Clinical forms

- Nontyphoidal enterocolitis

Infection with nontyphoidal salmonellae usually causes enterocolitis similar to that caused by other bacterial enteric pathogens.

The incubation period depends on the host and the inoculum is generally 12-36 hours (4-48h). In most cases, stools quantitatively rich, watery with mucus and streaks of blood, yellow-green, with fetid odor.
Febrile syndrome remains at high values of 2-5 days The diarrhea is typically self-limiting and resolves within 3-7 days.

Fever, abdominal cramping, chills, headache, and myalgia are common.

- Nontyphoidal focal disease

Focal disease is due to transient or persistent bacteremia. Almost any organ can be affected, with sites of preexisting structural abnormalities being the most vulnerable.

Clinical patterns

- As a particular form, salmonella can take appearance of:
  septicemia (blood poisoning form)
  influenza (flu-like shape)
  dysentery (as disenteric)
  typhoid fever (typhoid form)
  nosocomial form that appears on the background of other conditions
  holeriform form (with watery stools riziforme)
- Depending on the severity are:
  mild (as an acute gastritis)
  medium disease
  severe disease (with dehydration and shock)
  toxic disease (with algid collapse, nervous system involvement, hypothermia)
- Depending on age, are:
  form that appears in infants, which often can give sepsis with secondary outbreaks (otitis, bronhopneumonia, meningitis, angiocolitis, abscesses, osteomyelitis)
  elderly - more severe symptoms.

Typhoid fever
Clinical

The incubation period is 10-14 days

Onset period lasts one week and is characterized by a prodromic phase - with progressive alteration of the general condition and prolonged low-grade fever, frontal headache, malaise, myalgia, dry cough, anorexia, nausea , confusion, stupor
Typhoid fever with atypical symptoms may start and an organ affected by making the clinical picture of: pneumotyphos, pleurotyphos, meningotyphos, colotyphos, nefrotyphos. During the natural evolution of disease, fever has characteristic febrile "trapeze" curve described by Wunderlich, rarely seen today.

Average period lasts 14 days and is characterized by:

a) febrile syndrome
fever remains high at values of 39 - 40 ° C, the entire period with insignificant thermal oscillations, "plateau fever"

b) nervous syndrome -apathy, obnubilation, lying immobile, with disregard to the entourage. Maintain of headache and insomnia. Mild forms of the present stage is characterized by discrete nerve symptoms: headache, insomnia, apathy

Typhoid fever
Clinical

c.)Digestive Syndrome

- loss of appetite, thirst, dry mucous membranes. Tongue with roasted aspect "parrot tongue" the sabural deposit, with red edges .The lips are burned, dry, cracked. Pharynx present Duguet angina sometimes consisting of ovalar gray painless ulceration.The abdomen is sensitive to palpation, especially in right iliac fossa with flatulence, garguiments. Constipation is present in 1 / 3 of cases. Diarrhea in typhoid fever is characterized by liquid stools looking like" mashed peas" yellow greenish , with epithelial exfoliate.

d.)Cardiovascular syndrome

is characterized by decreases in blood pressure, dicrot pulse, sphygmo-thermal dissociation (also known as relative bradycardia or pulse-temperature deficit).Transition from bradycardia to tachycardia and cardiac noise changes, changes in ECG instalation of thyphos miocarditis

Typhoid fever
Clinical

e.)Hepatic-splenic syndrome:

hepato-splenomegaly especially in children

f.)Eruptive syndrome

-3rd week: rose spots (1-2 mm diameter on the skin), blanchable: duration: 2-5 days occurring mainly on the flanks and chest, especially between day 6th and 9th of disease "lenticular spots" (rozeola typhous) can be seen as well in disseminated TB or septicemia. Disappear within 3-4 days without a trace.

Decline of disease is characterized by gradual reduction of fever. Sometimes fever decreases in crisis with sweating and polyuria.

Convalescence is prolonged, there is the possibility of complications. Clinical and bacteriological recovery are not simultaneous. Relapses usually occur within 8-15 days of convalescence.

Typhoid fever  Lab studies

Stool culture - special medium MacConkey agar, eosin-methylene blue agar, agar HE

S.typhi-isolated from stool, urine, roseole, gastric or intestinal secretions, blood, bone marrow

Salmonella species are differentiated by conventional biochemical tests, serological patterns and patterns fagica

The Widal test is used to measure antibodies against O and H antigens of S typhi. Newer diagnostic tests (Typhidot, Tubex) allow direct detection of immunoglobulin M (IgM) antibodies against specific S typhi antigens

Blood : leukopenia, neutropenia, anemia

Typhoid fever Complication

Until the introduction of chloramphenicol to treat typhoid fever, complications were alarming, every organ may be interested in:

- pneumonia, pleuritis, meningo-encephalitis, myelitis, phlebitis, arthritis, cholecystitis, hepatitis, nephritis, endocarditis, pericarditis, purulent arthritis, hemolytic uraemic, skin suppurative complications.

- Intestinal bleeding
- Intestinal perforation mimic an acute abdomen

Typhoid fever
Differential diagnosis

- Non invasive disease
  - Viral enterocolitis
  - E. Coli enteropatogen
  - Arizona, Citrobacter
  - Clostridium perfrigens
  - Klebsiella
  - Cholera
- Invasive disease
  - E. Coli enterohemoragic
  - E. Coli enterotoxic
  - Shigella
  - Campylobacter
  - Yersinia enterocolitica
  - Vibrio parahaemoliticus

Typhoid fever is distinguished from other diseases: tuberculosis, septicemia, malaria, brucellosis, subacute endocarditis, infectious mononucleosis etc

Treatment

- Mild disease- self limited disease- simptomatic treatment -NO ATB - supress normal enteric flora,extends bacterial clearance and predispose to chronic portage

Severe disease -CIPROFLOXACIN

- Gastrointestinal nontyphoidal salmonellosis requiring therapy: 500 mg PO bid for 3-7 d
- Typhoid fever: 400 mg IV bid (switch to PO when tolerated) for a total course of 7-10 d

CEFOTAXIM,CEFTRIAXON Typhoid fever: 2-3 g IV qd for 7-14 d
AZITROMICIN,CLORAMFENICOL 7-14 days

Sometimes chronic portage- colecistectomy- GALLBLADDER REZERVOIR

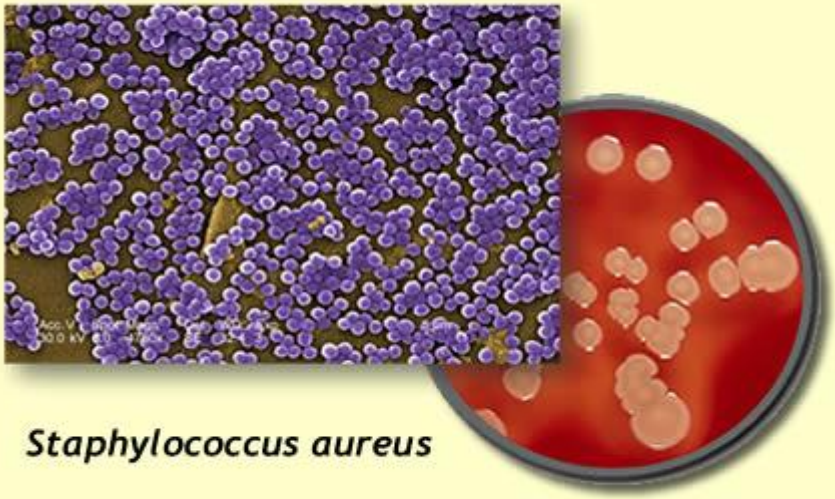
Vaccines for Typhoid Prevention

Two types of vaccines are available

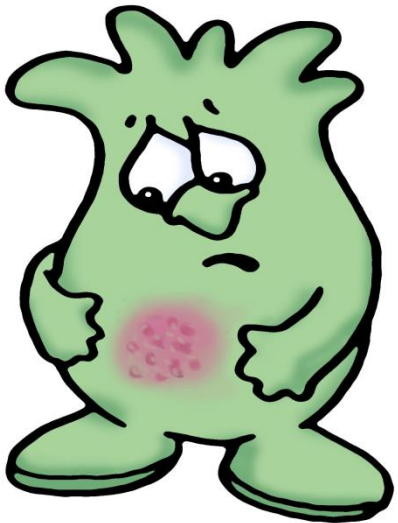
Oral and Inject able

- Oral – A live oral vaccine , one capsule on 1, 3, 5 days (three doses)
- The inject able vaccine, contains purified Vi polysaccharide antigen derived from S.typhi strain ty21

Given as single subcutaneous or intramuscular injection



Staphylococcus spp. gastrointestinal infections



Staphylococcus spp. gastrointestinal infections

Staphylococcus food poisoning occurs following the ingestion of food with preformed staphylococcal

ENTEROTOXIN

2 types of enterotoxin: A and B

a polypeptide structure

its production is enhanced by the presence of microorganisms in the intestine as E. coli, Proteus

heat resistant and is not destroyed by gastric juice

a neurotoxin that acts on peripheral and central vomiting center.

Acute enterocolitis caused by staphylococcus can take other 2 pathogenic models:

- Acute diarrheal disease as a result of pre-existing staphylococcal infection (staphylococcal skin, otitis, angina, bronchopneumonia, arthritis). Appears only in the neonate and small infant to 3 months.
- Pseudomembranous colitis occurs following administration of broad spectrum antibiotics for a long time. Is due to selection of resistant strains of staphylococcus, the destruction of intestinal flora by antibiotics.

Staphylococcus spp.
Gastrointestinal Clinical

The incubation period is short, from 30 min to 3-6 hours, because of the preformed toxin
Onset is usually abrupt, adynamia, with nausea, vomiting, abdominal cramps, dizziness, headache.
During the state period have repeated vomiting, abdominal cramps, and watery diarrheal stools, seromucoase. In severe forms - shock. Seizures may occur in young children, obnubilation, agitation. Fever is not common. The total duration of illness is 1-2 up to 4 days.

The neonate and small infant presents with gastroenterocolitis- pasty diarrheal stools, yellow gold, 3-5 per day, with mucositis. Diarrhea is accompanied by abdominal cramps, vomiting, flatulence, food refusal, agitation. There can progress to ulcerative colitis, which may be complicated by intestinal perforation and peritonitis.

Staphylococcus spp Gastrointestinal disease

Lab diagnosis -for the isolation of presumptive pathogenic staphylococci - Chapman medium- incriminated food, vomiting, stool

Differential diagnosis

other model of noninvasive enterocolitis

Prognosis is good in adults, lethality is less than 1%. It is more severe in infants less, because of the ulcero-suppurative and necrotic intestinal lesions.

Treatment

dietary recommandations- as all acute diarrheal diseases

drug therapy

Electrolite balance and antibiotic treatment if needed.

Acute diarrhea with Escherichia coli

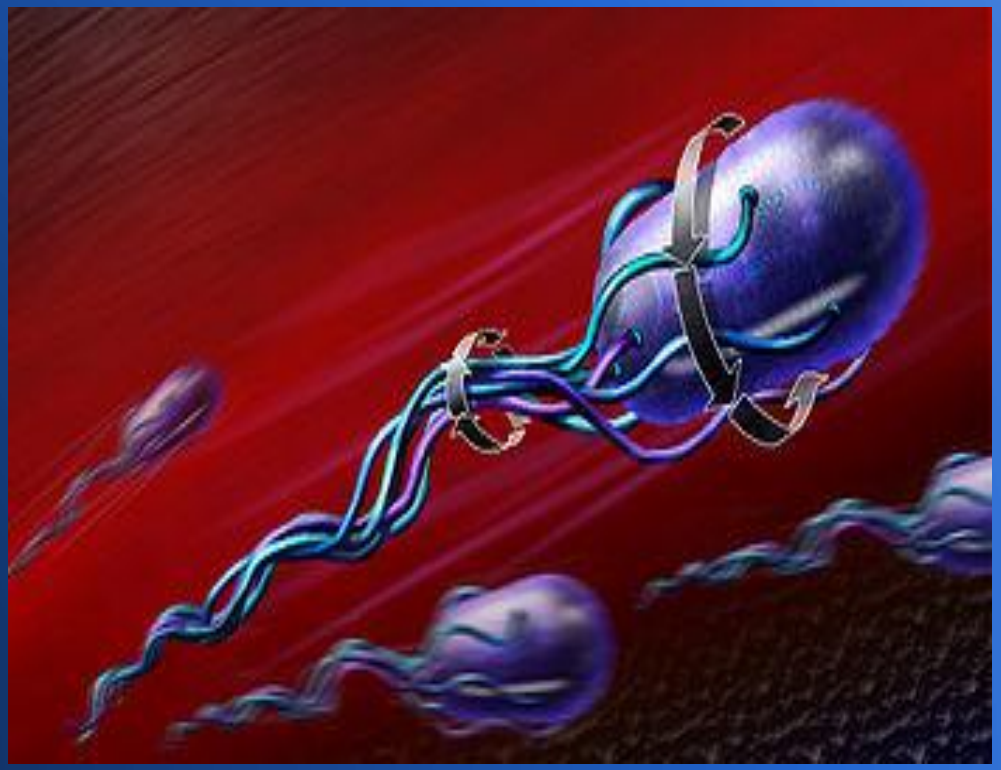
Escherichia coli is a Gram negative bacillus

Belong to Enterobacteriaceae family

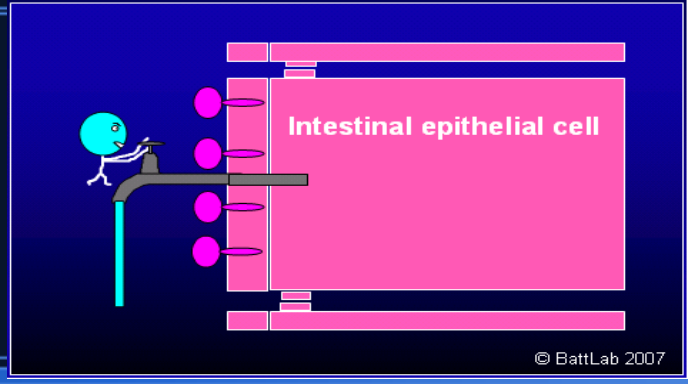
Antigenic structure is similar to the germs of this family, containing antigens A, H and K.

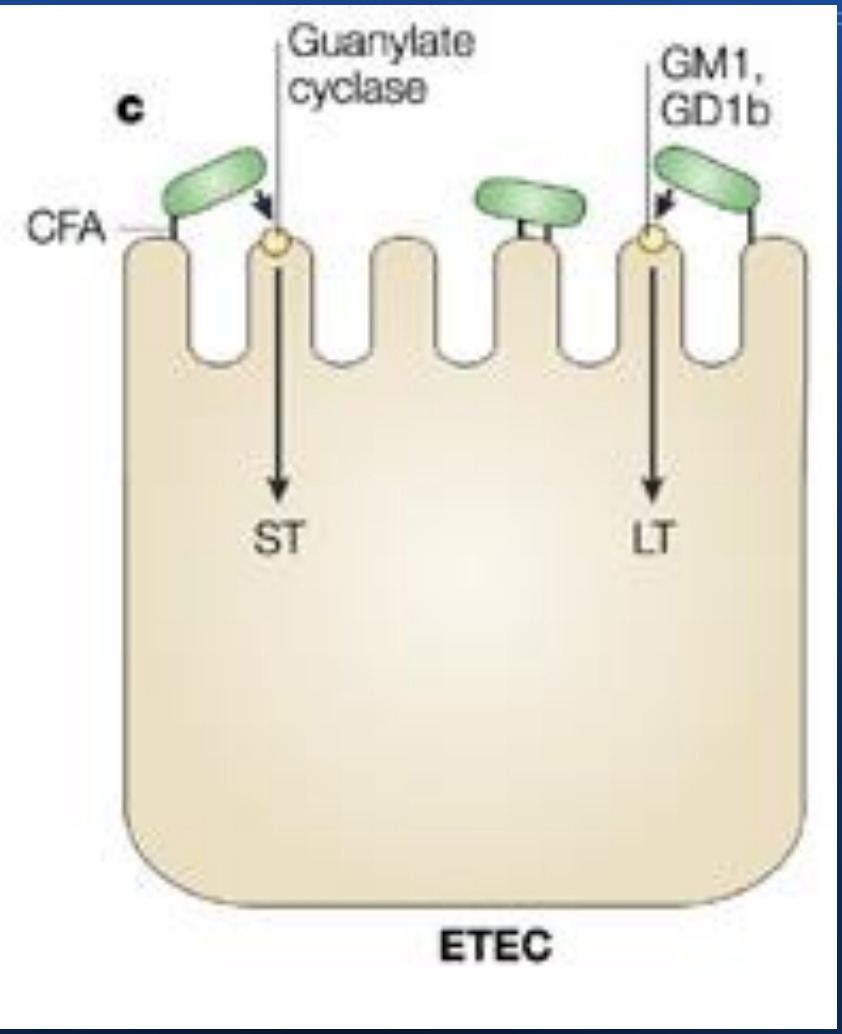
165 O serogroups, 54 H serotypes and 103 K serotypes .

The new nomenclature of each strain is known by the initials A, K, H, followed by a numer, indicating the serogroup and serotype .



Enterotoxigenic E. coli





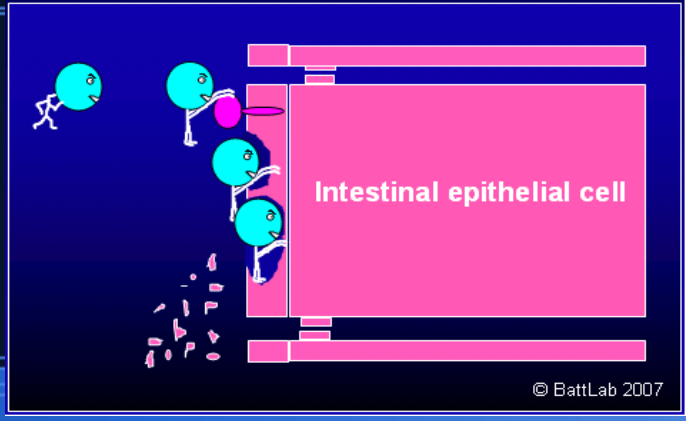
ETEC uses fimbrial adhesins to bind enterocyte cells in the small intestine

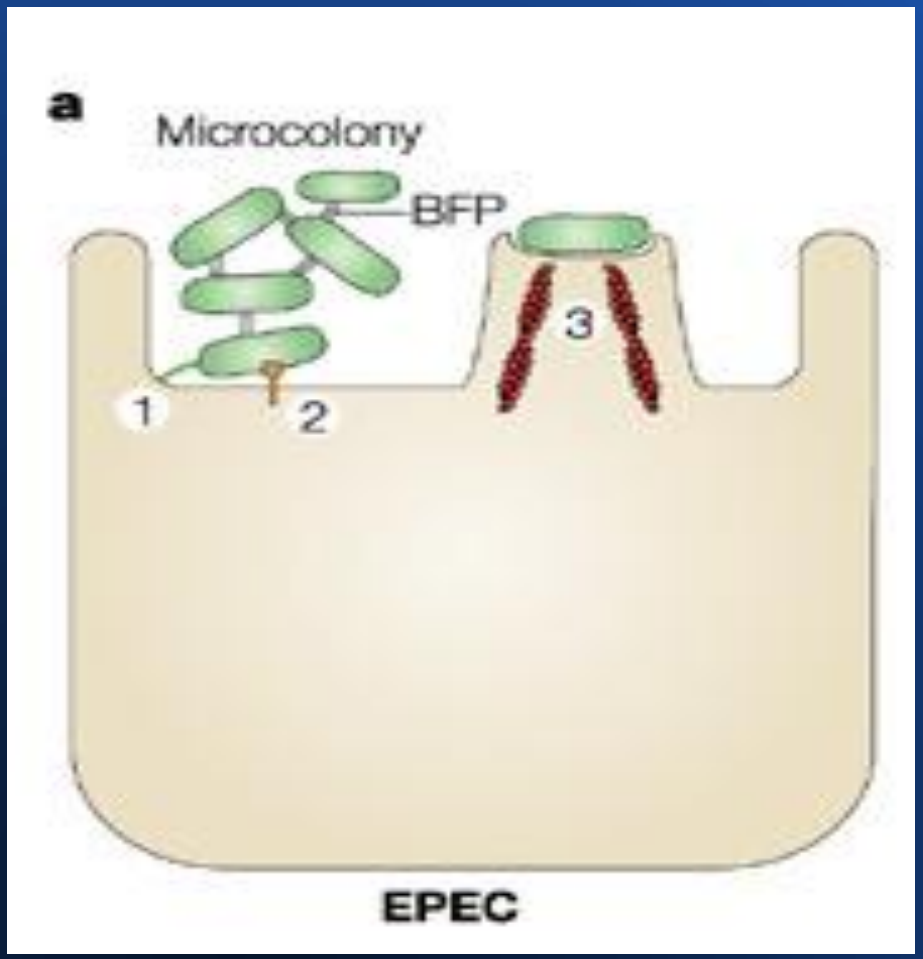
ETEC can produce two enterotoxins:

* the larger of the two proteins, LT enterotoxin, is similar to cholera toxin
* the smaller protein, ST enterotoxin causes cGMP accumulation in the target cells and a subsequent secretion of fluid and electrolytes into the intestinal lumen

ETEC strains are non-invasive, and they do not leave the intestinal lumen. ETEC is the leading bacterial cause of diarrhea in children in the developing world, as well as the most common cause of traveler's diarrhea

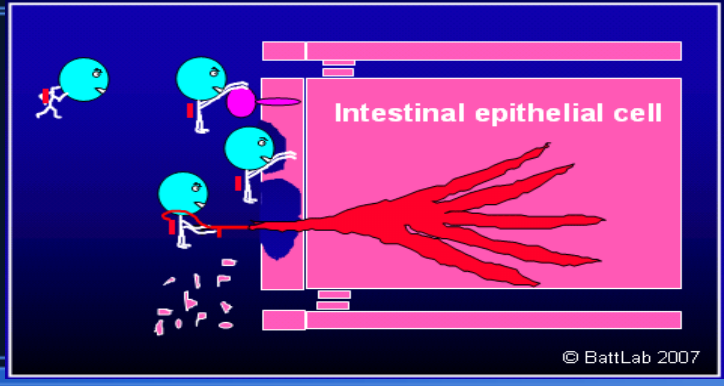
Enteropathogenic E.coli (EPEC)

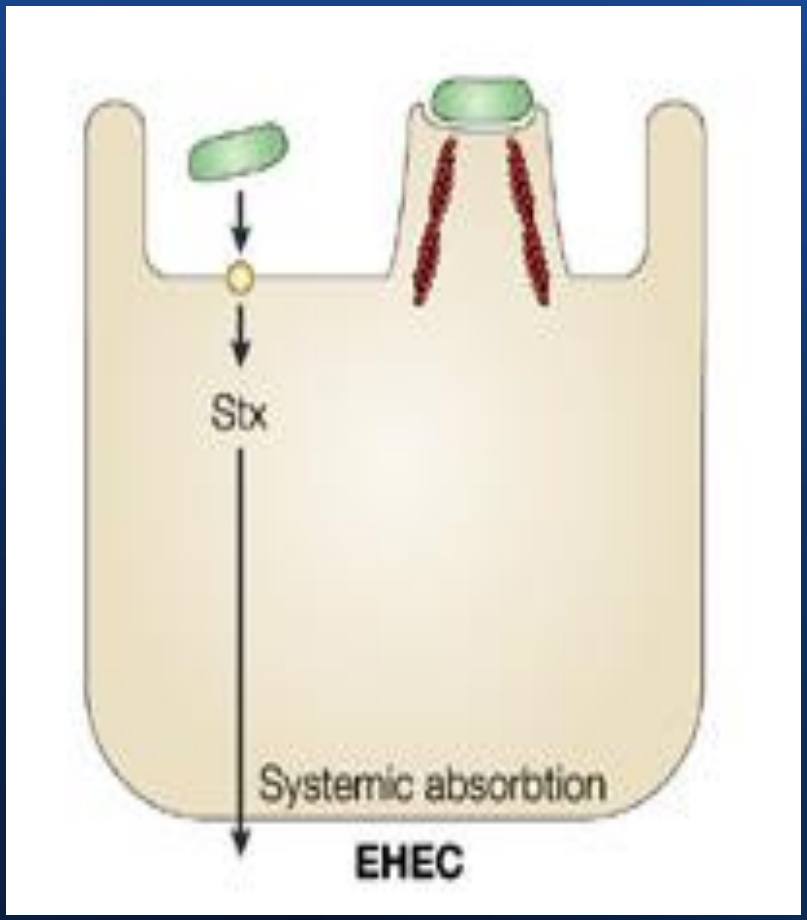




Like ETEC, EPEC also causes diarrhea, but the molecular mechanisms of colonization and etiology are different. EPEC lack fimbriae, ST and LT toxins, but they utilize an adhesin known as intimin, a virulence factor of EPEC and EHEC E. coli strains to bind host intestinal cells. This virotype has an array of virulence factors that are similar to those found in Shigella and may possess a shiga toxin. Adherence to the intestinal mucosa causes a rearrangement of actin in the host cell, causing significant deformation. EPEC cells are moderately-invasive (i.e. they enter host cells) and elicit an inflammatory response. Changes in intestinal cell ultrastructure due to "attachment and effacement" is likely the prime cause of diarrhea in those afflicted with EPEC.

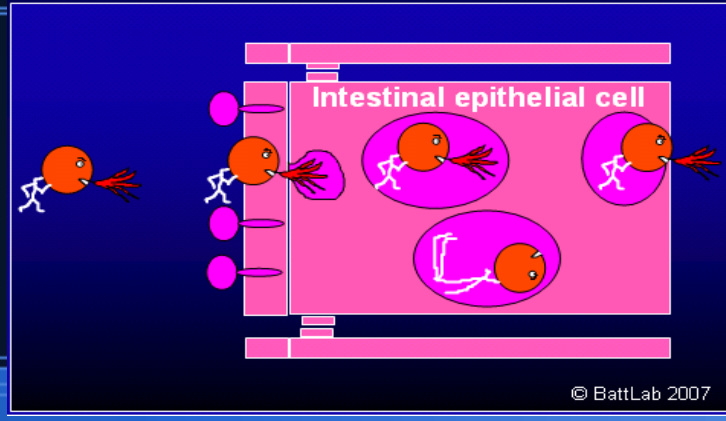
Enterohemorrhagic E. coli

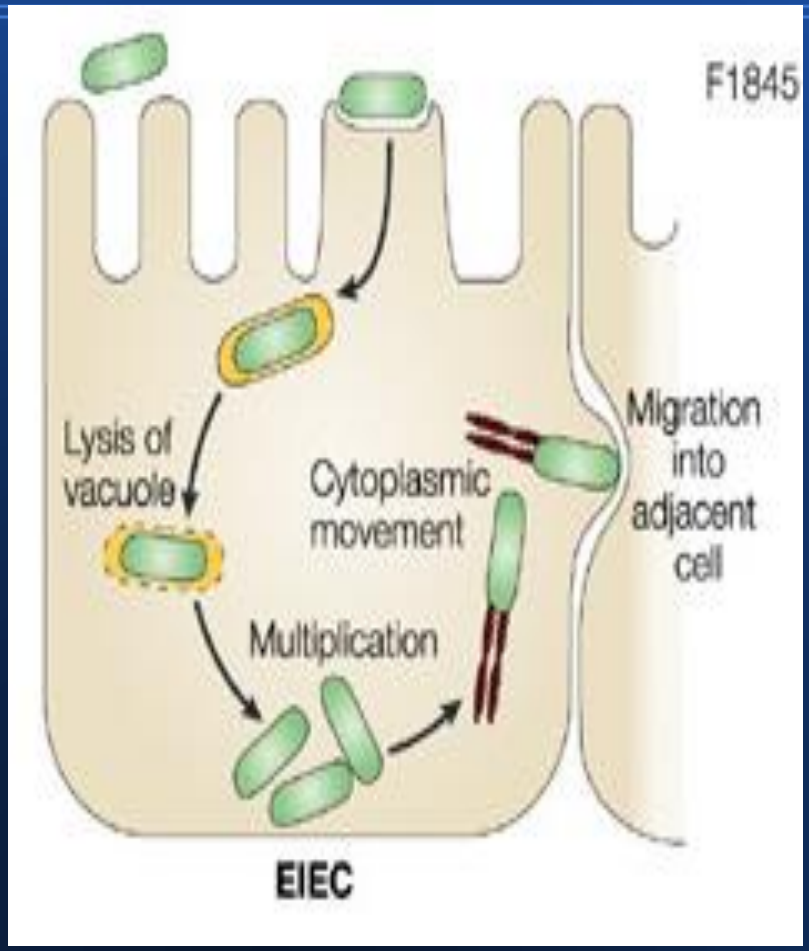




The most famous member of this virotype is strain O157:H7, which causes bloody diarrhea and no fever. EHEC can cause hemolytic-uremic syndrome and sudden kidney failure. It uses bacterial fimbriae for attachment (E. coli common pilus, ECP), is moderately-invasive and possesses a phage-encoded Shiga toxin that can elicit an intense inflammatory respons

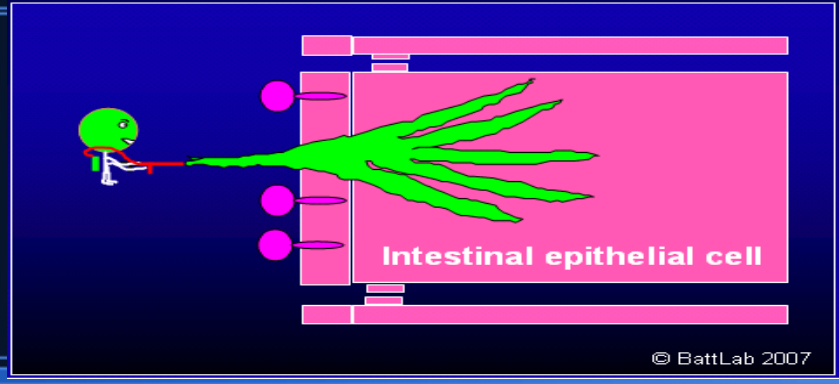
Enteroinvasive E. coli

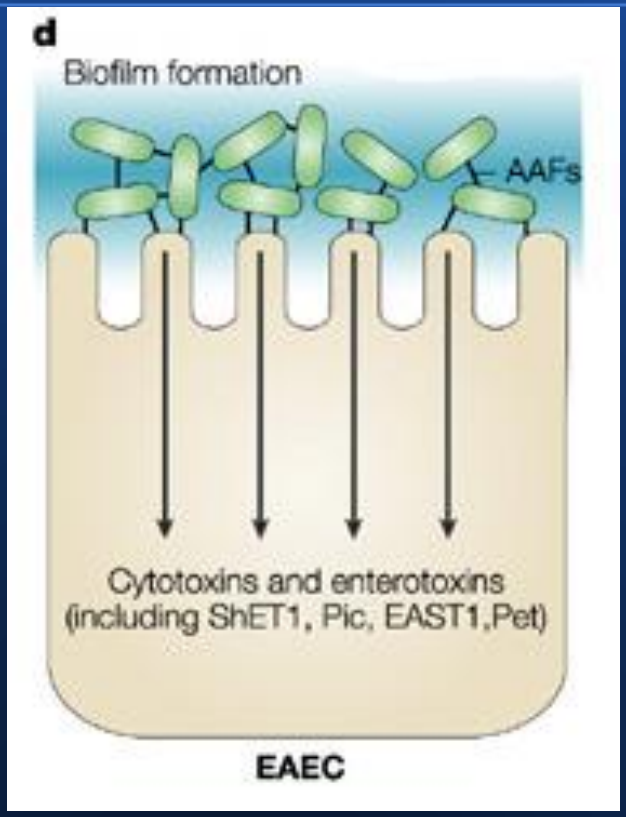




Enteroinvasive E. coli (EIEC) are able to invade and multiply within intestinal epithelial cells, resulting in cell destruction, intense inflammation, and ulceration of the intestinal lining. With symptoms of fever, cramps, vomiting, and bloody diarrhea, the disease closely resembles that caused by Shigella spp.EIEC infection causes a syndrome that is identical to Shigellosis with profuse diarrhea and high fever.

Enteroaggregative E. coli



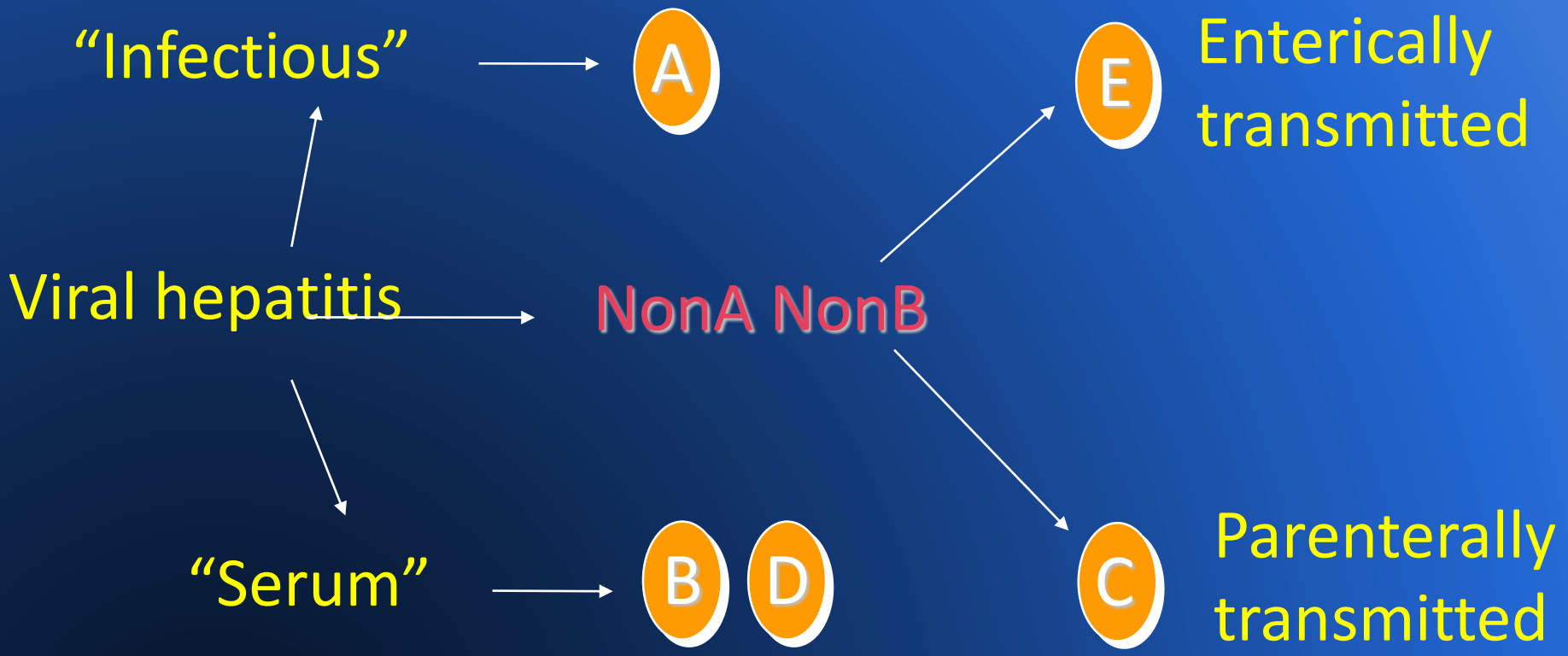


So named because they have fimbriae which aggregate tissue culture cells, EAEC bind to the intestinal mucosa to cause watery diarrhea without fever. EAEC are non-invasive. They produce a hemolysin and an ST enterotoxin similar to that of ETEC.

Thank you

Acute Viral Hepatitis

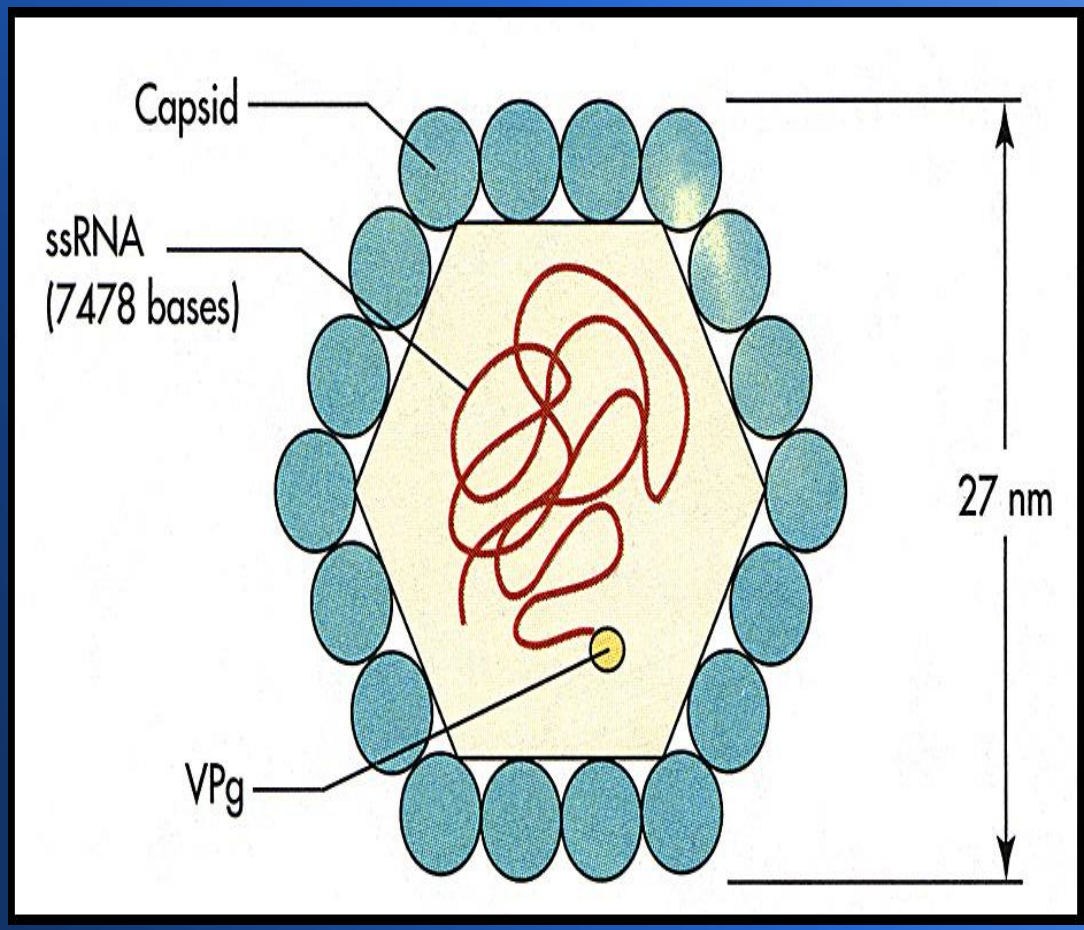
Viral Hepatitis - Perspectives



Hepatitis A
„Dirty hands” Disease

Hepatitis A virus

- is a 27 mm, icosahedral nonenveloped, positive-sense, linear ssRNA enterovirus formerly known as enterovirus 72
- member of the Picornaviridae family, genus : Hepatovirus
- One stable serotype only
- 4 genotypes exist, but in practice most of them are group 1



Hepatitis A Virus
Epidemiology

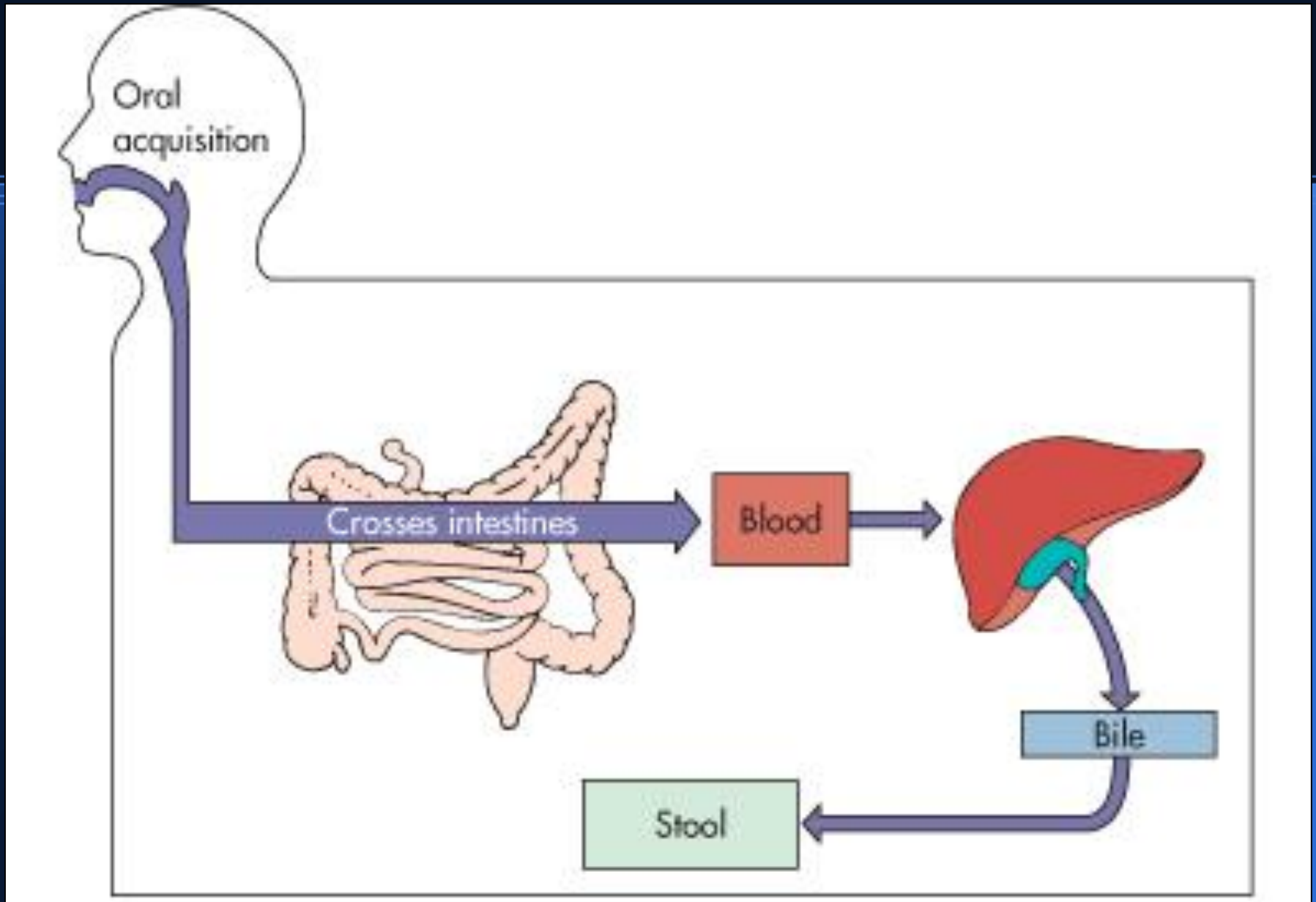
Reservoir: humans only natural hosts

Fecal-oral transmission,, percutaneous transmission occurs rarely

Increased risk : contacts of infected persons, household contacts of children in child-care centers, travel in endemic areas, contact with contaminated food or water, illicit parenteral drug use

Infection in early life occurs commonly in developing countries - the prevalence rate approaches 100% in children by the age of 5.

Immunity - Seropositivity for hepatitis A virus antibody protects individuals against reinfection



Hepatitis A Virus Pathogenesis

- Oral cavity→GI tract→liver via blood

Replicates in hepatocytes, released via bile to intestines 7-10 days prior to clinical symptoms.The virus is shed into the biliary tree and excreted in the feces. The development of an immunologic response to infection is accompanied by a predominantly portal and periportal lymphocytic infiltrate and varying degree of necrosis. Circulating antibodies are probably more important in limiting the spread of virus to uninfected liver cells.

Liver cell damage occurs through a cell-mediated immune response:

- Cytopathic injury to the hepatocytes--> release of ALT, AST
- Cholestatic jaundice from obstruction of billiary flow and damage to the hepatocytes--->increase of ALP (alkaline phosphatase), 5'nucleotidase, GGT, urobilinogen

Hepatitis A Virus

Clinical physical

- Incubation period: Average 30 days
  Range 15-50 days
- Jaundice by age group: <6 yrs, <10%
  6-14 yrs, 40%-50%
  >14 yrs, 70%-80%
- Complications: Fulminant hepatitis
  Cholestatic hepatitis
  Relapsing hepatitis
- Chronic sequelae: None

Hepatitis A Virus *Clinical history*

The incubation period is 2-6 weeks, with a mean of 4 weeks. Shorter incubation periods may result from higher total dose of viral inoculum.

Not every patient with fever, hepatomegaly, and jaundice has hepatitis A virus infection.

Hepatitis A is usually self-limitated subclinical or mild.

The most important determinant of severity of the illness is age at the infection occurs:

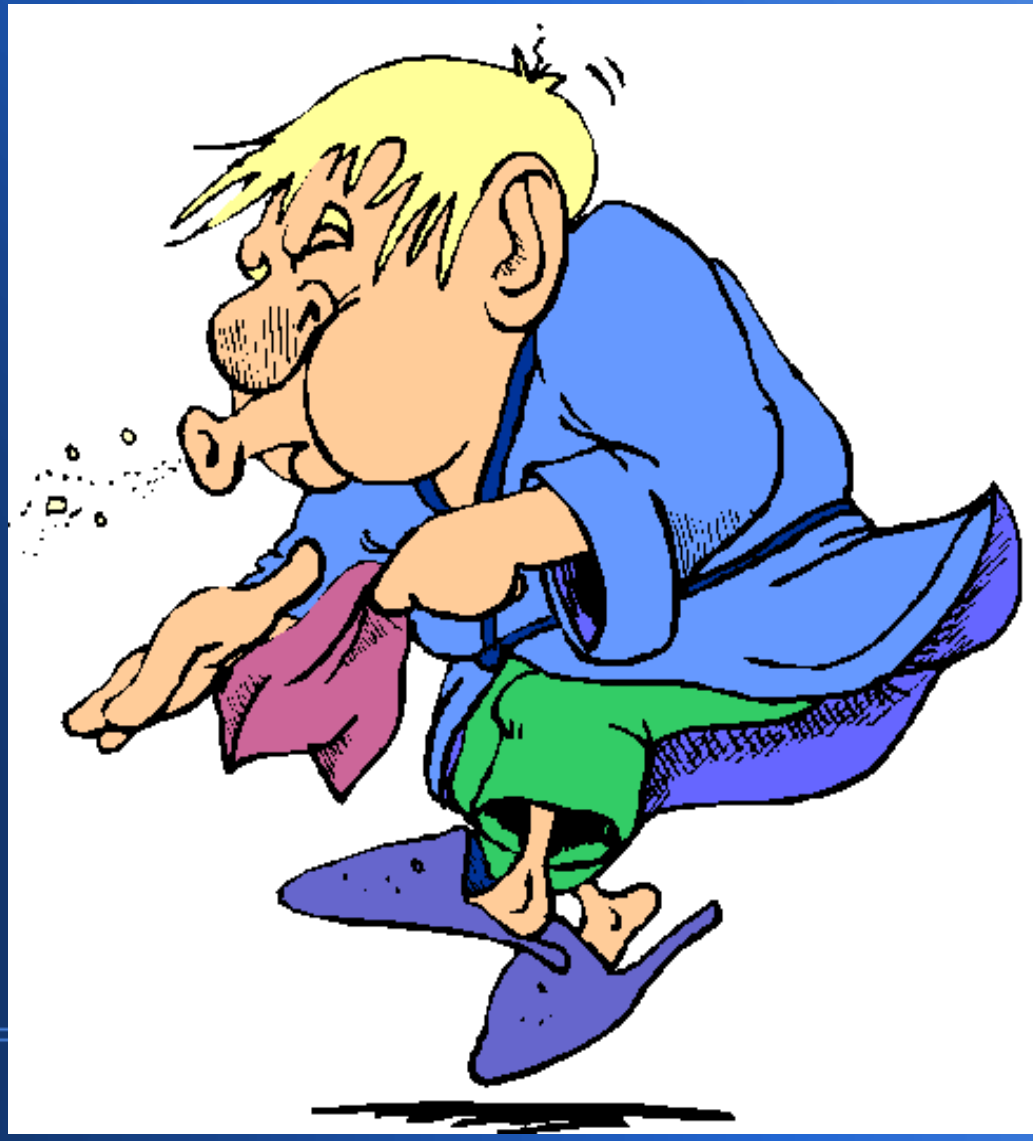
- Over 90% of infections in children younger than 5 years are silent, and the proportion of symptomatic infection increases with age;
- Severe disease may appear at patients over 45 years of age

Hepatitis A Virus — *Clinical history*

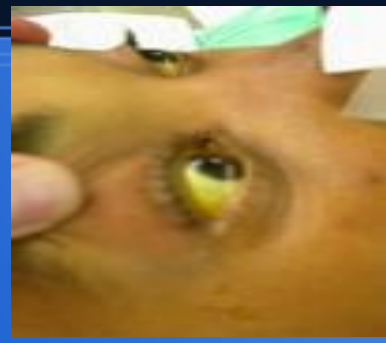
Prodrome

The onset of viral hepatitis can be sudden (most typical of hepatitis A) # insidious (more typical of type B or C).*Malaise* is the earliest and most common symptom.

"*influenza like*" onset with weakness, headaches, myalgia, chills, and fever, sore throat and cough, is most common with hepatitis A; this symptoms are short-lived (1 to 3 days) and are replaced by the more typical symptoms of anorexia, nausea, vomiting, distaste for cigarettes.



Hepatitis A Virus *Clinical history*



Icteric phase

Dark urine appears first (bilirubinuria).

Pale stool soon follows, although this is not universal.

Jaundice occurs in most (70-85%) adults with acute hepatitis A virus infection. Jaundice is less likely in children and is uncommon in infants. The degree of icterus also increases with age. *Icterus* can be detected if the bilirubin level exceeds 2,5 mg/dl. It is seen most easily in the sclera.

Abdominal pain occurs in approximately 40% of patients.Palpation of the abdomen often demonstrates a enlarged and tender liver.

Itch (pruritus), although less common than jaundice, is generally accompanied by jaundice.

Arthralgias and skin rash, are less frequent. Rash more often occurs on the lower limbs and may have a vasculitic appearance.

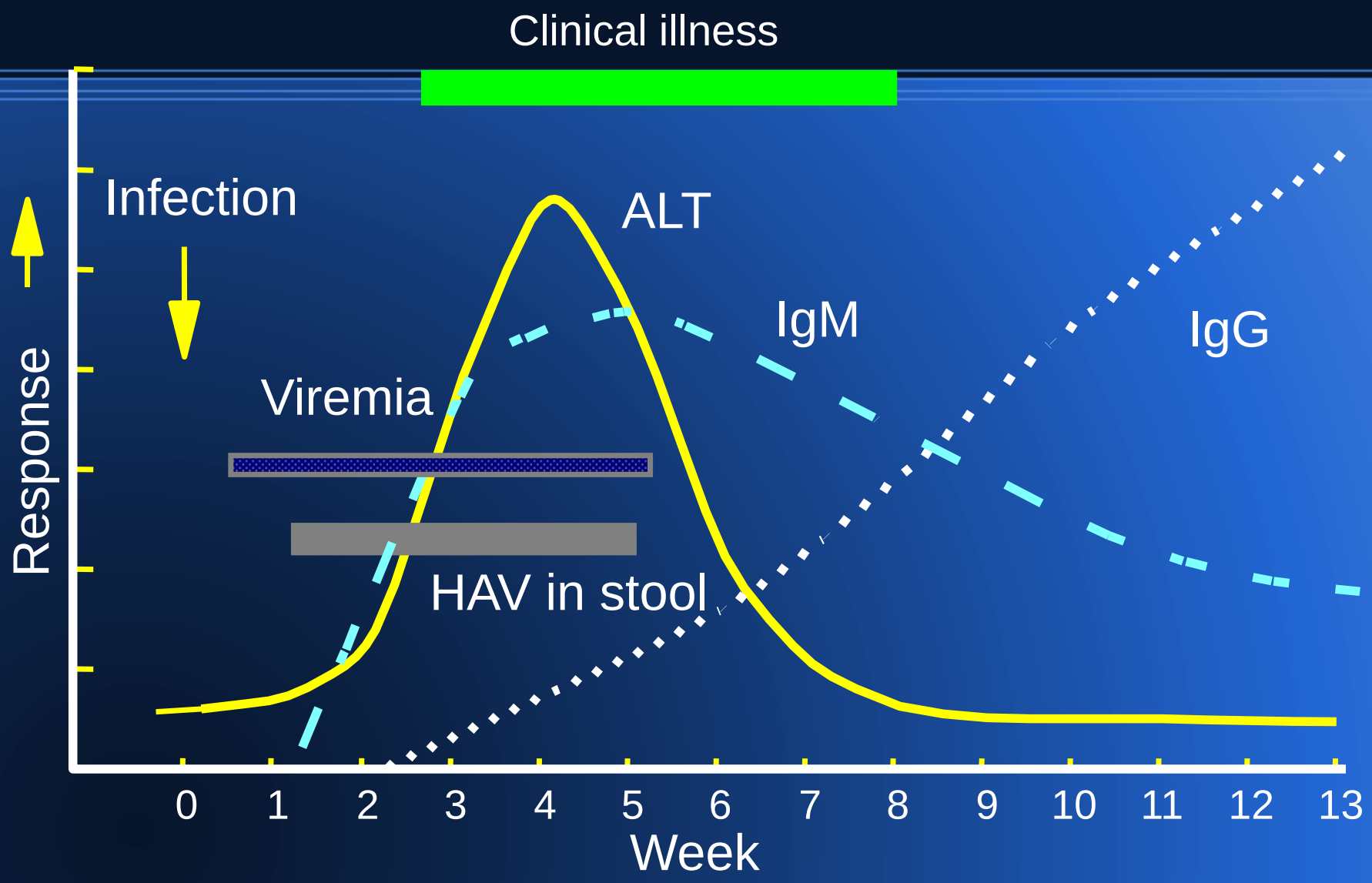
Hepatitis A Virus *Clinical history*

Relapsing hepatitis A

Relapsing hepatitis A is an uncommon sequela of acute infection, is more common in elderly persons, and is characterized by a protracted course of symptoms of the disease and a relapse of symptoms and signs following apparent resolution.

The virus is excreted in stools from 2 wk before to 1 wk after the onset of illness

EVENTS IN HEPATITIS A VIRUS INFECTION



Hepatitis A Virus *Laboratory diagnosis*

Liver enzymes - levels may exceed values of 10,000 mIU/mL, with ALT levels generally greater than AST levels- return to reference ranges over 5-20 weeks.

Rises in alkaline phosphatase, GGT, 5'nucleotidase, accompany the acute disease and may progress during the cholestatic phase

Bilirubin level rises soon after the onset of bilirubinuria and follows rises in ALT and AST levels -persistence beyond 3 months indicates cholestatic hepatitis A virus infection.

Prothrombin time- sensitive indicator of the damage of the liver- because of the short half life of this protein. When is prolonged, suspicion should be raised of severe liver necrosis that may progress to fulminant hepatic failure

Hepatitis A Virus — *Serologic diagnosis*

Anti-HAV (HAV Ab) The acute infection is diagnosed by the detection of HAV-IgM in serum by EIA, which is present at the onset of illness and disappears within 4 month. Thereafter IgG AbHAV is detectable. IgG persist for years and provides protective immunity.

Direct Detection – EM, RT-PCR of faeces. Can detect illness earlier than serology but rarely performed.

	Anti-HAV-IgM	Anti-HAV-IgG
Acute infection	+	-
Old infection (immune to HAV)	-	+
Incubation or no infection	-	-

Hepatitis A Virus **Complications**

Hepatic syntetic function decreases---> bleeding

Serum albumin level falls---> edema, ascites

Ammonia levels rise--->altered sensorium, stupor, coma

- Cholestasis
- Fulminant hepatitis
- Prolonged and relapsing disease
- Triggering of chronic active autoimmune hepatitis
- Autoimmune extrahepatic disease

Hepatitis A Virus ***Differential Diagnosis***

- An exacerbation of the underlying/chronic hepatitis
- Other infectious hepatitis (mononucleosis with EBV or CMV, leptospirosis)
- Toxic hepatitis (alcohol, acetaminophen, isoniazid, carbon tetrachloride)
- Nonspecific injury (shock, ischemia)
- Tumors and extrahepatic obstruction -Budd-Chiari Syndrome
- Acute HIV infection
- Drug-induced hypersensitivity reactions

Hepatitis A Virus **Treatment**

For acute cases of hepatitis A virus infection, therapy is generally supportive, with no specific treatment of acute uncomplicated illness. Initial therapy often consists of bed rest. The patient should probably not work during the acute phase of the illness.

Alcohol and major physical efforts avoidance during the acute illness and for 6 to 12 months after viral hepatitis.

Encourage an hepatoprotective diet: low fat diet, frequent, small feedings

Drugs: - symptomatic therapy for nausea, pain or sleeplessness may be needed.

- Vitamins B_1, B_6, K

Corticosteroids have sometimes been recommended for two situation in acute viral hepatitis: cholestatic hepatitis and fulminant hepatic failure

Hepatitis A Virus — *Prevention and prognosis*

- Hygiene (e.g., hand washing)
- Sanitation (e.g., clean water sources, chlorination)
- Immune globulin (pre- and post-exposure)
- ***Preexposure*** Travelers to endemic regions 0.02-0.04 mL/kg im.

  Post exposure ***(within 14 days)*** Household and other intimate contacts 0.02 mL/kg im
- Hepatitis A vaccine (pre-exposure)

Complete recovery without therapy is generally the rule

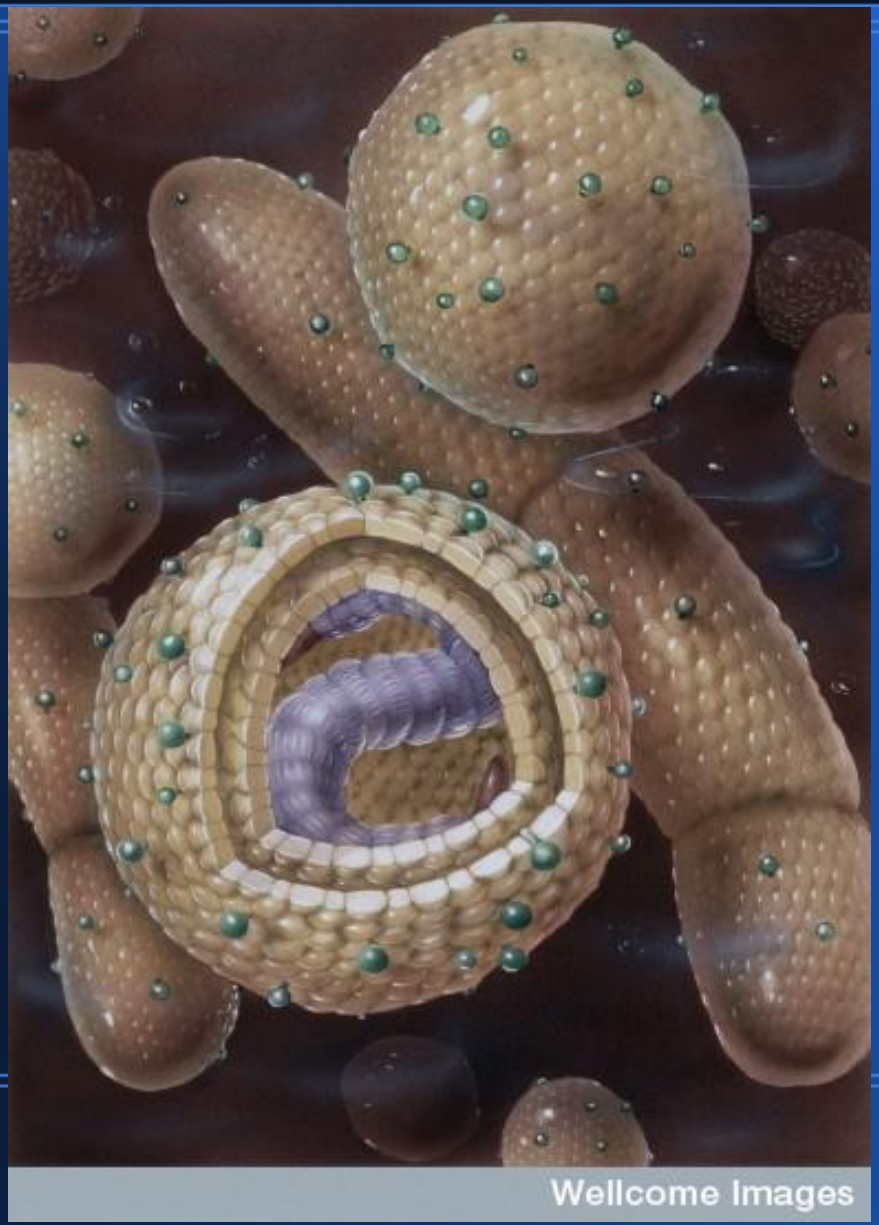
Hepatitis A Virus ***Prevention***

- Immuno globulin – provides short-term protection for up to 3 months, for pre-exposure prophylaxis for
- Hepatitis vaccine – for children older than 2 years, intramuscular two- dose schedule

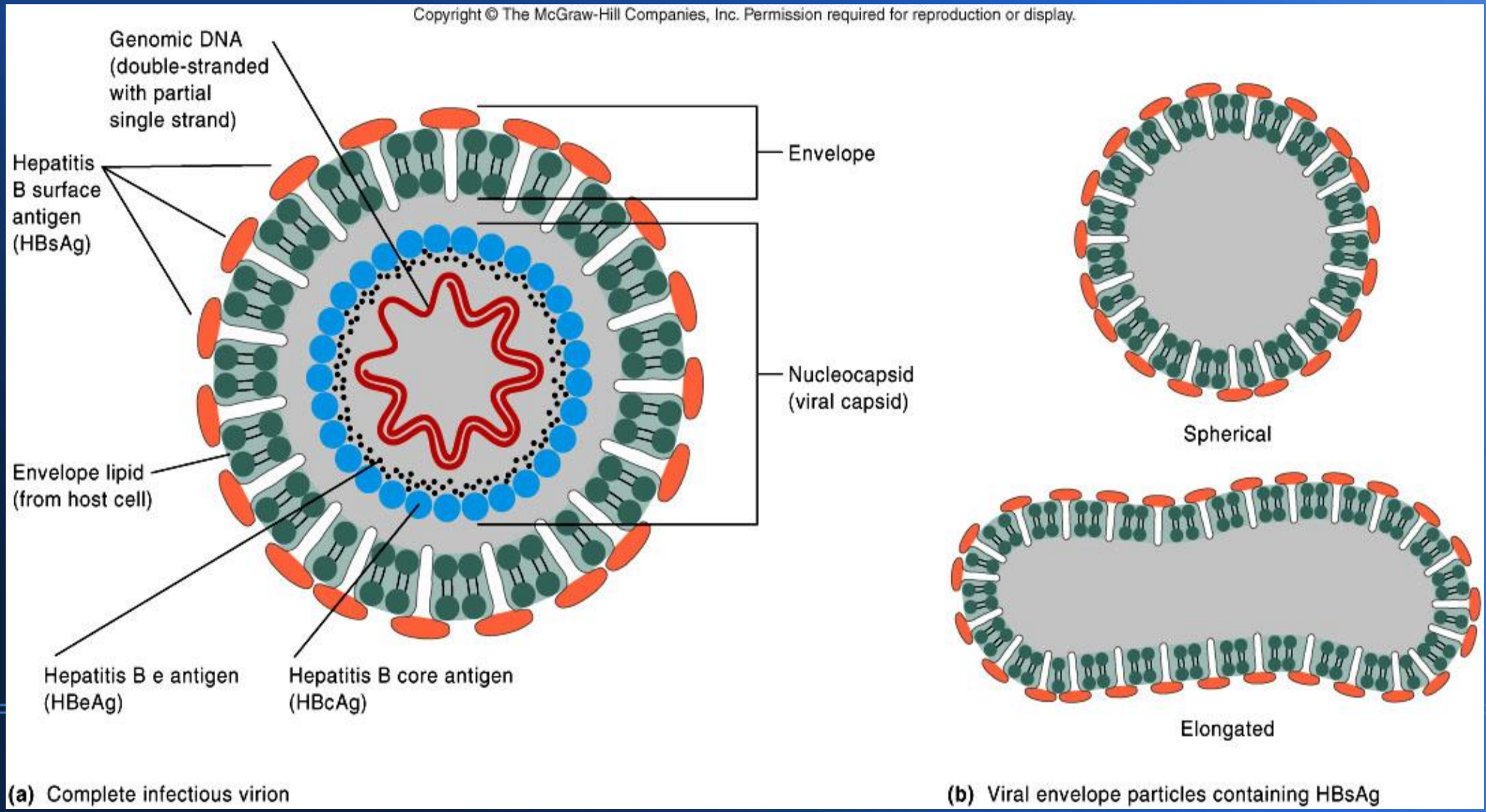
First dose protects for 1 year. To ensure that protection continues for at least 25 years, a second (booster) dose of the vaccine should be given 6 to 12 months after the first injection.

- Havrix and Vaqta – contain inactivated forms of hepatitis A virus and are safe for children older than 2 years as well as for most adults
- Twinrix – protects people age 18 and older against both hepatitis A virus (HAV) and the Hepatitis B virus (HBV)

Hepatitis B virus

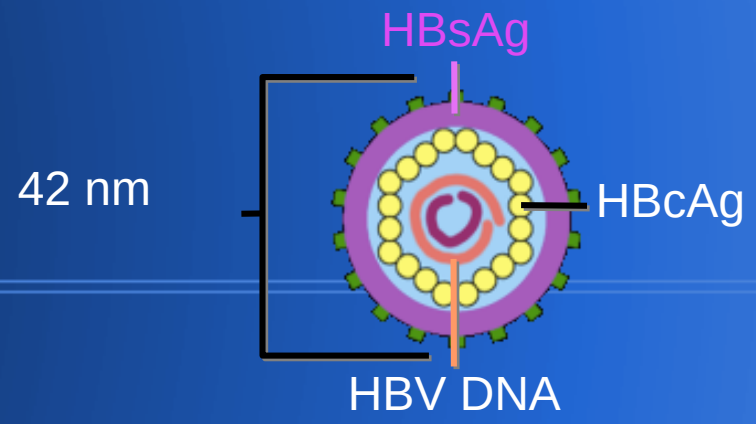


HBsAg = surface (coat) protein (4 phenotypes : adw, adr, ayw and ayr)
HBcAg = inner core protein (a single serotype)
HBeAg = secreted protein



Hepatitis B virus

- is a 42 mm, Spherical with Icosahedral symmetry double-stranded DNA
- member of the Hepadnaviridae family, genus : Orthohepadnavirus
- The surface of the virus includes two particles HbsAg: 22 nm spherical and one 22 nm wide tubular particle
- The inner portion of the virion contains HbcAg (the nucleocapsid that encodes the viral DNA- detectable only in liver cells, not in the blood) and HbeAg – MARKER of active viral replication.



Concentration of Hepatitis B Virus in Various Body Fluids

High	Moderate	Low/Not Detectable
blood	semen	urine
serum	vaginal fluid	feces
wound exudates	saliva	sweat
		tears
		Breast milk

Hepatitis B Virus
Epidemiology

World-wide there are 450 million persistant carriers of hepatitis B, 50 million of which are in Africa. Hepatitis B is parenterally transmitted

1) Blood

* blood transfusions, serum products
* sharing of needles, razors
* tattooing, acupuncture
* renal dialysis, organ donation

2) Sexual

3) Horizontal transmission in children, families, 'close personal contact'.

This is the major mode of transmission in South Africa where the majority of individuals become infected at between three and nine years of age.

4) Vertical transmission - perinatal transmission from a carrier mother to her baby

Hepatitis B Virus Pathogenesis

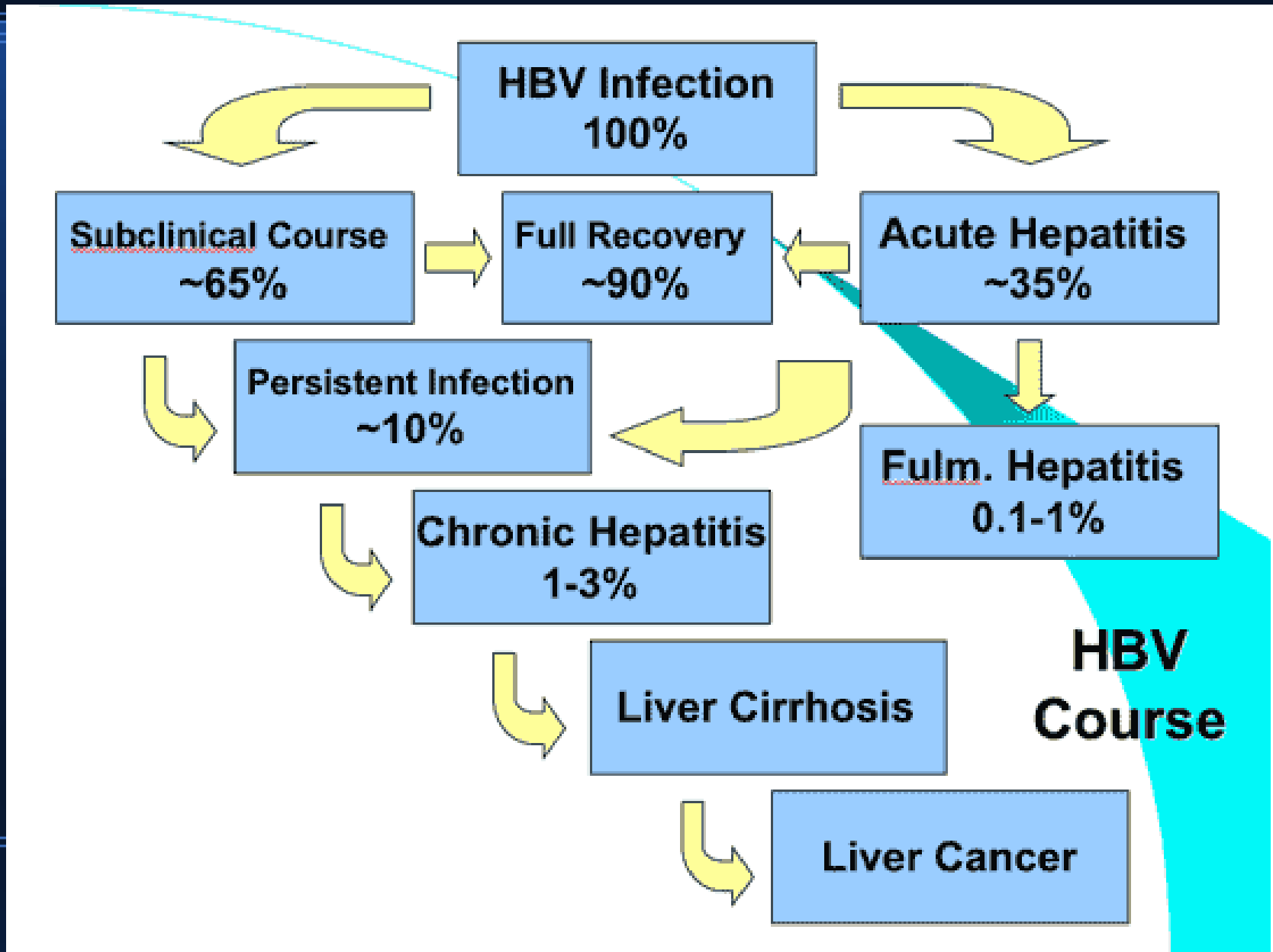
The first stage is immune tolerance. The duration of this stage for healthy adults is approximately 2-4 weeks and represents the incubation period. For newborns, the duration of this period is often decades. Active viral replication is known to continue despite little or no elevation in the aminotransferase levels and no symptoms of illness.

In the second stage, an inflammatory reaction with a cytopathic effect occurs. HBeAg can be identified in the sera, and a decline of the levels of hepatitis B virus (HBV) DNA is seen. The duration of this stage for patients with acute infection is approximately 3-4 weeks (symptomatic period).

In the third stage, the host can target the infected hepatocytes and the hepatitis B virus (HBV). Viral replication no longer occurs, and HBeAb can be detected. The HBV DNA levels are lower or undetectable, and aminotransferase levels are within the reference range. In this stage, an integration of the viral genome into the host's hepatocyte genome takes place. HBsAg still is present.

In the fourth stage, the virus cannot be detected and antibodies to various viral antigens have been produced.

The earlier the disease is acquired, the greater the chance of developing chronic hepatitis



Hepatitis B Virus ***ACUTE PHASE***

The incubation period is about 70 days (range 30 to 180 days)

Anicteric hepatitis is the predominant form of expression for this disease. The majority of the patients are asymptomatic. Patients with symptomatology have the same symptoms as patients who develop icteric hepatitis. Patients with anicteric hepatitis have a greater tendency to develop chronic hepatitis.

Icteric hepatitis is associated with a prodromal period, during which a serum sickness –like syndrome can occur. The symptomatology is more constitutional and includes the following: anorexia, nausea, vomiting, low-grade fever, myalgia, fatigability

Disordered gustatory acuity and smell sensations (aversion to food and cigarettes)

Right upper quadrant and epigastric pain (intermittent, mild to moderate)

Patients with hyperacute, acute, and subacute hepatitis may present with the following: hepatic encephalopathy, somnolence, disturbances in sleep pattern, mental confusion, coma

Hepatitis B Virus *CHRONIC PHASE*

Patients with chronic hepatitis can be healthy carriers without any evidence of active disease, and they also are asymptomatic.

Patients with chronic active hepatitis, especially during the replicative state, may complain of symptomatology such as the following:

Symptoms similar to those of acute hepatitis

- Fatigue
- Anorexia
- Nausea
- Mild upper quadrant pain or discomfort
- Hepatic decompensation

Hepatitis B Virus

PHYSICAL EXAM

- Low-grade fever
- Jaundice (10 d after the appearance of constitutional symptomatology and lasting for 1-3 mo)
- Hepatomegaly (mildly enlarged soft liver)
- Splenomegaly (5-15%)
- Palmar erythema (rarely)
- Spider nevi (rarely)

Some of patients (5 to 15%) experience a "*serum sickness-like syndrome*" at the onset of their B hepatitis. This consists of a triad of symptoms: fever, rash, and arthritis, a manifestation of immune-complex deposition.

The rash is maculo-papular, urticarial, with peripheral distribution ("acrodermatitis");

The arthritis is mild to moderate, nondeforming, polyarticular and migratory. Major joints involved are the elbows, wrists, knees, and small joints of the hands. Arthralgias probably are more common than frank arthritis.

Hepatitis B Virus *Laboratory diagnosis*

- High levels ALT and AST, at a range of 1000-2000 IU/mL, is the hallmark of this disease.
- Impaired synthetic function of the liver (ie, decreased albumin levels, increased bilirubin levels, and prolonged PT).
- Alkaline phosphatase (ALP), GGT, 5'nucleotidase, during the cholestatic phase levels may be elevated, but they are usually not more than 3 times the upper limit of normal.
- In the preicteric period (ie, before the appearance of jaundice), leukopenia (ie, granulocytopenia) and lymphocytosis

Hepatitis B Virus *Serologic diagnosis*

Several viral markers can be identified in the serum and the liver. HBsAg (Australian antigen) and HBeAg (marker of infectivity) are the first markers that can be identified in the serum. HBcAb (IgM) follows.

HBsAb

Are antibodies against HBsAg. They are the last antibodies to appear after infection and are an indicator that infection has been defeated. They neutralize HBV, providing protection against further infection. Therefore they are induced in vaccination by injection of HBsAg.

HBcAb

Antibodies against HBcAg (HBcAb) appear at about 8 weeks after infection (they are the first detectable antibodies). When HBcAb appears in the bloodstream the level of transaminases (AST and ALT) start to rise. Initial antibodies response is of IgM class then, after about 2 months it switches to IgG class. Therefore we found HBcAb of
IgM class when there is a recent infection (acute phase) and HBcAb of IgG class when infection is resolved. In chronic infection HBcAb IgM is persistently positive. These antibodies don't neutralize HBV, but they reveal if there was an infection (they don't appear after vaccination).

Hepatitis B Virus *Serologic diagnosis*

HBeAg

Is a peptide that is produced and becomes detectable in serum during HBV replication, like HBV DNA and DNA polymerase. In acute infection HBeAg is transiently present: it's generally detectable at the same time as HBsAg and disappears before it. Clearance of HBeAg indicates a favorable prognosis (virus stops its replication and there is no more liver damage). In chronic infection is positive during viral reactivation.

There are viral mutants of HBV that don't produce HBeAg. This mutants appear to be more aggressive. Patients HBeAg positive are highly infectious.

HBeAb

In acute infection, few weeks later clearance of HBeAg, antibodies against HBeAg (HBeAb) became detectable and transaminases start to drop. In chronic infection become positive when viral reactivation ends.

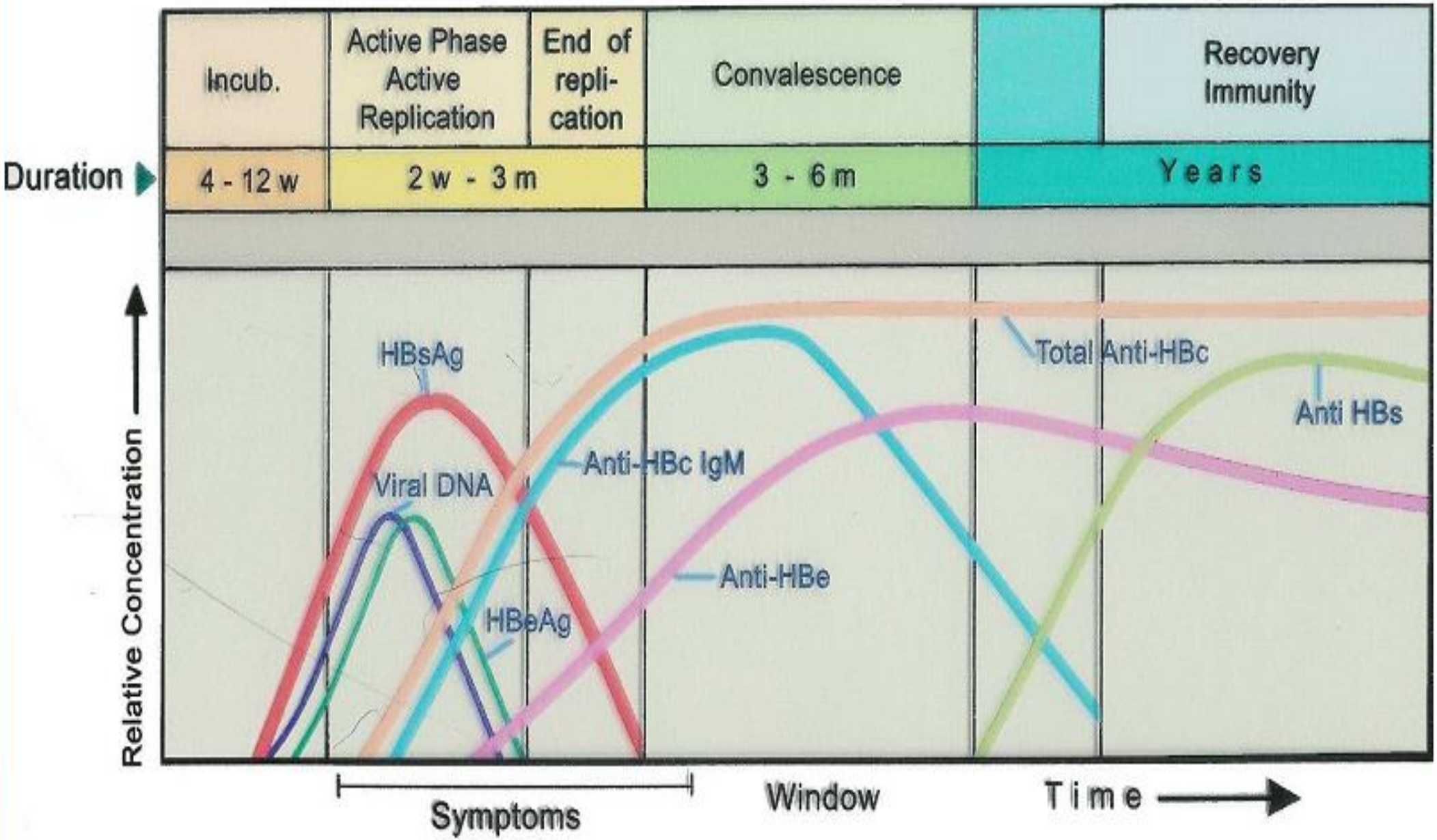
HBV DNA (PCR)

It's a test that detects HBV viral genome (DNA) in blood.

It becomes positive during viral replication : after infection (in acute hepatitis) and during viral reactivation (in chronic hepatitis).

	Acute hepatitis B	Recovery from acute hepatitis B	Chronic HBeAg + disease	Chronic HBeAG – disease	Successful Vaccination	Resistance to antiviral agents
HBsAg	✓ (may clear)		✓	✓		
Anti-HBs		✓			✓	
Anti-HBc IgM	✓					
Anti-HBc	✓	✓	✓	✓		
HBeAg	✓		✓			
Anti-HBe		✓ (in some cases)		✓		
DNA (PCR if required)	✓ (may be only marker during window period)		✓	✓		✓ (sequence pol region)

Serologic profile of HBV infection



Spectrum of Chronic Hepatitis B Diseases

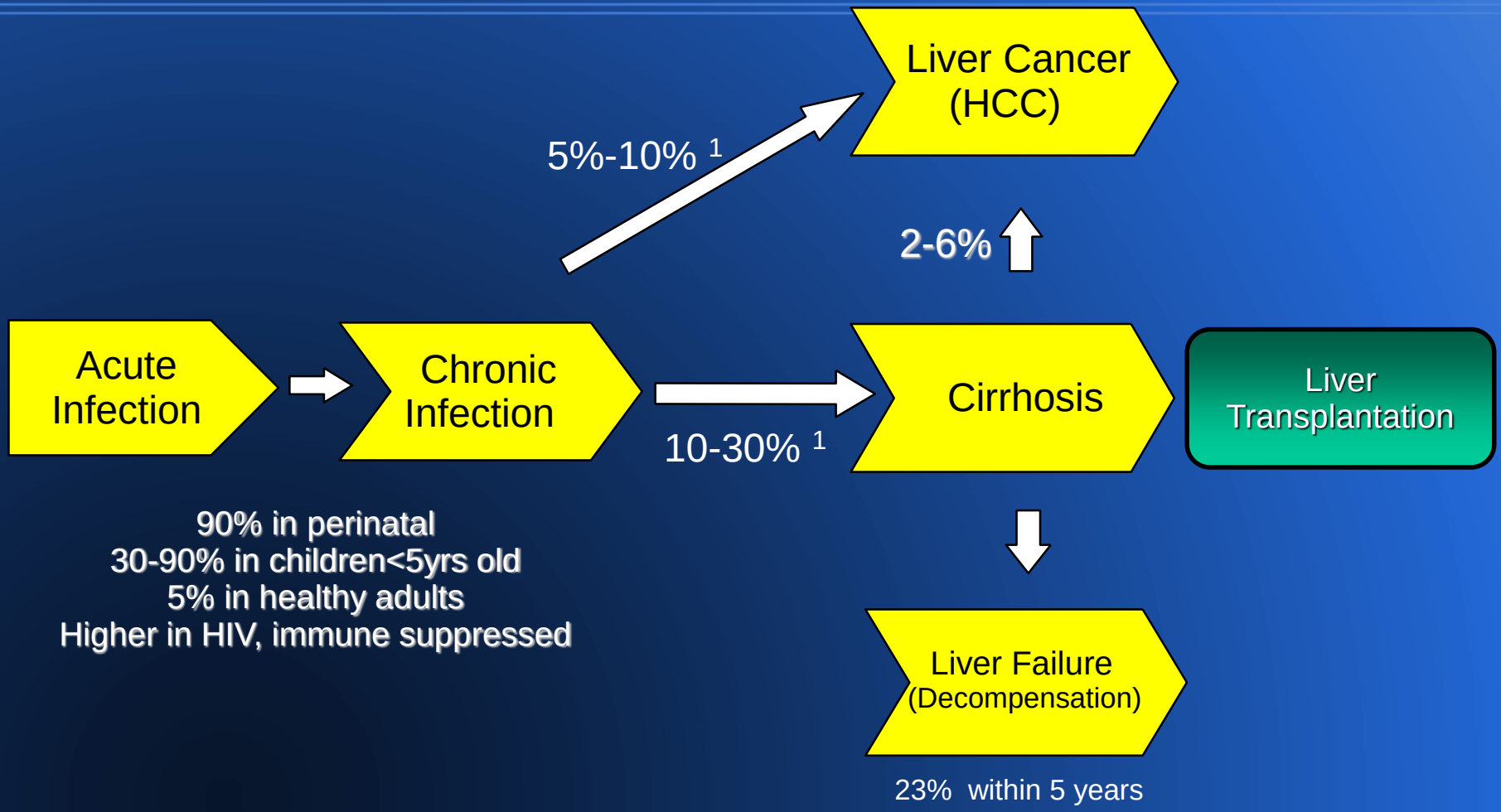
1Chronic Persistent Hepatitis - asymptomatic

2. Chronic Active Hepatitis - symptomatic exacerbations of hepatitis

3. Cirrhosis of Liver

4. Hepatocellular Carcinoma

Hepatitis B: Disease Progression



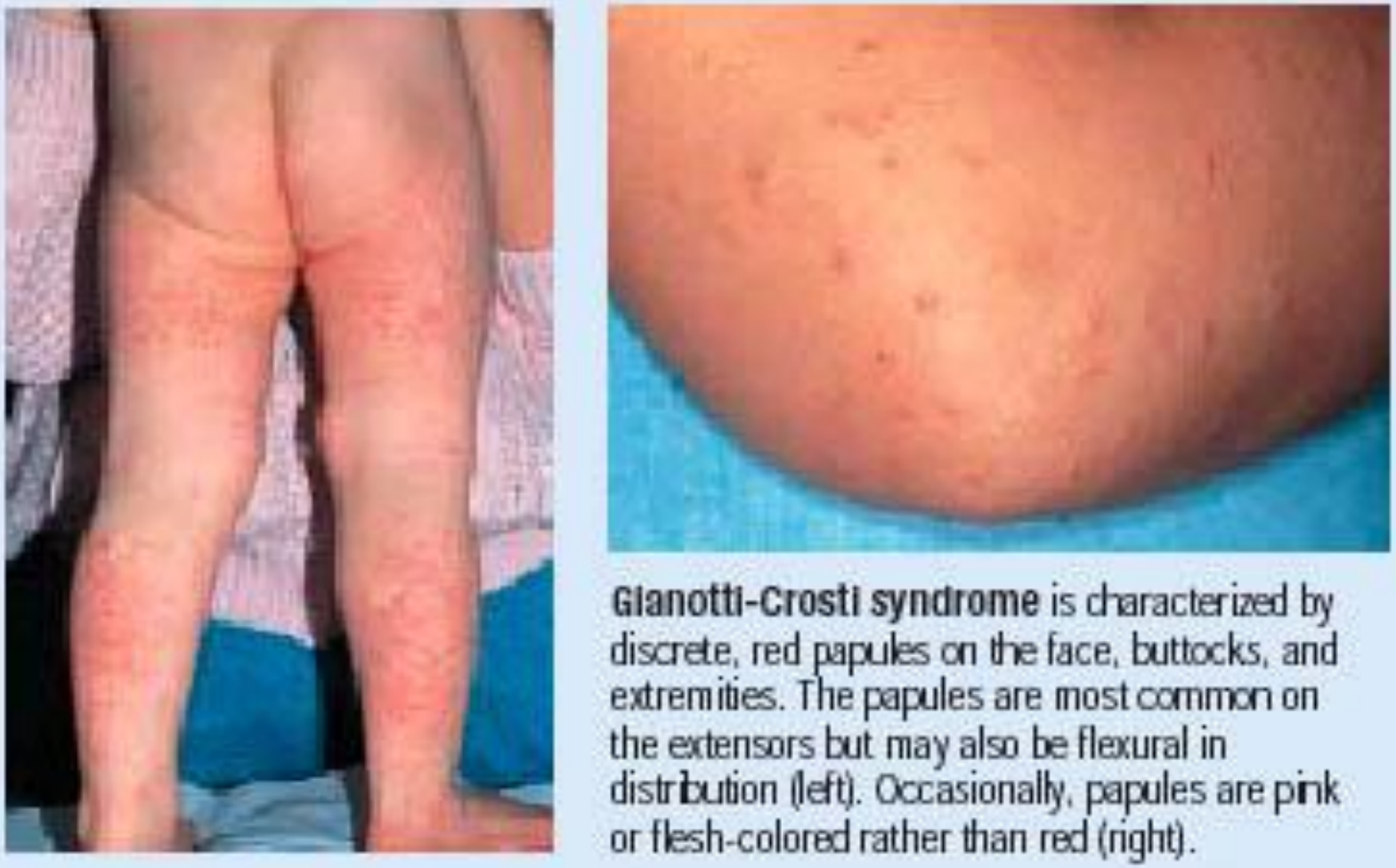
1. Torresi J et al. Gastroenterology. 2000.
2. Fattovich G et al. Hepatology. 1995.
3. Moyer LA et al. Am J Prev Med. 1994.
4. Perrillo R et al. Hepatology. 2001.

Hepatitis B Virus *Complications*

- Hepatocarcinoma
- Glomerulonephritis--membranous glomerulonephritis (MGN), mainly in children. However, membranoproliferative glomerulonephritis (MPGN) and, even more rarely, IgA nephropathy, have been identified.
- Polyarteritis nodosa
- Papular acrodermatitis, also recognized as Gianotti-Crosti syndrome
- Cardiopulmonary manifestations--Myocarditis, pericarditis, and arrhythmia occur primarily in patients with fulminant hepatitis.
- Joint and neurologic manifestations---Guillain-Barre syndrome, encephalitis, aseptic meningitis, and mononeuritis multiplex may occur in patients with acute hepatitis B disease.
- Arthralgias and arthritis (serum sickness) subcutaneous nodules may also occur, but these are rare.
- Hematologic and gastrointestinal tract manifestations
- Patients may develop pancreatitis.
- Diffuse intravascular coagulation may occur in

Gianotti-Crosti Syndrome

FIGURE 2



Gianotti-Crosti syndrome is characterized by discrete, red papules on the face, buttocks, and extremities. The papules are most common on the extensors but may also be flexural in distribution (left). Occasionally, papules are pink or flesh-colored rather than red (right).

Hepatitis B Virus ***Differential Diagnosis***

- Other Viral Hepatitis
- Alcoholic Hepatitis
- Autoimmune Hepatitis
- Cholangitis, Cirrhosis,Primary Sclerosing Cholangitis
- Hemochromatosis
- Hepatic Carcinoma, Primary
- Wilson Disease
- Congestive heart failure
- Drug hepatotoxicity

Hepatitis B Virus

Goals of treatment

- Reduce the risk of disease progression
- Reduce the risk of hepatocellular carcinoma

- Loss of HBeAg, HBeAg → HBeAb
- Undetectable HBV-DNA
  - (<10^5 copies/ml = 20,000IU/mL)
- Normalization of ALT
- Histologic Response
- HBsAg → HbsAb

} Virologic Response

Hepatitis B Virus **Treatment**

Medication

Currently, interferon alfa (IFN-a), lamivudine, telbivudine, adefovir, entecavir, and tenofovir are the main treatment drugs approved globally

Surgical Care

Orthotopic liver transplantation (OLT) is the treatment of choice for patients with fulminant hepatic failure who do not recover and for patients with end-stage liver disease.

Hepatitis B Virus — *Prevention and prognosis*

1) Active Immunization

Two types of vaccine are available:

- Serum derived - prepared from HBsAg purified from the serum of HBV carriers
- Recombinant HBsAg - made by genetic engineering in yeasts

Vaccination with a single dose must be repeated every 5-10 years

2) Passive Antibody

Hepatitis B immune globulin should be administered to non immune individuals following single episode exposure to HBV-infected blood.

Ideally within 3 hours. Probably not effective >7days post exposure

Hepatitis B Virus VACCIN

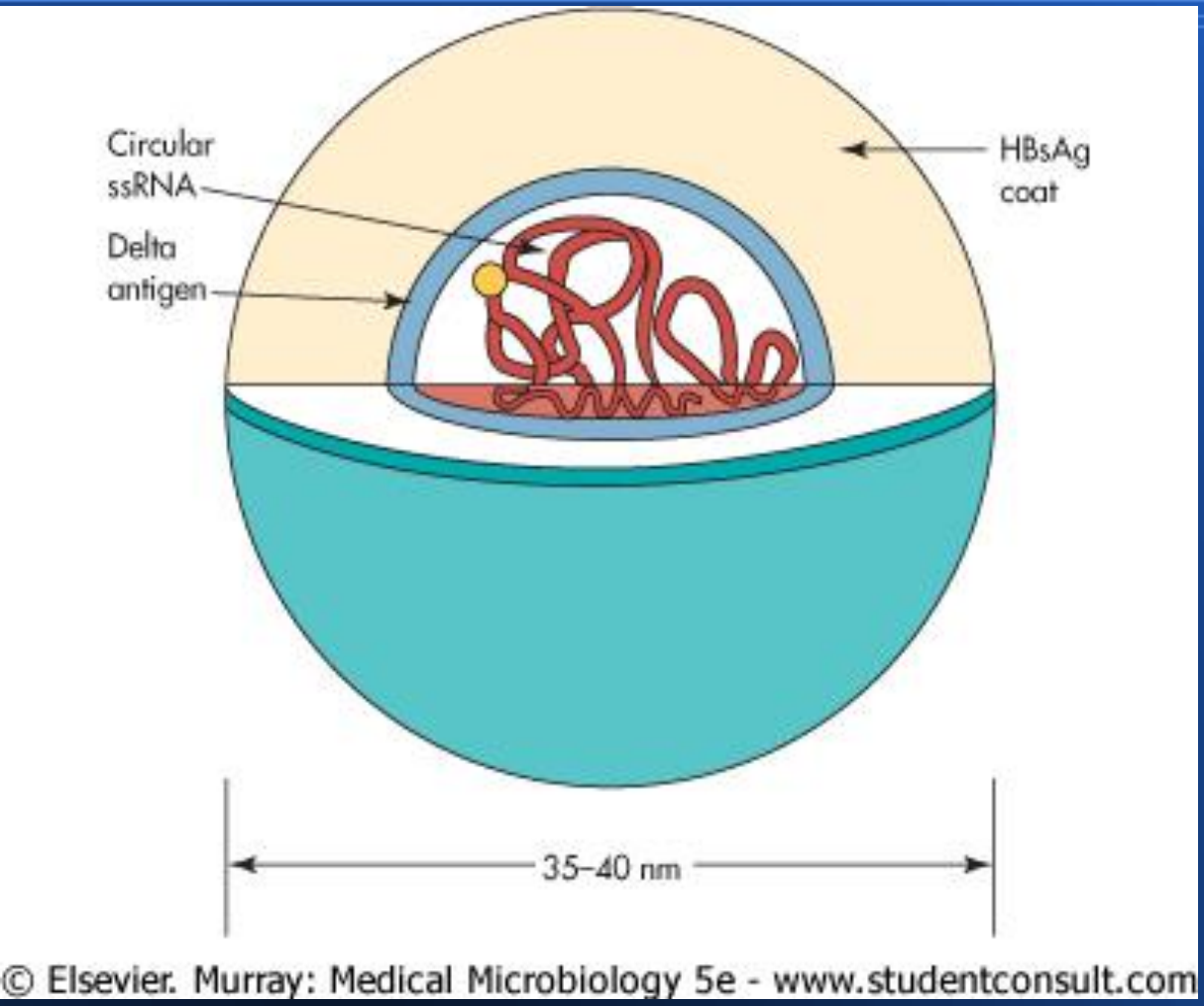
- Infants: several options that depend on status of the mother
  - If mother HBsAg negative: birth, 1-2m, 6-18m
  - If mother HBsAg positive: vaccine and Hep B immune globulin within 3-12 hours of birth, 1-2m, <6m
- Adults
  - 0,1, 6 months
- Vaccine recommended in
  - All those aged 0-18
  - Those at high risk

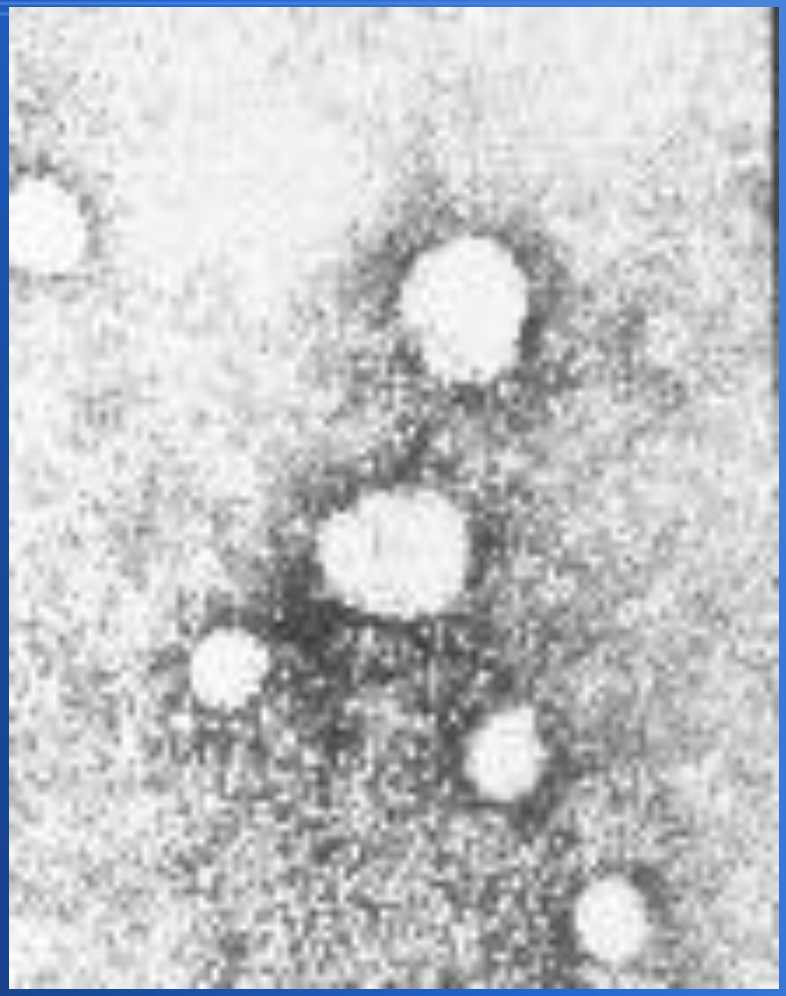
Hepatitis B Virus

High risk groups

- Persons with multiple sex partners or diagnosis of a sexually transmitted disease
- Sex contacts of infected persons
- Injection drug users
- Household contacts of chronically infected persons
- Infants born to infected mothers
- Infants/children of immigrants from areas with high rates of HBV infection
- Health care and public safety workers
- Hemodialysis patients

Hepatitis D (Delta) Virus





Hepatitis D Virus = Defective virus

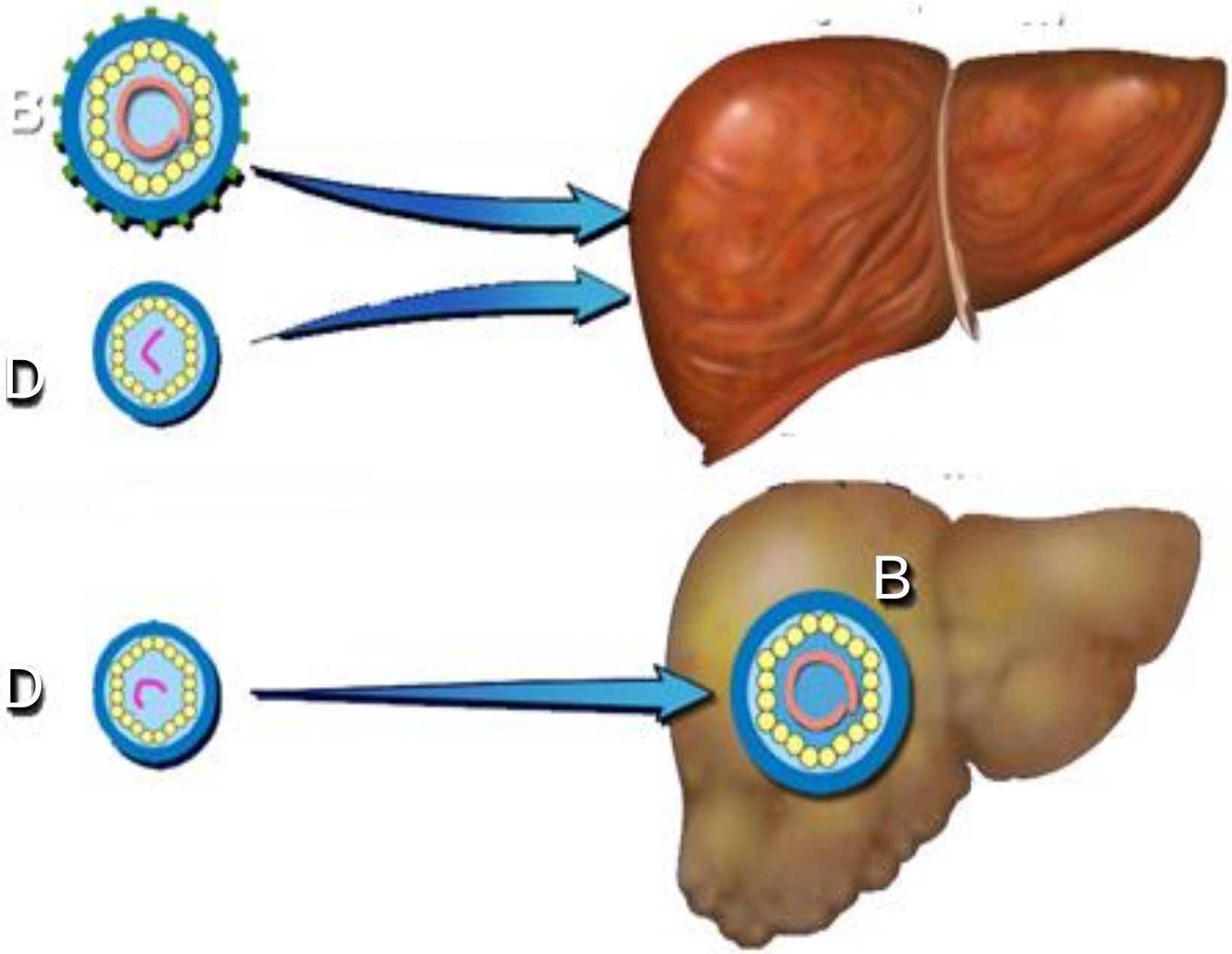
- HDV causes a unique infection that requires the assistance of viral particles from hepatitis B virus (HBV) to replicate and infect other hepatocytes - Incomplete RNA requires HBV for replication
- HDV infection occurs more commonly among adults than children. It is observed more commonly among patients with a history of intravenous drug use and in persons from the Mediterranean basin

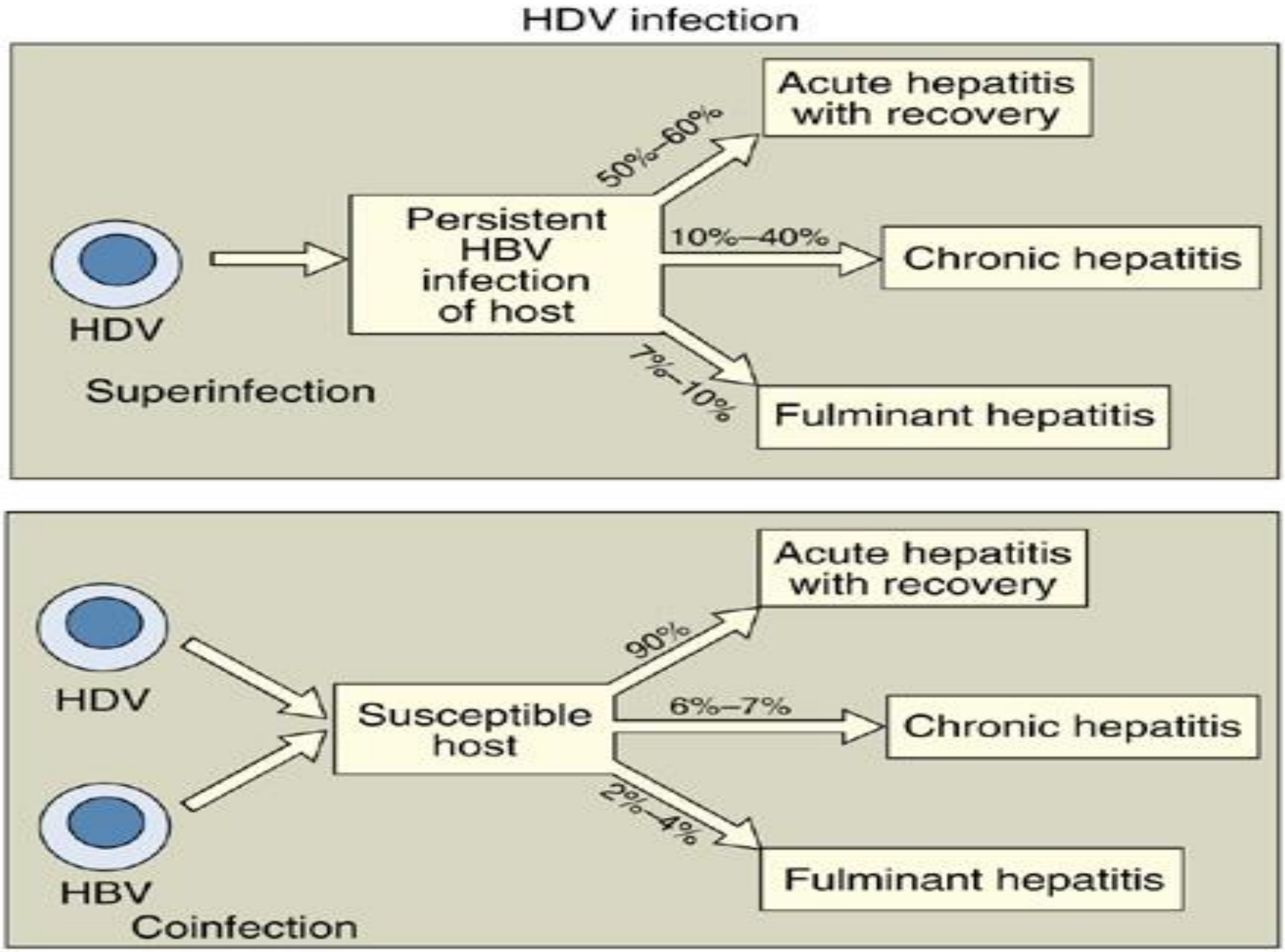
Hepatitis D Virus

Epidemiology

HDV is transmitted parenterally.
Risk factors include intravenous drug use and multiple blood transfusions.
Sexual transmission is less efficient than with HBV.

Modes of HDV infection




HDV infection
Acute hepatitis with recovery
50%–60%
Persistent HBV infection of host
10%–40%
Chronic hepatitis
HDV
Superinfection
7%–10%
Fulminant hepatitis
Acute hepatitis with recovery
90%
HDV
Susceptible host
6%–7%
Chronic hepatitis
2%–4%
HBV
Coinfection
Fulminant hepatitis

Hepatitis D Virus Pathogenesis

Immune mediated

- Co-infection with HBV and HDV is known as co-infection and results in fulminant liver failure in 1% of patients. Complete clinical recovery and clearance of HBV and HDV co-infection is the most common outcome. Chronic infection with HBV and HDV occurs in less than 5% of patients.
- Infection with HDV in a patient already HBsAg-positive is known as superinfection and results in fulminant liver failure in 5% of patients. Approximately 80-90% develop chronic HDV infection. These patients progress more rapidly to develop cirrhosis and may develop hepatocellular carcinoma.

Hepatitis D Virus *Clinical*

HDV infection is clinically indistinguishable from other forms of viral hepatitis.

As many as 90% of patients are asymptomatic.

The incubation period is 21-45 days but may be shorter in cases of superinfection.

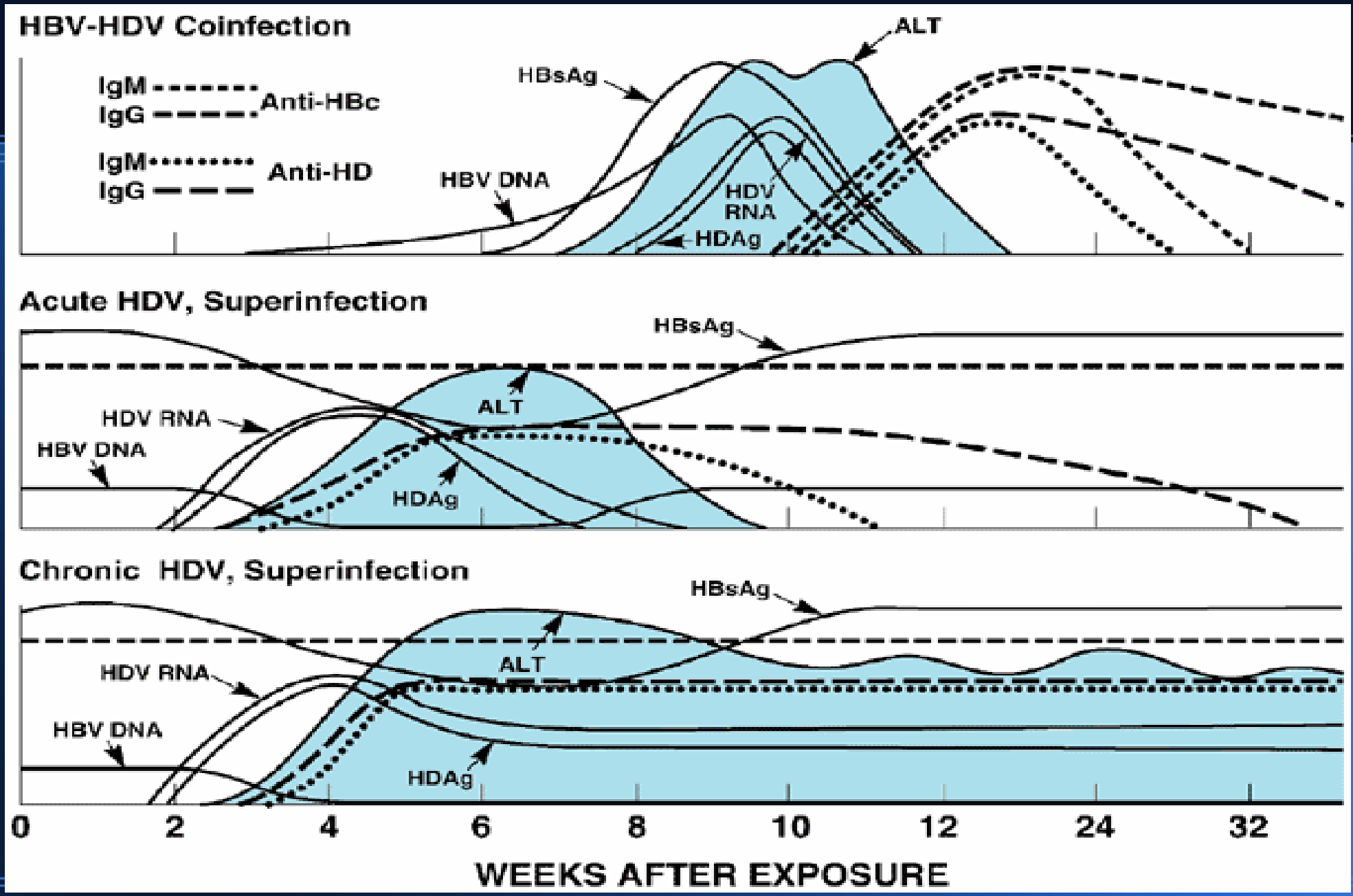
Symptoms include the following:

- Jaundice,dark urine,abdominal pain
- Nausea with vomiting
- Confusion, bruising, and bleeding (rare)
- Pruritus

Physical

Symptoms upon presentation include the following:

- Scleral icterus
- Fever
- Abdominal pain, usually right upper quadrant
- Tea-colored urine
- Encephalopathy (rare)
- Petechia with bruising (rare)


HBV-HDV Coinfection
IgM
IgG
Anti-HBc
IgM
IgG
Anti-HD
HBsAg
ALT
HBV DNA
HDV RNA
HDAg
Acute HDV, Superinfection
HBsAg
HDV RNA
HBV DNA
ALT
HDAg
Chronic HDV, Superinfection
HBsAg
HDV RNA
HBV DNA
ALT
HDAg
0
2
4
6
8
10
12
24
32
WEEKS AFTER EXPOSURE

Hepatitis D Virus — *Serologic diagnosis*

IgM anti-HBc and anti-HD are found in **co-infection** (the infection of HBV and HDV at the same time).

Superinfection in the infection of someone with pre-existing HBV infection with HDV; the markers of acute HBV are absent but the HBsAg and anti-HDV are present.

Hepatitis D Virus ***Prevention***

HBV-HDV Coinfection

Pre or postexposure prophylaxis to prevent HBV infection

HBV-HDV Superinfection

Education to reduce risk behaviors among persons with chronic HBV infection

Alpha interferon may help reduce hepatocellular damage

Hepatitis D Virus *Treatment*

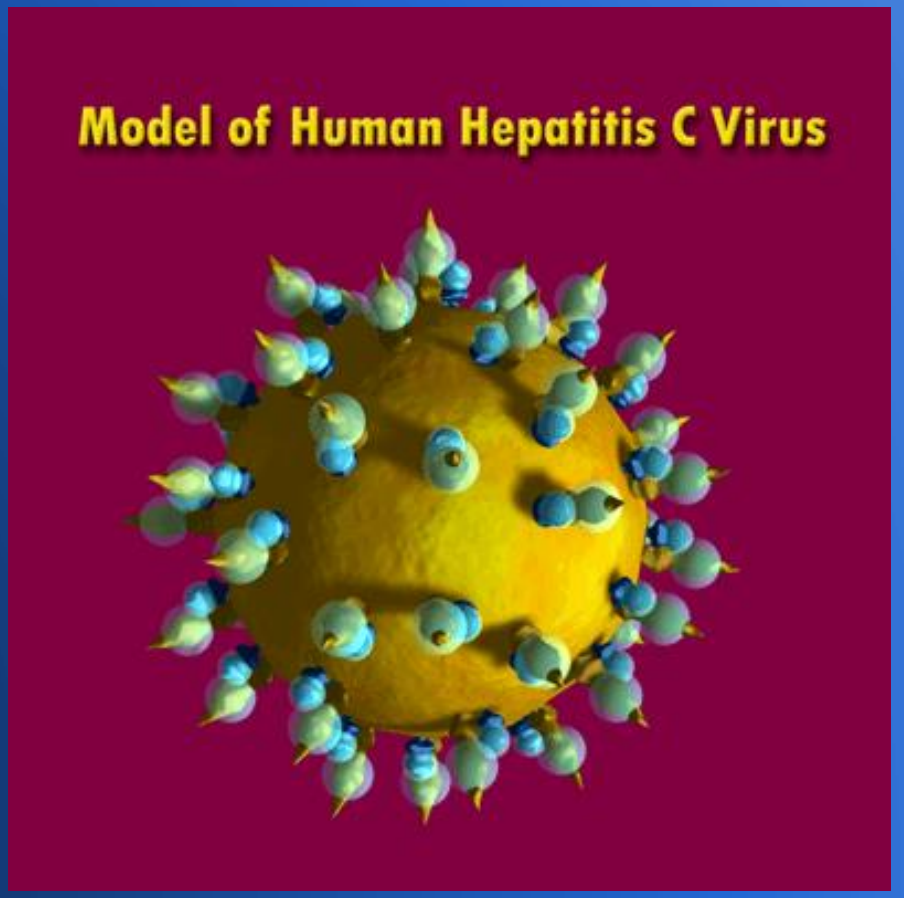
Treatment consists primarily of support. Observe synthetic liver function markers and mental status closely.

Antiviral therapy with interferon alfa can be considered in patients with chronic infection. The treatment course is usually at least one year.

Treatment is not needed for patients with co-infection, given the high spontaneous clearance rates.

Lamivudine, ribavirin, and corticosteroids have not been effective in treatment.

Hepatitis C

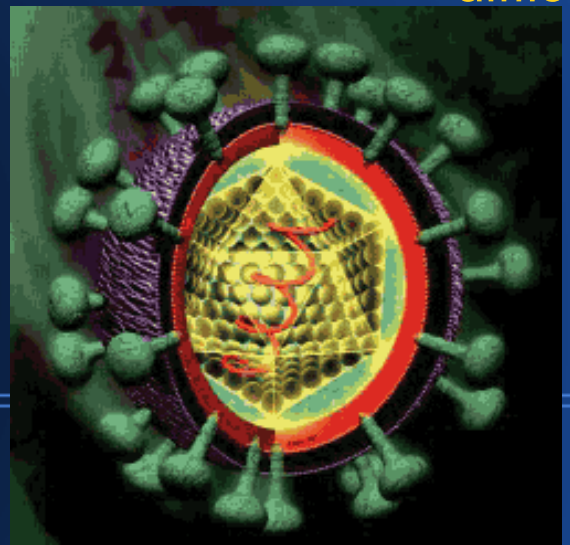


Hepatitis C Virus

HCV is a spherical, enveloped, 60 nm single-stranded RNA virus belonging to the Flaviviridae family and Flavivirus genus.

Six major HCV genotypes and numerous subtypes have been identified.

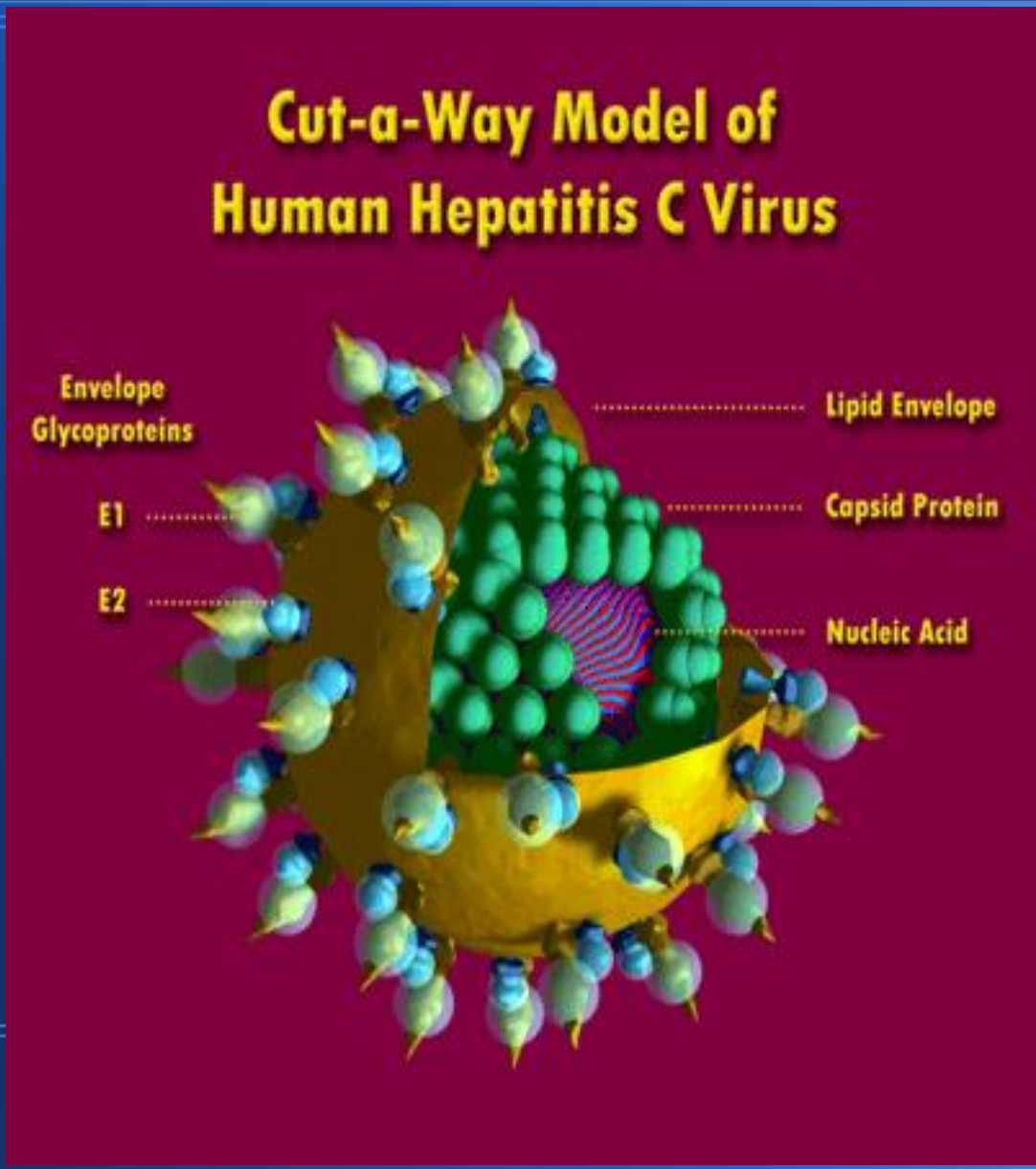
The major HCV genotype worldwide is genotype 1



RNA-dependent RNA polymerase, an enzyme critical in HCV replication, lacks proof-reading capabilities and generates a large number of mutant viruses known as quasispecies. HCV quasispecies pose a major challenge to immune-mediated control of HCV and may explain the variable clinical course and the difficulties in vaccine development.

Hepatitis C viruses particles and genome

- HCV can produce at least 10 trillion new viral particles each day.
- Structural components include the core and 2 envelope proteins, E1 and E2.
- Two regions of the E2 protein, designated hypervariable regions 1 and 2, have an extremely high rate of mutation



Hepatitis C Virus Epidemiology

- Injecting drug use
- Transfusion, transplant from infected donor
- Occupational exposure to bloodMostly needle sticks
- Iatrogenic (unsafe injections)
- Transmission only from women HCV-RNA positive at delivery
  - Average rate of infection 6%
  - Higher (17%) if woman co-infected with HIV
- Sex with infected partner
  - Multiple sex partners
- Could occur through percutaneous/mucosal exposures to blood

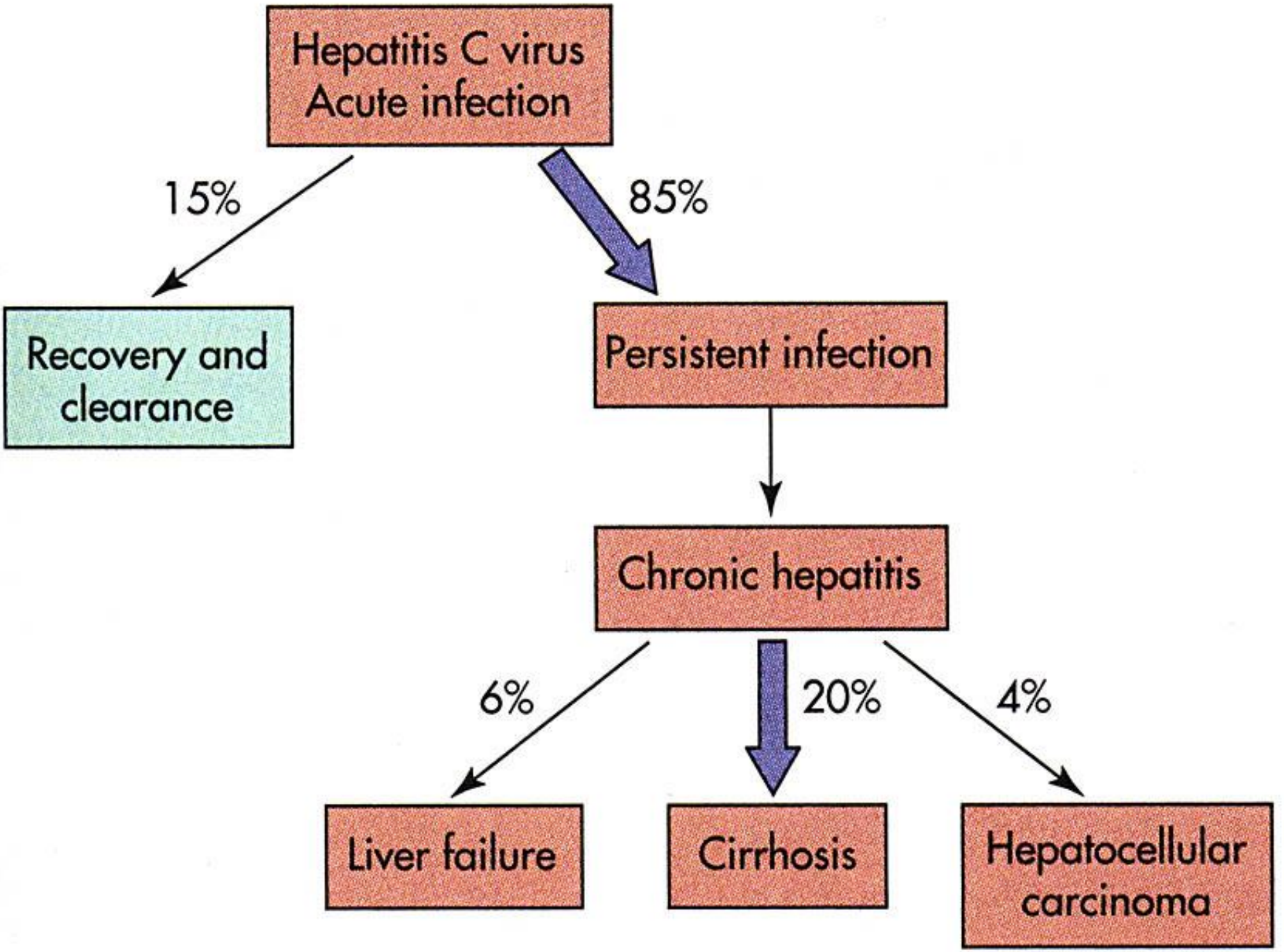
Hepatitis C Virus **Pathogenesis**

- Blood-borne pathogen that infects hepatocytes
- The natural targets of HCV are hepatocytes and, possibly, B lymphocytes. Viral clearance is associated with the development and persistence of strong virus-specific responses by cytotoxic T lymphocytes and helper T cells. In most infected people, viremia persists and is accompanied by variable degrees of hepatic inflammation and fibrosis.
- Like other chronic liver diseases (Hep B and chronic alcoholism), can cause hepatocellular carcinoma (HCC)

Hepatitis C Virus — Clinical features

Incubation period:	Average 6-7 wks Range 2-26 wks
Clinical illness (jaundice):	30-40% (20-30%)
Chronic hepatitis:	70%
Persistent infection:	85-100%

Immunity: No protective antibody response identified


Hepatitis C virus
Acute infection
15%
85%
Recovery and clearance
Persistent infection
Chronic hepatitis
6%
20%
4%
Liver failure
Cirrhosis
Hepatocellular carcinoma

Hepatitis C Virus — Clinical

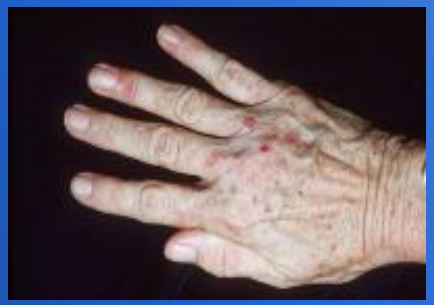
- Acute infection asymptomatic in over 80% of patients, when present, acute illness usually mild

  Acute symptoms include jaundice, nausea, abdominal pain, loss of appetite, dark urine

- Most patients do not have abnormal physical examination findings until they develop portal hypertension or decompensated liver disease.

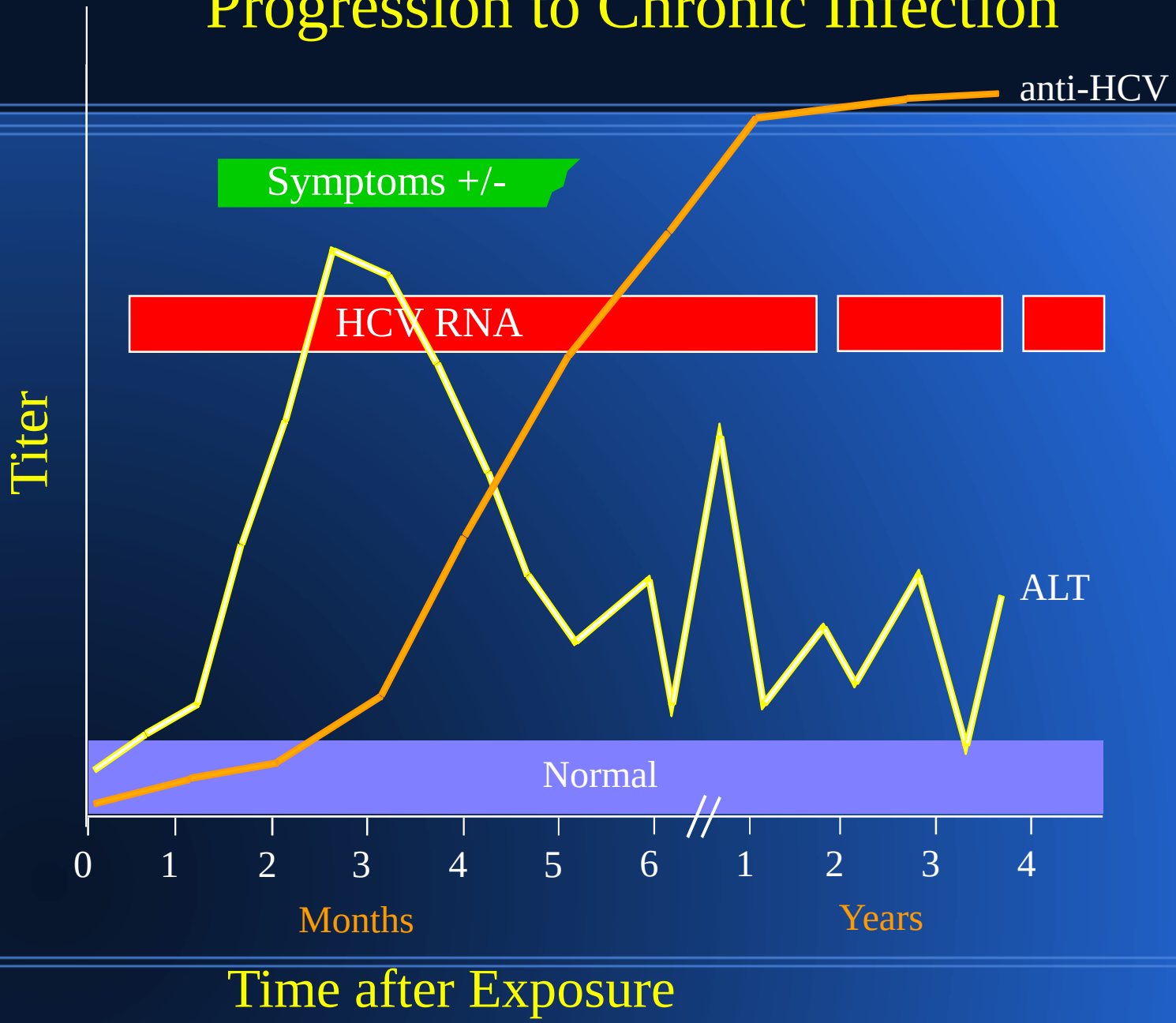
- One exception is patients with extrahepatic manifestations of HCV infection, such as porphyria cutanea tarda or necrotizing vasculitis.

Hepatitis C Virus Extrahepatic manifestations



- Seen with chronic infection
- Due to immune complexes
- Extrahepatic manifestations
  - Essential mixed cryoglobulinemia (vasculitis, skin rash, fatigue), Porphyria cutanea tarda, Membranoproliferative glomerulonephritis, Idiopathic thrombocytopenic purpura, Lichen planus, Keratoconjunctivitis sicca, Raynaud syndrome, Sjögren syndrome Porphyria cutanea tarda, Necrotizing cutaneous vasculitis

Serologic Pattern of Acute HCV Infection with Progression to Chronic Infection



Hepatitis C Virus — *Serologic diagnosis*

- HCV antibody - generally used to diagnose hepatitis C infection. Not useful in the acute phase as it takes at least 4 weeks after infection before antibody appears.
- HCV-RNA - various techniques are available e.g. PCR and branched DNA. May be used to diagnose HCV infection in the acute phase. However, its main use is in monitoring the response to antiviral therapy.
- HCV-antigen - an EIA for HCV antigen is available. It is used in the same capacity as HCV-RNA tests but is much easier to carry out.

Hepatitis C Virus **Treatment**

- Alfa interferon with Ribavirin for 6 months to 1 year
- Prevention – No vaccine -- general prevention to reduce transmission
- Interferon - may be considered for patients with chronic active hepatitis. The response rate is around 50% but 50% of responders will relapse upon withdrawal of treatment.
- Ribavirin - there is less experience with ribavirin than interferon. However, recent studies suggest that a combination of interferon and ribavirin is more effective than interferon alone.

Hepatitis C Virus — *Prognosis*

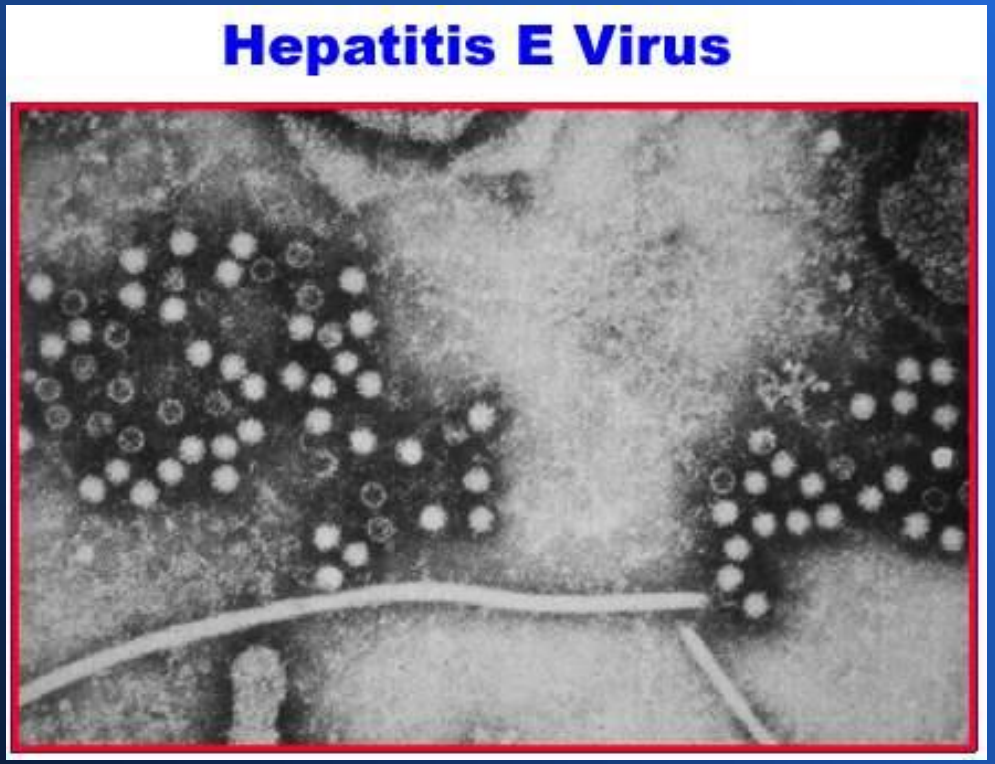
Genotyping – genotype 1 and 4 have a worse prognosis overall and respond poorly to interferon therapy.

Viral Load – patients with high viral load are thought to have a poorer prognosis. Viral load is also used for monitoring response to IFN therapy. A number of commercial and in-house tests are available.

Hepatitis C Virus — *Prognosis*

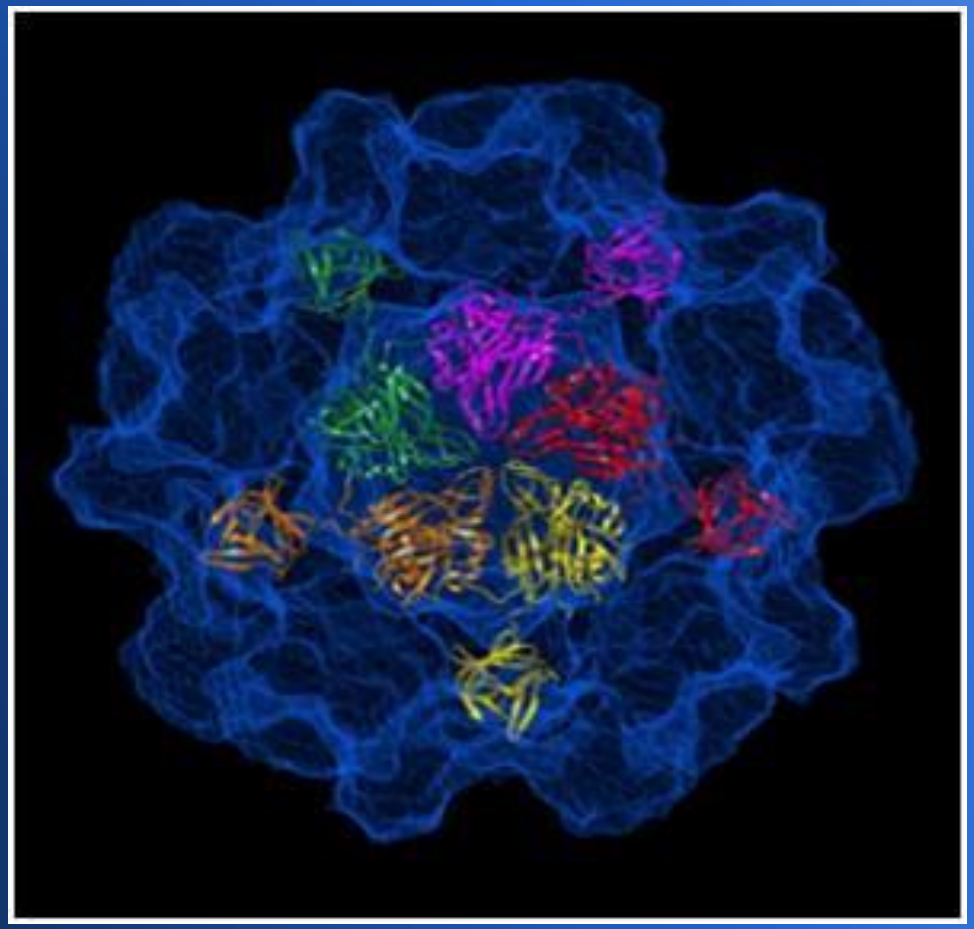
- Chronic infection develops in 70-80% of patients infected with HCV.
- Cirrhosis develops within 20 years of disease onset in 20% of those with chronic infection.
- HCC may develop at an average of 30 years after the onset of infection and is more common in the presence of cirrhosis, alcoholism, and HBV co-infection.

Hepatitis E Virus



Hepatitis E Virus

- Icosahedral and nonenveloped, unenveloped RNA virus, 32-34nm in diameter
- Calicivirus-like viruses
- Has not been isolate, but has been cloned using molecular techniques
- Hepatitis E is an RNA virus of the Caliciviridae family, genus Hepevirus. Four hepatitis E genotypes exist, and genotype 1 causes human disease.



Hepatitis E Virus *Epidemiology*

Hepatitis E virus (HEV) is an enteral transmitted infection that is typically self-limited.

Fulminant disease has been reported most frequently in pregnant women which increases during the second and third trimesters.

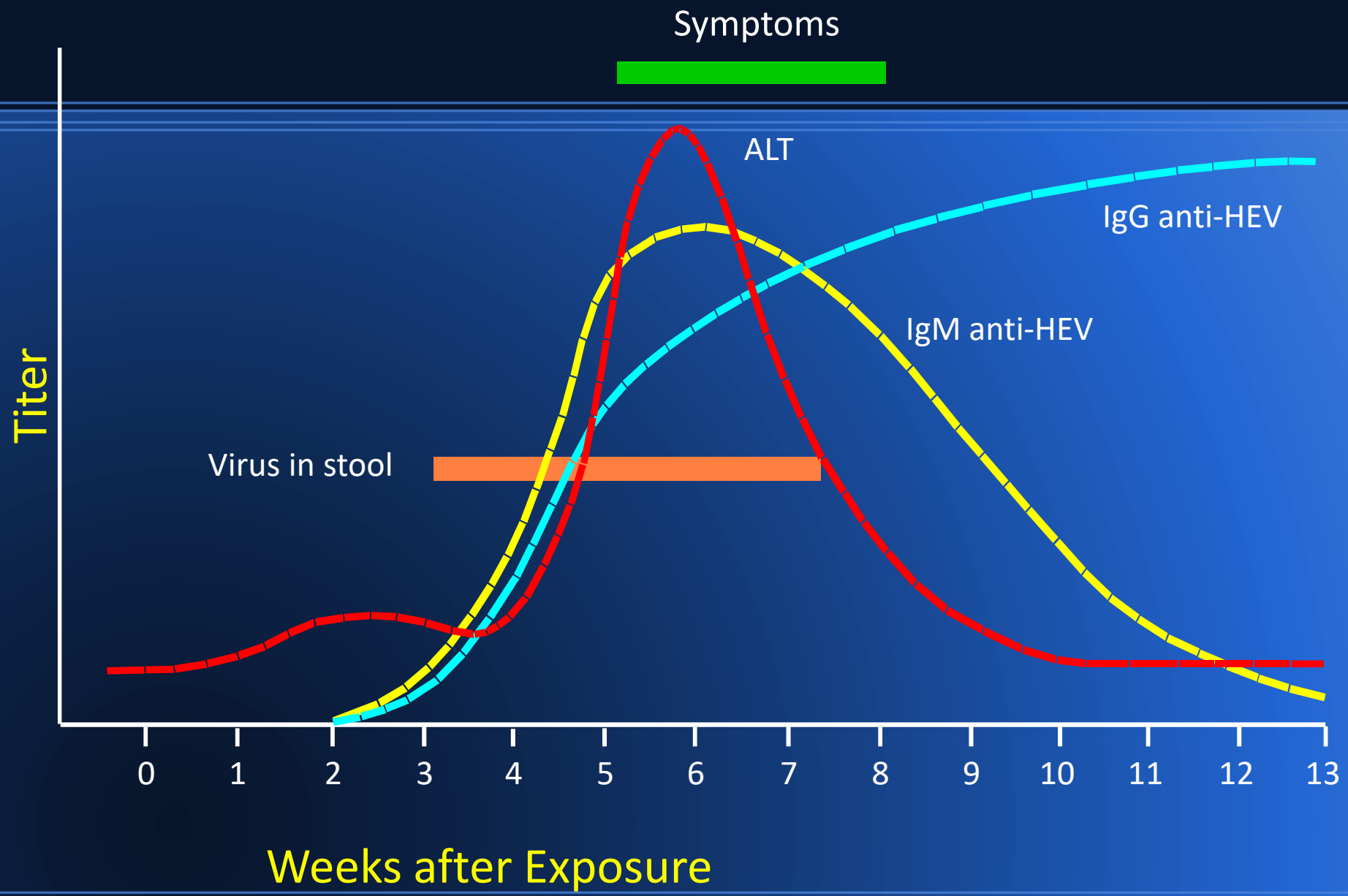
Most outbreaks associated with faecally contaminated drinking water, but a few food borne uncooked shellfish epidemics have been reported from China

Hepatitis E is the most common form of acute hepatitis in adult in highly epidemic regions of Asia.

Hepatitis E infection has recently been associated with chronic hepatitis in solid organ-transplant recipients

Minimal person-to-person transmission.

Hepatitis E Virus Infection



Hepatitis E Virus

Clinical features

- Incubation period: Average 40 days
Range 15-60 days
- Case-fatality rate: Overall, 1%-3%
Pregnant women, 15%-25%
- Illness severity: Increased with age
- Chronic sequelae: None identified

Hepatitis E Virus Pathogenesis and diagnosis

HEV appear to act as a cytopatic virus. The pathogenic findings are similar to the other hepatitis viruses.

Immune response

Specific IgM and IgG immune responses to HEV occur early in the infection, usually by the onset of clinical illness.

Serologic diagnosis can made at the time of presentation of the patient.

IgM anti-HEV disappears after several months;

IgG anti-HEV persist but appears to diminish in titer at a more rapid rate than antibody to HAV

Hepatitis E Virus Clinical

The incubation period ranges from 15 days to 60 days, and the course of infection has 2 phases termed prodromal and icteric

Hepatitis E cannot be differentiated from other types of viral hepatitis on the basis of clinical presentation. Clinically, the severity of HEV infections may cause from unapparent to fulminant. Most patients experience abdominal pain, nausea, vomiting, and fever.

Hepatitis E never progresses to chronicity.

Complication of hepatitis E are related to severe hepatitis in pregnancy:

High mortality of infected pregnant women 20% Reported causes of death 20% include encephalopathy and disseminated intravascular coagulation

Hepatitis E Virus Treatment and prevention

Therapy should be predominantly preventive, relying on clean drinking water, good sanitation, and proper personal hygiene.

Travelers to endemic areas should avoid drinking water or other beverages that may be contaminated and should avoid eating uncooked shellfish. Care should be taken while preparing uncooked fruits or vegetables

No immunoprophylaxis is available.

Prototype vaccines are being developed using animal models.

Once infection occurs, therapy is limited to support.

TABLE 62–1. Comparative Features of Hepatitis Viruses

Feature	Hepatitis A	Hepatitis B	Hepatitis C	Hepatitis D	Hepatitis E
Common name	"Infectious"	"Serum"	"Non-A, non-B–post-transfusion"	"Delta agent"	"Enteric non-A, non-B"
Virus structure	Picornavirus; capsid, RNA	Hepadnavirus; envelope, DNA	Flavivirus; envelope, RNA	Viroid-like; envelope, circular RNA	*Calicivirus*-like; capsid, RNA
Transmission	Fecal-oral	Parenteral, sexual	Parenteral, sexual	Parenteral, sexual	Fecal-oral
Onset	Abrupt	Insidious	Insidious	Abrupt	Abrupt
Incubation period (days)	15–50	45–160	14–180	15–64	15–50
Severity	Mild	Occasionally severe	Usually subclinical; 80% chronicity	*Co-infection* with HBV occasionally severe; *superinfection* with HBV often severe	Normal patients, mild; pregnant women, severe
Mortality	<0.5%	1%–2%	~4%	High to very high	Normal patients, 1%–2%; pregnant women, 20%
Chronicity/carrier state	No	Yes	Yes	Yes	No
Other disease associations	None	Primary hepatocellular carcinoma, cirrhosis	Primary hepatocellular carcinoma, cirrhosis	Cirrhosis, fulminant hepatitis	None
Laboratory diagnosis	Symptoms and anti-HAV IgM	Symptoms and serum levels of HBsAg, HBeAg, and anti-HBc IgM	Symptoms and anti-HCV ELISA	Anti-HDV ELISA	—

Thank you