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Particularly dangerous infections: cholera, plague, contagious hemorrhagic fevers (manual for english-speaking students of 5, 6 course of medical faculty)

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The manual reveals issues of pathogenesis, clinical course, diagnosis, differential diagnosis, treatment and prevention of particularly dangerous infections. There are given formulation of the concepts of particularly dangerous infections, observation, quarantine, described the tactic of doctor in contact with patients suspected of especially dangerous infections. There are presented tests, situational tasks on each of the themes with standard answers.

У навчальному посібнику розкриваються питання патогенезу, особливостей клінічного перебігу, діагностики, диференційної діагностики, лікування та профілактики особливо-небезпечних інфекцій. Дається формулювання понять особливо-небезпечних інфекцій, обсервації, карантину, описується тактика лікаря при зіткненні з хворим, підозрілим на особливо небезпечну інфекцію. Представлені тестові завдання, ситуаційні задачі по кожній з тем з еталонами відповідей на них.

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Content

Introduction

Particularly dangerous (quarantine) infections - a group of diseases which are subject to quarantine measures in accordance with international health regulations. Protective measures against import and spreading of infectious diseases from other countries were specified by the World Health Organization. Each country must have special system of measures aimed at prevention of import of infectious diseases from abroad, and if an infection is taken into a country, measures should be taken to prevent its spreading.

When people travel they can develop infections through food, water, insect bites, contact with animals or contact with other people. Often a person does not know they have developed an infectious disease until they become unwell days or weeks later. Symptoms of an infection might only develop, or become serious, after a person has returned to his country.

Some of the diseases at which quarantine measures are directed are rare and/or serious, such as Viral Haemorrhagic Fevers (VHFs). Some more familiar diseases are also important because outbreaks can occur if they are introduced by an unwell traveller. Some of these diseases include: cholera, highly pathogenic influenza, plague, rabies, severe acute respiratory syndrome (SARS), smallpox, viral haemorrhagic fever, yellow fever.

Isolation and quarantine help protect the public by preventing exposure to people who have or may have a contagious disease. *Isolation* separates sick people with a contagious disease from people who are not sick. *Quarantine* separates and restricts the movement of people who were exposed to a contagious disease to see if they become sick. Quarantine Stations, located at ports of entry and land border crossings, use these public health practices as part of a comprehensive Quarantine System that serves to limit the introduction of infectious diseases into the countries and to prevent their spread.

Unit 1. Cholera

Cholera is an intestinal infection caused by Vibrio cholerae. The hallmark of the disease is profuse secretory diarrhea. Cholera can be endemic, epidemic, or pandemic. Despite all the major advances in research, the condition still remains a challenge to the modern medical world. Although the disease may be asymptomatic or mild, severe cholera can cause dehydration and death within hours of onset.

Cholera is an ancient disease. Throughout history, populations all over the world have sporadically been affected by devastating outbreaks of cholera. Since 1817, 7 cholera pandemics have occurred. The pandemics originated from cholera's endemic reservoir in the Indian subcontinent. The first 6 occurred from 1817-1923 and were probably the result of V cholerae O1 of the classic biotype. Of these 6 pandemics, 5 affected Europe and 4 reached the United States, causing more than 150,000 deaths in 1832 and 50,000 deaths in 1866. The seventh pandemic of cholera, and the first in the 20th century, began in 1961; by 1991, it had affected 5 continents. The pandemic continues today. This seventh pandemic was the first recognized to be caused by the El Tor biotype of V cholerae O1. The pandemic originated from the Celebes Islands, Indonesia, and affected more countries and continents than the previous 6 pandemics. A new strain of cholera, V cholerae serogroup O139 (Bengal) emerged in the fall of 1992 and caused outbreaks in Bangladesh and India in 1993. Disease from this strain has become endemic in at least 11 countries. This disease is still common in other parts of the world, including the Indian subcontinent and sub-Saharan Africa. Epidemics occur after war, civil unrest, or natural disasters when water and food supplies become contaminated with V cholerae in areas with crowded living conditions and poor sanitation. The number of patients with cholera worldwide is uncertain because most cases go unreported, because most cases occur in remote areas of developing countries where definitive diagnosis is not possible; reporting systems often are

nonexistent in such areas; many countries with endemic cholera do not report at all.

Etiology.

V cholerae is a comma-shaped, gram-negative aerobic or facultatively anaerobic bacillus that varies in size from 1-3 µm in length by 0.5-0.8 µm in diameter (see the image below). Its antigenic structure consists of a flagellar H antigen and a somatic O antigen. The differentiation of the latter allows for separation into pathogenic and nonpathogenic strains. Although more than 200 serogroups of V cholerae have been identified, V cholerae O1 and V cholerae O139 are the principal ones associated with epidemic cholera.

Currently, the El Tor biotype of V cholerae O1 is the predominant cholera pathogen. Organisms in both the classical and the El Tor 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.

The clinical and epidemiologic features of disease caused by V cholerae O139 are indistinguishable from those of disease caused by O1 strains. Both serogroups cause clinical disease by producing an enterotoxin that promotes the secretion of fluid and electrolytes into the lumen of the small intestine. In nonendemic areas, the incidence of infection is similar in all age groups, although adults are less likely to become symptomatic than children. The exception is breastfed children, who are protected against severe disease because of less exposure and because of the antibodies to cholera they obtain in breast milk.

Epidemiology.

Cholera is usually transmitted through fecally contaminated water or food. Outbreaks can occur sporadically in any part of the world where water supply, sanitation, food safety, and hygiene are inadequate. WHO recommends improvements in water supply and sanitation as the most sustainable approach for protecting against cholera and other waterborne epidemic diarrheal diseases.

The source of infection is only a person: the patient and bacillicarrier. The infectious dose of V cholerae required to cause clinical disease varies by the mode of administration. If V cholerae is ingested with water, the infectious dose is 103 - 106 organisms. When ingested with food, fewer organisms (102 -104) are required to produce disease. Owing to the relatively large infectious dose, transmission occurs almost exclusively via contaminated water or food. Cholera has 2 main reservoirs, humans and water. V cholerae is rarely isolated from animals, and animals do not play a role in transmission of disease. Transmission occurs through fecal-oral spread of the organism through person-to-person contact or through contaminated water and food. Spread also occurs in households but can also occur in clinics or hospitals where patients with cholera are treated. Infection rates predictably are highest in communities in which water is not potable and personal and community hygiene standards are low. Asymptomatic carriers may have a role in transfer of disease in areas where the disease is not endemic. Although carriage usually is short-lived, a few individuals may excrete the organisms for a prolonged period. Malnutrition increases susceptibility to cholera. Because gastric acid can quickly render an inoculum of V cholerae noninfectious before it reaches the site of colonization in the small bowel, hydrochlorhydria or achlorhydria of any cause (including Helicobacter pylori infection, gastric surgery, vagotomy, use of H2 blockers for ulcer disease) increases susceptibility. The incidence of cholera appears to be twice as high in people with type O blood. The reason for this increased susceptibility is unknown.

Pathogenesis.

V cholerae O1 and V cholerae O139 cause clinical disease by producing an enterotoxin. The enterotoxin acts locally and does not invade the intestinal wall. This toxin 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 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. Unless the lost fluid and electrolytes are replaced adequately, the infected person may develop shock from profound dehydration and acidosis from loss of bicarbonate. Cholera causes bicarbonate loss in stools, accumulation of lactate because of diminished perfusion of peripheral tissues, and hyperphosphatemia. Acidemia results when respiratory compensation is unable to sustain a normal blood pH. Hypokalemia results from potassium loss in the stool, with a mean potassium concentration of approximately 3.0 mmol/L. Because of the existing acidosis, however, children often have normal serum potassium concentrations when first observed, despite severe total body potassium depletion. Hypokalemia develops only after the acidosis is corrected and intracellular hydrogen ions are exchanged for extracellular potassium. Hypokalemia is most severe in children with preexisting malnutrition who have diminished body stores of potassium and may be manifested as paralytic ileus. Rehydration therapy with bicarbonate-containing fluids can also produce hypocalcemia by decreasing the proportion of serum calcium that is ionized. Chvostek and Trousseau signs are often present, and spontaneous tetanic contractions can occur.

Signs and symptoms.

After a 24- to 48-hour incubation period (max – 5 days), symptoms begin with the sudden onset of painless watery diarrhea that may quickly become voluminous and is often followed by vomiting. The patient may experience

accompanying abdominal cramps, probably from distention of loops of small bowel as a result of the large volume of intestinal secretions. Fever is typically absent. However, most Vibrio cholerae infections are asymptomatic, and mild to moderate diarrhea due to V cholerae infection may not be clinically distinguishable from other causes of gastroenteritis. An estimated 5% of infected patients will develop cholera gravis, ie, severe watery diarrhea, vomiting, and dehydration.

Profuse watery diarrhea is a hallmark of cholera. Cholera should be suspected when a patient older than 5 years develops severe dehydration from acute, severe, watery diarrhea (usually without vomiting) or in any patient older than 2 years who has acute watery diarrhea and is in an area where an outbreak of cholera has occurred. Stool volume during cholera is more than that of any other infectious diarrhea. Patients with severe disease may have a stool volume of more than 250 ml/kg body weight in a 24-hour period. Because of the large volume of diarrhea, patients with cholera have frequent and often uncontrolled bowel movements. The stool may contain fecal material early in the course of clinical illness. The characteristic cholera stool is an opaque white liquid that is not malodorous and often is described as having a “rice water” appearance (ie, in color and consistency, it resembles water that has been used to wash or cook rice).

Vomiting, although a prominent manifestation, may not always be present. Early in the course of the disease, vomiting is caused by decreased gastric and intestinal motility; later in the course of the disease it is more likely to result from acidemia.

If untreated, the diarrhea and vomiting lead to isotonic dehydration, which can lead to acute tubular necrosis and renal failure. In patients with severe disease, vascular collapse, shock, and death may ensue. Dehydration can develop with remarkable rapidity, within hours after the onset of symptoms. This contrasts with disease produced by infection from any other enteropathogen. Because the dehydration is isotonic, water loss is proportional between 3 body compartments, intracellular, intravascular, and interstitial.

Clinical signs of cholera parallel the level of volume contraction.

According to clinical manifestations distinguish subclinical, mild, moderate, severe and very severe forms, determines the degree of dehydration: I degree, when patients lose fluid volume equal to 1-3% of body weight (erased and mild forms); II degree - losses amount 4-6% (moderate); III degree - 7-9% (severe); IV degree dehydration with loss of more than 9% corresponds to a very severe course of cholera. When cholera El Tor I degree of dehydration occurs in 50 -60% of patients, II - at 20-25%, III - at 8-10%, IV - at 8-10%.

The amount of fluid loss and the corresponding clinical signs of cholera are as follows: 1-3% loss of normal body weight - excessive thirst; 4-9% loss of normal body weight - postural hypotension, tachycardia, weakness, fatigue, dry mucous membranes or dry mouth; >9% loss of normal body weight - oliguria; glassy or sunken eyes; sunken fontanelles in infants; weak, thready, or absent pulse; wrinkled "washerwoman" skin; somnolence; coma.

Patients without clinically significant dehydration (< 4% loss of body weight) may have increased thirst without other signs of dehydration. In patients with moderate dehydration, cardiac output and vascular resistance are normal, and changes in interstitial and intracellular volume are the primary manifestations of illness. Skin turgor is decreased, as manifested by prolonged skin tenting in response to a skin pinch (the most reliable sign of isotonic dehydration), and a normal pulse. For the skin pinch, it is important to pinch longitudinally rather than horizontally and to maintain the pinch for a few seconds before releasing the skin.

Other signs of severe dehydration include tachycardia, absent or barely palpable peripheral pulses, and hypotension. Tachypnea and hypercapnia also are part of the clinical picture and are attributable to the metabolic acidosis that invariably is present in patients with cholera who are dehydrated.

Cholera sicca is an old term describing a rare, severe form of cholera that occurs in epidemic cholera. This form of cholera manifests as ileus and abdominal distention from massive outpouring of fluid and electrolytes into dilated intestinal

loops. Mortality is high, with death resulting from toxemia before the onset of diarrhea and vomiting. The mortality in this condition is high. Because of the unusual presentation, failure to recognize the condition as a form of cholera is common.

Laboratory diagnosis.

Laboratory diagnosis is required not only for identification but also for epidemiological purposes.

Non-specific tests. The major hematologic derangements in patients with cholera derive from the alterations in intravascular volume and electrolyte concentrations.

Hematocrit, serum-specific gravity, and serum protein are elevated in dehydrated patients because of resulting hemoconcentration. When patients are first observed, they generally have a leukocytosis without a left shift.

Serum sodium is usually 130-135 mmol/L, reflecting the substantial loss of sodium in the stool.

Serum potassium usually is normal in the acute phase of the illness, reflecting the exchange of intracellular potassium for extracellular hydrogen ion in an effort to correct the acidosis.

Hyperglycemia may be present, secondary to systemic release of epinephrine, glucagon, and cortisol due to hypovolemia.

Patients have elevated blood urea nitrogen and creatinine levels consistent with prerenal azotemia. The extent of elevation depends on the degree and duration of dehydration.

A reduced bicarbonate level (< 15 mmol/L) and an elevated anion gap occur as a result of increases in serum lactate, protein, and phosphate levels. The arterial pH is usually low (approximately 7.2). Calcium and magnesium levels are usually high as a result of hemoconcentration.

Microscopy of stool. Although observed as a gram-negative organism, the characteristic motility of Vibrio species cannot be identified on a Gram stain, but it is easily seen on direct dark-field examination of the stool.

Stool Culture. Many of the selective media used to differentiate enteric pathogens do not support the growth of V. cholerae. Colonies are lactose-negative, like all other intestinal pathogens, but sucrose-positive. When plated onto triple-sugar iron agar, the organism gives the nonpathogenic pattern of an acid (yellow) slant and acid butt because of fermentation of the sucrose contained in triple-sugar iron agar. Unlike other Enterobacteriaceae, V cholerae is oxidase-positive; hence, in countries where selective media are not available and cholera is not endemic, V cholerae should be suspected if any motile, oxidase-positive, gram-negative rod isolated on routine differential media from the stool of a patient with diarrhea produces an acid reaction on triple sugar iron agar. As Vibrio has the ability to grow at a high pH or in bile salts, which inhibit many other Enterobacteriaceae, peptone water (pH 8.5-9) or selective media containing bile salts are recommended to facilitate isolation and lab diagnosis. On thiosulfate-citrate-bile-sucrose-agar, the sucrose-fermenting V cholera grow as large, smooth, round yellow colonies that stand out against the blue-green agar.

Serological test. Specific antisera can be used in immobilization tests. A positive immobilization test result (ie, cessation of motility of the organism) is produced only if the antiserum is specific for the Vibrio type present; the second antiserum serves as a negative control. Vibrio antisera may be unavailable in countries where cholera is not endemic. In endemic regions, this is an excellent quick method of identification, even in small laboratories. Classic and El Tor biotypes also can be identified using the same method. This is useful for epidemiologic studies.

Treatment.

Rehydration is the first priority in the treatment of cholera. Rehydration is accomplished in 2 phases: rehydration and maintenance.

The goal of the rehydration phase is to restore normal hydration status, which should take no more than 4 hours. Set the rate of intravenous infusion in severely dehydrated patients at 50-100 mL/kg/hr. Lactated Ringer solution is preferred over isotonic sodium chloride solution because saline does not correct metabolic acidosis

The goal of the maintenance phase is to maintain normal hydration status by replacing ongoing losses. The oral route is preferred, and the use of oral rehydration solution (ORS) at a rate of 500-1000 mL/hr is recommended.

In areas where cholera is endemic, cholera cots have been used to assess the volume of ongoing stool losses. A cholera cot is a cot covered by a plastic sheet with a hole in the center to allow the stool to collect in a calibrated bucket underneath.

Use of such a cot allows minimally trained health workers to calculate fluid losses and replacement needs. The volume of stool is measured every 2-4 hours, and the volume of fluid administered is adjusted accordingly.

In the initial phase of therapy, urine losses account for only a small proportion of fluid losses, and the amount of fluid in the bucket is an adequate reflection of stool losses. With rehydration, urine should be collected separately, so that a vicious circle of increasing urine output and overhydration can be avoided.

The WHO has provided recommendations for fluid replacement in patients with dehydration. The recommendations include recommendations for fluid replacement for severe hydration, some dehydration, and no dehydration.

Severe dehydration

Administer intravenous (IV) fluid immediately to replace fluid deficit. Use lactated Ringer solution or, if that is not available, isotonic sodium chloride solution. If the patient can drink, begin giving oral rehydration salt solution (ORS) by mouth while the drip is being set up; ORS can provide the potassium, bicarbonate, and glucose that saline solution lacks.

For the treatment different polyionic solution are used. Most proven solution is "Trisol" (a solution of 5, 4, 1 or solution №1). To prepare the solution take bidistilled apyrogenic water, 1 liter of which was added 5 g of sodium chloride, 4 g sodium bicarbonate and 1 g of potassium chloride. A more effective solution is now considered "Kvartasol" containing 1 L of water 4.75 g of sodium chloride, 1.5 g potassium chloride, 2.6 g of sodium acetate and 1 g of sodium hydrogen carbonate. One can use a solution of "Acesol" - 1 liter pyrogen-free water 5 g sodium chloride, 2 g of sodium acetate, 1 g of potassium chloride. Solution "Chlosol" - 1 liter pyrogen-free water 4.75 g sodium chloride, 3.6 g of sodium acetate and 1.5 g of potassium chloride. Solution "Laktosol" containing 1 liter pyrogen-free water, 6.1 g sodium chloride, 3.4 g of sodium acetate lacquer, 0.3 g of sodium bicarbonate, 0.3 g potassium chloride, 0.16 g of calcium chloride and 0 1 g of magnesium chloride. World Health Organization recommended "WHO solution" - to 1 liter pyrogen-free water 4 g of sodium chloride, 1 g of potassium chloride, 5.4 g of sodium lactate and 8 g glucose.

Polyionic solutions are administered intravenously, previously heated to 38 - 40°C, with the speed in II degree of dehydration 40-48 ml / min, with severe (dehydration stage III-IV) administration of solutions begin with a speed of 80-120 ml / min.

For patients older than 1 year, give 100 mL/kg IV in 3 hours—30 mL/kg as rapidly as possible (within 30 min) then 70 mL/kg in the next 2 hours. For patients younger than 1 year, administer 100 mL/kg IV in 6 hours—30 mL/kg in the first hour then 70 mL/kg in the next 5 hours.

Monitor the patient frequently. After the initial 30 mL/kg has been administered, the radial pulse should be strong and blood pressure should be normal. If the pulse is not yet strong, continue to give IV fluid rapidly. Administer ORS solution (about 5 mL/kg/h) as soon as the patient can drink, in addition to IV fluid.

Reassess the hydration status after 3 hours (infants after 6 h). In the rare case that the patient still exhibits signs of severe dehydration, repeat the IV therapy already given. If signs of some dehydration are present, continue as indicated below for some dehydration. If no signs of dehydration exist, maintain hydration by replacing ongoing fluid losses.

Routes for parenteral rehydration

Accessing a peripheral vein is relatively easy, despite the severe dehydration. If a peripheral vein is not readily accessible, scalp veins have been used for initial rehydration. As the vascular volume is reestablished, a larger needle or catheter can be introduced in a peripheral vein.

Intraosseous routes have been used successfully in young children when veins cannot be accessed. The intraperitoneal route has been tried, but is not recommended.

ORS solution can be administered via nasogastric tube if the patient has some signs of dehydration and cannot drink or if the patient has severe dehydration and IV therapy is not possible at the treatment facility. WHO ORS contains the following: Sodium – 75 mmol/L , Chloride – 65 mmol/L, Potassium – 20 mmol/L, Bicarbonate – 30 mmol/L, Glucose – 111 mmol/L.

A risk of overhydration exists with intravenous fluids; it usually first manifests as puffiness around the eyes. Continued excessive administration of intravenous fluids can lead to pulmonary edema and has been observed even in children with normal cardiovascular reserve. Thus, it is important to monitor patients who are receiving intravenous rehydration hourly. Serum-specific gravity is an additional measure of the adequacy of rehydration.

Most patients absorb enough ORS solution to achieve rehydration, even when they are vomiting. Vomiting usually subsides within 2-3 hours, as rehydration is achieved.

Urine output decreases as dehydration develops and may cease. It usually resumes within 6-8 hours after starting rehydration. Regular urinary output (ie,

every 3-4 h) is a good sign that enough fluid is being given. Replace ongoing fluid losses until diarrhea stops.

When a patient who has been rehydrated with IV fluid or ORS solution is reassessed and has no signs of dehydration, continue to administer ORS solution to maintain normal hydration. The aim is to replace stool losses as they occur with an equivalent amount of ORS solution. The amount of ORS solution required to maintain hydration varies greatly among patients, depending on the volume of stool passed. It is highest in the first 24 hours of treatment and is especially large in patients who present with severe dehydration. In the first 24 hours, the average requirement of ORS solution in such patients is 200 mL/kg, but some patients may need as much as 350 mL/kg. Continue to reassess the patient for signs of dehydration at least every 4 hours to ensure that enough ORS solution is being taken. Patients with profuse ongoing diarrhea require more frequent monitoring. If signs of some dehydration are detected, the patient should be rehydrated as described earlier, before continuing with treatment to maintain hydration. Keep the patient under observation, if possible, until diarrhea stops or is infrequent and of small volume. This is especially important for any patient presenting with severe dehydration.

Antibacterial treatment

An effective antibiotic can reduce the volume of diarrhea in patients with severe cholera and shorten the period during which V cholerae O1 is excreted. In addition, it usually stops the diarrhea within 48 hours, thus shortening the period of hospitalization. Whenever possible, antibiotic therapy should be guided by susceptibility reports.

Empiric antimicrobial therapy must be comprehensive and should cover all likely pathogens in the context of the clinical setting. Although not necessarily curative, 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; fluid replacement is primary.

Emerging drug resistance in certain parts of the world is a concern, as some V cholerae strains contain plasmids that confer resistance to many antibiotics. In areas of known tetracycline resistance, therapeutic options include ciprofloxacin and erythromycin.

Antibiotic treatment is indicated for severely dehydrated patients who are older than 2 years. Begin antibiotic therapy after the patient has been rehydrated (usually in 4-6 h) and vomiting has stopped. No advantage exists to using injectable antibiotics, which are expensive. No other drugs should be used in the treatment of cholera. Antimicrobial agents typically are administered for 3-5 days. However, single-dose therapy with tetracycline, doxycycline, furazolidone, or ciprofloxacin has been shown effective in reducing the duration and volume of diarrhea. Because single dose doxycycline has been shown to be as effective as multiple doses of tetracycline, this has become the preferred regimen.

Antimicrobial therapy is an adjunct to fluid therapy of cholera and is not an essential component. However, it reduces diarrhea volume and duration by approximately 50%. The choice of antibiotics is determined by the susceptibility patterns of the local strains of V cholerae O1 or O139.

So, for the treatment of cholera follows are necessary:

- Evaluate the degree of dehydration upon arrival;

- Rehydrate the patient in 2 phases; these include rehydration (for 2-4 h) and maintenance (until diarrhea abates);

- Register output and intake volumes on predesigned charts and periodically review these data;

- Use the intravenous route only (1) during the rehydration phase for severely dehydrated patients for whom an infusion rate of 50-100 mL/kg/h is advised, (2) for moderately dehydrated patients who do not tolerate the oral route, and (3)

during the maintenance phase in patients considered high stool purgers (ie, >10 mL/kg/h);

- During the maintenance phase, use oral rehydration solution at a rate of 800-1000 mL/h; match ongoing losses with ORS administration ;

- Discharge patients to the treatment center if oral tolerance is greater than or equal to 1000 mL/h, urine volume is greater than or equal to 40 mL/h, and stool volume is less than or equal to 400 mL/h.

Diet. Resume feeding with a normal diet when vomiting has stopped. Malnutrition after infection is not a major problem, as it is after infection with Shigella species or rotavirus diarrhea. The catabolic cost of the infection is relatively low, anorexia is neither profound nor persistent, and intestinal enzyme activity remains intact after infection; hence, intestinal absorption of nutrients is near normal. There is no reason to withhold food from cholera patients. For replenishment of potassium in the diet is recommended to include in the near future, foods rich in potassium - dried apricots, bananas, oranges.

Prognosis.

Before the development of effective regimens for replacing fluids and electrolyte losses, the mortality in severe cholera was more than 50%. Mortality is higher in pregnant women and children. Mortality rates are lowest where intravenous therapy is available.

The basis for the statement convalescents are disappearance of diarrhea syndrome, the normalization of biochemical indices and negative results of bacteriological research feces conducted 48 hours after the end of antibiotic treatment for 3 consecutive days.

An attack of the classic biotype of V cholerae usually results in the generation of antibodies that protect against recurrent infection by either biotype. Those who have had El Tor cholera are not protected against further attacks. Attacks of V cholerae 01 do not lead to immunity against V cholerae 0139.

Prophylaxis.

Sensitive surveillance and prompt reporting contribute to the rapid containment of cholera epidemics. In many endemic countries, cholera is a seasonal disease, occurring every year usually during the rainy season. Surveillance systems can provide an early alert to outbreaks, which should lead to a coordinated response and assist in the preparation of preparedness plans. Education on specific hygiene practices is important in the prevention of cholera.

Education in environmental control is critical for the prevention of cholera. The source of V cholerae in nature is human excrement, and the most common vehicle of infection is water. Environmental control must focus on keeping these elements apart. In the developed world, much has been done in public health planning and in the engineering of water conservation and sewage disposal. However, in developing countries, contamination of water by human excrement is a daily hazard. Members of these populations experience a constant cycle of infection, excretion, and reinfection. Education about the sterilization of water and hand-washing techniques is critical but difficult. Contamination via food is also an important consideration. The source of this contamination is impure water used to wash or flush vegetables and fruit. Water contamination occurs via sewage or soil that is used to fertilize crops. In this situation, training food handlers is necessary.

Difficulties in implementing public health and personal preventive practices have stimulated the century-long search for vaccines. Experience with the parenteral vaccine has been disappointing. Because of a better understanding of the immune response to natural infection, researchers now know that the oral route of administration is better.

Persons who have been in contact with cholera patients are sent to the detention center, where carried out for 5 days under medical surveillance, admission - once bacteriological examination of faeces and appointed an emergency antibiotic (tetracycline (300 OOO IU 3 times daily) or doxycycline (0.2 g 1 time per day) for 4 days). Mass chemoprophylaxis is not justified because of the increased resistance of vibrio to antibiotics, growth in the number of carriers.

Cholera vaccination is no longer officially required for any international traveler, and the International Certificate of Vaccination no longer provides a special section for recording cholera immunization. The risk of an international traveler from a developed country contracting cholera is small (1 case in 500,000 travelers).

WHO has identified 3 oral vaccines. These are available in some countries but are used mainly by travelers.

One vaccine consists of a monovalent killed whole-cell V cholerae O1 with purified recombinant B-subunit of cholera toxoid (WC/rBS). Efficacy trials have shown that this vaccine is safe and confers 85-90% protection during 6 months in all age groups after administration of 2 doses, 1 week apart. Shanchol and ORCVAX are bivalent vaccines that are based on serogroups O1 and O139; however, they do not contain the bacterial toxin B subunit. Vaccine CVD 103-HgR is composed of attenuated V cholerae O1 prepared by recombinant DNA.

The vaccine is highly protective against moderate and severe cholera, and it is very well tolerated and extremely immunogenic. In addition, the rate and extent of vaccine excretion is minimal. Currently available vaccines are safe and provide 50-60% efficacy in preventing episodes of cholera in the first 2 years after the primary vaccination schedule.

Questions for self.

1. Why cholera refers to a group of particularly dangerous infections?
2. Who is the etiology of cholera, give them a description?
3. Who is the source of cholera epidemic and its meaning?
4. What are the mechanisms and factors of transmission of cholera.
5. What is the lead in the pathogenesis of cholera?
6. What determines the severity of the disease?
7. What material from the patient must be studied to identify cholera? Indicate laboratory methods.
8. Main principles of treatment of cholera.

9. The rules of discharging from the hospital.

10. Prevention of cholera.

Test tasks

1. Etiology of cholera is: A - virus; B - bacteria; C - protozoa; D - rickettsia; E - chlamydia.

2. How many biovars cholera has ?: A - one; B - two; C - three; D - four; E - seven.

3. Cholera is caused Vibrio serogroups: A - O-1; B - O-10; C - O-30; D - O-98; E - O-110.

4. How many serovars cholera El Tor has: A - one; B - two; C - three; D -12; E- 139.

5. Serovar Inaba contains antigenic fraction : A- AB; B – AC; C – BC; D - ABC; E - ABD.

6. Serovar Ogawa has subtype: A- AB; B - AC; C - BC; D - ABC; E - ABD.

7. Serovar Gikoshima has subtype: A- AB; B- AC; C- BC; D -ABC; E- ABD.

8. Vibrio El-Tor different from the vibrio cholerae classica by presence of: A- sensitivity to acids; B - liquefy gelatin; C - haemolytic properties; D - mobility; E- stability during boiling.

9. The optimal culture medium for cholera: A - Ploskirevs; B - Endo; C. Levins; D- bile; E - 1% peptone water.

10. V. cholera: A - forms spores; B- has the capsule; C - anaerobic; D- has flagellum; E- all right.

11. What properties Vibrio cholerae does not have?: A - mobility; B - invasive; C - adhesion; D- formation of enzyme; E - does not form spores.

12. Cholera belongs to: A - anthroponoses; B - zoonoses; C- zooantroponoses; D - sapronoses; E - all right.

13. The most intense source of cholera infection is: A - vibriocarriers; B patients with mild disease; C - with moderate course; D - with severe course; E- everything is right.
14. In epidemiological terms are particularly dangerous to patients: A- severe; B - with dehydration shock; C- with a moderate course; D- bacillicarriers; E- all right.
15. Among infected with El Tor cholera prevail: A - patient with severe course of the disease; B- with hypovolemic shock; C - with moderate course; D- with mild course; E- all are right.
16. What immunity is formed after cholera: A - bacterial; B - antitoxic; C non-sterile; D- antibacterial and antitoxic; E- immunity is not formed.
17. Immunity against cholera after disease persists during: A - no more than 1-2 years; B - 5 years; C- 7 years; D- 10 years; E – during all life.
18. The mechanism of transmission of cholera: A - airborne; B - fecal-oral; C- percutaneous; D- transmissible; E- all is right.
19. All ways of transmission of cholera are possible, except: A - water; B - food; C - contact-household; D- transmissible; E- only A and B.
20. Vibrio cholerae El Tor can persist long time in the body of all, except: A - fish; B- shrimp; C- oysters; D- frogs; E- rodents.
21. Vibrio actively proliferate in: A- stomach; B- small intestine; C- upper part of the large intestine; D- lower colon; E- throughout all gastrointestinal tract.
22. What contribute to vibrio colonization in intestinum: A- alkaline environment; B- enough protein; C- mobility vibrio; D- adhesion ability of vibrio; E- all is right.
23. Intracellular regulator (stimulant) of intestinal secretion is: A- cholinesterase; B- hyaluronidase; C- adenosine monophosphate; D- mucinases; E- all is right.

24. What is the basic criterion of the severity of cholera ?: A- degree of dehydration; B- concentration of agent in the small intestine; C- degree of hemodynamic disorders; D- multiplicity of defecation and vomiting; E- level of kidney failure.
25. What type of dehydration is developing in cholera? A- acute extracellular hypertension; B- acute intracellular isotonic; C- acute extracellular hypertension; D- intracellular acute hypertension; E acute extracellular hypotonic.
26. The mechanism of shock in cholera ?: A- decrease of circulating blood volume, increase of its density; B- electrolyte imbalance; C- change the acid-base status; D- microcirculatory disorder; E- all is right.
27. The activation of adenylate cyclase enterocytes leads to: A- strengthening extravasation of fluid into the intestine; B- activation neuraminidase; C- decrease absorption of fluid in the intestine; D- colonization vibrios; E- all is right.
28. The decrease in blood volume (CBV) in severe cholera leads to: A- spasm of peripheral vessels; B- oliguria; C- blood clots; D- hypoxia; E- all is right.
29. Deficiency of electrolytes in severe cholera leads to: A- cardiac weakness; B- arrhythmia; C- shortness of breath; D- cramps; E- all is right.
30. Hypokalemia in cholera is accompanied with: A- paresis of the intestine; B- bloating; C- "noise splashing" in the abdomen; D- cramps; E- all is right.
31. The incubation period for cholera is: A 1-2 hours; B- till 5 days; C 7-8 days; D- 21 days; E- 35 days.
32. In severe cholera patient's body temperature is: A- 40 ° C; B- 39 ° C; C- 38,5 ° C; D- 37,8 ° C; E- 35,8 ° C.
33. Diarrheal syndrome in severe cholera is characterized by: A- meager stool with mucus and blood; B- abundant green stool without impurities; C- abundant watery stools like "rice water»; D- stool as a "raspberry jelly"; E- all is right.

34. The patient with cholera has T-36,5 ° C, expressed weakness, watery stools (abundant and odorless), vomiting. Mucous membranes are dry, pale skin with reduced turgor (pinch goes slowly). Pulse 90 / min, BP - 95/50 mm Hg .The number of breaths 25/min. What is the severity of the disease ?: A- subclinical form; B- mild; C- moderate severity D- severe course; E- dehydration shock.

35. In a patient with cholera T-35,8 ° C. The skin is pale, cold, skin fold long time does not cracked down, spasms of the limbs and abdominal muscles. Cyanosis of the lips, earlobes, nose. On palpation - abdomen pain is absent, heightened rumbling is detected, splashing liquid. Pulse is 110 beats / min., thready. Blood pressure 80/35 mm Hg. Oliguria. What is the severity of the disease ?: A- subclinical form; B- within easy; C- moderate severity; D- severe course; E- cardiogenic shock.

36. The basic method of laboratory diagnosis of cholera: A- bacteriological; B- serological; C- bacterioscopic; D- virological; E- mycological.

37. To confirm the diagnosis of cholera examine: A- blood; B- feces; C- vomit; D- urine; E- feces and vomit.

38. In severe cholera all laboratory values are true, except: A- erythrocytosis; B- high hemoglobin; C- leucopenia; D- leukocytosis; E- relative density of urine is increased.

39. Choose the most objective indicator of severity of cholera: A- high hematocrit; B- low hematocrit; C- anemia; D- leucopenia; E- leukocytosis.

40. The drug of choice in etiotropic therapy of cholera: A- penicillin; B- tetracycline; C- ftalazol; D- hingamin; E- all is right.

41. To correct the deficiency volume of fluid in patients with severe cholera it is necessary: A- polyionic solutions; B- isotonic sodium chloride solution; C- 5-10% glucose; D- albumin; E- all are right.

42. Polyionic solutions include everything, except: A- Trisol; B- Kvartasol; C- Acesol; D- 5-10% glucose; E- Chlosol.

43. During parenteral rehydration of patients with dehydration shock temperature of fluids should be: A- 20-22 °; B- 25-30 °; C- 30-35 °; D- 36-37 °; E- 38-39 °.

44. In primary patients with dehydration rehydration solutions are administered a shock at the speed of: A 50 drops / min; B 100 drops / min; C 50 ml / min; D- 100 ml / min .; E- 150ml / min.

45. Discharging from hospital of convalescent cholera made after clinical cure and follow bacteriological research: A- bacteriological tests there is not necessary; B-negative blood culture result and stool culture; C-3 negative results copro- and urine culture; D- 3 negative stool culture results; E- 3 negative stool culture results and one bile culture.

46. Persons who have been in contact with cholera patients should be isolated for a period: A- is not necessary to isolate; B- 5 days; C- 7 days; D- 14 days; E- 1 month.

47. Persons who have been in contact with cholera patients, should be investigated: A- is not necessary; B- bacteriological tests of feces; C- bacteriological tests of feces and urine; D- bacteriological tests of bile; E- bacteriological tests of blood and stool.

48. The persons who were in contact with cholera patients should get 4 days of preventative treatment: A- tetracycline; B- chloramphenicol; C- erythromycin; D- ciprofloxacin; E- all are right.

49. For the purpose of the specific prevention of cholera following is used: A- immunoglobulin; B- vaccine; C- serum; D- only toxoid; E- tetracycline.

50. After 2 hours of administration Trisol parenterally to patient the discomfort in the heart region appeared, in the ECG - increase PQ, QRS, the level of potassium in the blood is 8 mg / dL. What correction therapy ?: A- Kvartasol; B- reopoligljukin; C- zhelatinol; D- Chlosol; E- Disol.

Situational tasks.

Task №1.

Patient K., 30 years old. Was ill acutely: T-36,5 ° C, a little weakness. Stool 5 times a day, liquid, pappy. Skin was clean, turgor was normal. Breathing is vesicular. Heart sounds are pure, pulse 90 / min, blood pressure 100/60 mm Hg . Abdomen was soft, painless. Meningeal signs were negative. General blood test: red blood cells 5 • 10^{12}/ L, leucocytes 6,1 • 10^{9} / L, hematocrit 48. Bacteriological tests of feces showed V. cholerae O1.

1. Make the preliminary diagnosis, explain it.
2. Tell the rules of discharging from hospital for patient.

Task №2

Patient A., 25 years old, came from India three days ago. He was ill acutely in the morning: T - 36,2 ° C, weakness, thirst, dry mouth, stool up to 10 times, profuse watery unclear white color and odorless. In the evening, he had profuse vomiting twice. Pale skin, skin fold crushes slowly. Single leg cramps. Breathing is vesicular, 23/min. Heart sounds were pure, pulse – 95/min, weak. BP - 80/50 mm Hg. Tongue was dry. Abdomen was soft, painless, rumbling along the intestine. The liver and spleen were not palpable. Meningeal signs were negative. Patient weight - 60 kg. General blood analysis: Erythrocytes 7x10^{12}/l, Hb - 148 g/l, leukocytes - 12.5 • 10^{9}/l. Specific gravity of plasma 1,044.

1. Make the preliminary diagnosis, explain it.
2. What laboratory data can confirm the diagnosis?
3. Prescribe the treatment for the patient.

Keys to tests

1 B	6 A	11 B	16 D	21 B	26 E	31 B	36 A	41 A	46 B
2 B	7 D	12 A	17 A	22 E	27 A	32 E	37 E	42 D	47 B
3 A	8 C	13 D	18 B	23 C	28 E	33 C	38 C	43 E	48 A
4 C	9 E	14 D	19 D	24 A	29 E	34 C	39 A	44 D	49 B
5 B	10 D	15 D	20 E	25 A	30 E	35 D	40 B	45 D	50 E

Answers to situational tasks:

№1:

1. Diagnosis: Cholera, mild course, dehydration I degree. Diagnosis is based on clinical and laboratory data: acute onset, normal body temperature, absence of abdominal pain, the stool is frequent, loose, mushy. Slight tachycardia, hypotension. Vibrio cholerae serogroup O1 isolated from faeces. dehydration I degree because hematocrit increased slightly (48 when normal is 45).

2. For discharging the patient from the hospital it is necessary:

• clinical cure (disappearance of diarrhea syndrome);

• presence of 3 negative results of bacteriological examination of feces carried out in 2 days after the treatment with antibiotics for 3 consecutive days.

№2:

1. Diagnosis: cholera, moderate dehydration (I degree). Diagnosis based on: clinical findings: acute onset, with normal body temperature, absence of abdominal pain, stool is frequent abundant odorless, in a few hours – vomiting. Data of objective research: pale skin, skin turgor is reduced. Cyanosis of the lips, leg cramps, tachycardia, hypotension. Rumbling along the intestine. Data of epidemiological anamnesis: three days ago he came back from India - a country,

endemic about cholera. Laboratory data: polycythemia, increased hemoglobin, high specific gravity of plasma.

2. It is necessary the bacteriological examination of feces and vomiting mass on the medium 1% peptone water. The diagnosis is confirmed by detection of Vibrio cholerae serogroup O1.

3. The first step is to to fill lost fluids and electrolytes. Considering the dehydration of II degree and the presence of vomiting in patients, the primary rehydration should be started with parenteral solutions. You can use Kvartasol or Trisol. The rate of introduction - 40 ml/min. As soon as the patient's condition will improve and vomiting will stop - continue with oral solt solution in the quantity required for correcting the subsequent losses with stool.

In order to impact on the agents use antibiotics. Prescribe to the patient erythromycin 0.5 g 4 times per day for 5 days.

Unit 2. Plague

Plague is worldwide in distribution, with most of the human cases reported from developing countries. Plague has caused large-scale epidemics, thereby changing the course of history in many nations. The first pandemic was believed to have started in Africa and killed 100 million people over a span of 60 years. In the Middle Ages, plague killed approximately one fourth of Europe's population. The pandemic that began in China in the 1860s spread to Hong Kong in the 1890s and was subsequently spread by rats transported on ships to Africa, Asia, California, and port cities of South America. In the early twentieth century, plague epidemics accounted for about 10 million deaths in India. As reported in National Geographic, mass graves of plague victims were recently discovered in an area of Venice called "Quarantine Island."

Etiology.

Plague is caused by the plague bacillus, rod-shaped bacteria referred to as Yersinia pestis. Y pestis is a nonmotile, pleomorphic, gram-negative coccobacillus that is nonsporulating. The bacteria elaborate a lipopolysaccharide endotoxin, coagulase, and a fibrinolysin, which are the principal factors in the pathogenesis of plague. The pathophysiology of plague basically involves two phases—a cycle within the fleas and a cycle within humans. After ingestion of infected blood, the bacteria survive in the midgut of the flea owing to a plasmid-encoded phospholipase D that protects them from digestive juices. The bacteria multiply uninhibited in the midgut to form a mass that extends from the stomach proximally into the esophagus through a sphincterlike structure with sharp teeth called the proventriculus. As a desperate measure, the flea then repeatedly tries to obtain a meal by biting a host, managing only to regurgitate the infected mass into host's bloodstream. However, the concept that the flea must be engorged before becoming infectious loses support when trying to explain the rapid rate of spread of disease during a plague epidemic.

Epidemiology.

Transmission to healthy person is carried out in various ways: transmissible, contact, alimentary, airborne. Transmissible transmission is realized through flea bites, infected during bloodsucking of sick rodents.

By contact person can become infected by removing the skins and butchering from infected animals. Alimentary way of infection associated with the consumption of meat of sick animals (rabbit, camel, etc.).

Human-to-human transmission is rare except during epidemics of pneumonic plague – airborne way.

The following are the modes of plague transmission in humans: bites by fleas; exposure to humans with pneumonic plague; handling of infected carcasses; scratches or bites from infected domestic cats; exposure to aerosols containing plague-causing bacilli.

Risk factors include the following:

- Flea bite;
- Contact with a patient or a potential host;
- Contact with sick animals or rodents;
- Residence in an endemic area of plague.
- Presence of a food source for rodents in the immediate vicinity of the home;
- Camping, hiking, hunting, or fishing;
- Occupational exposure (eg, researchers, veterinarians);
- Direct handling or inhalation of contaminated tissue or tissue fluids.
- Contact with a dog infected with Y pestis.

Animal reservoirs mostly include squirrels, rabbits, and prairie dogs. However, there has been an established role of domestic cats, dogs in the transmission of plague (in this scenario, transmission via inhalation was more common than in any other form of plague).

The risk of plague-related death depends on the type of plague and whether the infected individual receives appropriate treatment. The following are the mortality rates associated with the different types of plague: pneumonic plague 50-100%, bubonic plague 10-90%, septicemic plague - 20-25%.

Pathogenesis.

The causative agent is introduced into the human body through the skin or mucous membranes of the digestive tract and upper respiratory tract. Getting on the skin, the agent can cause inflammation at the site of deployment. The bacilli migrate to the regional lymph nodes, are phagocytosed by polymorphonuclear and mononuclear phagocytes, and multiply intracellularly. Survival and replication within macrophages is probably of greatest importance in early stages of the disease. Involved lymph nodes show dense concentrations of plague bacilli, destruction of the normal architecture, and medullary necrosis. Lymph nodes are increasing greatly and form a conglomerate - "bubo". With subsequent lysis of the phagocytes, bacteremia can occur and may lead to invasion of distant organs in the

absence of specific therapy. Loss of lymph node barrier function leads to a generalization of the process. It can develop septicemic (in the absence of bubo) or secondary form of septic involving all the internal organs and the formation of secondary buboes. Septic form of plague is accompanied by a massive bacteremia and toxemia complete suppression of the immune system. Hematogenous drift of plague bacteria in the lung tissue leads to the development of secondary plague pneumonia. Pneumonia is the beginning serosanguineous then necrotic character. The critical state in pneumonic form is due to infectious-toxic shock and acute respiratory failure.

The disease is accompanied by severe toxinemia. The toxins affect the central nervous system, causing severe neurotoxicosis on the cardiovascular system with the development of acute cardiovascular insufficiency. Cause disorders in the hemostatic system with the development of thrombohemorrhagic syndrome.

Clinical symptoms.

According to clinical manifestations localized and generalized forms are differentiated. Localized forms include: skin, skin-bubonic and bubonic. Generalized forms include: of primarily and secondary septic form; of primarily and secondary pulmonary form.

In all forms of the disease begins acutely. Body temperature with strong chills, increased to 39.5 - 40 ° C or more. Characterized by agonizing headache, dizziness, muscle-joint pain, fatigue, and sometimes vomiting. The appearance of the patient: a person hyperemic, puffiness. The conjunctiva and sclera injected on a transitional fold often petechial hemorrhages. Tongue dry, thickened, trembling, lined with thick white coating ("as if smeared with chalk"), oropharyngeal mucosa hyperemic. From the first days of the disease, the of CNS and cardiovascular system appear. Some patients has agitation, hallucinations frightening character, incoordination ("drunken walk"), slurring of speech, muscle tremors. Others - lethargy, stupor. Dyspnea. The boundaries of the heart enlarged, heart sounds are

dull. Tachycardia 120 - 140 per minute, heartbeat is irregular, progressive falling of BP.

Skin plague. in the place of the introduction of the pathogen the spot appears first, then papule, vesicle, pustule with serous-hemorrhagic content. Pustules are located on the solid base red-purple color and have significant morbidity. After opening the pustules ulcers are formed, the bottom of which is covered with a dark crust. Ulcers heal slowly, forming a scar.

Bubonic plague. This is the most common presentation of plague. The incubation period varies but usually ranges 2-6 days. There is a sudden onset of high fever, chills, and headache. Patients with this type also experience body aches, extreme exhaustion, weakness, abdominal pain, and/or diarrhea. Painful, swollen lymph glands (buboes) arise, usually in the groin (most common site), axilla, or neck. Inguinal buboes are the most common. Axillary, cervical, and epitrochlear buboes are almost always seen in cat-associated plague. Without intervention, this stage may lead to secondary pneumonic plague or meningitis or may disseminate and manifest as a sepsis picture.

Vesicles may be observed at the site of the infected flea bite. With advanced disease, papules, pustules, carbuncles, or an eschar may be observed in areas of the skin drained by the involved lymph nodes. A generalized papular rash of the hands and feet may be observed.

Buboes are unilateral, oval, extremely tender lymph nodes and can vary from 2-10 cm in size. Femoral lymph nodes are most commonly involved. Patients with an inguinal bubo walk with a limp, and the affected limb may be in a position of flexion, abduction, and external rotation. Patients resist any attempt to examine the involved lymph nodes. Enlargement of the buboes leads to rupture and discharge of malodorous pus.

Hepatomegaly and splenomegaly often occur and may be tender.

Pneumonic plague. Pneumonic plague is highly contagious and transmitted by aerosol droplets. This is often secondary to bubonic or septicemic plague.

However, primary pneumonic plague may be seen in laboratory workers, individuals exposed to an infected person, or those who have been exposed to a cat with pneumonic plague. There is an abrupt onset of fever and chills, accompanied by cough, chest pain, dyspnea, purulent sputum, or hemoptysis. Buboes may or may not be associated with pneumonic plague. Pneumonic plague causes fever, lymphadenopathy, productive sputum, and/or hemoptysis.

The ability for plague to be spread by aerosols makes Y pestis a potential agent of bioterrorism.

Meningeal plague. This is characterized by fever, headache, and nuchal rigidity. Buboes are common in meningeal plague. Axillary buboes are associated with an increased incidence of the meningeal form.

Pharyngeal plague. Pharyngeal plague results from ingestion of the plague bacilli. Patients experience sore throat, fever, pharyngeal erythema and painful cervical lymph nodes.

Septicemic plague. Septicemic plague is observed in elderly patients and causes a rapid onset of symptoms. Patients experience nausea, vomiting, abdominal pain, and diarrhea. Diarrhea may be the predominant symptom. Patients exhibit a toxic appearance and soon become moribund. Buboes are uncommon in septicemic plague, making the diagnosis elusive. Septicemic plague carries a high mortality rate and is associated with disseminated intravascular coagulation (DIC), multiorgan failure, and profound hypotension. Because of an overwhelming infection with the plague bacillus, patients with septicemic plague have a toxic appearance and may present with tachycardia, tachypnea, and hypotension. Hypothermia is common. Generalized purpura may be observed and can progress to necrosis and gangrene of the distal extremities. No evidence of lymphadenitis or bubo formation is apparent. Patients may die of a high-grade bacteremia.

Patients may has genitourinary/gastrointestinal plague and cutaneous plague (this manifests as purpura).

Complications.

Potential complications of plague include the following:

- Acute respiratory distress syndrome;
- Chronic lymphedema from lymphatic scarring;
- DIC;
- Septic shock;
- Superinfections of the buboes by Staphylococcus and Pseudomonas species.

Diagnosis.

The possibility of plague should be strongly considered in febrile patients from endemic areas who have history of exposure to rodents. Rapid recognition of the classic symptoms of this disease and laboratory confirmation are essential to instituting lifesaving therapy.

Non-specific tests. Leukocytosis with a predominance of neutrophils is observed, and the degree of leukocytosis is proportional to the severity of illness. Thrombocytopenia is common, and levels of fibrin degradation products may be elevated. Peripheral blood smear shows toxic granulations and Dohle bodies. Serum transaminase and bilirubin levels may be elevated. Proteinuria may be present, and renal function test findings may be abnormal. Hypoglycemia may be observed.

Specific tests. 27- 96% of blood cultures are positive for Y pestis in patients with bubonic plague and septicemic plague. Microbiology staff should be informed of the possibility of Y pestis agents in samples so that they can take adequate precautions when handling specimens.

Y pestis may be observed on a peripheral blood smear. Smear stained with Wright-Giemsa reveals rod-shaped bacteria. A Wayson stain demonstrates the typical "safety pin" appearance (bipolar staining) of the bacterium. Gram stain shows small gram-negative coccobacilli.

Lymph node aspirates often demonstrate Y pestis. In patients with pharyngeal plague, Y pestis is cultured from throat swabs.

Cerebrospinal fluid (CSF) analysis in meningeal plague may show pleocytosis with a predominance of polymorphonuclear leukocytes. Gram stain of CSF may show plague bacilli. Limulus test of CSF demonstrates the presence of endotoxin.

Gram stain of sputum often reveals Y pestis.

Direct immunofluorescence testing of fluid or cultures may aid in rapid diagnosis. A novel rapid diagnostic test capable of detecting miniscule amounts of Y pestis F1 antigen within 15 minutes has been developed and field tested in Madagascar. This test yields 100% sensitivity and specificity for Y pestis and other Yersinia species.

A passive hemagglutination test (performed on serum from a patient in acute or convalescent stages) with a 16-fold or greater increase in titer (single titer) suggests plague infection.

A 4-fold rise in antibody titers to the F-1 antigen of Y pestis also confirms infection.

A polymerase chain reaction (PCR) using primers derived from Y pestis plasminogen activator gene has been used to detect the pathogen in fleas, but the application of this method in humans is still a matter of speculation.

Aspiration of lymph node (bubo). Inject 1 mL of sterile saline into the bubo with a 20-gauge needle; after withdrawing several times, aspirate the fluid. Gram stain of the aspirate reveals gram-negative coccobacilli and polymorphonuclear leucocytes. Wayson stain of the aspirate shows plague bacilli as light-blue bacilli with dark-blue polar bodies. Examination of the aspirate of the fluid from the inguinal lymph nodes shows a characteristic bipolar appearance that resembles a closed safety pin.

Lumbar puncture. Lumbar puncture may be performed for CSF analysis.

Imaging Studies. Chest radiography reveals patchy infiltrates, consolidation, or a persistent cavity in patients with pneumonic plague. ECG reveals sinus tachycardia and ST-T changes. Nuclear imaging may help localize areas of lymphadenitis and meningeal inflammation.

Treatment.

Etiotropic treatment. Therapy must be comprehensive and cover all likely pathogens in the context of this clinical setting. Antibiotic selection should be guided by blood culture sensitivity whenever feasible. Untreated plague can progress to a fulminate illness with a high risk of mortality. Thus, early and appropriate antibiotic treatment is essential.

Streptomycin (15 mg/kg, up to 1 g intramuscularly every 12 h) - has been the drug of choice earlier. This aminoglycoside antibiotic recommended when less potentially hazardous therapeutic agents are ineffective or contraindicated. An in vitro comparison demonstrated that gentamicin (5 mg/kg intravenously or intramuscularly once daily) is comparable to or superior than streptomycin. Gentamicin has been used successfully in the treatment of human plague, is inexpensive, and can be dosed once daily.

Doxycycline is a recommended alternative in patients who cannot take aminoglycosides or in the event of a mass casualty scenario, making parenteral therapy unachievable. Because chloramphenicol attains high CSF concentrations, it has been used to treat CNS infections associated with plague, although no studies have been conducted for substantiation.

Studies in murine models have shown that fluoroquinolones demonstrate efficacy similar to that of the aminoglycosides. Fluoroquinolones are a reasonable alternative therapy. However, no clinical trials of fluoroquinolone therapy in human plague have been conducted. Levofloxacin, Moxifloxacin are indicated for treatment and prophylaxis of plague, including pneumonic and septicemic plague, caused by Yersinia pestis.

Trimethoprim-sulfamethoxazole has been used to treat bubonic plague; however, it is not considered first-line therapy. Beta-lactam antibiotics and macrolides should not be used.

Supportive therapy. Patients with advanced plague have a presentation of typical gram-negative sepsis and need antibiotic treatment for 10 days, along with

other supportive measures. Hemodynamic monitoring and ventilatory support are performed as appropriate. Intravenous fluids, epinephrine, and dopamine are implemented as necessary for correction of dehydration and hypotension.

Surgical Care. Enlarging or fluctuant buboes require incision and drainage.

Prognosis.

Untreated plague carries a mortality rate of approximately 50%; however, with appropriate therapy, the mortality rate drops to approximately 5%.

Prophylaxis.

Fleas always must be targeted for destruction before the rodents, because killing rodents may release into the environment massive amounts of infected fleas, which will be hungry for a blood meal and, in the absence of rodents, the fleas will seek out any warm-blooded animal, including humans and infect them. Pesticides have been successful in getting rid of rats and other animal hosts. Public education about how plague spreads is an important part of prevention.

Precautions. All patients with suspected plague and signs of pneumonia should be placed in strict respiratory isolation for 48-72 hours after antibiotic therapy is initiated and kept there until pneumonia has been ruled out or until sputum culture have shown negative findings.

Report patients thought to have plague to the local health department and to the WHO.

Patients with plague who are critically ill and require transfer to another facility should be transported under strict isolation precautions.

Alert laboratory personnel to the possibility of the diagnosis of plague. All fluid specimens must be handled with gloves and mask to prevent aerosolization of the infected fluids.

Postexposure prophylaxis (prophylactic antibiotic therapy).

It is recommended the short-term prophylactic antibiotic therapy in people who have been bitten by potentially infected rodent fleas during a plague outbreak.

Prophylactic antibiotic therapy is recommended in persons who have had close exposure to a person or an animal thought to have pneumonic plague. Sulfadoxine prophylaxis has been effective in outbreaks of pneumonic plague. The infection rate in contacts was 8.4% with this strategy. Recent studies have shown that doxycycline can be used as an alternative for sulfadoxine.

Preferred antibiotics for prophylaxis against plague include doxycycline 100 mg PO q12h for 14-21 days (for patients >8 y) or full-dose ciprofloxacin for 7 days. Chloramphenicol may be used as an alternative. To be effective, chemoprophylaxis must be initiated within 7 days of exposure. Levofloxacin may be prescribed as a 10-14 day regimen for either treatment or postexposure prophylaxis. Chloramphenicol may be used as an alternative. In a community experiencing a pneumonic plague epidemic, individuals with a temperature of 38.5°C or higher or newly onset cough should promptly receive parenteral antimicrobial therapy.

Vaccination. Plague vaccination is of limited use and is not mandatory for entry into any country. Plague vaccine is recommended for field workers in endemic areas and for scientists and laboratory personnel who routinely work with the plague bacterium.

Contacts with victims who have bubonic plague do not need preventive medication. But people who were in the same environment as those who are infected may need preventive antibiotics. Live and killed vaccines are used. The killed vaccine is composed of killed whole cells. It needs to be taken as 2 injections 1-3 months apart followed by the booster every 6 months until the patient is no longer considered to be at risk. A previously FDA-approved plague vaccine is no longer manufactured. It was useful against the bubonic form of plague but not the more serious pneumonic (lung) form of plague, which is the kind most often expected in a terrorist incident. A new vaccine effective against all varieties of plague is under development.

Patient Education. Report sick or dead animals to the local health department or law enforcement officials and wear gloves when handling potentially infected animals. Eliminate food sources and nesting places for rodents around homes, workplaces, and recreation areas and make homes rodent-proof. Personal protective measures include wearing protective clothing and applying insect repellents to clothing and skin to prevent flea bites. Restrain pet dogs and cats in areas endemic to plague and regularly treat pets to control fleas. Spraying of appropriate chemicals by health authorities may be necessary to kill fleas at selected sites during animal plague outbreaks.

Environmental sanitation. Efforts to control the animal reservoir and flea population may be effective in reducing transmission of plague bacteria. Remove food sources used by rodents. Rodent-proof homes, buildings, and warehouses. Trained professionals should apply chemicals to kill fleas and rodents. Trained professionals should fumigate cargo areas of ships and docks.

Questions for self.

1. Tell about the basic properties of the causative agent of plague.
2. What are the main sources of the plague in the natural foci and anthropurgic?
3. List the ways of transmission of plague.
4. Describe the basic pathogenesis of plague.
5. Describe the clinical forms of plague and give them a description.
6. With what diseases it is necessary to carry out the differential diagnosis of plague?
7. What are the results of laboratory tests confirmed the diagnosis of plague?
8. What specific therapy is indicated for the bubonic plague and generalized form?
9. Specify the order of admission and discharge of patients from the rules of the hospital.

10. What actions should be held in an epidemic hearth of plague?

Test tasks

1. What infections on clinical and epidemiological indications plague belongs to?: A - particularly dangerous; B- natural focal; C - quarantine; D - of Convention; E – all are right.

2. The causative agent of the plague is: A - Enterobacter; B - Neisseria; C - Spirochetes; D - Yersinia; E - Rickettsia.

3. For the causative agent of plague all true, except: A - motionless; B - does not form spores; C - facultative intracellular parasite; D - gram-positive; E - is resistant to environmental conditions.

4. Plague belongs to: A - anthroponoses; B - zooantroponoses; C - zoonoses; D - sapronoses; E- all are right.

5. For plague all ways of transmission are possible, except: A - transmissible; B - contact-household; C- parenteral; D- alimentary; E- airborne.

6. The main factor of transmission of plague are: A- mosquitoes; B - fleas; C - cockroaches; D- bugs; E - mites.

7. Intoxication in plague is caused by: A - hyaluronidase; B - neuraminidase; C - plasmocoagulase; D - endotoxin; E- all are right.

8. Localized forms of plague are all, except: A- skin; B- skin-bubonic; C- bubonic; D- pulmonary; E- all are right.

9. The incubation period in bubonic plague is: A 2-3 hours; B-1-6 days; C-10-14 days; D- 21 days; E- 35 days.

10. Pneumonic plague is characterized by: A - neurotoxicosis; B- cutting pains in the chest, coughing, shortness of breath; C - sputum is liquid, frothy, bloody; D- scarce physical signs; E- all are right.

11. The material for bacteriological study in plague can be: A - punctate from bubo; B - contents of vesicles, pustules, ulcers; C - sputum; D- blood; E- all are right.

12. What persons should be hospitalized and investigated?: A - patients with cutaneous form of plague; B- who was in contact with patients with pneumonic plague; C - who was in contact with patients with bubonic form; D- who was in contact with patients with septic form of plague; E- all are right.

13. Specific drugs for the treatment of plague are: A - gentamicin; B - ofloxacin; C- streptomycin; D- doxycycline; E- all are right.

14. The course of antibiotic treatment of plague is: A - 5 days; B- 10 days; C - 17 days; D- 30 days; E- 45 days.

15. Pathogenetic therapy of patients with severe bubonic plague include: A - fluid therapy - 40 ml/kg of body weight per day; B- crystalloid solutions; C- colloid solutions; D- steroids; E- all are right.

16. What form of plague is the most dangerous for others: A- skin; B- bubonic; C - skin and bubonic; D- pulmonary; E - all are right.

17. Term of isolation of contact with the plague: A- is not necessary; B- for 6 days; C - 14 days; D- 21 days; E- 1 month.

18. In what form of plague individually isolation of contacts is carried out?: A- skin; B - bubonic; C- skin and bubonic; D- pulmonary; E- all are right.

19. For the emergency prevention of contact with the plague, you can use: A - streptomycin; B - doxycycline; C- gentmicin; D- ofloxacin; E- all are right.

20. Specific prevention of plague is carried out by: A- immunoglobulin; B- killed vaccine; C- live vaccine; D- interferon; E- B and C are correct.

21. The symtoms of toxic encephalopathy from the first days of illness are typical for: A - lymphogranulomatosis, B - plague; C - anthrax; D- tularemia; E - purulent lymphadenitis.

22. What disease is characterized by a conglomerate of lymph nodes dense consistency, which soldered to the subcutaneous tissue, greatly painful?: A - lymphogranulomatosis; B - tularemia; C - plague; D - anthrax; E - erysipelas.

23. The phenomena of lymphangitis is not characteristic for: A - anthrax; B - erysipelas; C - plague; D - tularemia; E - acute purulent lymphadenitis.

24. What disease is characterized by the appearance of a patient (puffiness, severe redness of the face and mucous membranes, cyanosis) from the first day of the disease: A - tularemia; B - anthrax; C - erysipelas; D - plague; E – all are right.

25. What disease is characterized by ulcers located on solid ground, covered with a dark crust, very painful: A - plague; B - erysipeloid; C - erysipelas; D - anthrax; E - tularemia.

26. What disease is characterized by a painless ulcer, located on a dense ground covered with dark scab: A - tularemia; B - anthrax; C - plague; D - erysipelas; E - erysipeloid.

27. Patient N., 31 years old, hospitalized on the 2nd day of illness. T-40,8 °, excruciating headache. The skin is dry, hot. The face and conjunctiva are hyperemic. Greatly painful conglomerate soldered with the surrounding tissue is on the right axilla, the skin over it is tense. Diagnosis?: A - tularemia; B - lymphogranulomatosis; C - anthrax; D - plague; E - purulent lymphadenitis.

28. Patient A., 3 days ago came back from India. T-40,1 ° C, delusions, hallucinations with frightening character. Face is swelling, hyperemic, "eyes of raging bull." 2 pustules with hemorrhagic content is on the right hand, swelling, tenderness around. Axillary lymph nodes on the right are 4 cm in diameter, immobile, sharply painful. Diagnosis?: A - plague; B - anthrax; C - tularemia; D - erysipeloid; E - erysipelas.

29. Patient K., fell ill acutely: T-41,3 ° C, headache. Slurred speech, confused mind. Face is puffy, hyperemic, cyanotic. Tremor of tongue. Extensive, confluent hemorrhages purple-black are on the skin. Hemorrhages are on mucous membranes. Nose bleed. Pulse is 140 beats per minute, blood pressure 80/40 mm Hg. Oliguria. Diagnosis?: A - tularemia. B - plague; C - anthrax; D - erysipeloid; E - lymphogranulomatosis.

30. What drugs is paramount in the treatment of infectious-toxic shock in plague?: A - antibiotics; B - glucocorticoids; C - haemodesum; D - vitamins; E- inhibitors of proteolysis.

Situational task.

Patient K., 32 years old, recently returned from Thailand. On the third day of the disease the patient is restless, his speech is slurred. The body temperature is 40,2°C. Acutely painful ulcers 3-3.5 cm is on the skin of the right shin, covered with a dark crust, with red-purple inflammation around. Scant purulent serous discharging is exuded from under the scab. Dense sedentary tumor formation is palpable in the right groin, harshly painful during palpation. The skin over it is hyperemic, tense. The number of breaths – 36/min. Heart sounds are muffled, rhythmic. Pulse is 130 beats/min. BP - 90/60 mm Hg. Abdomen is soft, painless. Meningeal signs are negative.

1. What kind of disease you can think of? Explain the diagnosis.

2. How to confirm the diagnosis laboratory?

3. What measures are necessary to carry out in relation to contact with the sick with plague?

Keys to tests

1 E	2 D	3 D	4 B	5 C
6 B	7 D	8 D	9 B	10 E
11 E	12 E	13 E	14B	15 E
16 D	17 B	18 D	19 E	20 E
21 B	22 C	23 C	24 D	25 A
26 B	27 D	28 A	29 B	30 B

Answer to situational task:

1. Plague, skin-bubonic form, severe course. Diagnosis is based on history of the disease: harshly expressed intoxication (temperature of 40,2 ° C, the patient is restless, his speech is slurred, tachypnea, hypotension); data of objective research

(on the skin - acutely painful ulcers covered with a dark crust, with red-purple inflammatory roll around, in the groin palpable dense sedentary tumor formation, acutely painful during palpation); data of epidemiological anamnesis (returned from Thailand, a country which is endemic by plague).

2. It is necessary to investigate the punctate from bubo bacteriologically on the blood agar.

3. Medical practice, who reveal a plague patient, without leaving the room (before the arrival of the medical team), where the patient was identified, by telephone or through a messenger (who was not been in contact with the patient), informs the main doctor of the hospital about the plague-infected patient. Medical staff and other persons who were in direct contact with patients, should be isolated in the hospital for observation during 6 days. For the purpose of emergency prophylaxis one of antibiotics is used: doxycycline 0.1g 2 times per day, streptomycin 0.5g 2 times per day intramuscularly. After hospitalization final disinfection is carried out in foci.

Unit 3. Viral hemorrhagic fevers.

Viral hemorrhagic fevers (VHFs) are a group of febrile illnesses caused by RNA viruses from several viral families. These highly infectious viruses lead to a potentially lethal disease syndrome characterized by fever, malaise, vomiting, mucosal and gastrointestinal (GI) bleeding, edema, and hypotension. The four viral families known to cause VHF disease in humans include the Arenaviridae, Bunyaviridae, Filoviridae, and Flaviviridae.

Arenaviridae are spread to humans by rodent contact and include Lassa virus in Africa and several rare South American hemorrhagic fevers. Lassa virus is the most clinically significant of the Arenaviridae, accounting for serious morbidity and mortality in West Africa. Lassa fever first appeared in Lassa, Nigeria, in 1969. It has been found in all countries of West Africa and is a significant public health problem in endemic areas. In populations studied, Lassa fever accounts for 5-14%

of hospitalized febrile illnesses. Its natural reservoir is a small rodent whose virus-containing excreta is the source of transmission.

Filoviridae. The most notorious of the VHF viruses, including Ebola and Marburg viruses, belong to the Filoviridae family. Ebola virus first was described in 1976 after outbreaks of a febrile, rapidly fatal hemorrhagic illness were reported along the Ebola River in Zaire (now the Democratic Republic of the Congo) and Sudan. Sporadic outbreaks have continued since that time, usually in isolated areas of central Africa. An outbreak in Kikwit, Zaire, in 1995 led to 317 confirmed cases, with an 81% mortality rate. Two thirds of the patients were among health care workers caring for infected individuals. An outbreak in Uganda in late 2000 resulted in 425 cases and claimed 225 lives. In late 2012, 7 cases of Ebola virus infection were reported, including 4 deaths.

Marburg virus, named after the German town where it first was reported in 1967, is another highly pathogenic member of the Filoviridae family that is traced to central Africa. As in Ebola-Zaire, the natural host for the virus is likely the fruit bat. Marburg virus was determined to be the causative agent in a 2004-2005 outbreak of hemorrhagic fever in Angola that led to 252 confirmed cases and 227 deaths (90% case-fatality rate).

Flaviviridae. Yellow fever and dengue fever are the most well known diseases caused by flaviviruses. Both are mosquito-borne; yellow fever is found in tropical Africa and South America, and dengue fever is found in Asia, Africa, and the Americas. They are notable for their significant effect on prior military campaigns and their continued presence throughout endemic areas.

Due to a resurgence in the last 3 decades, dengue fever is now considered second only to malaria in terms of importance as a tropical disease. Transmission is via the bite of the infected female Aedes mosquito, although dengue can also be transmitted via transfusion.

Epidemiology. Since the natural reservoir for Ebola and Marburg viruses is unknown, contact with infected monkeys or humans is not a prerequisite for

transmission of infection. Direct contact with rodents infected with hemorrhagic fever viruses (eg, arenaviruses, hantaviruses) is not necessary for transmission of infection, since aerosolized excreta may transmit infection.

Contacts of patients with known viral hemorrhagic fever (VHF), especially family members or health care workers caring for infected patients, are at risk for infection if appropriate barrier precautions are not used. Transmission of VHF has occurred from the reuse of unsterile needles and syringes used for treatment of infected patients. Transmission of VHF also has occurred to individuals handling the deceased in preparation for burial. Because of their extreme pathogenicity and potential for transmission by fine-particle aerosol, VHF viruses are considered potential biological warfare agents.

Table 1. Viral Families Causing Viral Hemorrhagic Fever

Virus Family	Disease	Natural distribution	Usual source of human infection	Incubation period (days)
Arenaviridae	Lassa fever	Africa	Rodent	5-16
Filoviridae	Marburg and Ebola	Africa	Fruit bat	3-16
Flaviviridae	Yellow fever	Tropical Africa, South America	Mosquito	3-6

Lassa fever is responsible for an estimated 100,000-300,000 infections per year, with 5,000 deaths. Cases have been reported throughout West Africa, particularly in Nigeria, Sierra Leone, Guinea, and Liberia. Other arenaviruses are responsible for sporadic VHF outbreaks throughout South America.

Ebola virus appears sporadically in endemic areas of the former Zaire and Sudan. Ebola virus also has been reported in Gabon, the Ivory Coast, and Uganda. Outbreaks appear to propagate in hospital settings, often involving health care providers.

Yellow fever continues to be a serious problem in tropical areas of South America and Africa, where vaccination is not widespread. The World Health Organization estimates that approximately 200,000 cases per year occur in Africa.

Pathogenesis. The primary defect in patients with viral hemorrhagic fever (VHF) is that of increased vascular permeability. Hemorrhagic fever viruses have an affinity for the vascular system, leading initially to signs such as flushing, conjunctival injection, and petechial hemorrhages, usually associated with fever and myalgias. Later, frank mucous membrane hemorrhage may occur, with accompanying hypotension, shock, and circulatory collapse. The relative severity of the clinical presentation may vary depending on the virus in question, amount, and route of exposure.

In acute disease, patients are extremely viremic, and messenger ribonucleic acid (mRNA) evidence of multiple cytokine activation exists. In vitro studies reveal these cytokines lead to shock and increased vascular permeability, the basic pathophysiologic processes most often seen in viral hemorrhagic fever infection. Another prominent pathologic feature is pronounced macrophage involvement. Inadequate or delayed immune response to these novel viral antigens may lead to rapid development of overwhelming viremia. Extensive infection and necrosis of affected organs also are described. Hemorrhagic complications are multifactorial and are related to hepatic damage, consumptive coagulopathy, and primary marrow injury to megakaryocytes. Aerosol transmission of some viral hemorrhagic fever infections is reported among nonhuman primates and likely is a mode of transmission in patients with severe infection.

Multisystem organ failure affecting the hematopoietic, neurologic, and pulmonary systems often accompanies the vascular involvement. Hepatic involvement varies with the infecting organism and is at times seen with Ebola, Marburg and yellow fever. Bleeding complications are particularly prominent with Ebola, Marburg.

Clinical symptoms. Incubation periods for VHF vary from 2-21 days. The initial symptoms correspond to development of viremia and include: high fever, headache, fatigue, abdominal pain, myalgias, prostration.

In more advanced disease, signs and symptoms include the following: hematemesis and bloody diarrhea, generalized mucous membrane hemorrhage, rash, altered mental status and cardiovascular collapse (preterminal events).

Depending on the progress of the disease, patients with viral hemorrhagic fever (VHF) initially may present with minimal signs, suggesting a more benign viral syndrome. As the disease progresses, more classic findings are present as follows: fever, pharyngitis, conjunctival injection, nondependent edema, petechial rash, GI bleeding, hypotension and/or shock. Most hemorrhagic fevers can produce a variety of cutaneous findings that are principally caused by vascular instability and bleeding abnormalities. Such findings include flushing, petechiae, purpura, ecchymoses, and edema. The arenavirus causing Lassa fever results in the greatest amount of edema of any of the hemorrhagic fever viruses. Additionally, no bleeding abnormalities are present. The filoviruses (Marburg and Ebola) exhibit characteristic exanthems that are best seen in fair-skinned patients. Soft palatal hyperemia accompanies the flu-like prodrome and is followed between days 5 and 7 by a nonpruritic, centripetal, pinhead-sized papular, erythematous exanthem. Within 24 hours, this can develop into large and coalescent, well-demarcated, sometimes hemorrhagic macules and papules. In severe cases, hemorrhage exudes from mucous membranes, venipuncture sites, and body orifices.

Complications. Complications from viral hemorrhagic fever (VHF) infection include retinitis, orchitis, encephalitis, hepatitis, transverse myelitis, and uveitis.

In patients who recover from Lassa fever infection, deafness is the most common complication. Spontaneous abortion also is common.

Laboratory diagnosis.

Because of risks associated with handling infectious materials, perform the minimum necessary laboratory testing for diagnostic evaluation and patient care. Considerations in ordering lab tests are as follows:

- A complete blood count often indicates leukopenia and thrombocytopenia (these findings may not be present in Lassa fever);
- Elevated hepatic transaminases are observed in viral hemorrhagic fever (VHF) and are predictive of high mortality in Lassa fever infection
- Prothrombin time, activated partial thromboplastin time.
- A disseminated intravascular coagulation profile including fibrinogen level, fibrin degradation products, and platelet count may be useful.

Specific viral diagnosis can be made using serologic tests, including enzyme-linked immunosorbent assay (ELISA) and polymerase chain reaction. Difficult cases may require tissue cultures. Reverse transcriptase-PCR (RT-PCR) emerged as a very effective means for detecting Ebola virus in patient serum, plasma, and whole blood.

Treatment.

Fluid resuscitation and supportive care are the mainstays of emergency department therapy. Intravenous crystalloids, oxygen, and cardiac monitoring are the most appropriate initial steps in the treatment of patients in whom viral hemorrhagic fever (VHF) is suggested. Other measures include the following:

- Administer blood and blood products as clinically indicated;
- Avoid intramuscular injections and the use of aspirin or other anticoagulants;
- Minimize invasive procedures because of the risk associated with viral transmission from sharp objects.

No specific antiviral therapy is available for Ebola or Marburg virus infection. The use of convalescent serum (ie, sera from patients who have survived infection) is suggested as a possible therapy. Late during the 1995 Kikwit, Zaire, outbreak, 8 Ebola patients received blood transfusions from Ebola survivors. Of these, 7 survived. However, no clear evidence exists that links their survival directly to this

therapy. More recent efforts have focused on viral inhibition, including Ebola virus inhibition using selective estrogen receptor modulators.

Lassa fever have been treated effectively with intravenous and oral ribavirin. Because of this, ribavirin has been recommended as a potential treatment for other arenaviruses. Treatment is most effective when given early in the clinical course. Ribavirin also is recommended for postexposure prophylaxis. Other potential antiviral therapies against Lassa fever include novel benzimidazole compounds such as ST-193 and other related heterocyclic compounds.

The goals in the use of antivirals are to shorten the clinical course, prevent complications, prevent the development of latency and/or subsequent recurrences, decrease transmission, and eliminate established latency.

Ribavirin (Virazole) - nucleoside analog with antiviral activity; may significantly reduce mortality in Lassa fever if treatment begun within 6 d of onset. Load intravenously 30 mg/kg (up to 2 g), THEN 16 mg/kg (up to 1 g) x4 days, THEN 8 mg/kg (up to 500 mg) x6 days.

Prophylaxis.

Because most patients requiring prehospital evaluation and transport are in the early stages of the disease, universal precautions should be adequate. In patients with respiratory symptoms (eg, cough, rhinitis), use face shields and high-efficiency particulate air (HEPA) filter masks.

As the natural reservoirs for Ebola and Marburg virus infection remain unknown, no specific prevention measures are established. Recent studies have suggested that contact with fruits bats may be responsible for some cases of filovirus infection.

Efforts are under way in West Africa to educate people in high-risk areas about ways to decrease rodent populations, thereby reducing transmission of Lassa fever.

Strict barrier precautions in the treatment of patients with known or suspected viral hemorrhagic fever infection reduce nosocomial transmission.

Infection control measures include the following:

- Place patients in a private room;
- Prevent nonessential staff and visitors from entering the room;
- All staff entering the room should wear gloves and gowns;
- Persons coming within 3 feet of the patient should wear face shields or surgical masks with eye protection (including side shields); use HEPA filter masks if patients have prominent respiratory, GI, or hemorrhagic symptoms;
- If large amounts of blood or other body fluids are present in the environment, use leg and shoe coverings;
- Before exiting the room, discard all used protective barriers and clean shoes with a hospital disinfectant or solution of household bleach;
- If possible, use an anteroom for putting on and removing protective barriers and for storing supplies.

Recently proposed guidelines for the use of ribavirin for postexposure prophylaxis recommend the use of oral ribavirin (500-600 mg PO x7-10 days) exclusively for definitive, high-risk exposures, such as contaminated needlestick injury, mucous membrane or nonintact skin exposure with contaminated blood or body fluids, participation in emergency resuscitative procedures (eg, intubation, suctioning), or prolonged close contact in an enclosed space with infected patients without appropriate personal protective equipment.

The only established and licensed virus-specific vaccine against any of these viruses is the yellow fever vaccine. It is mandatory for those traveling into areas of Africa and South America where the disease is commonly found. Current trials are underway for further vaccines and antibody therapies. Yellow fever vaccine is readily available and is both safe and effective. Development of a Lassa virus vaccine is continuing at the CDC. A bivalent vaccine is being developed from the preexisting 17D yellow fever vaccine that would express not only yellow fever glycoproteins but also Lassa glycoproteins, theoretically stimulating a protective immune response against both viruses.

Although there is no approved vaccine for either Ebola or Marburg virus, significant progress has been made in developing an effective experimental vaccine using a vesicular stomatitis virus-based vaccine. Initial reports indicate that this effort may have been successful. Other recent efforts have focused on postexposure prophylaxis for filovirus exposure and have achieved success using a primate model. Other efforts to create a viable (and marketable) Ebola vaccine have led to the development of an experimental bivalent vaccine that confers protection against both rabies and Ebola virus.

3.1 Lassa fever

Lassa fever is an acute viral illness that occurs in west Africa. The illness was discovered in 1969 when two missionary nurses died in Nigeria. The virus is named after the town in Nigeria where the first cases occurred. The virus, a member of the virus family Arenaviridae, is a single-stranded RNA virus and is zoonotic, or animal-borne.

Lassa fever is endemic in parts of west Africa including Sierra Leone, Liberia, Guinea and Nigeria; however, other neighboring countries are also at risk, as the animal vector for Lassa virus, the "multimammate rat" (Mastomys natalensis) is distributed throughout the region.

The number of Lassa virus infections per year in west Africa is estimated at 100,000 to 300,000, with approximately 5,000 deaths. Unfortunately, such estimates are crude, because surveillance for cases of the disease is not uniformly performed. In some areas of Sierra Leone and Liberia, it is known that 10%-16% of people admitted to hospitals every year have Lassa fever, which indicates the serious impact of the disease on the population of this region.

Epidemiology. The reservoir, or host, of Lassa virus is a rodent known as the "multimammate rat" (Mastomys natalensis). Once infected, this rodent is able to excrete virus in urine for an extended time period, maybe for the rest of its life. Mastomys rodents breed frequently, produce large numbers of offspring, and are numerous in the savannas and forests of west, central, and east Africa. In addition,

Mastomys readily colonize human homes and areas where food is stored. All of these factors contribute to the relatively efficient spread of Lassa virus from infected rodents to humans. Transmission of Lassa virus to humans occurs most commonly through ingestion or inhalation. Mastomys rodents shed the virus in urine and droppings and direct contact with these materials, through touching soiled objects, eating contaminated food, or exposure to open cuts or sores, can lead to infection.

Direct contact with infected rodents is not the only way in which people are infected; person-to-person transmission may occur after exposure to virus in the blood, tissue, secretions, or excretions of a Lassa virus-infected individual. Casual contact (including skin-to-skin contact without exchange of body fluids) does not spread Lassa virus. Person-to-person transmission is common in health care settings (called nosocomial transmission) where proper personal protective equipment (PPE) is not available or not used. Lassa virus may be spread in contaminated medical equipment, such as reused needles.

Signs and symptoms of Lassa fever typically occur 1-3 weeks after the patient comes into contact with the virus. For the majority of Lassa fever virus infections (approximately 80%), symptoms are mild and are undiagnosed. Mild symptoms include slight fever, general malaise and weakness, and headache. In 20% of infected individuals, however, disease may progress to more serious symptoms including hemorrhaging (in gums, eyes, or nose, as examples), respiratory distress, repeated vomiting, facial swelling, pain in the chest, back, and abdomen, and shock. Neurological problems have also been described, including hearing loss, tremors, and encephalitis. Death may occur within two weeks after symptom onset due to multi-organ failure.

The most common complication of Lassa fever is deafness. Various degrees of deafness occur in approximately one-third of infections, and in many cases hearing loss is permanent. As far as is known, severity of the disease does not affect this complication: deafness may develop in mild as well as in severe cases.

Approximately 15%-20% of patients hospitalized for Lassa fever die from the illness. However, only 1% of all Lassa virus infections result in death. The death rates for women in the third trimester of pregnancy are particularly high. Spontaneous abortion is a serious complication of infection with an estimated 95% mortality in fetuses of infected pregnant mothers.

Because the symptoms of Lassa fever are so varied and nonspecific, clinical diagnosis is often difficult. Lassa fever is also associated with occasional epidemics, during which the case-fatality rate can reach 50% in hospitalized patients.

Diagnosis. Lassa fever is most often diagnosed by using enzyme-linked immunosorbent serologic assays (ELISA), which detect IgM and IgG antibodies as well as Lassa antigen. Reverse transcription-polymerase chain reaction (RT-PCR) can be used in the early stage of disease. The virus itself may be cultured in 7 to 10 days, but this procedure should only be done in a high containment laboratory with good laboratory practices. Immunohistochemistry, performed on formalin-fixed tissue specimens, can be used to make a post-mortem diagnosis.

Treatment. Ribavirin, an antiviral drug, has been used with success in Lassa fever patients. It has been shown to be most effective when given early in the course of the illness. Patients should also receive supportive care consisting of maintenance of appropriate fluid and electrolyte balance, oxygenation and blood pressure, as well as treatment of any other complicating infections.

Prevention. Primary transmission of the Lassa virus from its host to humans can be prevented by avoiding contact with Mastomys rodents, especially in the geographic regions where outbreaks occur. Putting food away in rodent-proof containers and keeping the home clean help to discourage rodents from entering homes. Using these rodents as a food source is not recommended. Trapping in and around homes can help reduce rodent populations; however, the wide distribution of Mastomys in Africa makes complete control of this rodent reservoir impractical.

When caring for patients with Lassa fever, further transmission of the disease through person-to-person contact or nosocomial routes can be avoided by taking preventive precautions against contact with patient secretions (called VHF isolation precautions or barrier nursing methods). Such precautions include wearing protective clothing, such as masks, gloves, gowns, and goggles; using infection control measures, such as complete equipment sterilization; and isolating infected patients from contact with unprotected persons until the disease has run its course.

Further, educating people in high-risk areas about ways to decrease rodent populations in their homes will aid in the control and prevention of Lassa fever. Other challenges include developing more rapid diagnostic tests and increasing the availability of the only known drug treatment, ribavirin. Research is presently under way to develop a vaccine for Lassa fever.

3.2 Marburg hemorrhagic fever

Marburg hemorrhagic fever (Marburg HF) is a rare but severe hemorrhagic fever which affects both humans and non-human primates. Marburg HF is caused by Marburg virus, a genetically unique zoonotic (or, animal-borne) RNA virus of the filovirus family. Marburg virus was first recognized in 1967, when outbreaks of hemorrhagic fever occurred simultaneously in laboratories in Marburg and Frankfurt, Germany and in Belgrade, Yugoslavia (now Serbia). Marburg HF typically appears in sporadic outbreaks throughout Africa. The virus is not known to be native to other continents, such as North America.

Epidemiology. The reservoir host of Marburg virus is the African fruit bat, Rousettus aegyptiacus. Fruit bats infected with Marburg virus do not to show obvious signs of illness. Primates (including humans) can become infected with Marburg virus, and may develop serious disease with high mortality. Further study is needed to determine if other species may also host the virus. This Rousettus bat is a sighted, cave-dwelling bat widely distributed across Africa. Given the fruit bat's wide distribution, more areas are potentially at risk for outbreaks of Marburg

HF than previously suspected. After this initial crossover of virus from host animal to humans, transmission occurs through person-to-person contact. This may happen in several ways: direct contact to droplets of body fluids from infected persons, or contact with equipment and other objects contaminated with infectious blood or tissues. Persons who have handled infected non-human primates or have come in direct contact with their fluids or cell cultures have become infected. Spread of the virus between humans has occurred in close environments and direct contacts. A common example is through caregivers in the home or in a hospital (nosocomial transmission).

Signs and symptoms. After an incubation period of 5-10 days, symptom onset is sudden and marked by fever, chills, headache, and myalgia. Around the fifth day after the onset of symptoms, a maculopapular rash, most prominent on the trunk (chest, back, stomach), may occur. Nausea, vomiting, chest pain, a sore throat, abdominal pain, and diarrhea may then appear. Symptoms become increasingly severe and can include jaundice, inflammation of the pancreas, severe weight loss, delirium, shock, liver failure, massive hemorrhaging, and multi-organ dysfunction. Because many of the signs and symptoms of Marburg hemorrhagic fever are similar to those of other infectious diseases such as malaria or typhoid fever, clinical diagnosis of the disease can be difficult, especially if only a single case is involved. The case-fatality rate for Marburg hemorrhagic fever is between 23-90%.

Laboratory diagnosis. If a person has the early symptoms of Marburg HF and there is reason to believe that Marburg HF should be considered, the patient should be isolated and public health professionals notified. Samples from the patient can then be collected and tested to confirm infection.

Antigen-capture enzyme-linked immunosorbent assay (ELISA) testing, polymerase chain reaction (PCR), and IgM-capture ELISA can be used to confirm a case of Marburg HF within a few days of symptom onset. Virus isolation may also be performed but should only be done in a high containment laboratory with

good laboratory practices. The IgG-capture ELISA is appropriate for testing persons later in the course of disease or after recovery. In deceased patients, immunohistochemistry, virus isolation, or PCR of blood or tissue specimens may be used to diagnose Marburg HF retrospectively.

Treatment. There is no specific treatment for Marburg hemorrhagic fever. Supportive hospital therapy should be utilized, which includes balancing the patient's fluids and electrolytes, maintaining oxygen status and blood pressure, replacing lost blood and clotting factors, and treatment for any complicating infections. Experimental etiotropic treatment is validated in non-human primates models, but have never been tried in humans.

Prophylaxis. Preventive measures against Marburg virus infection are not well defined, as transmission from wildlife to humans remains an area of ongoing research. However, avoiding fruit bats, and sick non-human primates in central Africa, is one way to protect against infection.

Measures for prevention of secondary, or person-to-person, transmission are similar to those used for other hemorrhagic fevers. If a patient is either suspected or confirmed to have Marburg hemorrhagic fever, barrier nursing techniques should be used to prevent direct physical contact with the patient. These precautions include wearing of protective gowns, gloves, and masks; placing the infected individual in strict isolation; and sterilization or proper disposal of needles, equipment, and patient excretions.

Marburg hemorrhagic fever is a very rare human disease. However, when it occurs, it has the potential to spread to other people, especially health care staff and family members who care for the patient. Therefore, increasing awareness in communities and among health-care providers of the clinical symptoms of patients with Marburg hemorrhagic fever is critical. Better awareness can lead to earlier and stronger precautions against the spread of Marburg virus in both family members and health-care providers. Improving the use of diagnostic tools is another priority. With modern means of transportation that give access even to

remote areas, it is possible to obtain rapid testing of samples in disease control centers equipped with Biosafety Level 4 laboratories in order to confirm or rule out Marburg virus infection.

3.3 Ebola hemorrhagic fever

Ebola hemorrhagic fever is a rare and deadly disease caused by infection with one of the Ebola virus species. Ebola can cause disease in humans and nonhuman primates (monkeys, gorillas, and chimpanzees). Ebola is caused by infection with a virus of the family Filoviridae, genus Ebolavirus. There are five identified Ebola virus species, four of which are known to cause disease in humans: Ebola virus (Zaire ebolavirus); Sudan virus (Sudan ebolavirus); Taï Forest virus (Taï Forest ebolavirus, formerly Côte d'Ivoire ebolavirus); and Bundibugyo virus (Bundibugyo ebolavirus). The fifth, Reston virus (Reston ebolavirus), has caused disease in nonhuman primates, but not in humans.

Ebola viruses are found in several African countries. Ebola was first discovered in 1976 near the Ebola River in what is now the Democratic Republic of the Congo. Since then, outbreaks have appeared sporadically in Africa.

Epidemiology. The natural reservoir host of Ebola virus remains unknown. However, on the basis of evidence and the nature of similar viruses, researchers believe that the virus is animal-borne and that bats are the most likely reservoir. Because the natural reservoir host of Ebola viruses has not yet been identified, the way in which the virus first appears in a human at the start of an outbreak is unknown. However, scientists believe that the first patient becomes infected through contact with an infected animal, such as a fruit bat or primate (apes and monkeys), which is called a spillover event. Person-to-person transmission follows and can lead to large numbers of affected people. In some past Ebola outbreaks, primates were also affected by Ebola and multiple spillover events occurred when people touched or ate infected primates. People get Ebola through direct contact (through broken skin or mucous membranes in, for example, the eyes, nose, or mouth) with:

- blood or body fluids (including but not limited to urine, saliva, sweat, feces, vomit, breast milk, and semen) of a person who is sick with or has died from Ebola,

- objects (like needles and syringes) that have been contaminated with body fluids from a person who is sick with Ebola or the body of a person who has died from Ebola,

- infected fruit bats or primates (apes and monkeys), and

- possibly from contact with semen from a man who has recovered from Ebola (for example, by having oral, vaginal, or anal sex).

Ebola is not spread through the air, by water, or in general, by food. However, in Africa, Ebola may be spread as a result of handling bushmeat (wild animals hunted for food) and contact with infected bats. There is no evidence that mosquitoes or other insects can transmit Ebola virus. Only a few species of mammals (e.g., humans, bats, monkeys, and apes) have shown the ability to become infected with and spread Ebola virus.

During outbreaks of Ebola, the disease can spread quickly within healthcare settings (such as a clinic or hospital). Exposure to Ebola can occur in healthcare settings where hospital staff are not wearing appropriate personal protective equipment. Dedicated medical equipment (preferably disposable, when possible) should be used by healthcare personnel providing patient care. Proper cleaning and disposal of instruments, such as needles and syringes, also are important. If instruments are not disposable, they must be sterilized before being used again. Without adequate sterilization of instruments, virus transmission can continue and amplify an outbreak.

Clinical symptoms. Symptoms may appear anywhere from 2 to 21 days after exposure to Ebola, but the average is 8 to 10 days. Symptoms of Ebola include: fever, severe headache, muscle pain, weakness, fatigue, diarrhea, vomiting, abdominal (stomach) pain, unexplained hemorrhage (bleeding or bruising).

Recovery from Ebola depends on good supportive clinical care and the patient’s immune response. People who recover from Ebola infection develop antibodies that last for at least 10 years.

Laboratory diagnosis. Diagnosing Ebola in a person who has been infected for only a few days is difficult because the early symptoms, such as fever, are nonspecific to Ebola infection and often are seen in patients with more common diseases, such as malaria and typhoid fever. However, a person should be isolated and public health authorities notified if they have the early symptoms of Ebola and have had contact with blood or body fluids from a person sick with or who has died from Ebola, objects that have been contaminated with the blood or body fluids of a person sick with or who has died from Ebola, infected fruit bats and primates (apes and monkeys), or semen from a man who has recovered from Ebola. Samples from the patient can then be collected and tested to confirm infection.

Ebola virus is detected in blood only after onset of symptoms, most notably fever, which accompany the rise in circulating virus within the patient's body. It may take up to three days after symptoms start for the virus to reach detectable levels. Laboratory tests used in diagnosis include: within a few days after symptoms begin - antigen-capture enzyme-linked immunosorbent assay (ELISA) testing, IgM ELISA, polymerase chain reaction (PCR),virus isolation; Later in disease course or after recovery - IgM and IgG antibodies; retrospectively in deceased patients - immunohistochemistry testing, PCR, virus isolation.

Treatment. Symptoms of Ebola and complications are treated as they appear. The following basic interventions, when used early, can significantly improve the chances of survival: providing intravenous fluids (IV) and balancing electrolytes (body salts), maintaining oxygen status and blood pressure, treating other infections if they occur. Experimental treatments for Ebola are under development, but they have not yet been fully tested for safety or effectiveness.

Recovery from Ebola depends on good supportive care and the patient’s immune response. People who recover from Ebola infection develop antibodies

that last for at least 10 years, possibly longer. It is not known if people who recover are immune for life or if they can become infected with a different species of Ebola. Some people who have recovered from Ebola have developed long-term complications, such as joint and vision problems. Even after recovery, Ebola might be found in some body fluids, including semen. The time it takes for Ebola to leave the semen is different for each man. For some men who survived Ebola, the virus left their semen in three months. For other men, the virus did not leave their semen for more than nine months.

Prophylaxis. No FDA-approved vaccine or medicine (e.g., antiviral drug) is available for Ebola.

If you travel to or are in an area affected by an Ebola outbreak, make sure to do the following:

- Practice careful hygiene. For example, wash your hands with soap and water or an alcohol-based hand sanitizer and avoid contact with blood and body fluids (such as urine, feces, saliva, sweat, urine, vomit, breast milk, semen, and vaginal fluids).

- Do not handle items that may have come in contact with an infected person's blood or body fluids (such as clothes, bedding, needles, and medical equipment).

- Avoid funeral or burial rituals that require handling the body of someone who has died from Ebola.

- Avoid contact with bats and nonhuman primates or blood, fluids, and raw meat prepared from these animals.

- Avoid facilities in West Africa where Ebola patients are being treated.

- Avoid contact with semen from a man who has had Ebola until you know Ebola is gone from his semen.

- After you return, monitor your health for 21 days and seek medical care immediately if you develop symptoms of Ebola.

Healthcare workers who may be exposed to people with Ebola should follow these steps:

- Wear appropriate personal protective equipment (PPE).
- Practice proper infection control and sterilization measures.
- Isolate patients with Ebola from other patients.
- Avoid direct, unprotected contact with the bodies of people who have died from Ebola.
- Notify health officials if you have had direct contact with the blood or body fluids, such as but not limited to, feces, saliva, urine, vomit, and semen of a person who is sick with Ebola. The virus can enter the body through broken skin or unprotected mucous membranes in, for example, the eyes, nose, or mouth.

3.4 Yellow fever.

Yellow fever virus is an RNA virus that belongs to the genus Flavivirus. This virus is found in tropical and subtropical areas in South America and Africa. The virus is transmitted to people by the bite of an infected mosquito. Yellow fever is a very rare cause of illness in U.S. travelers. Illness ranges in severity from a self-limited febrile illness to severe liver disease with bleeding.

Yellow fever disease is diagnosed based on symptoms, physical findings, laboratory testing, and travel history, including the possibility of exposure to infected mosquitoes. There is no specific treatment for yellow fever; care is based on symptoms. Steps to prevent yellow fever virus infection include using insect repellent, wearing protective clothing, and getting vaccinated.

Epidemiology. Yellow fever virus is transmitted to people primarily through the bite of infected Aedes or Haemagogus species mosquitoes. Mosquitoes acquire the virus by feeding on infected primates (human or non-human) and then can transmit the virus to other primates (human or non-human). People infected with yellow fever virus are infectious to mosquitoes (referred to as being "viremic") shortly before the onset of fever and up to 5 days after onset.

Yellow fever virus has three transmission cycles: jungle (sylvatic), intermediate (savannah), and urban.

The *jungle (sylvatic) cycle* involves transmission of the virus between non-human primates (e.g., monkeys) and mosquito species found in the forest canopy. The virus is transmitted by mosquitoes from monkeys to humans when humans are visiting or working in the jungle. In Africa, an *intermediate (savannah) cycle* exists that involves transmission of virus from mosquitoes to humans living or working in jungle border areas. In this cycle, the virus can be transmitted from monkey to human or from human to human via mosquitoes. The *urban cycle* involves transmission of the virus between humans and urban mosquitoes, primarily Aedes aegypti. The virus is usually brought to the urban setting by a viremic human who was infected in the jungle or savannah.

Clinical symptoms. The majority of persons infected with yellow fever virus have no illness or only mild illness.

In persons who develop symptoms, the incubation period (time from infection until illness) is typically 3–6 days.

The initial symptoms include sudden onset of fever, chills, severe headache, back pain, general body aches, nausea, and vomiting, fatigue, and weakness. Most persons improve after the initial presentation.

After a brief remission of hours to a day, roughly 15% of cases progress to develop a more severe form of the disease. The severe form is characterized by high fever, jaundice, bleeding, and eventually shock and failure of multiple organs.

Laboratory diagnosis. Diagnosis is usually based on blood tests that look for virus or antibodies that a person's immune system makes against the viral infection.

Treatment. No specific treatments have been found to benefit patients with yellow fever. Whenever possible, yellow fever patients should be hospitalized for supportive care and close observation.

Treatment is symptomatic. Rest, fluids, and use of pain relievers and medication to reduce fever may relieve symptoms of aching and fever.

Care should be taken to avoid certain medications, such as aspirin or other nonsteroidal anti-inflammatory drugs (e.g. ibuprofen, naproxen), which may increase the risk of bleeding.

Yellow fever patients should be protected from further mosquito exposure (staying indoors and/or under a mosquito net) for up to 5 days after the onset of fever. This way, yellow fever virus in their bloodstream will be unavailable to uninfected mosquitoes, thus breaking the transmission cycle and reducing risk to the persons around them.

Prognosis. The majority of infected persons will be asymptomatic or have mild disease with complete recovery. In persons who become symptomatic but recover, weakness and fatigue may last several months. Among those who develop severe disease, 20–50% may die. Those who recover from yellow fever generally have lasting immunity against subsequent infection.

Prevention. Avoid Mosquito Bites. Use insect repellent. When you go outdoors, use an insect repellent such as those containing DEET, picaridin, IR3535, or oil of lemon eucalyptus on exposed skin. Even a short time outdoors can be long enough to get a mosquito bite. Wear proper clothing to reduce mosquito bites. When weather permits, wear long-sleeves, long pants and socks when outdoors. Mosquitoes may bite through thin clothing, so spraying clothes with repellent containing permethrin or another repellent will give extra protection. Clothing pre-treated with permethrin is commercially available. Mosquito repellents containing permethrin are not approved for application directly to skin. Be aware of peak mosquito hours. The peak biting times for many mosquito species is dusk to dawn. However, Aedes aegypti, one of the mosquitoes that transmits yellow fever virus, feeds during the daytime. Take extra care to use repellent and protective clothing during daytime as well as during the evening and early morning. Staying in accommodations with screened or air-conditioned

rooms, particularly during peak biting times, will also reduce risk of mosquito bites.

Get Vaccinated if Recommended. Yellow fever vaccine is recommended for persons aged ≥ 9 months who are traveling to or living in areas at risk for yellow fever virus transmission in South America and Africa. Yellow fever vaccine may be required for entry into certain countries. Yellow fever vaccine is a live-virus vaccine that has been used for several decades. For most travelers, a single dose of yellow fever vaccine provides long-lasting protection and a booster dose of the vaccine is not needed. A single dose provides lifelong protection for most people.

Questions for self-control.

1. The etiology of hemorrhagic fevers.
2. Epidemiology of hemorrhagic fevers.
3. The pathogenesis of the disease and the major pathological changes.
4. What are the clinical manifestations of hemorrhagic fevers?
5. Complications and prognosis of hemorrhagic fever.
6. Methods of laboratory diagnosis of hemorrhagic fevers.
7. What are the principles of treatment of hemorrhagic fevers?
8. What are the preventive measures carried out in an epidemic focus of hemorrhagic fevers?

Test tasks

1. What hemorrhagic fever are the most dangerous in the epidemiological aspects? A - Omsk; B - yellow; C - dengue; D - Chikungunya; E - Ebola.

2. What hemorrhagic fever is contagious? A - yellow; B - Lassa; C - Ebola; D - Marburg; E - all of these.

3. What hemorrhagic fever is not a tick-borne? A - yellow; B - Crimea; C - Omsk; D - Kyasanur forest diseases; E - Argentina.

4. What a haemorrhagic fever transmitted by mosquitoes? A - Crimean; B - Tomsk; C - dengue; D- Ebola; E - Marburg.

5. What forms of thrombohemorrhagic syndrome are occurs in patients with hemorrhagic fever? A - fulminant; B - acute; C - latent; D - chronic; E - all of these.

6. In the pathogenesis of hemorrhagic fever the cells of what organs are damaged firstly? A - bronchial epithelium; B - epithelium cells of the circulatory system; C - lungs; D - CNS; E - spleen.

7. In the pathogenesis of hemorrhagic fevers what vasoactive components play the leading role? A - thrombocytes; B - kinins; C - adrenaline; D - cytokines; E- all of these.

8. What phase of thrombohemorrhagic syndrome is the most dangerous in the clinical plan? A – 1 stage; B - increasing DIC; C - full DIC; D - phase of thrombosis and occlusion; E - reconstructive phase.

9. Patient P., arrived from Zaire. Complains of trembling, intense headache, muscle pain and back pain, nausea, vomiting. Objectively: hyperemia and swelling of the face, neck, icterus sclera, photophobia. Puls - 120 min. Hepatomegaly. Preliminary diagnosis: A - yellow fever; B - malaria; C - plague; D - hemorrhagic fever with renal syndrome; E - leptospirosis.

10. The patient 25 years old, has the third day of the disease. Complains about high fever, headache, muscle pain, back pain, nausea. He has conjunctivitis, photophobia, lacrimation. The skin of the face and neck hyperemic, the skin is dry, hot. Sclera are subicterus. Pulse is frequent, soft. He returned from Africa 6 days ago, he was in the jungle. Diagnosis: A - leptospirosis; B - Flu, C - yellow fever; D - malaria E - hematuria.

11. A woman 29 years was ill a week ago with a headache, hyperthermia 40°C. She returned from South Africa a week ago, where she was bitten by mosquitoes. Here condition was grave, hemorrhagic rash on the skin and mucous membranes, nasal bleeding, jaundice, hepatosplenomegaly. What disease should be

suspected: A - yellow fever; B - malaria; C - plague; D - dengue fever; E - Ku fever.

12. The most reliable method of laboratory diagnosis of yellow fever is: A - isolation of the virus from the dead patient's blood, liver and brain of the; B - complement fixation titer 1:16 or higher; C - virus neutralization; D - hemagglutination inhibition; E - histology of liver biopsy.

13. The differential diagnosis of yellow fever is carried out with: A - viral hepatitis, B - leptospirosis; C - haemorrhagic fevers; D - malaria; E - all of the above.

14. In the treatment of yellow fever all these drugs are used, except: A - disintoxication solutions in a volume of 2 - 3 liters per day; B - glucocorticoids parenterally; C - cardiovascular agents (strophanthin, korglikon, camphor); D – antibiotics for secondary flora; E - specific immunoglobulin.

15. Prevention of yellow fever includes the following measures: A - isolation of patients in box-room for the first 5 days of illness; B - medical staff should work in overalls; C - destruction of mosquitoes - vectors in foci of epidemic; D - 17D vaccine vaccination of the population "Dakar", E - all of these.

16. Ebola virus in the human body is located in: A - blood; B - faeces; C - urine; D - semen; E - all biological fluids.

17. From what animals, who are sick with Ebola, a person can be infected? A - elephants; B – cat, C - snakes; D - monkeys; E - birds.

18. Ebola mainly is registered in: A- Africa; B - North America; C - Australia; D - Europe; E - South America.

19. What rash is usually develops in Ebola fever?: A - allergic, B - herpetic, C - vesicular; D - maculopapular; E - ulcers.

20. What early manifestation is characteristic for Ebola? A - rash; B - diarrhea, C - jaundice; D - high body temperature; E - orchitis.

21. The doctor who examined the patient with high fever in southern Sudan earlier, has fever, headache, muscle aches and joint pain, weakness, diarrhea. On

the 4th day of illness makulo- papular rash appeared on the body, on 5th day - blood vomiting, melena and hypotension. Diagnosis: A - Ebola; B - malaria; C - plague; D - leptospirosis; E - pseudotuberculosis.

22. The patient, who had returned from Zimbabwe, has fever 40°C, nosebleeds, which can not be stopped, blood tears, numerous hemorrhages, bruises. Diagnosis: A - malaria, B - typhus, C - Ebola, D - leptospirosis, E - pseudotuberculosis.

23. A man 23 years old, who returned from Guinea, has t 38-39,5°C. On the 3rd day of illness bloody vomiting, icterus of sclera and skin, hepatomegaly, oliguria appeared. Face is swollen, red, the vessels of sclera are injected. In urine protein and erythrocytes are present. What method is necessary to confirm the diagnosis: A - virology; B - serology; C - bacteriological; D - biological; E - skin and allergic test.

24. The man, who returned from Zaire, has fever, symptoms of intoxication, abdominal pain. On the third day of disease he has abundant makulla body rash, sore throat, erosive pharyngitis. On the 5th day - bleeding under the skin, nasal bleedings, melena. Which of the following data indicate about the poor prognosis of the disease?: A - thrombocytopenia; B - increase of ALT; C - leucopenia; D - decrease of hematocrit; E - mild anemia.

25. Etiotropic drug for Ebola: A - acyclovir; B - remantadin; C - is not invented; D - azithromycin; E - ribavirin.

26. Patient 2 days after returning from Venezuela, where he worked on agricultural works, has t 39-40° C, shivering, severe headache. On the third day of the disease he has serious condition, hyperemic face and sclera, edema of the eyelids. Pharynx is hyperemic. Then nosebleeds appear. Pulse 120/min. AD 100/70 mm Hg. Tongue is red and dry. Liver +1.5 cm. What pathogenetic therapy is necessary in this situation?: A - vikasol, GCS, detoxification; B - vikasol, glucose; C - α-aminocaproic acid and sorbents; D - hepatoprotectors, saline; E - detoxification.

27. Specific prevention of Ebola: A - intravenous ribavirin; B - vaccinations with live vaccines; C - immunoglobulin; D - vaccination with recombinant vaccines; E - is not invented.

28. Causative agent of Lassa fever belongs to: A - Bunyan Viruses; B - Flavio viruses; C - Filoviruses; D - Arenaviruses; E - Togaviridae.

29. Lassa fever is common in: A - South Africa; B - West Africa; C - North Africa; D - South America; E - South-East Asia.

30. The natural reservoir of Lassa fever is: A - multimammate rat; B - mouse vole; C - mites; D - mosquitoes; E - bats.

31. How Lassa fever can not be transmitted from person to person? A - sexually; B - parenteral; C - contact; D - airborne, E - wound.

32. What is not observed in patints with Lassa fever?: A - rash, swelling of the face, and neck; C - pleuritis, pericarditis; D - hepatitis; E - orchitis.

33. For Lassa fever it is characteristic the ulcers of: A - stomach; B – skin; C - oropharynx; D - duodenum; E - rectum.

34. Increased activity of what enzyme is the most unfavorable for the prognosis of Lassa fever? A - ALT, B - alkaline phosphatase; C - GGT; D - lactate dehydrogenase; E - AsAT.

35. What is detected in general analysis of blood in height of Lassa fever? A - aneosinophilia, B - lymphocytosis; C - lymphopenia; D - thrombocytosis; E - normal ESR.

36. What material is examined in patient with Lassa fever for confirming the diagnosis? A - blood and cerebrospinal fluid; B - blood and urine; C - sputum, stool; D - saliva, urine, feces; E - all biological fluids.

37. What etiotropic drug is used for Lassa fever?: A - acyclovir; B - anatoxin; C - ribavirin; D - ganciclovir; E - penicillin.

38. The duration of the isolation of patients with Lassa fever: A - 7 days from the onset of the disease; B - 14 days from the onset of the disease; C - for at least

21 days after infection; D - not less than 30 days from the onset of the disease; E - need not be insulated.

39. Soldier, who returned from Sierra Leone, is sick 3 days. During examination: t°-39°C, signs of erosive pharyngitis, hyperemia of face, conjunctivitis. Lassa fever was suspected. What control measures is necessary in the hearth ?: A - protective clothing for medical staff, rodent control, disinfection, isolation of patients; B - vaccination of contacts; C - emergency antibiotic prophylaxis; D - disinfection; E - introduction of specific serum.

40. The causative agent of Marburg fever belongs to: A - Adenovirus; B - Flavivirus; C - Filoviruses; D - Bunyaviridae; E - Togaviridae.

41. The natural reservoir of Marburg fever are: A rats; B - mice-vole; C - monkeys; D - dogs; E - mites.

42. Marburg fever in nature is registered in: A - Asia, B - South America; C - Australia; D – Africa; E - Europe.

43. What is the main mechanism of infection in fever Marburg? A - fecal-oral; B - vertical, C - transmissible; D - airborne; E - contact.

44. When diarrhea in fever Marburg does appear? A – on 3-4 day of disease; B - from the 1st day; C - on the second week; D - on the 3 week: E - on the 4th week.

45. Hemorrhagic syndrome in Marburg fever develops: A - at the onset of disease; B – on 2-3 day of disease; C - on 5-7 day; D - to the 2nd week; E - does not appear.

46. The rash in Marburg fever as a rule is? A - maculopapular; B - petechial, C - vesicular; D - pustular; E - urticarial.

47. Lab technician, who worked with the tissues from African monkeys, admitted to the hospital on the 3rd day of the disease in serious condition: severe headache, arthralgia, sore throat, temperature 40° C, diarrhea with blood. Macular rash on the face, conjunctivitis, erosive pharyngitis, confused consciousness.

Tachycardia and hypotension. Pain around the umbilicus. Diagnosis: A - fever of Marburg; B - plague; C - leptospirosis; D - yersiniosis; E - pseudotuberculosis.

48. Marburg virus in a patient can be isolated from human: A – blood; B - urine, C - hemorrhagic exudate; D - fluid anterior eye chamber; E - all answers are correct.

49. What is effective for etiotropic treatment of Marburg fever? A - acyclovir; B - remantadine, C - zanamivir; D - penicillin; E – does not exist.

50. The main preventive measure during contact with Marburg fever patient: A - vaccination with live vaccine; B - vaccination with recombinant vaccine; C - anatoxin; D - fluoroquinolones; E - protective suit.

Situational tasks.

Task №1

Patient A. 25 years old entered to the hospital on the third day of the disease with complaints about high fever, headache, muscle pain, back pain, nausea, vomiting. Objectively: icteric sclera, photophobia, lacrimation, hyperemic skin of the face and neck, the skin is dry, hot to the touch. Hepatomegaly. Pulse is frequent, soft. From epidemiological anamnesis: a week ago he returned from South Africa, where he was bitten by mosquitoes.

1. Preliminary diagnosis.
2. Diagnosis of the disease .
3. Medical tactic.
4. Preventive measures.

Task №2

The patient, 25 years, 3 days ago returned from Liberia. In the plane he has felt an indisposition, headache, sore throat. On arrival home he measured the body temperature, which was subfebrile. The patient did not apply for medical aid, to lower the temperature and reduce the headache he took aspirin. On the second day

of the disease symptoms of general malaise and headache increased, body temperature rose to 39,5 ° - 40 ° C. On admission patient had vomiting three times, first with food, then watery, diarrhea twice without pathological impurities, patient coughed often, sputum was with blood.

An objective examination: body temperature - 40 ° C, swelling of the face and neck, generalized lymphadenopathy, swelling of the posterior pharyngeal wall, hyperemic mucosa of the oropharynx with ulcers with a yellowish center and erythema around them. Respiratory rate 25 / min. Breathing is vesicular, in the lower lung - wet sounding wheezes. HR - 90 / min., BP 90/60 mm Hg. Heart sounds are muffled. Liver +7 cm, sensitive on palpation.

1. The preliminary diagnosis.
2. Plan of examination.
3. Conduct a differential diagnosis.
4. The treatment plan.

Task №3

The patient 26 years old appealed to the clinic. In objective examination of the patient revealed generalized lymphadenopathy was found, more pronounced increasing of cervical lymph nodes. On the skin hemorrhages of various sizes and other elements (roseola, papules, spots) are marked. Tachycardia, boundaries of the heart are dilated, heart sounds are muffled, blood pressure is lowered. There have dyspnea, cough, stabbing pains in his side, shortening of percussion sound, dry and wet wheezing, sometimes pleural friction rub. X-ray investigation: infiltrative changes in lungs, frequently a pleural effusion. Pronounced changes in the digestive system: necrotic pharyngitis, pain in the epigastric region, nausea, vomiting, rumbling and pain in the umbilical region, abundant watery stool. The liver is enlarged, painful on palpation, ascites. From the nervous system - severe headache, meningeal symptoms (the cerebrospinal fluid is normal), disorders of consciousness, dizziness, noise in ears.

1. Diagnosis.

2. Plan of examination.

3. Treatment plan.

Task №4

The patient 35 years fell ill acutely: fever, headache, generalized myalgia, prostration appeared. From the first days of illness vomiting and watery diarrhea appeared. On examination: symptoms of pharyngitis, conjunctivitis, inflammation of the genital organs. On the 4-5th day of illness maculo-papular rash appeared. Hemorrhagic diathesis, bleeding from the gums, small intestine, urinary tract appeared in the 2nd week. The vomiting was with blood. The signs of multiple organ lesions: liver, kidneys, myocardium. High fever decreased after 8-10 days of illness, but gave a second peak at the end of the 2nd week of the disease. Diarrhea was lengthy, continued after the normalization of body temperature, leading to dehydration.

1. Diagnosis.

2. Plan of examination.

3. Treatment plan.

Keys to test

1.E	11.A	21.A	31.D	41.C
2.E	12.A	22.C	32.E	42.D
3.A	13.E	23.A	33.C	43.E
4.C	14.E	24.A	34.E	44.A
5.E	15.E	25. C	35.C	45.C
6.B	16. E	26. A	36.E	46.E
7. E	17.D	27. E	37.C	47.A
8.C	18.A	28.D	38.D	48.E

9.A	19.D	29.B	39.A	49.E
10.C	20. D	30.A	40.C	50.E

Answers to situational tasks

№1

1. Yellow fever.

2. Complete blood count (leukopenia, neutropenia, thrombocytopenia, relative lymphocytosis, increased erythrocyte sedimentation rate). Biochemical analysis of blood (hyperbilirubinemia, hyperasotemia, increased potassium, increased activity of AST, ALT). Urinalysis (proteinuria, the presence of hyaline and granular cylinders, fresh and modified erythrocytes). Detection of antigen in the serum using monoclonal antibodies in ELISA. PCR.

3. Hospitalization into an insulated box. Strict bed rest, high-calorie light diet, based on organ pathology. Symptomatic therapy, detoxification, anti-shock and hemostatic drugs, taking into account the severity of a syndrome. Correction of acid-base balance.

4. Preventive measures include protection against mosquito bites in endemic areas, disinfestations and specific immunization for people who live in endemic areas, or people from non-endemic areas 10 days before the departure to the endemic area. Active prevention is performed with live attenuated 17D vaccine by single subcutaneous administration of 0,5ml in 1:10 dilution.

№2

1. Ebola fever.

2. General clinical research methods (complete blood count, urinalysis, coprogram), biochemical methods of investigation of blood, urine, cerebrospinal fluid, additional research methods (ECG, ultrasound of the heart and abdominal organs, radiography of the abdomen, fibrogastroduodenoscopy, MRI). The specific

diagnosis: identification of the virus by contamination of cells VERO E6 to guinea pigs intraperitoneally or intracerebral contamination to newborn mice, PCR, serological diagnosis: RNIF, ELISA - determination of IgM, IgG from 2nd week). The study of virus-containing material is carried out only in special laboratories in mode of operation with particularly dangerous infections.

3. Hemorrhagic fever with renal syndrome, yellow fever, typhus, tropical malaria, sepsis.

4. The specific treatment of this disease is not present. Pathogenetic treatment is aimed to reducing the symptoms of intoxication, hemorrhagic manifestations, elimination of hemodynamic disorders, anti-hemorrhagic shock, the other manifestations of the disease.

№3

1. Lassa fever.

2. General clinical research methods (complete blood count, urinalysis, coprogram), biochemical methods of investigation of blood, urine, cerebrospinal fluid, additional research methods (ECG, ultrasound of the heart and abdominal organs, radiography of the abdomen, fibrogastroduodenoscopy, MRI). The specific diagnosis: identification of the virus by contamination of cells VERO E6 to guinea pigs intraperitoneally or intracerebral contamination to newborn mice, PCR, serological diagnosis: RNIF, ELISA - determination of IgM, IgG from 2nd week). The study of virus-containing material is carried out only in special laboratories in mode of operation with particularly dangerous infections.

3. Obligatory hospitalization of patients to specialized infectious compartment under close confinement. Bed regime, the treatment is mainly symptomatic. Application of convalescents plasma is effective only in some cases in the first week of the disease. At its later introduction it is possible deterioration of the patient. Antibiotics, glucocorticoids are shown in case of complications. Etiotropic drugs and vaccines are developed. Using of ribavirin (virazole, ribamidil) in the

early phase of the disease oraly 1000 mg / day for 10 days or intravenously for 4 days reduces the severity and mortality.

№4

1. Marburg fever.

2. General clinical research methods (complete blood count, urinalysis, coprogram), biochemical methods of investigation of blood, urine, cerebrospinal fluid, additional research methods (ECG, ultrasound of the heart and abdominal organs, radiography of the abdomen, fibrogastroduodenoscopy, MRI). The specific diagnosis: identification of the virus by contamination of cells VERO E6 to guinea pigs intraperitoneally or intracerebral contamination to newborn mice, PCR, serological diagnosis: RNIF, ELISA - determination of IgM, IgG from 2nd week). The study of virus-containing material is carried out only in special laboratories in mode of operation with particularly dangerous infections.

3. Diet - lacto-vegetarian, mashed foods. Ribavirin for 10 days according to the scheme. Detoxification, hemostatic, rehydration, antiedematous replacement therapy.

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