INFECTIOUS DISEASES

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INTRODUCTION TO DIARRHEAL DISEASES

Diarrhea is one of the leading causes of death worldwide, accounting for nearly 2,5 million deaths annually. It is most common in developing countries and a less serious problem in the European region.

These disorders are usually self-limiting, but can be fatal in infants, elderly people, and immunocompromised hosts.

Nowadays the three most common bacterial causes of acute infectious diarrhea are *Salmonella*, *Shigella*, and *Campylobacter species*. Other important bacterial pathogens include *Escherichia coli*, *Vibrio cholerae* and *Yersinia enterocolitica*. Each of these pathogens has unique life cycle and virulence characteristics. The various causes of acute bacterial diarrhea are hard to distinguish clinically, and diagnosis requires isolation of the organism from stool culture.

SHIGELLOSIS

Etiology. *Shigella* organisms cause bacillary dysentery, a disease that has been described since early recorded history. *Shigella* organisms are small gram-negative rods that are members of the family *Enterobacteriaceae*, tribe *Escherichieae*, and genus *Shigella*.

They are nonmotile and nonencapsulated. The 47 serotypes of *Shigella* are divided into four groups, depending on serologic similarity and fermentation reactions: group A (*Shigella dysenteriae*), group B (*Shigella flexneri*), group C (*Shigella boydii*), and group D (*Shigella sonnei*).

Epidemiology. The organism is spread by fecal-oral contact; via infected food or water. *Sh. sonnei* and *Sh. flexneri* cause 90 % of the cases of shigellosis. *Sh. dysenteriae* can produce epidemic shigellosis.

Pathophysiology. *Shigella* species cause damage by 2 mechanisms: invasion of the colonic epithelium, which is dependent on a plasmid-mediated virulence factor, and production of enterotoxin, which is not essential for colitis, but enhances virulence.

The organism first takes up residence in the small intestine. After several days, it is cleared by the small intestine, but then invades the colon, where it causes an intense inflammatory response, forming microabscesses and mucosal ulcerations.

Clinical features. Symptoms of shigellosis include: acute bloody diarrhea, crampy abdominal pain, tenesmus, passage of mucus, fever (usually 1–3 days after exposure), occasionally vomiting (35 % prevalence), lower abdominal tenderness, normal or increased bowel sounds and dehydration (occasionally).

Diagnostic workup. Mildly elevated hematocrit, sodium, and urea nitrogen are indicative of volume depletion in cases of shigellosis. Leukocytosis is rare.

Main diagnostic way of shigellosis is positive finding on stool culture of a fresh fecal specimen.

Differential diagnosis: amebiasis, *Campylobacter* infections, cholera, viral gastroenteritis, *Clostridium difficile* colitis, colon cancer, Crohn disease, cryptosporidiosis, *Escherichia coli* infections, salmonellosis, yersiniosis.

Treatment. For public health reasons, most experts recommend treating any person whose stool culture is positive for *Shigella* species.

The cornerstone of the therapy is appropriate rehydration in cases of severe fluid losses. Use of antimicrobials shortens duration of illness and shedding, decreases risk of transmission person-to-person. If unknown antibiotic susceptibility: ciprofloxacin 500 mg or norfloxacin 400 mg or ofloxacin 200 mg all per os twice daily × 5 days. Alternatives (usual duration 5 days): ceftriaxone (1 g intravenous every 24 h), azithromycin (500 mg per os day 1, then 250 mg per os days 2–4), depending on susceptibility patterns. In southeast Asia, growing resistance seen to fluoroquinolones, azithromycin may be preferred.

Prevention. Following measures can help prevent the dissemination of shigellosis: use of safe drinking water, chlorination of unreliable water sources, strict handwashing, refrigeration and proper preparation and cooking of food. Food handlers must be treated with antibiotics and should not be involved in food preparation as long as stool cultures are positive for *Shigella*.

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SALMONELLOSIS

Salmonellosis is an infectious disease caused by different nontyphoidal serotypes of *Salmonella* genus, which is characterized by various clinical manifestations in range from asymptomatic carrying to septic forms and mainly occurs in gastrointestinal tract.

Etiology. *Salmonella* is an aerobic gram-negative bacillus that can grow readily on simple culture media. It is motile, and most strains do not ferment lactose. Members of the seven Salmonella subspecies can be serotyped into one of more than 2500 serotypes (serovars) according to antigenically diverse surface structures.

There are **three main antigens** in *Salmonella* structure:

– O-antigen (somatic);
– H-antigen (flagellar);
– Vi-antigen (superficial or capsule).

Epidemiology. Most of the cases of human salmonellosis are caused by *S. typhimurium*, *S. enteritidis*, *S. panama*, *S. infantis*, *S. newport*, *S. agona*, *S. derby*, *S. london*, etc. From a clinical standpoint, the simplest approach is to differentiate typhoidal salmonella (primarily *Salmonella typhi* and *S. paratyphi*) from the many nontyphoidal serotypes that primarily cause gastroenteritis named above.

Nontyphoidal *Salmonella* species infect both wild and domestic animals. Because chickens often excrete Salmonella in their stools and eggs, egg products and undercooked chicken are the foods most commonly associated with disease in human.

Pathophysiology. Salmonella infections begin with the ingestion of bacteria in contaminated food.

In experimental studies the median dose required to produce disease was approximately 10^6 bacteria. Gastric acidity represents the initial barrier to Salmonella colonization, and conditions that increase gastric pH significantly increase susceptibility to infection.

Main factors of pathogenicity are cholera-like enterotoxin and the lypopolysaccharyde endotoxin. Endotoxin may induce multiple effects in human organism: fever, microcirculation failure, even septic shock in complicated cases. The enterotoxin activates the adenylatecyclase of enterocytes, which leads to increase of cyclic AMF (adenosinemonophosphate) in cells. As a result normal transport of Na^+ and Cl^- ions through cell membrane of enterocyte is blocked increasing their concentration in lumen of the intestine. Because of the created osmotic gradient liquid leaves enterocytes and the watery diarrhea starts. In complicated cases failure of liquid-ion balance because of the loss of water amounts may result in decrease of blood volume, arterial blood pressure and hypovolemic shock. Disseminated intravascular coagulation can occur as a consequence of endotoxin influence on hemostasis and hypovolemia.

Clinical features. The incubation period depending on the host and the inoculum is generally 6–72 hours. There can be such clinical forms of salmonellosis:

– gastrointestinal (localised), which can occur in gastritic, gastroenteritic, gastroenterocolitic and enterocolitic variants;
– generalised forms: typhoid-like and septic variants;
– carrying of salmonella: acute, chronic and transient;
– subclinical forms.

Gastrointestinal forms are the most common, starting with nausea, vomiting, and diarrhea. In most cases stools are loose, of moderate volume, and without blood. In rare cases stool may be watery and of large volume (“cholera-like”) or of small volume associated with tenesmus (“dysentery-like”). Fever (38° to 39 °C), abdominal cramping, nausea, vomiting, and chills frequently are reported. Headache, myalgias, and other systemic symptoms also may occur.

Diarrhea is usually self-limited, typically lasting for 3 to 7 days. Diarrhea that persists for more than 10 days should suggest another diagnosis. If fever is present, it usually resolves within 48 to 72 hours.

Occasionally, patients require hospitalization because of dehydration, and death occurs infrequently.

Extraintestinal focal infections develop in approximately 5 % to 10 % of persons with Salmonella bacteremia (cardiorespiratory system, nervous system, bones, joints, hepatobiliary area).

Diagnostic workup. Infection with nontyphoidal *Salmonella* most often results in self-limited acute gastroenteritis that is indistinguishable from that caused by many other enteric bacterial pathogens. Freshly passed stool is the preferred specimen for isolation of nontyphoidal *Salmonella* species. Since stool carriage of *Salmonella* may be prolonged, the interpretation of positive results merits caution, and the diagnosis should be established only when accompanied by clinical findings that are typical of infection.

Modern blood culture systems are 80–100 % accurate in detecting bacteremia in salmonellosis. As the disease duration increases, the sensitivity of blood cultures decreases, while the sensitivity of stool isolation increases. Bone marrow aspirate and culture is superior to blood culture, since the bacterial concentration in bone marrow is 10 times that of peripheral blood. In patients who received antibiotic therapy prior to hospitalization, bone marrow aspirate may still be positive for *Salmonella* even if blood culture results are negative.

Differential diagnosis: *Campylobacter* infections, *Escherichia coli* infections, shigellosis, *Vibrio* infections, *Yersinia enterocolitica.*

Treatment. *Salmonella* gastroenteritis is usually a self-limited disease, and therapy primarily should be directed to the replacement of fluid and electrolyte losses. In a large meta-analysis, antimicrobial therapy for uncomplicated nontyphoidal *Salmonella* gastroenteritis, including short-course or single-dose regimens did not significantly decrease the length of illness, including duration of fever or diarrhea, and was associated with an increased risk of relapse, positive culture after 3 weeks, and adverse drug reactions. Immunocompromised persons, patients with severe clinical presentation, older than 50 years, with valve disease, severe atherosclerosis, cancer, AIDS, uremia, who develop *Salmonella* gastroenteritis may require antibiotic therapy to reduce the risk of extraintestinal spread.

Salmonella antibiotic treatment regimens: ciprofloxacin 500 mg per os twice daily × 5–7 days, ceftriaxone 2g per day intramuscular/intravenous × 5–7 days. Treatment may be prolonged for 14 days if deeply immunocompromised (or if relapsing disease).

After resolution of gastroenteritis, the mean duration of carriage of nontyphoidal *Salmonella* in the stool is 4 to 5 weeks and varies by *Salmonella* serotype. The chronic carrier state is defined as the persistence of *Salmonella* in

stool or urine for periods greater than 1 year. From 0.2 % to 0.6 % of patients with nontyphoidal *Salmonella* infection develop chronic carriage.

Prevention. The most cost-effective approach to the control of salmonellosis is attention to good personal hygiene and maintenance of time-temperature standards for food handling.

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FOOD POISONING (FOOD-BORNE DISEASE)

Etiology. Food poisoning is defined as an illness caused by the consumption of food or water contaminated with bacteria and/or their toxins. Most of the illnesses are mild and improve without any specific treatment. Some patients have severe disease and require hospitalization, aggressive hydration.

Examples of toxin-producing microorganisms, causing food poisoning, include *Clostridium perfringens, Bacillus cereus, Proteus vulgaris, Proteus mirabilis, Staphylococcus spp., Klebsiella spp., Citrobacter spp., Serratia spp.,* etc.

Epidemiology. Main way of spreading of the disease is with infected by toxins and/or bacteria food. Outbreaks are typical for food poisoning.

Pathophysiology. Diarrhea is caused by the action of enterotoxins on the secretory mechanisms of the mucosa of the small intestine, without invasion. This leads to large volume watery stools in the absence of blood, pus, or severe abdominal pain. Occasionally, profound dehydration may result. The enterotoxins may be either preformed in food before ingestion or produced in the gut after ingestion.

Clinical features. The incubation period ranges from hours to 1 day, depending on the cause and on how much was consumed. Enterotoxins can produce illness even when the microbes that produced them have been killed. Symptom appearance varies with the toxin but more often there is a rapid on-set, as in the case of enterotoxins of *Staphylococcus aureus* in which symptoms appear in 1–6 hours. This causes intense vomiting including or not including diarrhea lasting as long as 24–48 hours. Dry mouth, decreased axillary sweat, and decreased urine output indicate mild dehydration, whereas orthostasis, tachycardia, and hypotension indicate more severe volume depletion.

Diagnostic workup. Mainly the diagnosis is based on clinical and epidemiological data: acute start of the disease with symptoms of gastritis or gastroenteritis, short period of hyperthermia or its absence, short incubation period and

fast clinical course of disease, group of people may often become ill, connection with one type of food consumption normally exists, outbreaks of disease often happen.

Toxin presents in food, serum, and stool. Bacterial culture may be positive for enteric pathogens, such as *Salmonella, Shigella, and Campylobacter* organisms.

Differential diagnosis: salmonellosis, viral gastroenteritis, acute meningitis, poisoning with drugs, chemicals, mushrooms.

Treatment. Most food-borne illnesses are mild and improve without any specific treatment. No antibiotics indicated. Gastric lavage may be used to evacuate the toxins. The main objective is adequate rehydration and electrolyte supplementation. Oral rehydration is achieved by administering clear liquids and sodium-containing and glucose-containing solutions. Intravenous solutions are indicated in patients who are severely dehydrated or who have intractable vomiting. Enterosorbents do not alter the course of the disease or reduce fluid loss.

Prevention. The best way to prevent food poisoning caused by infectious agents is to practice strict personal hygiene, cook all foods adequately, avoid cross-contamination of raw and cooked foods, and keep all foods at appropriate temperatures. Stool cultures should be monitored in individuals working in hospitals, food establishments until they become culture-negative without antibiotics. These people should not return to work until that time.

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ESCHERICHIA COLI GASTROINTESTINAL INFECTIONS

Multiple strains of *E. coli* can cause diarrheal illness. These strains cannot easily be distinguished from the nonpathogenic strains of *E. coli* that normally colonize the bowel. Experimental serotyping methods are available that can identify specific lipopolysaccharide antigens (O-antigens) and flagellar antigens (H-antigens) associated with specific pathogenic characteristics. The diarrhea-causing *E. coli* strains are generally divided into five major classes based on their mechanisms of virulence:

1. Enterotoxigenic (ETEC) strains. Colonize the small bowel and produce a cholera-like or heatstable toxin that stimulates secretion of chloride, causing watery diarrhea. These organisms are most commonly encountered in developing countries and are contracted from water contaminated with human

sewage. These strains are a major cause of traveler's diarrhea. The differential diagnoses of *E. coli* traveler's diarrhea include rotavirus infection, Norwalk virus infection, *Salmonella* infection, and *Campylobacter* diarrhea.

2. Enteroaggregative (EaggEC or EAEC) strains. Adhere in large aggregates to human colonic mucosa and produce a low-molecular-weight enterotoxin that causes watery diarrhea. The diarrhea is often prolonged. These strains are contracted by ingesting contaminated water or food. Enteroaggregative E. coli is reported in developing countries and is the second most common cause of traveler's diarrhea. The differential diagnoses of EAEC include *Vibrio cholerae* infection and *Rotavirus* infection.

3. Enteropathogenic (EPEC) strains. Enteropathogenic Escherichia coli (EPEC) is usually associated with outbreaks and sporadic cases of severe infantile diarrhoea in the developing world, and less commonly with sporadic cases in developed countries. Very little number of cases indicates that EPEC is a foodborne pathogen for adults. EPEC are defined as E. coli belonging to serogroups epidemiologically implicated as pathogens but whose virulence mechanism is unrelated to the excretion of typical E. coli enterotoxins. Adhere to the small bowel and induce the polymerization of actin filaments to form a pedestal directly beneath the site of bacterial attachment. EPEC cause either a watery or bloody diarrhea, the former associated with the attachment to, and physical alteration of, the integrity of the intestine. Bloody diarrhea is associated with attachment and an acute tissue-destructive process, perhaps caused by a toxin similar to that of Shigella dysenteriae. Diarrhea may be prolonged, leading to dehydration, electrolyte imbalance and even fatal outcome.

The infective dose is presumably similar to other colonizers (greater than 10^6 total dose). These strains are transmitted by contaminated food or water and by person-to-person spread in nurseries. The differential diagnoses of EPEC also include *Vibrio cholerae* infection and *Rotavirus* infection.

4. Enterohemorrhagic (EHEC) strains, also called **Shiga toxin-producing E. coli (STEC).** The *E. coli* produces Shiga-like cytotoxins that inhibit protein synthesis and cause cell death. In certain strains, the toxin damages vascular endothelium in the bowel and glomeruli, causing hemorrhagic inflammatory colitis and the hemolytic uremic syndrome (HUS). HUS defined by triad of hemolytic anemia, thrombocytopenia, and renal failure. Seizures may be common.

The strain most commonly associated with this syndrome is O157:H7; however, other toxin-producing serotypes are being identified with increasing frequency. Cattle appear to be the primary reservoir, and the disease is most commonly associated with ingestion of undercooked contaminated ground beef. Less commonly, cases have developed after consumption of unpasteurized milk, spinach, lettuce, and commercial mayonnaise. A foodborne outbreak may be associated with raw tomatoes, cucumbers, and leaf salad. Patients present

with bloody diarrhea and a hemolytic uremic syndrome. The Germany outbreak in 2011 year was caused by a hybrid E. coli O104:H4 strain having characteristics of both STEC and EAEC strains. This infection is found primarily in industrialized nations and usually occurs during the summer months. The differential diagnoses of EHEC include *Shigella* infections, *Clostridium difficile* enterocolitis, ulcerative colitis/Crohn disease, ischemic colitis, diverticulosis, and appendicitis.

5. Enteroinvasive (EIEC) strains. Enteroinvasive Escherichia coli (EIEC) infection causes a syndrome that is identical to Shigellosis, with profuse diarrhea and high fever. EIEC are highly invasive, and they utilize adhesin proteins to bind to and enter intestinal cells. They produce no toxins, but severely damage the intestinal wall through mechanical cell destruction. Invade colonic epithelial cells by the same mechanisms that *Shigella* uses. These strains require ingestion of a large inoculum (10^8 organisms) to cause disease. Diarrhea caused by EIEC usually occurs within 12 to 72 hours following the ingestion of contaminated food. The illness is characterized by abdominal cramps, diarrhea, vomiting, fever, chills, and a generalized malaise. It is generally self-limiting with no known complications. Outbreaks are rare and are usually associated with contaminated foods in developing countries. The differential diagnoses of EIEC include shigellosis and amebic dysentery.

Diagnostic workup. Stool microscopy — gram stain results determine if the organism is gram-negative, but findings do not distinguish among the other aerobic gram-negative bacilli that cause similar infectious diseases.

Stool culture — *E. coli* is a gram-negative bacillus that grows well on commonly used media. It is lactose-fermenting and beta-hemolytic on blood agar. Serological methods may be helpful in distinguishing the *E. coli*.

Treatment. Treatment based on symptom severity includes rehydration and antibiotics. Antibacterial therapy may reduce duration of diarrhea:

– Enterotoxigenic *E. coli*: ciprofloxacin 500 mg per os twice daily × 3 days (for severe disease), rifamixin 200 mg per os every 8 hours × 3 days (for non-invasive disease).

– Enterohemorrhagic *E. coli*: if suspect — avoid antibiotics and antimotility agents, reserve antibiotics for severe illness. Antibiotics are not useful in enterohemorrhagic *E. coli* (EHEC) infection and may predispose to development of HUS.

– Traveller's diarrhea: if treatment required (severe): ciprofloxacin 500 mg per os twice daily; rifamixin 200 mg three times a day—all drugs given for 3 days, except bloody diarrhea × 5 days.

– Enteroinvasive *E. coli*: ciprofloxacin 500 mg per os twice daily; rifamixin 200 mg three times a day × 5 days. Antimotility agents are contraindicated in persons with enteroinvasive *E. coli* (EIEC) infection.

– Enteropathogenic *E. coli*: ciprofloxacin 500 mg per os twice daily × 3 days (for severe disease), rifamixin 200 mg per os every 8 hours × 3 days.

– Antimicrobials known to be useful in cases of traveler's diarrhea include fluoroquinolones, rifaximin and in some cases trimethoprim/sulfamethoxazole (TMP/SMZ). They shorten the duration of diarrhea by 24–36 h.

Prevention. Handwashing before eating, water purification, avoid raw fruits and vegetables unless peeled, choose steaming hot foods.

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CHOLERA

Etiology. Cholera is an intestinal infection caused by *Vibrio cholerae. V. cholerae* is a curved gram-negative bacillus which belongs to the family *Vibrionaceae* and shares common characteristics with the family *Enterobacteriaceae*. The antigenic structure of *V. cholerae* is similar to that of other members of the family *Enterobacteriaceae*, with a flagellar H-antigen and a somatic O-antigen. The O-antigen is used to classify *V. cholerae* further, into serogroups O1 and non-O1. Approximately 206 serogroups of *V. cholerae* have been identified to date, but only the serogroups O1 and O139 are associated with clinical cholera.

There are two biotypes of *V. cholerae* O1. The differences between the two biotypes of *V. cholerae* O1 are remarkable. The classic biotype, probably responsible for the first six pandemics of cholera, causes an approximately equal number of symptomatic and asymptomatic cases. In contrast, the El Tor biotype causes more asymptomatic infections, with a ratio between 20 and 100 asymptomatic infections to 1 symptomatic case. The classic biotype is quite rare nowadays, whereas the El Tor biotype is responsible for the current pandemic.

V. cholera O139 was the first non-O1 cholera serotype producing toxin found to be able to produce epidemic cholera. This serotype nowadays is mostly found in Asian, African countries, Carribean and south of Ukraine.

Gastroenteritis caused by so-called non-O1/O139 *V. cholerae* can have symptoms of differing severity ranging from mild diarrhea to severe watery diarrhea.

Epidemiology. Cholera can be an endemic, epidemic, or a pandemic disease. Initiation and maintenance of epidemic and pandemic disease by *V. cholerae* result from human infection and poor sanitation with assistance

from human migration and seasonal warming of coastal waters. Cholera has 2 main reservoirs — humans and water. Transmission occurs through fecal-oral spread of the organism through person-to-person contact or through contaminated water and food.

Pathophysiology. *V. cholerae* is not acid-resistant, it depends on its large inoculum size to withstand gastric acidity. *V. cholerae* cause clinical disease by producing an enterotoxin that promotes the secretion of fluid and electrolytes into the lumen of the small intestine. Enterotoxin is responsible for the increase in cyclic adenosine monophosphate (cAMP). cAMP blocks the absorption of sodium and chloride 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. 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.

Clinical features. Incubation period lasts 24–48 hours, symptoms begin with the sudden onset of painless watery diarrhea that may quickly become voluminous and is often followed by vomiting. Fever is typically absent.

However, most *Vibrio cholerae* infections nowadays are asymptomatic, and mild to moderate diarrhea due to *V. cholerae* infection may not be clinically distinguishable from other causes of gastroenteritis. Only an estimated 5 % of infected patients will develop cholera gravis — severe watery diarrhea, vomiting, and dehydration.

Profuse watery diarrhea is a hallmark of cholera. Stool volume during cholera is more than that of any other infectious diarrhea. The stool may contain fecal material early in the course of clinical illness. The characteristic cholera stool is a white liquid that is often described as a “rice water” (in color and consistency it resembles water that has been used to wash or cook rice).

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.

The World Health Organization (WHO) has classified dehydration in patients with diarrhea into the following 3 categories to facilitate treatment (table 1):

– severe;
– some (previously termed moderate, in the WHO criteria);
– none (previously termed mild, in the WHO criteria).

Table 1

WHO classification of dehydration

Sensorium	Eyes	Thirst	Skin pinch	Decision
Abnormally sleepy or lethargic	Sunken	Drinks poorly or not at all	Goes back very slowly (> 2 sec.)	If the patient has 2 or more of these signs, severe dehydration is present
Restless, irritable	Sunken	Drinks eagerly	Goes back slowly (< 2 sec.)	If the patient has 2 or more signs, some dehydration is present
Well, alert	Normal	Drinks normally, not thirsty	Goes back quickly	Patient has no dehydration

Diagnostic workup. According to WHO standard case definition, a case of cholera is suspected when the following conditions are met:

– In an area where the disease is not known to be present, a patient aged 5 years or older develops severe dehydration or dies from acute watery diarrhea;

– In an area with a noted cholera epidemic, a patient aged 5 years or older develops acute watery diarrhea, with or without vomiting.

Identification of the organism is possible by means of direct microscopic examination of stool along with Gram stain, culture, and serotype and biotype identification. Polymerase chain reaction (PCR) tests for identifying *V. cholerae* have been developed.

Differential diagnosis: *Escherichia coli* infections, other bacterial gastroenteritis, *Rotavirus* gastroenteritis.

Treatment. WHO guidelines include such steps in the treatment of a patient with suspected cholera:

1. Assess for dehydration (see Table 1).
2. Rehydrate the patient and monitor frequently, then reassess hydration status.
3. Maintain hydration; replace ongoing fluid losses until diarrhea stops.
4. Administer an oral antibiotic to the patient with severe dehydration.
5. Feed the patient.

The main goal of therapy is to restore the fluid losses caused by diarrhea and vomiting. Rehydration is accomplished in 2 phases: ***rehydration*** and ***maintenance***.

1. 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/hour. Lactated Ringer solution is preferred over isotonic sodium chloride solution because saline does not correct metabolic acidosis. After finishing the rehydration phase all signs of dehydration should have abated and the patient should pass urine at a rate of 0,5 ml/kg/hour or higher.

2. 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 at a rate of 500–1000 ml/hour is recommended.

The parenteral (intravenous) route should be restricted to patients with moderate and severe dehydration, those who do not tolerate the oral route.

An effective antibiotic can reduce the volume of diarrhea in patients with severe cholera and shorten the period during which *V. cholera* is excreted. Listed antibiotic regimens are possible to use:

– Ciprofloxacin 500 mg per os once to twice daily;
– Tetracycline 500 mg per os four times daily;
– Doxycycline 100 mg per os twice daily;
– Azithromycin 1000 mg per os × 1 dose;
– Ampicillin 500 mg per os four times daily.

One of the most prefered nowadays antibiotic regimens in treating cholera O1 or O139 in adults is ciprofloxacin 1000 mg per os once.

Hypovolemic shock treatment. Hypovolemic shock is a medical condition in which rapid fluid loss results in multiple organ failure due to inadequate circulating volume and subsequent inadequate perfusion. In hypovolemic shock the patient cannot replace the amount of fluid that was lost by drinking enough water, and the body is unable to maintain blood pressure and cardiac output. In all shock states, when waste products build up, increased acidosis occurs, and a worsening body environment leads to further organ failure. For a patient with hypovolemic shock due to gastroenteritis the following interventions should be carried out:

– intravenous access performed;
– oxygen as required;
– inotrope therapy (Noradrenaline, Dopamine), which increase the contractility of the heart muscle;
– rehydration therapy in two phases (described before). If improvement is not observed after 50–100 ml/kg/hour of fluid administration, other etiologies of shock (cardiac, anaphylactic, septic) should be considered.

Prevention. Providing clean water and ensuring proper management of excreta to avoid contamination of other water sources are important measures to reduce cholera transmission. Existing cholera vaccine still shows low efficacy, but improved from prior vaccine.

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INTESTINAL YERSINIOSIS

Etiology. *Yersinia enterocolitica* is a pleomorphic, gram-negative bacillus that belongs to the family *Enterobacteriaceae*. As a human pathogen, *Y. enterocolitica* is most frequently associated with enterocolitis, acute diarrhea, terminal ileitis, mesenteric lymphadenitis and pseudoappendicitis. Human clinical *Y. enterocolitica* infections start after ingestion of the microorganisms in contaminated food or water or by direct inoculation through blood transfusion.

Epidemiology. *Y. enterocolitica* is distributed widely throughout the world and can be isolated from multiple environmental sources, including fresh water, contaminated foods, and a wide range of wild and domestic animals. Outbreaks have been associated with raw vegetables; the surface of vegetables can become contaminated with pathogenic microorganisms through contact with soil, irrigation water and animals. Pasteurized milk and dairy products can also cause outbreaks because *Yersinia* can proliferate at refrigerated temperatures. Animal reservoirs of *Y. enterocolitica* include swine (principle reservoir), dogs, cats, cows, sheep, goats, rodents, foxes and birds. Reports of person-to-person spread are conflicting and are generally not observed in large outbreaks.

Pathophysiology. The alimentary tract is the portal of entry in most cases. As a foodborne pathogen, *Y. enterocolitica* can efficiently colonize and induce disease in the small intestine. Following ingestion, the bacteria colonize the lumen and invade the epithelial lining of the small intestine, resulting in the colonization of the underlying lymphoid tissues (Peyer patches). A direct lymphatic link between the Peyer patches and mesenteric lymph nodes may result in bacterial dissemination to these sites, resulting in mesenteric lymphadenitis or systemic infection.

Clinical features. The major clinical syndromes associated with *Y. enterocolitica* are enterocolitis, mesenteric adenitis, terminal ileitis, septicemia, and various immunoreactive conditions, especially reactive arthritis. The incubation period is 4–6 days, typically with a range of 1–14 days. Prodromal symptoms of malaise, anorexia, and headache may be present. The usual presentation of *Y. enterocolitica* infection includes diarrhea, low-grade fever, and abdominal pain lasting 1–3 weeks. Diarrhea may be bloody in severe cases. Vomiting is present in approximately 15–40 % of cases.

The existence of extraintestinal symptoms after a gastrointestinal illness may also indicate the possibility of yersiniosis. Reactive arthritis can occur after *Y. enterocolitica* infection. Myocarditis and glomerulonephritis may occur in postinfection period. Erythema nodosum may appear 2–20 days after the onset of fever and abdominal pain and resolve spontaneously in most cases in about a month, manifesting as painful, raised red or purple lesions, mainly on the patient's legs and trunk. *Y. enterocolitica* septicemia is reported most commonly in patients who have predisposing conditions, including alcoholism, diabetes mellitus, or an underlying immune defect.

Diagnostic workup. Yersinia may be isolated from stool, mesenteric lymph nodes, pharyngeal exudates, peritoneal fluid, or blood and from abscesses, depending on the clinical syndrome. Serologic tests are useful in diagnosing Yersinia infections. Agglutination tests, enzyme-linked immunosorbent assays, and immunoblotting tests are used. Stool culture is still the best way to confirm a diagnosis of *Y. enterocolitica*; the culture result is usually positive within 2 weeks of onset of disease.

Differential diagnosis: amebiasis, appendicitis, *Campylobacter* infections, *Clostridium difficile* colitis, Crohn disease, diverticulitis, inflammatory bowel disease, pseudotuberculosis, salmonellosis.

Treatment. Enterocolitis caused by *Y. enterocolitica* is usually self-limited. No antibiotic treatment in clinically stable cases may be indicated. Diarrhea should be managed with fluid and electrolyte replacement. Antimotility medications, which could lead to bacteremia, should be avoided.

Though in cases of severe *Y. enterocolitica* enterocolitis, antibiotics have shown some benefit in terms of shortening the duration of illness. Patient populations who should be considered for antibiotic therapy of intestinal yersiniosis include the following:

– severe clinical presentation;
– elderly patients;
– patients with diabetes;
– patients with cirrhosis;
– immunocompromised patients;
– patients with cancer who are receiving chemotherapy;
– healthcare and childcare workers who are at an increased risk of person-to-person spread.

In the above-named cases following antibiotic regimens are possible:

– ciprofloxacin 500 mg per os twice daily;
– combination of doxycycline 100 mg intravenous twice daily and gentamicin 5 mg/kg intravenous every 24 hours.

Resistance of *Y. enterocolitica* to ampicillin is often seen today, so it is not the best antibiotic to prescribe in such cases.

Prevention. Public health measures to control Yersinia infection should focus on safe food handling, processing, and preparation practices. Special attention should be given to protecting milk.

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PSEUDOTUBERCULOSIS

Pseudotuberculosis is an acute infectious disease of the zoonotic group, characterized by toxemia, fever, scarlet fever-like rash, lesions of other organs and systems.

Etiology. *Yersinia pseudotuberculosis*, a gram-negative bacterial pathogen. It primarily causes zoonotic infection in various hosts, including domestic animals and birds, but has been associated with food-borne infection in humans.

Epidemiology. Pseudotuberculosis is wide-spread in nature. Rodents are the most important source of infection. There are epizootics among them frequently. Besides, the cases of the disease occur among domestic animals (dogs, cats, great and small cattle). Soil plays a leading part in preservation of *Y. pseudotuberculosis* as species. The sick human is not a source of infection.

The principal route of infection is oral. The factors of transmission are food and water, contaminated by rodents. Vegetables, used without thermal treatment, are the most important source in transmitting the pathogen.

Pathophysiology. *Y. pseudotuberculosis* infections in humans are primarily acquired through the gastrointestinal tract after consumption of contaminated food products. The mucous membrane of intestinal tract is the portal of entry. The primary inflammation focus occurs in the small bowel, lymphatic system of the intestine, lymph nodes. Spreading of the pathogen and absorption of the toxins occurs from the local inflammation focus.

Clinical features. The incubation period of the disease fluctuates from 3 to 18 days. Clinical picture of the disease is polymorphic.

Usually the body temperature rises from the first days of the disease and fluctuates from subfebrile (in mild forms) to febrile (39–40 °C), which has remittent or intermittent nature and may be accompanied by febrile chill. Duration of fever may fluctuate from several days to 2–3 weeks, sometimes longer. There is headache, weakness, anorexia, insomnia.

Rash occurs in most of the patients and may appear in various terms (from the 2nd to 8th day of illness). It is characterized by polymorphism of its elements and various localization. It is most often minute, scarlet-fever-like on reddened skin and may be combined with macular, hemorrhagic, papular elements. Rash localisation is like the one in scarlet fever (on the lateral parts of the trunk, the internal and the back parts of legs, on the skin of the lower abdomen, in skin folds). Besides, rash may appear on the external surfaces of arms and forearms, on the knee and radiocarpal joints. Hyperemia and edema of skin on the face, hands and feet (symptoms of "hood", "gloves" and "socks")

occur frequently. Rash grows pale gradually during 1–5 days, more often on the 2nd–3rd day.

Desquamation of skin on the hands and feet is observed in 30 % of the patients after disappearance of rash. It usually occurs on the 5th–10th day after the onset of the disease.

Changes in pharynx are found in most of patients. They are characterized by hyperemia of palatal archs, soft palate, uvula, back walls of pharynx.

Lesion of gastro-intestinal tract is observed in more than a half of patients in the form of gastritis, gastroenteritis, enteritis, mesadenitis, ileitis.

Clinically the lesion of gastrointestinal tract is manifested by nausea, vomiting, watery stool, pains in epigastrium, right hypochondrium, near the umbilicus, in the right iliac region. Vomiting is usually single, inconstant; watery stool is 2–4 times a day, without pathological admixtures or with small admixture of mucus, its duration is from 1 to 3 days.

Affection of liver is observed in half of the patients and it is manifested by enlargement, ictericity of skin and sclerae. In blood serum there is an increasing of level of direct bilirubin, increasing of activity of transaminases, decreasing of prothrombin index.

Lesions of joints in pseudotuberculosis may develop in 50–70 % of patients. There are mainly arthralgias, but sometimes there is clinics of poly-arthritis; wrist, ankle and knee joints are most often involved in the process, shoulder and hip joints are more rarely involved.

Development of myocarditis and kidney lesions is possible.

Differential diagnosis: appendicitis, *Clostridium difficile* colitis, Crohn disease, other bacterial gastroenteritis, leptospirosis, acute pancreatitis, sepsis, typhoid fever, ulcerative colitis.

Diagnostic workup. Bacteriological verification of *Y. pseudotuberculosis* infection depends on acquisition of its culture from sources such as blood, feces, urine, cerebrospinal fluid, peritoneal fluid, synovial fluid etc. Serology tests — enzyme-linked immunosorbent assay (ELISA) and agglutination tests may be obtained; the antibodies may appear soon after the onset of illness and typically wane over 2–6 months. Paired serum specimens taken 2 weeks apart that indicate a 4-fold rise in agglutinating antibodies support the diagnosis. In single tests of serum titers of antibodies 1:200 and higher are taken into account.

Treatment. Clinically ill patients and septicemia patients may receive one of the possible regimens:

– Ciprofloxacin 500 mg per os twice daily;
– Doxycycline 100 mg intravenous twice daily;
– Gentamicin 5 mg/kg intravenous every 24 hours.

Duration of antibiotic therapy course is no less than 7 days, and in complicated and severe cases duration of the course is continued up to 10–14 days.

Because of the resistance of *Y. pseudotuberculosis* to ampicillin and its greater prevalence, this agent would not be a good choice for empiric therapy in a clinical situation where this organism could be present.

Prevention. Food-borne epidemics of *Y. pseudotuberculosis* infection can occur. Avoid ingestion of contaminated vegetables, water or unpasteurized milk.

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ROTAVIRAL INFECTION

Viruses account for over half the diarrheal episodes. Rotavirus outnumbers other viral causes of diarrhea by 4:1, causing around 50 % of those cases requiring hospitalization in the developed world.

Etiology and epidemiology. Rotaviruses constitute a genus within the *Reoviridae*, a family of nonenveloped, icosahedral animal viruses with double-stranded RNA genomes. There are seven major groups of rotavirus (A through G); human illness is caused primarily by group A and, to a much lesser extent, by groups B and C.

Found worldwide. Nearly all children are infected with rotavirus by 3–5 years of age. The highest incidence is between 6 month and 24 month old. Rotavirus can cause illness in parents and caretakers of children with rotavirus diarrhea, immunocompromised persons, travelers, and elderly individuals.

In temperate climates, rotavirus disease occurs predominantly during the cooler fall and winter months. In tropical settings, rotavirus disease occurs during the whole year, with less pronounced seasonal peaks.

Rotaviruses are relatively resistant to common handwashing agents and can survive for some time on hard surfaces and in water.

Transmission is faeco-oral (contaminated food, water, direct contact, or inhalation of aerosol from vomit or feces).

Pathogenesis. Rotaviruses infect and ultimately destroy mature enterocytes of the proximal small intestine. The loss of absorptive villous epithelium, coupled with the proliferation of secretory crypt cells, results in secretory diarrhea. Brush-border enzymes characteristic of differentiated cells are reduced, and this change leads to the accumulation of unmetabolized disaccharides and consequent osmotic diarrhea. A nonstructural rotavirus protein, NSP4, functions as an enterotoxin and contributes to secretory diarrhea by altering epithelial cell

function and permeability. In addition, rotavirus may evoke fluid secretion through activation of the enteric nervous system in the intestinal wall.

Clinical features. Incubation period lasts 1–2 days. Patients experience fever, vomiting, and watery bloodless diarrhea. Up to one-third of patients may have a temperature of > 39 °C. Gastrointestinal symptoms generally resolve in 3–7 days. In most severe cases isotonic dehydration develops.

Diagnosis. Illness caused by rotavirus is difficult to distinguish clinically from that caused by other enteric viruses. Because large quantities of virus are shed in feces, the diagnosis can usually be confirmed by a wide variety of rapid diagnostic tests (ELISA for rotavirus-specific antigen, latex agglutination kits) or by techniques for detecting viral RNA, such as gel electrophoresis, probe hybridization, or PCR.

Electron microscopy of feces is now rarely used.

Treatment. Standard oral rehydration therapy is successful in most children who can take oral fluids, but IV fluid replacement may be required for patients who are severely dehydrated or are unable to tolerate oral therapy because of frequent vomiting.

Antibiotics and antimotility agents should be avoided.

Prevention. Hand hygiene is a cornerstone preventive measure. Two oral vaccines are currently available (a multivalent bovine-human reassortant rotavirus-based vaccine, and a vaccine, based on a single attenuated human rotavirus strain).

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ENTEROVIRAL INFECTION

Enteroviruses are so named because of their ability to multiply in the gastrointestinal tract. Despite their name, these viruses are not a prominent cause of gastroenteritis.

Etiology and epidemiology. Enteroviruses is a genera in the *Picornaviridae* family. Originally, the human enteroviruses were divided into five subgenera based on differences in host range and pathogenic potential: polioviruses, group A coxsackieviruses, group B coxsackieviruses, echoviruses, and "newer" enteroviruses. A classification scheme based on RNA homology within the VP1 capsid protein coding region that replaces the traditional classification divides the genus *Enterovirus* into four species, designated enterovirus A through D.

Human enteroviruses contain a single-stranded RNA genome surrounded by an icosahedral capsid comprising four viral proteins. These viruses have no lipid envelope and are stable in acidic environments, including the stomach. They are resistant to inactivation by standard disinfectants (e. g., alcohol, detergents) and can persist for days at room temperature.

Enteroviruses are found worldwide, affects all age groups but highest infection rates are seen in children (secondary to exposure, hygiene, and immune status). Enteroviral infections occur throughout the year, but in temperate climates infections are more prevalent in the summer and autumn months. This seasonal periodicity is less pronounced in southern latitudes and disappears altogether in the tropics.

Most enteroviruses are transmitted by:

– fecal-oral route from fecally contaminated fingers or inanimate objects;

– ingestion of virus-contaminated food or water;

– direct inoculation from the fingers to the mucus membranes or skin leisons;

– airborne transmission.

Enteroviruses can be transmitted across the placenta from mother to fetus, causing severe disease in the newborn. Nosocomial spread of coxsackievirus and echovirus has taken place in hospital nurseries.

Pathogenesis. Enteroviruses infect humans via direct or indirect contact with virus shed from the gastrointestinal tract or upper respiratory tract. Whereas ingested virus implants and replicates in the pharynx and the distal intestine. After multiplication in submucosal lymphatic tissues, enteroviruses pass to regional lymph nodes and give rise to a transient “minor viremia.” This leads to infection and viral replication in reticuloendothelial tissue. Further replication of virus occurs in these reticuloendothelial sites, leading to a sustained “major” viremia that results in dissemination to target organs where tissue necrosis and inflammation occurs in proportion to the level of viral replication.

Clinical features. Incubation period lasts 3–10 days. Infection may be asymptomatic (90 % of infections) or cause an undifferentiated febrile illness, or a more characteristic syndrome.

The most common clinical manifestation is an ***undifferentiated febrile illness***. Patients present with an acute onset of fever, malaise, and headache. Occasional cases are associated with upper respiratory symptoms (e. g., sore throat, and occasionally cough or coryza), and some cases include gastrointestinal symptoms (e. g., nausea, vomiting, and diarrhea). Symptoms often last for 3–4 days, and most cases resolve in a week.

Enteroviruses cause most ***acute viral meningitis*** cases in both adults and children. The onset may be gradual or abrupt, and the typical patient has a brief prodrome of fever and chills. Headache is usually a prominent complaint. Meningismus, when present, varies from mild to severe. Kernig and Brudzinski

signs are present in only about one third of patients. Other symptoms of enteroviral infection can be present. The CSF is clear and under normal or mildly increased pressure. Differential cell counts of the CSF often reveal a high proportion of neutrophils, but the differential typically shifts to a predominance of lymphocytes during the initial 1 to 2 days of illness.

Encephalitis is a well-documented, although unusual, manifestation of nonpolio enterovirus central nervous system infection. Occasional highly inflammatory cases of enteroviral meningitis may be complicated by a mild form of encephalitis that is recognized on the basis of progressive lethargy, disorientation, and sometimes seizures. Less commonly, severe primary encephalitis may develop. Paralytic disease due to enteroviruses other than poliovirus occurs sporadically and is usually less severe than poliomyelitis.

Pleurodynia (Bornholm disease) is characterized by an acute onset of fever and spasms of pleuritic chest or upper abdominal pain. Chest pain is more common in adults, and abdominal pain is more common in children. Paroxysms of severe, knifelike pain usually last 15–30 min and are associated with diaphoresis and tachypnea. Fever peaks within an hour after the onset of paroxysms and subsides when pain resolves. The involved muscles are tender to palpation, and a pleural rub may be detected. The white blood cell count and chest x-ray are usually normal.

Enterovirus infection is the leading cause of ***exanthems*** in children. Rashes may be discrete (rubelliform) or confluent (morbilliform), beginning on the face and spreading to the trunk and extremities. A variety of other rashes have been associated with enteroviruses, including erythema multiforme and vesicular, roseolar, urticarial, petechial, or purpuric lesions.

Hand-foot-and-mouth disease (HFMD) present with fever, anorexia, and malaise; which are followed by the development of sore throat and vesicles on the buccal mucosa and often on the tongue and then by the appearance of tender vesicular lesions on the dorsum of the hands, sometimes with involvement of the palms. The vesicles may form bullae and quickly ulcerate. About one-third of patients also have lesions on the palate, uvula, or tonsillar pillars, and one-third have a rash on the feet (including the soles) or on the buttocks. The lesions usually resolve in 1 week.

Herpangina (enteroviral vesicular pharyngitis) presents as acute-onset fever, sore throat, dysphagia, and grayish-white papulovesicular lesions on an erythematous base that ulcerate. The lesions (usually 3–10) are present on the soft palate, anterior pillars of the tonsils, and uvula; and are concentrated in the posterior portion of the mouth. There are no exudates present.

Other manifestations of enteroviral infection include: acute haemorrhagic conjunctivitis, myocarditis/pericarditis, pneumonia, neonatal sepsis, and chronic meningoencephalitis in agammaglobulinemic and other immunocompromised patients.

Diagnosis. Diagnosis of herpangina and HFMD is clinical.

Isolation of enterovirus in cell culture is the traditional diagnostic procedure. A presumptive diagnosis of enteroviral infection can usually be reported by the laboratory within 2 to 5 days by identification of a characteristic cytopathic effect. The virus can be identified from respiratory secretions, skin lesions, stool, cerebrospinal fluid, pericardial fluid, or blood, depending on the clinical syndrome.

Serologic diagnosis of enterovirus infection is limited by the large number of serotypes and the lack of a common antigen. Demonstration of seroconversion may be useful. Serum should be collected and frozen soon after the onset of disease and again ~4 weeks later. Measurement of neutralizing titers is the most accurate method for antibody determination.

PCR tests are available.

Treatment. Most enterovirus infections are self-limited and do not require antiviral therapy. Exceptions include encephalitis, acute myocarditis, and infections in neonates and immunocompromised hosts that may be lifethreatening. The therapeutic options for these more serious infections include intravenous immune globulin and pleconaril (has not been licensed in the most countries). Desintoxication and supportive management (e. g. soft food for patients with mouth ulcers, antipyretics, etc.) is indicated in the vast majority of cases. Dehydration is used in cases with central nervous system involvement. Glucocorticoids are contraindicated.

In pleurodynia treatment includes the administration of nonsteroidal anti-inflammatory agents or the application of heat to the affected muscles.

Prevention. Preventive measures are directed to prevent continued faeco-oral, contact, or airborne spread (good hand-washing practices, individual towels, masks, isolation, etc.). Enteric precautions are indicated for 7 days after the onset of enterovirus infections.

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AMOEBIASIS

Amebiasis is a protozoal infection caused by *Entamoeba histolytica*. About 90 % of infections are asymptomatic, and the remaining 10 % produce a spectrum of clinical syndromes ranging from dysentery to abscesses of the liver or other organs.

Etiology and epidemiology. *E. histolytica* is one of several *Entamoeba* species that infect man. Other species are non-pathogenic and include *E. dispar*, *E. hartmani* and *E. coli*. The organism exists in two forms: the trophozoite (10–60 μm) and the cyst (5–20 μm).

About 10 % of the world's population is infected with *Entamoeba*, the majority with noninvasive *Entamoeba dispar*. Prevalence ranges from < 5 % in developed countries to 20–30 % in the tropics. Disease is seen at all ages and both sexes are equally affected.

E. histolytica is acquired by ingestion of viable cysts from fecally contaminated water, food, or hands.

Pathogenesis and life cycle. Ingestion of the cysts results in excystation in the small bowel. Trophozoites are formed which infect the colon and results in symptoms. During unfavorable conditions, the trophozoite encysts and cyst form is passed out in feces.

Most people infected with *E. histolytica* have no significant invasion of the colonic mucosa and are asymptomatic (cyst passers). Patients with colonic invasion have flask-shaped colonic ulcers. The pathogenesis of invasive amoebiasis requires adherence of trophozoites, direct cytolytic and proteolytic effects that damage tissue, and resistance of the parasite to host immune response.

Clinical features. The clinical features of amoebiasis can be divided into intestinal and extraintestinal forms.

Intestinal amoebiasis includes asymptomatic infection and symptomatic intestinal infection. Symptomatic amebic colitis develops 2–6 weeks after the ingestion of infectious cysts. A gradual onset of lower abdominal pain and mild diarrhea is followed by malaise, weight loss, and diffuse lower abdominal or back pain. Patients with full-blown dysentery may pass 10–12 stools per day. The stools contain little fecal material and consist mainly of blood and mucus. In contrast to those with bacterial diarrhea, fewer than 40 % of patients with amebic dysentery are febrile.

More fulminant intestinal infection, with severe abdominal pain, high fever, and profuse diarrhea, is rare and occurs predominantly in children. These patients may develop toxic megacolon. Uncommonly, patients develop a chronic form of amebic colitis, or amoeboma (annular lesion of the colon).

Extraintestinal amoebiasis includes hematogenous amoebic abscesses (liver, lungs, brain, etc.), and/or genitourinary disease.

Extraintestinal infection by *E. histolytica* most often involves the liver. Most patients are febrile and have right-upper-quadrant pain, which may be dull or pleuritic in nature and may radiate to the shoulder. Point tenderness over the liver and right-sided pleural effusion are common. Jaundice is rare.

The genitourinary tract may become involved by direct extension of amebiasis from the colon or by hematogenous spread of the infection. Painful genital ulcers, characterized by a punched-out appearance and profuse discharge, develop.

Symptoms and prognosis of extraintestinal abscesses depend on the size and location of the lesion.

Diagnosis and differential diagnosis. Stool microscopy remains the cornerstone of diagnosis but multiple specimens may need to be examined due to poor sensitivity. The definitive diagnosis of amebic colitis is made by the demonstration of hematophagous trophozoites of *E. histolytica*.

Colonoscopy and biopsy may be helpful in confirming the diagnosis in patient with colitis. Endoscopic features include punctuate hemorrhages and flask-shaped ulcers.

Serology is an important addition to the methods used for parasitologic diagnosis of invasive amoebiasis. Enzyme-linked immunosorbent assays (ELISAs) and agar gel diffusion assays are positive in more than 90 % of patients with symptomatic amoebiasis. Positive results in conjunction with the appropriate clinical syndrome suggest active disease because serologic findings usually revert to negative within 6–12 months. The interpretation of the indirect hemagglutination test is more difficult because titers may remain positive for as long as 10 years.

ELISA and PCR-based assays can be used to find amoebic antigen in feces.

Imaging studies (ultrasound, CT, MRI) are useful in patients with extraintestinal amoebic abscesses. Aspiration of the abscess yields a brown, odorless, sterile liquid, which may show trophozoites.

Differential diagnosis includes ulcerative colitis, carcinoma of the colon, Crohn's disease, diverticulitis, abdominal abscesses, irritable bowel syndrome, pyogenic abscesses, hepatoma, echinococcal liver cyst.

Treatment. The treatment of amoebiasis is complicated by a variety of clinical syndromes, varying sites of action of different drugs, and the availability of different drugs in different countries.

Intestinal amoebiasis should be treated with metronidazole 750 mg tid for 10 days or tinidazole 1 g bid for 3 days, followed by either of the following: iodoquinol for 20 days or paromomycin for 7 days.

Extraintestinal amoebiasis should be treated by metronidazole 750 mg tid for 10 days followed by iodoquinol for 20 days. In severely ill patients, emetine or dehydroemetine (less toxic one) may be added for the first few days.

For a large abscesses (> 3 cm), aspiration and needle drainage is indicated. Smaller abscesses resolve with medical treatment.

Asymptomatic disease (intra-luminal carriage) should also be treated by paromomycin, diloxanide furoate, or iodoquinol due to the risk of invasive disease.

Prevention. Avoid ingestion of contaminated water and food. In endemic areas boiling of water is necessary for its decontamination. Vegetables should be washed well with potable water or be treated with detergent and soaked in acetic acid or vinegar. Avoid sexual practices that involve faeco-oral contact.

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BALANTIDIASIS

Balantidiasis is caused by *Balantidium coli* — a large ciliated protozoal parasite that can produce a spectrum of bowel disease analogous to amebiasis. However, unlike *Entamoeba histolytica*, *B. coli* does not spread haematogenously to other organs.

Epidemiology. The parasite is widely distributed in the world. Most frequent geographical locations are Latin America, Southeast Asia and parts of the Middle East.

Since it infects pigs, cases in humans are more common where pigs are raised. Infective cysts can be transmitted from person to person and through water, but many cases are due to the ingestion of cysts derived from porcine feces in association with slaughtering, with use of pig feces for fertilizer, or with contamination of water supplies by pig feces.

Pathogenesis. Ingested cysts liberate *B. coli* trophozoites, which reside and replicate in the large bowel. They cause mucosal inflammation and ulceration, invading the distal ileal and colonic mucosa. Ulceration may be superficial or involve the full thickness of the bowel, leading to perforation. Invasion may be enhanced by hyaluronidase produced by the parasite.

Clinical features. Up to 80 % of persons carrying the organism are asymptomatic, but some have persisting intermittent diarrhea, and a few develop more fulminant dysentery.

Acute diarrhea with blood and mucus begins abruptly and is associated with nausea, abdominal discomfort in the hypogastrium and marked weight loss. There can be inflammatory changes and ulceration in the proctosigmoid region.

A chronic infection occurs with intermittent diarrhea and infrequent bloody stools.

Diagnosis. The diagnosis is made by microscopic detection of the trophozoite stage in stool or sampled colonic tissue.

Treatment. Tetracycline (500 mg q6h for 10 days) is effective against *B. coli*. Doxycycline, metronidazole, iodoquinol, and paromomycin are the alternatives. Surgery may be required for fulminant disease with perforation or abscess formation.

Prevention. The prevention and control of balantidiasis can be achieved through improvement of personal hygiene and better sanitary conditions.

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TYPHOID FEVER (TYPHUS)

Typhoid fever is a systemic disease characterized by fever and abdominal pain and caused by dissemination of *Salmonella typhi* or *Salmonella paratyphi*.

Epidemiology. In contrast to other Salmonella serotypes, the etiologic agents of enteric fever — *S. typhi* and *S. paratyphi* serotypes A, B, and C — have no known hosts other than humans. Most commonly, food-borne or water-borne transmission results from fecal contamination by ill or asymptomatic chronic carriers. Sexual transmission between male partners has been described. Health care workers occasionally acquire enteric fever after exposure to infected patients or during processing of clinical specimens and cultures. With improvements in food handling and water/sewage treatment, enteric fever has become rare in developed nations. Worldwide, however, there were an estimated 22 million cases of enteric fever, with 200,000 deaths annually. The incidence is highest (> 100 cases per 100,000 population per year) in south-central and Southeast Asia; medium (10–100 cases per 100,000) in the rest of Asia, Africa, Latin America, and Oceania (excluding Australia and New Zealand); and low in other parts of the world. A high incidence of enteric fever is correlated with poor sanitation and lack of access to clean drinking water. In endemic regions, enteric fever is more common in urban than rural areas and among young children and adolescents. Risk factors include contaminated water or ice, flooding, food and drinks purchased from street vendors, raw fruits and vegetables grown in fields fertilized with sewage, ill household contacts, lack of hand washing and toilet access, and evidence of prior *Helicobacter pylori* infection (an association probably related to chronically reduced gastric acidity). It is estimated that there is one case of paratyphoid fever for every four cases of typhoid fever, but the incidence of infection associated with *S. paratyphi* A appears to be increasing, especially in India.

Multidrug-resistant (MDR) strains of *S. typhi* emerged in 1989 in China and Southeast Asia and have since disseminated widely. These strains contain plasmids encoding resistance to chloramphenicol, ampicillin, and trimethoprim — antibiotics long used to treat enteric fever. With the increased use of

fluoroquinolones to treat MDR enteric fever, strains of *S. typhi* and *S. paratyphi* with reduced susceptibility to ciprofloxacin have emerged in India and Vietnam and have been associated with clinical treatment failure. Testing of isolates for resistance to the first-generation quinolone nalidixic acid detects most but not all strains with reduced susceptibility to ciprofloxacin. The incidence of enteric fever among U.S. travelers is estimated at 3–30 cases per 100,000. Of 1393 cases reported to the Centers for Disease Control and Prevention (CDC) in 1994–1999, 74 % were associated with recent international travel, most commonly to India (30 %), Pakistan (13 %), Mexico (12 %), Bangladesh (8 %), the Philippines (8 %), and Haiti (5 %). Likewise, of 356 cases reported in the United States in 2003, 74 % occurred in persons who reported international travel during the preceding 6 weeks. Only 4 % of travelers diagnosed with enteric fever gave a history of *S. typhi* vaccination within the previous 5 years.

Clinical features. Although fever is documented at presentation in > 75 % of cases, abdominal pain is reported in only 30–40 %.Thus a high index of suspicion for this potentially fatal systemic illness is necessary when a person presents with fever and a history of recent travel to a developing country.

The incubation period for *S. typhi* averages 10–14 days but ranges from 3 to 21 days, with the duration likely reflecting the inoculum size and the host's health and immune status. The most prominent symptom is prolonged fever (38.8–40.5 °C), which can continue for up to 4 weeks if untreated. *S. paratyphi* A is thought to cause milder disease than *S. typhi*, with predominantly gastrointestinal symptoms. However, a prospective study of 669 consecutive cases of enteric fever in Kathmandu, Nepal, found that the infections were clinically indistinguishable. In this series, symptoms reported on initial medical evaluation included headache (80 %), chills (35–45 %), cough (30 %), sweating (20–25 %), myalgias (20 %), malaise (10 %), and arthralgia (2–4 %). Gastrointestinal symptoms included anorexia (55 %), abdominal pain (30–40 %), nausea (18–24 %), vomiting (18 %), and diarrhea (22–28 %) more commonly than constipation (13–16 %). Physical findings included coated tongue (51–56 %), splenomegaly (5–6 %), and abdominal tenderness (4–5 %).

Early physical findings of enteric fever include rash ("rose spots"), hepatosplenomegaly (3–6 %), epistaxis, and relative bradycardia at the peak of high fever. Rose spots make up a faint, salmon-colored, blanching, maculopapular rash located primarily on the trunk and chest. The rash is evident in ~30 % of patients at the end of the first week and resolves without a trace after 2–5 days. Patients can have two or three crops of lesions, and Salmonella can be cultured from punch biopsies of these lesions. The faintness of the rash makes it difficult to detect in highly pigmented patients.

The development of severe disease (which occurs in ~10–15 % of patients) depends on host factors (immunosuppression, antacid therapy, previous exposure, and vaccination), strain virulence and inoculum, and choice of

antibiotic therapy. Gastrointestinal bleeding (10–20 %) and intestinal perforation (1–3 %) most commonly occur in the third and fourth weeks of illness and result from hyperplasia, ulceration, and necrosis of the ileocecal Peyer's patches at the initial site of Salmonella infiltration. Both complications are life-threatening and require immediate fluid resuscitation and surgical intervention, with broadened antibiotic coverage for polymicrobial peritonitis and treatment of gastrointestinal hemorrhages, including bowel resection. Neurologic manifestations occur in 2–40 % of patients and include meningitis, Guillain–Barre syndrome, neuritis, and neuropsychiatric symptoms (described as "muttering delirium" or "coma vigil"), with picking at bedclothes or imaginary objects.

Rare complications whose incidences are reduced by prompt antibiotic treatment include disseminated intravascular coagulation, hematophagocytic syndrome, pancreatitis, hepatic and splenic abscesses and granulomas, endocarditis, pericarditis, myocarditis, orchitis, hepatitis, glomerulonephritis, pyelonephritis and hemolytic uremic syndrome, severe pneumonia, arthritis, osteomyelitis, and parotitis. Up to 10 % of patients develop mild relapse, usually within 2–3 weeks of fever resolution and in association with the same strain type and susceptibility profile. Up to 10 % of untreated patients with typhoid fever excrete *S. typhi* in the feces for up to 3 months, and 1–4 % develop chronic asymptomatic carriage, shedding *S. typhi* in either urine or stool for > 1 year. Chronic carriage is more common among women, infants, and persons with biliary abnormalities or concurrent bladder infection with *Schistosoma haematobium*. The anatomic abnormalities associated with the latter conditions presumably allow prolonged colonization.

Diagnosis. Since the clinical presentation of enteric fever is relatively nonspecific, the diagnosis needs to be considered in any febrile traveler returning from a developing country, especially the Indian subcontinent, the Philippines, or Latin America. Other diagnoses that should be considered in these travelers include malaria, hepatitis, bacterial enteritis, dengue fever, rickettsial infections, leptospirosis, amebic liver abscesses, and acute HIV infection. Other than a positive culture, no specific laboratory test is diagnostic for enteric fever.

In 15–25 % of cases, leucopenia and neutropenia are detectable. Leukocytosis is more common among children, during the first 10 days of illness, and in cases complicated by intestinal perforation or secondary infection. Other nonspecific laboratory findings include moderately elevated liver function tests and muscle enzyme levels. The definitive diagnosis of enteric fever requires the isolation of *S. typhi* or *S. paratyphi* from blood, bone marrow, other sterile sites, rose spots, stool, or intestinal secretions. The yield of blood cultures is quite variable; sensitivity is as high as 90 % during the first week of infection and decreases to 50 % by the third week. A low yield in infected patients is related to low numbers of salmonellae (< 15 organisms/mL) and/or to recent antibiotic treatment. Unlike blood culture, bone marrow culture remains highly

(90 %) sensitive despite ≤ 5 days of antibiotic therapy. Culture of intestinal secretions (best obtained by a noninvasive duodenal string test) can be positive despite a negative bone marrow culture. If blood, bone marrow, and intestinal secretions are all cultured, the yield is > 90 %. Stool cultures, although negative in 60–70 % of cases during the first week, can become positive during the third week of infection in untreated patients.

Several serologic tests, including the classic Widal's test for "febrile agglutinins," are available. None of these tests are sufficiently sensitive or specific to replace culture-based methods for the diagnosis of enteric fever in developed countries. Polymerase chain reaction and DNA probe assays to detect *S. typhi* in blood are being developed.

Treatment. Prompt administration of appropriate antibiotic therapy prevents severe complications of enteric fever and results in a case-fatality rate of < 1 %. The initial choice of antibiotics depends on the susceptibility of the *S. typhi* and *S. paratyphi* strains in the area of residence or travel (table 2).

For treatment of drug-susceptible typhoid fever, fluoroquinolones are the most effective class of agents, with cure rates of ~98 % and relapse and fecal carriage rates of < 2 %. Experience is most extensive with ciprofloxacin. Short-course ofloxacin therapy is similarly successful against infection caused by nalidixic acid-susceptible strains. However, the increased incidence of nalidixic acid-resistant (NAR) *S. typhi* in Asia, which is probably related to the widespread availability of fluoroquinolones over the counter, is now limiting the use of this drug class for empirical therapy.

Table 2

The initial choice of antibiotics depends on the susceptibility of the *S. typhi* and *S. paratyphi* strains

Empirical Treatment	Ceftriaxone 1–2 g/d (IV) 7–14 Azithromycin 1 g/d (PO) 5
Fully Susceptible	Ciprofloxacin (first line) 500 mg bid (PO) 5–7 or 400 mg q12h (IV) Amoxicillin (second line) 1 g tid (PO) 14 or 2 g q6h (IV) Chloramphenicol 25 mg/kg tid (PO or IV) 14–21 Trimethoprim-sulfamethoxazole 160/800 mg bid (PO) 14
Multidrug-Resistant	Ciprofloxacin 500 mg bid (PO) 5–7 or 400 mg q12h (IV) Ceftriaxone 2–3 g/d (IV) 7–14 Azithromycin 1 g/d (PO) 5
Nalidixic Acid-Resistant	Ceftriaxone 1–2 g/d (IV) 7–14 Azithromycin 1 g/d (PO) 5 High-dose ciprofloxacin 750 mg bid (PO) 10–14 or 400 mg q8h (IV)

Patients infected with NAR *S. typhi* strains should be treated with ceftriaxone, azithromycin, or high-dose ciprofloxacin. However, high-dose fluoroquinolone therapy for NAR enteric fever has been associated with delayed resolution of fever and high rates of fecal carriage during convalescence. Ceftriaxone, cefotaxime, and (oral) cefixime are effective for treatment of MDR

enteric fever, including NAR and fluoroquinolone-resistant strains. These agents clear fever in ~1 week, with failure rates of ~5–10 %, fecal carriage rates of < 3 %, and relapse rates of 3–6 %. Oral azithromycin results in defervescence in 4–6 days, with rates of relapse and convalescent stool carriage of < 3 %.

Despite efficient in vitro killing of *Salmonella*, first- and second-generation cephalosporins as well as aminoglycosides are ineffective in treating clinical infections. Patients with persistent vomiting, diarrhea, and/or abdominal distension should be hospitalized and given supportive therapy as well as a parenteral third-generation cephalosporin or fluoroquinolone, depending on the susceptibility profile. Therapy should be administered for at least 10 days or for 5 days after fever resolution.

Severe enteric fever remains one of the few indications for glucocorticoid treatment of an acute bacterial infection. The 1–5 % of patients who develop chronic carriage of *Salmonella* can be treated for 4–6 weeks with an appropriate oral antibiotic. Treatment with oral amoxicillin, trimethoprim-sulfamethoxazole (TMP-SMX), ciprofloxacin, or norfloxacin is ~80 % effective in eradicating chronic carriage of susceptible organisms. However, in cases of anatomic abnormality (e. g., biliary or kidney stones), eradication often requires both antibiotic therapy and surgical correction.

Prevention. Theoretically, it is possible to eliminate the salmonellae that cause enteric fever since they survive only in human hosts and are spread by contaminated food and water. However, given the high prevalence of the disease in developing countries that lack adequate sewage disposal and water treatment, this goal is currently unrealistic. Thus travelers to developing countries should be advised to monitor their food and water intake carefully and to consider vaccination.

Two typhoid vaccines are commercially available:

1) Ty21a, an oral live attenuated *S. typhi* vaccine (given on days 1, 3, 5, and 7, with a booster every 5 years);

2) Vi CPS, a parenteral vaccine consisting of purified Vi polysaccharide from the bacterial capsule (given in one dose, with a booster every 2 years).

The old parenteral whole-cell typhoid/paratyphoid A and B vaccine is no longer licensed, largely because of significant side effects.

The minimal age for vaccination is 6 years for Ty21a and 2 years for Vi CPS. Currently, there is no licensed vaccine for paratyphoid fever.

A large-scale meta-analysis of vaccine trials comparing whole-cell vaccine, Ty21a, and Vi CPS in populations in endemic areas indicates that, although all three vaccines are similarly effective for the first year, the 3-year cumulative efficacy of the whole-cell vaccine (73 %) exceeds that of both Ty21a (51 %) and Vi CPS (55 %).

Although data on typhoid vaccines in travelers are limited, some evidence suggests that efficacy rates may be substantially lower than those for local popu-

lations in endemic areas. Both the CDC and the World Health Organization recommend typhoid vaccination for travelers to typhoid-endemic countries. Recent analyses from the CDC found that 16 % of travel-associated cases occurred among persons who stayed at their travel destination for ≤ 2 weeks.

Thus vaccination should be strongly considered even for persons planning short term travel to high-risk areas such as the Indian subcontinent.

In addition, since 1–4 % of patients with *S. typhi* infection become chronic carriers, it is important to monitor patients (especially childcare providers and food handlers) for chronic carriage and to treat this condition if indicated.

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HEPATITIS A

Definition. Hepatitis A virus (HAV) is an acute, most often self-limiting viral illness characterized as hepatitis and jaundice. HAV can sometimes be a fulminant illness.

Epidemiology:

1. Most common cause of acute viral hepatitis.
2. More likely to occur in patients age 5 to 14 years.
3. More likely to occur in Central and South America, Africa, India, the Middle East, and parts of Asia (lowest in the United States and Japan).

Risk Factors. Most commonly transmitted by oral-fecal route; however, no identified source occurs in approximately 50 % of cases.

1. Household or sexual contact (especially men who have sex with men).
2. Foreign travelers (particularly those to developing nations).
3. Contaminated food or water (particularly associated with green onions and strawberries).
4. Consumption of shellfish from contaminated water.
5. Daycare children and daycare workers.
6. Blood transfusion or blood products are very rarely associated with HAV.
7. Injection and noninjection drug use.

Microbiology. RNA picornavirus; *Hepatovirus* genus. Nonenveloped virus (a lack of a lipid envelope confers resistance to bile lysis in the small intestine and liver). Four genotypes and one serotype.

The coding region of the genome codes for 4 structural proteins and 7 nonstructural proteins.

The virus replicates through a RNA-dependent polymerase in hepatocytes and gastrointestinal epithelial cells.

Lifecycle of HAV:

1. Oral inoculation of fecally excreted virus.

2. Transportation across gastrointestinal epithelium to mesenteric veins of liver (viremia).

3. Taken up by hepatocytes, replicates, and shed into the bile canaliculi.

4. Transported to the intestine and excreted into the feces.

Clinical features of HAV.

Classic HAV. Acute onset of illness following an incubation period of approximately 1 month. The illness is typically self-limited (approximately 8 weeks) and consists of two phases:

1. Preicteric phase. Characterized by fever, malaise, and fatigue (influenzalike) and nausea, emesis, and diarrhea approximately 1 week prior to the appearance of dark urine.

2. Icteric phase. Characterized by jaundice and pale-colored stool. This phase is associated with hepatocyte injury (elevated aminotransferases) and eventual HAV clearance through cell-mediated and antibody-mediated processes. Commonly associated with hepatomegaly and splenomegaly.

Fulminant HAV. Characterized by worsening jaundice and development of encephalopathy. This form of HAV infection is rare but more common with the elderly (age greater than 49) and patients with chronic HBV and HCV.

Relapsing HAV. Uncommon, but characterized by recurrent HAV infection with a symptom-free interval.

Cholestasis HAV. Uncommon, but characterized as a prolonged course of HAV infection (over months) associated with fever, jaundice, and pruritus.

Patients may present clinically similar to acute acalculous cholecystitis.

Approach to the patient.

History. While the majority of adults are symptomatic, historical findings may be nonspecific. A complete history should be performed to review risk factors for HAV as well as for consideration of other causes of jaundice and hepatitis:

1. Autoimmune hepatitis/Systemic lupus erythematosus.

2. Alcohol hepatitis.

3. Medications: acetaminophen, isoniazid, rifampin, sulfonamides, and oral contraceptives.

4. Bacterial infections: syphilis, typhoid, Rocky Mountain spotted fever, Q fever, and leptospirosis.

5. Parasite infections: liver flukes.

6. Cholecystitis/choledocholithiasis.

7. Metastatic disease (e. g., colon cancer, pancreatic cancer).

8. Viral infections: CMV, EBV, HBV, HCV, VZV, HSV.

Physical examination. A complete physical examination should be performed, but areas to focus attention include:

1. Ophthalmic examination (to detect jaundice).

2. Neurologic examination (to evaluate mental status for signs of encephalopathy and asterixis).

3. Abdomen examination (to detect tender hepatomegaly and splenomegaly common in icteric phase of HAV).

4. Lymphatic examination (postcervical lymphadenopathy is occasionally observed in the icteric phase of HAV).

5. Dermatologic examination (to detect vasculitis as rarely can HAV be associated with cryoglobulinemia).

Laboratory studies.

1. Serum anti-HAV IgM and IgG. The preferred confirmatory test for HAV:

– Anti-HAV IgM. Detected 1 to 2 weeks after HAV exposure and remains elevated for 3 to 6 months;

– Anti-HAV IgG. Detected 5 to 6 weeks after HAV exposure, remains elevated lifelong, and confers protective immunity against HAV.

2. CBC (Complete blood count). Routinely ordered on hospitalized patients but nonspecific.

3. PT/PTT (Partial Thromboplastin Time). A prolonged PTT may reflect extensive liver necrosis and/or need for liver transplantations (especially if PTT is greater than or equal to 25 seconds).

4. LFT (Liver function tests). ALT and AST may be as high as 3100 ULN, alkaline phosphatase is only minimally elevated, and total bilirubin is rarely greater than 10 ng/dL. (Total bilirubin greater than or equal to10 ng/dL may suggest cholestasis HAV). ANA, ANCA, RPR and serum antibodies to typhoid, RMSF (Rocky Mountain spotted fever), Q fever, and leptospirosis may be helpful in cases mimicking HAV infection with abnormal LFTs.

5. Blood cultures are not recommended routinely. Cultures may be helpful in cases with a fever and a concern for cholecystitis or choledocholithiasis.

Radiographic Studies. A transabdominal US or CT scan may be helpful to demonstrate hepatomegaly and splenomegaly in association with HAV infection (common in icteric phase of HAV) but usually reserved to evaluate cases with concerns for cholelithiasis and choledocholithiasis.

Treatment. Virus-specific therapy is not available for HAV; therefore, treatment is mainly supportive measures, avoidance of hepatic toxins (less than 2 g/day acetaminophen), and alcohol, vaccination, and prevention. Indication for evaluation for liver transplantation includes:

1. Fulminant HAV.

2. Jaundice lasting more than 7 days before encephalopathy (indicating extensive liver necrosis). 3. Serum bilirubin greater than or equal to 17 mg/dL.

Prevention. Vaccination of high-risk patients, and postexposure prophylaxis.

Hand hygiene is most important for preventing transmission. Since the virus can survive as fomites and resist freezing, detergents, and acids. Environmental control of surfaces should include inactivation of HAV by formalin and/or chlorine.

Passive Immunization: immune globulin.

1. Provides short-term protection through passive antibody transfer. When used as preexposure prophylaxis (i. e., travelers):

– a single IM dose of 0.02 mL/kg protects for less than 3 months;

– a single IM dose of 0.06 mL/kg protects for 3 to 5 months

When used as postexposure prophylaxis within 2 weeks of exposure, a single IM dose of 0.02 mL/kg is 80 % to 90 % effective in preventing HAV.

2. Not contraindicated during pregnancy or lactation.

3. Consists of pooled plasma with anti-HAV (plasma is negative for HIV and treated to inactivate other viruses).

4. Do not give within 2 to 3 weeks following administration of live, attenuated vaccines (decreases immunogenicity of vaccine).

5. Wait 3 months for measles-mumps-rubella (MMR) vaccine administration following immunoglobulin administration and 5 months for varicella vaccine administration following immunoglobulin administration.

6. Immunoglobulin is recommended for:

– persons with a recent HAV exposure (less than 2 weeks) and no history of HAV vaccine; a single dose of immunoglobulin at 0.02 mL/kg. HAV vaccine can be administered at the same time but in a separate anatomic location;

– unvaccinated persons with regular household or sexual contact of individuals with serologically confirmed HAV;

– unvaccinated staff and attendees of child daycare centers or homes with greater than one case are identified in children or employees. During an outbreak (defined as cases involving 3 or more familes) IG should also be administered to unvaccinated household members of children in day care that wear diapers;

– for individuals age greater than 40 years, IG is preferred because of the absence of information regarding vaccine performance in this age group and because of the more severe manifestations of HAV A in older adults. Vaccine can be used if IG cannot be obtained. The magnitude of the risk of HAV transmission from the exposure should be considered in decisions to use vaccine or IG in this age group;

– for children aged less than 12 months, immunocompromised persons, persons with chronic liver disease, and persons who are allergic to the vaccine or a vaccine component, IG should be used.

Active Immunization: vaccination.

Two licensed vaccines, Havrix and Vaqta, are derived from formalin inactivated cell-cultured-propagated HAV. HAV vaccine also exists in combination with HBV vaccine (Twinrix). Usually provided as 2 intramuscular injections given 6 months apart.

Vaccination is recommended for the following:

– persons working or travel to high-risk areas;
– men who have sex with men;
– drug use history (injection or noninjection);
– history of chronic HBV and HCV (increased risk of fulminant HAV);
– HAV research laboratory workers;
– children (all children age 12 to 23 months as routine vaccination).

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HEPATITIS B

Definition. Hepatitis B virus (HBV) is either an acute, self-limited or chronic infection that can be characterized by hepatitis and jaundice. HBV can also be a fulminant illness in less than 1 % of cases.

Epidemiology. The prevalence of HBV is higher in Southeast Asia, Pacific Basin (i. e., Japan, Australia, and New Zealand), Sub-Saharan Africa, the Amazon Basin, the Middle East, and Eastern Europe where infection is more commonly obtained by perinatal transmission (mother-to-child at birth or during infancy).

Risk factors. Most commonly transmitted by sexual contact as well as percutaneous injuries or needle puncture, and perinatal (mother-to-child at birth or during infancy).

1. Injection drug use.
2. Health care workers.
3. Sexual or household contact with HBV positive person (HBsAg positive).
4. Men who have sex with men.
5. Blood or blood product transfusion.
6. Infants born to HBV-positive mothers (HBsAg positive).
7. HIV infection.
8. Comorbid illnesses needing chemotherapy or immunosuppression treatment (these are more commonly associated with reactivation of HBV rather than as a risk to acquire the virus).
9. Travel to high-risk areas.
10. People born in Asia, Africa, and other regions with moderate or high rates of Hepatitis B.

11. Unvaccinated people whose parents are from regions with high rates of HBV.

12. Hemodialysis.

Microbiology. DNA virus; *Hepadnavirus*. Covalently closed circular DNA with four reading frames:

1. Presurface-surface. Codes three surface antigens:

– HBsAg — most commonly tested for infection;

– M protein — unknown function;

– L protein — important for host cell binding and virion assembly/release.

2. Precore core. Codes two main antigens:

– HBcAg — commonly used in serology;

– HBeAg — a marker for viral replication but has no direct role for replication or assembly.

3. P coding region. Codes for viral polymerase.

4. X coding region. Involved with host cell signal transduction and required for replication and spread of virus.

The cardinal feature of viral replication is by reverse transcription (similar to HIV).

Eight different genotypes (A–H).

Double-shelled virus with an outer lipoprotein envelope (susceptible to bile acid lysis).

HBV predominantly infects liver cells and lymphocytes.

Viral life cycle and pathogenesis

Primary HBV infection. More commonly is an asymptomatic, self-limited illness that is not directly cytotoxic to cells.

1. HBV is transmitted in blood and secretions to primarily infect liver cells.

2. HBsAg becomes detected in the blood following a 4- to 10-week incubation period. Viremia is established during this period of detection. Patients are infectious.

3. HBcAg and anti-HBc IgM then begin to appear in the blood.

4. HBeAg usually becomes detectable. Some patients may be HBeAg negative due to gene mutations that either reduce or eliminate production of the antigen.

5. HBV replication is not directly cytotoxic to liver cells, but liver injury and symptoms are related to both the antiviral cytotoxic T-cell response and cytokines (eg, tumor-necrosis factor).

6. In most cases involving adults, inflammatory cytokines (e. g., interferongamma and tumor necrosis factor [TNF]-alpha) and an immunological response result in the disappearance of HBsAg, HBcAg, and HBeAg, and the presence of anti-HBs (HBsAb) indicates recovery and immunity. However, low levels of HBV-DNA may remain detectable but are not considered infectious. In cases of acquisition during infancy, most cases (up to 95 %) will not clear the virus and become a chronic infection.

Persistent (chronic) HBV infection. In some patients the primary infection does not resolve (5 %).

1. Characterized by persistent circulating HBsAg greater than or equal to 6 months. Antibodies to HBsAg are still produced but are undetected due to excess HBsAg in persistent infection.

2. HBeAg is detectable in some cases (except HBeAg-negative patients) but may disappear with the development of anti-HBe antibodies. The detection of HBeAg in the blood usually indicates high viral replication and viremia (patients are highly infectious). While anti-HBe antibodies suggest lower infectivity and reduced viral replication, low levels of HBV-DNA might remain detectable.

3. Persistent infection may be classified as:

– Asymptomatic chronic HBV carriers. Patients have normal LFTs and liver biopsy.

HBeAg-negative carriers have a good prognosis.

HBeAg-positive carriers with or without anti-HBe antibodies have a high risk of hepatocellular carcinoma.

– Symptomatic chronic HBV infection. Patients have abnormal LFTs and liver biopsy with the risk of progression to cirrhosis (estimated to be 20 % in 5 years) and/or hepatocellular cancer.

Clinical features of HBV infection.

Acute HBV Infection. Usually lasts 2 to 4 months.

Symptoms. Typically nonspecific and include fatigue, anorexia (poor appetite), nausea, emesis, generalized or right upper quadrant abdominal pain, fever, jaundice, and dark urine (due to elevated urobilirubin).

Signs. Most commonly involve right upper quadrant tenderness (liver tenderness), hepatomegaly, splenomegaly, scleral icterus.

Chronic HBV infection. Most patients remain asymptomatic but might develop signs or symptoms related to hepatic cirrhosis. These include: fatigue, weakness, anorexia, gynecomastia, palmar erythema, renal insufficiency, thrombocytopenia, anemia, and coagulopathy.

Extrahepatic HBV manifestations:

1. Polyarteritis nodosa. Small-vessel vasculitis characterized by neuropathy, dermatologic ulcers, fevers, hypertension, and abdominal pain.

2. Glomerulonephritis. Most commonly membranous glomerulonephritis characterized by hematuria and proteinuria.

Approach to the patient.

History. Adults are symptomatic in 30 % to 50 % of cases (children are rarely symptomatic); therefore, HBV should be included in the differential diagnosis of patients being evaluated for abdominal pain, fever, and jaundice (immunosuppressed patients or elderly may be asymptomatic). The history should focus on HBV risk factors and consideration for other etiologies.

Physical examination. A complete physical examination should be performed, but areas to focus attention include:

1. Ophthalmologic examination (to detect jaundice).

2. Neurologic examination (to detect asterixis and other signs of encephalopathy).

3. Abdomen examination (to detect hepatomegaly and splenomegaly).

Laboratory studies.

1. The diagnosis of HBV usually involves the evaluation of HBsAg, HBsAb, HBcAb, and HBeAg/HBeAb. Tests should be performed with acute infection and 6 months following acute infection. Interpretation is presented within the table 3.

Table 3

HBV serological markers interpretation

HBsAg	HBcAB	HBsAB	Status
–	–	–	Susceptible
–	–	+	Vaccinated
–	+	+	Natural infection but patient immune
+	+	–	Acute (if ≤ 6 months) or chronic (if ≥ 6 months); HBcAB IgM is also considered an indicator of acute infection.

2. HBV DNA. Values vary based on clinical status and are more useful in chronic HBV treatment plans.

3. Liver biopsy. Important for therapy with chronic HBV.

4. CBC. Routinely ordered but nonspecific. Anemia and thrombocytopenia may indicate chronic liver disease.

5. Basic Metabolic Panel. Renal insufficiency may be associated with chronic liver disease.

6. Liver function tests. Aminotransferase levels might be elevated but vary with status. In general, ALT greater than AST greater than Alkaline phosphatase. Albumin level may be low with chronic liver disease.

7. Prothrombin time/Partial thromboplastin time. Prolonged in chronic liver disease or cirrhosis.

8. Serum alpha-fetoprotein. Marker of hepatocellular cancer (HCC) usually performed one to two times per year in those individuals at high risk for HCC. The following patients should be screened for HCC:

– asian males greater than 40 years;
– asian females greater than 50 years;
– all cirrhotic hepatitis B carriers;
– family history of HCC.

For noncirrhotic hepatitis B carriers not listed above, the risk of HCC varies depending on the severity of the underlying liver disease, and current and past hepatic inflammatory activity. Patients with high HBV DNA concentrations and those with ongoing hepatic inflammatory activity also remain at risk for HCC.

9. Blood cultures. Not recommended routinely.

Radiographic studies. A transabdominal US or CT scan may be helpful to demonstrate hepatomegaly and splenomegaly in acute infection as well as demonstrate cirrhosis or screen for hepatocellular carcinoma in chronic infection.

Treatment.

Goals of therapy:

1. Reduction of viremia. Despite either self-limited HBV infection or seroconversion with treatment of chronic HBV, circulating viral DNA persists at low levels.

2. Reduction of hepatic dysfunction. Normalization of aminotransferase levels (Alanine transaminase (ALT)) are most commonly used for evaluation.

3. Successful therapy is defined as reduction or normalization of ALT, loss of circulating HBeAg, seroconversion to anti-HBe, and reduction of circulating viral DNA (less than 10–100).

4. Cure of HBV is rare but defined as complete resolution of HBV circulating viral DNA, HBsAg clearance, and HBsAb seroconversion; however, HBV DNA persist in hepatocytes.

Predictors for the response to HBV therapy:

1. Elevated ALT level.
2. Low HBV DNA level.
3. Mild-to-moderate histology grading on liver biopsy.
4. Serotype (genotypes B and C are more likely to be associated with spontaneous resolution; genotype A treated with pegylated interferon is more likely to result in seroconversion).
5. Certain oral therapies are more likely to be associated with resistance in the YMDD motif of DNA polymerase domain C (lamivudine, telbivudine, and adefovir). Adefovir resistance is associated with B and D domain mutations. Resistance to lamivudine is sufficiently high to limit clinical utility in some cases.

Indications for therapy.

The indications for treatment are generally the same for both HBeAg-positive and HBeAg-negative CHB. This is based mainly on the combination of three criteria:

– Serum HBV DNA levels.
– Serum ALT levels.
– Severity of liver disease.

Patients should be considered for treatment when they have HBV DNA levels above 2000 IU/ml, serum ALT levels above the upper limit of normal (ULN) and severity of liver disease assessed by liver biopsy (or non-invasive markers once validated in HBV infected patients) showing moderate to severe active necroinflammation and/or at least moderate fibrosis using a standardized scoring system.

In patients who fulfil the above criteria for HBV DNA and histological severity of liver disease, treatment may be initiated even if ALT levels are normal.

Indications for treatment may also take into account age, health status, family history of HCC or cirrhosis and extrahepatic manifestations.

The need for liver biopsy and treatment should be considered separately in the following subgroups of patients:

– Immunotolerant patients: HBeAg-positive patients under 30 years of age with persistently normal ALT levels and a high HBV DNA level, without any evidence of liver disease and without a family history of HCC or cirrhosis, do not require immediate liver biopsy or therapy. Follow-up at least every 3–6 months is mandatory. Consider liver biopsy or even therapy in such patients over 30 years of age and/or with a family history of HCC or cirrhosis.

– HBeAg-negative patients with persistently normal ALT levels (ALT determinations at least every 3 months for at least 1 year) and HBV DNA levels above 2000 but below 20,000 IU/ml, without any evidence of liver disease, do not require immediate liver biopsy or therapy (B1). Close follow-up with ALT determinations every 3 months and HBV DNA every 6–12 months for at least 3 years is mandatory (C1). After 3 years, they should be followed for life like all inactive chronic HBV carriers. Evaluation of the severity of fibrosis by a non-invasive method, such as Fibroscan, might be useful in such cases.

– Patients with obviously active CHB: HBeAg-positive and HBeAg-negative patients with ALT above 2 times ULN and serum HBV DNA above 20,000 IU/ml may start treatment even without a liver biopsy. In such patients, liver biopsy may provide additional useful information, but it does not usually change the decision for treatment. A non-invasive method for the estimation of the extent of fibrosis and most importantly to confirm or rule out cirrhosis is extremely useful in patients who start treatment without liver biopsy.

– Patients with compensated cirrhosis and detectable HBV DNA must be considered for treatment even if ALT levels are normal.

– Patients with decompensated cirrhosis and detectable HBV DNA require urgent antiviral treatment with NA(s). Significant clinical improvement can be associated with control of viral replication. However, antiviral therapy may not be sufficient to rescue some patients with very advanced liver disease who should be considered for liver transplantation at the same time.

Agents for therapy:

1. Pegylated interferon alfa-2a and -2b (alfa-2b mostly in USA). A subcutaneously injected immunomodulating agent that is considered first-line treatment for compensated disease. The usual dose is 180 mcg by subcutaneous injection weekly for 48 weeks.

The benefit of this agent is: no drug resistance, and likelihood of seroconversion (HBV DNA suppression is less profound than oral therapies). Patients with high ALT, genotype A and low-level HBV DNA tend to respond best to interferon therapy. Tenofovir and entecavir are oral therapies that are also options considered as first-line therapies for compensated HBV.

Oral therapies are the only option for treating decompensated HBV liver disease but are in some cases as effective as injectable pegylated interferon in compensated disease and patients who previously have not responded to nonpegylated interferon. Oral therapies are nucleotide or nucleoside analogues that inhibit the reverse transcription from HBV RNA to DNA during the virus replication life cycle. In general, oral therapy requires a longer duration for seroconversion, and all agents need monitoring of serum creatinine and dose adjustment for renal disease.

Available oral therapies include:

2. Lamivudine 100 mg PO q24 hours. Usually well tolerated but is no longer considered first-line therapy due to resistance (up to 70 % after 5 years) in the YMDD (tyrosine (Y)-methionine (M)-aspartic acid (D)-aspartic acid (D)) motif of the HBV DNA polymerase and also may be a reason to change therapy. This agent can be used with HIV coinfection.

3. Adefovir 10 mg PO q24 hours. An effective alternative in lamivudine-resistant HBV but is the least potent and slowest to suppress viral DNA. This agent has HIV activity at higher doses but is limited due to nephrotoxicity.

4. Entecavir 0.5 mg PO q24 hours is generally well tolerated, and the development of resistance is usually not of clinical significance in treatment-naive patients. This agent has some activity for HIV.

5. Tenofovir 300 mg PO q24 hours is generally well tolerated and considered a preferred first-line therapy. Resistance rates have currently not been documented in patients after 6 years of follow-up, and this agent can be used with HIV coinfection.

6. Telbivudine 600 mg PO q24 hours is more commonly associated with elevated creatine kinase (CK) levels and peripheral neuropathy, but resistance is low.

Currently, the combination of HBV therapies with the hope of reducing resistance and improving markers of HBV infection has not shown an increased efficacy in treatment.

Prevention. Infants born to HBsAg-negative mothers should receive vaccine (these vaccines are HBsAg) (Recombivax HB, Energix-B). The second dose should be administered at least 1 month after the first dose. The third dose should be given at least 2 months after the second, but not before the age of 6 months.

Infants born to HBsAg-positive mothers should receive 0.5 mL of hepatitis B immunoglobulin (HBIG) within 12 hours of birth and either vaccine at a separate site. Second dose is recommended at the age of 1–2 months and the third dose at 6 months.

Infants born to mothers whose HBsAg status is unknown should receive either within 12 hours of birth. The second dose of vaccine is recommended at the age of 1 month, and the third dose at 6 months. Blood should be drawn

at the time of delivery to determine the mother's HBsAg status; if it is positive, the infant should receive HBIG as soon as possible (no later than the age of 1 week). Dosage and timing of subsequent vaccine doses should be based on the mother's HBsAg status.

Children and adolescents who have not been vaccinated against hepatitis B in infancy may begin the series with the first opportunity. Those who have not previously received three doses of hepatitis B vaccine should initiate or complete the series during the 11- to 12-year-old visit, and unvaccinated older adolescents should be vaccinated whenever possible. The second dose should be administered at least 1 month after the first dose, and the third dose should be administered at least 4 months after the first dose and at least 2 months after the second dose.

For unvaccinated persons sustaining an exposure to HBV, postexposure prophylaxis with a combination of HBIG and HBV vaccine is recommended.

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HEPATITIS C

Epidemiology. Approximately 3 % of the world population is infected with hepatitis C virus (HCV). While the prevalence is estimated at 1 % in the Belarus, the prevalence in Egypt is estimated at > 20 %. The most common mode of transmission is through contaminated blood.

Risk factors. Persons more likely to be infected with HCV include:

1. IVDU (intravenous drug use).
2. Recipient of blood transfusion or organ transplant prior to 1992.
3. Persons infected with HIV born to HCV-infected mother.
4. Persons with hemophilia receiving clotting factors prior to 1987.
5. Multiple sexual partners and/or divorced or separated.
6. Body piercing, body tattooing, and commercial barbering.
7. Poverty and/or education level less than 12 years.
8. Health care workers.
9. Persons receiving hemodialysis.

Following a needle-stick injury, the likelihood of acquiring a bloodborne infection from an infected host follows the rule of three: 30 % hepatitis B virus, 3 % HCV, and 0.3 % HIV.

Microbiology/virology. RNA virus of the family of *Flaviviridae* (similar to West Nile virus, yellow fever virus, and Dengue virus).

HCV can be divided into six genotypes from PCR sequence analysis of the 5' noncoding region. Determining the genotype is important for treatment and treatment duration. HCV genotype 1 is the most commonly found genotype in the United States and Europe. The HCV genome encodes a single polyprotein that produces both structural proteins and regulatory proteins. A structural protein that encodes the virus envelope, E2 envelope protein, contains a binding site for CD81 on hepatocytes and B-lymphocytes (the primary cells in which the HCV virus replicates). In vivo replication rates of HCV are much greater than HIV or HBV infection.

Clinical features of HCV infection.

Acute infection. Patients are generally asymptomatic, and the infection usually goes undiagnosed at this stage. However, a minority of patients (less than or equal to 20 %) develop symptomatic hepatitis that usually consists of: jaundice, malaise, and/or nausea. Acute infection is defined as less than 6 months duration. Of those acutely infected, 15 % to 25 % may spontaneously clear the infection. Spontaneous clearance of HCV is higher in symptomatic acute infection (presumed secondary to a robust immune response). Fulminant hepatitis/hepatic failure is very rare.

Chronic infection. In the majority of patients the infection becomes chronic with a slow interval development (20–30 years) of hepatic cirrhosis and/or hepatocellular carcinoma (estimated to be 20 % of those with chronic infection). Hepatocellular carcinoma rarely occurs without cirrhosis. Chronic infection is defined as an infection of greater than 6 months duration. The most common manifestation is fatigue but can also be associated with findings of cirrhosis.

1. Anorexia.
2. GI bleeding.
3. Altered mental status (hepatic encephalopathy or asterixis).
4. Jaundice.
5. Palmar erythema and/or spider angiomas.
6. Ascites and splenomegaly.
7. Testicular atrophy or gynecomastia.
8. Dupuytren’s contractures.

Patients with HCV infection can develop diabetes due to insulin resistance.

Extrahepatic manifestations. Most conditions are associated with either an autoimmune or lymphoproliferative disorder in association with chronic hepatic HCV infection.

1. Lymphoproliferative:

– Non-Hodgkin B-cell lymphoma.

2. Autoimmune:

– type II or III cryoglobulinemia and/or vasculitis;
– membranoproliferative glomerulonephritis;
– lichen planus;

– Sicca (Sjogren) syndrome;
– porphyria cutanea tarda.

Approach to the patient.

History. Acute HCV infection is often missed, but infection should be suspected in patients with an elevated alanine aminotransferase (ALT) and exposure risk (see risk factors above).

Chronic infection with HCV should always be included in the differential diagnosis of patients being evaluated for:

1. Abnormal liver chemistry (ALT greater than or equal to AST).
2. Anemia and thrombocytopenia.
3. Findings suggestive of cirrhosis (see Section III.B).

Physical examination. A complete examination should be performed, but areas of specific focus include:

1. Conjunctival examination (to detect jaundice).
2. Vascular examination (to detect signs of vasculitis and lymph node enlargement).
3. Neurologic examination (to detect encephalopathy or asterixis).
4. Abdominal examination (to detect ascites, cirrhosis, or splenomegaly).
5. Dermatological examination (to detect rash or vasculitis).

Laboratory studies:

1. CBC. Patients with chronic HCV may have anemia. Thrombocytopenia usually occurs in patients with hepatic cirrhosis. Pancytopenia is also a complication of combined HCV treatment.
2. BMP. Routinely ordered. Membranoproliferative glomerulonephritis should be suspected if creatinine is elevated.
3. Liver function test. An ALT:AST ratio greater than or equal to 2:1, elevated alkaline phosphatase and bilirubin level as well as a low albumin may suggest HCV. Liver chemistries are unreliable for predicting the severity of hepatic HCV, and normal results cannot rule out HCV-related liver disease or cirrhosis. However, an AST: platelet ratio greater than or equal to 1.5 has a high positive predictive value (88 %) for liver fibrosis calculated as: AST level 3 100/platelet count
4. PT/PTT. An elevated PT may suggest cirrhosis.
5. TSH. HCV therapy can induce an autoimmune thyroiditis; therefore, a baseline TSH may be helpful.
6. Urinalysis. Findings of glomerulonephritis may suggest HCV.
7. Uric acid level. Hyperuricemia can be a complication of HCV treatment; therefore, a baseline uric acid level may be helpful.
8. ESR and CRP. Values are nonspecific but may be elevated with HCV.

Radiographic studies. Transabdominal ultrasound is adequate to evaluate for cirrhosis and splenomegaly as well as ascites.

Diagnosis of acute and chronic hepatitis C.

The diagnosis of acute and chronic HCV infection is based on the detection of HCV RNA by a sensitive molecular method (lower limit of detection < 15 international units [IU]/ml). Anti-HCV antibodies are detectable by enzyme immunoassay (EIA) in the vast majority of patients with HCV infection, but EIA results may be negative in early acute hepatitis C and in profoundly immunosuppressed patients. Following spontaneous or treatment-induced viral clearance, anti-HCV antibodies persist in the absence of HCV RNA but may decline and finally disappear in some individuals.

The diagnosis of acute hepatitis C can be confidently made only if seroconversion to anti-HCV antibodies can be documented, since there is no serological marker which proves that HCV infection is in the de novo acquired acute phase. Not all patients with acute hepatitis C will be anti-HCV positive at diagnosis. In these cases, acute hepatitis C can be suspected if the clinical signs and symptoms are compatible with acute hepatitis C (ALT > 10 times the upper limit of normal, jaundice) in the absence of a history of chronic liver disease or other causes of acute hepatitis, and/or if a likely recent source of transmission is identifiable. In all cases, HCV RNA can be detected during the acute phase although brief periods of undetectable HCV RNA may occur.

The diagnosis of chronic hepatitis C is based on the detection of both HCV antibodies and HCV RNA in the presence of signs of chronic hepatitis, either by elevated aminotransferases or by histological changes of chronic hepatitis C. Since, in the case of a newly acquired HCV infection, spontaneous viral clearance is very rare beyond four to six months of infection, the diagnosis of chronic hepatitis C can be made after that time period.

HCV viral load. Quantification of the viral load is relevant to therapy as a pretreatment viral load less than 800,000 IU/mL is associated with a sustained response to treatment.

HCV viral genotype. Genotyping can help predict the therapy outcome as genotypes 1 and 4 are more resistant to treatment (and require a longer duration) than genotypes 2 and 3.

Thus, HCV-RNA testing should be performed with: 1) a positive anti-HCV, 2) patients considered for treatment, 3) patients with unexplained liver disease or immunosuppression with a negative anti-HCV as PCR is usually positive within 1 to 2 weeks of acute HCV. HCV genotype should be ordered in patients considered for therapy.

Liver biopsy testing. The diagnostic gold standard is to assess the level of liver inflammation and fibrosis. The liver biopsy is a histologic assessment for the grade (defines the extent of necroinflammatory activity) and the stage (establishes the extent of fibrosis or the presence of cirrhosis) in hepatic disease.

Thus, a liver biopsy should be considered in patients with chronic HCV for prognosis or treatment considerations.

Treatment of HCV. The goal of treatment is to prevent complications and death from HCV. Decisions for treatment should be made jointly by patients and clinicians. Factors that need to be considered are current level of liver fibrosis and inflammation, likelihood of continuous fibrosis progression and probability of treatment response, and side effects.

Who should be treated?

All treatment-naive and -experienced patients with compensated disease due to HCV should be considered for therapy.

Treatment should be prioritized for patients with significant fibrosis (METAVIR score F3 to F4).

Treatment is justified in patients with moderate fibrosis (METAVIR score F2).

In patients with no or mild disease (METAVIR score F0-F1), the indication for and timing of therapy can be individualized.

Patients with decompensated cirrhosis who are on the transplant list should be considered for IFN-free, ideally ribavirin-free therapy.

Factors that negatively affect prognosis include: 1) advanced age, 2) obesity (BMI 25), 3) HIV infection, 4) immunosuppression (transplant, corticosteroids), 5) patients who consume 50 g alcohol/day, 6) bridging fibrosis on biopsy, 7) symptomatic cryoglobulinemia.

The current recommended therapy in Belarus for genotypes other than 1 is pegylated interferon alfa-2a or -2b combined with ribavirin. For genotype 1, an HCV protease inhibitor such as boceprevir or telaprevir is added to pegylated interferon alfa and ribavirin.

The most common side effects from treatment include:

1. Pegylated interferon:

– influenza-like illness (fatigue, headache, fever, and rigors);

– neutropenia (ANC less than or equal to 1.5 units), anemia (HBG less than or equal to 10 g/dL), or thrombocytopenia;

– autoimmune thyroiditis;

– anxiety, insomnia, psychosis, suicidal ideation;

– depression (usually respond to SSRI antidepressants).

2. Ribavirin:

– lymphopenia;

– hemolytic anemia;

– hyperuricemia;

– rash.

3. Protease inhibitors:

– anemia;

– leukopenia;

– telaprevir: rash;

– boceprevir: dysgeusia.

Contraindications to therapy include: 1) uncontrolled depression or other neuropsychiatric illness, 2) untreated thyroid disease, 3) pregnancy, 4) age less than or equal to 2, 5) active autoimmune disease, 6) decompensated liver disease, 7) severe anemia, 8) recent organ transplantation, 9) active cardiac disease.

The most important treatment objective is the achievement of sustained virologic response (SVR) to treatment defined as a negative HCV RNA PCR 6 months following the completion of therapy.

Early viral kinetics can help predict the likelihood of achievement of SVR and in the case of HCV genotype 1 helps determine the duration of treatment. Achieving an undetectable HCV RNA PCR at four weeks of treatment — also called rapid virologic response (RVR) — is associated with high rates of SVR.

Patients with HCV genotype 1 who are treated with telaprevir-based triple therapy (in conjunction with pegylated interferon alfa-2a or -2b and ribavirin, can be treated for 24 weeks if the HCV RNA PCR is undetectable at 12 and 24 weeks of treatment. The same group of patients treated with boceprevir-based triple therapy can be treated for 28 weeks — provided they are treatment naïve — if HCV RNA PCR is undetectable at 8 and 24 weeks.

All other genotype 1-infected patients generally require extended treatment courses of up to 48 weeks. Patients with genotypes 2 and 3 can generally be treated with pegylated interferon alfa-2a or -2b combined with ribavirin for 24 weeks. Despite the use of a third agent — an HCV protease inhibitor — and sometimes longer treatment courses, patients with genotype 1 have a lower rate of SVR (about 70–75 %) compared to patients with genotypes 2 and 3 (79–84 % SVR).

Acute HCV infection. Symptomatic patients. A waiting period of 12 weeks has been suggested as patients may have spontaneous recovery. If no spontaneous recovery is observed, suggested treatment includes:

– genotype 1 and 4 and/or HIV coinfection: peginterferon alfa-2b 1.5 mcg/kg or peginterferon alfa-2a 180 mcg weekly for 24 to 48 weeks;

– genotype 2 and 3 without HIV coinfection: same as above but 24 weeks;

– asymptomatic patients. Treated the same as symptomatic patients except there is no 12-week waiting period.

Chronic HCV infection.

Genotype 1a or 1b.

Patients with genotypes 1a or 1b can be treated with pegylated interferon alfa-2a or -2b combined with ribavirin for 48–72 weeks.

Protease inhibitors 1st genotype. Peginterferon alfa-2a 180 mcg SQ weekly with ribavirin 1000 mg (less than or equal to 75 kg of body weight) or 1200 mg (greater than or equal to 75 kg) or peginterferon alfa-2b 1.5 mcg/kg SQ weekly with ribavirin 800 mg (less than or equal to 65 kg) or 1000 mg (greater than or equal to 65–85 kg) or 1200 mg (greater than or equal to 85 kg)] plus [telaprevir 750 mg three times a day or boceprevir 800 mg three time a day]. Duration of

treatment ranging between 24 and 48 weeks to be determined with response-guided therapy depending on early viral kinetics. Telaprevir is always used for 12 weeks and boceprevir from 24 to 48 weeks.

Genotype 2 and 3. Peginterferon alfa-2b 1.5 mcg/kg or peginterferon alfa-2a 180 mcg SQ weekly with ribavirin 800 mg for 24 weeks. Some patients may need therapy extended to 48 weeks.

Available new drugs and dosage regimens (approved by EMA and FDA before the end of 2014) (at this point only for 1–3 genotypes).

Sofosbuvir. Patients infected with **HCV genotype 1** can be treated with a combination of weekly pegylated IFN-α, daily weight-based ribavirin (1000 or 1200 mg in patients < 75 kg or ≥ 75 kg, respectively), and daily sofosbuvir (400 mg) 12 weeks.

Patients infected with HCV **genotype 1** who are **IFN intolerant** or -ineligible can be treated with daily weightbased ribavirin (1000 or 1200 mg in patients < 75 kg or ≥ 75 kg, respectively), and daily sofosbuvir (400 mg) 24 weeks. This combination should be proposed to these patients exclusively when no other IFN-free option is available.

Simeprevir. Patients infected with **HCV genotype 1** can be treated with a combination of weekly pegylated IFN-α, daily weight-based ribavirin (1000 or 1200 mg in patients < 75 kg or ≥ 75 kg, respectively), and daily simeprevir (150 mg). This combination is not recommended in patients infected with sub-type 1a who have a detectable Q80K substitution in the NS3 protease sequence at baseline, as assessed by population sequencing (direct sequence analysis).

Simeprevir should be administered 12 weeks in combination with pegylated IFN-α and ribavirin. Pegylated IFN-α and ribavirin should then be administered alone for an additional 12 weeks (total treatment duration 24 weeks) in treat-ment-naive and prior relapser patients, including cirrhotics, and for an additional 36 weeks (total treatment duration 48 weeks) in prior partial and null responders, including cirrhotics. HCV RNA levels should be monitored on treatment. Treatment should be stopped if HCV RNA level is ≥ 25 IU/ml at treatment week 4, week 12 or week 24.

Daclatasvir. Patients infected with **HCV genotype 1**, subtype 1b can be treated with a combination of weekly pegylated IFN-α, daily weight-based ribavirin (1000 or 1200 mg in patients < 75 kg or ≥ 75 kg, respectively) and daily daclatasvir (60 mg) 24 weeks. This combination should not be proposed to patients infected with HCV genotype 1, subtype 1a, given the preliminary data available, pending results of on-going large-scale studies.

Daclatasvir should be administered 12 weeks in combination with pegylated IFN-α and ribavirin. Daclatasvir should be continued in combination with pegylated IFN-α and ribavirin an additional 12 weeks (total duration 24 weeks) in patients who do not achieve an HCV RNA level < 25 IU/ml at week 4 and undetectable at week 10. Pegylated IFN-α and ribavirin should be continued

alone between week 12 and 24 (total duration 24 weeks) in patients who achieve an HCV RNA level <25 IU/ml at week 4 and undetectable at week 10.

Patients infected with **HCV genotype 1** can be treated with an **interferon-free combination** of daily **sofosbuvir** (400 mg) and daily **simeprevir** (150 mg) for 12 weeks. Preliminary results do not indicate a major advantage of adding ribavirin to this regimen. However, adding daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively) should be considered in patients with predictors of poor response to anti-HCV therapy, especially prior non-responders and/or patients with cirrhosis.

Patients infected with **HCV genotype 1** can be treated with an **interferon-free combination** of daily **sofosbuvir** (400 mg) and daily **daclatasvir** (60 mg) 12 weeks in treatment-naive patients or 24 weeks in treatment experienced patients, including those who failed on a triple combination of pegylated IFN-α, ribavirin and either telaprevir or boceprevir (pending data with 12 weeks of therapy in treatment-experienced patients). Preliminary results do not indicate a major advantage to adding ribavirin to this regimen. However, adding daily weight-based ribavirin (1000 or 1200 mg in patients < 75 kg or ≥ 75 kg, respectively) should be considered in patients with predictors of poor response to anti-HCV therapy, especially prior non-responders and/or patients with cirrhosis.

Patients infected with **HCV genotype 2** must be treated with daily weight-based ribavirin (1000 or 1200 mg in patients < 75 kg or ≥ 75 kg, respectively), and daily sofosbuvir (400 mg) 12 weeks. Therapy should be prolonged to 16 or 20 weeks in patients with cirrhosis, especially if they are treatment experienced. Alternatively, cirrhotic and/or treatment-experienced patients could be treated with weekly pegylated IFN-α, daily weight-based ribavirin (1000 or 1200 mg in patients < 75 kg or ≥ 75 kg, respectively), and daily sofosbuvir (400 mg) 12 weeks.

Patients infected with **HCV genotype 3** can be treated with a combination of weekly pegylated IFN-α, daily weight-based ribavirin (1000 or 1200 mg in patients < 75 kg or ≥ 75 kg, respectively), and daily sofosbuvir (400 mg) 12 weeks.

Patients infected with **HCV genotype 3** can be treated with daily weight-based ribavirin (1000 or 1200 mg in patients < 75 kg or ≥ 75 kg, respectively), and daily sofosbuvir (400 mg) 24 weeks. This therapy is suboptimal in treatment-experienced cirrhotics, who should be proposed an alternative treatment option.

Patients infected with **HCV genotype 3** can be treated with an **interferon-free combination** of daily sofosbuvir (400 mg) and daily daclatasvir (60 mg) 12 weeks in treatment-naive patients or 24 weeks in treatment-experienced patients (pending data with 12 weeks of therapy in treatment-experienced patients). Preliminary results do not indicate a major impact of adding ribavirin to this regimen. However, adding daily weight-based ribavirin (1000 or 1200 mg

in patients < 75 kg or ≥ 75 kg, respectively) should be considered in patients with predictors of poor response to anti-HCV therapy, especially prior non-responders and/or patients with cirrhosis.

Prevention. IG is ineffective in preventing hepatitis C and is no longer recommended for postexposure prophylaxis in cases of perinatal, needle stick, or sexual exposure. Although prototype vaccines that induce antibodies to HCV envelope proteins have been developed, currently, hepatitis C vaccination is not feasible practically. Genotype and quasispecies viral heterogeneity, as well as rapid evasion of neutralizing antibodies by this rapidly mutating virus, conspire to render HCV a difficult target for immunoprophylaxis with a vaccine.

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HEPATITIS E

Etiology and epidemiology. Previously labeled epidemic or enterically transmitted non-A, non-B hepatitis, hepatitis E virus (HEV) is an enterically transmitted virus that occurs primarily in India, Asia, Africa, and Central America; in those geographic areas, HEV is the most common cause of acute hepatitis.

This agent, with epidemiologic features resembling those of hepatitis A, is a 32- to 34-nm, nonenveloped, HAV-like virus with a 7600-nucleotide, single-strand, positive-sense RNA genome.

All HEV isolates appear to belong to a single serotype, despite genomic heterogeneity of up to 25 % and the existence of five genotypes, only four of which have been detected in humans; genotypes 1 and 2 appear to be more virulent, while genotypes 3 and 4 are more attenuated and account for subclinical infections. Contributing to the perpetuation of this virus are animal reservoirs, most notably in swine. There is no genomic or antigenic homology, however, between HEV and HAV or other picornaviruses; and HEV, although resembling caliciviruses, is sufficiently distinct from any known agent to merit a new classification of its own as a unique genus, *Hepevirus*, within the *Hepeviridae* family.

The virus has been detected in stool, bile, and liver and is excreted in the stool during the late incubation period; immune responses to viral antigens occur very early during the course of acute infection. Both IgM anti-HEV and IgG anti-HEV can be detected, but both fall rapidly after acute infection, reaching low

levels within 9–12 months. Currently, serologic testing for HEV infection is not available routinely.

This type of hepatitis, identified in India, Asia, Africa, the Middle East, and Central America, resembles hepatitis A in its primarily enteric mode of spread. The commonly recognized cases occur after contamination of water supplies such as after monsoon flooding, but sporadic, isolated cases occur. An epidemiologic feature that distinguishes HEV from other enteric agents is the rarity of secondary person-to-person spread from infected persons to their close contacts. Infections arise in populations that are immune to HAV and favor young adults. In endemic areas, the prevalence of antibodies to HEV is ≤ 40 %. In nonendemic areas of the world, such as the United States, clinically apparent acute hepatitis E is extremely rare; however, the prevalence of antibodies to HEV can be as high as 20 % in such areas. Several reports suggest a zoonotic reservoir for HEV in swine.

Clinical features. Generally, incubation periods for hepatitis E range from 14–60 days (mean, 5–6 weeks). The generalized clinical symptoms and laboratory features are similar to hepatitis A.

The most feared complication of viral hepatitis is fulminant hepatitis (massive hepatic necrosis); fortunately, this is a rare event. In outbreaks of waterborne hepatitis E in India and Asia, the case-fatality rate is 1–2 % and up to 10–20 % in pregnant women.

Patients usually present with signs and symptoms of encephalopathy that may evolve to deep coma. The liver is usually small and the PT excessively prolonged. The combination of rapidly shrinking liver size, rapidly rising bilirubin level, and marked prolongation of the PT, even as aminotransferase levels fall, together with clinical signs of confusion, disorientation, somnolence, ascites, and edema, indicates that the patient has hepatic failure with encephalopathy. Cerebral edema is common; brainstem compression, gastrointestinal bleeding, sepsis, respiratory failure, cardiovascular collapse, and renal failure are terminal events. The mortality rate is exceedingly high (> 80 % in patients with deep coma), but patients who survive may have a complete biochemical and histologic recovery. If a donor liver can be located in time, liver transplantation may be life-saving in patients with fulminant hepatitis.

Progression to chronic liver disease. Does not occur.

Prevention. Whether IG prevents hepatitis E remains undetermined. A recombinant vaccine has been developed and is undergoing clinical testing.

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HEPATITIS D (Delta virus)

Etiology and epidemiology. The delta hepatitis agent, or HDV, is a defective RNA virus that coinfects with and requires the helper function of HBV (or other hepadnaviruses) for its replication and expression. Slightly smaller than HBV, delta is a formalinsensitive, 35- to 37-nm virus with a hybrid structure. Its nucleocapsid expresses delta antigen, which bears no antigenic homology with any of the HBV antigens, and contains the virus genome. The delta core is "encapsidated" by an outer envelope of HBsAg, indistinguishable from that of HBV except in its relative compositions of major, middle, and large HBsAg component proteins. The genome is a small, 1700-nucleotide, circular, single-strand RNA (minus strand) that is nonhomologous with HBV DNA (except for a small area of the polymerase gene) but that has features and the rolling circle model of replication common to genomes of plant satellite viruses or viroids.

Although complete hepatitis D virions and liver injury require the cooperative helper function of HBV, intracellular replication of HDV RNA can occur without HBV. Genomic heterogeneity among HDV isolates has been described; however, pathophysiologic and clinical consequences of this genetic diversity have not been recognized.

HDV can either infect a person simultaneously with HBV (**co-infection**) or superinfect a person already infected with HBV (**superinfection**); when HDV infection is transmitted from a donor with one HBsAg subtype to an HBsAg-positive recipient with a different subtype, the HDV agent assumes the HBsAg subtype of the recipient, rather than the donor. Because HDV relies absolutely on HBV, the duration of HDV infection is determined by the duration of (and cannot outlast) HBV infection. HDV antigen is expressed primarily in hepatocyte nuclei and is occasionally detectable in serum.

During acute HDV infection, anti-HDV of the IgM class predominates, and 30–40 days may elapse after symptoms appear before anti-HDV can be detected. In self-limited infection, anti-HDV is low titer and transient, rarely remaining detectable beyond the clearance of HBsAg and HDV antigen.

In chronic HDV infection, anti-HDV circulates in high titer, and both IgM and IgG anti-HDV can be detected. HDV antigen in the liver and HDV RNA in serum and liver can be detected during HDV replication.

Infection with HDV has a worldwide distribution, but two epidemiologic patterns exist.

In Mediterranean countries (northern Africa, southern Europe, the Middle East), HDV infection is endemic among those with hepatitis B, and the disease is transmitted predominantly by nonpercutaneous means, especially close personal contact.

In nonendemic areas, such as the United States and northern Europe, HDV infection is confined to persons exposed frequently to blood and blood products,

primarily injection drug users and hemophiliacs. HDV infection can be introduced into a population through drug users or by migration of persons from endemic to nonendemic areas.

Thus, patterns of population migration and human behavior facilitating percutaneous contact play important roles in the introduction and amplification of HDV infection. Occasionally, the migrating epidemiology of hepatitis D is expressed in explosive outbreaks of severe hepatitis, such as those that have occurred in remote South American villages as well as in urban centers in the United States. Ultimately, such outbreaks of hepatitis D — either of coinfections with acute hepatitis B or of superinfections in those already infected with HBV — may blur the distinctions between endemic and nonendemic areas. On a global scale, HDV infection is declining. Even in Italy, an HDV-endemic area, public health measures introduced to control HBV infection resulted during the 1990s in a 1.5 %/year reduction in the prevalence of HDV infection.

Clinical features. The clinical and laboratory features of chronic HDV infection are similar to hepatitis B. Generally, incubation periods for hepatitis B and D from 30–180 days (mean, 8–12 weeks). Infection with HDV can occur in the presence of acute or chronic HBV infection; the duration of HBV infection determines the duration of HDV infection. When acute HDV and HBV infection occur simultaneously, clinical and biochemical features may be indistinguishable from those of HBV infection alone, although occasionally they are more severe. As opposed to patients with acute HBV infection, patients with chronic HBV infection can support HDV replication indefinitely. This can happen when acute HDV infection occurs in the presence of a nonresolving acute HBV infection. More commonly, acute HDV infection becomes chronic when it is superimposed on an underlying chronic HBV infection. In such cases, the HDV superinfection appears as a clinical exacerbation or an episode resembling acute viral hepatitis in someone already chronically infected with HBV. Superinfection with HDV in a patient with chronic hepatitis B often leads to clinical deterioration.

Patients with simultaneous acute hepatitis B and hepatitis D do not necessarily experience a higher mortality rate than do patients with acute hepatitis B alone; however, in several recent outbreaks of acute simultaneous HBV and HDV infection among injection drug users, the case-fatality rate has been ~5 %. In the case of HDV superinfection of a person with chronic hepatitis B, the likelihood of fulminant hepatitis and death is increased substantially. Although the casefatality rate for hepatitis D has not been defined adequately, in outbreaks of severe HDV superinfection in isolated populations with a high hepatitis B carrier rate, the mortality rate has been recorded in excess of 20 %.

The most feared complication is fulminant hepatitis (massive hepatic necrosis).

Although acute hepatitis D infection does not increase the likelihood of chronicity of simultaneous acute hepatitis B, hepatitis D has the potential for

contributing to the severity of chronic hepatitis B. Hepatitis D superinfection can transform inactive or mild chronic hepatitis B into severe, progressive chronic hepatitis and cirrhosis; it also can accelerate the course of chronic hepatitis B. Some HDV superinfections in patients with chronic hepatitis B lead to fulminant hepatitis. Although HDV and HBV infections are associated with severe liver disease, mild hepatitis and even inactive carriage have been identified in some patients, and the disease may become indolent beyond the early years of infection.

Chronic hepatitis D (HDV) may follow acute co-infection with HBV but at a rate no higher than the rate of chronicity of acute hepatitis B. That is, although HDV co-infection can increase the severity of acute hepatitis B, HDV does not increase the likelihood of progression to chronic hepatitis B. When, however, HDV superinfection occurs in a person who is already chronically infected with HBV, long-term HDV infection is the rule and a worsening of the liver disease the expected consequence. Except for severity, chronic hepatitis B plus D has similar clinical and laboratory features to those seen in chronic hepatitis B alone. Relatively severe chronic hepatitis, with or without cirrhosis, is the rule, and mild chronic hepatitis is the exception. Occasionally, mild hepatitis or even, rarely, inactive carriage occurs in patients with chronic hepatitis B plus D, and the disease may become indolent after several years of infection.

A distinguishing serologic feature of chronic hepatitis D is the presence in the circulation of antibodies to liver-kidney microsomes (anti-LKM).

Diagnosis. The presence of HDV infection can be identified by demonstrating intrahepatic HDV antigen or, more practically, an anti-HDV seroconversion (a rise in titer of anti-HDV or de novo appearance of anti-HDV). Circulating HDV antigen, also diagnostic of acute infection, is detectable only briefly, if at all. Because anti-HDV is often undetectable once HBsAg disappears, retrospective serodiagnosis of acute self-limited, simultaneous HBV and HDV infection is difficult.

Early diagnosis of acute infection may be hampered by a delay of up to 30–40 days in the appearance of anti-HDV. When a patient presents with acute hepatitis and has HBsAg and anti-HDV in serum, determination of the class of anti-HBc is helpful in establishing the relationship between infection with HBV and HDV. Although IgM anti-HBc does not distinguish absolutely between acute and chronic HBV infection, its presence is a reliable indicator of recent infection and its absence a reliable indicator of infection in the remote past. In simultaneous acute HBV and HDV infections, IgM anti-HBc will be detectable, while in acute HDV infection superimposed on chronic HBV infection, anti-HBc will be of the IgG class. Tests for the presence of HDV RNA are useful for determining the presence of ongoing HDV replication and relative infectivity.

Progression to chronic liver disease. The risk of progression to cirrhosis, and the incidence of HCC are increased by HDV superinfection in a patient already infected with HBV.

Treatment of HDV. PEG-IFN is the only drug effective against HDV. The efficacy of PEG-IFN therapy can be assessed during treatment (after 3–6 months) by measuring HDV RNA levels (C2). More than 1 year of therapy may be necessary, as there may be some benefit from treatment prolongation. However, the optimal duration of therapy is not well defined. Around 25–40 % of treated patients have a sustained off-treatment virological response with undetectable HDV RNA and accompanying improvement in histology, while some also lose HBsAg. However, it has not been defined how long patients need to be HDV RNA negative after the end of therapy before sustained virological response is achieved. Nucleoside/nucleotide analogues (NA) do not impact HDV replication and related disease. However, NA treatment might be considered in some patients who have active HBV replication with persistent or fluctuating serum HBV DNA levels above 2000 IU/ml.

Prevention. Infection with hepatitis D can be prevented by vaccinating susceptible persons with hepatitis B vaccine. No product is available for immunoprophylaxis to prevent HDV superinfection in HBsAg carriers; for them, avoidance of percutaneous exposures and limitation of intimate contact with persons who have HDV infection are recommended.

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HEPATITIS G

Two flaviviruses, hepatitis G virus (HGV) and hepatitis GB virus type C (HGBV-C), have recently been described and subsequently been shown to be virtually identical isolates of the same virus. HGV is distributed worldwide, and can be transmitted by blood transfusion.

Prevalence in blood donors is ~1.7 % (USA), but is higher in groups with risk factors for other blood-borne viruses, e. g. 11 % in Japanese HCV patients, ~20 % in some studies of dialysis patients.

The exact role, if any, of HGV in producing disease in humans remains unclear, and there is no clear evidence that it causes hepatitis.

Anti-HGV antibodies appear to be highly associated with viral clearance and protection from reinfection. Evidence is accumulating for a protective effect of chronic HGV infection on patients coinfected with HIV.

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HEPATOCELLULAR CARCINOMA (HCC)

Hepatocellular carcinoma (HCC) currently has the fifth highest incidence rate among tumors worldwide, a rate expected to continue to increase over the next several decades. The majority of patients with HCC have cirrhosis of the liver, with chronic hepatitis B and C as the major agents of etiology. Despite advances in technology, the prognosis of patients with HCC has shown little improvement over time, most likely because most patients are diagnosed at advanced stages. HCC meets the criteria established by the World Health Organization for performing surveillance in those at risk for developing this tumor (patients with cirrhosis of the liver).

The decision to screen an at-risk population for cancer is based on well-established criteria. Although the overall goal is to reduce morbidity and mortality from cancer, the objective of screening is the utilization of a relatively simple and inexpensive examination in a large number of individuals to determine whether or not they are likely to develop the cancer for which they are being screened. Screening is the one-time application of an examination that allows detection of a disease at a stage in which curative intervention may achieve the goal of reducing morbidity and mortality. Surveillance refers to the continuous monitoring of disease occurrence (using the screening examination) within a population to accomplish the same goals of screening.

The incidence rate of HCC is the fifth highest among solid tumors worldwide as is the death rate. In the 2007 annual report to the nation on the status of cancer, liver cancer had the thirteenth highest incidence rate among tumors in the United States and had the largest increase in incidence of all solid tumors from 1995 to 2004. The incidence of HCC has been rising in both Europe and the United States, largely due to the growing prevalence of hepatitis C cirrhosis. HCC is the third most common cause of cancer-related deaths worldwide, resulting in over 500,000 deaths per year. In the United States, HCC is the eighth most common cause of cancer-related death at 8.5 deaths per 100,000 but has the largest increase in mortality of all solid tumors from 1995 to 2004. Despite advances in technology and the available treatments, the 5-year survival rate in 1996 showed little improvement from the 5-year survival rate in 1985 (5 % vs 4 %).

Cirrhosis has been recognized as the most important risk factor for the development of HCC. HCV and hepatitis B virus (HBV) are the major agents of etiology that lead to the development of HCC. Alcoholic cirrhosis is another well-established major etiologic risk factor for the development of HCC. Recently, an association between nonalcoholic liver disease and HCC was made, but there have been no cohort studies evaluating the natural history of nonalcoholic fatty liver disease. Other etiologies of chronic liver disease, such as hemochromatosis, primary biliary cirrhosis, autoimmune hepatitis, and alpha-1 antitrypsin deficiency, are less common causes of chronic liver disease, with

prevalence rates of 1–8 % in patients with HCC. Furthermore, improvements in the survival of patients with cirrhosis due to better specialty care may further increase the number of individuals at risk for developing HCC.

The annual risk of developing HCC among patients with cirrhosis is between 2 % and 7 % and appears to be a cumulative risk. Among patients with cirrhosis, male gender, older age, alcohol and tobacco consumption, obesity, and diabetes are factors associated with an increased risk of HCC. In patients with chronic HBV infection, a baseline HBV DNA level of greater than 100,000 copies/mL increases the risk of HCC 10-fold. This biologic gradient of HCC risk in relation to HBV DNA level suggests that persistent viral replication increases the risk of HCC. A prospective cohort study of patients with cirrhosis found that prothrombin activity less than 75 % of baseline, age of more than 55 years, platelet count less than 75, and presence of HCV were independent risk factors for developing HCC. When the researchers stratified patients into a high-risk group (presence of these factors) and a low-risk group (absence of risk factors), the 5-year cumulative incidence of HCC was 30 % for the high-risk group and 4 % for the low-risk group ($P < 0.0001$).

Advantages of Treating Occult Hepatocellular Carcinoma.

The effectiveness of HCC treatment depends upon the disease stage at the time of diagnosis. The Barcelona Clinic Liver Cancer (BCLC) staging system has been recommended as the main determinant of prognosis and the treatment guide for patients with HCC. For early-stage tumors (BCLC stage A), surgical resection has provided 5-year survival rates of 70 % in carefully selected patients with preserved hepatic function, no evidence of portal hypertension, and single small asymptomatic tumors (< 5 cm in maximal diameter). Liver transplantation is the preferred method of treatment for patients not amenable to surgical resection but only for those restricted to the Milan criteria (single nodule < 5 cm or < 3 nodules each < 3 cm in diameter). The 5-year survival rate reported for liver transplantation is 74 %. Ablative treatments, specifically percutaneous ethanol injection and radiofrequency ablation, have demonstrated 5-year survival rates of 37 % in BCLC stage A patients not amenable to resection or transplantation. It is estimated that approximately 30 % of patients with HCC are currently diagnosed at early stages at which these therapies can be administered. Curative therapies exist for patients with early-stage HCC, and an efficacious surveillance program is critical for the identification of HCC at early stages.

Acceptance of the Target Population and Healthcare Professionals.

Surveillance for HCC appears to be acceptable to patients with cirrhosis. Such data are indirectly derived from cohort studies showing that only approximately 3–18 % of cirrhotic patients were noncompliant with ultrasound and AFP surveillance, which compares favorably with the 67 % noncompliance rate seen with colonoscopy surveillance for colon cancer screening. HCC surveillance

also appears to be well accepted by physicians. In a national survey of 554 members of the American Association for the Study of Liver Diseases, 84 % of respondents indicated that they routinely screen patients with cirrhosis for HCC using AFP and ultrasound.

Standardization of Recall Procedures.

A consensus conference offered guidelines on how to investigate abnormalities of the commonly used screening examinations AFP and ultrasound in patients with cirrhosis. Computed tomography (CT), magnetic resonance imaging (MRI), and contrast-enhanced ultrasound are the major diagnostic modalities used to establish the diagnosis of HCC without the need for histopathologic examination. The main imaging characteristic for HCC is the finding of arterial enhancement of the lesion followed by washout of contrast in the delayed venous phases. If the screening ultrasound shows a nodule of less than 1 cm in maximal diameter, repeat ultrasound is recommended because of the low probability of having HCC. When the lesion is at least 1 cm on ultrasound or the AFP is more than 20 ng/mL, cross-sectional imaging techniques (CT or MRI) or contrast-enhanced ultrasound should be performed, given the high likelihood of HCC.

The guidelines state that HCC can be accurately diagnosed by imaging if characteristic findings are seen on two modalities for lesions less than 2 cm in diameter. However, if the imaging characteristics are atypical for HCC, liver biopsy is recommended in order to establish the diagnosis. For nodules of at least 2 cm in diameter, HCC can be accurately diagnosed if the imaging characteristics are seen on one imaging test. A negative biopsy in these patients does not rule out HCC and sometimes may require repetition. Therefore, appropriate recall modalities do exist to evaluate abnormal surveillance tests.

Achieving An Acceptable Level of Hepatocellular Carcinoma Screening Accuracy.

The ideal marker for HCC would be specific for HCC and undetectable in premalignant liver disease (ie, cirrhosis regardless of the etiology). In addition, such a marker would be easily measurable and reproducible, minimally invasive, and acceptable to patients and physicians. Both radiographic and serologic examinations are currently utilized for HCC surveillance.

Ultrasound has been recommended as the primary radiologic screening examination for HCC. It is the least expensive, and it is noninvasive and widely available, which makes it an attractive screening examination. There have been no randomized controlled trials in patients with cirrhosis to date assessing the efficacy of ultrasound as a screening examination. The sensitivity for the detection of early-stage HCC ranges from 29 % to 100 %, whereas its specificity ranges from 94 % to 100 %. The high degree of operator dependence, differences in the equipment, and body habitus significantly limit ultrasound from being the best surveillance examination for HCC.

AFP has been the most widely utilized serologic examination for HCC screening. The operating characteristics of AFP are dependent on the cutoff level chosen to support the diagnosis of HCC. At higher cutoff levels, the test is more specific for HCC but at a cost of decreased sensitivity; conversely, at lower cutoff levels, AFP becomes increasingly sensitive but with a higher rate of false-positives.

Therefore, **a level greater than 20 ng/mL** has become the most commonly used cutoff in clinical practice to trigger a recall examination for the diagnosis of HCC, though various other cutoffs have been studied.

Even at the optimal cutoff level in this study, the sensitivity was only 60 %, whereas the specificity was 90.6 %. In addition, serum AFP values are frequently elevated among patients with chronic HCV with advanced hepatic fibrosis even in the absence of HCC, with levels declining after antiviral therapy.

AFP alone is not sufficient for the surveillance of HCC in patients with cirrhosis. In hepatitis B carriers, the combination of ultrasound and AFP increased the sensitivity of HCC detection, when compared to either examination alone, from 71 % with ultrasound alone to 79 % when **ultrasound and AFP were used together**.

Chronic elevations of AFP have also been shown to increase the risk of developing HCC among patients with cirrhosis and among hepatitis B carriers. Although better examinations are needed to improve the detection of early-stage HCC, AFP offers benefits in the surveillance of patients with cirrhosis and leads to diagnosis in approximately half of patients with HCC as well as the determination of their risk of developing the tumor.

Other tumor markers have been studied for the detection of HCC. **Des-gamma carboxy-prothrombin (DCP)** is an abnormal prothrombin protein generated as a result of an acquired defect in the posttranslational carboxylation of the prothrombin precursor in malignant hepatic cells. The sensitivities for detecting HCC ranged from 23 % to 57 % for DCP compared to 14 % to 71 % for AFP. Overall, **AFP and DCP had equal sensitivity, but DCP had better specificity**.

Reducing Mortality From Hepatocellular Carcinoma.

At the present time, ultrasound with AFP is the recommended strategy for the surveillance of patients with cirrhosis.

Treatment.

A proportion of patients in each stage do not fulfil all the criteria for the treatment allocation. In those cases, it is advised to offer the patient the next most suitable option within the same stage or the next prognostic stage. For instance, patients at BCLC A failing local ablation should be offered chemoembolization. Similarly, patients at BCLC B stage non-responding to chemoembolization — at least two cycles of treatment — should be offered sorafenib.

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LIVER CIRRHOSIS

Cirrhosis is a late stage of hepatic fibrosis that has resulted in widespread distortion of normal hepatic architecture. Cirrhosis is characterized by regenerative nodules surrounded by dense fibrotic tissue. Symptoms may not develop for years and are often nonspecific (eg, anorexia, fatigue, weight loss). Late manifestations include portal hypertension, ascites, and, when decompensation occurs, liver failure. Diagnosis often requires liver biopsy. Cirrhosis is usually considered irreversible. Treatment is supportive.

Cirrhosis is a leading cause of death worldwide. The causes of cirrhosis are the same as those of fibrosis. In developed countries, most cases result from chronic alcohol abuse or chronic hepatitis C. In parts of Asia and Africa, cirrhosis often results from chronic hepatitis B. Cirrhosis of unknown etiology (cryptogenic cirrhosis) is becoming less common as many specific causes (e. g., chronic hepatitis C, steatohepatitis) are identified. Injury to the bile ducts also can result in cirrhosis, as occurs in mechanical bile duct obstruction, primary biliary cirrhosis, and primary sclerosing cholangitis.

Pathophysiology. There are 2 primary ingredients: Hepatic fibrosis and regenerating liver cells.

In response to injury and loss, growth regulators induce hepatocellular hyperplasia (producing regenerating nodules) and arterial growth (angiogenesis). Among the growth regulators are cytokines and hepatic growth factors (e. g., epithelial growth factor, hepatocyte growth factor, transforming growth factor-α, tumor necrosis factor). Insulin, glucagon, and patterns of intrahepatic blood flow determine how and where nodules develop.

Angiogenesis produces new vessels within the fibrous sheath that surrounds nodules. These vessels connect the hepatic artery and portal vein to hepatic venules, restoring the intrahepatic circulatory pathways. Such interconnecting vessels provide relatively low-volume, high-pressure venous drainage that cannot accommodate as much blood volume as normal. As a result, portal vein pressure increases. Such distortions in blood flow contribute to portal hypertension, which increases because the regenerating nodules compress hepatic venules.

The progression rate from fibrosis to cirrhosis and the morphology of cirrhosis vary from person to person. Presumably, the reason for such variation is the extent of exposure to the injurious stimulus and the individual's response.

Complications. Portal hypertension is the most common serious complication of cirrhosis, and it, in turn, causes complications, including GI bleeding from esophageal, gastric, or rectal varices and portal hypertensive gastropathy. In patients with cirrhosis, portal hypertension can also lead to ascites, acute kidney injury (hepatorenal syndrome), and pulmonary hypertension (portopulmonary hypertension). Ascites is a risk factor for spontaneous bacterial peritonitis. Portopulmonary hypertension can manifest with symptoms of heart failure. Complications of portal hypertension tend to cause significant morbidity and mortality.

Cirrhosis can cause other cardiovascular complications. Vasodilation, intrapulmonary right-to-left shunting, and ventilation/perfusion mismatch can result in hypoxia (hepatopulmonary syndrome).

Progressive loss of hepatic architecture impairs function, leading to hepatic insufficiency; it manifests as coagulopathy, acute kidney injury (hepatorenal syndrome), and hepatic encephalopathy. Hepatocytes secrete less bile, contributing to cholestasis and jaundice. Less bile in the intestine causes malabsorption of dietary fat (triglycerides) and fat-soluble vitamins. Malabsorption of vitamin D may contribute to osteoporosis. Undernutrition is common. It may result from anorexia with reduced food intake or, in patients with alcoholic liver disease, from malabsorption due to pancreatic insufficiency.

Blood disorders are common. Anemia usually results from hypersplenism, chronic GI bleeding, folate deficiency (particularly in patients with alcoholism), and hemolysis.

Cirrhosis results in decreased production of prothrombotic and antithrombotic factors. Hypersplenism and altered expression of thrombopoietin contribute to thrombocytopenia. Thrombocytopenia and decreased production of clotting factors can make clotting unpredictable, increasing risk of both bleeding and thromboembolic disease (even though INR is usually increased). Leukopenia is also common; it is mediated by hypersplenism and altered expression of erythropoietin and granulocyte-stimulating factors.

Hepatocellular carcinoma frequently complicates cirrhosis, particularly cirrhosis resulting from chronic hepatitis B or C, hemochromatosis, alcohol-related liver disease, α_1-antitrypsin deficiency, or glycogen storage disease.

Histopathology. Cirrhosis is characterized by regenerating nodules and fibrosis. Cirrhosis can be micronodular or macronodular. Micronodular cirrhosis is characterized by uniformly small nodules (< 3 mm in diameter) and thick regular bands of connective tissue. Typically, nodules lack lobular organization; terminal (central) hepatic venules and portal triads are distorted. With time, macronodular cirrhosis often develops. The nodules vary in size (3 mm to 5 cm in diameter) and have some relatively normal lobular organization of portal triads and terminal hepatic venules. Broad fibrous bands of varying thickness surround the large nodules. Collapse of the normal hepatic architecture is

suggested by the concentration of portal triads within the fibrous scars. Mixed cirrhosis (incomplete septal cirrhosis) combines elements of micronodular and macronodular cirrhosis. Differentiation between these morphologic types of cirrhosis has limited clinical value.

Clinical features. Cirrhosis may be asymptomatic for years. One third of patients never develop symptoms. Often, the first symptoms are nonspecific; they include generalized fatigue (due to cytokine release), anorexia, malaise, and weight loss. The liver is typically palpable and firm, with a blunt edge, but is sometimes small and difficult to palpate. Nodules usually are not palpable.

Clinical signs that suggest a chronic liver disorder or chronic alcohol use but are not specific for cirrhosis include muscle wasting, palmar erythema, parotid gland enlargement, white nails, clubbing, Dupuytren contracture, spider angiomas (< 10 may be normal), gynecomastia, axillary hair loss, testicular atrophy, and peripheral neuropathy. Once complications of cirrhosis develop, decompensation inexorably ensues.

Diagnosis. Liver function tests, coagulation tests, CBC, and serologic tests for viral causes:

– Sometimes biopsy (eg, when clinical and noninvasive tests are inconclusive or when biopsy results may change management).

– Identification of cause based on clinical evaluation, routine testing for common causes, and selective testing for less common causes.

General approach. Cirrhosis is suspected in patients with manifestations of any of its complications, particularly portal hypertension or ascites. Early cirrhosis should be considered in patients with nonspecific symptoms or characteristic laboratory abnormalities detected incidentally during laboratory testing, particularly in patients who have a disorder or take a drug that might cause fibrosis. Testing seeks to detect cirrhosis and any complications and to determine its cause.

Laboratory tests. Diagnostic testing begins with liver function tests, coagulation tests, CBC, and serologic tests for viral causes (e. g., hepatitis B and C). Laboratory tests alone may increase suspicion for cirrhosis but cannot confirm or exclude it. Liver biopsy becomes necessary if a clear diagnosis would lead to better management and outcome.

Test results may be normal or may indicate nonspecific abnormalities due to complications of cirrhosis or alcoholism. ALT and AST levels are often modestly elevated. Alkaline phosphatase and γ-glutamyl transpeptidase (GGT) are often normal; elevated levels indicate cholestasis or biliary obstruction. Bilirubin is usually normal but increases when cirrhosis progresses, particularly in primary biliary cirrhosis. Decreased serum albumin and a prolonged PT directly reflect impaired hepatic synthesis — usually an end-stage event. Albumin can also be low when nutrition is poor. Serum globulin increases in cirrhosis and in most liver disorders with an inflammatory component. Anemia is

common and usually normocytic with a high RBC distribution width. Anemia is often multifactorial; contributing factors may include chronic GI bleeding (usually causing microcytic anemia), folate nutritional deficiency (causing macrocytic anemia, especially in alcohol abuse), hemolysis, and hypersplenism. CBC may also detect leukopenia, thrombocytopenia, or pancytopenia.

Diagnostic imaging. Imaging tests are not highly sensitive or specific for the diagnosis of cirrhosis by themselves, but they can often detect its complications. In advanced cirrhosis, ultrasonography shows a small, nodular liver. Ultrasonography also detects portal hypertension and ascites. CT can detect a nodular texture, but it has no advantage over ultrasonography. Radionuclide liver scans using technetium-99m sulfur colloid may show irregular liver uptake and increased spleen and bone marrow uptake. MRI is more expensive than other imaging tests and has little advantage.

Identification of the cause. Determining the specific cause of cirrhosis requires key clinical information from the history and examination, as well as selective testing. Alcohol is the likely cause in patients with a documented history of alcoholism and clinical findings such as gynecomastia, spider angiomas (telangiectasia), and testicular atrophy plus laboratory confirmation of liver damage (AST elevated more than ALT) and liver enzyme induction (a greatly increased GGT). Fever, tender hepatomegaly, and jaundice suggest the presence of alcoholic hepatitis. Detecting hepatitis B surface antigen (HBsAg) and IgG antibodies to hepatitis B (IgG anti-HBc) confirms chronic hepatitis B. Identifying serum antibody to hepatitis C (anti-HCV) and HCV-RNA points to hepatitis C.

Most clinicians also routinely test for the following:

– Autoimmune hepatitis: Suggested by a high antinuclear antibody titer (a low titer is nonspecific and does not always mandate further evaluation) and confirmed by hypergammaglobulinemia and the presence of other autoantibodies (e. g., anti-smooth muscle or anti-liver/kidney microsomal type 1 antibodies).

– Hemochromatosis: Confirmed by increased serum Fe and transferrin saturation and possibly results of genetic testing.

– α_1-Antitrypsin deficiency: Confirmed by a low serum α_1-antitrypsin level and genotyping

If these causes are not confirmed, other causes are sought:

– Presence of antimitochondrial antibodies (in 95 %) suggests primary biliary cirrhosis.

– Strictures and dilations of the intrahepatic and extrahepatic bile ducts, seen on magnetic resonance cholangiopancreatography (MRCP), suggest primary sclerosing cholangitis.

– Decreased serum ceruloplasmin and characteristic copper test results suggest Wilson disease.

– The presence of obesity and a history of diabetes suggest nonalcoholic steatohepatitis.

Liver biopsy. If clinical criteria and noninvasive testing are inconclusive, liver biopsy is usually done. For example, if well-compensated cirrhosis is suspected clinically and imaging findings are inconclusive, biopsy should be done to confirm the diagnosis. Sensitivity of liver biopsy approaches 100 %. Nonalcoholic fatty liver disease (NAFLD) may be evident on ultrasound scans. However, nonalcoholic steatohepatitis (NASH) often associated with obesity, diabetes, or the metabolic syndrome, requires liver biopsy for confirmation. In obvious cases of cirrhosis with marked coagulopathy, portal hypertension, ascites, and liver failure, biopsy is not required unless results would change management. In patients with coagulopathy and thrombocytopenia, the transjugular approach to biopsy is safest. When this approach is used, pressures can be measured and thus the transsinusoidal pressure gradient can be calculated.

Monitoring. All patients with cirrhosis, regardless of cause, should be screened regularly for hepatocellular carcinoma. Currently, abdominal ultrasonography is recommended every 6 month, and if abnormalities compatible with hepatocellular carcinoma are detected, contrast-enhanced MRI or triple-phase CT of the abdomen (contrast-enhanced CT with separate arterial and venous phase images) should be done.

Upper endoscopy to check for gastroesophageal varices should be done when the diagnosis is made and then every 2 to 3 years. Positive findings may mandate treatment or more frequent endoscopic monitoring.

Prognosis. Prognosis is often unpredictable. It depends on factors such as etiology, severity, presence of complications, comorbid conditions, host factors, and effectiveness of therapy. Patients who continue to drink alcohol, even small amounts, have a very poor prognosis. The Child-Turcotte-Pugh scoring system uses clinical and laboratory information to stratify disease severity, surgical risk, and overall prognosis (table 4).

Table 4

Child-Turcotte-Pugh Scoring System

Clinical or Laboratory Factor	Degree of Abnormality	Points Assigned*
Encephalopathy (grade†)	None	1
	1–2	2
	3–4	3
Ascites	None	1
	Mild (or controlled by diuretics)	2
	At least moderate despite diuretic treatment	3
PT (seconds prolonged)	< 4	1
	4–6	2
	> 6	3
or		
INR	< 1.7	1
	1.7–2.3	2
	> 2.3	3

Clinical or Laboratory Factor	Degree of Abnormality	Points Assigned*
Albumin (g/dL)	> 3.5	1
	2.8–3.5	2
	< 2.8	3
Bilirubin (mg/dL)	< 2	1
	2–3	2
	> 3	3

* Risk (grade) is based on the total number of points: low (A) — 5–6; moderate (B) — 7–9; high (C) — 10–15. †Encephalopathy is graded based on symptoms: 1 — sleep disturbances; impaired concentration; depression, anxiety, or irritability; 2 — drowsiness, disorientation, poor short-term memory, uninhibited behavior; 3 — somnolence; confusion; amnesia; anger, paranoia, or other bizarre behavior; 4 — coma.

However, the Child-Turcotte-Pugh scoring system has limitations; for example, assessments of the severity of ascites and encephalopathy are subjective; interrater reliability of results is thus decreased. In contrast, the Model for End-Stage Liver Disease (MELD) score estimates the severity of end-stage liver disease, regardless of cause, based solely on objective results of laboratory tests: serum creatinine, serum total bilirubin, and INR. The MELD score is used to determine allocation of available organs to liver transplant candidates.

Treatment. In general, treatment is supportive and includes stopping injurious drugs, providing nutrition (including supplemental vitamins), and treating the underlying disorders and complications. Doses of drugs metabolized in the liver should be reduced. All alcohol and hepatotoxic substances must be avoided. Withdrawal symptoms during hospitalization should be anticipated in patients who have cirrhosis and have continued to abuse alcohol. Patients should be vaccinated against viral hepatitis A and B unless they are already immune.

Patients with varices need therapy to prevent bleeding. No evidence supports treating small esophageal varices. Medium and large esophageal varices should be treated prophylactically with nonselective β-blockers or endoscopic banding (ligation). If gastric varices are not amenable to endoscopic banding and do not respond to nonselective β-blockers, balloon-occluded retrograde transvenous obliteration or endoscopic cyanoacrylate injection may be used. Transjugular intrahepatic portosystemic shunting (TIPS) should be considered if patients have complications of portal hypertension that are refractory to standard treatments, including ascites and recurrent variceal bleeding.

Liver transplantation is indicated for patients with end-stage liver disease or hepatocellular carcinoma.

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MENINGOCOCCAL INFECTION

Meningococcal infection is caused by the *Neisseria meningitidis* which may result in local (carriage or nasopharingitis) and systemic infection: meningitis, meningococcemia and rare clinical variants.

Etiology and epidemiology. *Neisseria meningitidis* (also known as meningococcus) is a gram-negative, "coffee-corne"-like diplococci, which has unstable to temperature endotoxine (LPS). These bacteria frequently live in a person's upper respiratory tract without causing visible signs of illness. There are 13 different types of meningococci, but most infections are caused by types A, B, C, Y, W-135. These 5 types are responsible for 95 % clinical cases of meningococcal disease. Meningococci are spread through respiratory and throat secretions (close contact, kissing, sneezing, cough).

Neisseria meningitidis is carried, usually harmlessly, in nose and throat of 3–10 % of the population. These are healthy "carriers". Bacteria are passed from person-to-person by close prolonged contact (family contact, barracks, campus et al.). Cigarette smoking, both active and passive, appears to increase the risk of developing meningococcal disease. Contact with saliva from the front of the mouth (for example, when sharing drinks or cigarettes) has not been shown to cause meningococcal disease.

Morbidity is 1–2 on 100 000 population in European Countries. There is so-called "meningococcal belt" in Western and Central Africa, were morbidity is much higher. But after successful use of vaccination it has strike tendency of decrease now.

Most cases of meningococcal meningitis occur in children 4–24 month of age and teens. But it is very important to remember that this disease can occur in any age. Meningococcus is one of the most common cause of bacterial meningitis in children and adults. Before vaccination it was the leading cause of bacterial meningitis among children in Europe. Infectious diseases tend to spread quickly wherever large groups of people gather together. Also there are certain medical situations and diseases, which put people at increased risk of meningococcal disease, such as not having a spleen.

Pathogenesis. Meningococcal disease occurs when the bacteria "invades" the body from the throat or nose. Then it can spread hematogeniously and pass through blood-encephalitic barrier. However, most of people become healthy "carriers" or has nasopharingitis after contact with Neisseria meningitides.

Clinical features and diagnosis. Meningococcal infection has unique place in modern clinical practice. First, because it can cause fulminant disease with quick fatal onset among previously healthy people (mostly young). Clinical manifestations of meningococcal disease can be variable, ranging from transient fever to fulminant disease with death. It may be meningitis, septicemia (meningococcemia), joint infection, eye infection, pneumonia.

Meningococcal nasopharyngitis is one of the local forms of infection (the other is carriage). Common manifestation is subfebrile fever, symptoms of cold, sore throat.Hyperplasia of lymphoid pholiculles at the back surface of pharyngs may occur. Diagnosis is confirmed bacteriologically. Meningococcal nasopharyngitis has a significant role in spread of meningococcal infection.

Meningitis and meningococcemia are the most important variants of meningococcal diseases. Clinical diagnosis of meningitis is usually based on the most typical symptoms. The symptoms include: sudden onset, fever, headache (witout effect from common used analgetics), stiff neck. Some authors prefer to underline "meningococcal triada" – fever, headache and vomiting. There are often additional symptoms, such as weakness, confusion, hyperstesia, photophobia et al.

The symptoms of meningococcal meningitis can appear very quickly or during some days. Typically they develop within 3–7 days after exposure. In infants, it is sometimes very difficult to find classical symptoms of meningitis. There may be only fever and usually vomiting. But headache (infants!), and neck stiffness may be absent or difficult to notice. Such patients may appear to be slow, weak, inactive, irritable, then fall into confusion and convulsions. In young children, it is necessary to look at the reflexes, which can also be a sign of meningitis.

Meningeal signs (stiffness neck, Brudzinsky and Kernig symptoms and other) are of great diagnostic importance. But they fluctuate because of the patient's reactivity and can depend on age, immunologic status, physical conditions.

The pathophysiological base of meningitis is bacterial intoxication and progressive brain edema.

Possible complications of meningitis are: brain damage, hearing loss, hydrocephalus, subdural effusion, myocarditis, seizures.

If meningitis is possible, a lumbar puncture should be done to remove a sample of spinal fluid (cerebrospinal fluid, or CSF) for testing. CT of brain is also important, X-ray of the chest is necessary.

Laboratory diagnostic: full blood cells count and differential; biochemistry tests — glucose, urea, bilirubin, ALT and electrolytes; lumbar puncture, cerebrospinal fluid analysis (cells, protein, glucose) and bacterioscopy; bacteriological culture of cerebrospinal fluid and blood; meningococcal PCR of cerebrospinal fluid and if blood cultures have been obtained post-antibiotics. There is typical increasing of neutrophyls in liquore at meningococcal meningitis.

Meningococcemia (Meningococcal Septicemia) is the most severe variant of meningococcal infection. In fatal cases, deaths can occur in as little as a few hours (fulminant meningococcemia). During meningococcal septicemia, the bacteria enter the bloodstream and multiply, cause disseminated intravascular coagulation (DIC), damage the walls of the blood vessels and causing bleeding into the skin and inner organs. The main sign is sudden outbreak

of fever and increasing of intoxication. The signs of intoxication are mostly severe, but in early period of the disease, the status of the patient could be compensated. The most important symptom of meningococcemia is hemorrahic rash, which usually appears in the first 4–15 hours of the disease. Other symptoms may include: fatigue, vomiting, cold hands and feet, severe aches or pain in the muscles, joints, chest or abdomen, sometimes diarrhea, in the later stages, a dark purple rash. The main complications of meningococcemia are septic shock and polyorganic insuffiency.

At the early period of meningococcemia, pinpoint red spots (petechiae) appears. At the late stage of the disease, or in fulminant meningococcemia, purple bruise-like areas (purpura) cover skin of the patient. Hypotension, cold extremities, confusion are the signs of septic shock. But, the condition is most life threatening in those who have: disseminated intravascular coagulopathy — a severe bleeding disorder, kidney failure, myocarditis, pericarditis, ARDS, severe damage to adrenal glands that can lead to low blood pressure (Waterhouse–Friderichsen syndrome).

Main signs of the septic shock are: hypotension (!), paleness, later mental status changes.

So, possible complications of meningococcemia are: arthritis, DIC, inflammation of blood vessels in the skin (cutaneous vasculitis) and gangrene due to lack of blood supply, and, of course, septic shock.

Blood tests should be done to confirm meningococcemia. Such tests should include blood culture (if possible with bacterioscopy), complete blood count with differentiation, clotting studies (PT, PTT).

Other tests that may be done: lumbar puncture to get a sample of spinal fluid for CSF culture and Gram stain test, sometimes skin biopsy and urinalysis.

Treatment. Meningococcal disease can be treated with antibiotics, but adequate medical attention is extremely important. Meningococcal meningitis is very serious diagnosis and can be fatal for patient, mostly when therapy started late.

– IV antibiotics should be given as soon as meningococcal disease is suspected (if IV access cannot be obtained within 15 minutes, IM or IO administration is warranted).

– If possible collect blood cultures prior to antibiotic administration. But if it is impossible to organize quick collection of blood culture — starting antibiotic therapy is in priority.

– Ceftriaxone IV/IM or Cefotaxime IV is the first choice antibiotic. If unavailable, use penicillin IV/IM. The dosage of Ceftriaxone or Cefotaxime is maximal, dosage of penicillin is 300 000 IU/kg/daily.

– Other investigations should not delay antibiotic therapy.

– Breathing support.

– Fluids (IV).

– Dehydration (diuretics).

Meningococcemia is a medical emergency. Patients should be admitted to the intensive care unit of the hospital, where they are closely monitored.

Antibiotics should be started as soon as possible. Early antibiotic treatment improves outcome. Penicillin in high doses is almost always effective. Ceftriaxone and cefatoxime are the most commonly used antibiotics for meningococcal infection. If the patient is allergic to penicillin, chloramphenicol may be used also. Sometimes corticosteroids may be used, especially in children.

Treatment includes also: breathing support, clotting factors or platelet replacement (if necessary), fluids intravenously, corticosteroids (shock), antyhypotensions (shock), wound care for areas of skin necrosis.

Prevention. People who are in close contact with patient should be given antibiotics to prevent infection. Such people are: household members, roommates, people, who are in close and long-term contact with patient.

Vaccination is the best existing defense against meningococcal disease.

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RABIES

Definition. Rabies is an acute almost always fatal disease of the central nervous system caused by virus that is transmitted to humans by infected animals.

Etiology. Rabies virus is an enveloped virus with an RNA genome (the genus *Lyssavirus*, the family *Rhabdoviridae*). There is antigenic variation between various strains of rabies virus that helps in the identification of the source of infection.

Epidemiology. Rabies virus can infect most mammals and is registered worldwide. The majority of cases occur in underdeveloped countries (especially India, China and the Middle East) and among the children. Risk groups include people who work with animals, hunters and laboratory workers.

This infection is generally transmitted to humans by the bite of a rabid animal. The main sources of rabies are domestic animals (dogs and cats, rarely other farm animal) and different wildlife animals (bats, raccoons, skunks, foxes, wolves, small rodents etc.). Wild dogs, skunks, raccoons, foxes, and bats have the highest risk of infection. Rarely the source of rabies may be nonbite direct exposures with aerosolized bat excreta within caves and transplanted human organs.

Pathogenesis. Virus is inoculated by the bite of a rabid animal and replicates in skeletal muscle cells (incubation period — postexposure prophylaxis has the greatest effectiveness). Then it binds to nicotinic acetylcholine receptors at neuromuscular junctions and travels within axons in peripheral nerves via retrograde axonal transport. Rabies virus reaches the spinal cord, replicates in motor neurons and local dorsal root ganglia and then rapid ascent to the brain. Infection of the brain neurons is accompanied by mild inflammation and neuronal dysfunction with character clinical features of rabies. Finally rabies virus centrifugally spreads along nerves to salivary glands, skin, cornea and other organs. Rabies virus replication in salivary glands results in viral excretion in the saliva of rabid animals.

Clinical manifestations. The average incubation is usually 1–3 months (vary from 2 weeks to more than 1 year). After an asymptomatic incubation period clinical rabies progresses through three general phases: a prodrome, an acute neurologic phase and coma/death.

Prodromal features. The prodrome lasts 2 to 10 days. Patients may note paresthesias, pain or pruritis at the site of the initial bite. They also have constitutional symptoms and signs (low-grade fever, malaise, nausea, vomiting, sore throat etc).

Acute neurologic period. Two acute neurologic forms of rabies are seen in humans: encephalitic in 80 % and paralytic in 20 %. This stage lasts about 1 week and progresses to coma and death.

Encephalitic form features include fever, confusion, hallucinations, muscle spasms, hyperactivity, seizures and autonomic dysfunction (hypersalivation, excessive perspiration, gooseflesh, pupillary dilation and/or priapism). Episodes of hyperexcitability are typically followed by periods of complete lucidity that become shorter as the disease progresses. The typical features of rabies encephalitis are early brainstem involvement which results in the classic symptoms of hydrophobia and aerophobia (involuntary, painful contraction of the diaphragm and accessory respiratory, laryngeal, and pharyngeal muscles in response to swallowing liquids (hydrophobia) or a draft of air (aerophobia). Coma followed within days by death is the rule unless the course is prolonged by supportive measures. With supportive measures late complications may be registered (water disbalance, noncardiogenic pulmonary edema and cardiac arrhythmias due to brainstem dysfunction and/or myocarditis).

Paralytic form of rabies is characterized by early and prominent muscle weakness, often beginning in the bitten extremity and spreading to produce quadriparesis and facial weakness. Sphincter involvement is common but sensory involvement is usually mild. Patients with paralytic rabies generally survive a few days longer than is typical in encephalitic rabies, but multiple-organ failure develops even with aggressive supportive care.

Laboratory diagnosis. Examination of cerebrospinal fluid often reveals mild mononuclear cell pleocytosis with a mildly elevated protein level. CT head scans are usually normal, MRI brain scans sometimes show signal abnormalities in the brainstem or other areas but these findings are variable and nonspecific. Electroencephalograms show only nonspecific abnormalities.

To confirm the diagnosis rabies-specific tests may be employed such as serological detection of rabies-specific antibodies in serum of a previously unimmunized persons (but sometimes absent even in late stages of the disease) and CSF (always confirm the rabies even in immunized persons), direct fluorescent antibody testing of brain tissues, corneal impressions or skin biopsy samples from the nape of the neck and detection of rabies virus by PCR in fresh saliva samples, CSF and tissue. Viral cultures of saliva and CSF are often positive but do not help in the diagnosis because of the length of time these cultures take to develop. Biopsy of the brain should reveal Negri bodies or intracytoplasmic inclusions (most commonly in pyramidal cells in the hippocampus). If it's possible may be useful to capture the animal in order to test its central nervous system for virus.

Treatment. There is no established treatment for rabies. Different measures were used in a healthy survivor with confirmed rabies (antiviral therapy, ketamine and therapeutic coma) with intermittent success. For most patients only a palliative approach is used.

Prevention. *Preexposure prophylaxis*. Public health measures taken to decrease the risk of disease in domestic animals had great success in developed countries. Travelers to endemic regions for rabies should be alerted to the risks. People at high risk (travelling into high risk locations were animal contact is possible) may be immunized prior to any potential exposure.

Postexposure prophylaxis. Rabies is transmitted through the saliva of sick animals. Usually animals will be sick or become sick within 10 days of an attack. As bites from potentially rabid bats often go unnoticed, anyone who has while sleeping possibly been exposed to a bat should be treated as if they have been bitten. Whenever possible the animal should be recovered and either quarantined or killed and sent to the laboratory for examination.

The wound must be scrubbed with soap as soon as possible after the bite. Vaccination should be given as soon as possible for a high-risk bite. Passive antibody administration with human rabies immune globulin at a dose of 20 IU/kg should be given. One-half of the dose should be administrated around the wound and the other half given intramuscularly in the thigh or upper outer buttocks. Vaccination should be given in 1-mL doses on days 0, 3, 7, 14 and 28 in the deltoid area.

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DIFFERENTIAL DIAGNOSIS OF CNS INFECTIONS

Classification and definitions. Classification of CNS infections includes:

1. *Meningitis* — inflamation of the brain coverings (pia and arachnoid meninges).
2. *Encephalitis* — diffuse inflamation of the brain parenchyma.
3. *Myelitis* — diffuse inflamation of the spinal cord matter.
4. *Brain (spinal cord) abscess* — localised purulent inflamation of the brain (spinal cord).
5. *Epidural abscess* — localised purulent inflamation in epidural space of CNS.
6. *Subdural empyema* — purulent inflamation in subdural space of CNS.

Sometimes patients may have inflamation of the meninges and the brain parenchyma (meningoencephalitis), of the meninges and the spinal cord matter (meningomyelitis) or even meningomyeloencephalitis.

Meningitis — may be purulent (bacterial) or aseptic (bacterial, viral, parasytic).

Table 5

Etiology of infectious meningitis

<table>
<tr><th colspan="2">Purulent meningitis</th><th>Aseptic meningitis</th></tr>
<tr><th colspan="2">Age</th><th>Viral</th></tr>
<tr><td>< 1 month</td><td>Streptococcus agalactiae, Escherichia coli, Listeria monocytogenes, Klebsiella species</td><td rowspan="4">Enteroviruses (most common)
Herpes simplex virus 2 (HSV 2)
Tick-borne encephalitis virus (TBE)
Lymphocytic choriomeningitis virus
Human immunodeficiency virus
Mumps
Adenovirus
Parainfluenza virus type 3
Influenza virus</td></tr>
<tr><td>1–23 months</td><td>S. agalactiae, E. coli, Haemophilus infuenzae, Streptococcus pneumoniae, Neisseria meningitidis</td></tr>
<tr><td>2–50 years</td><td>S. pneumoniae, N. meningitidis</td><td>Bacterial</td></tr>
<tr><td>> 50 years</td><td>S. pneumoniae, N. meningitidis, L. monocytogenes,
aerobic gram-negative bacilli</td><td rowspan="2">Mycobacterium tuberculosis
Treponema pallidum
Borrelia burgdorferi s.l.
Leptospira spp.
Mycoplasma pneumoniae
Chlamydophila psittaci
Rickettsia rickettsii
Ehrlichia spp.
Anaplasma spp.</td></tr>
<tr><td>Immunocompromised state</td><td>S. pneumoniae, N. meningitidis, L. monocytogenes,
aerobic gram-negative bacilli (including P. aeruginosa)</td></tr>
</table>

Purulent meningitis		Aseptic meningitis
Basilar skull fracture	*S. pneumoniae, H. infuenzae, S. pyogenes*	**Protozoa and helminths**
Head trauma; postneurosurgery	*Staphylococcus aureus*, coagulase-negative staphylococci (especially *S. epidermidis*), aerobic gram-negative bacilli (including *P. aeruginosa*)	*Naegleria fowleri* *Angiostrongylus cantonensis* *Baylisascaris procyonis* *Taenia solium* (cysticercosis) *Toxocara* spp. *Strongyloides stercoralis*
		Fungal
		Cryptococcus neoformans *Coccidioides immitis* *Histoplasma capsulatum* *Blastomycetes dermatididis* *Aspergillus* spp.

There are also some *non-infectious causes of meningitis*: intracranial Tumors and Cysts, medications, systemic Illnesses (like systemic lupus erythematosus, Vogt–Koyanagi–Harada syndrome, Behcet's disease, CNS vasculitis), procedure-related (postneurosurgery, spinal anesthesia, intrathecal injections), neoplasm (esp. breast, lung), neurosarcoidosis.

Key symptoms and signs: fever, severe headache (without improvement with analgetics), nausea and sometimes vomiting, lethargy, hyperesthesia (photophobia, hyperacusia) and meningeal signs (neck stiffness, Kernig and Brudzinski signs).

NB! Meningeal signs occur only in about 50 % of cases of bacterial meningits and less often in cases of aseptic meningitis, so these signs are neither highly specific nor highly sensitive. We have to perform lumbar punction in every patient with severe headache and fever without any obvious causes of his condition.

If severe meningitis stay untreated, the meningeal inflamation will lead to diffuse brain dysfunction, edema of brain parenchyma and herniation with coma and death.

Diagnosis:

– lumbar puncture with investigation of cerebrospinal fluid (CSF): cytology, biochemistry (glucose, protein, lactate level), bacterioscopy and bacteriology, PCR;

– in patients with purulent meningitis in addition to previous examination — blood culture;

– CT or MRI of the brain — only if there are other indications (not informative for the diagnosis of meningitis, may be used for excluding of contraindications for lumbar puncture, encephalitis, brain abscess etc).

Encephalitis.

The most common etiology of encephalitis — viral:

– herpesviruses (herpes simplex virus 1 and varicella-zoster virus — the most common causes of viral encephalitis, Epstein–Barr virus, cytomegalovirus, HHV6);

– tick-borne encephalitis virus;

– enterovirus (most often enterovirus 71);

– human immunodeficiency virus;

– rabies;

– West Nile virus;

– polyomavirus (JC);

– rare: influenzae virus, adenovirus, parvovirus B19, lymphocytic choriomeningitis virus, mumps etc.)

Sometimes encephalitis may be caused by bacteria (most common *Listeria spp., Mycoplasma pneumoniae, Borrelia burgdorferi* s.l., *Bartonella spp.*), parasites (*Naegleria fowleri*, *Acanthamoeba*, *Balamuthia*) or may be non-infectious: autoimmune (anti-NMDA, anti-VKG), paraneoplastic and so on.

Key symptoms and signs: fever, confusion, personality change, altered mental status, seizures, focal neurologic signs.

Diagnosis:

1. Brain imaging (MRI is more preferable, CT).

2. Lumbar puncture + investigation of CSF (including PCR for herpes simplex encephalitis, varicella-zoster encephalitis).

3. Serology (for example in case of tick-borne encephalitis, West Nile encephalitis, HIV; preferably use paired serum for detection of acute and convalescent titers of antibody).

4. Brain biopsy in exceptional cases.

Myelitis and spinal epidural abscess.

Primary myelitis can present as one of three discrete clinical patterns with different etiology:

a) anterior poliomyelitis (inflammation involving the gray matter): poliovirus 1,2,3, nonpolio enterovirus (*Coxsackie* A, B), echovirus, West Nile virus;

b) leukomyelitis (inflammation involving the white matter): HIV-1, HTLV-1, herpesviruses (CMV, EBV, HSV, VZV);

c) transverse myelitis (inflammation of an entire cross section of the spinal cord): VZV, spirochetes, schistosomiasis.

The most common cause of spinal epidural abscess is *S. aureus*.

Key symtoms and signs: fever, back pain, limb weakness or sensory changes, bowel or bladder dysfunction.

Diagnosis:

– Lumbar puncture and investigation of CSF for suspected myelitis but *not for spinal epidural abscess*.

– MRI of the spine at the level suggested by the clinical exam.

Brain abscess and subdural empyema.

Etiology of brain abscess and subdural empyema depends on the primary sources of infection which are associated with specific microorganisms:

– paranasal sinuses: *Streptococcus spp.* (especially *S. milleri*), *Haemophilus spp., Bacteroides spp., Fusobacterium spp.*

– odontogenic sources: *Streptococcus spp., Bacteroides spp., Prevotella spp., Fusobacterium spp., Haemophilus spp.*

– otogenic sources: *Enterobacteriaceae, Streptococcus spp., Pseudomonas aeruginosa, Bacteroides spp.*

– lungs: *Streptococcus spp., Fusobacterium spp., Actinomyces spp.*

– urinary tract: *Pseudomonas aeruginosa, Enterobacter spp.*

– penetrating head trauma: *Staphylococcus aureus, Enterobacter spp., Clostridium spp.*

– neurosurgical procedures: *Staphylococcus spp., Streptococcus spp., Pseudomonas aeruginosa, Enterobacter spp.*

– endocarditis: Viridans streptococci, *S. aureus.*

Key symptoms and signs: headache, focal neurologic deficits, in case of increased intracranial pressure — papilledema, naused and vomiting. Fever, chills and other signs of infection usually do not occur.

Diagnosis: contrast-enhanced CT or MRI may show a ring-enhancing lesion or lesions and surrounding brain edema. If the diagnosis is in doubt a stereotaxic brain biopsy will confirm that the lesion is an abscess. Lumbar puncture is not usually performed because abscess creates an intracranial mass with edema so there is a risk of brain herniation. If the abscess is well-encapsulated, protein may be increased, but cell counts are usually low and cultures are usually negative, so the diagnostic usefulness of LP is limited.

Lumbar puncture (LP).

Lumbar puncture is essential for diagnosis in most cases of meningitis and encephalitis (but not for abscess or empyema). The test is sensitive and specific for most organisms.

Investigation of cerebrospinal fluid in cases of meningitis and encephalitis includes:

– cell count and differential (lympocytes, neutrophils, red blood cells and their morphology, sometimes eosinophils);

– biochemical investigation (total protein, glucose);

– gram stain and CSF latex agglutination (detection of cryptococcal antigens, *H. influenzae, N. meningitidis, S. pneumoniae, E. coli, L. monocytogenes* antigens);

– bacterial culture;

– PCR for bacterial and viral pathogens.

Relative contraindications to lumbar puncture:

1. Space-occupying intracranial lesions or obstructive hydrocephalus. The risk is that removing fluid from the lumbar space would exacerbate a pressure differential between intracranial compartments and lead to brain herniation. Careful examination of the patient for signs of increased intracranial pressure (e. g. papilledema) or an emergency non-contrast CT scan of the head.

2. Severe bleeding.

3. Spinal epidural abscess.

Possible complications of lumbar puncture:

– Post LP Headache. Occurs in 20 % of patients, caused by leakage of fluid through the hole made in the dura. Diagnosis is obvious — the headache is severe when standing but immediately goes away on lying down. Treatment is bedrest with the head lower than the hole and drink plenty of fluids, sometimes may be useful hypodermic injection of 1 % caffeine solution or drink coffee.

– Meningitis (very rare). Should occur only if there is some break in sterile technique.

– Contamination of the CSF sample.

– Brain herniation. It may be in case of space-occupying intracranial lesions or obstructive hydrocephalus. See possible contraindications to lumbar puncture before the procedure.

Table 6

Typical CSF formulas in different meningitis

Meningitis	Bacterial	Viral	Fungal	Tuberculous
Opening pressure	normal or high	normal	normal or high	usually high
WBC count (cells/mm^3)	1,000–10,000	< 1000	20–500	50–500
PMN (%)	> 80	< 20	< 50	~20
Protein (g/L)	very high (> 1 g/L)	normal or < 1 g/L	high (> 1 g/L)	high (> 1 g/L)
Glucose	low	normal	usually low	very low
Gram stain	60–90 % positive	negative	negative	acid fast based stain positive in 40–80 %

In case of traumatic LP is typical the clearing of blood with successive collection tubes; microscopically red blood cells are round and fresh, CSF is clear after centrifugation.

In case of subarachnoid hemorrhage the most typical findings are:

– an elevated opening pressure and an elevated red blood cell (RBC) count that does not diminish from CSF tube one to tube three;

– microscopically — crenated morphology of red blood cells;

– xanthochromia (pink or yellow tint of CSF which represents hemoglobin degradation products) after centrifugation of CSF (but sometimes xanthochromia can also occurs with increased CSF concentrations of protein 1,5 g/L and more, systemic hyperbilirubinemia and traumatic lumbar puncture with more than 100.000 red blood cells/μL).

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LYME DISEASE

Definition. Lyme borreliosis or Lyme disease (LD) is caused by a spirochete, *Borrelia burgdorferi sensu lato*, which is transmitted by ticks of the *Ixodes ricinus* complex. It's a multisystem illness which affects primarily the skin, nervous system, heart and joints.

Etiology. *B. burgdorferi sensu lato* is a fastidious gram-negative bacterium. There are a lot of genomospecies of *B. burgorferi s.l.* but the LD is caused primarily by three pathogenic genospecies: *B. burgdorferi sensu stricto*, *Borrelia garinii* and *Borrelia afzelii*. All three genospecies are found in Europe.

Epidemiology. The principal vectors of LD in Europe, including Belarus, — *Ixodes ricinus*, in Asia — *I. persulcatus*, in USA — *I. scapularis* and *I. pacificus*. These ticks may transmit other diseases as well (tick-borne encephalitis, anaplasmosis, erlichiosis, babesiosis et al.). Ticks of the *I. ricinus* complex have larval, nymphal and adult stages. They require a blood meal at each stage. The risk of infection in a given area depends largely on the density of these ticks as well as their feeding habits and animal hosts. Because of the small size of ticks most patients do not remember the preceding tick bite.

LD is now the most common vector-borne infection in the United States and Europe. During recent years the number of cases in the Europe (including Belarus) has increased dramatically. In Europe the highest reported frequencies of the disease are in the middle of the continent and in Scandinavia.

Pathogenesis. After tick bite and injection of the bacteria into the human skin *B. burgdorferi s.l.* may migrate outward, producing erythema migrans (first stage of infection, early localised infection). In some patients without antibacterial treatment *B. burgdorferi s.l.* may spread hematogenously or in the lymph

to other organs but more preferably in distant sites of skin, heart, joints and nervous system (second stage of infection, early disseminated infection). On the third stage of infection (late infection) *B. burgdorferi s.l.* may persists in enriched with collagen organs and tissues for many months and years, preferably in skin, joints and nervous system.

On the first stage of infection only localized immune response to *B. burgorferi* is typical but on the second and third stages of LD systemic immune response always activates. In some patients after erythema migrans reinfection may occur when patients are treated with antibiotics. In such cases the immune response is not adequate to provide protection from subsequent infection. Patients who develop an expanded immune response to the spirochete over a period of months have protective immunity for a period of years and do not acquire the infection again.

Clinical features. Incubation period varies from 3 to 32 days (about 1 month).

Stage 1 (early localized infection). At the site of the tick bite erythema migrans (EM) occurs. It usually begins as a painless red macule or papule that expands slowly to form a large annular lesion with a bright red outer border and partial central clearing. EM can be located anywhere but the thigh, groin and axilla are particularly common sites. Approximately 20 % of patients do not exhibit this characteristic skin manifestation of early localised infection but it may be associated with infections by other *Borrelia* species (for example, *B. miyamotoi*).

Stage 2 (early disseminated infection). *B. burgdorferi s.l.* often spreads hematogenously or more rarely lymphogenously to many sites within days or weeks after the onset of EM. In these cases patients may develop fever, profound malaise and fatigue and different abnormalities such as:

1) secondary annular skin lesions similar to the initial EM (secondary EMs);

2) arthralgias of large joints with migratory character of pain, migratory pain in tendons, bursae, muscles or bones and rare lyme arthritis;

3) unexpected arrythmia and fluctuating degree of atrioventricular block (up to complete heart block), rare acute myopericarditis or pancarditis;

4) early neuroborreliosis (aseptic meningitis with severe headache, mild stiffness of the neck, nausea and lymphocytic pleocytosis with slightly elevated protein level but with normal glucose in CSF, cranial neuritis more often with n. facialis palsy (uni- or bilateral) and motor or sensory radiculoneuropathy; if the patient has aseptic meningitis with radiculoneuritis — it's Bannwarth syndrome).

The early signs and symptoms of LD are typically intermittent and changing and even in untreated patients these symptoms usually become less severe or disappear within several weeks.

Stage 3 (late infection). This stage develops in patients without previous antibiotic treatment on stage 1 and 2 and may be manifest as:

1) frank Lyme arthritis with intermittent attacks of oligoarticular arthritis in large joints (especially the knees) lasting for weeks or months. Sometimes a few small joints or periarticular sites may also be affected. In a small percentage of cases involvement of large joints becomes chronic and may lead to erosion of cartilage and bone.

2) acrodermatitis chronica atrophicans (the skin lesions which are usually found on the distal surface of an arm or leg, first begin insidiously with reddish-violaceous discoloration and then over a period of years they become sclerotic or atrophic).

3) late neuroborreliosis (subtle encephalopathy affecting memory, mood, or sleep, encephalomyelitis often with clinical and MRI picture resembling multiple sclerosis, axonal polyneuropathy).

Laboratory diagnosis. LD is usually diagnosed by the recognition of a characteristic clinical picture with serologic confirmation (two step approach — ELISA as a screening, immunoblot if positive or equivocal ELISA for confirmation of diagnosis). But there are some important problems with serologic diagnosis:

1) It's important that serologic testing may yield negative results during the first several weeks of infection (during the first stage of LD — erythema migrans) but most patients have a positive antibody response to *B. burgdorferi s.l.* after that time and always during second and third stages of infection. So EM is a pathognomonic symptom of LD and no need for laboratory confirmation of diagnosis.

2) Patients with previous Lyme disease even after adequate antibiotic treatment often remain seropositive for years. So for treated patients with LD no need for recurrent laboratory investigations. Only resolution of clinical signs of LD is necessary to define that antibacterial treatment was clinically successful.

3) About 10–25 % of patients in endemic areas by LD are seropositive because of asymptomatic infection. If these individuals subsequently develop another illness, the positive serologic test for Lyme disease may cause diagnostic confusion. No need for serologic screening of patients without compatible clinical signs of LD as in such patients the probability of a false-positive serologic result is higher than that of a true-positive result.

4) In persons with illness of > 1 month's duration, a positive IgM test result alone is likely to be false-positive and therefore should not be used to support the diagnosis of LD.

The culture of *B. burgdorferi* in BSK medium is rarely used in clinical practice because it's a laborious and costly ineffective method but it may be used in research studies. PCR has high sensitivity only for the detection of *B. burgdorferi* DNA in joint fluid and in biopsy material from EM but it's insensitive for detection of *B. burgdorferi s.l.* in CSF, blood and urine samples.

Treatment. The various manifestations of Lyme disease including early neuroborreliosis can usually be treated successfully with orally administered antibiotics; the exceptions are objective late neurologic abnormalities and third-degree atrioventricular heart block, which are generally treated with IV antibiotics. For early localized and disseminated Lyme disease doxycycline is first-choice antibiotic. Amoxicillin, cefuroxime axetil and azythromycin are second-, third-and fourth-choice alternatives, respectively. For patients with late infection ceftriaxone intravenously is the drug of choice.

For patients with EM a 14-day course of therapy is generally sufficient; for patients with early disseminated infection, a 21-day course is recommended; for patients with late infection a 30 days of ceftriaxon intravenously is recommended in case of late neuroborreliosis or oral doxycycline or amoxicillin for 30–60 days for the initial treatment of Lyme arthritis. Among patients with arthritis who do not respond to oral antibiotics, re-treatment with IV ceftriaxone for 28 days is appropriate.

Prevention. Protective measures may include the avoidance of tick-infested areas, the use of repellents and tick checks. Currently there are no any commercially available vaccines for the prevention of LD. In areas which are high endemic for LD postexposure prophylaxis with a single 200 mg dose of doxycycline given within 72 h after the tick bite may be administered.

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TICK-BORNE ENCEPHALITIS

Definition. Tick-borne encephalitis (TBE) is a disease caused by tick-borne encephalitis virus which is transmitted mainly by *Ixodes spp.* ticks and may manifest as a fever, aseptic meningitis, meningoencephalitis and other rare CNS abnormalities.

Etiology. Tick-borne encephalitis virus (TBEV) is a member of the genus *Flavivirus*, family *Flaviviridae* (RNA viruses). TBEV consists of 3 subtypes: 1) the Central European TBEV (Western subtype); 2) Siberian TBEV; 3) Russian spring-summer TBEV (Far Eastern subtype). The last two viruses are more virulent and cause more severe forms of TBE than European TBEV.

Epidemiology. The main vector of European TBEV is *Ixodes ricinus*, of the Siberian and Far Eastern TBEV — *Ixodes persulcatus*. The reservoir of TBEV in nature is small mammals. TBEV is transmitted from the saliva of infected ticks within minutes of the tick bites (but only two-thirds of patients report tick bite). Human cases of TBE in Europe occur between April and October with a peak in June and July according to seasonal activity of *I. ricinus*.

Sometimes TBEV can occasionaly be transmitted after an intake of unpasteurised milk products from viremic livestock (in Belarus via unpasteurised goat milk).

Pathogenesis. The pathogenesis of TBE is characterized by a biphasic course: the first viremic phase with unspecified clinical picture (fever, fatigue, malaise, arthralgia, etc.) and the second phase with invasion of CNS.

Clinical features. Incubation period varies from 4 to 30 days (median 8 days) after tick bite. Typically the TBE has biphasic course. The median duration of the first stage of illness is 5 days (range 2–10) with up to 7 day symptom-free interval to the second phase.

In the first viraemic stage the dominant symptoms are fever, fatigue, general malaise, headache and body pain. Investigation of blood may show leucopenia and thrombocytopenia and slightly raised serum transaminases

In the second neuroinvasive stage recurrence of fever is typical and some clinical forms of CNS involvement may occur:

1) aseptic meningitis (fever, headache, nause, vomiting, meningial signs — neck stiffness, Kernig's signs);

2) meningoencephalitis (clinical picture of meningitis + ataxia, tremor, altered consciousness, rarely seizures, hemiparesis and cranial nerve paralysis);

3) a flaccid poliomyelitis-like paralysis (usually affects the arms, shoulders and levator muscles of the head, rarely with subsequent development of monoparesis, paraparesis and tetraparesis;

4) myeloradiculitic form (severe pain in the back and limbs, weak muscle reflexes and sensory disturbances).

In Russian spring-summer TBE the encephalitic syndrome sometimes begins without a remission and has more severe manifestations than in European TBE, mortality is high and major sequel (most notably lower motor neuron paralyses of the proximal muscles of the extremities, trunk, and neck) are common.

Cerebrospinal fluid (CSF) analyses in patients with TBE reveal moderate pleocytosis with two-thirds of patients having 100 leucocytes per μL or less and with an initial predominance of polymorphonuclear cells which is later changed to an almost 100 % mononuclear cell dominance. Two-thirds of patients have a moderate increased CSF protein. MRI abnormalities are seen in up to $^{1}/_{5}$ of patients with lesions in the thalamus, cerebellum, brainstem, and nucleus caudatus. In almost 80 % of patients with TBE there are unspecific EEG abnormalities.

Laboratory diagnosis. TBE is usually diagnosed with the recognition of a characteristic clinical picture (biphasic course, first stage — fever and unspecific symptoms, symptom-free interval and second stage — CNS involvment) with serologic confirmation (ELISA for detection of IgM antibodies). In the viremic phase of infection TBEV may be isolated from blood or detected by PCR. In the neuroinvasive phase PCR of CSF is insensitive method of laboratory diagnosis.

Treatment. No specific treatment for TBE exists. Corticosteroid therapy may result in a more rapid reduction of fever but prolonged hospitalization. Use of TBE human immune globulin therapy is controversial (some studies of its effectiveness show beneficial effects with more rapid convalescence but some studies show harmful effects with the exacerbation of disease and poor outcome). So only supportive treatment of TBE is recommended (dehydratation therapy for treatment of cerebral edema, analgetics, antipyretics etc).

Prevention. Protective measures for the prevention of TBE may include the avoidance of tick-infested areas, the use of repellents and the avoidance of unpasteurised goat and sheep milk in endemic areas.

Tick-borne encephalitis can be prevented by active immunisation. Vaccination should be used in persons likely to experience exposure in an endemic area during the season of transmission.

Passive immunisation with hyperimmune IgG against TBEV has been frequently used in some countries as postexposure prophylaxis. Because of the absence of well documented effectiveness this immunisation can no longer be recommended.

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MALARIA

Definition. Malaria is a vector-borne disease transmitted by the female Anopheles mosquito and is caused by protozoan parasite *Plasmodium spp.*

Etiology. Five *Plasmodium* species cause human infection:

– *P. falciparum* occurs in Africa, Papua New Guinea, Haiti and East Asia, can invade red blood cells of all ages, may be drug-resistant and is responsible for most severe, life-threatening infections;

– *P. vivax* (occurs in Central and South America, India, North Africa and East Asia) and *P. ovale* (occurs in West Africa) cause clinically similar, milder infections. They produce hypnozoites and may cause relapse months after the initial infection;

– *P. malaria* (occurs mostly in Africa) rarely causes acute illness in normal hosts, doesn't produce hypnozoites but may persist in the bloodstream for years;

– *P. knowlesi* (occurs in Southeast Asia) causes malaria in macaques and has recently been recognised as a cause of human malaria. Microscopically it resembles *P. malariae* but can cause fatal disease (like *P. falciparum*).

P. falciparum and *P. vivax* account for 95 % of the malaria.

Life cycle. Human infection begins when an anopheline mosquito inoculates plasmodial sporozoites from its salivary gland during a blood meal. Motile sporozoites are carried rapidly via the bloodstream to the liver where they invade hepatic parenchymal cells and begin a period of asexual reproduction (intrahepatic or preerythrocytic schizogony or merogony). By this amplification process a single sporozoite eventually may produce from 10,000 to > 30,000 daughter merozoites. In *P. vivax* and *P. ovale* infections, a proportion of the intrahepatic forms do not divide immediately but remain dormant for a period ranging from 3 weeks to a year or longer before reproduction begins. These dormant forms, or hypnozoites, are the cause of the late relapses.

The swollen infected liver cell eventually bursts, discharging motile merozoites into the bloodstream. These then invade the red blood cells (RBCs), become trophozoites and multiply six- to twentyfold every 48–72 h. By the end of the 48-h intraerythrocytic life cycle (72 h for *P. malariae*), the parasite has consumed nearly all the hemoglobin and grown to occupy most of the RBC. It is now called a schizont. Multiple nuclear divisions have taken place (schizogony or merogony) and the RBC then ruptures to release 6–30 daughter merozoites, each potentially capable of invading a new RBC and repeating the cycle.

After a series of asexual cycles (*P. falciparum*) or immediately after release from the liver (*P. vivax, P. ovale, P. malariae*) some of the parasites develop into morphologically distinct, longer-lived sexual forms (gametocytes) that can transmit malaria. After being ingested in the blood meal of a biting female anopheline mosquito the male and female gametocytes form a zygote in the insect's midgut. This zygote matures into an ookinete, which penetrates and encysts in the mosquito's gut wall. The resulting oocyst expands by asexual division until it bursts to liberate myriad motile sporozoites, which then migrate in the hemolymph to the salivary gland of the mosquito to await inoculation into another human at the next feeding.

Epidemiology. Every year 300–500 million people suffer from this disease and 1,5–3,0 million die (mostly children). Malaria occurs througout most of the tropical regions of the world and affects people in more than 100 countries.

Malaria is mainly transmitted via the bite of a female *Anopheles spp.* mosquito. Other comparatively rare mechanisms for transmission include: congenitally-acquired disease, blood transfusion, sharing of contaminated needles in intravenous drug usage and organ transplantation.

Pathogenesis. After the merozoites invade the red blood cells they cause hemolysis of parasitized red blood cells that activates cytokines. There are some additional mechanisms that contribute to the pathogenesis of severe *Plasmodium falciparum* malaria:

– cytoadherence — adherence of parasitized red blood cells to the vascular endothelium is mediated by *P. falciparum*-infected erythrocyte membrane protein 1 (PfEMP1), which binds to specific endothelial receptors (thrombospondin, CD36, ICAM-1, VCAM1 etc). This results in periferal sequestration of parasites which protects them from removal from the circulation as they pass through the spleen and oxidant damage as they pass through the lungs;

– osetting — PfEMP1 also binds to complement receptor-1 resulting in clustering of unparasitized red cells around parasitized red cells;

– hyperparasitaemia (> 5 %) is associated with a greater risk of death, particularly in non-immune patients. Reasons for this include moreovere metabolic effects (hypoglycaemia and lactic acidosis).

Clinical features. Malaria is a very common cause of fever in tropical countries. The first symptoms of malaria are nonspecific (headache, fatigue, abdominal discomfort and muscle aches) followed by fever are all similar to the symptoms of a respiratory viral illness. In some instances a prominence of headache, chest pain, abdominal pain, arthralgia, myalgia or diarrhea may suggest another diagnosis. Although headache may be severe in malaria there is no neck stiffness or photophobia resembling that in meningitis. While myalgia may be prominent it is not usually as severe as in dengue fever and the muscles are not tender as in leptospirosis or typhus. Nausea, vomiting, and orthostatic hypotension are common.

The classic malarial paroxysms includes 3 stages:

1) “cold or chilling stage” — severe chills;

2) “hot stage” — high temperature;

3) “sweating stage” — resolution of fever, intense sweat and fatigue.

Malarial paroxysms occur at regular intervals are relatively unusual and suggest infection with *P. vivax* or *P. ovale* (tertian — fever spikes evere 2 days) or *P. malaria* (quartan — fever spikes every 3 days).The fever is always irregular and often constant in *P. falciparum* malaria.

In nonimmune individuals with acute malaria the spleen takes several days to become enlarged. Slight enlargement of the liver is also common. Mild jaundice is common among adults; it may develop in patients with otherwise uncomplicated falciparum malaria and usually resolves over 1–3 weeks.

Complications of malaria: cerebral malaria, pulmonary oedema, severe anaemia, hypoglycaemia, uraemia, lactic acidosis.

Laboratory diagnosis. Initial examination: anemia, thrombocytopenia, increased lactate dehydrogenase and reticulocytes.

Confirmatory tests:

1) thick and thin blood smears stained by Giemsa stain and examined under light microscopy (thick smear is useful for confirmation of diagnosis, thin smear — for identification of *Plasmodium* species and quantification of parasites);

2) rapid dipstick tests targeting malaria antigens (these tests detect plasmodial lactate dehydrogenase, some of them enable distinction of species);

3) polymerase chain reaction (PCR) and other molecular techniques (not widely available).

Treatment. The mainstay of therapy — antimalarials drugs but successful treatment is threatened by increasing drug resistance. The main classes of drug are: quinoline derivates (chloroquine, quinine, mefloquine, halofantrine); antifolates (pyrimethamine, sulfonamides); ribosomal inhibitors (tetracycline, doxycycline, clindamycin); artemisinin derivates (artemisinin, artemether, artesunate).

In case of *P. vivax*, *P. malaria*, *P. ovale*, chloroquine-susceptible *P. falciparum* the choice of treatment is chloroquine phosphate. In case of *P. falciparum* malaria (chloroquine-resistant or unknown susceptibility to chloroquine) — combination therapy (artemether-lumefantrine, atovaquone-proguanil, dyhydroartemisinin-piperaquine, artesunate+mefloquine, quinine + doxycycline or clindamycin).

Supportive therapy — careful management of seizures, pulmonary oedema, acute renal failure, lactic acidosis is essential in severe malaria. Exchange transfusion may be helpful in hyperparasitaemia.

Prevention. General measures — reducing vector-human contact with use of insecticide-impregnated bed nets or insect repellents containing DEET.

Chemoprophylaxis starting 1 week prior to exposure, during exposure and for 4 weeks following exposure (for chloroquine-susceptible *P. falciparum*, *P. malariae*, *P. vivax*, *P. ovale* malaria — chloroquine, for chloroquine-resistant *P. falciparum* malaria — atovaquone-proguanil, mefloxine, doxycycline).

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EPIDEMIC (LOUSE-BORNE) TYPHUS AND BRILL–ZINSSER DISEASE

Definition. Epidemic typhus (ET) is an infectious disease caused by *Rickettsia prowazekii* which is transmited by human body louse and manifests with fever, rash and CNS abnormalities. Brill–Zinsser disease is a recrudescent illness occurring years after acute epidemic typhus probably as a result of waning immunity.

Etiology. The causative agent of epidemic typhus is *R. prowazekii* — an obligately intracellular small gram-negative coccobacillus.

Epidemiology. The human body louse (*Pediculus humanus corporis*) lives in clothing under poor hygienic conditions and usually in impoverished cold areas. Lice acquire *R. prowazekii* when they ingest blood from a rickettsemic patient. The rickettsiae multiply in the midgut epithelial cells of the louse and are shed in the louse's feces. The infected louse leaves a febrile person and deposits infected feces on its subsequent host during its blood meal; the patient autoinoculates the organisms by scratching. Currently epidemic typhus predominates in regions affected by wars and disasters.

Eastern flying-squirrels (*Glaucomys volans*) and their lice and fleas maintain *R. prowazekii* in a zoonotic cycle. Sporadically the fleas can transmit the infection to humans.

Pathogenesis. After transcutaneous entry of infective louse feces *R. prowazekii* spreads throughout the body via the bloodstream or lymphatics, enters endothelial cells and proliferates by binary fission. It results in endothelial injury via both cellular swelling and necrosis. The consequence of that is widespread vasculitis with increased vascular permeability, edema, and activation of humoral inflammatory and coagulation mechanisms. This rickettsia-induced vasculitis may also be accompanied by mural and intimal thrombosis and microscopic areas of hemorrhage. Involvement of the microcirculation can produce diffuse myocarditis as well as damage to muscle, spleen, kidneys and brain.

The molecular basis for Brill–Zinsser disease, defined as the recrudescence of epidemic typhus years after the initial episode, remains unclear.

Clinical features. Incubation period varies from 7 to 14 days after exposure of infected lice.

The onset of illness is abrupt, with prostration, severe headache, fever rising rapidly to 38.8–40.0 °C and some nonspecific symptoms (cought, severe myalgias, abdominal pain, nausea and diarrhea). The face is edemaous, flushed. Photophobia with considerable conjunctival injection ("rabbit's eyes") and petechial rash on conjunctiva (symptom of Kjary–Aucyne) is typical. Before the rash appearance enanthema (small hemorrhages) on the basis of uvula is marked (Rosenberg's symptom). In the majority of patients splenomegaly is marked on the 3–4 day of the disease.

A rash begins on the upper trunk and in the axillary folds usually on the 5th day and then becomes generalized, involving the entire body except the face, palms and soles. Initially this rash is nonconfluent pink macular but without treatment it becomes maculopapular and petechial and sometimes confluent.

Complications of ET include skin necrosis and gangrene of the digits, interstitial pneumonia, myocarditis, renal insufficiency, meningitis and meningoencephalitis etc.

Laboratory abnormalities in most patients include jaundice, elevated serum aminotransferases and thrombocytopenia.

Brill–Zinsser disease is generally a mild illness. Severe symptoms and death are rare primarily occurring in elderly and debilitated patients. The onset of Brill–Zinsser disease is typically abrupt with chills, fever, headache and malaise. Nonspecific gastrointestinal and pulmonary symptoms may be present. Rash in most patients typically begins four to six days after the onset of symptoms, is often scant or evanescent and is only rarely petechial.

Laboratory diagnosis. The laboratory diagnosis of ET generally relies on the detection of antibodies with a fourfold rise in titer in convalescence. Usually a diagnostic titer is detected during the second week of illness. The standard serologic method is indirect immunofuorescence assay and an IgG titer of 1:128 or an IgM titer of 1:32 confrms the diagnosis. The *Proteus vulgaris* OX-19 agglutination (Weil–Felix reaction) is poorly sensitive and nonspecific but it may be useful when it is the only method available in a developing country. Also PCR and immunohistochemical detection of *R. prowazekii* in blood or tissue may be used for the definitive laboratory confirmation of the ET.

Treatment. Doxycycline (200 mg/d, given in two divided doses) is administered orally or — if the patient is comatose or vomiting — intravenously. Although under epidemic conditions a single 200-mg dose has proved effective, treatment is generally continued until 2–3 days after defervescence. Pregnant patients should be evaluated individually and treated with either chloramphenicol (60–75 mg/kg/day in four divided doses) early in pregnancy or doxycycline late in pregnancy. Although fuoroquinolones, rifampin and some of the newer macrolides show inhibition of growth of *R. prowazekii* in cell culture none has been proved to be effcacious clinically.

Prevention. Prevention of epidemic typhus involves control of body lice. Clothes should be changed regularly and insecticides (for example, permethrin) should be used to control the louse population. No vaccine is currently available for the prevention of ET.

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PLAGUE

Plague is one of the most virulent and potentially lethal bacterial diseases known, and fatality rates remain high among patients who are not treated in the early stages of infection.

Etiology and epidemiology. Plague is an acute zoonotic infection caused by *Yersinia pestis*, a gram-negative, aerobic, bipolar-staining bacillus that belongs to the family Enterobacteriaceae.

Plague has worldwide distribution except in Australia and Antarctica. Most cases occur in poor, developing countries. Plague occurs in widely scattered foci, where its usual hosts are various wild rodents and human-associated rats. Prairie dogs, ground squirrels and domestic cats are also animal reservoirs of the plague.

The World Health Organization reports 1,000–3,000 cases per year. During the recent years cases of the disease have been reported annually from the Madagascar, Congo, Tanzania, China, Vietnam, Peru and the USA. Although most cases are now sporadic, occurring singly or in small clusters, the potential for outbreaks and epidemic spread remains.

Infection is transmitted to humans typically by: 1) flea bite and infrequently, 2) direct contact with infected animal tissues (scratches/bites, handling of carcasses), 3) inhalation of aerosolized bacteria from animals, an infected human host with pneumonic plague, or laboratory specimen.

Because of its virulence and transmissibility, *Y. pestis* is considered an important potential agent of biological terrorism that requires special countermeasures to protect the public's health.

Pathogenesis. The inoculated bacteria are firstly captured by tissue macrophages, and then undergo intracellular multiplication within them followed by lysis of macrophages, bacterial release, and dissemination through lymphatic system and bloodstream. Via lymphatic system bacteria spread to regional lymph nodes with inflammation and necrosis with creation of buboes. Hematogenous spread leads to sepsis and multiorgan disease.

Classification and clinical features. Incubation period is generally between 2–8 days. The principal clinical forms of plague are: 1) ***bubonic***, 2) ***septicemic***, 3) ***pneumonic***. Bubonic plague is almost always caused by the bite of an infected flea but occasionally results from direct contact with infectious materials. Septicemic and pneumonic plague can be either primary or secondary to metastatic spread. Unusual forms include ***plague meningitis***, ***endophthalmitis***, ***lymphadenitis*** at multiple sites, and primary plague ***pharyngitis***.

Bubonic plague. Patients experience chills; fever, with temperatures that rise within hours to 38–40 °C; myalgias; arthralgias; headache; and a feeling of weakness. Soon — usually within 24 h — the patient notices tenderness and pain in one or more regional lymph nodes proximal to the site of inoculation of

yersinia. Because fleas most often bite the legs, femoral and inguinal nodes are most commonly involved; axillary and cervical nodes are next most commonly affected. Within hours, the enlarging bubo (up to 10 cm in diameter) becomes progressively painful and tender, sometimes exquisitely so. The patient usually guards against palpation and limits movement, pressure, and stretch around the affected bubo. The surrounding tissue often becomes edematous, sometimes markedly so, and the overlying skin may be erythematous, warm, and tense. On careful examination skin lesions (most common, papules, vesicles, or pustules) are found distal to the affected lymph nodes in as many as one fourth of patients with bubonic plague, presumably representing sites of the infective flea bites.

Septicemic plague. Primary septicemic plague develops in the absence of a detectable bubo or plague pneumonia. The diagnosis often is not suspected until preliminary blood culture results are reported to be positive by the laboratory. Secondary septicemic plague occurs as a complication of the bubonic or pneumonic plague.

By the time of examination, patients are typically prostrate and lethargic but may exhibit restlessness or agitation. Temperatures are usually elevated in the range of 38.5 °C to 40 °C. Occasionally, patients are delirious with high fever. Pulse rates are increased to 110 to 140 beats per minute. Blood pressure is characteristically low, owing to vasodilation. Petechiae, ecchymoses, bleeding from puncture wounds and orifices, and gangrene of acral parts are manifestations of disseminated intravascular coagulation. Adult respiratory distress syndrome (ARDS) can occur at any stage of septicemic plague. The liver and spleen are often palpable and tender.

Septic patients often present with gastrointestinal symptoms of nausea, vomiting, diarrhea, and abdominal pain, which may confound the correct diagnosis.

Refractory hypotension, renal shutdown, obtundation, and other signs of shock are preterminal events.

Pneumonic plague. Primary inhalation pneumonia is a rare but serious threat to unprotected persons in direct and close respiratory contact with the symptomatic patient. Secondary plague pneumonia is complications of bubonic plague. Both primary and secondary pneumonic plague are a malignant pneumonia with rapid advance and is often complicated by sepsis and its consequences. Patients with plague pneumonia experience rapidly advancing tachypnea, dyspnea, hypoxia, chest pain, cough, hemoptysis, and general signs of endotoxemia. The sputum is often purulent but may be watery, frothy, and copious, and may be blood-tinged or grossly hemorrhagic, and it usually contains large numbers of plague bacilli. Radiographs show patchy bronchopneumonia, cavities, or confluent consolidation, and the radiologic findings may be more impressive than indicated by physical examination.

Other syndromes. Plague meningitis is a rare complication. It may occur as a delayed manifestation of inadequately treated bubonic plague or as a manifestation of acute early disease. Plague meningitis is characterized by fever, headache, sensorial changes, meningismus, and cerebrospinal fluid pleocytosis with a predominance of polymorphonuclear leukocytes. Bacteria are frequently demonstrable with a Gram or Wayson stain of spinal fluid sediment, and endotoxin has been demonstrated in spinal fluid with the limulus test.

Plague can produce pharyngitis resembling acute tonsillitis. The anterior cervical lymph nodes are usually inflamed, and *Y. pestis* may be recovered from a throat culture or by aspiration of a cervical bubo. This is a rare clinical form of plague that follows the inhalation or ingestion of plague bacilli. Asymptomatic pharyngeal colonization with *Y. pestis* has been reported in close contacts of pneumonic plague cases.

Diagnosis and differential diagnosis. Plague should be included in the differential diagnosis of an acute febrile illness in a patient who was recently in a plague-endemic area and at risk of exposure to infected animals or their fleas.

Appropriate diagnostic specimens include blood cultures and other materials as indicated, such as bubo aspirates, sputum, tracheobronchial washes, swabs of skin lesions or pharyngeal mucosa, and cerebrospinal fluid. A variety of appropriate culture media (including brain-heart infusion broth, sheep blood agar, chocolate agar, and MacConkey agar) should be inoculated with a portion of each specimen. For each specimen, at least one smear should be examined immediately with Wayson or Giemsa stain and at least one with Gram's stain.

In patients with negative cultures, plague can be confirmed by serologic tests: passive hemagglutination test (4-fold increase between acute and convalescent antibody titers), ELISA based serologic tests (IgG and IgM antibodies to F1 antigen). Rapid antigen test based on F1 antigen detection using monoclonal antibodies also seems promising for rapid presumptive diagnosis at the bedside, even when performed under primitive field conditions.

Polymerase chain reaction has been studied in respiratory specimens, but is not routinely available as a diagnostic tool.

Chest radiographs should be obtained to rule out plague-associated damage (patchy or lobar pneumonia that progresses to cavitation, pleural effusions, mediastinal or hilar lymphadenopathy, or acute respiratory distress syndrome).

Patients with plague typically have white blood cell counts of 10,000–25,000/ L, with a left shift. Modest thrombocytopenia is usually present, and fibrin-fibrinogen split products are often detected, even in patients without frank disseminated intravascular coagulation.

Differential diagnosis includes: streptococcal or staphylococcal lymphadenitis, other bacterial skin abscesses, cat scratch disease, incarcerated inguinal hernia, chancroid and lymphogranuloma venereum, streptococcal skin infection, anthrax, tularemia, hantavirus pulmonary syndrome.

Treatment. Without treatment, plague is fatal in more than 50 % of bubonic cases and in nearly all cases of septicemic or pneumonic plague. Effective antibiotic therapy should be given immediately after obtaining diagnostic specimens. Streptomycin (30 mg/kg/day bid IM for 7 days or at least 3 days after remission of fever and other symptoms) has been considered the drug of choice since its introduction in the 1940s. Where streptomycin is not available for immediate use, an acceptable alternatives are gentamicin (2.5 mg/kg bid IM), tetracycline (0.5–1 g qid orally), doxycycline (0.1 g bid IV), chloramphenicol (0.5 g qid IV), ciprofloxacin (0.4 g bid IV).

Patients initially given IV antibiotics may be switched to oral regimens upon clinical improvement. Such improvement is usually evident 2–3 days after the start of treatment, even though fever may continue for several days.

The patient's hemodynamic status should be monitored closely and shock managed according to general principles used to combat endotoxic shock.

Buboes usually recede during the first week of antibiotic treatment, but it may be several weeks before they completely resolve; occasionally, they enlarge or become fluctuant, requiring incision and drainage. The aspirate is usually sterile, but persistence of viable *Y. pestis* in buboes after apparent clinical cure has been reported. This persistence has not been associated with relapse of systemic plague.

Prevention. Personal protective measures include the avoidance of areas with known epizootic plague (in which warning signs may be posted) and of sick or dead animals; the use of repellents, insecticides, and protective clothing when at risk of exposure to rodents' fleas; and the wearing of gloves when handling animal carcasses. Short-term antibiotic prophylaxis is recommended for persons known to have had close contact with a patient with suspected or confirmed pneumonic plague. Tetracycline (2 g/d orally divided in 2–4 doses for 7 days), doxycycline (100–200 mg orally bid for 7 days) or trimethoprim/sulfamethoxazole (160/800 mg bid for 7 days) are the most suitable antimicrobial agents for post-exposure prophylaxis.

Vaccination is indicated for high risk individuals (laboratory workers, ecologists, field workers in high risk areas). Primary vaccine series: 3 doses given at 0, 1–3 and 5–6 month intervals. Booster doses: up to 3 doses at 6 month intervals depending on antibody response and continuing risk of exposure. Additional boosters at 1–2 year intervals for continued risk may be given.

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TULAREMIA

Tularemia is primarily a disease of wild animals and persists in contaminated environments, ectoparasites, and animal carriers. Human infection is incidental and responsible for a number of syndromes that range from a plague-like ulceroglandular illness to pneumonia.

Etiology and epidemiology. Tularemia is caused by *Francisella tularensis* — a small (0.2 μm by 0.2–0.7μm), gram-negative, pleomorphic, nonmotile, non-spore-forming bacillus. They are more uniformly rod-shaped during logarithmic growth, during which they tend to exhibit bipolar staining with Gram or Giemsa methods.

The organism is virulent, and small numbers of organisms on the skin can invade and lead to systemic illness. *F. tularensis* is resistant to freezing and may persist for weeks in dead animals, is inactivated by heat.

The two main biovars of *F. tularensis* — *tularensis* (type A) and *holarctica* (type B) — are both found in the world. Type A produces more serious disease in humans; without treatment, the associated fatality rate is ~5 %. Type B produces a milder, often subclinical infection that is usually contracted from water or marine mammals.

Infection in humans can occur by one of the following routes:

– bite from an arthropod vector (tick or mosquito);
– skin contact with an infected carcass;
– inhalation of the organism (particularly by laboratory workers);
– ingestion of meat contaminated with the bacterium;
– bite from the animal (including pets) that harbor the organism in the oropharynx.

Pathogenesis. After inoculation into site of entry, *F. tularensis* multiplies locally and produces primary affect (i. e., an erythematous, tender, or pruritic papule when enter via the skin). The bacteria also spread to regional lymph nodes, producing lymphadenopathy (buboes), and, with bacteremia, may spread to distant organs.

Infection with *F. tularensis* stimulates the host to produce antibodies. However, this antibody response probably plays only a minor role in the containment of infection. In contrast, cell-mediated immunity, which develops over 2–4 weeks, plays a major role in containment and eradication. Macrophages, once activated, can kill *F. tularensis*. Recovery from infection generally renders the patient resistant to reinfection.

Classification and clinical features. The incubation period varies from 2 to 10 days. Tularemia often starts with a sudden onset of fever, chills, headache, and generalized myalgias and arthralgias. Fever may be associated with a pulse-temperature deficit. About 20 % of patients develop a generalized maculopapular rash, which occasionally becomes pustular. The clinical manifestations of tularemia have been divided into 7 forms: 1) ulceroglandular tularemia, 2) glandular tularemia, 3) oculoglandular tularemia, 4) oropharyngeal tularemia, 5) gastrointestinal tularemia, 6) pulmonary tularemia, and 7) typhoidal tularemia.

Ulceroglandular & glandular tularemia. These two forms of tularemia account for ~75–85 % of cases. Within 2–5 days (range, 1–10 days) after inoculation into the skin, *F. tularensis* produces an erythematous, tender, or pruritic papule. It evolves over several days into an painful ulcer with sharply demarcated edges and a yellow exudate. The ulcer gradually develops a black base, and simultaneously the regional lymph nodes become tender and severely enlarged. The ulcer is erythematous, indurated, and nonhealing, with a punched-out appearance that lasts 1–3 weeks. The affected lymph nodes may become fluctuant and drain spontaneously, but usually the condition resolves with effective treatment.

The predominant form in children involves cervical or posterior auricular lymphadenopathy. In adults, the most common form is inguinal/femoral lymphadenopathy.

Glandular tularemia is differentiated from the ulceroglandular form of the disease by the absence of identifiable skin lesion.

Oculoglandular tularemia. In ~1 % of patients, the portal of entry for *F. tularensis* is the conjunctiva. Usually, the organism reaches the conjunctiva through contact with contaminated fingers. The inflamed conjunctiva is painful, with numerous yellowish nodules and pinpoint ulcers. Purulent conjunctivitis with regional lymphadenopathy (preauricular, submandibular, or cervical) is evident. Because of debilitating pain, the patient may seek medical attention before regional lymphadenopathy develops. Corneal perforation may occur.

Oropharyngeal & gastrointestinal tularemia. Oral inoculation may result in acute, exudative, or membranous pharyngitis associated with cervical lymphadenopathy or in ulcerative intestinal lesions associated with mesenteric lymphadenopathy, diarrhea, abdominal pain, nausea, vomiting, and gastrointestinal bleeding. Infected tonsils become enlarged and develop a yellowish-white pseudomembrane, which can be confused with that of diphtheria. The clinical severity of gastrointestinal tularemia varies from mild, unexplained, persistent diarrhea with no other symptoms to a fulminant, fatal disease.

Pulmonary tularemia. Associated with inhalation of the organism or hematogenous spread. Patients with pneumonia usually have a nonproductive cough and may have dyspnea or pleuritic chest pain. Roentgenograms of

the chest usually reveal bilateral patchy infiltrates (described as ovoid or lobar densities), lobar parenchymal infiltrates, and cavitary lesions. Pleural effusions may have a predominance of mononuclear leukocytes or polymorphonuclear neutrophils and sometimes red blood cells. Empyema may develop.

Typhoidal tularemia. The source of infection in typhoidal tularemia is usually associated with pharyngeal and/or gastrointestinal inoculation or bacteremic disease. Typhoidal tularemia is usually associated with a huge inoculum or with a preexisting compromising condition. Fever usually develops without apparent skin lesions or lymphadenopathy. In the absence of a history of possible contact with a vector, diagnosis can be extremely difficult High continuous fevers, signs of endotoxemia, and severe headache are common. The patient may be delirious and may develop prostration and shock.

F. tularensis infection has been associated with meningitis, pericarditis, hepatitis, peritonitis, endocarditis, osteomyelitis, and sepsis and septic shock with rhabdomyolysis and acute renal failure. In the rare cases of tularemia meningitis, a predominantly lymphocytic response is demonstrated in cerebrospinal fluid.

Diagnosis and differential diagnosis. When patients in endemic areas present with fever, chronic ulcerative skin lesions, and large tender lymph nodes, a diagnosis of tularemia should be made presumptively, and confirmatory diagnostic testing and appropriate therapy should be undertaken. When the possibility of tularemia is considered in a nonendemic area, an attempt should be made to identify contact with a potential animal vector.

Diagnosis is often made serologically. Tularemia tube agglutination test and microagglutination test are the standard methods. A presumptive diagnosis is supported by an acute tube agglutination titer of 1:160 or more, or an acute microagglutination titer of 1:128 or more. But definitive serologic diagnosis requires a fourfold or greater rise in titer between acute and convalescent specimens.

The organism is rarely seen on Gram-stained smears or in tissue biopsies and does not grow in routinely plated cultures. The medium of choice is cysteine- glucose-blood agar.

A variety of polymerase chain reaction (PCR) methods can also be used to detect *F. tularensis* DNA.

The leukocyte count and sedimentation rate may be normal or elevated. Thrombocytopenia, hyponatremia, elevated serum transaminases, increased creatine phosphokinase, myoglobinuria, and sterile pyuria are occasionally found.

The characteristic presentation of ulceroglandular tularemia does not pose a diagnostic problem, but a less classic progression of regional lymphadenopathy or glandular tularemia must be differentiated from other diseases (pyogenic bacterial infection, sporotrichosis, tuberculosis, syphilis, anthrax, rat-bite fever, plague, lymphogranuloma venereum, cat-scratch disease).

Oropharyngeal tularemia can resemble and must be differentiated from pharyngitis due to other bacteria or viruses, including diphtheria. Tularemia pneumonia may resemble any atypical pneumonia. Typhoidal tularemia may resemble a variety of other infections, including typhoid fever and other *Salmonella* bacteremias, ehrlichiosis, brucellosis, tuberculosis, sarcoidosis, etc.

Treatment. The drug of first choice for the treatment of all forms of tularemia except meningitis is streptomycin (7.5 to 10 mg/kg bid IM) for 7 to 14 days, although gentamicin (3-5 mg/kg/d IV) is an acceptable substitute. Fluoroquinolones (ciprofloxacin and moxifloxacin) are the another treatment option for mild to moderate tularemia. Tetracycline and chloramphenicol are to be used with caution due to the high rate of relapse after treatment with these agents.

Additional treatment includes desintoxication and symptomatic therapy.

Surgical therapies are limited to drainage of abscessed lymph nodes and chest tube drainage of empyemas.

Prevention. A live attenuated vaccine is available for people at high risk of infection. It does not provide complete protection but reduces the severity of the disease.

Gloves, masks, and protective eye covers should be worn when skinning and dressing wild animals and when disposing of dead animals brought home by household pets. Wild game should be cooked thoroughly before ingestion. Wells or other waters that are contaminated by dead animals should not be used.

The most important measure to avoid tick bites in infested areas is wearing clothing that is tight at the wrists and ankles and that covers most of the body. Chemical tick repellants may also be of benefit.

Antibiotic prophylaxis after potential exposures of *unknown risk*, such as tick bites, is not recommended. Either doxycycline (0.1 g bid) or ciprofloxacin (0.5 g bid) given orally for 14 days is recommended for adults with suspected or proven *high-risk* exposure to *F. tularensis*.

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ANTHRAX

Anthrax is a worldwide disease of domesticated and wild animals that secondarily may occur in humans. Estimates of worldwide cases vary widely, but it is estimated by the World Health Organization that there are between 2000 and 20,000 human cases per year.

Etiology and epidemiology. *Bacillus anthracis*, the causative agent of anthrax, is a large (1–1.5 × 3–8 μm), gram-positive bacillus with rapid, non-hemolytic growth on blood agar that readily forms spores in the presence of oxygen. The spores are extremely hardy and may survive in certain soil conditions for decades. Although spores have demonstrated viability in soil for decades and even longer in bones from an archeological site, in most environments, where the organism must compete with other soil-dwelling bacteria, they typically survive only for months and rarely more than 4 years.

Animals are infected when they graze on fields or grain contaminated with spores or through the bites of flies that have fed on infected carcasses.

Human cases usually are associated with exposure to infected animals or contaminated animal products. Numerous products have been implicated in transmission to humans including wool, hair, bone and bone meal, meat, horns, and hides. The source may not be readily evident as the animal product may have been processed, e. g., goat-skin drums, wool-based tapestries, and bone meal-based fertilizers. In developing countries, the major risk is with exposure to contaminated soil. Transmission from flies has also been documented.

Pathogenesis. *B. anthracis* spores introduced into the host are ingested at the exposed site by macrophages and then germinate into vegetative forms that produce the virulence factors. *B. anthracis* has 3 known virulence factors: an antiphagocytic capsule and 2 protein toxins (known as edema factor and lethal factor). Lethal factor and edema factor are named for the effects they induce when injected into experimental animals.

Classification and clinical features. The three primary forms of anthrax are dependent on the route of exposure: 1) cutaneous, 2) inhalational (pulmonary), 3) gastrointestinal. Bacteremia secondary to any of the primary forms of anthrax may lead to seeding of any site, including the central nervous system with the resulting hemorrhagic meningoencephalitis.

Cutaneous anthrax. Naturally occurring anthrax infections in humans are, in more than 95 % of cases, cutaneous disease. After the introduction of anthrax spores into the skin, often with just trivial trauma, there is an incubation period of 1–10 (more commonly 3–5) days, leading to the development of a small, pruritic papule at the inoculation site. The majority of lesions are on exposed areas of the head, neck, and extremities. A day or two after the formation of the papule, vesicles containing a clear to serosanguineous fluid form around the lesion and may become quite large, 1–2 cm in diameter. There is no purulence, and

the lesions remain painless. The vesicles are thin roofed and easily rupture, leading to formation of a dark brown, turning to black, eschar at the base of a shallow ulcer. The ulcer is typically surrounded by an area of induration, and in some cases non-pitting edema may be marked.

In uncomplicated cases lesions slowly heal over a period of 1–3 weeks and the eschar loosens and falls off, typically without leaving a scar. Antibiotics do not affect the evolution of the skin lesions. In most cases, patients report associated headache, malaise and low-grade fever even if the infection does not progress to bacteremia.

Inhalational (pulmonary) anthrax. Incubation period lasts 1–6 days. The first symptoms occur in the early prodromal stage with a "flu-like" illness characterized by low-grade fever, malaise, fatigue, and myalgias. Headache may be prominent, the fatigue may be profound, and blurred vision and photophobia occur in some cases. Dry cough and mild precordial discomfort are also seen in some patients. Patients may experience a biphasic illness during which they feel somewhat improved after the 2–3 days of the prodromal illness, while others progress directly to the intermediate-progressive stage associated with high fever, declining pulmonary status, respiratory distress, dyspnea, marked diaphoresis, pleuritic chest pain, and confusion or syncope. Mediastinal widening and pleural effusions are noted radiographically.

Gastrointestinal anthrax. Typically incubation period lasts 1–5 days. Oropharyngeal anthrax demonstrates symptoms and signs at the site of inoculation in the mouth or pharynx of swelling, severe pharyngitis, dysphagia, odynophagia, fever, and in some cases, respiratory distress due to marked edema and lymphadenitis. An ulcer may be observed in the mouth, the pharynx, the tonsil, or the tongue. Pseudomembranes often form over the ulcer after the first week, bringing diphtheria into the differential diagnosis. Although significant neck swelling is seen in all oropharyngeal cases, massive facial and neck edema is occasionally seen.

Intestinal disease occurs with infection of the stomach or bowel wall. The patient presents with nausea, vomiting, and fever, followed by severe abdominal pain often manifested as a surgical abdomen. Many cases will be associated with hematemesis, massive ascites, and bloody diarrhea.

Meningitis is an uncommon sequel of cutaneous anthrax but a frequent complication of the rarer inhalational or gastrointestinal disease, occurring in up to 50 % of cases of the former. The hallmark of anthrax meningitis is its hemorrhagic component associated with large gram-positive bacilli. CNS involvement may also include parenchymal brain hemorrhage and subarachnoid hemorrhage possibly owing to a diffuse cerebral arteritis or necrotizing vasculitis. As might be expected from anthrax infections in other sites, cerebral edema may also be prominent.

Initial symptoms include abrupt onset of severe headache, malaise, fever, chills, nausea, and vomiting. Meningeal signs such as nuchal rigidity may be absent early in the course but develop as the patient deteriorates. Seizures, delirium, and coma usually follow within hours. Death was inevitable in the pre-antibiotic era but is currently estimated at approximately 95 % of cases.

Diagnosis and differential diagnosis. Culture of B. anthracis (vesicle fluid, sputum, blood, stool, cerebrospinal fluid) remains the gold standard for the diagnosis of anthrax infections.

Gram stains of vesicular lesions can reveal the organism — a large, encapsulated, Gram-positive rod in short chains.

A rapid enzyme-linked immunosorbent assay (ELISA) can be used for anthrax serological diagnosis. Acute and convalescent serum samples should be obtained for serology at 0–7 days of illness and at 14–28 days.

A number of rapid PCR assays have been developed. Some of these can be used on either clinical or environmental samples. Caution must be used in interpreting these results, as false-positive and -negative results may occur.

Chest X-ray film in pulmonary anthrax often reveals diffuse infiltrates and effusions. Widening of the mediastinum is seen late in the disease.

The differential diagnosis of cutaneous anthrax includes tularemia, scrub typhus, rat bite fever, blastomycosis, ringworm acquired from animals, and mycobacterial infection with *Mycobacterium marinum*. Gastrointestinal anthrax should be differentiated with Shigella, Yersinia or Campylobacter infections, pulmonary anthrax — wide array of bacterial and viral processes.

Treatment. Ciprofloxacin 500 mg PO b.i.d. or doxycycline 100 mg PO b.i.d. for 7–10 days for localized or uncomplicated cases of naturally acquired cutaneous anthrax.

Inhalational and gastrointestinal anthrax should be treated by IV ciprofloxacin 400 mg q12h (first line) or doxycycline 100 mg q12h (second line) and, in case of fulminant bacteremia, 1 or 2 additional antimicrobials, such as rifampin, vancomycin, penicillin, ampicillin, chloramphenicol, imipenem, clindamycin, and clarithromycin. The course of antibiotic treatment has to last 60 days. Early and aggressive pleural fluid drainage is recommended for all cases of inhalational anthrax. A human IgG1λ monoclonal antibody directed against a component of the anthrax toxin (raxibacumab) can also be used in patients with symptomatic inhalational anthrax.

Prevention. Prevention measures include vaccination of livestock in endemic areas, decontamination of imported hides and animal hair, vaccination of the individuals from the high-risk groups (laboratory workers, persons who work with imported animal hides or furs, persons who handle potentially infected animal products in high-incidence areas, military personnel deployed to areas with high risk for exposure to organisms).

Anthrax vaccine adsorbed is approved for ages 18–65 and should be effective against all known strains of B. anthracis. Vaccine is given IM in 5 doses at 0, 4 weeks, and 6, 12, and 18 months plus annual boosters.

Patients with a likely inhalational exposure history, but no symptoms, are candidates for postexposure prophylaxis with either ciprofloxacin 500 mg PO b.i.d. or doxycycline 100 mg PO b.i.d. for 60 days. CDC guidelines state patients should also receive 3 doses of anthrax vaccine (0, 2 weeks, 4 weeks). Prophylactic medications are not indicated for prevention of cutaneous anthrax.

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BRUCELLOSIS

Brucellosis is a zoonotic infectious disease of both wild and domestic animals. Humans are the accidental host of the pathogen and develop a systemic disease of acute or insidious onset.

Etiology and epidemiology. Human brucellosis is caused by strains of *Brucella*, aerobic, small, gram-negative, unencapsulated, nonsporulating rods or coccobacilli. In vivo, brucellae behave as facultative intracellular parasites.

B. melitensis is the commonest cause of symptomatic disease in humans and is acquired from sheep, goats, and camels. *B. abortus* is usually acquired from cattle or buffalo, *B. suis* — from swine but has one variant enzootic in reindeer and caribou and another in rodents, *B. canis* — from dogs. *B. ovis*, which causes reproductive disease in sheep, and *B. neotomae*, which is specific for desert rodents, have not been clearly implicated in human disease. Other brucellae have been isolated from marine mammals, and two new nomen species, *B. cetaceae* and *B. pinnipediae*, have been proposed.

Brucellosis exists in animals worldwide but is especially prevalent in the Mediterranean basin, the Arabian peninsula, the Indian subcontinent, and in parts of Central Asia, Africa, Mexico, and Central and South America.

Routes of transmission from animal to human include: 1) direct contact with infected animals or their secretions through cuts or abrasions in the skin or conjunctiva, 2) inhalation of contaminated aerosols, 3) ingestion of unpasteurized dairy products. In areas where drinking animal blood or ingesting raw liver are traditions, foodborne infection from other than dairy products is possible. Person-to-person transmission of brucellosis is unusual; however, rare cases

in which sexual and vertical transmission was suspected have been reported. In addition, blood transfusions and bone marrow transplants can be sources of brucellosis. Brucellae are potential airborne biologic weapon.

Pathogenesis. Exposure to brucellosis elicits both humoral and cell-mediated immune responses. Antibodies promote clearance of extracellular brucellae by bactericidal action and by facilitation of phagocytosis by polymorphonuclear and mononuclear phagocytes; however, antibodies alone cannot eradicate infection. Organisms taken up by macrophages and other cells can multiply within them and establish persistent intracellular infections. Brucellae within macrophages and monocytes become localized in organs of the reticuloendothelial system, such as the lymph nodes, liver, spleen, and bone marrow. Subsequent hematogenous spread may result in chronic localizing infection at almost any site, although the reticuloendothelial system, musculoskeletal tissues, and genitourinary system are most frequently targeted. Both acute and chronic inflammatory responses develop in brucellosis, and the local tissue response may include granuloma formation with or without necrosis and caseation. Abscesses may also develop, especially in chronic localized infection.

Clinical features. Attempts to categorize the disease into acute, subacute, and chronic according to the length or severity of symptoms are purely arbitrary. When involvement of a specific organ predominates, the disease is often termed focal or localized.

The symptoms of brucellosis are nonspecific (e. g., fever, sweats, malaise, anorexia, headache, generalized aches, arthralgias, weight loss). The onset can be insidious or acute, generally beginning within 2 to 8 weeks after inoculation. An undulant or “wave-like” fever pattern is apparent in patients who are untreated for long periods of time, leading to the name undulant fever for brucellosis. Some patients report malodorous sweat and a peculiar taste in the mouth. Depression is common and often out of proportion to the severity of other symptoms.

Hepatomegaly, splenomegaly, and lymphadenopathy may be found. A significant proportion of patients (20–50 %) have osteoarticular involvement, including spondylodiscitis. Symptoms due to orchitis and/or epididymitis also may be manifestations of brucellosis in a considerable proportion (5–25 %) of patients. in general, brucellosis may affect any organ of the body and present occasionally as a localized infection (i. e., pneumonia, endocarditis. etc.).

Sequelae are also variable, and include granulomatous hepatitis, anaemia, leukopenia, thrombocytopenia, meningitis, uveitis, and optic neuritis.

Diagnosis and differential diagnosis. Brucellosis should come to the mind of a physician when he or she sees a patient from an endemic area with a febrile illness of acute or insidious onset, especially if there are manifestations of osteoarticular involvement.

Definitive diagnosis of brucellosis is made with the culture of the pathogen from blood, bone marrow or other tissue specimens. Cultures should be kept for at least 4 weeks when brucellosis is a possibility.

In the absence of bacteriologic confirmation confirmation, a presumptive diagnosis can be made by serologic tests. Raised (1:160) or a rising antibody titre in symptomatic patients suggests the diagnosis of active brucella. Demonstration of antibodies with various tests including standard tube agglutination test, mercaptoethanol test, classic Huddleson, Wright, and/or Bengal/Rose reactions. False-negative serologic tests for brucellosis may be due to the prozone phenomenon. False-positive results may be obtained due to cross-reactions (*Yersinia enterocolitica*, *Vibrio cholera*, *Francisella tularensis*). Attention also should be paid to the fact that IgG antibodies against Brucella species may be found in all forms (acute, recurrent, or chronic) of the infection. An ELISA to detect antibodies against Brucella is more reliable for the diagnosis.

Molecular techniques/real-time PCR has been developed.

An abdominal ultrasound or CT/MRI of the abdomen will detect enlarge lymph nodes and organomegaly. Radiological alterations in infected vertebrae — the Pedro Pons sign (preferential erosion of antero-superior corner of lumbar vertebrae) and marked osteophytosis are suspicious of brucellic spondylitis.

A liver biopsy may disclose granulomatous hepatitis.

Treatment. Currently, the combination of doxycycline (200 mg/day PO for 6 weeks) plus gentamicin (5 mg/kg/day IM for 7 days) provides excellent results. The combination of doxycycline (200 mg/day PO for 6 weeks) plus rifampin (600 to 900 mg/day PO for 6 weeks) offers the advantage of an all-oral regimen, but it is not advised in cases with complications, such as spondylitis, central nervous system involvement, and endocarditis. Trimethoprimsulfamethoxazole is useful for treating children younger than 8 years of age, in whom tetracycline is contraindicated, in combination with other drugs, such as rifampin, a quinolone, or an aminoglycoside. Both trimethoprim-sulfamethoxazole and rifampin appear to be safe drugs for treating brucellosis during pregnancy. Quinolone combinations are suboptimal.

Corticosteroids are often recommended for neurobrucellosis; however, in the absence of controlled studies, efficacy is unproven.

Valve replacement is usually necessary in cases of *Brucella* endocarditis.

Prevention. The prevention of human brucellosis depends on the elimination of the disease in animals. Vaccination of cattle and identification of sick animals are the mainstay of such an approach. Also human should avoid contact with infected animals.

Good standards of hygiene in the production of raw milk and its products, or pasteurization of all milk, will prevent brucellosis acquired from ingestion of milk.

No safe vaccine is available for professions at risk.

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LEPTOSPIROSIS

Leptospirosis is a zoonosis of global distribution, caused by infection with pathogenic spirochetes of the genus *Leptospira*.

Etiology and epidemiology. Historically, the genus *Leptospira* was classified into two species, *L. interrogans* and *L. biflexa*, comprised of pathogenic and nonpathogenic strains, respectively. Within each species, large numbers of serovars were differentiated using agglutinating antibodies. Although more-recent DNA analysis does not correlate well with the above mentioned serological classification. There are currently 18 species, including pathogens, nonpathogenic saprophytes, and species of indeterminate pathogenicity (e. g., *L. inadai*). Some species contain both pathogenic and nonpathogenic strains. However, for clinical and epidemiologic reasons, it is still more practical to use a classification system based on serologic differences.

Leptospirosis affects at least 160 mammalian species. It is maintained in nature by chronic renal infection of carrier animals. Rodents, especially rats, are the most important reservoir, although other wild mammals as well as domestic and farm animals may also harbor leptospires. Humans are incidental hosts and onwards transmission is rare. The main mode of disease transmission to humans is through the contact of the abraded skin or of mucous membranes with water, vegetation, or soil contaminated with urine of infected animals (e. g. canoeing, swimming in lakes and rivers, farming), but also food and drink consumption.

The peak incidence occurs in the rainy season in tropical regions and the late summer to early fall in temperate regions. Outbreaks may follow periods of excess rainfall.

Pathogenesis. The pathogenesis of leptospirosis is incompletely understood. After gaining entry via the skin or mucous membranes, there is widespread hematogenous dissemination of leptospires and penetration of tissue barriers, including invasion of the central nervous system and aqueous humor of the eye. Transendothelial migration of spirochetes is facilitated by a systemic vasculitis. The direct endothelium affliction may lead to hemorrhage.

Leptospiraemia particularly affects the liver and kidney causing centrilobular necrosis and jaundice or interstitial nephritis and tubular necrosis, respectively. Renal failure may occur. The list of affected organs also includes muscles (oedema and/or focal necrosis).

When antibodies are formed, leptospires are eliminated from all sites in the host except the eye, the proximal renal tubules, and perhaps the brain, where they may persist for weeks or months. The systemic immune response is effective in eliminating the organism but may also produce symptomatic inflammatory reactions.

Clinical features. Incubation period is usually 7–12 days (range 2–25 days). The majority of patients (90 %) develop mild disease without jaundice (anicteric form); 5–10 % develop the severe form, Weil's disease (icteric form). Disease is biphasic: the first leptospiremic phase lasts 4–7 days; the second phase ("immune" or "leptospiruric phase") starts after 1–3 days period of improvement, is characterized by immunological symptomatic inflammatory reactions and lasts up to a month. The distinction between the first and second phases is not always clear, and milder cases do not always include the second phase.

Anicteric form. Leptospirosis may present as an acute influenza-like illness, with fever, chills, severe headache, conjunctival suffusion, nausea, vomiting, and myalgias (especially in the calves, back, and abdomen). Less common features include sore throat and rash. Mental confusion may be evident. Pulmonary involvement, manifested in most cases by cough and chest pain and in a few cases by hemoptysis, is not uncommon. Less common findings include muscle tenderness, lymphadenopathy, pharyngeal injection, rash, hepatomegaly, and splenomegaly. The rash may be macular, maculopapular, erythematous, urticarial, or hemorrhagic. Mild jaundice and or renal impairment (pyuria, haematuria, proteinuria) may be present.

Most patients become asymptomatic within 1 week. After an interval of 1–3 days, the illness recurs in a number of cases. Symptoms are more variable than during the first (leptospiremic) phase. Usually the symptoms last for only a few days, but occasionally they persist for weeks. Often the fever is less pronounced and the myalgias are less severe. An important event during the immune phase is the development of aseptic meningitis.

Iritis, iridocyclitis, and chorioretinitis — late complications that may persist for years — can become apparent as early as the third week but often present several months after the initial illness.

Icteric form (Weil's disease). Icteric form, the most severe form of leptospirosis, is characterized by jaundice, renal dysfunction, and hemorrhagic diathesis; by pulmonary involvement in many cases; and by mortality rates of 5–15 %.

The onset of illness is no different from that of less severe leptospirosis; however, after 4–9 days, jaundice as well as renal and vascular dysfunction generally develop. Although some degree of defervescence may be noted after the first week of illness, a biphasic disease pattern like that seen in anicteric leptospirosis is lacking.

Hepatomegaly and tenderness in the right upper quadrant are usually detected. In contrast to patients with acute viral hepatitis, those with leptospirosis typically have elevated serum levels of bilirubin and alkaline phosphatase as well as mild increases (up to 200 U/L) in serum levels of aminotransferases. Splenomegaly is found in 20 % of cases.

Renal failure may develop, often during the second week of illness. Hypovolemia and decreased renal perfusion contribute to the development of acute tubular necrosis with oliguria or anuria.

Hemorrhagic manifestations including epistaxis, petechiae, purpura, and ecchymoses are found commonly, while severe gastrointestinal bleeding and adrenal or subarachnoid hemorrhage are detected rarely.

Pulmonary involvement occurs frequently, resulting in cough, dyspnea, chest pain, and blood-stained sputum and sometimes in hemoptysis or even respiratory failure.

Rhabdomyolysis, hemolysis, myocarditis, pericarditis, congestive heart failure, cardiogenic shock, adult respiratory distress syndrome, necrotizing pancreatitis, and multiorgan failure have all been described during severe leptospirosis.

The erythrocyte sedimentation rate is usually elevated. In anicteric leptospirosis, peripheral leukocyte counts range from 3000 to 26,000/ L, with a left shift; in Weil's disease, leukocytosis is often marked. Mild thrombocytopenia occurs in up to 50 % of patients and is associated with renal failure.

Diagnosis and differential diagnosis. Leptospirosis should be considered as diagnostic possibility in every febrile patient at risk for the infection due to occupation or recreational activities.

Leptospires can be isolated from blood and/or CSF during the first 10 days of illness and from urine for several weeks beginning at ~1 week. Cultures most often become positive after 2–4 weeks, with a range of 1 week to 6 months. For isolation of leptospires from body fluids or tissues, Ellinghausen–McCullough–Johnson–Harris (EMJH) medium is useful. Quantitative PCR assays to detect leptospiral DNA have been also developed.

Dark-field examination of blood or urine frequently results in misdiagnosis and should not be used.

Serology is a mainstay of the diagnosis. A definite diagnosis of leptospirosis is based on seroconversion or a rise in antibody titer in the microscopic agglutination test (MAT). A positive MAT is considered to be a fourfold increase in antibody titre, or a switch from seronegative to a titre of 1:100 or over. In addition to

the MAT the ELISA and various rapid tests (based on lateral flow, (latex) agglutination, or ELISA methodology) with diagnostic value have been developed.

Leptospirosis should be differentiated from other febrile illnesses associated with headache and muscle pain, such as dengue, malaria, enteric fever, viral hepatitis, influenza, Hantavirus infections, and rickettsial diseases.

Treatment. Treatment should be initiated as early as possible. In milder cases, oral treatment with doxycycline or amoxicillin should be considered. For severe cases of leptospirosis, intravenous administration of penicillin G, ampicillin, or ceftriaxone is recommended. Patients with severe leptospirosis and renal failure may require dialysis. Those with Weil's disease may need transfusions of whole blood and/or platelets. Steroids have been used in severe case of leptospirosis, especially when the respiratory or renal system has been afflicted but there is no consensus on this use. Intensive care may be necessary.

Prevention. Measures for controlling leptospirosis include avoidance of exposure to urine and tissues from infected animals, vaccination of animals, and rodent control.

Chemoprophylaxis with doxycycline (200 mg once a week) has appeared to be efficacious to some extent but is indicated only in cases of accidental lab exposure or military/adventure travel.

Vaccines are available against specific serovars.

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VIRAL HAEMORRHAGIC FEVERS

Viral haemorrhagic fevers (VHF) are severe, potentially life-threatening diseases caused by the members of several viral families (table 7).

Table 7

Virus	Source or vector	Distribution
Arenaviridae		
Junin (Argentine HF)	Rodent	Northern part of Buenos Aires province
Machupo (Bolivian HF)	Rodent	Northeastern Bolivian savannah
Guanarito (Venezuelan HF)	Rodent	Venezuelan cleared forest areas
Lassa HF	Rodent	West Africa

Virus	Source or vector	Distribution
Bunyaviridae		
Crimean-Congo HF	1) Ticks; 2) Contact with infected animals	The Commonwealth of Independent States, Middle East, Africa
HF with renal syndrome (Hantavirus)	Rodent	Parts of China, Asia, Russia and Europe
Rift valley fever	Mosquito	Sub-Saharan Africa
Filoviridae		
Ebola fever	Bats	Democratic Republic of Congo, Republic of Congo, Sudan, Liberia, Guinea, Nigeria, Cote d'Ivoire, Sierra Leone, Gabon, Uganda
Marburg fever	Unknown	Uganda, Western Kenya
Flaviviridae		
Yellow fever	Human or monkey, via mosquito	South America, sub-Saharan Africa
Dengue fever	Human, via mosquito	Asia, sub-Saharan Africa, South America
Omsk HF	Tick	Russia
Kyansanur forest disease	Tick	India
Togaviridae		
Chikungunya fever	Mosquito	Africa, Asia

Clinical features. VHF should be considered in a patient with a febrile illness who has returned from endemic country within 3 weeks. Early clinical features usually are mild and non-characteristic: fever, cough, headache, sore throat, nausea, vomiting, weakness, abdominal and chest pains. Severe features present a few days later and include: haemorrhage, encephalopathy, hepatitis, shock.

Differential diagnosis. In patients returned from "malaria belt" countries malaria should be excluded as soon as possible. Typhoid fever and rickettsial infections should also be considered.

Management and infection control. Place of treatment depends on the risk, clinical progress, and local protocols. Minimum-risk patients (i. e., patients who has not been in an endemic area or left it more than 3 weeks before symptom onset) are usually managed in a standard side room. The other patients with suspected VHF should be isolated and full special precautions taken in acquiring and transporting samples.

There are no specific treatments, except ribavirin for Lassa fever and HF with renal syndrome. Management is supportive.

Infection control precautions aim to prevent secondary infection of other patients and/or staff. Gloves, water-repellant aprons, face visors, and masks should be used. Sharps and other contaminated equipment should be disposed of extremely carefully.

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HAEMORRHAGIC FEVER WITH RENAL SYNDROME

This disease, the first to be identified as a haemorrhagic fever (HF), is widely distributed over Europe and Asia. HF with renal syndrome (HFRS) is the most important form of HF today, with > 100,000 cases of severe disease in Asia annually and milder infections numbering in the thousands as well.

Etiology and epidemiology. HFRS is caused by *Hantaviruses* (a genera of *Bunyaviridae* family). These agents are fundamentally parasites of wild rodents and insectivores. Each of the presently recognized viral species has a single major rodent host species. ***Hantaan*** virus, the cause of severe HFRS in Korea, China, and eastern Russia, is carried by the striped field mouse, *Apodemus agrarius*. ***Dobrava*** virus associated with *Aedes flavicollis* is the major cause of severe HFRS in the Balkans, and related viruses cause similarly severe disease in other areas of the former Soviet Union. Another hantavirus, ***Seoul*** virus, is found worldwide in *Rattus norvegicus*. Bank voles, *Clethrionomys glareolus*, are the reservoir-vectors of ***Puumala*** virus, the cause of a milder form of HFRS termed nephropathia epidemica in Scandinavia, the western former Soviet Union, and Europe. This species becomes chronically infected despite an immune response that eliminates viremia, and its members excrete virus in urine and saliva for weeks or months.

Aerosols of virus-contaminated rodent urine or perhaps feces are thought to represent the principal vehicle for the transmission of Hantaviruses; disease has also followed the bite of infected rodents (saliva contains virus). Patients with Hantavirus diseases are not infectious.

Most cases occur in rural residents or vacationers; the exception is Seoul virus disease, which may be acquired in an urban or rural setting or from contaminated laboratory rat colonies. Disease is maximal in "highrodent" years, when suburban residents may be exposed to disposing of infected rodents. The incidence of HFRS may be the highest in summer or in fall and early winter.

Pathogenesis. The process by which hantaviruses cause multisystem organ dysfunction syndrome is unclear. Hantavirus disease is mainly microvascular in nature and endothelium is the predominant cell type involved. Endothelial damage or dysfunction leads to capillary engorgement, leakage of erythrocytes and increased permeability. Recent studies implicated the disease process as being immunologically based, with lymphocytes playing a key role, especially T-cells. Lymphocyte induction of migrating macrophages and other inflammatory cells results in the production of cytokines which in turn increases vascular permeability.

Thrombocytopenia, defects in platelet function, transient disseminated intravascular coagulation and increased vascular fragility are all thought to play a key role in the disease.

Clinical features. The incubation period, typically 2 weeks, may vary from 5 to 42 days. The hallmarks of clinical infection by Hantaviruses are fever, thrombocytopenia, and acute renal insufficiency pathologically typical of acute interstitial nephritis. In the severe form of HFRS exemplified by Hantaan virus infection or Dobrava virus in Europe, patients who survive full-blown disease progress through the febrile stage with myalgia, lasting 3 or 4 days; the hypotensive stage, often associated with shock and lasting from a few hours to 48 h; the oliguric stage with renal failure, lasting 3–10 days; and the polyuric stage with diuresis and hyposthenuria.

The febrile stage is initiated by the abrupt onset of fever, headache, severe myalgia, thirst, anorexia, and often nausea and vomiting. Photophobia, retroorbital pain, and pain on ocular movement are common, and the vision may become blurred with ciliary body inflammation. Flushing over the face, the V area of the neck, and the back is characteristic, as are pharyngeal injection, periorbital edema, and conjunctival suffusion. Petechiae often develop in areas of pressure, the conjunctivae, and the axillae. Back pain and tenderness to percussion at the costovertebral angle reflect massive retroperitoneal edema. Laboratory evidence of mild to moderate disseminated intravascular coagulation is present. Other laboratory findings include proteinuria and active urinary sediment.

The hypotensive stage is ushered in by falling blood pressure and sometimes by shock. The relative bradycardia typical of the febrile phase is replaced by tachycardia. Leukocytosis with a left shift develops, and thrombocytopenia continues. The renal circulation is congested and compromised from local and systemic circulatory changes resulting in necrosis of tubules, particularly at the corticomedullary junction, and oliguria.

During the oliguric stage, hemorrhagic tendencies continue, probably in large part because of uremic bleeding defects. The oliguria persists for 3–10 days before the return of renal function marks the onset of the polyuric stage, which carries the danger of dehydration and electrolyte abnormalities.

The fatality rate in severe HFRS caused by Hantaan or Dobrava viruses averages about 5 %.

The milder form of HFRS caused by Puumala virus and often referred to as nephropathia epidemica is rarely hemorrhagic and is fatal in less than 1 % of clinical cases. Abdominal pain and hyposphenuria may be manifestations. Up to 90 % of Puumala virus infections are asymptomatic. Proteinuria, creatinine level elevation, and leukocytosis, although common, are much less severe than for Hantaan virus infection.

Seoul virus also causes a mild to moderately severe HFRS in Eurasia with more prominent hepatic involvement than classic HFRS.

Diagnosis. The diagnosis is readily made by IgM-capture ELISA, which should be positive at admission or within 24–48 h thereafter. The isolation of virus is difficult, but reverse transcription-PCR of a blood clot collected early in the clinical course or of tissues obtained postmortem will give positive results. Immunohistochemical staining of tissues can also be valuable.

Treatment. Ribavirin was effective in the treatment of HFRS. Early management of hantavirus patients should avoid excessive administration of fluids. Vascular leak leads to extravasation into retroperitoneal tissues; cardiotonic drugs should be used early because of the hemodynamic profile of decreased cardiac output and increased systemic vascular resistance. Patients with severe HFRS may require hemodialysis or peritoneal dialysis during the oliguric phase, and plasma protein or whole blood, or both, may be useful in treating hemorrhage or shock, or both. Heparin is not recommended for the treatment of presumptive or incipient disseminated intravascular coagulation in HFRS.

Prevention. There is no vaccine in general use, and prevention is by public health measures to reduce vector numbers, and personal avoidance.

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EBOLA HAEMORRHAGIC FEVER

Ebola HF is a severe, often fatal disease in humans and nonhuman primates (such as monkeys, gorillas, and chimpanzees).

Etiology and epidemiology. Ebola HF is caused by infection with a virus of the family *Filoviridae*, genus *Ebolavirus*.

There are five identified subspecies of Ebolavirus. Four of the five have caused 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.

The natural reservoir host of ebolaviruses remains unknown. However, on the basis of available evidence and the nature of similar viruses, researchers believe that the virus is zoonotic with bats being the most likely reservoir. Four of the five subspecies occur in an animal host native to Africa, Reston virus — to the Philippines.

The virus is spread through direct contact (through broken skin or mucous membranes) with 1) a sick person's blood or body fluids (urine, saliva, feces, vomit, and semen); 2) objects (such as needles) that have been contaminated with infected body fluids; 3) infected animals.

Pathogenesis. The precise mechanisms by which filoviruses cause the most severe forms of VHF are unclear, but there is marked hepatic involvement, DIC and shock, producing extremely high fatality rates (30–90 %). As with other VHF infections fluid imbalance and platelet abnormalities indicate endothelial cell and platelet damage or dysfunction. Infected monocyte and/or macrophages have been shown in in-vitro models to secrete TNF which has the ability to increase vascular endothelial cell damage. The data currently available support mediator-induced vascular damage that leads to increased permeability and shock observed in severe cases. Hemorrhage is likely to be caused by reticuloendothelial system damage that cannot be repaired because of platelet and coagulation malfunctions.

Clinical features. Incubation period is from 2 to 21 days after exposure to ebolavirus, although 8–10 days is most common. Ebola HF begins with the abrupt onset of fever (greater than 38.6 °C), usually accompanied by myalgia and headache. The fever is joined by some combination of nausea and vomiting, abdominal pain, diarrhea, chest pain, cough, and pharyngitis. Other common features include photophobia, lymphadenopathy, conjunctival injection, jaundice, and pancreatitis. Central nervous system involvement is often manifested by somnolence, delirium, or coma. As the disease progresses, wasting becomes evident, and bleeding manifestations such as petechiae, hemorrhages, ecchymoses around needle puncture sites, and mucous membrane hemorrhages occur in half or more of the patients. A characteristic maculopapular rash occurs 7–10 days (range 1–21 days) after onset of the clinical disease.

In the second week, the patient defervesces and improves markedly or dies in shock with multiorgan dysfunction, often accompanied by disseminated intravascular coagulation, anuria, and liver failure. Convalescence may be protracted and accompanied by arthralgia, orchitis, recurrent hepatitis, transverse myelitis, or uveitis.

Clinical laboratory findings in the early acute phase include lymphopenia followed by neutrophilia, marked thrombocytopenia and abnormal platelet aggregation. Serum aspartate aminotransferase and alanine aminotransferase are elevated (AST levels more than ALT levels).

Diagnosis. The clinical diagnosis of Ebola should be considered in patients who show acute, febrile illness and have traveled in known epidemic or suspected endemic areas, particularly when hemorrhagic signs are present.

Antigen-detection ELISA is a sensitive, robust diagnostic modality. Seroconversion occurs around day 8 to 12. Virus isolation from blood and RT-PCR of blood specimen are also effective during acute stages. Skin biopsies

are an extremely useful adjunct in postmortem diagnosis of infection with Ebola virus because of the presence of large amounts of viral antigen.

In convalescence, virus has been isolated from semen for several weeks and from anterior chamber fluid in a case of late uveitis.

Treatment. If there are reasons to believe that Ebola HF should be considered, the patient should be isolated. No specific vaccine or medicine is available. Treatment is limited to the provision of intensive nursing and effective control of blood volume and electrolyte balance. Shock, renal failure, depletion of blood clotting factors, severe bleeding and oxygen depletion must be managed.

Human interferon and human convalescent plasma have been used to treat patients, but their efficacy is not proved. In addition, a recombinant inhibitor of the tissue factor-activated factor VII complex improved survival in one study and should also be considered in severe cases.

Prevention. Properly sterilized injection equipment, protection from body fluids and skin contact during preparation of the dead, and routine barrier nursing precautions are probably adequate in most cases.

An adenovirus-vectored Ebola glycoprotein gene has proved protective in nonhuman primates and is undergoing trials in humans.

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SEPSIS

Sepsis is a systemic, deleterious host response to infection. Severe sepsis and septic shock are major healthcare problems, affecting millions of people around the world each year, killing one in four (and often more), and increasing in incidence. Similar to polytrauma, acute myocardial infarction, or stroke, the speed and appropriateness of therapy administered in the initial hours after severe sepsis develops are likely to influence outcome.

Etiology and epidemiology. In the USA an annual incidence for severe sepsis is approximately 3 cases per 1000 (2.26 cases/100 hospital discharges), what is equivalent to 751 000 cases each year. Severe sepsis was responsible for 0.61 % of all hospital admissions but 11 % of admissions to intensive care in the Netherlands. Similar data showed a point prevalence for severe sepsis in ICU admissions of 28.7 % in the UK and 27 % in France. In Australia and New

Zealand severe sepsis has been estimated in 0.77 per 1000 of the population and is responsible for 11.8/100 ICU admissions. In surveys performed in ICUs in the United States, Europe and Russia approximately 70 % to 95 % of the cases of sepsis in adults occurred in individuals who were already hospitalized for other reasons, i. e. were healthcare-associated.

Although the median age for patients with a sepsis-related hospital discharge diagnosis is approximately 60 years, the attack rate is very high among infants (more than 500 cases per 100,000 population per year), with low-birth-weight newborns experiencing particularly high risk. Sepsis incidence and sepsis-related mortality decrease after the first year of life and then increase steadily with increasing age. The mortality of sepsis varies because of variations in infection prevalence, case definition, ICU facilities and patient populations. In an analysis of four large sepsis trials, 14-day mortality averaged 26 % and 28-day mortality 42 %.

A 2009 review of an international registry of patients with severe sepsis demonstrates some basic characteristics of the septic disease process on the basis of data from more than 11,000 patients from 37 countries. The lung was the primary source of the infection in 47 % of the patients, followed by the abdomen (23 %) and urinary tract (8 %). A substantial proportion of the patients had comorbidities, including diabetes (24 %), chronic lung disease or cancer (16 %), congestive heart failure (14 %), and renal insufficiency (11 %). Of these patients, 57 % had gram-negative infections, 44 % had gram-positive infections, and 11 % had fungal infections (some had mixed infections, so the total is > 100 %). According to the international agreement viruses and parasites are possible but uncommon sepsis-associated pathogens.

Community-acquired sepsis due to classical bacterial pathogens, such as *Neisseria meningitidis*, *Streptococcus pneumoniae* or *Streptococcus pyogenes*, is much less frequently encountered nowadays than is healthcare-associated sepsis triggered by commensal microbes that infect individuals whose epithelial barriers or other antimicrobial defenses have been compromised by injury or illness. The main gram-negative pathogens in healthcare associated sepsis are *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Enterobacteriaceae spp.* (*Klebsiella pneumoniae, Escherichia coli, Serratia marcescens*, etc.), *Stenotrophomonas maltophilia, Burkholderia cepacia*. *Staphylococcus aureus*, coagulase-negative staphylococci, and enterococci are their companions among gram-positives. *Candida spp.* and less frequently *Aspergillus spp.* are key fungal agents of healthcare-associated sepsis in patients without hematological malignances.

Pathogenesis. A bacterial pathogen typically enters a sterile site in which the resident cells detect the invader and initiate the inflammatory response. When a limited number of bacteria invade, the local responses are sufficient to clear the pathogens. Antigen presenting cells (APCs) such as macrophages and dendritic cells can alert the host to the presence of infection through the recogni-

tion of pathogen associated molecular patterns, which are conserved microbial molecules that are present in a broad array of bacteria, fungi, and viruses. Such molecules are recognized by pathogen recognition receptors (PRRs) on APCs. PRRs activate intracellular transduction pathways, i. e. via nuclear factor kappa (NF- kb). Activated NF- kb moves from the cell cytoplasm to the nucleus, binds to transcription sites and induces activation of an array of genes for acute-phase proteins, proinflammatory cytokines, inducible nitric oxide synthase (iNOS), coagulation factors, and enzymatic activation of cellular proteases. Once activated, the innate immune system initiates the inflammatory response by secreting cytokines and chemokines, inducing the expression of costimulatory molecules in order to recruit immune cells to the site of infection and to trigger the adaptive immune response. Additional cells are typically recruited to the site of inflammation to assist with the eradication of the pathogen. The cytokines secreted by the resident inflammatory cells stimulate the synthesis of adhesion molecules on the surface of endothelial cells. Circulating white blood cells transiently bind to the endothelial cells, and then are recruited through the vascular wall to the site of inflammation.

Microbial antigen is presented to T cells by APCs, in conjunction with other cell-surface proteins and costimulatory molecules. When the appropriate signals are received, effector CD4+ T cells secrete cytokines, such as interferon (IFN)-γ, that activate phagocytotic cells to kill intracellular bacteria and interact with B cells, which then produce antimicrobial antibodies.

The first step in phagocytic-cell killing of microorganism involves phagocytosis of the pathogen. When pathogens enter the host, they are typically opsonized, that is, covered with host proteins including antibodies and fragments of complement. The pathogen recognition receptors localized on the surface of the neutrophil (complement and receptors for the Fc portion of immunoglobulin, Toll-like receptors) assist phagocytosis by recognizing the opsonized proteins on the surface of the bacteria. The phagocytosed bacteria is typically inside a vacuole, the phagosome, which fuses with specific intracellular granules to form the phagolysosome. Fusion of the neutrophil granules with the bacteria creates a hostile local environment, with decreased pH and potent proteases that focus on killing the pathogen. Macrophages phagocytosed bacteria also produce a range of proinflammatory cytokines (interleukin (IL)-1β, tumor necrosis factor (TNF), and IL-6, as well as chemokines such as IL-8), which initiate the innate immune system's response to the pathogen.

Sepsis develops when the inflammatory response to infection rises to such a level that physiologic alterations within the host occur leading to systemic inflammatory response syndrome development due to hyper production of proinflammatory cytokines (so called hyperinflammatory stage of sepsis or cytokine storm). This response is sometimes termed an exuberant or exaggerated inflammatory response, but this may not be an appropriate characterization.

The bacterial load may be of such magnitude (or the bacteria may be so virulent) that a strong inflammatory response appropriately matches the powerful bacterial stimulus, yet the "collateral damage" it simultaneously produces cannot be compensated for by the septic patient.

Being firstly hyperinflammatory condition, cytokine storm leads to the synthesis of anti-inflammatory cytokines (IL-10, IL-1 receptors antagonist, transforming growth factor beta, steroids, etc.) in order to control and balance inflammation. Simultaneously, septic patients experience a significant decline in the number of lymphocytes through apoptosis, increased expression of the inhibitory costimulatory molecules (ligands or receptors to anti-inflammatory cytokines) on the remaining T cells and downregulation of the proinflammatory ones, leading therefore to alteration of the signals received from APCs and anergy in surviving macrophages and dendritic cells. The ensued severe immune depression is termed compensatory anti-inflammatory response syndrome (CARS) and is characterized by the domination of anti-inflammatory cytokines, inability to eradicate invading pathogens and susceptibility to secondary nosocomial infections.

Additionally, dysfunctions in coagulation develop during the course of sepsis and lead to inappropriate intravascular fibrin deposition. When the natural balance of coagulation (fast onset and fast multilayered inhibition) is unbalanced during disease, small clots form faster than they can be broken down, and they lodge in the microvascular beds of organs. The paradox of developing disseminated intravascular coagulation (DIC) is that the patients are undergoing nearly unrestricted clotting and, as a result, are at high risk for bleeding due to the consumption coagulopathy (platelets and coagulation factors are consumed faster than they can be replaced).

The above mentioned changes result in the homeostasis alterations consisting in uncontrolled cascade of pathologic reactions in coagulation and inflammatory systems. These reactions occur simultaneously, potentiate each other and lead to endothelial damage, frustration of microcirculation, DIC syndrome and multi-organ failure.

Classification and clinical features. Diagnosis in patients suffering from sepsis is currently based on a clinical classification (SIRS criteria) and divided into: 1) ***sepsis***, 2) ***severe sepsis***, 3) ***septic shock***.

According to this classification sepsis is defined as infection, documented or suspected, plus two or more of the SIRS manifestations (table 8).

Table 8

Systemic inflammatory response syndrome (SIRS) manifestations

General variables
Fever (> 38.3 °C)
Hypothermia (core temperature < 36 °C)
Heart rate > 90/min^{-1} or more than two SD above the normal value for age
Tachypnea
Altered mental status

General variables
Significant edema or positive fluid balance (> 20 mL/kg over 24 hr)
Hyperglycemia (plasma glucose > 140 mg/dL or 7.7 mmol/L) in the absence of diabetes
Inflammatory variables
Leukocytosis (WBC count > 12,000 μL^{-1})
Leukopenia (WBC count < 4000 μL^{-1})
Normal WBC count with greater than 10 % immature forms
Plasma C-reactive protein more than two SD above the normal value
Plasma procalcitonin more than two SD above the normal value
Hemodynamic variables
Arterial hypotension (SBP < 90 mm Hg, MAP < 70 mm Hg, or an SBP decrease > 40 mm Hg in adults or less than two SD below normal for age)
Organ dysfunction variables
Arterial hypoxemia (PaO_2/FiO_2 < 300)
Acute oliguria (urine output < 0.5 mL/kg/hr for at least 2 hrs despite adequate fluid resuscitation)
Creatinine increase > 0.5 mg/dL or 44.2 μmol/L
Coagulation abnormalities (INR > 1.5 or aPTT > 60 s)
Ileus (absent bowel sounds)
Thrombocytopenia (platelet count < 100,000 μL^{-1})
Hyperbilirubinemia (plasma total bilirubin > 4 mg/dL or 70 μmol/L)
Tissue perfusion variables
Hyperlactatemia (> 1 mmol/L)
Decreased capillary refill or mottling

WBC = white blood cell; SBP = systolic blood pressure; MAP = mean arterial pressure; INR = international normalized ratio; aPTT = activated partial thromboplastin time.

PaO2/FiO2 – arterial oxygen partial pressure / fractional inspiredoxygen

Adapted from M. M. Levy [et al.] 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Crit. Care Med. 2003. Vol. 31. P. 1250–1256.

Severe sepsis is defined as sepsis plus sepsis-induced organ dysfunction or tissue hypoperfusion (any of the signs stated in the table 9 thought to be due to the infection).

Table 9

Manifestations of severe sepsis

Sepsis-induced hypotension (systolic blood pressure (SBP) < 90 mm Hg or mean arterial pressure (MAP) < 70 mm Hg or a SBP decrease > 40 mm Hg or less than two standard deviations below normal for age in the absence of other causes of hypotension
Lactate above upper limits laboratory normal
Urine output < 0.5 mL/kg/hr for more than 2 hrs despite adequate fluid resuscitation
Acute lung injury with PaO_2/FiO_2 < 250 in the absence of pneumonia as infection source
Acute lung injury with PaO_2/FiO_2 < 200 in the presence of pneumonia as infection source
Creatinine > 2.0 mg/dL (176.8 μmol/L)
Bilirubin > 2 mg/dL (34.2 μmol/L)
Platelet count < 100,000 μL
Coagulopathy (international normalized ratio > 1.5)

Adapted from M. M. Levy [et al.] 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Crit. Care Med. 2003. Vol. 31. P. 1250–1256.

Septic shock is defined as sepsis-induced hypotension not responding to fluid resuscitation.

Besides the above mentioned positions there are two definitions included into this sepsis classification — ***bacteremia*** and ***multi-organ dysfunction syndrome*** (MODS). Bacteremia is defined as viable bacteria cultured from bloodstream without clinical signs of infection. Multi-organ dysfunction syndrome is defined as failure of two or more inner organs and/or systems.

Additionally sepsis can be classified by pathogen, place of occurrence and localization of primary infection site:

***By pathogen*:**

1. Bacterial.
2. Viral.
3. Parasitic.
4. Helminthic.

***By place of occurrence*:**

1. Community-acquired.
2. Healthcare-associated.

***By localization of on the primary infection site*:**

1. Urosepsis.
2. Intraabdominal.
3. Odontogenic.
4. Pulmonary.
5. …
6. Cryptogenic.

Symptoms that suggest the onset of sepsis are often nonspecific and include sweats, chills or rigors, breathlessness, nausea and vomiting or diarrhea, and headache. Confusion may be found in 10–30 % of patients, especially the elderly, and sepsis-related encephalopathy is associated with a poorer clinical outcome. There may be specific localizing symptoms or signs to suggest the underlying pathology, such as cough, dysuria or meningism, but in many cases there are no clues.

With progression to severe sepsis and shock there is increasing evidence of organ dysfunction; the key physical signs and physiologic changes indicating this are encapsulated in table 5, 6. Remember that sepsis is a dynamic evolving clinical picture and frequent re-evaluation of the patient is essential.

The characteristic patient is febrile, tachypneic, tachycardic with warm peripheries and a bounding arterial pulse, hypotensive, disoriented and oliguric. With impending circulatory collapse the patient may develop peripheral vasoconstriction with cool peripheries and a prolonged capillary refill time.

Some patients, particularly the elderly or immunocompromised, have a more subtle presentation necessitating a high index of suspicion to recognize early disease. Most patients are febrile but severe sepsis may present with hypothermia.

Focal physical signs may help to identify the site of infection, for example renal angle tenderness, pulmonary consolidation, new cardiac murmur or finding an intra-abdominal mass.

If the patient is hypotensive, other causes of shock such as cardiac dysfunction (including myocardial infarction and cardiac tamponade), hypovolemia and redistributive shock from pancreatitis and physical injuries need to be considered. Remember that hypotension in sepsis is often multifactorial and sepsis may complicate or coexist with other causes of shock.

Diagnosis. Routine investigations may show leucopaenia, thrombocytopaenia, and lactic acidosis.

Cultures should be taken preferably before antimicrobial therapy if it causes no significant delay (> 45 mins) in the start of antimicrobial(s). At least 2 sets of blood cultures (both aerobic and anaerobic bottles) should be obtained before antimicrobial therapy with at least 1 drawn percutaneously and 1 drawn through each vascular access device, unless the device was recently (< 48 hrs) inserted. Cultures of potential sources should also be taken. If invasive candidiasis is considered in differential diagnosis of cause of infection the 1,3 beta-D-glucan assay or mannan and anti-mannan antibody assays should be used.

Imaging studies should be performed promptly to confirm a potential source of infection.

Additional option in sepsis diagnosis is presented by biomarkers (molecules that are correlated with disease states or states of altered physiology). In human sepsis, several inflammation-associated biomarkers, such as procalcitonin (PCT), interleukine-6 (IL-6) and C-reactive protein (CRP), are claimed to be either of diagnostic value or correlated with death.

Treatment.

1. Source Control

A specific anatomical diagnosis of infection requiring consideration for emergent source control should be sought and diagnosed or excluded as rapidly as possible, and intervention should be undertaken for source control within the first 12 hours after the diagnosis is made, if feasible.

If intravascular access devices are a possible source of severe sepsis or septic shock, they should be removed promptly after other vascular access has been established.

2. Antimicrobial Therapy

Initial empiric anti-infective therapy should be administered within the first hour of recognition of sepsis. It includes one or more drugs that have activity against all likely pathogens (bacterial and/or fungal or viral etc.) and that penetrate in adequate concentrations into tissues presumed to be the source of sepsis. The choice of agents depends on the clinical presentation, i. e. community or hospital-acquired, neutropenia level, colonization with drug-resistant microorganisms.

Combination empirical therapy is often restricted to neutropenic patients with severe sepsis and for patients with difficult-to-treat, multidrug-resistant bacterial pathogens such as *Acinetobacter and Pseudomonas spp.* Antimicrobial regimen should be reassessed daily for potential de-escalation. Empiric combination therapy should not be administered for more than 3–5 days. De-escalation to the most appropriate single therapy should be performed as soon as pathogen and its susceptibility profile is known.

Duration of therapy is typically 7–10 days; longer courses may be appropriate in patients who have a slow clinical response, undrainable focci of infection, bacteremia with *S. aureus*; some fungal and viral infections or immunologic deficiencies, including neutropenia.

3. Resuscitation

Goals during the first 6 hours of resuscitation:

a) central venous pressure 8–12 mm Hg;

b) mean arterial pressure (MAP) ≥ 65 mm Hg;

c) urine output ≥ 0.5 mL/kg/hr;

d) central venous (superior vena cava) or mixed venous oxygen saturation 70 % or 65 %, respectively.

In patients with elevated lactate levels targeting resuscitation to normalize lactate.

A number of therapeutic measures directed to reach the abovementioned goals includes: fluid therapy (crystalloids, mainly), glucose control (blood glucose level ≤ 10 mmol/L), deep vein thrombosis prophylaxis, stress ulcer prophylaxis, adequate nutrition and replacement of altered organs functions (i. e., mechanical ventilation, renal replacement therapies, etc.).

In septic shock patients vasopressors (preferably norepinephrine) and corticosteroids (preferably hydrocortisone) should be added. Inotropic therapy (i. e., dobutamine infusion) can be administered or added to vasopressor (if in use) in the presence of (a) myocardial dysfunction as suggested by elevated cardiac filling pressures and low cardiac output, or (b) ongoing signs of hypoperfusion, despite achieving adequate intravascular volume and adequate mean arterial pressure.

Prevention. A number of measures may be implemented to prevent sepsis:

– infection control measures;

– management of high-risk patients (e. g. bone marrow transplant patients) in a protective environment;

– active or passive immunoprophylaxis (e. g. pneumococcal vaccine).

– selective oral decontamination (chlorhexidine gluconate) and selective digestive decontamination (rifaximin, aminoglycosides per os) should be introduced as a method to reduce the incidence of ventilator-associated pneumonia.

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ERYSIPELAS

Erysipelas is a superficial cutaneous process, usually restricted to the dermis but with prominent lymphatic involvement. Usually affects children, infants, and the elderly. Predisposing factors include skin lesions (surgical incisions, trauma or abrasions, dermatologic diseases such as psoriasis, or local fungal infections), venous stasis, neurologic disorders, diabetes mellitus, and alcohol abuse.

Etiology. It is almost always caused by β-hemolytic streptococci. In most cases the infecting agent is the group A streptococci (*Streptcoccus pyogenes*), but similar lesions can be caused by streptococci of group C or G. Rarely, group B streptococci or *S. aureus* may be the culprits.

Clinical features. Usually occurs on the face or the legs. The cutaneous lesion begins as a localized area of painful erythema and swelling and then spreads rapidly with advancing red margins, which are raised and well demarcated from adjacent normal tissue. There is marked edema, often with bleb formation, and in facial erysipelas the eyes are frequently swollen shut. The cutaneous inflammation is accompanied by chills, fever, and general toxicity. Flaccid bullae may develop during the second or third day of illness, but extension to deeper soft tissues is rare.

Diagnosis and differential diagnosis. The diagnosis is based on clinical signs of the disease. Erysipelas is distinguished clinically from other forms of cutaneous infection by two features: the lesions are raised above the level of the surrounding skin, and there is a clear line of demarcation between involved and uninvolved tissue.

The differential diagnosis is limited. Early on, the lesions of facial herpes zoster, contact dermatitis or giant urticaria may be confused with erysipelas. Lesions resembling erysipelas may occur in patients with familial Mediterranean fever. Cutaneous lesions similar in appearance to those of erysipelas may occur

on the hands of patients who sustain cuts or abrasions while handling fish or meats. This entity, known as erysipeloid of Rosenbach and caused by *Erysipelothrix rhusiopathiae*, is usually unaccompanied by fever or systemic symptoms.

Treatment. Penicillin, either parenterally or orally, depending on clinical severity, is the treatment of choice. If staphylococcal infection is suspected, a flucloxacillin, clindamycin, cefazoline or erythromycin should be selected.

Additional treatment includes oral or parenteral desintoxication therapy, and non-steroid anti-inflammatory drugs for pain and fever relief (if necessary).

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BOTULISM

Definition. Botulism is a paralytic disease caused by potent neurotoxins elaborated by *Clostridium botulinum*.

There are 3 clinical forms of botulism:

1) food-borne botulism — from ingestion of preformed toxin in food contaminated with *Cl. botulinum*;

2) wound botulism — from toxin produced in wounds contaminated with *Cl. botulinum*;

3) intestinal botulism — from ingestion of spores and production of toxin in the intestine of infants (infant botulism) or adults (rare).

Etiology. *Cl. botulinum* — a heterogeneous group of anaerobic gram-positive organisms that form spores and elaborates the most potent bacterial toxin. Rare strains of other clostridial species — *Cl. butyricum* and *Cl. baratii* — have been found to produce toxin. *Cl. botulinum* can be found in soil and marine environments throughout the world.

Different types of *Cl. botulinum* A through G have been distinguished by the antigenic specificities of their toxins. Toxin types A, B, E and rarely F cause disease in humans; type G (from *Cl. argentinense*) has been associated with sudden death but not with neuroparalytic illness in a few patients in Switzerland. Toxin types C and D cause disease in animals.

Epidemiology. Human botulism occurs worldwide. Food-borne botulism is associated primarily with home-canned food (particularly mushrooms, vegetables, meat) and fish (espesially toxin E). Commercial products occasionally cause outbreaks. Food-borne botulism can occur when: 1) food to be preserved is contaminated with spores, 2) preservation does not inactivate the spores but

kills other putrefactive bacteria that might inhibit growth of *Cl. botulinum* and provides anaerobic conditions at a pH and temperature that allow germination and toxin production, 3) food is not heated to a temperature that destroys toxin before being eaten. One of the most significant sourse of spores in intestinal botulism in infants is contaminated honey.

Botulinum toxin because of its extraordinary potency may be a threat as an agent of bioterrorism that could be acquired by inhalation or ingestion. Iatrogenic botulism can follow cosmetic or therapeutic use of toxin.

Pathogenesis. Botulinum neurotoxin whether ingested, inhaled or produced in the intestine or a wound, enters the vascular system and is transported to peripheral cholinergic nerve terminals, including neuromuscular junctions, postganglionic parasympathetic nerve endings and peripheral ganglia. The central nervous system is not involved. Steps in neurotoxin activity include binding, internalization in endocytic vesicles, translocation to the cytosol and proteolysis resulting in a blockage of the release of the neurotransmitter acetylcholine. Cure follows sprouting of new nerve terminals.

Clinical manifestations. *Food-Borne Botulism*. The incubation period is usually 18–36 h but depending on toxin dose can range from a few hours to several days. After ingestion of food containing toxin illness varies from a mild condition for which no medical care is sought to very severe disease that can result in death within 24 h. Symmetric descending paralysis is characteristic and can lead to respiratory failure and death.

Usually first signs of the disease is cranial nerves involvement produces diplopia, dysarthria, dysphonia and/or dysphagia. Then symmetric weakness progresses from the head to involve the neck, arms, thorax and legs. Dizziness, blurred vision, dry mouth and tongue are common. Ptosis is frequent; the pupillary reflexes may be depressed and fixed or dilated pupils may be noted. The gag reflex may be suppressed. Nausea, vomiting and abdominal pain may precede or follow the onset of paralysis. Paralytic ileus, severe constipation and urinary retention are common.

Patients with botulism are generally alert and oriented and typically they have no fever. There are no any sensory abnormalities and the neurologic findings are symmetric.

Type A disease is generally more severe than type B and mortality rates from botulism are higher among patients older than age 60 than among younger patients. With improved respiratory and intensive care the case-fatality rate in food-borne illness has been reduced to ~7.5 % and is low in infant botulism as well. Some patients experience residual weakness and autonomic dysfunction for as long as a year after disease onset.

Wound Botulism. Wound botulism occurs when the spores contaminating a wound germinate and form vegetative organisms that produce toxin. This rare condition resembles food-borne illness except that the incubation period is

longer (about 10 days) and gastrointestinal symptoms are lacking. Wound botulism has been documented after traumatic injury involving contamination with soil; in injection drug users, for whom black-tar heroin use has been identified as a risk factor; and after cesarean delivery. The illness has occurred even after antibiotics have been given to prevent wound infection. When present fever is probably attributable to concurrent infection with other bacteria. The wound may appear benign.

Intestinal botulism. In intestinal botulism toxin is produced in and absorbed from the intestine after the germination of ingested spores. Intestinal botulism in infants (infant botulism) is the most common form of botulism. The severity ranges from mild illness to fulminant severe paralysis with respiratory failure. Intestinal botulism involving adults is uncommon. The patient may have a history of gastrointestinal disease, gastrointestinal surgery or recent antibiotic therapy. Toxin and organisms may be identified in the stool.

Laboratory diagnosis. The most cases of botulism must be diagnosed clinically in patients with symmetric descending paralysis who are afebrile and mentally intact. The bulbar musculature is involved initially but sensory findings are absent and deep tendon reflexes remain intact. A careful travel and activity history, as well as a dietary history, should be taken in any suspected botulism case. Patients should also be asked whether they know of other persons with similar symptoms.

The demonstration of toxin in serum by bioassay in mice is definitive diagnosis but this test may give negative results, particularly in wound and infant botulism and it is performed only by specific laboratories. The demonstration of *Cl. botulinum* or its toxin in vomitus, gastric fluid or stool is strongly suggestive of the diagnosis because intestinal carriage is rare. Isolation of the organism from food without toxin is insufficient grounds for the diagnosis. Wound cultures yielding the organism are suggestive of botulism.

Treatment. Patients should be hospitalized and monitored closely both clinically and by spirometry, pulse oximetry and measurement of arterial blood gases for incipient respiratory failure. Intubation and mechanical ventilation should be strongly considered when the vital capacity is < 30 % of predicted especially when paralysis is progressing rapidly and hypoxemia with absolute or relative hypercarbia is documented.

If there is no ileus laxatives and enemas may be used to purge the gut of toxin; gastric lavage had also to be used as soon as possible. The use of antibiotics to eliminate an intestinal source of possible continued toxin production isn't of proven value.

In food-borne illness **equine antitoxin** should be administered as soon as possible. Treatment should not await laboratory analyses which may take days. The trivalent antitoxin preparation (types A, B and E) is used when the type of

toxin isn't known. In case of outbreaks with known type of toxin monovalent antitoxin may be used.

After testing for hypersensitivity to horse serum antitoxin is given (intravenously or intramuscularly); repeated doses are not considered necessary. Anaphylaxis and serum sickness are risks inherent in use of the equine product and desensitization of allergic patients or use of high doses of corticosteroids (240-300 mg of prednisolone) before the antitoxin may be required.

Treatment of infant botulism requires supportive care and administration of human botulism immune globulin (not available in Belarus). Neither equine antitoxin nor antibiotics have been shown to be beneficial.

In wound botulism equine antitoxin is administered. The wound should be thoroughly explored and debrided and an antibiotic such as penicillin should be given to eradicate *Cl. botulinum* from the site

Prevention. A pentavalent vaccine (types A through E) is available for use in highly exposed individuals. Spores are highly resistant to heat but can be inactivated by exposure to high temperature (116–121 °C) and pressure as in steam sterilizers or pressure cookers used in accordance with the manufacturer's instructions. Toxin is heat-labile and can be inactivated by exposure to a temperature of 85 °C for 5 min.

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TETANUS

Definition. Tetanus is an infectious disease caused by *Cl. tetani* exotoxin (tetanospasmin) and characterized by increased muscle tone and spasms. There are several clinical forms of tetanus: generalized (most common), localized and neonatal.

Etiology. *Cl. tetani* is an anaerobic motile gram-positive rod that forms spores. Vegetative cells of *Cl. tetani* can produce exotoxin that causes different forms of tetanus in people. Tetanospasmin is formed in vegetative cells and released at the moment of their autolysis. It finally consists of a heavy chain which mediates binding to and entry into nerve cells and a light chain which blocks neurotransmitter release.

Epidemiology. *Cl. tetani* is found worldwide in soil, in the inanimate environment, in animal and occasionally human feces. Spores may survive for years in some environments and are resistant to various disinfectants and to

boiling for 20 min. Vegetative cells are easily inactivated and are susceptible to several antibiotics, including metronidazole and penicillin.

Most causes of tetanus follow an acute injury (puncture wound, laceration, abrasion or other trauma). The disease may complicate chronic conditions such as skin ulcers, abscesses and gangrene. Tetanus has also been associated with burns, frostbite, middle-ear infection, surgery, abortion, childbirth, body piercing and drug abuse. In some cases no injury or portal of entry can be identified.

Tetanus occurs sporadically and almost always affects unimmunized persons or partially immunized persons. This disease is common in areas where soil is cultivated, in rural areas, in warm climates, during summer months and among males. In countries without a comprehensive immunization program tetanus occurs predominantly in neonates and other young children.

Pathogenesis. Toxin production of *Cl. tetani* starts after contamination of wounds with low oxidation-reduction potential (with devitalized tissue, foreign bodies or active infection) with spores of this bacterium and their germination. Toxin released in the wound binds to peripheral motor neuron terminals, enters the axon and is transported to the nerve-cell body in the brainstem and spinal cord by retrograde transport. Then it migrates across the synapse to presynaptic terminals where it blocks release of the inhibitory neurotransmitters glycine and γ-aminobutyric acid (GABA) and causes such clinical features as spasms and rigidity. Recovery requires sprouting of new nerve terminals.

In local tetanus only the nerves supplying the affected muscles are involved. Generalized tetanus occurs when toxin released in the wound enters the lymphatics and bloodstream and is spread widely to distant nerve terminals.

Clinical manifestations. The median time of tetanus onset after injury is 7 days (varied between 3 and 14 days).

Generalized tetanus, the most common form of the disease, is characterized by increased muscle tone and generalized spasms.

Typically the patient first notices increased tone in the masseter muscles (trismus). Dysphagia or stiffness and pain in the neck, shoulder and back muscles appears concurrently or soon thereafter. The subsequent involvement of other muscles produces a rigid abdomen and stiff proximal limb muscles; the hands and feet are relatively spared. Sustained contraction of the facial muscles results in a grimace or sneer (risus sardonicus) and contraction of the back muscles produces an arched back (opisthotonos). Trismus, risus sardonicus and dysphagia is the classical tetanus triad.

Some patients develop paroxysmal violent painful generalized muscle spasms that may cause cyanosis and threaten ventilation. These spasms occur repetitively and may be spontaneous or provoked by even the slightest stimulation. A constant threat during generalized spasms is reduced ventilation, apnea and laryngospasm. Mentation is unimpaired.

Autonomic dysfunction commonly complicates severe cases and is characterized by hypertension, tachycardia, dysrhythmia, hyperpyrexia, profuse sweating, peripheral vasoconstriction and increased plasma and urinary catecholamine levels.

There are some grades of tetanus severity: mild (muscle rigidity and few or no spasms), moderate (trismus, dysphagia, rigidity and spasms) or severe (frequent explosive paroxysms).

The most prominent complications of the disease: sudden cardiac arrest, aspiration pneumonia, fractures, muscle ruptures, deep-vein thrombophlebitis, pulmonary emboli, decubitus ulcers and rhabdomyolysis.

Neonatal tetanus usually occurs as the generalized form and is usually fatal if left untreated. It develops in children born to inadequately immunized mothers, frequently after unsterile treatment of the umbilical cord stump. Its onset generally comes during the first 2 weeks of life.

Local tetanus is a rare form in which manifestations are restricted to muscles near the wound.

Mortality rates now in generalized tetanus about 10 %. The outcome is poor in neonates and the elderly and in patients with a short incubation period, a short interval from the onset of symptoms to admission or a short period from the onset of symptoms to the first spasm (period of onset). Outcome is also related to the extent of prior vaccination.

The course of tetanus extends over 4–6 weeks and patients may require prolonged ventilator support. Increased tone and minor spasms can last for months but recovery is usually complete.

Laboratory diagnosis. The diagnosis of tetanus is based entirely on clinical findings. Tetanus is unlikely if a reliable history indicates the completion of a primary vaccination series and the receipt of appropriate booster doses. Wounds should be cultured in suspected cases. However *Cl. tetani* can be isolated from wounds of patients without tetanus and frequently cannot be recovered from wounds of those with tetanus.

Cerebrospinal fluid examination yields normal results. Electromyograms may show continuous discharge of motor units and shortening or absence of the silent interval normally seen after an action potential. Nonspecific changes may be evident on the electrocardiogram.

Muscle enzyme levels may be raised. Serum antitoxin levels of ≥ 0.1 IU/mL (as measured by ELISA) are considered protective and make tetanus unlikely.

Treatment. The goals of therapy are to eliminate the source of toxin, neutralize unbound toxin and prevent muscle spasms while monitoring the patient's condition and providing support — especially respiratory — until recovery.

1. Patients should be admitted to a quiet room in an intensive care unit, where observation and cardiopulmonary monitoring can be maintained continuously but stimulation can be minimized. Protection of the airway is vital.

2. Antitoxin given to neutralize circulating toxin and unbound toxin in the wound effectively lowers mortality; toxin already bound to neural tissue is unaffected. Human tetanus immune globulin (TIG) is the preparation of choice and should be given promptly (3000–6000 units intramuscular usually in divided doses). Additional doses are unnecessary because the half-life of antitoxin is long. Equine tetanus antitoxin (TAT) may be an alternative, it is cheaper than human antitoxin but the half-life is shorter and its administration commonly elicits a hypersensitivity reaction and serum sickness.

3. Wounds should be explored, carefully cleansed and thoroughly debrided.

4. Antibiotic therapy (penicillin 10-12 million units IV daily or metronidazole 500 mg every 6 hours IV for 10 days; also active clindamycin, erythromycin) is administered to eradicate vegetative cells — the source of toxin.

5. Supportive care: control of muscle spasms (diazepam, lorazepam — first-line agents, barbiturates, chlorpromazine — second-line agents, form spasms unresposive to medications or threaten ventilation — therapeutic paralysis with a nondepolarizing neuromuscular blocking agent and mechanical ventilation etc); respiratory care (intubation or tracheostomy with or without mechanical ventilation); correction of autonomic dysfunction (labetolol, esmolol, clonidine, verapamil, morphine sulfate, parenteral magnesium sulfate).

Prevention. The cornestone — is active immunization. All partially immunized and unimmunized adults should receive vaccine as should those recovering from tetanus (because immunity is not induced by the small amount of toxin required to produce disease).

Proper wound management requires consideration of the need for: 1) passive immunization with TIG, 2) active immunization with vaccine depending of the severity of wounds and current immunization status of patient. Vaccine and antibody should be administered at separate sites with separate syringes.

For neonatal tetanus preventive measures include maternal vaccination even during pregnancy, efforts to increase the proportion of births that take place in the hospital and the provision of training for nonmedical birth attendants.

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DIPHTHERIA

Definition. Diphtheria is an acute infectious disease caused by exotoxin of *Corynebacterium diphtheriae*. Most commonly it attacks pharynx and other organs of upper respiratory tract and may be accompanied by systemic complications (myocarditis, polyneuropathy).

Etiology. *C. diphtheriae* is a gram-positive, unencapsulated, nonmotile, nonsporulating bacillus. It has a characteristic club-shaped bacillary appearance and typically form clusters of parallel rays. Different microbiological media for isolation of *C. diphtheriae* may be used (most often medium with tellurite). Human isolates of *C. diphtheriae* may display nontoxigenic (tox−) or toxigenic (tox+) phenotypes. Some bacteriophages carries the structural gene (tox) encoding diphtheria toxin are responsible for toxigenic conversion of tox− *C. diphtheriae* to the tox+ phenotype.

Epidemiology. The main route of transmission for *C. diphtheriae* is via the aerool route during close contact. The organism may colonize the respiratory tract without causing disease. Other rare route of transmission are direct contact via different objects (toys, towels, dishes) or alimentary (via milk).

The only reservoir of *C. diphtheria* in nature is humans. In temperate climate respiratory diphtheria is most common during winter months. Immunity induced by vaccination during childhood but gradually decreases in adulthood so some older adults have antitoxin titers below the protective level. In addition to older age and lack of vaccination risk factors for illness include alcoholism, low socioeconomic status and crowded living conditions. During the 1990s in the states of the former Soviet Union a large diphtheria epidemic caused > 150,000 cases and > 5000 deaths. The epidemic was attributed to failure of the public health infrastructure to effectively vaccinate the population.

Pathogenesis. Diphtheria toxin produced by toxigenic strains of *C. diphtheriae* is the primary virulence factor in clinical disease. It consists of two chains — A fragment and B fragment. The toxin is produced in the pseudomembranous lesion and is taken up into the bloodstream through which it is distributed to all organ systems. Once bound to its cell surface receptor by B fragment, the toxin is internalized by receptor-mediated endocytosis and enters the cytosol. Delivery of the A fragment into the eukaryotic cell cytosol results in irreversible inhibition of protein synthesis by NAD+-dependent ADP ribosylation of elongation factor 2. The eventual result is the death of the cell.

Characteristic pathologic findings of diphtheria include mucosal ulcers with a pseudomembranous coating composed of fibrin and neutrophils. Initially white and firmly adherent in advanced diphtheria the pseudomembranes turn gray and even green or black as necrosis progresses. Mucosal ulcers result from toxin-induced necrosis of the epithelium accompanied by edema, hyperemia and vascular congestion of the submucosal base. A fibrinosuppurative exudate from

the ulcer develops into the pseudomembrane. Ulcers and pseudomembranes in severe respiratory diphtheria may extend from the pharynx into medium-sized bronchial airways. Expanding and sloughing membranes may result in fatal airway obstruction.

Clinical features. Diphtheria may be symptomless or rapidly fatal. The mean incubation period is 2–4 days (varies from 1 to 7 days).

Anterior nares diphtheria. The infection is localized to the anterior nasal area and is manifested by unilateral or bilateral serous or serosanguineous discharge that erodes the adjacent skin, resulting in small crusted lesions. The membrane may be seen in the nose.

***Tonsillar and pharyngeal diphtheria*.** Tonsillar diphtheria is the most common presentation and the most toxic form. The clinical diagnosis of tonsillar diphtheria is based on the constellation of mild sore throat, adherent tonsillar, pharyngeal or nasal pseudomembranous lesions and low-grade (usually rarely exceeding 38 °C) fever. The pseudomembranous lesion is most often located in the tonsillopharyngeal region. The diphtheritic pseudomembrane is gray or whitish and sharply demarcated. Unlike the exudative lesion associated with streptococcal pharyngitis the pseudomembrane in diphtheria is tightly adherent to the underlying tissues. Attempts to dislodge the membrane may cause bleeding. The regional cervical lymph nodes are enlarged.

In case of pharyngeal diphtheria the exudate may extend beyond the tonsils to the adjacent structures of the pharynx (uvula, hard palate, back of the throat etc.). A few patients develop massive swelling of the tonsils and present with "bull-neck" diphtheria which results from massive edema of the submandibular and paratracheal region and is further characterized by foul breath, thick speech, stridorous breathing and often septic shock (toxic or malignant diphtheria).

Laryngeal and bronchial diphtheria. Pseudomembranes in the larynx, trachea and bronchi may slough and obstruct the airway with appearance of a hoarse voice, barking cough and stenotic respiration. Children are particularly prone to airway obstruction because of their small airways.

Some patients may be carriers of *C. diphtheriae* who have positive cultures for *C. diphtheriae* and either are asymptomatic or have symptoms but lack pseudomembranes.

***Cutaneous diphtheria*.** This form of diphtheria most often characterized by punched-out ulcerative lesions with necrotic sloughing or pseudomembrane formation on the extremities. The diagnosis requires cultivation of *C. diphtheriae* from lesions. Patients usually seek medical attention because of nonhealing or enlarging skin ulcers which may be associated with a preexisting wound or dermatoses such as eczema, psoriasis and venous stasis disease.

Complications. Polyneuropathy and myocarditis are most common toxic manifestations of diphtheria.

Myocarditis occurs in 10–15 % of patients with diphtheria 1 to 2 weeks after the initial sore throat. The onset is insidious, the patient exhibits a weak, rising pulse, distant heart sounds and profound weakness and lethargy. Overt signs of heart failure can occur. The most common ECG changes are flattening or inversion of T waves, bundle branch block or intraventricular block and disorders of rhythm. For diagnosis of myocarditis serial determination of cardiac enzyme concentrations and echocardiogram may be useful.

Neurologic manifestations may appear during the first or second week of illness typically beginning with dysphagia, nasal regurgitation and nasal dysarthria and progressing to other signs of cranial nerve involvement, including weakness of the tongue, facial numbness, ciliary and oculomotor paralysis. Ciliary paralysis manifests as blurred vision due to paralysis of pupillary accommodation with a preserved light reflex. Cranial neuropathy may be followed by respiratory and abdominal muscle weakness requiring artificial ventilation. Several weeks later (sometimes as cranial neuropathy is improving) a generalized sensorimotor polyneuropathy may appear. Gradual improvement is the rule in patients who survive the acute phase.

Laboratory diagnosis. The diagnosis of diphtheria is based on clinical signs and symptoms plus laboratory confirmation. The presence of a pseudomembrane should prompt consideration of diphtheria. Laboratory diagnosis is based on bacteriological cultivation of *C. diphtheriae* from the site of infection using selective media. Pharyngeal and nasal swabs should be submitted to the laboratory for culture as early as possible because it takes a long time (about 3 days) to differentiate *C. diphtheriae* from other nasopharyngeal commensal corynebacteria and to detect tox+ *C. diphtheriae*. In Belarus all patients with exudative tonsillopharyngitis who seek medical attention must be examined for possible diphtheria.

Treatment. Prompt administration of diphtheria antitoxin (a horse antiserum) is critical in the management of respiratory diphtheria. The antitoxin is effective in reducing the extent of local disease, the risk of complications and a mortality risk. Because diphtheria antitoxin cannot neutralize cell-bound toxin prompt initiation is very important. The use of antitoxin includes a test dose to rule out immediate type hypersensitivity. Patients who exhibit hypersensitivity require desensitization or use of high doses of corticosteroids intravenously before a full therapeutic dose of antitoxin is administered.

Antibiotics (benzyl penicillin, ampicillin, erythromycin, rifampicin or clindamycin for 5–7 days) are used in the management of diphtheria primarily to prevent transmission to other susceptible contacts. Eradication of *C. diphtheriae* should be documented at least 1 day after antimicrobial therapy is complete. A repeat throat culture 2 weeks later is recommended.

Patients in whom diphtheria is suspected should be hospitalized in respiratory isolation rooms with close monitoring of cardiac and respiratory function.

A cardiac workup is recommended to assess the possibility of myocarditis. In patients with extensive pseudomembranes consultation with an anesthesialogist or an ear, nose and throat specialist is recommended because of the possibility that tracheostomy or intubation will be required.

Prevention. At present diphtheria toxoid vaccine is coadministered with tetanus and pertussis vaccine (DTaP) for children before 1 year old with subsequent revaccinations. Individuals with an antitoxin titer of > 0.01 unit/mL are at low risk of diphtheria disease. In populations where a majority of individuals have protective antitoxin titers the carrier rate for toxigenic strains of *C. diphtheriae* decreases and the overall risk of diphtheria among susceptible individuals is reduced. Nevertheless individuals with nonprotective titers may contract diphtheria through either travel or exposure to individuals who have recently returned from regions where the disease is endemic.

Close contacts of diphtheria cases should undergo throat and nasal culture to determine whether they are carriers. After samples for throat culture are obtained antimicrobial prophylaxis should be considered for all close contacts even those who are culture-negative. The options are 7–10 days of oral erythromycin or one dose of IM benzathine penicillin G. Contacts of diphtheria cases who have an uncertain immunization status should receive the appropriate diphtheria toxoid-containing vaccine. Carriers of *C. diphtheriae* in the community should be treated and vaccinated when identified.

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CHLAMYDIA INFECTIONS

Etiology. *Chlamydia* and *Chlamydophila* are nomotile, obligate intracellular prokaryotic organisms. In the current schema they are classified in the order *Chlamydiales*, which contains only one family, the *Chlamydiaceae*, and two genera, *Chlamydia* and *Chlamydophila*.

Within this family there are four currently recognized species: *Chlamydophila pecorum*, *Chlamydophila psittaci*, *Chlamydia trachomatis* and *Chlamydophila pneumoniae*. All except *C. pecorum* have been associated with human disease.

Psittacosis. Psittacosis is a systemic infection that frequently causes pneumonia. The causative agent of psittacosis is *Chlamydophila psittaci*.

Epidemiology. *C. psittaci* is common in birds and domestic animals. Infection is therefore a hazard to pet owners. The infection is generally spread by the respiratory route, by direct contact or aerosolization of infective discharges or dust. Rarely, the bird may spread the infection by a bite.

Pathophysiology. All chlamydiae have a unique life cycle that uses an extracellular infectious form, the elementary body (EB), and an intracellular replicative form, the reticulate body (RB).

Clinical features. The disease begins after an incubation period of 5 to 15 days with nonproductive cough, fever, headache, and chest film abnormalities more dramatic than would be suggested by the physical findings. The illness ranges in severity from an inapparent or mild disease to a fatal systemic illness with prominent respiratory symptoms.

Diagnosis. The total white blood cell count is usually normal or slightly elevated. Appearance on the chest film is abnormal in approximately 75 % of patients and is usually more abnormal than auscultation would predict.

Laboratory diagnosis depends mainly on serology: microimmunofluorescence (MIF) and complement-fixing (CF) methods are used.

Differential diagnosis: meningitis, community-acquired pneumonia, pulmonary embolism, endocarditis, vasculitis, septicemia, brucellosis and polymyositis.

Treatment. Possible regimens may include: azithromycin 250–500 mg per os daily × at least 7 days; doxycycline 100 mg twice daily or tetracycline 500 mg four times a day for 10 days.

Prevention. Avoid close contacts with birds if possible. Infected birds should be treated with tetracycline, chlortetracycline, or doxycycline for at least 45 consecutive days. There is no documented protection after infection, and second infections are possible.

Chlamydophila pneumoniae.

Etiology. *C. pneumoniae* appears to be a common human respiratory pathogen. Obligate intracellular bacteria.

Epidemiology. The mode of transmission occurs through patients infected respiratory secretions.

Clinical presentation. Major cause of respiratory infections: community-acquired pneumonia, pharyngitis, sinusitis, bronchitis.

May cause atypical pneumonia, manifests as upper respiratory tract infection (rhinitis, laryngitis) + cough + patchy infiltrate, slow onset and prolonged presentation with cough more than 2 weeks.

Diagnosis. Most common serological method is MIF serology. PCR use looks promising.

Treatment. Treatment possibilities include macrolides, doxycycline or levofloxacin for at least 7 days: azithromycin 250–500 mg per os once daily or clarithromycin 500 mg twice daily; doxycycline 100 mg twice daily per os; levofloxacin 750 mg every 24 hours.

Prevention. There are no effective specific preventive measures, prophylactic antibiotic use after close contact with patient being discussed.

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MYCOPLASMA INFECTIONS

Etiology. *Mycoplasma* organisms are prokaryotes that lack a cell wall. They are bounded by a cell membrane containing sterols, substances not found in other bacteria or viruses. Because of their small size and deformable membrane, they are able to pass through filters with pore sizes that retain other bacteria. Therefore, when first discovered, they were thought to be viruses.

Member of *Mollicutes* class, among the smallest known free-living bacteria. The family *Mycoplasmataceae* is composed of two genera responsible for human infection, *Mycoplasma* and *Ureaplasma*. *M. pneumoniae* is one of the most common causes of atypical pneumonia in humans.

Mycoplasma pneumoniae infection.

Pathophysiology and epidemiology. *M. pneumoniae* attach to the surface of ciliated and nonciliated epithelial cells. *M. pneumoniae* infection is spread from one patient to another by respiratory droplets produced by coughing.

Clinical features. *Mycoplasma pneumonia* infection has an incubation period of 2 to 3 weeks. *Mycoplasma pneumoniae* onset often gradual with dry cough, prominent headache, fever, malaise and sore throat. Cough may last 4–6 wks. The frequency and severity of cough increase over the next 1 to 2 days and may become debilitating. On physical examination, the general appearance is that of a patient who is not terribly ill. In fact, this disease is the paradigm of the term "walking pneumonia". Examination of the chest in patients with *Mycoplasma pneumonia* is often unrevealing, even in those patients with severe, productive cough. Disparity between physical findings and radiographic evidence of pneumonia in this condition may be the greatest of any of the atypical pneumonia syndromes.

Diagnosis. Problematic diagnosis since culture difficult, serology insensitive at time of presentation. *Mycoplasma* IgM are commonly negative first 7–10 days Sputum PCR probably best for rapid, accurate diagnosis but availability limited.

Normal white blood cell count and clear chest exam despite pneumonia on X-ray should prompt consideration of atypical pneumonias, esp. *Mycoplasma*.

Differential diagnosis. Other causes of community-acquired pneumonia should be discussed.

Treatment. Antibiotics can shorten the duration of illness, though cough may continue for weeks. Prolonging light cough without other symptoms of active infection should not be estimated as a cause of restarting or prolonging antibiotic treatment. Usual duration of antibiotics is 7–14 days. Possible choices include: Azithromycin 250–500 mg per os once daily; Clarithromycin 250 mg per os every 12 hours; Erythromycin 250 mg per os four times a day; Levofloxacin 500 mg per os once daily; Moxifloxacin 400 mg per os once daily; Doxycycline 100 mg per os twice daily.

Prevention. In case of outbreak in a closed environment there are data of effectiveness of Azithromycin 250–500 mg per os daily for 5 days to reduce secondary attack rate.

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INFLUENZA

Etiology. There are three main types of influenza virus: Types A, B and C. The influenza A and B viruses that routinely spread in people (human influenza viruses) are responsible for seasonal flu epidemics each year. Influenza A viruses can be broken down into sub-types depending on the genes that make up the surface proteins neuraminidase (N) and hemagglutinins (H). Over the course of a flu season, different types (A & B) and subtypes (influenza A) of influenza circulate and cause illness. There are 18 different hemagglutinin subtypes and 11 different neuraminidase subtypes. (H1 through H18 and N1 through N11, respectively). Influenza B viruses are not divided into subtypes, but can be further broken down into lineages and strains. Currently circulating influenza B viruses belong to one of two lineages: B/Yamagata and B/Victoria.

The internationally accepted naming convention for influenza viruses was accepted by WHO in 1979 and published in February 1980 in the Bulletin of

the World Health Organization. The naming approach uses the following components:

– the antigenic type (e. g., A, B, C);

– the host of origin (e. g., swine, equine, chicken, etc. For human-origin viruses, no host of origin designation is given);

– geographical origin (e. g., Denver, Taiwan, etc.);

– strain number (e. g., 15, 7, etc.);

– year of isolation (e. g., 57, 2009, etc.).

For influenza A viruses, the hemagglutinin and neuraminidase antigen description in parentheses (e. g., (H3N2), (H5N1).

Aerosol transmission is the main route of the influenza spread. It may occur 1 day before the onset of symptoms and last until the 5^{th} day of the symptomatic illness. Thus, it may be possible for transmission to occur via asymptomatic persons or persons with subclinical disease, who may be unaware that they have been exposed to the disease.

Avian influenza (H5N1, H7N9, H7N7 et al.) is rare in humans in developed and other countries.

Pathogenesis. The main targets of the influenza virus are the columnar epithelial cells of the trachea, bronchi and bronchioles. Hemagglutinin (HA) binds to galactose-bound sialic acid on the surface of host cells. The HA binding site is highly conserved between subtypes of the influenza virus. Cleavage of the virus from the binding site at the host cell is essential and is mediated by the neuraminidase. In humans, the replication of the influenza virus is usually restricted to the airways epithelial cells due to the limited expression of a serine protease, produced by nonciliated bronchial epithelial cells and which cleaves the HA precursor in HA1 and HA2 polypeptides, rendering the virions infectious. Replication and virions production occurs within hours after virus entry. Human influenza leads to complex cytopathic effects due to downregulation of host cell protein synthesis and apoptosis, predominantly in the the airways epithelial cells.

Clinical features. The incubation period of influenza is 2 days long on average but may range from 1 to 4 days in length. The presentation of influenza virus infection varies, but the main syndromes are: intoxication and catharal. Signs and symptoms include: fever, sore throat, myalgias, frontal or retro-orbital headache, nasal discharge, weakness and severe fatigue, cough and other respiratory symptoms (tracheitis is one of the most common symptom of influenza), tachycardia and red watery eyes.

Complications: Children aged less than 1 year and adults aged more than 65 years, pregnant woman, and people of any age with comorbid illnesses are at highest risk. Pulmonary complications (pneumonia) of influenza are the most common ones and include primary influenza and secondary bacterial infection. *Streptococcus pneumoniae* and *Staphylococcus aureus*, including methicillin-

resistant strains, are important causes of secondary bacterial pneumonia with high mortality. During influenza season, treatment of pneumonia should include empiric coverage for this pathogen. Neuromuscular and cardiac complications are unusual but may manifest in persons of any age.

Diagnosis. Influenza has traditionally been diagnosed on the basis of clinical criteria, but rapid diagnostic tests, which have a high degree of specificity but only moderate sensitivity, are becoming more widely used. The criterion standard for diagnosing influenza A and B is a viral culture of nasopharyngeal samples or throat samples. In elderly or high-risk patients with pulmonary symptoms, chest radiography should be performed to exclude pneumonia.

Treatment. Only these medicines have proved clinical effect for influenza treatment:

– oseltamivir 75 mg — 2 times daily in capsules for 5 days;

– zanamivir 10 mg — 2 times daily ingalations for 5 days.

Two other antiviral medicines Rematadine and Amantadine were used in past and are not effective now because of viral resistance.

Rest until disease is fully resolve, fluids in the case of intoxication, acetaminophen against temperature (aspirin is strictly contraindicated in children before 18, because of Reye syndrome).

Prevention. Prevention of influenza is the most effective management strategy. Influenza A and B vaccine is administered each year before flu season.

Traditionally, the vaccine is trivalent (i. e., designed to provide protection against 3 viral subtypes, generally an A-H1, an A-H3, and a B).

In addition to vaccination, other public health measures are also effective in limiting influenza transmission in closed environments. Enhanced surveillance with daily temperature taking and prompt reporting with isolation through home medical leave and segregation of smaller subgroups decrease the spread of influenza.

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PARAINFLUENZA

Etiology. Human Parainfluenza viruses (HPIVs) are paramyxoviruses of the family *Paramyxoviridae*.

Their pathogenic spectrum includes upper and lower respiratory tract infections: common cold with fever, laryngotracheobronchitis (croup), bronchiolitis, and pneumonia. HPIVs are one of the most frequent causes of community-acquired respiratory tract infections of variable severity in adults.

Pathogenesis. HPIV transmission occurs via direct inoculation of contagious secretions from the hands or via large-particle aerosols into the eyes and nose. Prolonged survival of HPIV on skin, cloth, and other objects emphasizes the importance of fomites in nosocomial spread. Respiratory epithelium appears to be the major site of virus binding and subsequent infection. Although immunity to HPIV infection is long-lasting, reinfection may occur many times throughout life and at variable intervals, even in the presence of neutralizing antibodies.

Clinical features. The incubation period of HPIV infection generally lasts 1–7 days. Patients with HPIV infection typically present with a history of coryza and low-grade fever; they then develop the classic barking cough. On physical examination, HPIV infection is associated with a broad range of findings, which may include fever, nasal congestion, pharyngeal erythema, nonproductive to minimally productive cough, inspiratory stridor, rhonchi, rales, and wheezing. Systemic flulike symptoms are not common in HPIV-infected patients, but adult patients more frequently present with flulike symptoms compared with children.

Diagnosis. The white blood cell count is usually normal; however, lymphocytosis may be noted. The diagnosis of HPIV infection can be confirmed in either of the following 2 ways:

1) isolation and identification of the virus in cell culture or direct detection of the virus in respiratory secretions by means of immunofluorescent assay, enzyme-linked immunosorbent assay (ELISA), or polymerase chain reaction (PCR) assay;

2) demonstration of a significant rise in specific immunoglobulin G (IgG) antibodies between appropriately collected paired serum specimens or in specific immunoglobulin M (IgM) antibodies in a single serum specimen.

Differential diagnosis: adenoviruses, atypical pneumonia, influenza.

Treatment. No specific antiviral agents have been established as beneficial for treating human parainfluenza virus (HPIV) infections; however, ribavirin is sometimes given. Ribavirin appears safe but is expensive. Its efficiency and effectiveness have not been clearly demonstrated in large, randomized, placebo-controlled trials. At present, routine use of ribavirin cannot be recommended.

Rest until disease is fully resolve, fluids in the case of intoxication, acetaminophen against temperature.

Anti-inflammatory drugs help reduce the inflammation in case of croup.

Prevention. Currently, there are no effective vaccines for prevention of infections by HPIVs.

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ADENOVIRUS INFECTIONS

Etiology. Adenoviruses are DNA viruses often found in human and animal populations. They survive long periods outside a host, and stay endemic throughout the year. Possessing 52 serotypes, adenovirus is recognized as the etiologic agent of various diverse syndromes.

Pathogenesis. The site of entry generally determines the site of infection; respiratory tract infection infections result from droplet inhalation, while gastrointestinal tract involvement results from fecal-oral transmission. After acute adenovirus infection there may be chronic or latent infection, the exact mechanism of which is unknown, which frequently involves asymptomatic infection of lymphoid tissue.

High contagiousness of adenovirus is facilitated by very high levels of viral particles in the sputum or oral secretions of infected adults.

Clinical features. The major clinical variants of adenovirus infection include: acute respiratory disease (ARD), pharyngoconjunctival fever, epidemic keratoconjunctivitis, acute hemorrhagic cystitis and gastroenteritis. Adenovirus infections may be dangerous and have special clinical features in immunocompromised hosts.

Acute respiratory disease. Fever, rhinorrhea, cough, and sore throat, usually lasting 3–5 days, are typical symptoms of adenoviral ARD.

Pharyngoconjunctival fever. The classic presentation is characterized by fever, sore throat, coryza, and red eyes. Upper respiratory tract symptoms may precede ocular findings or may be absent.

Epidemic keratoconjunctivitis. Highly contagious, with approximately 10 % transmission in household contacts via hands. After a 5–8 days incubation period, an insidious onset of unilateral red eye occurs, spreading to involve both eyes. Patients have photophobia, tearing, and pain (indicating corneal involvement).

Acute hemorrhagic cystitis. Acute hemorrhagic cystitis usually affects children aged 5–15 years but may also affect immunosuppressed adults. Dysuria, frequency, and grossly bloody urine are reported.

Gastroenteritis. Fever and watery diarrhea are usually limited to 1–2 weeks.

Diagnosis. Antigen tests based on indirect immunofluorescence assays may be used for direct examination of tissue specimens.

Serology is not always useful in clinical practice: a 4-fold rise in acute titers to convalescent titers is diagnostic.

PCR is being used with high specificity on various specimens (respiratory, tissue, urine, blood) to identify adenovirus.

Treatment. Currently, specific therapy for adenovirus infection, other than supportive and symptomatic treatment, is not recommended. Most infections are self-limited in the setting of a normal immune response. Treatment of adenovirus infections in immunocompromised patients is widely discussed.

Prevention. Vaccination against certain strains of adenovirus exists but has been limited in most countries because of the increased risk of clinically significant disease and potential for hospitalization. Effective isolation procedures, handwashing and hygiene may prevent the spread of adenovirus.

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RESPIRATORY SYNCYTIAL VIRUS INFECTION

Etiology. Respiratory syncytial virus (RSV) is one of the major causes of lower respiratory tract illness. RSV belongs to the family *Paramyxoviridae*. RSV is a medium-sized RNA virus. Most frequent RSV clinical manifestations are bronchiolitis, pneumonia, tracheobronchitis.

Pathogenesis. Infection with RSV is primarily acquired through close contact with an infected individual or direct inoculation into the eyes and nose of infectious secretions. RSV replicates in respiratory epithelium. Spread of the virus down the respiratory tract occurs through cell-to-cell transfer of the virus along intracytoplasmic bridges (syncytia) from the upper to the lower respiratory tract.

Clinical features. The illness may begin with upper respiratory symptoms and progress rapidly over 1–2 days to the development of diffuse small airway disease characterized by cough, coryza, wheezing and rales, low-grade fever. Among healthy adults RSV infection is symptomatic in 84 % and 22 % have lower respiratory tract manifestations (pneumonia or bronchiolitis). In comparison to influenza infection occurring in these same individuals, fever is less frequent, but earache and sinus pain and a persistent productive cough are significantly more common with RSV infection.

Diagnosis. Secretions can be analyzed for RSV in the laboratory by means of culture, antigen-revealing techniques, or polymerase chain reaction (PCR).

Treatment. For most of the patients symptomatic care has to be given, fever control, and adequate fluid intake. In case of immunocompromised patients (i. e. transplant recipients, chemotherapy patients) RSV-immunoglobulin may be prescribed. One of the new treatment possibilities for immuno-

compromised patients with RSV is palivizumab, a humanized monoclonal antibody directed against the F (fusion) protein of RSV.

Prevention. Special preventive measures against RSV are not indicated for healthy adults.

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RHINOVIRUS INFECTION

Etiology. The rhinoviruses (RVs) are among the most common of the pathogens that infect humans. These viruses have been implicated in 30 % to 50 % of all cases of acute respiratory disease and are the most important cause of the common cold. RVs are small RNA viruses of the *Picornaviridae* family. More than 100 different serotypes have been identified until now.

Pathogenesis. Rhinovirus infections occur throughout the year, but usually there are distinct peaks of illness in the fall and spring. Delivery of virus to the nasal mucosa can potentially occur either by aerosols or by direct contact. Rhinovirus preferentially infects the upper respiratory tract.

Clinical features. The incubation period is 12–72 hours. Nasal dryness or irritation may be the first symptom of RV infection. A sore throat or throat irritation is also a common initial symptom and is frequently the most intense of the early symptoms. This is followed by nasal discharge, nasal congestion, and sneezing, which intensify over the next 2–3 days. Nasal secretions typically become thicker and colored after the first few days of illness. Other associated complaints include headache, facial and ear pressure. Systemic signs and symptoms, such as fever and malaise, are unusual.

Diagnosis. If findings from a thorough history and physical examination are consistent with a viral etiology and no complications are noted, an additional laboratory workup is rarely necessary.

Treatment. Rhinovirus infections are predominantly mild and self-limited; thus, treatment is generally focused on symptomatic relief and prevention of person-to-person spread and complications. Symptomatic treatment with analgesics, decongestants, antihistamines usually needed.

Prevention. Because infection is spread by hand-to-hand contact, autoinoculation, and, possibly, aerosol particles, it is important to emphasize appropriate handwashing, avoidance of finger-to-eyes or finger-to-nose contact.

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HIV-INFECTION

The history of Acquired Immune Deficiency Syndrome (AIDS) started in 1981. The human immunodeficiency virus (HIV) was identified as the cause of this condition in 1983. After that HIV-infection became the most serious problem of world health and led to so huge scientific and human progress which has never happened before.

According to published by WHO in 2014 World health statistics, an estimated 2.3 million people were newly infected with HIV in 2012 — representing a 33 % decline compared with the 3.4 million new infections estimated for 2001. People living in sub-Saharan Africa accounted for 70 % of all new infections. As access to antiretroviral therapy (ART) improves, the population living with HIV increases as fewer people die from AIDS-related causes. In 2012, an estimated 35.3 million people were living with HIV — with 9.7 million people in low- and middle-income countries receiving ART. It has been estimated that during the period 1995–2012, ART cumulatively averted 5.5 million deaths in such countries. Globally, an estimated 1.6 million people died of HIV/AIDS in 2012; down from the peak of 2.3 million in 2005.

HIV virology and pathogenesis of disease. HIV is enveloped RNA virus of the retrovirus family. As other lentiviruses it produces slowly progressed disease with long period of latency and CNS involvement. There are two HIV types: HIV-1 and HIV-2. HIV-1 is responsible for the majority of infection in the world, whereas HIV-2 occurs mainly in West Africa, associated with lower transmissible capacity and slower clinical progression.

The HIV-1 virion is composed of:

– envelope — host cell membrane with inserted HIV-1 proteins (e. g. glycoprotein (gp) 120 and gp 41);

– matrix — mainly protein (p)17;

– core, containing viral RNA connected with p7, three main enzymes (reverse transcriptase, protease, and integrase) and structural p6 and p24.

Several stages of virus lifecycle has been found as the targets for antiviral medicinal agents.

Infection is started by *binding* of gp120 to CD4 molecules which are situated on the surface of some T cells, macrophages and microglial cells. The binding demands cooperation with so-called co-receptors (CCR5 or CXCR4). Than the viral core releases into host cell cytoplasm as the result of *fusion* of viral envelope with cell cytoplasm. Reverse *transcription* produces viral cDNA and integrates it into the host genome to make proviral DNA. After appropriate stimulation viral mRNA *transcripts* and new virions are released by budding. The presence of latent non-integrated provirus in quiescent non-activated T-cells, monocytes, macrophages and glial cells makes impossible the complete eradication of virus by the use of contemporary antiviral drugs.

The replication of retroviruses is prone to mistakes which provides spontaneous mutations. Some of them are useful for virus and allow him to escape antivirals. As a result drug resistant virions will be selected under drug pressure and cause the failure of ART.

HIV replication induce the decline of functionality and dying of CD4 cells, which lead to various immune disfunction. The decrease of CD4 T cells count is hallmark of diseases and predispose to opportunistic infections. Opposite increasing of CD8 T cells count, B-cell hyperactivation and hypergammaglobulinaemia reflects the attempts to compensate immunologic imbalance. Monocytes-macrophages disfunction contributes in the onset of diseases caused by intracellular pathogens (e. g. M. tuberculosis). HIV-associated CNS disease connects with the latency of virus in microglia. Candida infections can be observed at all stages of HIV infection, it is predisposed by the insufficiency of neutrophil activity.

The individual course of HIV infection depends on many host and viral factors.

Epidemiology. The next transmission routes of HIV are main:

– unsafe sex with infected partner;

– sharing injection devices and other consumables with HIV positive person;

– vertical transmission from HIV-infected mother to her child (in the time of pregnancy, at delivery, or through breastfeeding);

The transmission due to blood products transfusion is extremely rare in countries where all donors are screened for HIV.

The long period of investigations has clearly demonstrated that everyday living contacts (sharing use of bath or tableware etc.) or contacts infected blood or other body fluids with intact skin cannot cause HIV transmission.

Transmission risk is proportional to the level of HIV viremia (viral load (VL)). The highest VL there are in recently infected people or in the late stage of diseases. Risky behavior means the exchange of body fluids like blood or semen with many people over days. This kind of lifestyle leads to inevitable meeting with highly contagious recently infected person. Current sexually transmitted

disease (STD), including genital herpes ulcers, increases the probability to transmit HIV. The probability of infection per sexual contact depends on many factors (sexual practice, VL, the presence of STD, circumcision and other) and ranges from 0.03 to 7.5 %.

Intravenous drug users become infected through sharing injection paraphernalia. This route of transmission has been predominant in Eastern Europe until recent time and continues to play leading role in the increasing of HIV prevalence in this region.

Without any prophylactic measures the mother-to-child transmission of HIV happens up to 40 %. Comprehensive approach (ART for pregnant women before labor and antiretroviral prophylaxis for newborn after, elective cesarian section and the substitution of breastfeeding) decreased vertical transmission to 1–2 %.

The risk of professional exposure of HIV is around 0.3 % per each needle stick injury and it is considerably higher for hollow needle injury than surgeon's one. Timely started post-exposure antiretroviral prophylaxis effective prevents infection.

The natural course of HIV-infection is observed in the absence of ART (figure 1).

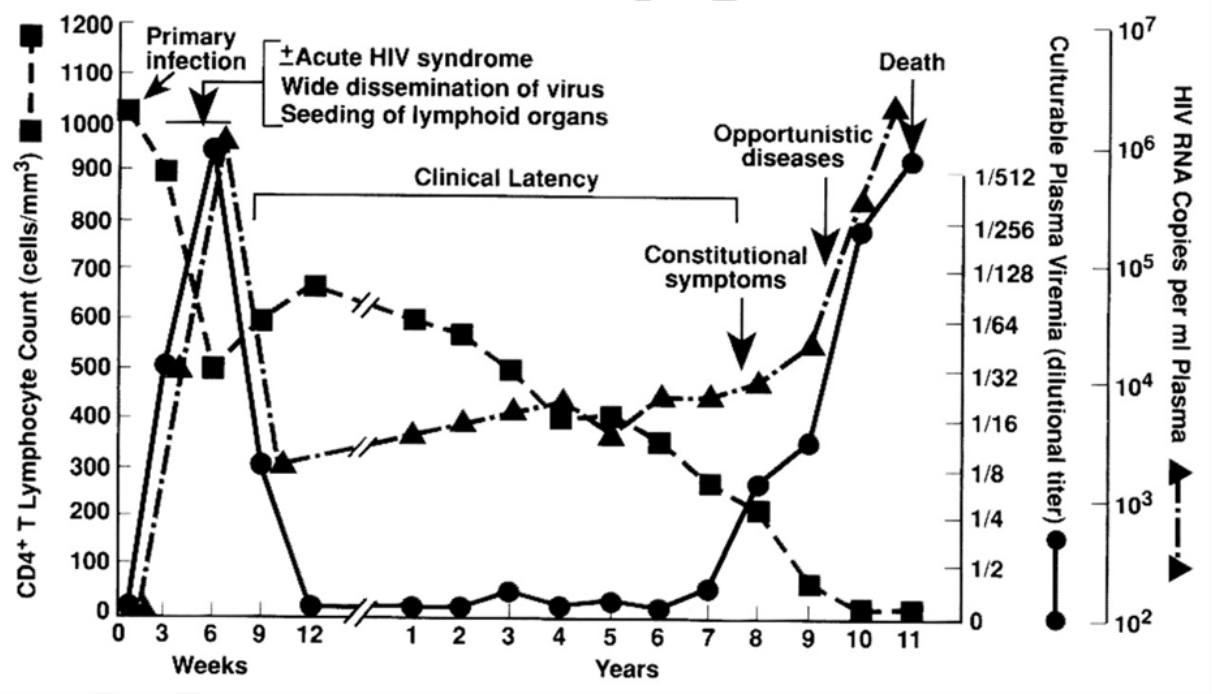

Figure 1. The natural course of HIV (Fauci A. S., Pantaleo G., Stanley S., Weissman D. Immunopathogenic Mechanisms of HIV Infection. Ann Intern Med. 1996. Vol. 124(7). P. 654–663)
N.B! For children other values apply

There are several definition concerning the periods of natural course of HIV-infection.

– *primary infection* includes two conditions:

• *acute HIV infection* — plasma HIV RNA typically very high (> 10,000 copies/ml) with negative result of HIV antibodies by ELISA and negative or indeterminate result of Western Blot (< 3 bands positive); acute HIV infection is often accompanied by the manifestations of acute retroviral syndrome;

• *early HIV infection* can be established by confirmed recent (less than 6 months) seroconversion (regardless of the presence of clinical signs);

– *acute retroviral syndrome* — condition with various clinical presentations (fever, adenopathy, pharyngitis, rash, hepatosplenomegaly — mononucleosis-like illness, as well as nausea, diarrhea, headache, trash and neurologic symptoms (aseptic meningitis, Guillain-Barré syndrome)) which can manifest in 2–3 weeks after infection;

– *recovery and seroconversion* is going on next 2–4 weeks with recovery of CD4 count and cutback in plasma HIV VL to a set point; high level of CD4 count and low VL at set point can be attributed to slow follow diseases progression;

– *asymptomatic chronic HIV infection* prolongs average 8 years when CD4 count gradually declines without any special clinical presentations;

– *symptomatic HIV infection* — the developing of bacterial pneumonia, pulmonary tuberculosis, cancers, idiopathic thrombocytopaenic purpura and other conditions listed in category B according to CDC classification or in clinical stage 3 by WHO classification (see below);

– *AIDS* — opportunistic infections occur and CD4 count becomes less than 200 cells/mcL.

Classifications of HIV-infection. There are two main classifications of HIV-infections elaborated by Center for Disease Control and Prevention (CDC, USA, table 10) and World Health Organization (WHO).

Table 10

Classification of HIV diseases according to the 1993 CDC classification for adult and adolescents

CD4 T cells	Asymptomatic or acute HIV diseases	Symptomatic but not categories A or C	AIDS defining ilness
> 500/mcL	A1	B1	C1
200–499/mcL	A2	B2	C2
< 200/mcL	A3	B3	C3

Category A consists of one or more of the conditions listed below in an adolescent or adult (greater than or equal to 13 years) with documented HIV infection. Conditions listed in Categories B and C must not have occurred.

– asymptomatic HIV infection;

– persistent generalized lymphadenopathy;

– acute (primary) HIV infection with accompanying illness or history of acute HIV infection.

Category B. Category B consists of symptomatic conditions in an HIV-infected adolescent or adult that are not included among conditions listed in clinical Category C and that meet at least one of the following criteria: a) the conditions are attributed to HIV infection or are indicative of a defect in cell-mediated immunity; or b) the conditions are considered by physicians to have a clinical course or to require management that is complicated by HIV infection. Examples of conditions in clinical Category B include, but are not limited to:

– bacillary angiomatosis;

– candidiasis, oropharyngeal (thrush);

– candidiasis, vulvovaginal; persistent, frequent, or poorly responsive to therapy;

– cervical dysplasia (moderate or severe)/cervical carcinoma in situ;

– constitutional symptoms, such as fever (38.5 °C) or diarrhea lasting greater than 1 month;

– oral hairy leukoplakia;

– herpes zoster (shingles), involving at least two distinct episodes or more than one dermatome;

– idiopathic thrombocytopenic purpura;

– listeriosis;

– pelvic inflammatory disease, particularly if complicated by tubo-ovarian abscess;

– peripheral neuropathy.

Category C. AIDS defining conditions:

– Bacterial infections, multiple or recurrent[1];

– Candidiasis of bronchi, trachea, or lungs;

– Candidiasis of esophagus[2];

– Cervical cancer, invasive[3];

– Coccidioidomycosis, disseminated or extrapulmonary;

– Cryptococcosis, extrapulmonary;

– Cryptosporidiosis, chronic intestinal (> 1 month's duration);

– Cytomegalovirus disease (other than liver, spleen, or nodes), onset at age > 1 month;

– Cytomegalovirus retinitis (with loss of vision)[†];

– Encephalopathy, HIV related;

[1] Only among children aged < 13 years. (CDC. 1994 Revised classification system for human immunodeficiency virus infection in children less than 13 years of age. MMWR 1994;43[No. RR-12]).

[2] Condition that might be diagnosed presumptively.

[3] Only among adults and adolescents aged > 13 years. (CDC. 1993 Revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. MMWR 1992;41[No. RR-17]).

– Herpes simplex: chronic ulcers (> 1 month's duration) or bronchitis, pneumonitis, or esophagitis (onset at age > 1 month);

– Histoplasmosis, disseminated or extrapulmonary;

– Isosporiasis, chronic intestinal (> 1 month's duration);

– Kaposi sarcoma[2];

– Lymphoid interstitial pneumonia or pulmonary lymphoid hyperplasia complex[1 2];

– Lymphoma, Burkitt (or equivalent term);

– Lymphoma, immunoblastic (or equivalent term);

– Lymphoma, primary, of brain;

– Mycobacterium avium complex or Mycobacterium kansasii, disseminated or extrapulmonary[2];

– *Mycobacterium tuberculosis* of any site, pulmonary[2 3], disseminated[2], or extrapulmonary[2];

– Mycobacterium, other species or unidentified species, disseminated[2] or extrapulmonary[2];

– *Pneumocystis jirovecii* pneumonia[2];

– Pneumonia, recurrent[2 3];

– Progressive multifocal leukoencephalopathy;

– Salmonella septicemia, recurrent;

– Toxoplasmosis of brain, onset at age > 1 month[2];

– Wasting syndrome attributed to HIV.

In 2008 CDC revised and simplified HIV disease classification (table 11).

Table 11

Classification of HIV disease (CDC, 2008)

Stage	AIDS-defining illness (category C, 1993)	CD4 cell count
1	None	> 500/mcL or ≧ 29 %
2	None	200–499/mcL or 14–28 %
3 (AIDS)	Documented AIDS-defining ilness	< 200/mcL or < 14 %
Unknown	No information available	No information available

One of the main principles of CDC classification is impossibility to reclassification upward upon the improvement of person condition or his immunologic status.

At the same time in most low- and middle income countries specialists use treatment recommendations and classification of HIV disease elaborated by WHO.

Classification of HIV infection according to WHO, 2007:

Clinical stage 1 (asymptomatic regarding HIV-associated symptoms, corresponds to CD4 > 500 c/mcL):

– asymptomatic;

– persistent generalized lymphadenopathy;

Clinical stage 2 (mild HIV-associated symptoms, corresponds to CD4 350–499 c/mcL):

– moderate unexplained weight loss (< 10 % of presumed or measured body weight);

– recurrent respiratory tract infections sinusitis, tonsillitis, otitis media and pharyngitis);

– herpes zoster;

– angular cheilitis;

– recurrent oral ulceration;

– papular pruritic eruptions;

– seborrhoeic dermatitis;

– fungal nail infections.

Clinical stage 3 (advanced HIV-associated symptoms, corresponds to CD4 200–349 c/mcL):

– unexplained severe weight loss (> 10 % of presumed or measured body weight);

– unexplained chronic diarrhea for longer than one month;

– unexplained persistent fever (above 37.6 °C intermittent or constant, for longer than one month);

– persistent oral candidiasis;

– oral hairy leukoplakia;

– pulmonary tuberculosis (current);

– severe bacterial infections (such as pneumonia, empyema, pyomyositis, bone or joint infection, meningitis or bacteraemia);

– acute necrotizing ulcerative stomatitis, gingivitis or periodontitis;

– unexplained anaemia (< 80 g/L), neutropaenia (< 0.5×10^9/L) or chronic thrombocytopaenia (<50×10^9/L per litre);

Clinical stage 4 (severe HIV-associated symptoms, corresponds to CD4 < 200 c/mcL):

– HIV wasting syndrome;

– *Pneumocystis* pneumonia;

– Recurrent severe bacterial pneumonia;

– Chronic herpes simplex infection (orolabial, genital or anorectal of more than one month's duration or visceral at any site);

– Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs);

– Extrapulmonary tuberculosis;

– Kaposi's sarcoma;

– Cytomegalovirus infection (retinitis or infection of other organs);

– Central nervous system toxoplasmosis;

– HIV encephalopathy;

– Extrapulmonary cryptococcosis including meningitis;

– Disseminated non-tuberculous mycobacterial infection;

– Progressive multifocal leukoencephalopathy;
– Chronic cryptosporidiosis (with diarrhea);
– Chronic isosporiasis;
– Disseminated mycosis (coccidiomycosis or histoplasmosis);
– Recurrent non-typhoidal Salmonella bacteraemia;
– Lymphoma (cerebral or B-cell non-Hodgkin) or other solid HIV-associated tumors;
– Invasive cervical carcinoma;
– Atypical disseminated leishmaniasis;
– Symptomatic HIV-associated nephropathy or symptomatic HIV-associated cardiomyopathy.

WHO classification is based predominantly on clinical symptoms, because of increased, although not universal, availability of CD4+ T-lymphocyte testing. CDC recommends using only immunologic criteria for staging, with the exception of stage 3. WHO presents four clinical stages for disease classification, whereas CDC presents three, combining WHO stages 2 and 3 into CDC stage 2. Pulmonary tuberculosis is AIDS defining condition according to CDC classification, on the other hand it belongs to 3 stage according to WHO classification. Despite these differences both classifications' stages can still be compared.

HIV testing. There are many laboratory methods to determine HIV-infection.

HIV serology tests detect antibodies to the virus. These tests are most commonly used. The *screening tests* are based on the principles of antigene-antibody binding detected by *enzyme immunosorbent assay* (EIA, ELISA). After receiving reactive screening test result the next blood sample must be taken for the performing *confirmatory test*. Two separate samples need to exclude sample confusion. The term "positive" shouldn't be used regarding screening test result, only "reactive" or "negative". As confirmatory test a *Western Blot* (immunoblot) is usually carried out. Western Blot test strip contains separated by molecular weight viral proteins. After interaction with a patient plasma antibodies a corresponding band spectrum occurs on the test strip. An immunoblot test is considered positive when at least two or three bands are visible. Alternative screening tests, based on the same principle, are immunofluorescence assay, rapid tests and home kits.

The methods of *viral detection* are used to diagnose HIV-infection when serological tests can be false-negative (early infection, agammaglobulinaemia) or misleading (determination of HIV status in newborns). HIV-1 DNA PCR detects proviral DNA in peripheral CD4 cells, being the most sensitive it is able to identify 1–10 copies of DNA. HIV RNA PCR detects viral genome in plasma with 95–98 % sensitivity. Both tests can be used as confirmatory. The main scope of quantitative plasma HIV RNA (VL) detection is diagnosis acute HIV infection (before seroconversion and in neonates) and monitoring of ART.

P 24 antigen detection almost is not used nowadays for diagnosis of acute HIV infection because it has much more lower sensitivity compared with HIV PCR. Currently used the 4th generation screening tests combine the detection of HIV antibody and p24 antigene.

HIV testing shouldn't be perform without appropriate counseling before and after procedure. HIV testing and counseling according to WHO recommendation (2013) should be voluntary and adhere to the five C's: consent, confidentiality, counseling, correct test results and connection to care, treatment and prevention services.

Treatment. The first antiretroviral agent zidovudin was introduced in 1988. But mono therapy with one nucleoside analog, than dual therapy with the same class drugs was made the diseases progression only a little bit slowly. High Active Antiretroviral Treatment (HAART) has started to employ since 1996 after introducing of new drug class — protease inhibitors. HAART means the using of antiretroviral drugs combination from at least two different classes.

There are five classes of antiretroviral agent:

1) nucleoside or nucleotide reverse transcriptase inhibitors (NRTIs);
2) non-nucleoside reverse transcriptase inhibitors (NNRTIs);
3) protease inhibitors (PIs);
4) entry inhibitors:
– co-receptor antagonists ;
– fusion inhibitors;
5) integrase inhibitors (IIs).

Now it can be declared, that timely started HAART is able to restore estimated before infection life span of people living with HIV.

ART must be started for all patients with CD4 < 350 cells/mcL or with symptomatic diseases or AIDS (stage 3 or 4 by WHO or category B or C by CDC). Regarding the persons with CD4 350–500 cells/mcL there is not common opinion, but the general trend is to treat them. ART also should always be started in some special situation regardless CD4 count:

– pregnancy;
– HIV nephropathy;
– HBV infection requiring treatment.

ART can be recommended on a case-by-case basis:

– fast immunodeficiency progression especially in older people;
– concomitant non-AIDS defining cancer and other.

To treat or not to treat primary infection remains the topic of active research. The treatment in this phase can lead to more robust CD4 recovery, and on the other hand untimely problems with drug toxicity and HIV resistance.

ART can be offered to HIV positive partner in a serodiscordant couple for sexual transmission prevention and consequently for a safe conception.

Usually prescribed HAART regimen contains 2NRTI+NNRTI or 2NRTI+PI. For example, according WHO recommendation the regimen of the first choice is tenofovir (TDF)+emtricitabine (FTC)+efavirenz (EFV). But any HAART regimen should be individualized to result the best therapeutic response, tolerability and adherence, it could be possible only in the case of minimal toxicity and drug interaction. To avoid drug resistant and to achieve the best potency people in therapy must permanently support the highest adherence to treatment. As for NNRTI based regimen patient must consistently take 95 % prescribed doses and shouldn't miss more then one dose running. Low adherence results the suboptimal viral suppression and creates favorable conditions for the selection of viral subpopulation accumulated drug resistance mutations regarding to using drugs.

The treatment success or failure are determined using virologic, immunologic and clinical criteria. The virologic success is defined as VL decline below the level of detection (depending on assay, usually < 50 copies/mL) and the retention of this result. Regardless of VL at the ART start VL must reduce by 1 $\log_{10}$ in 4 weeks and be undetectable in six months at the latest.

Immunologic success is evaluated by the CD4 count dynamics. Usually cells count grows 50–100 cells/mcL per year, but the speed is depend on many factors. There are so-called immunologic non responders who don't restore CD4 count despite of virologic success.

Clinical failure of treatment means the onset of new AIDS defining condition after ART starting. Sometimes it could be the result of the immune reconstitution inflammatory syndrome (IRIS) when at the time of ART initiation there is occult opportunistic infection or neoplasm which become unmasked as efficient treatment recovers immunity and the ability to demonstrate inflammatory reactions. So virologic success is the most appropriate for the assessment the efficacy of ART regimen.

OPPORTUNISTIC INFECTIONS — DIAGNOSING AND TREATMENT

Opportunistic infections (OIs) remain the big problem in the country with high HIV prevalence and inappropriate HIV testing strategy. After HAART introducing the life expectancy of individuals diagnosed with OIs became longer, but in the same time the personal prognosis can be poor. Some of conditions (PML, primary brain lymphoma) don't have adequate treatment even today. Many clinicians and laboratory specialists are unfamiliar with OIs' presentations and unable to recognize rare pathogens. As the immunodeficiency become worse the possibility to diagnosed more than one OI in patient become more realistic. Many OIs have approximate CD4 cut-off (table 12), that is the CD4 count, above which particular conditions are unlikely. But, exceptions are nevertheless possible.

Table 12

OIs, diagnosis, treatment and prophylaxis (only first line regimens are presented)

OI (CD4 cut-off)	Diagnostics	Treatment	Prophylaxis
Pulmonary tuberculosis (TB) (no CD4 cut-of)	Chronic symptoms: (lasting at least 2–3 weeks) cough, haemoptysis, shortness of breath, chest pain, weight loss, fever, night sweats; PLUS EITHER positive sputum smear; OR negative sputum smear; AND compatible chest radiograph (including but not restricted to upper lobe infiltrates, carita-tion, pulmonary fibrosist shrinkage. No evidence of extrapulmo-nary disease. Definitive diagnosis — Isola-tion of M. Tuberculosis on sputum culture or histology of lung biopsy (with compatible symptoms)	Depends on suscepti-bility of TB isolate or if culture is not available — on the previous treatment result and suspected resistance. Dosages are based on patient weight, periodicity of drugs intake — on CD4 count and treatment phase, duration of treatment depends on disease form (pulmo-nary or disseminated) and resistance pattern. For pulmonary TB caused susceptible MBT there is main 4 drugs regimen: iso-niazid (INH) + rifam-picin (RIF) + etham-butol + pyrazinamide for 2 months, than INH+RIF for 4 months. General recommenda-tion is to start ART in 2–8 weeks after TB treatment initiation	Adults and adoles-cents living with HIV who have an unknown or posi-tive tuberculin skin test status and are unlikely to have active TB should receive at least six months of isoniazid (INH at 300 mg/day or 5 mg/kg/day) pre-ventive therapy (IPT). IPT should be given to such individuals irrespective of the degree of im-munosuppression, and also to those on ART, those who have previous-ly been treated for TB and pregnant women
Extrapulmonary (disseminated) TB (CD4 < 100 c/mcL)	Systemic illness (such as fever, night sweats, weakness and weight loss). Other evidence for extrapulmonary or disseminated tuberculosis varies by site: Pleural, pericar-dia, peritoneal involvement, meningitis, mediastinal or abdominal lymphadenopathy or ostetis. Discrete peripheral lymph node Mycobacterium tuberculosis infection (espe-cially cervical) is considered a less severe form of extra pulmonary tuberculosis. Definitive diagnosis — M. tu-berculosis isolation or compat-ible histology from appropriate site or radiological evidence of miliary tuberculosis; (diffuse uniformly distributed small miliary shadows or micronodules on chest X-ray)		

OI (CD4 cut-off)	Diagnostics	Treatment	Prophylaxis
Pneumocystis pneumonia (PCP) (CD4 < 250 c/mcL)	Dyspnoea on exertion or nonproductive cough of recent onset (within the past three months), tachypnoea and fever; AND Chest X-ray evidence of diffuse bilateral interstitial infiltrates; AND No evidence of bacterial pneumonia; bilateral crepitations on auscultation with or without reduced air entry. Definitive diagnosis — cytology or immunofluorescent microscopy of induced sputum or bronchoalveolar lavage or histology of lung tissue	Trimethoprim sulfamethoxazole (TMP-SMX) 480 mg if PaO_2 > 70 mmHg and able to take po meds — 4 tabs q8h; if PaO_2 < 70 mmHg and severe ill — TMP-SMX 15–20 mg of TMP component/kg/day IV + prednisolone 40 mg po q12h × 5 d, than 40 mg po q24h × 5 d, than 20 mg po q24h × 11 d Treatment duration is 21 days	Primary and secondary TMP-SMX 480 mg 1–2 tab q24h, or 960 mg 3 times weekly until CD4 > 200 c/mcL at least 3 months. TMP-SMX 960 mg regimen also protects against toxoplasmosis and other bacterial infections
Cerebral toxoplasmosis (CD4 < 100 c/mcL)	Recent onset of a focal nervous system abnormality consistent with intracranial disease or reduced level of consciousness AND response within 10 days to specific therapy. Confirmed diagnosis — positive serum toxoplasma antibody AND single or multiple intracranial mass lesion on neuroimaging (computed tomography or magnetic resonance imaging)	TMP-SMX 10 mg of TMP component/kg/day IV or po × 6 wks	Primary prophylaxis — TMP-SMX 480 mg 1–2 tab q24h, secondary — with on half of therapeutic dosage of TMP-SMX, 960 mg q24h is also possible regimen
Extrapulmonary cryptococcosis (including meningitis) (CD4 < 100 c/mcL)	Meningitis: usually subacute, fever with increasing severe headache, meningism, confusion, behavioral changes that respond to cryptococcal therapy. Definitive diagnosis — isolation of Cryptococcus neoformans from extrapulmonary site or positive cryptococcal antigen test on cerebrospinal fluid or blood	Induction therapy: amphotericin B 0,7 mg/kg IV q24h (or liposomal amphotericin B 4 mg/kg IV q24h) + flucitosine 25 mg/kg po q6h × 2 weeks; than consolidation therapy: fluconazole 400 mg po q24h to complete a 10-weeks course or until CSF culture sterile	Secondary prophylaxis is mandatory with fluconazole 200 mg/day po until CD4 count rises to > 100 c/mcL and is sustained for 6 months

OI (CD4 cut-off)	Diagnostics	Treatment	Prophylaxis
Cytomegalovirus disease (other than liver, spleen or lymph node) (CD4 < 50 c/mcL)	Retinitis only: may be diagnosed by experienced clinicians. Typical eye lesions on fundoscopic examination: discrete patches of retinal whitening with distinct borders, spreading centrifugally, often following blood vessels, associated with retinal vasculitis, haemorrhage and necrosis. Definitive diagnosis — compatible histology or cytomegalovirus demonstrated in cerebrospinal fluid by culture or DNA (by polymerase chain reaction)	Initial treatment for CMV infection should include optimization of ART ganciclovir 5 mg/kg IV q12h or foscarnet 90 mg/kg q12h 14–21 d (3–6 wks for esophagitis/colitis). For CMV of CNS most would use combination ganciclovir and foscarnet	Primary is not generally recommended, secondary — valganciclovir 900 mg po q24h or foscarnet 90 mg/kg q24h IV for CMV retinitis and encefalitis, for CMV colitis and esophagitis may not be necessary except after relapses, until CD4 > 100 c/mcL at least for 6 months
Candidiasis (CD4 < 100 c/mcL for esophageal candidiasis)	Persistent oral candidiasis can be diagnosed clinically — persistent or recurring creamy white curd-like plaques that can be scraped off (pseudomembranous) or red patches on tongue, palate or lining of mouth, usually painful or tender (erythematous form). Esophageal candidiasis — recent onset of retrosternal pain or difficulty on swallowing (food and fluids) together with oral candidasis. Definitive diagnosis — macroscopic appearance at endoscopy or bronchoscopy, or by microscopy or histology	Oropharyngeal candidiasis — fluconazole 100–200 mg daily for 7–14 days candida esophagitis — fluconazole 200–400 mg daily for 14–21 days	ART prevents disease relapses, primary prophylaxis is not generally recommended, especially with CD4 > 200 c/mcL. Secondary prophylaxis, if required, for oropharyngeal form — fluconazole 100 mg thrice weekly, or 200 mg thrice weekly for recurrent esophageal candidiasis
Atypical mycobacteriosis (mycobacterium avium-intracellularae complex MAC or MAI) (CD4 < 50 c/mcL)	No presumptive clinical diagnosis. Diagnosed by finding atypical mycobacterial species from stool, blood, body fluid or other body tissue, excluding the lungs	Clarithromycin 500 mg q12h or azithromycin 600 mg q24h + ethambutol 15–25 mg/kg/day+/- rifabutin 300 mg q24h	Primary — azithromycin 1200 mg weekly or clarithromycin 500 mg q24h, if CD4 < 50–100 c/mcL, secondary —clarithromycin 500 mg q12h or azithromycin 600 mg q24h + etambutol 15 mg/kg/day.

OI (CD4 cut-off)	Diagnostics	Treatment	Prophylaxis
			Prophylaxis can be discontinued if CD4 > 100 c/mcL consistently on ART
Chronic herpes simplex virus infection (orolabial, genital or anorectal) of more than one month or visceral infection of any duration. (CD4 < 250 c/mcL)	Painful, progressive anogenital or orolabial ulceration; lesions caused by recurrence of herpes simplex virus infection and reported for more than one month. History of previous episodes. Visceral herpes simplex virus requires definitive diagnosis — positive culture or DNA (by polymerase chain reaction) of herpes simplex virus or compatible cytology or histology	Mucocutaneous mild disease — aciclovir 400 mg po q8h 7–14 d, severe or systemic — aciclovir 5 mg/kg IV q8h 5–10 d than aciclovir 400 mg po q8h until lesions have completely healed. For encefalitis — aciclovir 10 mg/kg IV q8h 10 d	Primary is not recommended; secondary — only if recurrence are frequent or severe aciclovir 400 mg po q12h or 200 mg po q8h indefinitely
Kaposi's sarcoma (no cut-off)	Typical gross appearance in skin or oropharynx of persistent, initially flat, patches with a pink or violaceous colour, skin lesions that usually develop into plaques or nodules. Definitive diagnosis — macroscopic appearance at endoscopy or bronchoscopy, or by histology	Effective ART has best chance of preventing progression of Kaposi's sarcoma or occurrence of new lesion	
HIV encephalopathy (CD4 < 200 c/mcL)	Disabling cognitive and/or motor dysfunction interfering with activities of daily living, progressing over weeks or months in the absence of a concurrent illness or condition other than HIV infection that might explain the findings. Diagnosis of exclusion: and neuroimaging	Effective ART	
Progressive multifocal leukoencephalopathy (PML) (CD4 < 250 c/mcL)	No presumptive clinical diagnosis. Progressive nervous system disorder (cognitive dysfunction, gait/speech disorder, visual loss, limb weakness and cranial nerve palsies) together with hypodense white matter lesions on neuroimaging or positive polyomavirus JC polymerase chain reaction on cerebrospinal fluid	Not developed. ART increases survival	Effective ART

OI (CD4 cut-off)	Diagnostics	Treatment	Prophylaxis
Chronic cryptosporidiosis (with diarrhoea lasting more than one month) (CD4 < 100 c/mcL)	No presumptive clinical diagnosis. Cysts identified on modified Ziehl-Nielsen stain microscopic examination of unformed stool	Effective ART is the best and one and only therapy; other therapy approved for immunocompetent patients is not validated in HIV patients	
Lymphoma (cerebral (CD4 < 50 c/mcL) or B cell non-Hodgkin (no cut-off))	No presumptive clinical diagnosis. Histology of relevant specimen or, for central nervous system tumours, neuroimaging techniques	complex antitumoral treatment + ART there are exceptional cases of survival	Effective ART

The treatment of OIs is a priory unsuccessful without timely initiated ART. But in the same time the problems of toxicity and drug interaction rise up.

Many countries in the world have simultaneously two epidemics — HIV and tuberculosis (TB). In 2012, an estimated 8.6 million people developed tuberculosis and 1.3 million died from the disease (including 320 000 deaths among HIV-positive people). Infection with HIV is the strongest risk factor for developing active tuberculosis disease. Many countries have made considerable progress in addressing the tuberculosis and HIV co-epidemic. However, less than half of notified tuberculosis patients had a documented HIV test result in 2012, with only 57 % of those who tested positive being on ART or started on ART.

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HERPES VIRUS INFECTIONS

Etiology. Herpes viruses are double string DNA-containing enveloped viruses. They are divided into three groups:

– alfa-herpesviruses — herpes simplex viruses types 1 and 2 (HSV-1, HSV-2) and varicella zoster virus (VZV);

– beta-herpesviruses — cytomegaloviruse (CMV), human herpes virus types 6 and 7 (HHV-6 and HHV-7);

– gamma-herpesviruses — Epstein-Barr virus (EBV) and human herpes virus types 8 (HHV-8).

Morphologically similar herpes viruses have many common features and pathology mechanisms, otherwise they are quite differ by clinical manifestations. After acute primary infection the life long virus latency starts. All herpes viruses use specific mechanism allowing to evade immune response. Severe and life-treating forms of infection usually affect immunocompromised patients. Almost all of them (except HHV-7) are able to cause neurologic complications.

HSV 1 AND 2

Epidemiology and pathogenesis. HSVs infect many types of cells. Within some of the cells viruses complete their replication which becomes apparent by cytopathic effects. After acute infection HSV exists in a latency state within certain nervous cells.

HSV-infection is ubiquitous and affects only humans. Almost all adults are infected by the middle age with HSV-1. The probability to contract HIV-2 depends on sexual activity of an individual and their partners as well as other concomitant sexual transmitted infections (STIs).

Infection happens by close mucosal or skin contact with individual shedding virus in the skin or mucosa perhaps inapparently. After its inoculation

virus replicates locally, than spreads to the nerve ganglia via the axons (most commonly HHV-1 affects trigeminal and HHV-2 — sacral nerve root ganglia). In the ganglia the second phase of replication occurs followed by wide subsequent dissemination along sensory nerves. Virus and host factors as well as the route of transmission all contribute to unclear mechanisms of virus reactivation which is less severe in immunocompetent hosts than the primary infection.

Clinical features:

• Cutaneous and mucosal features:

– pharyngitis and gingivostomatitis are the most common forms of acute infection observed generally in children. Painful oral and pharynx mucosal ulcers are accompanied by fever, malaise and cervical lymphadenopathy. This form of HSV-infection has been attributed to up to 75 % of cases of erythema multiforme;

– recurrent herpes labialis is the well known typical manifestation of the HSV-1 reactivation. It may range from asymptomatic to severe mucositis and perioral skin involvement in immunocompromised hosts or to persistent ulceration in AIDS patients;

– herpetic whitlow is characterized by painful edema, erythema and vesicles on a finger and often happens as the result of auto-inoculation (existing labial or genital infection) or of an environmental contact (health workers exposure);

– herpes gladiatorum appears as mucocutaneous diseases contracted by sportsmen through the close person to person contact or through sport equipment (e. g. mat).

• Visceral infection is the results of viremia which leads to multiple organs involvement. Severe disseminated infection in the third trimester of pregnancy associated with high neonatal morbidity. More rarely the dissemination could be manifested as single organ affection (pneumonitis or esophagitis) predominantly in immunocompromised patients.

• Encephalitis caused by HSV-1 is one of the most serious CNS infection. Primary infection (in patients of 5–30 years old) and reactivation (in older group, > 50 years) or re-infections (in adult on the whole) produce the quite acute predominantly temporal encephalitis. Short prodrome is possible with fever, behavioral changes and headache. In untimely diagnosed and treated cases seizures and coma occur. Death and severe disability are frequent without appropriate treatment. Diagnosis is made by PCR DNA HSV in CSF (at least one of two examination in early disease). MRI is more sensitive than computerized tomography (CT), especially in early disease. Unilateral encephalitis brain lesions, predominantly in temporal lobe, can be considered as sufficient evidence of possible HSV encephalitis.

• Meningitis is usually caused by HSV-2. More often it accompanies or follows (in 3–10 days) genital herpes or can be independent process. This

meningitis is usually benign in immunocompetent individuals and lasts for 4–7 days. The HSV-2 cause of this aseptic meningitis can be confirmed by PCR DNA in CSF.

Diagnosis. For herpes ulceration — virus isolation or less sensitive antigen detection are appropriate if other causes are suspected. PCR HSV DNA in CSF is the main assay for CNS involvement. Serology is useful assay only for carriers detection.

Treatment. Acute and recurrent mucocutaneous forms, including genital herpes, can be treated with oral acyclovir or valacyclovir or famciclovir. Daily suppression of recurrent infection is indicated in immunocompromised patients or in the case of very frequent relapses (> 6 per year). For this purpose all listed drugs can be used.

The treatment of herpes encephalitis must be started with acyclovir (10 mg/kg q8h IV) as soon as possible. The treatment duration is 14–21 days or until the diagnosis is completely rule out. Severe and disseminated forms also demand intravenous treatment.

VZV

Epidemiology and pathogenesis. Despite the other herpes viruses with their variety of clinical presentation VZV can cause two main clinical form:

– primary infection — chickenpox (varicella);

– fix in localization recurrence — shingles (herpes zoster).

VZV can infect only humans. It is one of the most contagious virus, the infection is respiratory and generally (90 %) occurs in childhood. The infectious period lasts from 48 hours before rash appearance until 5 days after last rash wave occurrence. After infection the virus becomes latent in dorsal ganglia reactivated and caused shingles in all ages, but more often in elderly or immunocompromised.

Clinical features:

– Chickenpox has acute onset after incubation (10–14 days). Main clinical signs are fever and rash which has several consecutive stages: maculopapules, vesicles, pustules and scabs. Lesions firstly occur on the face and trunk and then spread to extremities. Mucosa of pharynx and vagina can be involved. Skin lesions are often extensive in adults. Immunocompromised children also have severe skin affection and high risk of visceral involvement.

Complications — secondary bacterial skin infection, acute cerebellar ataxia (may be severe, but benign in children), encephalitis (0.2 % cases, may be life-threatening in adult), cerebral angiitis, meningitis, transverse myelitis, pneumonitis (may be life-threatening in immunocompromised and in pregnant women in 2^{nd} and 3^{rd} trimesters), hepatitis, myocarditis.

– Herpes zoster declare itself as unilateral grouped vesicular lesson distributed in 1–2 dermatomes. In many cases prodrome with pain in the affected

area precedes 2–3 days before eruption. Sensitive nerves and ganglions involvement has different manifestations — eyelids, keratitis, oral mucosa involvement, Ramsay-Hunt syndrome (vesicles in the external auditory meatus, ipsilateral facial palsy, lost of taste to the anterior two-third of tongue as a result of geniculate ganglionitis), encephalitis, cerebral angiitis, paralysis. Immunocompromised patients often suffer from disseminated cutaneous and visceral forms with long period of recovery. HIV positive have higher risk of retinitis and chronic progressive encephalitis.

Post-herpetic neuralgia is the common consequence of herpes zoster in patients older than 50 years. In some of them pain can be debilitating and demands long additional treatment.

Diagnosis. Vesicles fluid investigation with PCR VZV DNA can be demanded for differentiation from impetigo, other viral skin lesion (HSV, Coxakie). Seroconversion allows to diagnose acute infection. PCR VZV DNA of CSF is necessary to prove CNS involvement.

Treatment. Chickenpox can not be treated with antivirals in healthy children. Adolescents and adults presented within 24 hour of rash onset should be treated with oral acyclovir or valacyclovir or famciclovir (doses are higher as compared with HSV). For the treatment of pregnant women (over 20 weeks' gestation) only acyclovir are licensed. Severe (hemorrhagic) and disseminated forms demand intravenous treatment with acyclovir (10–12 mg/kg q8h 7 days).

Shingles should be treated in all patients and the same antiviral agents can be used, but valacyclovir is preferable (1000 mg 3 times per day during 7 days). Intravenous acyclovir is the drug of choice in immunocompromised hosts with severe, disseminated or CNS-complicated involvement forms.

EBV

Epidemiology and pathogenesis. EBV is the most common cause of infectious mononucleosis. Infectious mononucleosis (IM) or mononucleosis-like illness is the syndrome of pharyngitis and/or tonsillitis, fever, lymphadenopathy with atypical lymphocytosis. The second common cause of IM is CMV, but in can be also observed in patients with primary HIV, acute toxoplasmosis, rubella, viral hepatitis.

Besides of IM EBV is associated with Burkitt's lymphoma.

EBV usually spreads via close contacts. There are two age group of higher incidence — children (before 5 years old) and adolescents.

After infection of B lymphocytes and the cells of oropharyngeal epithelia incubation may last up to 50 days. In the course of immune response during IM there is production of many antibodies against viral antigen as well as unrelated antigen which can be found on other animals' cells (heterophile antibodies). Less frequently antibody can be synthesized against platelets, neutrophils and ampicillin.

Clinical features. Infection can be asymptomatic, especially in young children. Abrupt disease onset is possible, but usually it follows on 1–2 weeks prodrome of malaise.

Along with aforementioned symptoms of IM some additional signs can be observed — rash as the consequence of ampicillin treatment (90–100 % treated) or as independent event (5 %), hepatomegaly, splenomegaly, face edema. Pharyngitis can be exudative with palatal petechiae and tonsillar can be able to obstruct the airway. Abdominal pain can be provoked by fast enlargement of liver and/or spleen. The risk of spontaneous splenic rupture exists. Almost in 90 % of patients there are biochemical signs of hepatitis, but only 5 % have a jaundice.

Complete recover takes a lot of time despite of fever disappearance in 10–14 days.

Possible complication:

– neurological — Guillain–Barré, optic neuritis, Bell's palsy, encephalitis, meningitis, cerebellitis — generally benign with high rate of complete recovery;

– haematological — thrombocytopenia, splenic rupture (0.2 %), autoimmune haemolitic anemia (1 %);

– other — interstitial nephritis, pericarditis, myocarditis.

EBV-associations were found with some neoplastic disorders, such as nasopharyngeal carcinoma, Burkitt's lymphoma, and in last time with Hodgkin's and polyclonal both B- and T-cell lymphomas. In HIV positive people EBV causes oral hairy leukoplakia, B-cell lymphomas and lymphoid interstitial pneumonia in children.

Diagnosis. Atypical lymphocytosis is not specific only for EBV and diagnosis should be confirmed by other tests. Heterophile antibodies detection is the principle of some old and quite chip agglutinin tests which are replaced by newer and more sensitive and specific assays. Serological identification of EBV specific antibodies allow to confirm diagnosis and define its period. Epstein–Barr virus nuclear antigen (EBNA) and antiviral capsid antigen (VCA) antibody are the main markers of infection.

aVCAIgM+ and EBNA-indicate acute infection, aVCAIgM remains positive for 4–8 weeks.

aVCAIgG+, aVCAIgM-, EBNA+ mean infection between 3–12 months ago; this pattern can retain for life.

Treatment. In immunocompetent patients infection is usually self-limited and does not require specific treatment. Antiviral drugs couldn't demonstrate any benefits for acute disease treatment, regardless in vitro activity of acyclovir and ganciclovir against EBV. Corticosteroids can be indicated as the component of the treatment of complications listed above with the exception of splenic rupture which needs surgical operation.

CMV

Epidemiology and pathogenesis. Being the largest among herpes viruses as the result of its replication CMV produces in the nucleus of infected cells the big inclusions useful in microscopic detection. As other herpes viruses after primary infection CMV persists in many types of cells and reactivates in immunocompromised hosts. Some secondary cases may be caused by reinfection.

Clinical features. Young people acquire CMV usually via the close contact and develop subclinical infection or mononucleosis-like illness milder than with EBV. The heterophile agglutinin tests remain negative. Older immunocompromised patients often became infected by transfusion and their primary infection is frequently complicated with interstitial pneumonia, hepatitis, Guillain–Barré syndrome, meningoencephalitis, myocarditis, thrombocytopenia and hemolytic anemia.

The frequency of CMV in HIV positive people dramatically decreased as the result of the introducing of high active antiretroviral treatment. CMV retinitis is the most common manifestation; among other can be listed polyradiculopathy, esophagitis, colitis, pancreatitis and cholecystitis. CD4 cut off for CMV diseases is < 100 cells/mcL.

Transplant recipients get CMV with transplanted organ or via transfused blood components. CMV is the commonest and the most serious opportunistic infection in this patients. CMV pneumonitis in bone marrow recipients and CMV hepatitis in liver recipients are the most problematic forms.

Diagnosis. Serology tests — the rising of titers or seroconversion — are the evidence of current infection.

PCR detected CMV DNA replaced viral culture and antigene identifying assay. The finding of CMV in saliva or urine does not necessary indicate active infection, because seropositive individuals can produce virus lifelong. On the other hand CMV DNA detection in CSF, blood and cells proves active infection. Detection of CMV infected cells containing bodies inclusions in biopsy material is the most reliable confirmation of end-organ disease.

Treatment. Primary infection in immunocompetent patients does not require antiviral treatment.

Ganciclovir, valganciclovir, foscarnet and cidofovir are active against CMV and used in immunocompromised patients with evidences of end-organ disease. There are several approaches to antiviral prophylactic in solid organ recipients.

HHV-6

HHV-6 is the cause of roseola (also known as exanthem subitum or six disease).

Epidemiology and pathogenesis. The main route of infection is the saliva exchange and almost everybody by 2 years is infected. After penetration through

oropharynx virus replicates in regional lymph nodes and mononuclears, ager that it gets many organs including CNS.

Clinical features. Incubation lasts 5–15 days.

– Infantile fever — benign and the most common disease form consisted in fever without rash sometimes with periorbital edema.

– Exanthem subitum or six disease affects infants and young children. Fever and upper mild respiratory tract symptoms have acute onset and continue 3–5 days, after that light-rose slightly elevated papules appear. Sometimes rash onset concurs with fever cessation. The rash lasts 1–2 days and can be accompanied by lymphadenopathy, cough, vomiting and diarrhea. For the most infants diseases are well tolerated or asymptomatic

– Encephalitis as the result of acute infection may be alone or accompanies roseola.

– Other features — mononucleosis like illness, hepatitis. There is attempt to link HHV-6 and chronic fatigue syndrome.

In immunocompromised hosts virus DNA can be found in blood and other body fluids and occasionally with other pathogens (e. g. CMV), but the direct causative role of HHV-6 in opportunistic infections or neoplasms has been not proved.

In the course of HIV-infection HHV-6 accelerates CD4 expression and promotes their infection by HIV-1, in turn HIV-associated immune suppression furthers HHV-6 spread. In the same time there is not any evidence that HHV-6 either causes any opportunistic infection or lead to progression of AIDS.

Diagnosis. Diagnosis is not needed in the case of exanthem subitum so it is self-limited process. Lab evaluation is performed for encephalitis or hepatitis diagnosis and in immunocompromised patients or organ recipients. Paired sera investigation better helps for acute infection diagnosis than IgM assays.

Treatment. There aren't controlled trials proving antiviral agents effectiveness. In vitro aciclovir is inactive, on gancilovir there is variable response and foscarnet is able to inhibit HHV-6

HHV-7

The exact role of HHV-7 has been still unclear. Nearly everybody's infected by 5 years. It is supposed HHV-7 would cause similar fever and rash as HHV-6.

HHV-8

HHV-8 firstly was recognized in the association with Kaposi's sarcoma (KS) in HIV positive patients. Virus predominantly transmit through sexual contact. Acute infection is asymptomatic and the sites of viral replication are no known.

Regarding KS the treatment with antiviral agent active against herpes virus is ineffective. Antiretroviral treatment along may be sufficient in the case of

middle skin lesions. Extensive KS or with visceral organ involvement (gastrointestinal or pulmonary) needs for combination chemotherapy.

HHV-8 also associated with several other neoplasms — primary effusion lymphoma and Castelman's disease. Both of them more often are seen in AIDS patients.

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CHARACTERISTICS OF CHILDHOOD INFECTIOUS DISEASES IN ADULTS

CHICKENPOX

Etiology. Varicella-zoster virus (VZV) causes two distinct clinical diseases. Varicella, more commonly called chickenpox, is the primary infection and results from exposure of a person susceptible to the virus. Recurrence of infection results in the more localized phenomenon known as *herpes zoster*, often referred to as *shingles*, a common infection among the elderly and immunocompromised.

VZV is a member of the *Herpesviridae* family and shares structural characteristics with other members of the family; it contains centrally located double-stranded DNA with a surrounding envelope.

Chickenpox is an acute infectious disease, characterized by vesicular eruption with transparent liquid on skin and mucous membrane. Overall, chickenpox is a disease of childhood, because 90 % of cases occur in children younger than 13 years.

Epidemiology. Humans are the only known reservoir for VZV. Chickenpox follows exposure of the susceptible or seronegative person to VZV. Virus is spread by the respiratory route and replicates in the nasopharynx or upper respiratory tract. Patients are a source of infection from the last (1–2) days of the incubation period up to the ninth day from appearance of the elements of the rash. The patient is not infective at the stage of formation and separation of crusts. Many clinicians believe that chickenpox can be contracted in individual cases from herpes zoster patients. Infection is transmitted by air-droplet route, and can be conveyed over quite considerable distances.

Susceptibility to chickenpox is very high, practically universal. Stable lifelong immunity follows one attack; second attacks are extremely rare.

Pathophysiology. The portal of entry is the mucous membrane of the upper respiratory tract. After an incubation period, the virus circulating in the blood localizes by preference in the skin owing to its dermotropism. Vacuolization leads to the formation of fresh vesicles.

It is possible that the chickenpox virus may persist in the body of human for a long period of time. It may probably be retained in the cells of the intervertebral ganglia after the human recovers from chickenpox. The latent infection may persist for years and revive when the general condition has favorable background for its development (various diseases, injuries, intoxications, etc.). The virus then becomes activated in older children or adults and has clinical manifestation as herpes zoster.

Clinical features. Chickenpox is generally a benign, self-limited disease in immunocompetent persons. The risk of severe presentation increases by more than 15-fold for adults.

The incubation period averages 14 days (11–21 days). Prodromal signs are usually absent or mild (subfebrile temperature, and a certain general discomfort for 12–24 hours).

The outbreak of rash happens with a rise of temperature or follows a few hours later; but the first vesicles often appear at normal temperature. There is no definite order of appearance of the rash; it may develop on the face, scalp, trunk or limbs.

At first maculo-papular, the elements very quickly turn (within a few hours) into vesicules, round or oval, differ in size from a pinpoint to a large pea, and are seated superficially; their wall is tense, and they are filled with a clear fluid; umbilication is seen in only individual lesions. A narrow erythematous corona surrounds the vesicles. Vesicles dry up in one or two days, forming flat brown crusts that are shed in one to three weeks, leaving no scars. Since chickenpox eruption does not develop at once, but comes out in crops at intervals of 24 to 48 hours, it is polymorphous, i. e. the lesions are in different stages of development (papules, vesicles, crusts) at any time on a given area of the skin. The itch is disturbing.

In some patient's eruption is often seen on the mucous membranes of the mouth, nasopharynx, larynx, and genital organs.

The rise of temperature in chickenpox usually usually goes up to 38 °C, and may become high (39 °C or 40 °C). The temperature curve is irregular, each peak reflecting the dynamics of the eruption

The most frequent CNS complication is encephalitis, which can be life threatening in adults.

Another complication that occurs more commonly in adults and in immunocompromised persons is varicella pneumonitis.

Diagnosis. The diagnosis of chickenpox is usually made by history and physical examination. Confirmation of the diagnosis is possible through the demonstration of either seroconversion or serologic rises.

Differential diagnosis: scarlet fever, measles, dermatologic diseases, allergic skin reactions.

Treatment. The medical management of chickenpox in the normal host is directed toward reduction of complications. For chickenpox, hygiene is important, including bathing, and closely cropped fingernails to avoid a source for secondary bacterial infection.

Oral acyclovir therapy in normal children, adolescents, and adults shortens the duration of lesion formation by about 1 day, reduces the total number of new lesions by approximately 25 %, and diminishes constitutional symptoms in one third of patients. Adolescents and adults can receive up to 800 mg 5 times a day. Normal children/adolescents (uncomplicated) still usually require no antiviral treatment. Immunosuppressed patients should receive intravenous acyclovir in dose 10 mg/kg every 8 hours × 7–10 days.

Prevention. In the normal host, prophylaxis of chickenpox is achieved via vaccination. In the immunocompromised person who has not been previously exposed to chickenpox, the administration of varicella-zoster immunoglobulin (VZIG) has been shown to be useful for both prevention and amelioration of symptomatic chickenpox in high-risk persons. Recent guidelines also recommend administration of VZIG to a pregnant woman who is known to be seronegative and who has had a significant exposure.

There is a live attenuated varicella vaccine. Varicella vaccine is recommended for healthy varicella-susceptible children and adults.

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MEASLES

Etiology. Measles, an acute infection caused by rubeola virus, is highly contagious and usually seen in children. Measles virus (MV) belongs to the genus *Morbillivirus* of the family *Paramyxoviridae*. MV is an enveloped, nonsegmented, single-stranded RNA virus. Countries in which measles vaccine is widely used have experienced a marked decrease in the incidence of disease. Measles has long been regarded as an illness of childhood. When it occurs in adults, it is often a more severe illness.

Epidemiology. The source of infection in measles is a sick person. Measles is an airborne virus that is spread by direct contact with droplets from respirato-

ry secretions of infected persons. It is one of the most communicable of the infectious diseases, most infectious during the late prodromal phase of the illness, when cough is at its peak. The susceptibility of humans to measles is very high.

Pathophysiology. The portal of entry of measles is the mucous membrane of the upper respiratory tract, and possibly the conjunctiva. The principal pathological changes attending measles are inflammatory processes in the nasopharynx, respiratory organs, and skin.

Clinical features. The incubation period of measles is 10 to 14 days; it is often longer in adults than in children. A prodromal phase lasting several days begins after the incubation period. Measles are manifested by malaise, fever, anorexia, conjunctivitis, and respiratory symptoms such as cough and nasopharyngitis. Toward the end of the prodrome, just before the appearance of the rash, *Belsky–Filatov–Koplik's* spots appear. These spots mostly break out on the mucosa on the line of opposition of the molar teeth, and less commonly on the lip inner surfaces and on the gums, occasionally on the conjunctiva. Each element looks like a whitish papule, the size of a poppy-seed, surrounded by a narrow band of hyperemia, or areola. The spots persist for two or three days. The presence of *Belsky–Filatov–Koplik's* spots is a pathognomonic measles symptom found in no other disease; the disease diagnosis can be based on this symptom long before the outbreak of eruption.

The appearance of the rash coincides with the rise of temperature. Its first elements are found behind the ears and in the centre of the face. Within 24 hours it spreads rapidly over the whole face, neck, and upper part of the chest. On the second day the exanthema rapidly spreads over the trunk and the proximal parts of the extremities, and on the third day covers the limbs. This order of succession in the spread of the eruption is typical of measles. At first the elements of the rash look like pink papules of a soft consistency, the size of a grain of millet or buckwheat. Within a few hours each papule becomes surrounded by a zone of bright erythema. Soon adjacent maculopapules become confluent, forming large blotches of irregular outline, with the initial papules in the centre. Large maculopapular elements have a tendency to fuse further. The rash exanthema usually persists for three days; from the fourth day it begins to fade in the order of its appearance.

One of the most common complications in adults is encephalitis after measles; it may be acute or chronic. Acute measles encephalitis manifests with a resurgence of fever during convalescence and frequently with headaches, seizures and changes in the state of consciousness.

Diagnosis. Diagnosis is usually clinical based on acute febrile illness, characteristic rash and/or *Belsky–Filatov–Koplik's* spots. Measles serology IgM helpful for acute infection from 4^{th} day of rash appeared, while IgG is used to screen immune status. Tissue/secretions/blood/urine may be cultured for virus. The blood picture shows leukopenia and neutropenia.

Differential diagnosis: influenza, rubella, scarlet fever, drug rash.

Treatment. Mainly supportive care: fluids in the case of intoxication, acetaminophen against temperature.

Prevention. Immunity to measles after an attack of the disease appears to be lifelong. Similarly, after measles vaccination, immunity is of many years' duration and probably lifelong in most persons. MMR vaccine (measles-mumps-rubella) introducing is the main prevention method in population.

At the present time, gamma-globulin is only used for prophylactic purposes in a small number of children who were in contact with the measles patients and are 3-months to one year of age. Gamma-globulin is given not later than 6 days from the day of contact.

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RUBELLA

Etiology. Rubella (German measles) is an acute exanthematous viral infection of children and adults. Rubella virus is classified in the *Togaviridae* family on the basis of its single-stranded RNA genome.

Epidemiology. Rubella virus is spread in droplets that are shed from respiratory secretions of infected persons. Patients are most contagious while the rash is erupting, but they may shed virus from the throat from 10 days before until 15 days after the onset of the rash. Only modestly communicable.

Clinical features. Incubation 12–23 days. Less severe than measles, sometimes called "3-day measles", but main public health risk is congenital rubella syndrome (CRS).

Age is the most important determinant of the severity of rubella. Children have milder disease than adults. The major clinical manifestations of postnatal rubella are adenopathy, which may last several weeks, and rash. The rash of rubella begins on the face and moves down the body. It is maculopapular but not confluent, may desquamate during convalescence and may be absent in some cases. An enanthem consisting of petechial lesions on the soft palate (Forschheimer's spots) has been described for rubella. The rash may be accompanied by mild pharyngitis and conjunctivitis. Usually the rash lasts 3 to 5 days. Fever, if present, rarely lasts beyond the first day of rash. The complications of postnatal rubella are uncommon.

Rubella in pregnancy. Rubella can be a disastrous disease in early gestation and can lead to fetal death, premature delivery, and an array of congenital

defects. The effects of rubella virus on the fetus are, to a large extent, dependent on the time of infection; in general, the younger the fetus when infected, the more severe the illness.

The specific signs and symptoms of congenital rubella may be classified as temporary (e. g., low birth weight), permanent (e. g., deafness), and developmental (e. g., myopia). The most common manifestations are deafness, cataract or glaucoma, congenital heart disease, and mental retardation.

Diagnosis and differential diagnosis. Because rubella is usually a mild disease with nonspecific symptoms, it is often difficult to diagnose clinically. The disease has been confused with other infections such as scarlet fever, mild measles, infectious mononucleosis, toxoplasmosis and certain enteroviral infections.

Blood analysis may reveal only leukopenia and atypical lymphocytes. Virus isolation from throat swabs, urine, synovial fluid, or other body secretions is an acceptable method for diagnosis. However, this technique is time-consuming and expensive. The laboratory diagnosis of postnatal rubella is most conveniently made serologically. These include enzyme-linked immunosorbent assay (ELISA), passive latex agglutination test. A demonstration of specific IgG on one serum sample is evidence of immunity to rubella. Acute rubella infection may be diagnosed either by a demonstration of specific IgM in one serum sample or by a fourfold or greater increase in rubella antibody titer in acute and convalescent specimens assayed in the same test.

For a serologic diagnosis of congenital rubella in the neonatal period, antibody to rubella virus should be measured in both infant and maternal sera. If rubella IgM is detected in a newborn infant's serum, then transplacental rubella infection has occurred. Congenital rubella infection has been diagnosed by the following tests or procedures: placental biopsy at 12 weeks, demonstration of rubella antigen with monoclonal antibody, cordocentesis and detection of RNA by in situ hybridization and PCR. It may also be diagnosed by the presence of specific IgM in fetal blood, but this may not be detectable until as late as 22 weeks of gestation.

Treatment. Often mild illness that necessitates no therapy. Fever, arthritic complaints may be treated syptomatically.

Prevention. After an attack of rubella, lifelong protection against the disease develops in most persons. The persistence of specific antibody for as long as 14 years after immunization has also been demonstrated. Vaccine indications: infants over 12 months, susceptible adolescents and adults, emphasising on non-pregnant women of childbearing age.

Immunisation against rubella in pregnancy: the observed risk for congenital rubella after immunization therefore is reported as zero; however, the theoretical maximal risk could be as high as 1 % to 2 %. It is recommended that women avoid pregnancy for 28 days after rubella vaccination. Although it is not

recommended that rubella vaccine be administered to women who are pregnant, the currently recognized minimal theoretical fetal risk does not mandate automatic termination of a pregnancy.

Post-exposure prophylaxis for pregnant patients: if nonimmune exposed to rubella, and abortion not a consideration if rubella develops, some authorities suggest immunoglobulin therapy, though scant evidence for this recommendations.

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MUMPS

Mumps is an acute generalized viral infection that occurs primarily in school-aged children and adolescents. The disease is benign and self-limited, with one third of affected persons having subclinical infection. As is characteristic of many viral infections, mumps is usually a more severe illness in adults than in children and more commonly leads to extrasalivary gland involvement in these older patients.

Etiology. Mumps virus is a member of the *Paramyxoviridae* family.

Epidemiology. Humans are the only known natural host; the virus is naturally transmitted via direct contact, droplet nuclei and enters through the nose or mouth. More intimate contact is needed to transmit mumps than for measles or chickenpox. The period of peak contagion is just before or at the onset of parotitis.

Clinical features. The incubation period of mumps averages 16 to 18 days, with a range of 2 to 4 weeks. Characteristically, the prodromal symptoms are nonspecific and include low-grade fever, anorexia, malaise, and headache.

Within 1 day, the nature of the illness becomes apparent when the patient complains of an earache, and tenderness can be elicited by palpation of the parotid. The involved gland is soon visibly enlarged and progresses to a maximum size over the next 2 to 3 days. Usually the second parotid gland enlarges 1 or 2 days after the other; however, mumps results in unilateral parotitis alone in one quarter of patients with salivary gland involvement. The Stensen's duct is frequently edematous and erythematous. During the first 3 days of illness, the patient's temperature may range from normal to 40 °C.

After parotid swelling has reached its peak, pain, fever, and tenderness rapidly resolve, and the parotid gland returns to normal size within 1 week.

Involvement of the other salivary glands may occur in conjunction with parotitis in up to 10 % of cases but is rare as the sole manifestation of mumps infection.

Central nervous system involvement is one of the most common extrasalivary gland manifestation of mumps in adults. Meningitis and encephalitis may occur.

Epididymo-orchitis is the most common extrasalivary gland manifestation in the adults. It develops in 20 % to 30 % of adult male with mumps infection and is bilateral in one of six of those with testicular involvement. Genital examination reveals warmth, swelling, and tenderness of the involved testicle and erythema of the scrotum. The testis may be enlarged to three to four times its normal size. When testes are examined months to years later, some degree of atrophy is noted in 50 % of patients.

Pancreatitis may manifest by severe epigastric pain and tenderness accompanied by fever, nausea, and vomiting.

Diagnosis. Historically, the diagnosis of mumps has been made on the basis of a history of exposure and of parotid swelling and tenderness accompanied by mild to moderate constitutional symptoms.

The WBC and differential counts in mumps are normal, or there may be a mild leukopenia with a relative lymphocytosis.

The definitive diagnosis of mumps depends on serologic studies, viral isolation from nasopharynx or parotid duct swab, or PCR assay.

Serogy criteria of mumps are: positive IgM or 4 × rise IgG in serum. Acute titer or IgM assay should be done within 5 days of illness onset. If negative, delayed responses to IgM have been reported, so recommendations are for repeat IgM assessment 2–3 weeks after onset of symptoms.

Differential diagnosis: enteroviral infection, influenza, acute HIV, bacterial infection (*S. aureus*), drug reaction, tumor, Sjogrens syndrom.

Treatment. Self-limited; symptomatic treatment is needed.

Management of orchitis is purely symptomatic. Bed rest, analgesics, support of the inflamed testis with a “bridge”, and ice packs make the patient feel more comfortable. There is no convincing evidence that the use of steroids produces more rapid resolution of the orchitis or prevents subsequent atrophy.

Prevention. MMR usually used as vaccine for mumps. All children older than 12 months should be immunized.

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ENTEROBIASIS

Enterobiasis is highly prevalent, particulary in temperate climate. This infection is most common in young children and institutionalized populations.

Etiology and epidemiology. *Enterobius vermicularis* (pinworm) is a small, white thread-like worm which inhabits the caecum and ascending colon. The gravid females migrate at night to the perianal/perineal region where they deposit their eggs. The eggs become infective within hours and are transferred to night clothes, bedding, dust, and air. The most common mode of transmission is by hand-to-mouth passage. From ingested eggs, larvae hatch and mature into adults. This life cycle takes ~1 month, and adult worms survive for ~2 months. Self-infection results from perianal scratching and transport of infective eggs on the hands or under the nails to the mouth. Because of the ease of person-to-person spread, pinworm infections are common among family members.

Clinical features. Most infected patients are asymptomatic. In the others the most common symptoms are perianal/perineal puritus and disturb sleep. Heavy infections have been claimed to cause abdominal pain and weight loss.

Occasionally, pinworms may cause ectopic disease (e. g. appendicitis, salpingitis, ulcerative bowel lesions). Eosinophilia is uncommon.

Diagnosis. Diagnosis is based on cellophane-tape slide (scotch-tape) test for identification of characteristic elongated oval shaped eggs. All family members of an affected individual should be screened for infection.

Treatment. Infected children and adults should be treated with albendazole (400 mg once), mebendazole (100 mg once), or pyrantel pamoate (11 mg/kg once; maximum, 1 g), with the same treatment repeated after 2 weeks. Treatment of household members is advocated to eliminate asymptomatic reservoirs of potential reinfection.

Prevention. Good personal hygiene is a cornerstone prophylactic measure.

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ASCARIASIS

Ascariasis is the most common human helminthic infection affecting more than 1 billion people globally.

Etiology and epidemiology. Ascariasis is caused by *Ascaris lumbricoides* (white or reddish yellow roundworm; 15–35 cm in length) and is found world-

wide. Transmission typically occurs through fecally contaminated soil and is due either to a lack of sanitary facilities or to the use of human feces as fertilizer. With their propensity for hand-to-mouth fecal carriage, younger children are most affected. Infection outside endemic areas, though uncommon, can occur when eggs on transported vegetables are ingested.

Adult worms live in the lumen of the small intestine. Female worm produces up to 200 000 ova/day, which pass with the feces. Ascarid eggs become infective after several weeks of maturation in the soil and can remain infective for years. After infective eggs are swallowed, larvae hatched in the intestine penetrate its wall, migrate through the circulation to the lungs, break into the alveoli, ascend the bronchial tree, and return via swallowing to the small intestine, where they develop into adult worms. Adult worms live for 1–2 years.

Clinical features. Most patients are asymptomatic. Clinical features depend on the site and intensity of infection.

During the lung phase of larval migration, patients may develop an irritating nonproductive cough and burning substernal discomfort that is aggravated by coughing or deep inspiration. Dyspnea and blood-tinged sputum are less common. Fever is usually reported. Eosinophilia develops during this symptomatic phase and subsides slowly over weeks. Chest x-rays may reveal evidence of eosinophilic pneumonitis (Löffler's syndrome), with rounded infiltrates a few millimeters to several centimeters in size. These infiltrates may be transient and intermittent, clearing after several weeks.

In established infections, adult worms in the small intestine can cause malnutrition, malabsorption, steatorrhoea. In heavy infections, particularly in children, a large bolus of entangled worms can cause pain and small-bowel obstruction. Single worms may cause disease when they migrate into aberrant sites. A large worm can enter and occlude the biliary tree, causing biliary colic, cholecystitis, cholangitis, pancreatitis, or (rarely) intrahepatic abscesses.

Diagnosis. Stool microscopy usually confirms the diagnosis by finding eggs that are oval shaped and thick shelled.

During the early transpulmonary migratory phase, when eosinophilic pneumonitis occurs, larvae can be found in sputum or gastric aspirates before diagnostic eggs appear in the stool. The eosinophilia that is prominent during this early stage usually decreases to minimal levels in established infection.

Treatment. Albendazole (400 mg once), or mebendazole (100 mg bid PO for 3 days is effective against ascariasis. In pregnant women pyrantel pamoate should be used.

Partial intestinal obstruction should be managed with instillation of piperazine citrate through the nasogastric tube (piperazine narcotizes the worms and helps to relieve symptoms) and nasogastric suction. Complete obstruction requires immediate surgical intervention.

Prevention. Prophylactic measures include proper hand washing after defecation and before handling food; proper washing, peeling, or cooking of all fresh fruits and vegetables before consumption.

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OPISTHORCHIASIS

Etiology and epidemiology. Opisthorchiasis is caused by trematode helminthes *Opisthorchis felineus* and *Opisthorchis viverrini*. They are common liver flukes of cats and dogs that are occasionally transmitted to humans.

About 2 million people in the former Soviet Union are infected with *O. felineus* (predominantly in Siberia), while *O. viverrini* is found in Thailand.

Life cycle. The adult flukes inhabit the biliary tract where they deposit small (30×14 μm) yellow-brown operculated eggs, which are fully embryonated when they pass out of the body in feces into fresh water. The eggs are ingested by snails, inside of which they hatch into miracidia that develop and replicate to produce large numbers of cercariae. Cercariae are once again released into the water and penetrate susceptible freshwater fish where they encyst as metacercariae. Humans are infected by ingestion of raw or undercooked fish. The metacercariae excyst in the duodenum and migrate to the bile ducts.

Clinical features. Mild or moderate infection is usually asymptomatic but eosinophilia may exist. Symptomatic illness is more common in patients aged 20–40 years with heavy infection.

An acute illness is characterized by fever, abdominal pain, hepatomegaly, urticaria, and eosinophilia and develops 2 to 4 weeks after the initial exposure. Increased liver enzymes and enhancing hypodense nodules on CT scan have been reported usually.

Irritation of bile duct walls by the helminthes and their metabolic products leads to inflammation (cholangitis) and thickening of bile duct walls and localized obstruction in about 10 % of persons with heavy chronic infections (1,000 to 25,000 or more eggs per gram of stool). Patients complain of right upper quadrant discomfort, anorexia, and weight loss. On physical examination, the liver is palpable and firm.

Chronic symptoms of dyspepsia, fatigue, and vague abdominal pain may occur as well.

Infection caused by *O. viverrini* is considered to be the risk factor of cholangiocarcinoma.

Diagnosis. Opisthorchiasis is diagnosed by finding eggs in the stool or by identifying adult worms during surgery or endoscopic retrograde cholangiopancreatography.

Serology and PCR-based assays are not widely available outside endemic areas or research laboratories.

Ultrasonography, CT, or MRI scans can demonstrate dilation and stricture of bile ducts, thickening of the gallbladder wall, and stones.

Treatment and prevention. Praziquantel (25 mg/kg tid for 1 to 2 days) is the drug of choice. Albendazole (10 mg/kg/day for 7 days) can also be used. Rarely, surgery is needed for biliary tract obstruction.

Prevention of infection can be achieved by freshwater fish freezing or adequate cooking.

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ECHINOCOCCOSIS

Etiology and epidemiology. Echinococcosis has two forms: hydatid (unilocular) cyst disease, caused by *Echinococcus granulosus*, and alveolar cyst disease, caused by *Echinococcus multilocularis*. In addition, polycystic echinococcosis is caused by either *Echinococcus vogeli* or *Echinococcus oligarthrus*. Infection in humans is caused by the larval stage of the tapeworm *Echinococcus spp.*

Infection is acquired by ingestion of parasite eggs excreted by tapeworm-infected animal (canines, incl. domestic dogs, sheep, cattle, pigs, horses, camels). Once in the intestinal tract, the eggs hatch to form oncospheres that penetrate the mucosa and enter the circulation. Oncospheres then encyst in host viscera, developing over time to form mature larval cysts. *E. granulosus* larvae develop into fluid-filled unilocular hydatid cysts. Daughter cysts develop develop within the main cyst capsule. The cysts expand slowly over a period of years. The larval form of *E. multilocularis* is quite different: the parasite is always multilocular, and daughter vesicles progressively invade the host tissue by peripheral extension. *E. vogeli* infections are similar to alveolar cyst disease, whereas *E. oligarthrus* infections appear less aggressive.

E. granulosus is prevalent worldwide. *E. multilocularis* is found in northern forest areas of Europe, Asia, and North America and in the Arctic regions, *E. vogeli* and *E. oligarthrus* — in South America.

Clinical features. The hydatid cysts of *E. granulosus* usually affect the liver (50–70 %) or the lungs (23–30 %). It should be taken to the note that they can affect any other organ, but more rarely.

Symptoms are often absent, and in many cases infection is detected only incidentally by imaging studies. When symptoms do occur, they are usually due to the mass effect of the enlarging cyst in a confined space or rupture into adjacent organs. Cyst rupture may cause severe allergic reactions or seeding to distant organs.

Alveolar cyst disease is relatively more aggressive with tumor-like invasion of adjacent organs and metastasis to distant ones. Symptoms are usually of gradual onset, referring to the organ involved, which is most commonly the liver. Complications include biliary tract disease, portal hypertension, and Budd–Chiari syndrome.

Diagnosis. Infection usually is suspected based on imaging studies (ultrasonography, CT, and MRI) and may be confirmed by a specific enzyme-linked immunosorbent assay (ELISA) or Western blot serology.

Eosinophilia is not a consistent or reliable finding.

Treatment. Optimal treatment of symptomatic, complicated hydatid cysts is surgical resection to remove the cyst in toto. An intermediate intervention for inoperable cysts has been developed, known as the PAIR procedure (**p**uncture under CT/ultrasound guidance, **a**spiration, **i**nfusion of scolicidal agents, and **r**easpiration). For prophylaxis of secondary peritoneal echinococcosis due to inadvertent spillage of fluid during PAIR, the administration of albendazole (15 mg/kg daily in two divided doses) should be initiated at least 4 days before the procedure and continued for at least 4 weeks afterward.

Wide surgical resection (e. g., hepatic lobectomy or liver transplantation — to ensure total removal of the cyst) is the treatment of choice for *E. multilocularis* infection. Adjuvant albendazole therapy to reduce cyst size before surgery or limit intraoperative spread is also recommended. For inoperable cases, indefinite mebendazole or albendazole therapy remains the single option.

Prevention. Prevention of echinococcosis depends on interrupting the parasite life cycle. In endemic areas, it can be prevented by administering praziquantel to infected dogs, by denying dogs' access to infected animals. Anti-*Echinococcus* vaccine can also significantly reduce infection rate in farm animals (sheep and pigs), which may further lower the level of peridomestic transmission.

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TRICHINELLOSIS

Definition. Trichinellosis is a parasitic disease caused by a roundworm of the genus *Trichinella*.

Etiology. Eight species of *Trichinella* are recognized as causes of infection in humans. The most common infections are caused by *T. spiralis*, which can be found in pigs, rodents, horses, bears and foxes. Some other pathogenic *Trichinella* species includes *T. pseudospiralis, T. nativa, T. nelsoni, T. britovi, T. murrelli* etc.

Life cycle and epidemiology. Trichinellosis has a worldwide geographic distribution causing a major public health problem in many parts of the world. *T. spiralis* is found primarily in the Europe, United States, South America and South Asia. This illness is common in developing countries where many outbreaks are reported each year as a result of consumption of undercooked pork or wild animals. Although the disease is rare in the western world, outbreaks are reported in Europe and the United States, especially among immigrants who continue to eat undercooked meat or when there are breakdowns of veterinary services. Most infections are caused by ingestion of wild or domestic pork, but cases have been reported after ingestion of infected meat from other animals including horses, bears, walruses, rodents, dogs, lions, panthers and crocodiles. Game animals as sources of infection have increased greatly in both developing and developed countries.

The life cycle includes enteral and parenteral phase.

Enteral phase. Humans are infected after eating encysted *Trichinella* larvae present in raw or inadequately cooked meat. The cyst walls are digested by acid-pepsin digestion in the stomach, larvae are released and pass into the small intestine. The larvae invade the small intestine epithelial wall, molt four times and develop into adult worms. The males die after copulation, and the females produce 500 to 1500 newborn larvae that are deposited into the mucosa of the duodenal wall over a 2- to 3-week period before their expulsion in the fecal stream.

Parenteral phase. Newborn larvae enter the bloodstream and seed various organs including myocardium, lungs, brain, pancreas and lymph nodes, but only the larvae that invade the skeletal muscle survive. The individual muscle fibers invaded by the *Trichinella* larvae show degeneration and necrosis and heavy infiltration with lymphocytes and eosinophils. The larvae are encysted within a few weeks, and the cyst wall may calcify over time. Although host immune responses may help to expel intestinal adult worms, they have little effect on muscle-dwelling larvae.

Clinical manifestations. Clinical symptoms of trichinellosis arise from the successive phases of parasite enteric invasion, larval migration and muscle encystment. Most light infections (with < 10 larvae per gram of muscle) are asymptomatic, whereas heavy infections (which can involve > 50 larvae per gram of muscle) can be lifethreatening.

Invasion of the gut by large numbers of parasites occasionally provokes diarrhea during the first week after infection; abdominal pain, constipation, nausea or vomiting also may be prominent.

Symptoms due to larval migration and muscle invasion begin to appear in the second week after infection. The migrating *Trichinella* larvae provoke a marked local and systemic hypersensitivity reaction, with fever and hypereosinophilia. Periorbital and facial edema is common, as are hemorrhages in the subconjunctivae, retina, and nail beds ("splinter" hemorrhages). A maculopapular rash, headache, cough, dyspnea or dysphagia sometimes develops. Myocarditis with tachyarrhythmias or heart failure and, less commonly, encephalitis or pneumonitis may develop and accounts for most deaths of patients with trichinellosis.

Upon onset of larval encystment in muscle 2–3 weeks after infection symptoms of myositis with myalgias, muscle edema and weakness develop, usually overlapping with the inflammatory reactions to migrating larvae. The most commonly involved muscle groups include the extraocular muscles, the biceps and the muscles of the jaw, neck, lower back and diaphragm. Peaking ~3 weeks after infection symptoms subside only gradually during a prolonged convalescence.

Diagnosis. In the enteric phase a history of ingesting raw or undercooked meat is helpful in differentiating parasitic infection from other causes of gastroenteritis. Blood eosinophilia develops in > 90 % of patients with symptomatic trichinellosis and may peak at a level of > 50 % between 2 and 4 weeks after infection. Serum levels of muscle enzymes, including creatine phosphokinase, are elevated in most symptomatic patients.

Serological diagnosis of trichinellosis (ELISA) in the enteric phase and early into the parenteral phase can be difficult because diagnostic antibody test results are commonly not positive until 3 to 5 weeks after infection. Even with negative *Trichinella* antibody test results, a febrile illness accompanied by headache, periorbital and facial edema and myalgias is suggestive of trichinellosis in persons with a compatible food history. Elevated blood levels of muscle enzymes such as creatine phosphokinase (CPK) as well as elevated eosinophil counts in the peripheral blood increase the probability even further.

The muscle biopsy (at least 1 g of involved muscle, preferably near tendon insertions) may be also used for confirmation of the illness but sensitivity of this method to identify diagnostic encysted *Trichinella* larvae in infected muscle will

be dependent on the degree of muscle involvement and choice of the area for biopsy.

A multiplex PCR has been developed for the unequivocal differentiation of *Trichinella* species and genotypes but it is not commercially available.

Treatment. Most lightly patients recover uneventfully with bed rest, antipyretics and analgesics. In case of moderate and severe disease albendazole 400 mg orally twice a day for 8 to 14 days or mebendazole 200–400 mg three times a day 3 days, then 400 mg three times a day 8–14 days is recommended. For prevention of systemic symptoms that can occur after treatment with albendazole or mebendazole prednisone is useful (the optimum dose is uncertain but 1 mg/kg for 5 days per os without tapering is probably sufficient). Aggressive supportive treatment and perhaps higher doses of steroids are warranted in those with life-threatening complications such as myocarditis, encephalitis or pneumonitis.

Prevention. Education regarding consumption of raw domestic and sylvatic animals that can be carriers of *Trichinella* parasites (if not properly tested for larvae as part of inspection) is an important component of prevention. In addition, careful control of farming techniques for pigs with veterinary oversight and use of certified feedstuff are needed.

Larvae may be killed by cooking pork until it is no longer pink or by freezing it at –15 °C for 3 weeks.

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FEVER OF UNKNOWN ORIGIN

Fever of unknown origin (FUO) is a medical condition requires that the patient have:

1) an illness that has lasted least 3 weeks;

2) fever of more than 38.3 °C on several occasions;

3) no diagnosis reached after routine workup for 3 days in hospital or after 3 or more outpatient visits.

Determining the cause of FUO remains one of the greatest challenges in infectious diseases. This problem requires a team approach in which all caregivers repeatedly share their daily findings and continually generate and test new

hypotheses. The team should be led by an expert, that is, a physician with extensive expertise in infectious diseases and many years of clinical experience.

Before launching different diagnostic tests for determination of FUO cause the physician must carefully document that the patient fulfills the criteria for FUO:

1) patient should be instructed to measure both 6-AM and 6-PM temperature to rule out an exaggerated circadian rhythm;

2) an electronic thermometer should always be used to exclude the possibility of factitious fever;

3) although the exact pattern of fever isn't helpful in most cases for identifying the fever's case, in patients with the highest fever in early morning miliary tuberculosis, typhoid fever and periarteritis nodosa should be strongly considered.

Causes of FUO. The possible cases of FUO can be classified into four major categories: infections, neoplasms, autoimmune disorders and miscellaneous causes (drug fever, factitious fever, familial Mediterranean fever, pulmonary emboli etc.).

Infectious causes of FUO (up to 40 % of all FUO) include:

1. Abscesses (particularly abdominal abscesses that may persist for prolonged periods before being diagnosed).
2. Osteomyelitis (particularly of the vertebral bodies, mandibule and air sinuses).
3. Subacute bacterial endocarditis (for successful diagnosis is very important a careful physical examination to determine the audible cardiac murmur, draw 3 sets of blood cultures before the antibiotic therapy and use transesophageal cardiac echo to visualize the vegetations).
4. Biliary system infections (may have no right upper quadrant tenderness and pain).
5. Urinary tract infections (in absence of related symptoms as dysuria, frequency of flank pain).
6. Tuberculosis (especially miliary — most common in patients in elderly or immunocompromised, particularly with HIV and on high-dose corticosteroids or TNF inhibitor therapy; bone marrow culture and computer tomography of the lungs are useful for right diagnosis).
7. Spirochetal infection: leptospirosis, *Borrelia spp.*
8. Brucellosis (history of animal exposure or eating unpasteurized cheese).
9. Rickettsial infections (a history of camping, hunting or other outdoor activities in areas endemic for these infections should raise the possibility).
10. Chlamydia psittaci (may resemble mononucleosis-like syndrome; *C. psittaci* is usually contracted from birds, including pigeons, and poultry).
11. Epstein–Barr virus and cytomegalovirus (especially in elderly).
12. Some fungal infections (*Cryptococcus spp.*, histoplasmosis).

13. Parasites (nonfalciparum forms of malaria, toxoplasmosis and trypanosomiasis).

Neoplastic causes of FUO (up to 25 % of all FUO) include:

1. Lymphoma (especially Hodgkin, may be non-Hodgkin — the most commonly reported causes of fever in elderly patients; Pel-Ebstein fever is typical — 1 week patient may be afebrile and the following week may bring hectic fevers, in some cases high and similar to fever in sepsis);

2. Leukemia (older patients in the aleukemic or preleukemic phase of their disease may have little or no evidence of leukemia on peripheral smear);

3. Hypernephroma (according to last data this solid tumor isn't so frequent cause of FUO as previously suppose);

4. Primary hepatocellular carcinoma (but tumors that metastasize to liver rarely cause fever);

5. Atrial myxoma (this is a rare disorder that is associated with fever and can mimic infective endocarditis; small pieces of the atrial tumor can break off and embolize to the periphery, causing small infarcts similar to those observed in infective endocarditis).

Autoimmune diseases as a causes of FUO (up to 10–20 % of all FUO) include:

1. Systemic lupus erythematosus (was a frequent cause in early series of FUO cases but now antinuclear and anti-DNA markers readily identify SLE).

2. Adult-onset Still's disease (one of the most frequent autoimmune cause of FUO in younger patients; key clinical features include an evanescent macular rash, arthralgias and a sore throat and high fevers; high peripheral white blood cells, markedly elevated serum ferritin and severe elevated erythrocyte sedimentation rate are typical; a diagnosis by exclusion).

3. Hypersensitivity angiitis.

4. Polymyalgia rheumatica, combined with temporal arteritis (very common cause of FUO in elderly patients; in case of polymyalgia rheumatica proximal muscle weakness and high erythrocyte sedimentation rate are typical; often in such patients also temporal arteritis concomitantly presents with temporal headaches and visual complaints).

5. Polyarteritis nodosa.

6. Mixed connective tissue disease.

7. Subacute thyroiditis (should be considered if the thyroid is tender and serum antithyroid antibodies are elevated).

8. Kikuchi's disease (self-limiting autoimmune disorder occurs in young Asian females and is associated with generalized lymphadenopathy and prolonged fever; diagnosis is made by lymph node biopsy).

Miscellaneous causes of FUO (up to 10 % of all FUO) include:

1. Drug fever (the most common miscellaneous cause of FUO; most often quinidine sulfate, procaine amide, sulfonamides and penicillins).

2. Factitious fever (must always be considered in female patients with a medical background; often these patients inject themselves with stool or saliva, causing polymicrobial bacteremia and fever).

3. Familial Mediterranean fever (a genetic disorder associated with recurrent serositis primarily of the abdominal cavity, rare with pleuritis and pericarditis).

4. Pulmonary emboli (must be excluded in all patients with risk for thrombophlebitis who present with FUO; small recurrent pulmonary emboli may not result in respiratory complaints and may simply present as fever).

Up to 10 % of patients with FUO had no explanation for their condition. In many of these cases fever spontaneously resolved over 3 to 6 months without harmful consequences.

Approach to diagnosis of FUO.

History of FUO. History play a critical role in narrowing the differential diagnosis and in deciding on the most appropriate diagnostic tests. A review of all symptoms associated with the illness needs to be periodically updated. Symptoms often are transient and are recalled by the patient only after repeated questioning. History of tuberculosis, family history (to exclude genetic disorders), animal exposure, home environment, occupational and travel exposure and list of all medications, including over-the-counter and natural organic remedies, must be included.

Physical examination of FUO. Careful repeat physical examination is frequently helpful. Particular attention should be paid to the skin examination (embolic or vasculitic lesions or evidence of physical manipulation), the nail beds (small splinter-shaped infarcts), the joint motion and the presence of effusions, the eyes (conjunctival petechiae, conjunctivitis, punctate corneal lesions, uveitis, optic nerve changes and retinal or choroidal abnormalities). Thorough palpation all lymph nodes needs to be repeatedly performed, documenting the consistency, size and tenderness. Cardiac examination should be repeated daily, listening for cardiac murmurs and pericardial rubs. The abdomen also should be palpated daily to detect new masses, areas of localized tenderness and hepato- or splenomegaly.

Basic diagnostic tests. All patients with FUO should receive a series of basic diagnostic tests including complete blood count with differential; HIV antibody and antigen test; liver function test, LDH, CPK; antinuclear antibodies and rheumatoid factor; C-reactive protein or erythrocyte sedimentation rate; urinalysis and urine culture; 3 sets of blood cultures; serum protein electrophoresis; tuberculin skin test of interferon γ release assay; chest and abdominal CT scan.

The subsequent diagnostic approach is based on patients history, physical examination and preliminary laboratory tests and may include different microbiological methods, invasive diagnostic procedures and high-yield imaging

studies. An iterative approach to testing is the most effective course of action. Clinicians need to focus on diagnostic tests that are likely to have a high yield. They must review each new potential diagnostic clue and assess its significance in relationship to the patient's other positive findings.

Treatment of FUO. Once true fever has been documented, antipyretics can be administered in most cases of FUO to relieve some of the patient's symptoms while the diagnostic workup is pursued. To avoid repeated shifting of the thermal set point and recurrent shivering and chills antipyretics (paracetamol, ibuprofen, etc.) must be administered at the proper time intervals to maintain therapeutic levels. Antibiotics are contraindicated until a specific diagnosis is made. Use of an empiric antibiotic trial often delays diagnosis and is rarely curative. Corticosteroids may be used empirically only when an autoimmune disorder appears to be the most likely explanation for FUO and when infection causes of FUO has been excluded because they can markedly exacerbate bacterial, mycobacterial, fungal or parasitic infections.

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HEALTHCARE-ASSOCIATED INFECTIONS

Health care–associated infections (HAI) are those that are not present or incubating at the time when patients enter a clinic or hospital. In general, they become manifest ≥ 48 h after initial patient care. They also include infections present at hospital admission or within 48 hours of admission in patients that fulfilled any of the following criteria: received intravenous therapy at home, wound care or specialized nursing care in the previous 30 days; attended a hospital or hemodialysis clinic or received intravenous chemotherapy in the previous 30 days; were hospitalized in an acute care hospital for ≥ 2 days in the previous 90 days, resided in a nursing home or long-term care facility. Occupational infections among healthcare staff are also classified as HAI. Hospital-acquired infections are caused by viral, bacterial, and fungal pathogens; the most common types are bloodstream infection (BSI), pneumonia (e. g., ventilator-associated pneumonia [VAP]), urinary tract infection (UTI), and surgical site infection (SSI).

Although comprehensive data on infection rates after clinic visits are lacking, it is known that 5–10 % of patients admitted to acute care hospitals in the developed countries will acquire a nosocomial infection.

Infectious agents causing healthcare-associated infections may come from endogenous or exogenous sources. Endogenous sources include body sites normally inhabited by microorganisms. Examples include the nasopharynx, GI, or genitourinary tracts. Exogenous sources include those that are not part of the patient. Examples include visitors, medical personnel, equipment and the healthcare environment.

Risk factors for nosocomial infections include:

– extremes of age;
– chronic disease (including diabetes, renal failure, and malignancy);
– immunodeficiency;
– malnutrition;
– medications (e. g., recent antibiotics, proton pump inhibitors, and sedatives);
– colonization with pathogenic strains of flora;
– breakdown of mucosal/cutaneous barriers, including trauma and battle wounds;
– anesthesia.

The leading causes of nosocomial bloodstream infections, in order from most common to least common, are coagulase-negative staphylococci, *Staphylococcus aureus*, enterococci, and *Candida* species.

Early-onset nosocomial pneumonia, which manifests within the first 4 days of hospitalization, is most often caused by community-acquired pathogens, such as *Streptococcus pneumoniae* and *Haemophilus* species. Late-onset pneumonias most commonly are due to *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Enterobacter* species, *Klebsiella pneumoniae*, and *S. aureus*.

The most common pathogens in UTIs are *Escherichia coli*, nosocomial gram-negative bacilli, enterococci, and *Candida*. Almost all nosocomial UTIs are associated with preceding instrumentation or indwelling bladder catheters. UTIs generally are caused by pathogens that spread up the periurethral space from the patient's perineum or gastrointestinal tract or via intraluminal contamination of urinary catheters. Pathogens come occasionally from inadequately disinfected urologic equipment and rarely from contaminated supplies.

The most common pathogens in postoperative wound infections are *S. aureus*, coagulase-negative staphylococci, and enteric and anaerobic bacteria. In rapidly progressing postoperative infections, which manifest within 24–48 h of a surgical procedure, the level of suspicion regarding group A streptococcal or clostridial infection should be high.

Rotavirus is the most common cause of acute gastroenteritis in hospitalized children, with greatest susceptibility in children younger than 3 years. Aside from having nonbloody diarrhea, patients may present with fever, vomiting, and abdominal cramps. Other viruses that can cause hospital-associated gastroenteritis

include norovirus and adenoviruses. Gastroenteritis due to adenovirus can be especially debilitating in immunocompromised patients.

Clostridium difficile is the most important bacterial cause of healthcare-associated gastroenteritis. Associated clinical conditions include asymptomatic carriage, diarrhea, and pseudomembranous colitis. Diagnosis is suspected in a patient with diarrhea and recent history of antibiotic use (especially cephalosporins and clindamycin).

Diagnostic and treatment approaches. In addition to the presence of systemic signs and symptoms of infection (e. g., fever, tachycardia, tachypnea, skin rash, general malaise), the localization of healthcare-associated infections may be suggested by various instrumental procedures. If healthcare-associated infection is suspected, culture should be taken and then antibiotic therapy administered based on supposed pathogens depending on disease localization (see scheme below). Indwelling catheters should be removed if possible, to avoid persistence and recurrence of infection. Antibiotics with coverage against all possible gram-positive and gram-negative organisms should be empirically started and then tailored after obtaining culture results according to clinical response and susceptibility pattern of isolated organisms.

Laboratory investigations should be guided by the results of a detailed physical examination and review of systems. Caution should be taken when interpreting laboratory results because not all bacterial or fungal growth on a culture are pathogenic. Growth on cultures may reflect simple microbial colonization. Consider the following:

– clinical presentation of the patient;

– reason for obtaining the test;

– the process by which the specimen was obtained (e. g., a urine culture obtained through a newly placed Foley catheter is less likely to be contaminated by microbial colonization);

– the presence of other supporting evidence of infection (e. g., the significance of bacterial growth on tracheal aspirate culture is strengthened by the presence of radiographic changes and clinical signs compatible with pneumonia).

Antifungal therapy (e. g., fluconazole, caspofungin, voriconazole, amphotericin B) and antiviral therapy (eg, ganciclovir, acyclovir) can be added to empiric antimicrobial coverage, if disseminated fungal or viral infections are suspected.

Prevention. Prevention efforts should address both patient-specific and facility-related risk factors: 1) appropriate hand hygiene; 2) antibiotic stewardship; 3) infection control; 4) hospital-based surveillance programs; 5) employee education on HAIs; 6) minimization of invasive procedures; 7) isolation of known pathogen carriers.

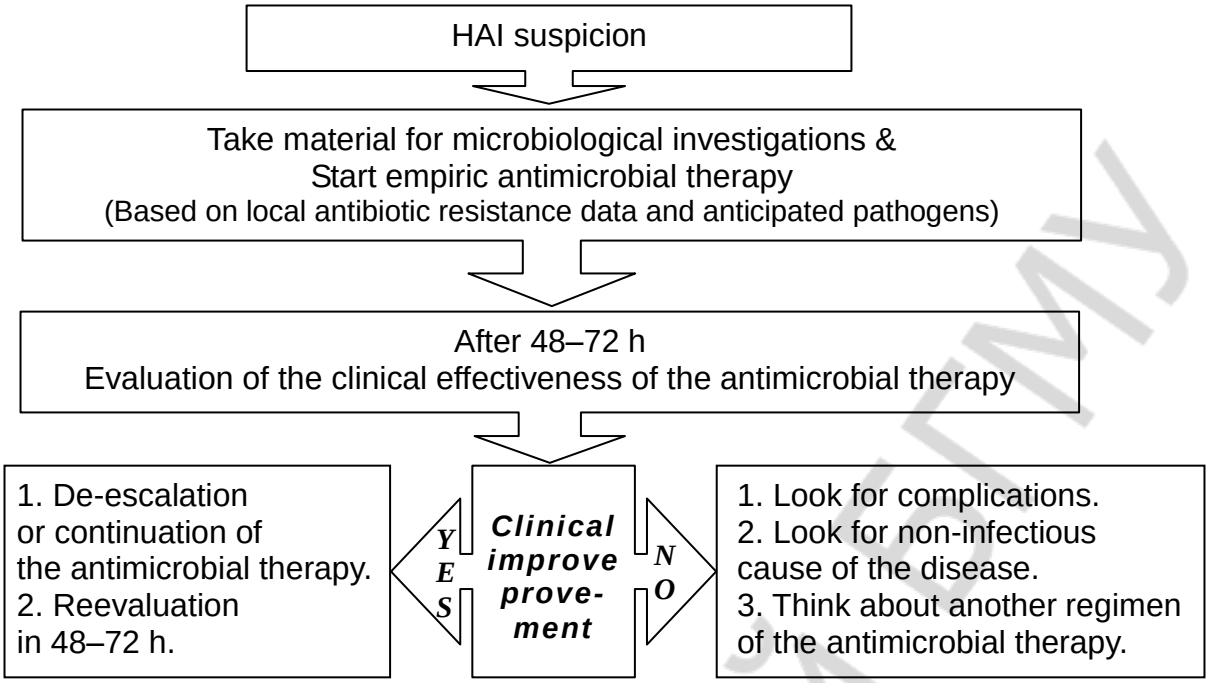

Figure 2. Basic scheme of diagnostic and treatment approaches in health care-associated infections

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