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Travel-Related Infectious Diseases

Whether you are cruising in the Caribbean, volunteering in the Third World, or seeing travelers at home in your emergency department, travel-related infectious diseases, such as malaria, cysticercosis, typhoid fever, Dengue fever, and amebiasis, may need to be in the differential diagnosis. This lecture will serve as an introduction to tropical emergency medicine.

- List the most common causes of travel-related infectious diseases.
- Discuss the recognition and treatment of malaria, cysticercosis, typhoid fever, diarrhea, amebiasis, and Dengue fever.

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FACULTY

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INTRODUCTION

Developing countries have a drastically different burden of illness than the rest of the world. The major health problems of these regions are related to poverty, malnutrition, lack of hygiene, overpopulation, and warm climates. Although many tropical diseases have been eliminated from temperate regions, international travel and migration will result in increasing imported tropical diseases in the United States. In addition, many tropical diseases are common wherever standards of personal and environmental hygiene are low. Only to this extent are many of these diseases considered "tropical." Each year, 8 million Americans travel to developing countries. These travelers often return with malaria, typhoid, cholera, and other exotic diseases. For example, over one thousand cases of falciparum malaria are reported to the CDC annually, along with thousands of cases of other imported tropical diseases. The objectives of this lecture are to review the general approach to patients with infectious tropical diseases and to discuss specific diseases that are commonly seen in travelers returning from developing countries and could result in significant morbidity and mortality if not rapidly diagnosed and treated in the emergency department.

GENERAL APPROACH

The vast majority of imported diseases are infectious in origin and the most common presenting symptoms are fever, gastrointestinal, respiratory, and/or central nervous system complaints. Other common features of tropical disease are rash, adenopathy, hepatosplenomegaly, anemia, and eosinophilia. For any of these clinical features, it is important to obtain a complete travel or migration history, with information concerning destination of travel, duration of stay, stopovers, activities, diet, immunizations prior to travel, chemoprophylaxis, compliance with chemoprophylaxis, and similar illness in travel party. The key is to assess the patient's exposure and risk to potential travel-related diseases.

Diseases that should be seriously considered will depend primarily on the place and time of travel. Knowledge of the geographic distribution and incubation periods of certain tropical infectious diseases is helpful in establishing differential diagnoses. Unfortunately, many infectious diseases have variable incubation periods depending on the patient's immune status and potential partial suppression from chemoprophylaxis. There are, however, certain life-threatening illnesses that are widespread in tropical regions and must be considered in any traveler or immigrant from these areas. **The most important is malaria**, but others include hepatitis, typhoid, typhus, dengue, and meningococcal meningitis.

Physical examination must be comprehensive with particular attention directed at the abdomen, liver, spleen, lymph nodes, skin, and the CNS. High fever, shock, hemorrhagic manifestations, severe diarrhea, dyspnea, CNS disturbances, indicate the patient may have acquired the disease outside the U. S.

Laboratory examinations of value when evaluating tropical diseases include complete blood counts, differentials, absolute eosinophil counts, thick and thin blood smears for malaria, microscopic examinations of stool for ova and parasites, stool cultures, ESRs, specific serological examinations, PPD, VDRL, HIV and chest radiographs. The most essential laboratory test for the evaluation of the overseas traveler or immigrant is the microscopic examination of a blood smear for the

presence of malaria parasites.

Anemia and eosinophilia are common hematological findings of parasitic diseases. Although elevated eosinophil counts are found with allergies, malignancies, and connective tissue disorders, in the tropics, eosinophilia is specifically associated with helminthic infections. Eosiniphilia is defined as an absolute count of greater than 500/mm^3, and is calculated by multiplying the percentage of eosinophils in the differential count by the total granulocyte count.

Case Number 1:

27-year old Nigerian male student, returning to the U.S. visiting Nigeria for one month. Complaints included intermittent fever with chills, abdominal pain, vomiting, headache, and generalized malaise for five days. Physical examination revealed tachycardia, with a pulse of 110 per minute, and a temperature of 103.5^oF. The abdomen was soft and without tenderness, but the spleen was palpable 1.5 cm below the left costal margin.

Diagnosis - MALARIA

Malaria is the one of the most common infectious diseases in the world, and is prevalent throughout the tropics and present in some subtropical areas. Malaria causes 270 million new cases and nearly two million deaths per year, with most of these deaths occurring in children. Malaria is caused by four species of the protozoan plasmodium parasite: *Plasmodium falciparum, P. vivax, P. ovale,* and *P. malariae*. Worldwide, *P. vivax* is most prevalent, but *P. falciparum* (also known as malignant or pernicious malaria) predominates in sub-Saharan Africa.

Malaria is usually transmitted through the bite of the female anopheline mosquito. Transmission can also occur through transfusion, transplantation, intravenous drug use, and congenitally through the placenta of gravid women to the fetus. The female anopheline mosquito directly injects sporozoites from her salivary glands during a blood meal. Sporozoites enter liver cells and divide by asexual fission (schizogony) to form merozoites. The liver cell then ruptures releasing thousands of merozoites that invade RBCs and repeat the asexual reproductive cycle. Ruptured RBCs release merozoites to continue the cycle. After several cycles, some RBC parasites differentiate into gametocytes that are ingested by the mosquito and undergo sexual reproduction in the abdomen of the mosquito to form sporozoites. These migrate to the salivary glands to await inoculation into another human at the next blood meal. Sporozoites from *P. vivax* and *P. ovale* can remain dormant in hepatocytes (called hynozoites) causing relapses months to years after the original mosquito bite. Typically, the incubation period is from 8 to 30 days.

Infections with all four species have many clinical features in common. Fever is the most common symptom and is usually irregular until the illness has continued for a week or more. Regular periodic fever depends on synchronized schizogony (probably related to immune response of the host). Anemia, splenomegaly, headache, arthralgias, diarrhea, and jaundice are also common. The patient may be hypotensive. Typically, there is no rash or lymphadenopathy.

P. falciparum is the most severe form and is responsible for almost all of the complications and deaths related to malaria. These complications include: cerebral malaria, hypoglycemia, pulmonary edema, hemolytic anemia, renal failure, and septicemia. The exceptions are splenic rupture and severe anemia that are associated with *P. vivax*, and nephrosis that can follow *P. malariae* infections. The increased morbidity and mortality of P. falciparum malaria is related the ability of this species to invade, utilize, and destroy erythrocytes of all ages (although immature forms are preferred), causing a high degree of parasitemia and hemolysis. *P. vivax*

and *P. ovale* merozoites attack only reticulocytes and very young erythrocytes; while *P. malariae* is limited to only mature erythrocytes. Moreover, erythrocytes containing *P. falciparum* parasites develop membrane changes that result in adherence to the capillary endothelium of the affected end organ producing local tissue damage.

Cerebral malaria is the most important and lethal complication of *P. falciparum*. It usually occurs in children and non-immunes, and results in a diffuse disturbance of consciousness, seizures, or focal neurological signs. If untreated, cerebral malaria usually progresses to coma and death. This is caused by localized disturbances of intracerebral circulation from microcirculatory obstruction in the capillaries. Hypoglycemia may mimic cerebral malaria.

The diagnosis of malaria is made on clinical suspicion and confirmed by identification of malaria parasites on thick and thin blood films. The thick film is much more sensitive because RBCs are piled upon each other 10 to 20 deep and lysed, allowing far more cells to be examined at a time. The thin film is utilized to identify the species. Once malaria is identified in the blood film, the most important distinction is between *P. falciparum* and other species since this will greatly influence treatment. A negative film does not exclude malaria. Blood examination should be repeated every 12 hours since parasitemia may fluctuate. A positive film does not prove the patient is suffering from malaria. Parasitemia may be a completely incidental finding in the indigenous population of endemic areas. If malaria is suspected, treatment should not be delayed while awaiting the blood films. Because of the sequestration of malaria schizont, the degree of parasitemia may not accurately reflect the percentage of RBCs infected.

Supportive treatment includes reducing the temperature, rehydration, treatment of seizures, and monitoring hemoglobin levels. Specific treatment is directed at terminating the parasitemia as rapidly as possible. Chloroquine is used in non-falciparum malaria, followed by primaquine to clear the hypnozoites in *P. vivax* and *P. ovale*. Intravenous quinine or quinidine is used for P. falciparum (cardiac dysrhythmia and hypoglycemia are the major side effects). Exchange transfusion is used in extremely severe P. falciparum infections with high parasitemia levels. Steroids are contraindicated. The patient should be adequately hydrated, but overhydration should be avoided to prevent pulmonary edema. Blood glucose levels should be monitored. Improvement is monitored with repeated blood films.

Case Number 2:

22 year-old American male recently returned from six months of missionary work in Kenya. He complained of frontal headache, fever, anorexia, abdominal discomfort, and constipation for 10 days. He also noted a dry cough and muscular aches and pains. His temperature was 102.4^{o}F and pulse was 72/min. Scattered rhonchi were noted throughout both lung fields, the abdomen was soft and diffusely tender with positive bowel sounds but no guarding or rigidity. The spleen was palpable 2 cm below the costal margin.

Diagnosis - TYPHOID (ENTERIC FEVER)

Typhoid and enteric fever are caused by *Salmonella typhi*, a Gram-negative flagellated bacillus. This organism is found throughout the world where personal hygiene and community sanitation is poor. Infection is transmitted by ingestion of contaminated water or food and is largely dose related. Infection rates and incubation periods are dose related. For example, 10^5 organisms may cause a relatively low attack rate with a fairly long incubation period, but an infecting dose of 10^6 organisms increases the attack rate to 95% and greatly shortens the incubation period. High gastric acidity opposes infection. *S. typhi* can multiply in suitable foods

maintained at a favorable temperature, greatly enhancing the risk of spread from infected food handlers. The most important reservoirs are asymptomatic human carriers.

After ingestion, the organisms attach to the small intestine, penetrate, multiply, and are transported by the lymphatics to lymph glands where they enter the bloodstream. Organisms then spread to the bone marrow, spleen, liver, and ball bladder. *S. typhi* organisms multiply in macrophages. Although diffuse multi-organ involvement can occur, pathological changes are greatest in the intestinal lymph follicles, the largest of which are the Peyer's patches. These follicles become hyperplastic, and if inflammation does not resolve, necrosis occurs and the patches ulcerate within 7-10 days. The incubation period is about two weeks, but can vary from less than a week to more than three weeks.

Fever and headache are the common early symptoms and progress during the first week resulting in prostration. This is followed by abdominal pain, constipation, diarrhea, malaise, anorexia, and generalized aches and pains. Constipation is more common than diarrhea. Hepatomegaly, splenomegaly, meningismus, confusion, delirium, and deafness are all common signs of typhoid, but depend on the severity of the illness. The pulse is disproportionately slow compared to the fever and may not reach 100 beats/min even when the temperature is 40^{o}C. Rose spots can only be seen on fair-skinned patients and are found after one week. They take the form of scanty pink macules found mainly on the trunk.

Complications may develop as the illness progresses, and may follow a clinical mild attack. Patients with typhoid complications are often difficult diagnostic problems because they may present with the complication rather than the symptoms of typhoid fever. Intestinal bleeding and perforation are the most common complications, occurring in about 5% of patients, and result from necrosis and ulceration of the small bowel. Hemorrhage, hemolytic anemia, DIC, pneumonia, meningitis, myocarditis, acute cholecystitis, renal failure and skeletal complications are also found with typhoid fever. Radiographs should be obtained to rule out free intraperitoneal air.

Blood, stool, and urine cultures can be used to isolate S. typhi, but frequently have a low yield. Bone marrow culture is the most sensitive test, positive in 90 to 95% of cases, and can be used in patients who have been pretreated with antibiotics. Serodiagnosis is less reliable than culture. The white blood cell count is normal or decreased with increased percentage of band forms. Aminotransferases and bilirubin concentrations are frequently elevated.

Effective drugs include chloramphenicol, amoxicillin, trimethoprim-sulfamethoxazole, ceftriaxone, and ciporfloxacin. Patients with severe typhoid, (with delirium, coma, shock, or DIC) should be given intravenous glucocorticoids such as dexamethasone, 3 mg/kg as a loading dose over 30 minutes followed by 1 mg/kg every 6 hours for 48 hours. Patients who are dehydrated will require intravenous saline. Significant intestinal bleeding requires transfusion.

In the past, parenteral typhoid vaccine prepared from killed bacteria was recommended for travel to tropical countries. A live oral vaccine is now available and reported to be as effective as the parenteral vaccine.

Case Number 3:

24 year-old American student returned to the United States after a two month vacation in Thailand. The day after his return he developed a fever with severe headache, myalgias, and sore eyes. On the fourth day the fever resolved, however, two days later the fever recurred and he noticed a rash on his body. Examination revealed a diffuse macular rash on the chest and abdomen. Small axillary lymph nodes were palpable. The temperature was 100.5^{o}F.

Diagnosis - DENGUE

Urban dengue occurs in nearly all tropical countries and is transmitted to humans by *Aedes aegypti* mosquitoes. A form of sylvanic dengue exists but this is mostly confined to forest primates. Urban dengue transmission in the American, African, and Indian tropical regions is mainly associated with classical dengue fever. In Southeast Asia, dengue infection can manifest as a hemorrhagic fever and shock syndrome.

The incubation period is 5 to 8 days. The initial fever begins abruptly and lasts 4 to 5 days. It is associated with severe musculoskeletal pains, fever, retro-orbital headache, nausea, vomiting, diarrhea, anorexia, and malaise. There can also be flushing of the face, puffiness of the eyelids, and conjunctivitis, often referred to as dengue facies. The patient often complains of pain on the movement of the eyes. The fever then recurs and is classically associated with maculopapular rash that begins on the trunk and spreads to the limbs and face. After the rash appears, the temperature begins to fall and recovery begins. Pronounced bradycardia, often lasting for weeks, is common. Epistaxis, petechiae, and purpuric lesions, although uncommon, may occur at any stage of the disease. Treatment is supportive, aspirin should be avoided.

Dengue hemorrhagic fever-dengue shock syndrome has most often been observed in children. DHF-DSS is similar to dengue but with significantly more severe symptoms. In addition, ecchymosis, epistaxis, hematemesis, melena, and hematuria are often seen. The major causes of bleeding are DIC and capillary damage. Shock is a bad prognostic sign and requires intravenous fluid resuscitation. Initial therapy should consist of lactated Ringer's or isotonic saline.

Case Number 4:

36 year-old Hispanic female, recently immigrated from Mexico, presented with complaints of fever, slight cough, chills, mild RUQ pain, and myalgias for 18 days. The patient was treated at a local clinic with cephalexin for one week without resolution of the symptoms. On examination the vital signs were normal. There was slight tenderness on palpation over the RUQ, but no palpable liver margin. The leukocyte count was 12.4 with 70% segs and the ESR was 110 mm.

Diagnosis - AMEBIASIS

Amebiasis is an infection caused by *Entamoeba histolytica*. It is found in all parts of the world where sanitation is poor, particularly in Asia, Africa, and Latin America. There have been estimates that as much as 10 percent of the world's population harbors *E.histolytica*. The organism may behave as a parasite (by harming the host) or as a commensal (when it does no harm to the host). *E. histolytica* is spread via fecal-oral transmission. Man is the only reservoir and source of infection. Man swallows the cyst in contaminated food or water and several small amebae are released into the gut.

E.histolytica usually causes no harm, feeding on bacteria and other food residues and multiplying by binary fission. Not all strains are capable of tissue invasion, so finding amebae in the stools of a patient with diarrhea does not prove the diarrhea was caused by the amebae. Most of the asymptomatic infections are due to non-pathogenic strains. Pathogenic trophozoites show greater motility and increased RBC phagocytic capacity. These strains can invade the intestinal mucosa causing ulcerations in the bowel wall and give rise to the various clinical manifestations of invasive amebiasis. Through blood-borne spreading, they may produce extraintestinal lesions such as amebic liver abscess, amebic brain abscess,

and amebic skin ulcerations.

Acute rectocolitis (amebic dysentery) is characterized by intense abdominal pain, tenesmus, loose watery blood-stained stools, and mild fever. Children are more likely to have high fever, anorexia, irritability, and vomiting resulting in severe dehydration.

Necrotizing colitis is the severe form of intestinal amebiasis that progresses rapidly from a non-specific gastroenteritis to a fulminant stage. It is more common in the elderly, malnourished, and immune compromised patients, and often seen after a mild case of amebiasis is inappropriately treated with corticosteroids. Necrotizing colitis is characterized by rectal bleeding and abdominal pain. Fever may be high, and nausea and vomiting may be present. Colonic perforation, peritonitis, and septicemia are common at the end stage.

Postdysenteric colitis is seen in a small percent of patients with acute rectocolitis after the dysenteric symptoms have resolved. The patient may continue to have intermittent watery diarrhea that gradually subsides without treatment after several months or years.

Amebomas are protrusions into the colonic lumen characterized by thickening of the intestinal wall accompanied by a thin and ulcerated mucosa. They are most often found in the cecum and ascending colon, and are often misdiagnosed as carcinomas, colonic TB, or Crohn's disease.

Amebic skin ulcerations may develop when the skin is in prolonged contact with amebae from any source. They are particularly common when an ALA drains through the skin or when the perineum is chronically exposed following amebic dysentery.

Amebic liver abscesses (ALA) are the most common extraintestinal form of invasive amebiasis. They are found in all age groups, but are more common between 20 and 60 years of age. There is about 5 to 1 higher frequency in males to females. Often, there is no previous history of colitis, dysentery, or even diarrhea. In countries in which amebiasis is prevalent, ALA is a frequent and severe complication. For example, it has been estimated that 1 to 2 percent of all patients admitted to general hospitals in Mexico have ALA. In addition, ALA has been found in 5.8 percent of 3000 autopsies in a large hospital in Mexico City. ALA is caused by amebae entering the liver via the portal vein, developing through the coalescence of several small abscesses. Most abscesses (83%) develop in the right lobe, and although there may be more than one abscess, most cases of ALA have only one lesion (80%). Surrounding the pus is an area of compressed but otherwise normal liver tissue in which the trophozoites are feeding on the liver cells and actively dividing. If not treated, the abscess will grow until it reaches a surface through which it can discharge, such as the skin, the peritoneum, the pleural cavity, or the pericardium. Rupture can lead to formation of a cutaneous sinus, amebic empyema, amebic peritonitis, or amebic pericarditis. The common symptoms include severe RUQ pain (sometimes referred to the right shoulder), spiking fever, cough, anorexia, weight loss, and breathlessness. Physical examination reveals a tender enlarged liver and tenderness over the right lower intercostal spaces with dullness to percussion and decreased breath sounds in this area. Localized edema or tenseness of the skin may be seen when the abscess approaches the surface. Pallor and mild jaundice may also be found.

The cornerstone in the diagnosis of invasive amebiasis is the microscopic observation of cysts and trophozoites of *E. histolytica* in stools or from scrappings of the colonic mucosa taken by rectosigmoidoscopy. Trophozoites containing RBCs are the best evidence of the invasive and pathogenic nature of that particular strain. Serological testing is also useful since antibodies are found in most cases of invasive amebiasis. With ALA, anemia and a leukocytosis of >15,000 cells per cubic mm is often found. The ESR is usually above 50 mm/hr. Liver function tests seldom show

consistent or significant changes, however, about 10% of patients have an elevated conjugated bilirubin. A raised right hemidiaphragm with a pleural effusion on chest X-ray is also a frequent finding. Ultrasonography and computed tomography are indicated for confirmation of ALA and to rule out other hepatic lesions.

The aim of drug treatment in all forms of invasive amebiasis is to kill all amebae from the bowel lumen. Metronidazole (Flagyl) is the most effective drug in the tissues, but is less effective in the lumen of the colon. Diloxanide furoate (Furamide) is the most effective luminal amebicide and is given in conjunction with metronidazole in cases of invasive amebiasis and ALA, and alone for the treatment of asymptomatic carriers. Aspiration of the ALA is indicated when there is localized swelling or bulging of the rib cage or abdominal wall, when there is marked local tenderness, or when there is a failure to respond to conservative treatment.

Case Number 5:

20 year-old Hispanic male presented with new onset grand mal seizure. Patient immigrated from El Salvador two years ago and has been intermittently employed as a construction worker. No history of recent head trauma or chemical exposure. Vital signs and physical examination were normal.

Diagnosis - CYSTICERCOSIS

Man is the definitive host of the *Taenia solium* tapeworm. Since pig is the normal intermediate host, *Taenia solium* is found all over the world where people eat raw or undercooked pork. The tapeworm is obtained by ingesting contaminated pork. Cysticercosis is acquired by ingesting *T. solium* eggs from fecally contaminated food. Fecal contamination of hands may cause autoinfection. There are commonly no symptoms at all in light infections. The worms usually encyst in muscle and subcutaneous tissue with minimal inflammatory response. The first indication of infection is often the finding of small (0.5-1.0 cm) swellings beneath the skin or on X-ray when they have calcified in skeletal muscle. Cerebral cysticercosis usually presents as epilepsy three or more years after initial infection. The human brain may be invaded by one or several cysticersi. In the majority of cases less than 10 cysticersi are present. The symptomatology of cerebral cysticercosis is characterized by three basic syndromes: seizures, intracranial hypertension, and psychiatric disorders. Focal neurological symptoms may also develop.

Diagnosis of tapeworm is made by finding *Taenia* eggs in the stool. Identifying the proglottid differentiates pork from beef tapeworm. Diagnosis of cysticercosis is made by identification of calcified cysts by CT or X-ray. Calcification in muscles usually appears 3-5 years after initial infection. Calcification of cysticerci in the brain occurs 10 or more years after infection. Various immunodiagnostic tests are available.

Treatment of the tapeworm is with niclosamide, which kills the worm and allows it to be expelled intact. Treatment of neurocysticercosis is with praziquantel or albendazole. This will lead to remission of symptoms and regression of the cysts. During and shortly after treatment, there may be severe headaches and aggravation of symptoms. The reaction around the dying cysts could lead to dramatic complications such as acute obstructive hydrocephalus. For this reason, praziquantel must only be given under careful supervision. Steroids are frequently added in order to prevent serious complications due to cerebral edema which may develop as a reaction to damaged cysticerci.

Case Number 6:

31 year-old Ghanaian boy presented with a two-day history of fever and headache. The day of presentation, the father noticed a sudden change in his mood, with irritability and extreme agitation.

Diagnosis - RABIES

With the exception of a few isolated geographical regions, rabies is distributed throughout the world as a zoonosis. Transmission typically occurs through the penetration of broken skin or intact mucosa by the rabies virus after contact with saliva from an infected animal. Most human rabies is transmitted by the domestic dog; however, in Central and South America the main transmitter is the vampire bat.

The virus multiplies at the site of inoculation and is transmitted to the CNS via the nerve trunks. In the CNS, the virus proliferates in the nerve cells of the brain and peripheral ganglia causing a fatal meningoencephalitis. The virus also spreads to the salivary glands completing the transmission cycle. The incubation period can vary from two weeks to over two years, but the majority of cases are between 20 and 90 days. Severe and proximal bites will have shorter incubation periods. Symptoms usually begin with fever, headache, anxiety, and insomnia. Frequently, the patient will have pain or paresthesia at the site of the inoculating bite. Rabies in man has two clinical presentations, *furious* and *paralytic*. Furious rabies is the most common and is seen in 80 percent of the cases. This form presents with painful spasms of the throat muscles that are precipitated by attempts to swallow. The spasms spread to involve the respiratory, neck, and back muscles. During the attacks, the patient is extremely irritable and appears to be in severe pain and is markedly terrified. Between attacks, the patient appears normal. Death is inevitable once the first symptoms appear and usually occurs 5 to 10 days later. In paralytic (also known as *dumb*) rabies, the patient develops an acute progressive ascending myelitis with flaccid paralysis. Death is the result of paralysis of the respiratory muscles and may be delayed up to 4 weeks.

Diagnosis is made post-mortem and is accomplished through examination of fixed brain tissue for the characteristic Negri inclusion bodies. Microscopic fluorescent antibody examination of the brain is both quicker and more sensitive, but requires fresh, unfixed tissue.

Death is inevitable once symptoms appear. No case of person-to-person transmission to a health care worker has ben documented. However, the patient's saliva, urine, and respiratory secretion are potentially infective. It is therefore prudent to use barrier precautions during the care of patients with rabies, including goggles. Post-exposure treatment should be given as soon as possible after the exposure. The objectives are to inactivate the virus at the inoculation site by proper wound care, and to produce effective antirabies antibody levels as quickly as possible. The wound should be cleansed thoroughly with soap and water as soon as possible, followed by irrigation with 70% alcohol or 1% quaternary ammonium compound to reduce the viral inoculum size. Active immunity is induced by human diploid cell vaccine (HDCV) and rabies immune globulin (RIG) is used to provide immediate passive immunity. Both should be given in combination on days 0, 3, 7, 14, and 28. Postexposure prophylaxis is most likely to be effective if it can be started within the first 24 hours.

Case Number 7:

31 year-old Peruvian female with severe diarrhea and vomiting beginning two days ago during a flight returning to the United States from Peru. The diarrhea was profuse, watery, and without mucus or blood. The patient also complained of

cramping abdominal pain, weakness, muscle aches, and mild fever.

Diagnosis - CHOLERA

Until recently, epidemic cholera was confined almost entirely to the tropical countries of Africa, Asia, and the Pacific region. South America had been free of epidemic cholera throughout the 20th century. In January 1991, an outbreak of cholera surfaced in Peru and quickly spread to several countries of South and Central America. Through 1993, this epidemic caused more than 950,000 cases of cholera and claimed 8,622 lives. Although the last major epidemic of cholera in the United States was in 1873, a small number of cases of endemic cholera occur periodically along the Gulf Coast. Because of superior sanitation and hygiene, epidemic cholera is not likely to arise in the U.S. again. However, as the most recent cholera epidemic continues to spread throughout South and Central America, sporadic cases, and even small outbreaks, will continue to be seen in North America.

Cholera is an acute bacterial infection of man caused by the gram negative, comma-shaped bacillus *Vibrio cholerae* and is transmitted by the fecal-oral route, usually by the ingestion of water or food contaminated with human feces. Cholera can also be transmitted through the ingestion of raw or uncooked shellfish and other seafood from waters that have been contaminated with human sewage. Although cholera is extremely sensitive to desiccation and able to survive only a few hours on dry surfaces, its viability on various foodstuffs can be up to several days. The incubation period is usually one to five days, but may be as short as a few hours. The infective dose is normally high, but a lower inoculum may be infective if gastric acid secretion is low or neutralized.

There are two biotypes of *V. cholerae*, El Tor and classical. El Tor differs from classical in that the former usually causes less severe symptoms. Both types, however, are capable of endemic and epidemic cholera. The cholera vibrios are characterized by a special 01 antigen and are termed 0 group 1. This group is capable of producing a specific enterotoxin (cholera toxin) that blocks sodium absorption and enhances secretion of chloride by direct stimulation of adenyl cyclase in the epithelial cells. *V. cholerae* multiplies rapidly in the small intestine. Infection results in inflammation, but the mucosal epithelium remains intact. Since no ulceration occurs, it is unusual to find blood or pus in the stool. The excessive secretion of large volumes of protein-free fluid, similar to plasma, except with higher potassium and bicarbonate concentrations, results in dehydration, hypokalemia, hemoconcentration and metabolic acidosis.

Cholera infection varies from asymptomatic carrier to acute onset of diarrhea leading rapidly (within a few hours) to dehydration, circulatory collapse, and death. The majority of infections of *V. cholerae* are mild or asymptomatic. Severe cholera is only seen in a small minority of cases. Typically, there is the sudden onset of profuse, painless, watery diarrhea that is without blood, but is flecked with mucus. This results is the classical "rice water stool." In most cases, vomiting follows shortly after the onset of diarrhea. With severe dehydration (8 to 10%), there is drying of the mucous membranes, poor skin turgor, sunken eyes and cheeks, and decreased urine output. Hypovolemia and shock follow quickly. Muscle cramps of the abdomen and extremities, caused by electrolyte disturbances, may also be seen. Fever is unusual, but is more frequently seen in children. If the patient survives, the rate of purging begins to decline after the first day and usually stops within five days from the onset. Complications of severe cholera are related to circulatory failure and electrolyte imbalance. They include sepsis, shock, anuria, renal failure, acidosis, hypokalemia, cardiac arrhythmias, myocardial infarct, altered consciousness, and cerebrovascular accidents. In children, hypoglycemia may occur during rehydration and can quickly be corrected with the administration of IV glucose. Seizure is a

common manifestation of hypoglycemia in children with severe cholera.

Confirmation of the diagnosis is made by isolation of toxigenic *V. cholerae* serotype 01 from fecal specimen using thiosulfate citrate bile salts sucrose (TCBS) culture medium. Specimens should be collected directly by means of a rectal swab or sterile catheter to avoid contamination.

The main emphasis of treatment is the correction of dehydration, metabolic acidosis, and hypokalemia. In underdeveloped countries, oral rehydration and maintenance therapy is usually sufficient in patients with mild dehydration who are able to drink. Oral rehydration salt (ORS) solutions use combinations of electrolytes and carbohydrates to facilitate the absorption of sodium and water. ORS is available premixed with water or in premeasured packets. If unavailable, home-made ORS solutions can be prepared using 3.5 grams of sodium chloride, 2.5 grams of sodium bicarbonate, 1.5 grams of potassium chloride, and 20 grams of glucose in one liter of water. Forty grams of sucrose (table sugar) may be substituted for 20 grams of glucose if this is not available. With mild to moderate dehydration 50 to 100 ml/kg is recommended during the first four hours for rehydration, followed by maintenance of fluids lost through continued diarrhea. Early feeding should begin as soon as tolerated to avoid complications of poor nutrition. Oral rehydration is not recommended for patients with intractable vomiting, high stool output, bloody diarrhea, severe diarrhea or its complications.

In moderate to severe cases of cholera, especially those complicated by vomiting, aggressive intravenous fluid therapy is required for rehydration. In addition, maintenance fluids should be added to match fluid losses from continued purging and vomiting. Because of its similarity to the composition of the diarrhea and its rapid availability, Ringer's lactate is the solution of choice. However, if acidosis or hypokalemia is severe or persistent, supplemental bicarbonate or potassium should be required. When vomiting ceases and the patient is hemodynamically stable, fluids may be continued by mouth. Since circulatory collapse and death can occur within a few hours, patients who have severe diarrhea and/or are unable to tolerate large amounts of oral fluids should be admitted for intravenous rehydration. Because of potentially severe complications and their inability to maintain strict hygiene, all children with cholera should be admitted to a hospital. Adequate rehydration therapy can reduce the death rate of severe cholera to less than 1%. Antidiarrheal and antisecretory agents are potentially harmful and are not recommended.

Antibiotics are effective and are used to shorten the course of symptoms, decrease purging volume, lessen rehydration requirements, and eliminate vibrios from the stool. Tetracycline is the drug of choice, and is effective in reducing the duration and volume of diarrhea. Norfloxacin has been found to be highly effective against multiple strains of pathogenic vibrio species in vitro, and clinically effective for *V. cholerae* in vivo.

Although there have been no reported cases of secondary transmission of cholera in the United States, potential contacts should be advised concerning proper hygiene, and should seek immediate medical attention if they develop gastrointestinal symptoms. Tetracycline and doxycycline have been found to confer protection to family contacts and are recommended as soon as the index case is identified for three to five days. Untreated asymptomatic carriers are usually free of cholera within two weeks. Long-term carriers exits, but they are very rare and found only through large population studies.

Previous infection with cholera provides at least short-term (one to three years) protection against reinfection. Although a parenteral vaccination has been available for several decades, it is not particularly effective and the duration is short-lived. Therefore, it is not recommended for travelers to cholera prevalent areas. Recent field trials of oral vaccines have been shown to provide significant protection

to cholera, but their effectiveness is also limited, lasting only three to six months. These oral vaccines are not currently available.

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