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In light of an increasing internationally mobile community, the primary care physician may see patients who have recently traveled overseas. This article highlights the manifestations of diseases that, although we may not see them often, can fool us with confusing symptoms. Having lived overseas for six years, I watched my two young daughters cough up Ascaris worms and comforted my wife through a bout of dengue, locally known as "breakbone fever." Some of the "exotic" diseases covered in this issue, like West Nile virus, can be found right here at home. Awareness is the first step to a correct diagnosis.

—The Editor

Uncommon but Important Infectious Diseases

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Malaria

Worldwide, malaria is clearly the most deadly vector-borne illness. Each year, 300-500 million new cases of malaria occur, with approximately 1.5-2.7 million deaths annually,[1] most in young children in sub-Saharan Africa. Roughly 1300 cases and 10 deaths per year are diagnosed in returning U.S. travelers.[2] The majority of these cases occur in patients who have not taken chemoprophylaxis.[3]

Without proper treatment, severe malaria can progress from a few flu-like symptoms to coma and death in as little as 12-48 hours.[4] It is suggested that "any patient who has potentially been exposed to malaria, however briefly, and presents with fever or unexplained systemic illness should be assumed to have life-threatening malaria until proven otherwise."[5]

History. The Centers for Disease Control (CDC) was established in 1946 and was responsible for efforts that eradicated malaria in the United States. However, localized outbreaks of mosquito-borne malaria have been documented as recently as 2003.[6] Currently, the vast majority of cases of malaria currently

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diagnosed in the United States are in returning travelers.

Pathology. Malaria is caused by the protozoan Plasmodium, of which there are four species: *P. falciparum*, *P. vivax*, *P. ovale*, and *P. malaria*. Falciparum malaria accounts for up to 95% of the deaths worldwide, even though it represents only 50% of the infections.[5] Both *P. vivax* and *P. ovale* produce dormant forms that can persist in the liver of infected people and resurface in several months or up to years after initial infection (longest recorded relapse time was 30 years).[7] *P. falciparum* is most common in Africa, East Asia, Haiti, and the Amazon, while *P. vivax* is the dominant species in Central America, the Middle East, India, and Southeast Asia.[8]

Infection begins when a human is bitten by an infected mosquito of the Anopholes species, which are most often active at dusk/night. The incubation period typically is 1-3 weeks but can be highly variable, ranging from several days or up to a year. Patients taking chemoprophylaxis may have delayed onset of illness and milder symptoms. Once inside the body, the malaria protozoan feeds on hemoglobin and other red blood cell (RBC) proteins, which results in lysis of the RBCs, causing anemia. *P. falciparum* infection produces a higher level of parasitemia than the others and also changes the RBC surface so that it adheres to capillary beds and slows blood supply to the vital organs. Thus the brain, kidneys, liver, gut, placenta, etc., are at risk of focal ischemia, thrombosis, and infarction. This effect explains the widely varied clinical symptoms observed (cerebral malaria, acute renal failure, etc.). Patients slowly develop immunity living in an endemic area, which is why most fatal cases of malaria occur in children (or travelers) who have not yet attained protective immunity. After leaving the endemic area, immunity that took years to develop wanes in only about six months.

Signs and Symptoms. Depending on the species of Plasmodium, fever cycles begin and repeat at regular intervals (72 hours [quartan] for *P. malaria* and 48 hours [tertian] for the other three). However, the regular cycle of fevers does not fully develop until the infection is well established. More commonly, the patient presents with vague flu-like symptoms (low-grade fever, headache, malaise, abdominal pain without tenderness, vomiting, diarrhea, muscle aches) with several fever spikes throughout a 24-hour period. Less commonly, patients complain of shortness of breath or chest pain. On physical examination, hepatomegaly and splenomegaly are seen in roughly 25-35%, with jaundice evident in 16%.[9] Lymphadenopathy and rash are not common. Likewise, elevated white blood cell count (WBC) is unusual (< 5% of cases) in acute malaria.[10]

Progression to severe malaria is a life-threatening complication. Severe malaria is defined by the World Health Organization (WHO) as malaria infection and one or more of the signs listed in Table 1. Unfortunately, severe malaria is most common in travelers (non-immune patients) or in primigravida women. Once this stage is reached, even with modern intensive care unit (ICU) treatment, the mortality rate is greater than 30%.[12] Cerebral malaria, a type of malaria-induced encephalitis, is the most common cause of death in severe malaria.[13] Non-cardiogenic pulmonary edema occurs less often than cerebral malaria but has an 80% mortality rate.[14] Acute renal failure is rare in children, but is seen in 30% of non-immune adults with *P. falciparum*.[9]

Diagnosis. One must maintain a high degree of suspicion in patients with a history of travel to an endemic area and any history of fever. Cases of "runway malaria" exist where it is suspected that an infected mosquito has been transported by airplane and

Executive Summary

- Consider malaria in any febrile patient who has recently traveled to endemic areas, no matter how brief the exposure.
- Dengue fever presents with similar symptoms to malaria, but 50% of patients will develop a rash.
- Typhus causes a systemic vasculitis macropapular or petechial rash sparing the face, palms, and soles.
- Typhoid fever classically presents with a prodrome of headache, abdominal pain, cough, and myalgias. Classic symptoms include fever, abdominal pain, and hepatosplenomegaly.
- West Nile virus, now seen in most states in the United States, most often causes only a flu-like illness. However, an encephalitis or flaccid paralysis can occur following the early symptoms.
- There has been spread of "tropical" disease through increased travel to previously isolated areas. Spread can occur through human-to-human contact, but there is also the concern of spread through infected insects transported on aircraft.

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Table 1. Signs of Severe Malaria[11]

- Prostration—inability to sit up without help
- Coma/mental status changes
- Respiratory distress/pulmonary edema
- Seizures
- Hemodynamic instability
- Coagulopathy
- Acute renal failure
- Hypoglycemia (easily overlooked)
- Acidosis
- Jaundice
- Anemia (hemoglobin < 5 g/dL)
- Patients with high parasitemia high risk for severe malaria
  - > 2% non-immune patient
  - > 5% semi-immune patient

may cause disease when released at the destination airport.[15] Thus, any international traveler ill enough to require admission may require screening as well. Table 2 summarizes some of the pitfalls in making the diagnosis. While most patients become ill in the first month, some may take months (even years) to present. Table 3 summarizes high-risk travel that is associated with malaria.

Classically, the gold-standard for diagnosis of malaria is peripheral blood smear and identification of the parasites with a microscope (thick or thin smear with Giemsa stain). CDC recommends obtaining smears every 12-24 hours for three consecutive days before considering malaria excluded.[16] Rapid detection tests (RDTs) using antibody detection techniques exist, but only one of these tests is currently approved for use in the United States (BinaxNOW Malaria). In cases of high suspicion, one should consider empiric therapy while waiting for test results.[17]

Treatment. Treatment of malaria depends on the species of Plasmodium with which the patient is infected and the severity of the illness. Resistance to anti-malarial drugs varies geographically. Obviously any acutely ill patient with suspected malaria should be admitted. Further, admission is advised for all children, pregnant women, and non-immune adults (most travelers). Anyone with malaria complications (*see Table 1*) or high parasite loads (> 2% in non-immune or > 5% in semi-immune patients) should be admitted to an ICU.[5] Volume resuscitation, fever control, seizure control (phenobarbital prophylactically, benzodiazepines for treatment), serum glucose supplementation, and early hemodialysis for renal failure are the mainstays of treatment.

Patients diagnosed with malaria should be started on appropriate anti-malarial drugs (usually chloroquine, quinine, or artesunate combined with doxycycline, tetracycline, or clindamycin). However, the exact regimen to use is best decided in consultation with an infectious disease specialist. Patients with severe malaria should be given anti-malaria drugs intravenously, with quinidine and artesunate being the only choices. Parenteral quinidine is cardiotoxic, and its use is recommended only in an ICU setting with cardiology consultation. The Malaria Hotline is available from the CDC 8 AM - 4:30 PM Eastern time at 770-488-7788, and on-call malaria specialists are available after hours as well at 770-488-7100.

Prevention. More than 50% of the cases of imported malaria between 1992 and 2001 (2,616 cases) involved travelers who took no prophylaxis,[18] but more recent reviews show even higher numbers of non-compliance (96% of 1579 cases).[3]

Prophylaxis is taken for 1-2 weeks prior to travel, once weekly on the same day of the week during travel, and for 4 weeks after completion of travel. Taking prophylaxis does not ensure protection. More than 70% of the cases (351 people) of imported malaria in the United States between 1995 and 2001 were due to malaria prophylaxis failure.[18] Most "failures" are from not taking the proper doses or due to drug-resistance issues. In addition to medication, one should employ netting, screens, and repellent as well. The CDC maintains a good resource web site for information of malaria prophylaxis (www.cdc.gov/malaria/travel/index.htm).

Dengue Fever

Like malaria, dengue is mosquito-borne, with a similar global distribution. Historically, it was only found in Africa, but it has spread to all tropical regions of the world as a result of international trade. There are an estimated 50-100 million cases of dengue fever annually.[19] Of these cases, about 250,000 develop dengue hemorrhagic fever, resulting in about 24,000 deaths. Dengue fever tends to occur in outbreaks or epidemics, and the attack rates can be as high as 70-90% during an outbreak.[20] In only 6 years (1995-2001), the number of cases reported in Central/South America doubled. The majority of recent major epidemics have occurred in Central/South America (Mexico, Guatemala, El Salvador, Nicaragua, Columbia, Brazil) and the Caribbean. As with malaria, many of the dengue fever cases occur in children.

Dengue fever is becoming more common in ill returning travelers. Small outbreaks of dengue were detected in Laredo, TX, in 2005 as a result of dengue spreading across the Rio Grande from Nuevo Laredo, Mexico.[21]

Pathology. Dengue fever is caused by an RNA virus of the Flavivirus genus. The virus is transmitted directly by mosquito from another infected human, and there are no natural animal reservoirs. Currently there are four different virus serotypes, and unfortunately infection with one serotype does not provide protective immunity from the others. Initial infection with the virus (classic dengue fever) typically is not lethal, but the second infection with another serotype can produce the lethal form of dengue: dengue hemorrhagic fever or dengue shock syndrome. For reasons that remain unclear, hemorrhagic fever complications appear to be more common in whites and Asians than in blacks, in females than in males, and in well nourished than in malnourished children.[22]

The dengue virus is transmitted to humans from the Aedes species of mosquito, which are active in the daytime. They are found in urban areas, which puts all travelers to endemic areas at risk. The incubation period varies from 3-14 days, with an aver-

Table 2. Pitfalls in Making the Diagnosis of Malaria

Signs/Symptoms Are Varied

1. Only 1/3 of infected travelers will develop regular fever cycles (48-72 hrs).
   a. It may also take several days to weeks for this to occur.
2. Most patients present with flu-like symptoms.
   a. Moderate fever with multiple spikes in a 24-hour period
   b. Headache, malaise, GI symptoms, muscle aches
3. Lymphadenopathy and rash are uncommon
4. In 98% of cases, WBC is normal or low but band count may be elevated.
5. Eosinophilia is rare unless there is GI parasite co-infection.
6. Failure to consider malaria as a diagnosis
7. Malaria can present after travel to "safe" areas.
8. Onset of symptoms may be delayed.
   a. *P. falciparum* infections usually become symptomatic within 8 weeks.
   b. *P. vivax* infections may take months to cause symptoms.
   c. Chemoprophylaxis can also delay/blunt symptoms.
   d. Chemoprophylaxis does not guarantee malaria prevention.
9. Initial tests may not be accurate.
   a. One negative smear is not diagnostic.
   b. Unfamiliarity with tests used may produce false negatives.
   c. Must obtain blood smears every 12-24 hours for 3 consecutive days to rule it out

Table 3. High Risk Travel Associated with Malaria

- Younger travelers to sub-Saharan Africa
- Rural travel, camping/working outdoors
- Travel during the rainy season
- Stay at altitudes < 1500 m
- Visiting friends/relatives (especially in West Africa)
- Stay for > 3 weeks
- Work as missionary or volunteer
- History of prior chemoprophylaxis side effects
- Failure to use proper netting, repellents, or chemoprophylaxis

age of 4-7 days. The virus primarily attacks hepatocytes and endothelial cells.

Signs and Symptoms. Classic dengue fever produces a flu-like syndrome with high fever, headache, arthralgias, and a generalized macular blanching rash. The rash is a helpful clue to distinguish dengue from malaria, in which rashes are uncommon. Symptoms return with fever and rash beginning simultaneously. In the second phase, the rash is mobilliform, maculopapular, sparing the palms and soles, with occasional desquamation. Small (< 1 cm) islands of normal or "spared" skin often are noted in the midst of the rash.[19] The fever in the second phase typically is not as high and lasts another 2-5 days.

Another hallmark of dengue fever is the severe arthralgias, leading to the term "breakbone fever."[20] The pain begins after the first fever onset, increases in severity with time, and may last several weeks. The most common sites affected are the legs, large joints, and lumbar spine. Interestingly, the bony pain is not present in dengue hemorrhagic fever or dengue shock syndrome.

The more severe form of dengue is dengue hemorrhagic fever. On the third to seventh day of illness around the end of the first phase, an abrupt shock syndrome develops. Patients develop abdominal pain with restlessness, hypothermia, mental status changes, and a sudden drop in platelet count. Thrombocytopenia contributes to spontaneous hemorrhage, ranging from petechiae to life-threatening gastrointestinal bleeding. Epistaxis, bleeding from gums, and menorrhagia also are noted. Hypotension and narrowed pulse pressures are noted, indicating intravascular volume depletion from increased capillary permeability. Loss of fluid into extracellular spaces rather than frank hemorrhage is the usual cause of shock.

The mortality of untreated dengue hemorrhagic fever can be as high as 50%, but ICU support can lower the number to < 5%.[23] Most deaths occur from cardiovascular collapse and/or adult respiratory distress syndrome (ARDS). Although children respond to aggressive fluid resuscitation, it recently has been suggested that more refractory cases may be a result of depressed cardiac output, the cause of which is yet to be determined.[24] Serum troponin is not elevated in these patients, so it does not appear to result from direct myocyte damage by the virus.

Diagnosis. In most cases, fever that begins after 2 weeks following departure from endemic areas or lasts longer than 10 days is not likely to be dengue fever.

The WHO has listed clinical criteria that support the diagnosis of dengue fever. (*See Table 4.*) WHO dengue hemorrhagic fever criteria include: recent history of fever, hemorrhagic complications, thrombocytopenia and hematocrit > 20% average for patient's sex, age and population.

Fortunately, laboratory tests can provide clues, as leukopenia (< 5000/mm^3), neutropenia (< 3000/mm^3), thrombocytopenia (seen in 50% of cases), or mildly elevated AST levels (> 60 U/mL) often are present.[25] Hematocrit levels should be monitored, as levels rising > 20% often precede development of shock.[20] Likewise, platelet counts < 100,000 cells/µL are seen before initial fever defervescence and onset of shock. Ultimately, proof of diagnosis depends on isolation and identification of the virus by PCR or ELISA tests.

Treatment. Uncomplicated dengue fever can be managed with fever control and fluid replacement. Patients presenting with signs of hemorrhagic fever or shock should be managed aggressively. Patients with a history of repeated travel to endemic areas should be observed for possible development of complications. In most cases, the patient will be admitted for diagnosis confirmation and inpatient observation. Patients who survive the first 48 hours of shock syndrome recover rapidly and do not experience relapse.

Rickettsial Diseases

Currently, rickettsial diseases consist of three main types of illnesses: spotted fevers, typhus, and Q fever. Spotted fevers (e.g., Rocky Mountain spotted fever) are transmitted via tick bites,

Table 4. Diagnostic Criteria for Dengue Fever

Acute fever with 2 or more of the following:
- Headache, retro-orbital pain
- Myalgias
- Arthralgias
- Rash
- Hemorrhagic complications

Case occurred at the same time as other confirmed cases.

while the typhus group of diseases is transmitted via fleas/lice, and Q fever is not vector-borne. Regardless of the type of rickettsial disease, treatment with doxycycline is usually the first-line therapy, with fluoroquinolones or macrolides as alternatives. Eschars seen at the site of the vector insect bites are common in all rickettsial diseases (except Q fever), and are caused by the high level of organisms present there.

Spotted Fevers. Rickettsial organisms cause a variety of spotted fevers, including Rocky Mountain spotted fever, Mediterranean spotted fever, African tick-bite fever, north Asian tick typhus, Queensland tick typhus, Japanese spotted fever, and flea-borne spotted fever. Spotted fevers are named for the rash that accompanies the other symptoms. These diseases are found around the globe except Antarctica. Cases are transmitted from infected animals (dogs, cows, other mammals) by tick bites. Often, the history of tick bite is absent, as transmission also can occur via the bite of immature forms whose bites go unnoticed. Most cases are seen in warmer months.

Typhus. Typhus is a group of illnesses (epidemic typhus, murine typhus, scrub typhus) caused by rickettsial organisms and transmitted to humans by lice or fleas. Epidemic typhus tends to occur during natural disasters or in areas of war/poverty.[26] A few cases have been reported in the eastern United States in recent years in patients who had close contact with flying squirrels.[27]

Symptoms of epidemic typhus appear after an incubation period of 8-16 days. The organism invades endothelial cells and produces a multi-system vasculitis. Most patients experience abrupt onset of fever, headache, myalgias, conjunctival injection, and rash. The rash is maculopapular or petechial and involves the entire body except for the face, palms, and soles. Regional lymphadenopathy is seen near the louse bites. Unless antibiotics are initiated, the symptoms progress to delirium, cough, gangrene, coma, and death in a median 12.5 days after symptom onset.[26] The mortality rate for untreated epidemic typhus varies from 20% (healthy patients) to 60% (elderly, pre-existing disease). With antibiotic treatment, the rate lowers to 3-4%. Patients who survive without antibiotic therapy recover about 14 days after onset of symptoms. Some patients, even with treatment, develop occult infection termed Brill-Zinsser disease. They harbor low levels of rickettsia in their bodies and may develop recurrent typhus months or even years later, although the course of recurrent disease is milder than epidemic typhus.

Most cases are diagnosed via rising antibody titers, but these are not present until the second week of illness. Doxycycline (100 mg BID for 7-10 days) is the treatment of choice, while chloramphenicol (60-75 mg/kg/day divided into 4 doses) is an effective alternative.[26]

Murine typhus is a similar infection caused by a different species of rickettsia and is transmitted to humans from infected rat flea bites. Isolated cases are seen in the United States (Texas, southern California) associated with cats and opossums. Murine typhus is seen primarily in port cities located in subtropical and temperate coastal areas. Cases recently have been reported in travelers returning from Hong Kong, China, Brazil, and Indonesia.[28] Symptoms are similar to epidemic typhus, although the fatality rate is less (1-4%). Definitive diagnosis is via rising antibody titers, but distinction from epidemic typhus can be difficult due to shared antigens. Treatment is with doxycycline or chloramphenicol.

Scrub typhus is caused by another rickettsial species and transmitted by infected mites (chiggers). It is endemic in southern and eastern Asia (Japan, China, Korea), as well as Indonesia, India, and the Philippines. An estimated 1 million people are infected each year.[29] Symptoms are similar to epidemic typhus, although the rash is less severe and often overlooked. Fatality rates can vary from 3% to 60% without treatment, but treatment with doxycycline or chloramphenicol greatly improves recovery.

Q Fever. Q fever is caused by *Coxiella burnetii,* and the disease is endemic in many parts of the world. It is one of the diseases that has been mentioned as a bioterrorism agent. Of note, this organism recently was reclassified as a protobacteria (distantly related to Legionella).[30] It is particularly common in southern Spain.[31] It is also endemic in the United States, causing 60-70 cases per year in recent years. The disease primarily affects those in close contact with livestock (cattle, sheep, and goats) who breath the organisms into their lungs directly from close contact with animal body fluids (urine, feces, milk, amniotic fluid). No inoculation eschars are seen. The incubation time is variable, but the average time is 18-21 days (range of 9-40 days).[32] Only about 50% of infections manifest with clinical symptoms, and mortality of acute infection is generally < 1%. Acute infection symptoms are those of pneumonitis with fever, headache, myalgias, cough, and pleuritic chest pain. For reasons that are unclear, some patients progress to chronic illness (lasting > 6 months) and are at risk for complications of hepatitis and endocarditis. Diagnosis is through rising antibody titers. Treatment is with doxycycline (100 mg BID for 14-21 days).

Schistosomiasis

Schistosomiasis is found in a total of 74 countries in Africa, South America, Asia, the Middle East, and the Caribbean. However, 80% of cases today are seen in sub-Saharan Africa.[33] Prevalence in endemic areas can approach 50%, and even short-term travelers to these areas are at risk of infection. Dams and irrigation projects have introduced the disease into new areas, and transmission has been reported even in large urban areas in Africa and Brazil.[34] Outbreaks of schistosomiasis also have been reported in adventure travelers on river trips in Africa and among Peace Corps volunteers.[35] There are an estimated 400,000 people

Table 5. Symptoms of Chronic Schistosomiasis

- **Intestinal form:** abdominal pain, bloody diarrhea
- **Hepatic form:** hepatomegaly, portal hypertension, liver failure
- **Urinary form:** hematuria, obstructive hydronephrosis/ hydroureter, bladder cancer
- **Central nervous system:** epilepsy, increased intracranial pressure, spinal cord lesions
- **Pulmonary:** cor pulmonale

with schistosomiasis currently in the United States, and they occasionally present with complications of chronic infection.[36] However, the disease cannot be passed on here, as the snail species required to complete the parasites' life cycle is not found in the United States.

People become infected when they enter fresh water containing the free-swimming larval form that can penetrate normal skin. In people with previous infection, a self-limited inflammatory reaction produces a papular dermatitis (swimmer's itch) that can begin only a few hours after infection.[33] Once in the body, larvae migrate into large veins of the liver, mesentery, or ureters depending on the species. After about 2-8 weeks, eggs are produced that pass from the intestines or urine into fresh water to infect specific snail hosts, which in turn release the free-swimming larvae. Once eggs begin to be released, many people develop an acute systemic reaction termed Katayama fever or acute schistosomiasis. The retention of the eggs produces the clinical disease of chronic schistosomiasis. Four major species migrate to produce hepatobiliary or gastrointestinal disease (*S. mansoni*, *S. intercalatum*, *S. mekongi*, and *S. japonicum*) and one to produce urinary disease (*S. haematobium*).

Systemic symptoms begin about 2-8 weeks after initial exposure to contaminated water but can take up to 12 weeks to appear. The delay between fresh-water exposure and onset of symptoms can make the connection difficult to discern. Symptoms and physical findings include fever, myalgias, fatigue, abdominal pain, bloody diarrhea, lymphadenopathy, hepatomegaly, non-productive cough, and suspicious laboratory findings of patchy pulmonary infiltrates with eosinophilia are seen. Higher nocturnal fevers and eosinophilia suggest parasitic infection and may be the only specific clues to acute schistosomiasis.[37] Most patients' symptoms resolve spontaneously in 2-10 weeks, but some develop persistent abdominal pain, diarrhea, dyspnea, and weight loss.

Symptoms of chronic schistosomiasis usually appear 2-10 years after initial infection and correlate with the area of the body infected. (*See Table 5.*) They result from inflammation and scarring produced by chronic egg retention.

Diagnosis is via microscopic examination of stool or urine for eggs. Serologic antibody detection is available at the CDC, but it cannot distinguish between active or past infections. Early treatment is crucial to prevent complications of long-term infection; even a single pair of worms is thought to be able to produce severe complications (i.e., transverse myelitis) over time.[33] Praziquantel (Biltricide 40-60 mg/kg/d PO divided BID to TID for 3-6 days) is the drug of choice, and just a single treatment can cure 65-90% of patients or reduce egg production by 90%.

Typhoid Fever

Typhoid fever is caused by infection with Salmonella typhi and paratyphoid fever by *S. paratyphi*. Both diseases are clinically similar, although paratyphoid symptoms generally are less severe and are collectively known as enteric fever. Typhoid fever now is seen mostly in developing countries with poor sanitation.[38] There are an average of 400 cases per year in the United States, with 72% of these diagnosed in travelers, most of whom went to India or Latin America (Mexico).[39] Travel to India carries the highest risk (18 fold higher).[40] About 1-4% of untreated individuals can become chronic carriers of the bacteria. The most infamous carrier was "Typhoid Mary," who unknowingly spread typhoid fever while she worked as a cook in New York in the early 1900s.

After bacteria are ingested, they invade the enteric mucosa and can spread to the lymphatic tissue (Peyer's patches), spleen, liver, and bone marrow. Use of antacids, proton pump inhibitors, history of gastrectomy, and immune deficiency all increase risk of infection. The incubation period varies, with an average of 7-14 days (3-60 day range). Untreated, symptoms usually last around four weeks, though patients given antibiotics recover rapidly over just 2-3 days. Early clinical symptoms consist of headache, abdominal pain, anorexia, dry cough, and myalgias that often precede the fever. Ironically, constipation occurs with equal frequency as diarrhea and is thought to result from hypertrophy of Peyer's patches. Classic physical findings include fever, abdominal pain, and enlarged liver and/or spleen. Fever may be absent during the first week, but it rises to a sustained high fever in weeks 2-4. Abdominal distension appears in the second week and peaks in the third week. Classically, "rose spots" appear in about 30-50% of cases and are subtle salmon-colored blanching maculopapular lesions about 1-4 cm in size.[38] Relative bradycardia with the fever is also suggestive of typhoid fever. Conjunctivitis and rales also are reported in about half of cases. Intestinal bleeding is the most common complication (12% in one series)[41] and may precede perforation, which occurs at heavily infected Peyer's patches. If patients do not die from intestinal perforation, GI bleeding, myocarditis, or sepsis, they begin to improve in the fourth week, although the recovery is slow and relapses are seen in 10% of cases.[38] Mortality can be as high as 90% without antibiotics, but their early use reduces this to < 1%.

Laboratory diagnosis is by culture of a Salmonella species. *S. typhi* can be cultured from blood (70% successful), stool (30% successful), urine, and the rose spots, but bone marrow aspirates have the highest sensitivity (80-95%) and remain a good source even after several days of antibiotic treatment.[42] Presumptive treatment should be started as soon as the disease is suspected. Ciprofloxacin is no longer effective against species from Southeast Asia, and alternatives include ceftriaxone (Rocephin) for severe cases or trimethoprim/sulfamethoxazole (Bactrim) for mild cases.[43]

Leishmaniasis

Leishmania are intracellular parasites transmitted by the bite of sand flies. The three main types of disease caused are visceral (most dangerous), cutaneous, and mucocutaneous. Cutaneous leishmaniasis is more common than the visceral form. The same species of Leishmania can produce more than a single clinical syndrome.

Leishmania are found in most of the world (also in the United States along the Mexican border), except for Australia, the Pacific Islands, and Antarctica. The vast majority of cases are clustered in several regions: 90% of visceral leishmaniasis is in eastern India, Bangladesh, Brazil, Nepal, and Sudan; 90% of mucocutaneous cases are from Brazil, Bolivia, and Peru; and 90% of the cutaneous cases are from Iran, Iraq, Saudi Arabia, Syria, Afghanistan, Brazil, and Peru.[44] Soldiers in Iraq and Afghanistan have frequent encounters, coining the term "Baghdad boil" for cutaneous disease. More than 500 cases in soldiers have been reported between 2002 and 2004. One estimate is that up to 10% of those deployed to the Persian Gulf may have leishmaniasis.[45] Cases have been documented to occur via blood transfusion[46] or needle sharing in IV drug users.[47] Treatment is complicated due to the drugs used and frequent treatment failures; consultation with ID specialists is recommended.

Visceral Leishmaniasis. The visceral form of leishmaniasis is the most severe. It is also called Kala-azar or black fever. Travel to eastern India, Bangladesh, Brazil, Nepal, and Sudan are the main areas of risk. Travelers with HIV/AIDS, though, are at much higher risk (about 100-1000 times higher)[48] The average incubation period is 3-8 months but can be as short as 10 days or more than 1 year.[45] Protozoa move to infect the spleen, liver, and bone marrow, and patients develop fevers, anorexia, weight loss, abdominal distension, hepatomegaly, and splenomegaly. Primarily in cases from India, hyperpigmentation develops on the hands, feet, abdomen, and face (hence the term black fever). Bone marrow involvement causes pancytopenia with severe anemia and leukopenia that can prompt opportunistic infections. Without treatment, the majority of cases prove fatal. Diagnosis is difficult and is typically through visualization of parasites (or culture) from bone marrow aspiration or liver or spleen biopsy. Serum antibody ELISA tests also are available. The first choice for treatment is amphotericin B (AmBisome) for 4-6 weeks. Miltefosine is a new oral agent being used with success in India, where resistance is 40%.[44]

Yellow Fever

In 1900, Dr. Walter Reed first confirmed Carlos Finley's idea that yellow fever was transmitted by mosquitoes. The last outbreak in the United States occurred in 1905 in New Orleans. Currently, yellow fever is still endemic to Africa and South America, with most of the cases in sub-Saharan Africa.

An effective live-attenuated vaccine was developed in 1937 and is still used today. It is effective, with side effects of low-grade fevers, malaise, and injection-site reactions seen in fewer than 5% of individuals. The vaccine can be given to older people, but patients older than 70 years of age have a 13-fold increased risk of this complication.[49] Yellow fever vaccination is required by many countries for entry by anyone traveling to or with stopover in Africa and South America. Currently no vaccinations are required to return to the United States.[50]

Pathology and Symptoms. Yellow fever is caused by an RNA virus of the Flavivirus genus. It is transmitted to humans by mosquitoes. Unfortunately, these mosquitoes are found throughout urban areas in endemic areas, with the highest risk of transmission in the rainy seasons. Once a person is bitten, the virus infects many tissues, including the liver, kidneys, lymph nodes, spleen, and bone marrow.

After a short incubation period of 3-6 days, a variety of symptoms can result, ranging from mild illness to hemorrhagic fever and rapid death. Nearly 90% of infections are mild or asymptomatic, but more serious cases occur in about 15% of patients, in whom mortality can be as high as 50%.[51] ICU care can lower this number in many cases to about 5%.[52] The first or acute phase of yellow fever begins with fever, headaches, and myalgias. Conjunctival injection, facial flushing, and relative bradycardia with the fever (Faget's sign) are seen.[20] Symptoms abate after about 3-4 days but will return in 24 hours to 2-3 days in the 15% who progress to the life-threatening stage or toxic phase of yellow fever.

The toxic phase is characterized by return of high fever, headache, low-back pain, abdominal pain, vomiting, and somnolence (or period of intoxication). Jaundice appears as liver damage increases, giving the disease its name. Spontaneous hemorrhage is common with epistaxis, gum bleeding, GI bleeding, and petechiae/purpuric rashes. Renal and hepatic failure (hepatorenal syndrome) is a common cause of death and typically occurs within 7-10 days after symptom onset. Those who do survive take many weeks to fully recover from residual fatigue.[20]

Diagnosis and Treatment. While there are few clinical findings that suggest yellow fever, the relative bradycardia seen with the high fever (Faget's sign) can be a clue when present. Strict questioning of the patient about the vaccine is important because, when used, the vaccine is very effective and provides protective immunity in 95% of recipients within one week.[53]

Common laboratory abnormalities include mildly low WBCs or neutrophil counts, signs of coagulopathy (elevated prothrombin times, low fibrinogen levels, low hemoglobin, and thrombocytopenia), rising liver enzymes and bilirubin levels, and elevated serum creatinine. Albuinuria is a consistent finding that helps differentiate yellow fever from other causes of viral hepatitis.[20] Ultimately, the diagnosis can be confirmed only by ELISA or PCR tests that detect the presence of the specific virus or by direct culture of the virus. Liver biopsy also can confirm the diagnosis but should be avoided in coagulopathic patients.

Treatment is supportive, as there are no specific treatments for yellow fever. All patients who do not progress to the toxic phase of the illness survive without sequelae. Of the 15% who progress to the toxic phase, 50% mortality is common without treatment. Aggressive fluid resuscitation, ventilation, dialysis, and management of disseminated intravascular coagulation can reduce this number to 5%.

West Nile Encephalitis

West Nile encephalitis was first recognized in 1937. The virus came to the forefront, though, in 1999, when it caused a series of deaths among wild crows and exotic birds.[54] Later that year, the virus was isolated from 59 individuals in the eastern United States. By 2002, the disease had spread across the United States to the Pacific.[20] Since 1999, there have been 19,525 cases reported in the United States, causing 771 deaths.[55] In 2007, cases of West Nile disease were reported from 43 states, with the largest numbers in Colorado (576), California (379), and North Dakota (369). To date, only Washington, Alaska, and Hawaii have not reported cases.

West Nile disease is caused by another species of Flavivirus. It is transmitted to humans by the bite of infected mosquitoes, usually of the Culex species. The virus exists in the wild, primarily in bird populations (especially crows, jays, and sparrows) but also can infect other mammals (cats, dogs, horses, etc.). The virus also can be transmitted by infected blood products or by organ donation.

The majority of infections in humans are asymptomatic, with only 20-40% of people developing clinical symptoms.[55] When symptoms do occur, they are seen after a 2- to 14-day incubation. Most people develop flu-like disease with fever, cough, sore throat, headache, myalgias, vomiting, and diarrhea that lasts 3-6 days. Fewer than 1% of infected people progress to severe neuroinvasive disease.[55] Besides neurologic complications, myocarditis, hepatitis, and pancreatitis also have been reported.[20]

Those who progress to neurologic disease develop a flu-like prodrome lasting 1-7 days. They seem to improve before relapsing with more severe symptoms. When neurologic disease develops, it is clinically indistinguishable from other forms of viral encephalitis. Patients can have signs of meningeal irritation (headache, stiff neck, photophobia) or develop delirium and focal neurologic signs (dysarthria, tremor, seizures, ataxia). Encephalitis (63% of cases) is more common than meningitis (29%), and some patients develop only headache (8%).[54] Case fatality rates range from 4-14%, with most deaths in the United States occurring in older patients.[20]

West Nile also is known to cause a flaccid paralysis that can follow 1-2 weeks after the flu-like illness.[55] The onset is rapid, with peak weakness occurring in only a few hours. Minimal or no sensory changes are noted, and bowel/bladder function is affected only in a minority of patients.[56] Unfortunately, recovery from flaccid paralysis is highly variable, with some studies reporting only 30% recovering the ability to walk after one year, while in other cases some patients recovered completely in a matter of weeks.[55]

Currently, no tests can identify West Nile infection while patients are still in the ED. ELISA tests for serum IgM antibodies are required.

Trypanosomiasis

Trypanosomiasis is caused by infection with protozoa of the Trypanosoma genus, and there are two distinct disease forms in humans. American trypanosomiasis (Chagas' disease) is caused by *Trypanosoma cruzi*, and African trypanosomiasis (sleeping sickness) is caused by *Trypanosoma brucei*.

African Trypanosomiasis (Sleeping Sickness). The West African version has a more delayed onset, with symptoms developing months to a year after the first bite. After symptoms develop in West African disease, it proceeds similarly to the East African version.

East African trypanosomiasis follows a more acute course. A painless inflammatory lesion at the bite site develops about a week after the bite. Even without treatment, this usually resolves spontaneously over a few weeks. About 3 weeks after being bitten, intermittent fevers, myalgias, general lymphadenopathy, rash, and headache occur. Like Chagas' disease, the heart can be involved at this stage with pericarditis and conduction disease.

Stage II develops when the parasites reach the central nervous system and may progress rapidly or may take months to years to develop. Persistent headaches, with behavioral changes, weight loss, and the characteristic disruption of sleep patterns (daytime somnolence, nighttime insomnia) the disease is named after are seen. Movement disorders, such as choreiform movements, fasciculations, ataxia, slurred speech, and tremors can prompt misdiagnosis with Parkinson's disease. Ultimately, the disease is fatal if untreated.

Definitive diagnosis relies on direct detection of the parasite in blood or tissue serologic antibody testing. Treatment is obtained through the CDC.

American Trypanosomiasis (Chagas' Disease). American trypanosomiasis, or Chagas' disease, is transmitted to humans from the bite of the kissing bug. People can become infected when the kissing bug bites, obtains a blood meal, and then defecates nearby. The protozoans are in high concentration in the bug's feces and are then rubbed into the nearby, itching wound. Pregnant women can transmit the disease to their fetuses. Muscle tissue is most affected by *T. cruzi* infection, especially cardiac muscle, resulting in dilated cardiomyopathy as well as conduction system abnormalities. Apical aneurysms and mural thrombi are common. The esophagus and colon are the other tissues most commonly affected. Only 10-30% of people with chronic infection will become symptomatic.[57]

Two distinct clinical syndromes result from infection: the acute and chronic disease. Incubation periods are about 7-10 days and last between 3-8 weeks without treatment. Symptoms consist of localized swelling (chagoma) at the site of the insect bite, with localized lymphadenopathy. Systemic symptoms of fever, malaise, anorexia, and facial/extremity edema can be seen. Rarely, patients will develop meninngoencephalitis or congestive heart failure in the acute infection, and fatalities can result. Chronic Chagas' disease can take years to decades to produce symptoms, which consist of right heart failure, arrhythmias, or achlasia (megaesophagus).

Diagnosis of acute infection can be made by observing a fresh drop of anticoagulated blood at 400 x magnification for moving *T. cruzi*. When blood smears are not diagnostic, culture may be needed to prove infection, but this can take several weeks. PCR tests are useful to diagnose acute/chronic infections but are not

sensitive enough for screening of donated blood.[58] Treatment is only available through the CDC.[57]

Viral Hemorrhagic Fevers (Ebola, Lassa, Marburg)

At least 18 different species of viruses are known to cause hemorrhagic fever syndromes: arenaviruses (Lassa, Bolivian, Argentine, Brazilian hemorrhagic fevers), bunyaviruses (Hantavirus, Congo-Crimean hemorrhagic fever, Rift Valley fever), filoviruses (Ebola and Marburg fevers), and Flaviviruses (Dengue and yellow fever). All are RNA viruses in which humans are not the natural host, they cause human disease in sporadic outbreaks, and, with few exceptions, they have no specific treatment. Some of these viruses (Ebola, Lassa, Marburg) are so contagious they are classed as Category A bioterrorism agents comparable to anthrax and smallpox.[59] This section will focus on the Ebola, Lassa, and Marburg fevers.

Ebola. Ebola fever is highly fatal in humans, with case fatality rates of 40-89%, and so far has been limited to infrequent outbreaks in sub-Saharan Africa (Congo, Gabon, Sudan, and Uganda). Very little is known about the virus, and the natural animal reservoir remains unidentified. Epidemics appear mysteriously, rapidly infect humans (and primates), and their spread is only limited by their deadly clinical course.

Ebola virus is highly infectious, and human-to-human aerosol spread through close contact with the infected patient or with their body fluids is well documented in those caring for these patients.[60] Even persons preparing the dead for burial have become infected, presumably just by touching of the skin.[60] Recent work shows that a few human Ebola infections remain asymptomatic, possibly due to a strong early immune response in these lucky individuals.[61] After exposure to the virus, incubation periods range from only 5-10 days. Early symptoms include abrupt onset of fever, myalgias, headache, abdominal pain, diarrhea, and pharyngitis with herpetic lesions. Later, patients develop a maculopapular rash that evolves into petechiae with spontaneous bleeding from all mucosal sites and venipuncture sites. Severe conjunctival injection and bleeding also are seen.[62] Most patients die from cardiovascular collapse and metabolic acidosis, but some improve markedly in the second week. Culture of the virus is diagnostic but must be performed in a level 4 biosafety facility. Otherwise, PCR detection of viral antigen or ELISA detection of antibodies is used. Currently there are no recommended antiviral drugs used to treat Ebola infections; treatment is strictly supportive.

Marburg Fever. This virus is closely related to the Ebola virus. Bats are the implicated natural reservoir, but so far no live virus from animals has been isolated.[60] Clinically, Marburg fever is very similar to Ebola, although mortality in some outbreaks has been lower (25-30%).[62] As with Ebola, there is no specific treatment, and the virus is highly contagious.

Lassa Fever. Lassa fever epidemics have been reported in West Africa (Nigeria, Liberia, Sierra Leone, and Guinea) with case fatality rates up to 50%. A case of Lassa fever was seen in New Jersey in 2004. It is estimated that between 100,000 and 300,000 cases (5,000 deaths) occur every year in West Africa. Only 1 in 20 infections leads to significant symptoms/hospitalization.[63]

The natural reservoir for Lassa virus is a small rodent. The exact mechanism of transfer to humans is unclear but likely occurs from contact, ingestion, or aerosol spread from the rat's urine or stool or by handling the rodents as they are prepared for food.[64] Infected people are highly contagious, and contact with their body fluids, tissue, or even intact skin can transmit the virus.

Symptoms begin after 7-12 days, and a variety of symptoms can be seen. In order of decreasing frequency, they include retrosternal chest pain (perhaps from pericarditis), sore throat, back pain, cough, abdominal pain, vomiting, diarrhea, conjunctivitis, and facial edema.[65] Mucosal bleeding is seen less often than with Ebola or Marburg. In some patients, encephalitis and/or meningitis complications occur. Diagnosis can be suggested by elevated serum aspartate transaminase (AST) levels, but serologic ELISA confirmation is required for accurate diagnosis. Patients who die from infection do so in the second week from cardiovascular collapse and pulmonary edema.

Ribavirin has been shown to be an effective treatment.[66] Ribavirin now is recommended as effective for chemoprophylaxis in those exposed to infected patients.

Cholera

Cholera is a contagious diarrheal illness capable of causing epidemics and pandemics.[67] Regional epidemics occur yearly. The overwhelming majority (66%) of recent cases are from Africa, followed by Southeast Asia (17%).[68] Although cholera is primarily a disease of poor sanitation, developed countries such as the United States, Canada, and Australia have reported endemic cases.[69] The U.S. cases were associated with raw seafood on the Gulf Coast, and cases were reported in association with hurricanes Katrina and Rita.[70]

Symptoms begin after a 24- to 48-hour incubation period, and the watery diarrhea ("rice water stools") can produce mild to life-threatening dehydration. Stool volume has been measured at > 250 mL/kg in the first 24 hours.[67] Vomiting can be present, complicating oral rehydration attempts. Clinical symptoms will vary with degree of dehydration. If untreated, cholera can cause death in 1-3 days from dehydration with a reported mortality of 50%.[67]

Diagnosis is by visualization of mobile V. cholerae in the stool, by culture, or by PCR testing. Treatment centers on rehydration, with restoration of fluid losses in the first 2-4 hours followed by maintenance until diarrhea slows. Fluid requirements in the restoration phase can be extreme, up to 100 mL/kg/hr (7 liters for 70-kg person).[67] Antibiotics are optional but do shorten the course of illness and limit fluid losses. Tetracycline resistance is spreading, and resistance to ciprofloxacin also has been reported in India. Erythromycin and azithromycin have been used with success.

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Physician CME Questions

20. The incubation time of malaria is:
    A. < 1 week
    B. 1-2 weeks
    C. 2-4 weeks
    D. 4-8 weeks
    E. > 8 weeks
    F. all of the above

21. Signs of severe malaria include all of the following *except*:
    A. coma/mental status changes.
    B. eosinophilia.
    C. coagulopathy.
    D. jaundice.

22. Unlike malaria, dengue fever causes:
    A. high fever.
    B. arthralgias.
    C. headache.
    D. rash.

23. Which of the following precedes the development of dengue shock syndrome?
    A. Anemia
    B. Rise in hemotocrit
    C. Thrombocytopenia
    D. Leukopenia

24. Typhus has been seen in the United States associated with which animal?
    A. Dog
    B. Rabbit
    C. Groundhog
    D. Flying squirrel

25. Typhoid fever is most common after travel to:
    A. India.
    B. New Orleans.
    C. Dominican Republic.
    D. New York City.

26. Which of the following is not associated with typhoid?
    A. Breakback fever
    B. Rose spots
    C. Relative bradycardia
    D. Splenomegaly

27. Bagdad boil seen in soldiers in Iraq and Afghanistan is caused by:
    A. malaria.
    B. dengue fever.
    C. leishmaniasis.
    D. Chagas' disease.

28. Yellow fever vaccine:
    A. causes more reactions in children than older adults.
    B. is nearly 100% effective.
    C. provides cross-over immunization for other diseases caused by Flavivirus.
    D. may cause jaundice in 5%.

29. The flaccid paralysis caused by West Nile virus:
    A. occurs 1-2 weeks after the flu-like illness.
    B. precedes the illness by 5-6 days.
    C. reverses in all patients effected within 1 week.
    D. reverses in all patients effected within 24 hours.

CME Instructions

Physicians participate in this continuing medical education program by reading the article, using the provided references for further research, and studying the questions at the end of the article. Participants should select what they believe to be the correct answers, then refer to the list of correct answers to evaluate their knowledge. To clarify confusion surrounding any questions answered incorrectly, please consult the source material. *After completing this activity, you must complete the evaluation form that will be provided at the end of the semester and return it in the reply envelope provided to receive a certificate of completion.* When your evaluation is received, a certificate will be mailed to you.

Primary Care Reports

CME Objectives

To help physicians:

• summarize the most recent significant primary care medicine-related studies;

• discuss up-to-date information on all aspects of primary care, including new drugs, techniques, equipment, trials, studies, books, teaching aids, and other information pertinent to primary care;

• evaluate the credibility of published data and recommendations; and

• describe the pros and cons of new testing procedures.

CME Answer Key

20. F; 21. B; 22. D; 23. B; 24. D; 25. A; 26. A; 27. C; 28. B; 29. A

In Future Issues:

Headache

Clinical Briefs in
Primary Care
The essential monthly primary care update
By Louis Kuritzky, MD
Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Infectious Disease Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports.*
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VapoRub Revisited

Source: Abanses JC, et al. Vicks VapoRub induces mucin secretion, decreases ciliary beat frequency, and increases tracheal mucus transport in the ferret trachea. *Chest* 2009;135:143-148.

THOSE OF US IN THE BABY-BOOMER generation may recall in the 1940s-50s the application of a generous quantity of some Vicks® VapoRub-type salve (VvR) to the chest wall as a time-honored remedy that grandma suggested for the common cold. Toxicity of VvR, rather than efficacy, was the subject of this publication.

As with essentially any therapeutic agent, there is always the potential for adverse effects. Based upon a single case report of a toddler who developed respiratory distress subsequent to peri-nasal application of VvR, Abanses et al investigated potential adverse physiologic effects of VvR by experiments in ferrets.

VvR resulted in increased mucin secretion and decreased ciliary beat frequency (as observed by video microscopy), the combination of which could lead to small-airway obstruction. The authors report upon studies of menthol (an ingredient of VvR) in adults, in which, despite a decrease in nasal airflow, subjects universally report improved nasal symptoms; this change is attributed to the cooling effect of menthol in the nasal passages, which the brain interprets as increased airflow across the nostrils.

VvR appears to be a generally safe remedy, but case reports suggest caution in young children. The case presented here was initially treated as asthma; clinicians might consider asking about VvR use in children who present with new, otherwise unexplained symptoms of respiratory distress. ■

Prostate Cancer Risk with Testosterone Replacement

Source: Shabsigh R, et al. Testosterone therapy in hypogonadal men and potential prostate cancer risk: A systematic review. *Int J Impot Res* 2009;21:9-23.

GROWTH AND DEVELOPMENT OF THE prostate is recognized to be testosterone (TST)-dependent. Clinicians have long held concerns that TST therapy might not only worsen symptoms of benign prostatic hyperplasia (BPH), but also stimulate the development, growth, proliferation, or aggressiveness of prostate cancer (PCa). Some of this concern stems logically from the observation that TST deprivation has salutary effects on prostate cancer growth.

This systematic review of 44 articles using FDA-approved agents was unable to directly provide a definitive answer to the question of whether TST replacement increases risk of PCa, but provides other interesting insights. First, trials of hypogonadal men treated with TST have not evidenced an increased risk for PCa; if anything, a protective effect may occur. Second, TST-treated men with a history of PCa did not experience more recurrences or metastases. Third, TST did not appear to influence Gleason scores when PCa was detected.

The authors conclude, "There is no evidence that TST increases risk of prostate cancer in hypogonadal men." Of some concern, however, are the case reports of aggressive PCa in recipients of a non-FDA-approved supplement containing TST, estradiol, chrysin, and elk velvet antler. ■

The Suicidal Process: Time to Intervene?

Source: Deisenhammer EA, et al. The duration of the suicidal process. *J Clin Psychiatry* 2009;70:19-24.

SUICIDE HAS BEEN IN THE TOP CAUSES of death in the United States for more than 20 years, usually ranking among the top 10. Clinicians would like to play a useful role in suicide prevention, yet data are sparse to inform about the interval between first suicidal ideation and a suicide attempt. Deisenhammer et al attempted to bridge this knowledge gap with a study of persons with failed suicide attempts, all of whom (n = 82) were interviewed within 72 hours of attempted suicide.

Most (83%) subjects were alone at the time of suicide conceptualization, and almost half reported the time from first suicide conception to attempt was 10 min or less. Nonetheless, during this brief interval, most (77%) had some contact (usually by telephone) with friends or family, and the majority indicated their wish to die or (according to their subjective reports) hinted at their death wish.

Interviews with subjects did not provide any insight as to what might have deterred the suicide attempt. Nonetheless, the fact that most suicidal subjects did make contact with others leaves open the possibility that some component of interpersonal communication has the potential to change the course of suicide attempts. ■

BNP to Guide Treatment of Heart Failure

Source: Pfisterer M, et al. BNP-guided vs symptom-guided heart failure therapy. *JAMA* 2009;301:383-392.

For Americans aged 65 or older, congestive heart failure (CHF) remains the most common diagnosis for hospital admission. Despite advances in therapy, the outcome of CHF remains daunting, with 5-year mortality rates as high as many malignancies. Because brain natriuretic peptide (BNP) reflects left ventricular wall stress, it can be useful to assist in diagnosis of CHF. Additionally, some, but not all, clinical trials have suggested that intensification of therapy to achieve optimization of BNP is associated with improved outcomes. The Trial of Intensified vs Standard Medical Therapy in Elderly Patients with Congestive Heart Failure (TIME-CHF) was devised to provide a more definitive comparison between the success of treatment intensification based upon symptoms vs level of BNP.

Patients with CHF (n = 499) were randomized to BNP-directed management (titrate treatment until BNP < 400 ng/mL) vs symptomatic management (intensify treatment until NYHA class II symptoms or better). Follow-up for the primary endpoint—hospitalization-free survival—was 18 months.

The BNP group experienced more aldosterone antagonists use, as well as more frequent increases in dose and utilization of ACE inhibitors and ARBs. However, there was no difference in the primary endpoint. In subjects age < 75 years, there was a reduction in mortality favoring BNP-directed management; however, because this was a secondary endpoint and the primary endpoint did not achieve statistical significance, it must be considered exploratory, not established. BNP-guided intensification of treatment is no more effective than standard symptom-directed methods. ■

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Clopidogrel and CV Events: One Size Does NOT Fit All

Source: Simon T, et al. Genetic determinants of response to clopidogrel and cardiovascular events. *N Engl J Med* 2009;360:363-375.

Utilization of clopidogrel (CPG) in patients with acute coronary syndromes (ACS is well established. Similarly, long-term prophylaxis with CPG for secondary prevention of CV events is evidence-based: The CAPRIE trial indicated that CPG is marginally superior to aspirin for endpoint reduction, and the PROFESS trial demonstrated that ER-dipyridamole/aspirin (Aggrenox®) failed to meet the non-inferiority threshold when compared to CPG for stroke prevention.

Residual risk in persons receiving CPG remains substantial, suggesting that perhaps the efficacy of CPG is not universal; i.e., some subjects might metabolize CPG differently than others, leading to different levels of efficacy (or adverse effects).

The French Registry of Acute ST-Elevation and Non-ST-Elevation Myocardial Infarction (FAST-MI) study enrolled ACS patients on CPG, and studied the relationship of genetic variants that result in variations in absorption, activation, and biologic activity of CPG. Next, the relationship between these genetic variants and adverse outcomes (death, stroke, MI) were studied.

The most important genetic variant appeared to be at the P450 2C19 gene. Those with 2 loss-of-function 2C19 genes were almost 4 times as likely to have a CV event over the next year as those without. The P450 2C19 gene is utilized for metabolism of CPG to its active metabolite; lesser antiplatelet activity would be anticipated in persons with impaired P450 2C19 activity. These results support the findings of another trial in the same issue of *The New England Journal of Medicine* that identified increased CV risk in persons with reduced 2C19 P450 functionality. ■

Estrogen + Progesterone and Breast Cancer

Source: Chlebowski RT, et al. Breast cancer after use of estrogen plus progestin in postmenopausal women. *N Engl J Med* 2009;360:573-587.

The Women's Health Initiative (WHI) provided convincing evidence that the use of estrogen + progesterone (E+P) in postmenopausal women is associated with an increased risk of breast cancer (BrCa). The outcomes of this clinical trial motivated large numbers of women and their clinicians to rethink the risk-benefit balance of hormone therapy (HT), evoking a sea-change in prescribing habits.

Despite the acknowledged association between E+P and BrCa in WHI, a concomitant decline in use of mammography following the WHI news invited the possibility that post-WHI, less BrCa screening might have influenced the observed BrCa decline rather than simply less E+P use. To study this issue, WHI investigators evaluated two data sets: the original WHI population (n = 16,608 women without BrCa at baseline) and a second observational study population (n = 41,449 without BrCa at baseline). The observational study group did not receive advice about whether to use E+P, but were informed about the results of the interventional WHI when it became available. In the observational WHI population, more than 16,000 women were taking E+P at baseline.

Long-term follow-up of the observational WHI population showed an increased incidence of BrCa in women who had used E+P. BrCa incidence in this population declined subsequent to HT discontinuation. This suggests the possibility that some early breast cancers may regress or disappear if HT is stopped. The data did not, however, provide a meaningful association between lesser use of mammography and reduced BrCa. ■

PHARMACOLOGY WATCH

Supplement to *Clinical Cardiology Alert*, *Clinical Oncology Alert*, *Critical Care Alert*, *Infectious Disease Alert*, *Internal Medicine Alert*, *Neurology Alert*, *OB/GYN Clinical Alert*, *Primary Care Reports*, *Travel Medicine Advisor*.

Warfarin May Be First to Apply Pharmacogenetics

In this issue: Individualization of therapy with pharmacogenetics; the rate vs rhythm debate; the FDA's Risk Evaluation and Mitigation Strategy; FDA actions.

Individualization with pharmacogenetics

Get used to the word "pharmacogenetics" — the discipline of studying genetic variation and its effect on responses to drugs. Warfarin dosing may be one of the first clinical applications of pharmacogenetics as it now appears that genetic testing may help predict an individual patient's response to the oral anticoagulant. Warfarin dosing can vary as much as 10 times from individual to individual, and currently, slow titration with frequent testing is the only way to safely initiate therapy. A new study, however, uses pharmacogenetic testing to estimate the appropriate warfarin dose. Reviewing data from more than 4000 patients, algorithms were developed based on clinical variables only or clinical variables plus genetic information (CYP2C9 and VKORC1). Compared to algorithms employing clinical data alone, algorithms employing genetic information more accurately identified a larger proportion of patients who would require low-dose (49.4% vs 33.3%; $P < 0.001$) or high-dose warfarin (24.8% vs 7.2%; $P < 0.001$). The authors conclude that pharmacogenetic algorithms for estimating the appropriate initial dose of warfarin produces recommendations that are significantly closer to the required stable therapeutic dose than algorithms derived from clinical data alone or a fixed-dose approach, particularly for those that require 49 mg or more per week or 21 mg or less per week. (*N Engl J Med* 2009;360:753-764). Although pharmacogenetic testing is not yet widely available and may be difficult to obtain prior to initiating warfarin therapy, an accompanying editorial states "pharmacogenetics has the potential to increase benefit and reduce harm in people whose drug responses are not 'average.'" (*N Engl J Med* 2009;360:811-813).

The rate vs rhythm debate

Rate control vs rhythm control for atrial fibrillation continues to be debated with most of the evidence falling on the side of rate control in recent years, primarily because of adverse effects from anti-arrhythmics. A new drug may change that however. Dronedarone, a derivative of amiodarone, lowers the hospitalization rate and death rate in atrial fibrillation according to a new phase 3 study. More than 4600 patients with atrial fibrillation and one additional risk factor for death (diabetes, stroke, CHF) were randomized to dronedarone 4 mg twice a day or placebo. The primary outcome was first hospitalization due to cardiovascular event or death. After follow-up of 21 months, 30% of patients in the treatment group and 31% patients in the placebo group stopped the drug prematurely due to adverse events. The primary outcome occurred in 31.9% of patients in the dronedarone group vs 39.4% in the placebo group (hazard ratio, 0.76; 95% confidence interval,

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0.69-0.84; $P < 0.001$). Five percent (5%) of people died in the treatment group vs 6% in the placebo group ($P = 0.18$). Deaths from cardiovascular causes were 2.7% in the dronedarone group vs 3.9% in the placebo group ($P = 0.03$). The treatment group had higher rates of bradycardia, QT interval prolongation, nausea, diarrhea, rash, and increased creatinine levels. Dronedarone was not associated with higher rates of thyroid or pulmonary-related adverse events. The authors conclude that dronedarone reduced the risk of hospitalization due to cardiovascular events or death in patients with atrial fibrillation (*N Engl J Med* 2009;360:668-678). Dronedarone is not yet approved in this country, and is being evaluated for other cardiac arrhythmias as well as atrial fibrillation. A trial in heart failure (ANDROMEDA) was terminated early because of increased mortality associated with dronedarone (*N Engl J Med* 2008;358:2678-2687).

New rules for opioid prescribing

The FDA is considering new tightened restrictions on use of opioid drugs. Manufacturers of these drugs will be required to have a Risk Evaluation and Mitigation Strategy to ensure that "the benefits of the drugs continue to outweigh the risks." The affected opioids include fentanyl, hydromorphone, methadone, morphine, oxycodone, and oxymorphone. This is in response to raising rates of misuse and abuse of these drugs as well as accidental overdoses, which have increased in the last 10 years. The agency plans to have a number of meetings later this year that will include patient groups, federal agencies, and other non-government institutions. Part of the strategy is to make sure that physicians prescribing these products are properly trained in their safe use.

In February, the American Pain Society-American Academy of Pain Medicine Opioids Guidelines Panel published clinical guidelines for the use of chronic opioid therapy and chronic noncancer pain. The guideline was commissioned because of the increased use of chronic opioid therapy for noncancer pain and the high risk for potentially serious harm associated with these drugs including opioid-related adverse effects. The guideline's recommendations include: Before initiating chronic opioid therapy (COT), clinicians should conduct a history, physical, and appropriate testing including assessment of risk for substance abuse, misuse, or addiction. A benefit-to-harm evaluation should be performed and documented before starting COT and on an ongoing basis for all patients on COT. Informed consent should be obtained when initiating therapy, and a continuing discussion with the patient regarding therapy should include goals, expectations, risks, and alternatives. Clinicians may consider a written COT management plan. Patients should be reassessed periodically including monitoring of pain intensity and levels of functioning.

For high-risk patients or those who have engaged in aberrant drug-related behaviors, clinicians should periodically obtain urine drug screens or other information to confirm adherence to the plan of care. For patients at risk of addiction, mental health or addiction specialists should be consulted, and if aberrant drug-related behaviors continue, referral for assistance in management or discontinuation of COT should be considered. The guideline also deals with dose escalations, use of methadone, treatment of opioid-associated adverse effects, cognitive impairment associated with COT that may affect driving and workplace safety, use in pregnancy, and state and federal laws that govern the medical use of COT (*J Pain* 2009;10:113-130).

FDA Actions

The FDA has issued a public health advisory regarding the risk of progressive multifocal leukoencephalopathy (PML) associated with use of efalizumab (Raptiva®) for the treatment of psoriasis. Four cases have been reported (3 have been confirmed). The FDA is recommending that health care professionals monitor patients on efalizumab, as well as those who have discontinued the drug, for signs and symptoms of neurologic disease.

The FDA has reaffirmed its position regarding cholesterol-lowering drugs stating that "elevated amounts of low-density lipoprotein … are a risk factor for cardiovascular diseases … and that lowering LDL cholesterol reduces the risk of these diseases." The statement is in response to results from the ENHANCE trial, which indicated that there was no significant difference between simvastatin plus ezetimibe (Vytorin®) vs simvastatin alone (Zocor®) in reducing carotid atherosclerosis. There was, however, a greater reduction in LDL in the Vytorin group vs the Zocor group (56% reduction vs 39% reduction, respectively). The statement from the FDA suggests that the results of ENHANCE do not change the FDA's position that greater LDL lowering is beneficial, and recommends that patients currently on Vytorin or other cholesterol-lowering medications should not change their therapy. The update is available on the FDA's web site at www.FDA.gov. ■