



Recognizing and treating new and emerging infections encountered in everyday practice

STEVEN M. GORDON, MD

SUMMARY Although infectious diseases were once considered a diminishing threat, new pathogens are constantly challenging the health care system. This article reviews the clinical presentation, diagnosis, and treatment of seven emerging infections that primary care physicians are likely to encounter.

KEY POINTS Parvovirus B19 attacks erythrocyte precursors; infection is usually benign and self-limiting but can cause aplastic crises in patients with chronic hemolytic disorders. ■ Hemorrhagic colitis due to *Escherichia coli* O157:H7 infection can lead to the hemolytic-uremic syndrome, especially in children; it also can cause thrombotic thrombocytopenia purpura. ■ *Chlamydia pneumoniae* causes a mild pneumonia that resembles mycoplasmal pneumonia. ■ Bacillary angiomatosis primarily affects immunocompromised patients, especially those infected with human immunodeficiency virus (HIV). At least two organisms can cause bacillary angiomatosis: *Bartonella henselae* and *Bartonella quintana*. ■ Hantavirus pulmonary syndrome is spread by exposure to the droppings of infected rodents. ■ Contrary to previous thought, HIV continues to replicate throughout the course of the illness and does not have a latency phase. ■ Ehrlichiosis is a tick-borne disease that resembles Rocky Mountain spotted fever.

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From the Department of Infectious Diseases, The Cleveland Clinic Foundation.

Address reprint requests to S.M.G., Department of Infectious Diseases, Desk S-32, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195. E-mail address: gordons@cesmtp.ccf.org

INFECTIONOUS DISEASES, predicted earlier in this century to be eliminated as a public health problem, remain the chief cause of death worldwide and a significant cause of death and morbidity in the United States.¹ Challenging the US public health system are several newly identified pathogens (eg, human immunodeficiency virus [HIV], *Escherichia coli* O157:H7, hepatitis C) and a resurgence of old diseases presumed to be under control (eg, tuberculosis, syphilis). Further, multiple-drug resistance in strains of pneumococci, gonococci, enterococci, staphylococci, salmonella, and mycobacteria undermines efforts to control the diseases they cause.² This paper gives an overview of some old and new emerging infectious diseases of significance to primary care clinicians.

WHAT IS AN 'EMERGING' INFECTION?

Emerging infections either have newly appeared or are rap-

idly increasing in incidence or geographic range. Recent examples include outbreaks of plague in Surat, India and of Ebola virus infection in Zaire.

Most emerging infections are not caused by genuinely new pathogens. Complex ecological, environmental, and demographic factors precipitate the emergence of disease by placing nonimmune people in increased contact with a pathogen or its natural host or by promoting dissemination. The current volume, speed, and reach of international travel make the emergence of infectious diseases truly a global problem.

PARVOVIRUS B19

Parvovirus B19, a single-stranded DNA virus, was discovered serendipitously in 1975 by electron microscopy during a study of transfusion-associated hepatitis. It is the smallest DNA virus known to infect mammalian cells, measuring approximately 25 nm (by comparison, Herpes virus measures 160 nm, HIV 225 nm). Parvovirus B19 replicates only in human erythroid progenitor cells, and has been propagated in the laboratory in bone marrow, peripheral blood, fetal liver cells, and a few hematopoietic cell lines with erythroid characteristics. The virus is heat-stable and can be transmitted via blood products.

Parvovirus B19 is the only parvovirus known to infect humans, and causes a wide spectrum of illnesses (see below).³

Erythema infectiosum (fifth disease)

This illness has been recognized since the late 19th century, when communicable diseases that cause rashes were classified using a numbering system (1, measles; 2, scarlet fever; 3, rubella; 4, Duke's disease or epidemic pseudoscarlatina; 5, erythema infectiosum; and 6, roseola)—hence the name “fifth disease.” Erythema infectiosum is usually a mild childhood illness characterized by a facial rash (called “slapped-face disease” because it features reddened cheeks) and a lace-like rash on the trunk and extremities. The rash may recur after exposure to nonspecific stimuli such as temperature changes, sunlight, and emotional stress. Usually, the patient is otherwise well when the rash appears but reports mild systemic symptoms that began 1 to 4 days previously. The symptoms are usually self-limiting but may persist for several months.

Polyarthralgia syndrome

Arthritic symptoms, which are more common in adults, may be the sole manifestation of parvovirus B19 infection. Rubella and parvovirus B19 infection cause similar clinical syndromes in young women, but now that the incidence of rubella is decreasing and rubella vaccines have been modified to eliminate arthritis-causing strains, parvovirus arthropathy may be more common. Adults seldom have the typical slapped-cheek appearance, and only 50% have a rash. Within several days after infection a symmetrical, self-limiting polyarthritis suddenly appears that most often affects the hands. Like other viral arthritides, parvovirus arthritis is thought to be immune-mediated.

Aplastic crisis in patients with hemolytic disorders

Parvovirus B19 preferentially parasitizes erythroid precursors in the bone marrow, transiently suppressing production of red blood cells. This suppression usually does not decrease the hematocrit in healthy people, as the infection is self-limiting and brief. However, in patients with chronic hemolytic disorders (eg, thalassemia, sickle cell anemia), who depend on a high rate of production of erythrocytes, or in patients with chronic immunosuppression (eg, in patients with HIV infection), parvovirus B19 infection may result in acute aplastic anemia.⁴

Parvovirus infection in pregnancy

Parvovirus B19 can cross the placenta and infect the fetus, leading to hydrops fetalis and, sometimes, fetal loss. Because of the considerable (and understandable) public concern, it is important to counsel pregnant patients that the risk to the fetus is relatively low, as the illness is usually self-limiting in immunocompetent patients. There is currently no recommendation to routinely screen pregnant women for parvovirus B19 infection. Parvovirus infection is *not* an indication for therapeutic termination of pregnancy. The American Association of Pediatricians does recommend that pregnant health care workers avoid caring for patients at high risk for active parvovirus B19 infections (patients admitted to the hospital with aplastic anemia or known parvovirus B19 infections).

Diagnosis

Unlike most viruses, parvovirus B19 infects one highly differentiated cell type, the human erythro-

progenitor. The P antigen, a cellular receptor on the erythrocyte, has recently been identified as the parvovirus B19 virus receptor.⁵ Persons without the P antigen are naturally resistant to parvovirus B19 infection.⁶ Of note, parvovirus B19 may also infect endothelial cells. This ability may allow transfusion through the placenta and also may contribute to the facial rash of fifth disease.

Parvovirus B19 infection can be diagnosed by isolating the virus's DNA from peripheral white blood cells (using polymerase chain reaction [PCR] technology) or by serologic testing for specific IgG or IgM (using radioimmunoassay and enzyme immunoassay based on the antibody capture principle with solid-phase polystyrene beads). In a patient with anemia and a low reticulocyte count, the presence of a giant pronormoblast in a bone marrow aspirate is very suggestive of parvovirus B19 infection.

Treatment

Immunoglobulin has been used to treat aplastic anemia caused by parvovirus B19 infection in immunocompromised patients.

E COLI O157:H7

E coli O157:H7 is a gram-negative bacterium first identified as a pathogen in 1982 during an outbreak of severe bloody diarrhea traced to contaminated hamburgers.⁷ In January 1993 a large outbreak affected 700 persons who ate undercooked hamburgers served in restaurants in the Puget Sound area in Washington.

Bacteriology of *E coli O157:H7*

The letters and numbers O157:H7 identify certain antigens found on the surface of *E coli* similar to those found on salmonellae. Three types of antigens—O, K, and H—are useful in classifying *E coli*. The O antigens are somatic, located on the lipopolysaccharide cell wall. The K antigens are located on the polysaccharide capsule and are heat-stable. The H antigens are located on the flagella and are heat-labile. Thus, *E coli O157:H7* has an O antigen of serotype 157 and an H antigen of serotype 7.

This strain differs from other strains of *E coli* by not fermenting sorbitol in less than 24 hours and by not producing a beta-glucuronidase. It does not grow well or at all at 44°C to 45°C and does not have any unusual heat resistance.

E coli O157:H7 is a verotoxigenic *E coli* (VTEC). Verotoxins cause diarrhea and are similar to the Shiga toxin produced by *Shigella* in classic dysentery. Because the clinical signs of *E coli O157:H7* infection involve hemorrhagic colitis, the organism is also referred to as an enterohemorrhagic *E coli* (EHEC). Of note, according to an ongoing study from the Centers for Disease Control and Prevention (CDC), *E coli O157:H7* causes more cases of bloody diarrhea in the United States than *Shigella* does, accounting for 8% of them.⁸ However, although more attention has been focused on *E coli O157:H7*, *Shigella dysenteriae* is likely the most common cause of the hemolytic-uremic syndrome in children worldwide.

Clinical presentation

E coli O157:H7 infection causes abdominal pain and watery diarrhea, followed within a few days by bloody diarrhea (hence the name "hemorrhagic colitis"). The bloody diarrhea corresponds to the dysentery phase of shigellosis, although *E coli O157:H7* does not cause true dysentery because it does not invade enterocytes. Sequelae include both the hemolytic-uremic syndrome and thrombotic thrombocytopenia purpura.

The organism is particularly pathogenic for children, and about 5% of the children who contract diarrhea from this organism also experience the hemolytic-uremic syndrome as a complication. Those who survive may suffer permanent renal damage and chronic renal insufficiency.

Diagnosis

E coli O157:H7 can be isolated only during the acute phase of the illness and may not be detectable 5 to 7 days after the onset. Screening requires culture in sorbitol MacConkey (SMAC) medium, in which *E coli O157:H7*, which does not ferment sorbitol, forms white colonies. In 1993, the Council of State and Territorial Epidemiologists recommended that clinical laboratories culture all bloody stools, and optimally all diarrheal stools, for *E coli O157:H7*. The Cleveland Clinic's clinical microbiology laboratory performs this screening with all stool cultures.

Prevention

Investigations of outbreaks have linked most cases with consumption of undercooked ground beef, although other foods, including roast beef, raw

milk, salami, water, and apple cider have been implicated. Federal guidelines require commercially prepared meat to be cooked to an internal temperature of 140°F just before it is removed from the grill.

Treatment

Antibiotics have no effect on the course of the bloody diarrhea or on the sequelae of *E coli* O157:H7 infection. There is some evidence suggesting that patients with hemolytic-uremic syndrome do worse when treated with antibiotics.⁸

CHLAMYDIA PNEUMONIAE TWAR STRAIN

C pneumoniae has now been established as a third species of *Chlamydia* (along with *Chlamydia trachomatis* and *Chlamydia psittaci*) on the basis of DNA, immunologic, and ultrastructural studies.⁹ Only one strain, Taiwan acute respiratory agent (TWAR), has been identified, first isolated in 1965 from the eye of a Taiwanese child and in 1983 from a college student with pharyngitis.

Because *C pneumoniae* is difficult and perhaps even hazardous to isolate, a TWAR-specific monoclonal antibody microimmunofluorescent test has played a key role in defining the epidemiology of *C pneumoniae* infection. The test can differentiate between IgM and IgG antibodies; the former is usually lost 2 to 6 months after infection, but IgG antibody persists. The seroprevalence rates are low in children and increase with age.

Several studies have linked TWAR with acute respiratory diseases, including pneumonia, bronchitis, pharyngitis, and sinusitis. During a 5-year period at the University of Washington Student Health Center, *C pneumoniae* infection was diagnosed in 22 students and accounted for almost 10% of all diagnosed pneumonias and 20% of radiographically-proven pneumonias. Two studies of community-acquired pneumonia in Canada and Pittsburgh demonstrated TWAR antibodies in 6% of 660 patients, making TWAR the third or fourth most common recognized cause of pneumonia in these studies. Pathologic studies of uncomplicated TWAR pneumonia are limited because the illness is usually not fatal.

Clinical presentation

TWAR causes a variety of relatively mild respiratory infections that lack any distinctive clinical presentation; most common to date has been pneu-

monia. Rales are almost invariably present, but signs of consolidation are less common. Chest radiographic films usually reveal a single pneumonic infiltrate of modest size. At present, microbiologic studies are of little help in establishing the diagnosis.

Diagnosis

TWAR-specific antibody tests are the easiest way to confirm a diagnosis. Because the clinical syndrome of pneumonitis caused by TWAR is not distinctive, TWAR is included among an array of pathogens in the differential diagnosis of mild pneumonia in young adults. The most common pathogen producing a similar illness is *Mycoplasma pneumoniae*.

Treatment

No studies of antibiotic therapy for TWAR infections have been performed, but limited clinical experience suggests that erythromycin may not be adequate. Based upon experience with other chlamydial infections, tetracycline at 2 g/day for 10 to 14 days is suggested.

BACILLARY ANGIOMATOSIS AND OTHER BARTONELLA-ASSOCIATED DISEASES

Bacillary angiomatosis is a newly recognized infectious disease primarily affecting immunocompromised patients, especially those infected with HIV.¹⁰

Clinical presentation

Bacillary angiomatosis derives its name from the vascular proliferation seen on histologic examination of affected tissues (including the skin, bone, liver, spleen, and brain) and from the presence of bacillary organisms on silver-stain or electron microscopy. The incidence of infection is unknown. This disease is probably a zoonosis associated with exposure to cats (or to fleas on the cats). The most commonly described cutaneous lesions are nodular "raspberry-like" tender papules or subcutaneous nodules that occasionally resemble Kaposi's sarcoma.

Recent molecular microbiologic investigations have confirmed that at least two organisms can cause bacillary angiomatosis: *Bartonella* (formerly *Rochalimaea*) *henselae* and *Bartonella quintana* (the louse-born agent of trench fever). Other clinical manifestations associated with these organisms include bacillary peliosis or hepatitis, relapsing fever

with bacteremia, infective endocarditis, and cat-scratch disease.

Researchers are gaining a greater understanding of the epidemiology and natural history of opportunistic infections caused by *Bartonella*. Recent reports of *B quintana* bloodstream infections and infective endocarditis in HIV-negative, alcoholic, homeless men emphasize the need for heightened clinical awareness as well as for increased surveillance to detect and characterize these fastidious pathogens.^{11–13}

Diagnosis

The differential diagnosis of subcutaneous and cutaneous lesions in HIV-infected patients is broad and includes a variety of disseminated opportunistic infections as well as neoplastic and dermatologic conditions. The differential diagnosis of cutaneous vascular lesions includes pyoderma gangrenosum, Kaposi's sarcoma, verruga peruana (a late manifestation of infection with *Bartonella bacilliformis*), and bacillary angiomatosis.

The presence of bacillary organisms on Warthin-Starry staining suggests the diagnosis of bacillary angiomatosis, but a definitive diagnosis requires the demonstration of the organisms in tissue or culture. *Bartonella* is a small, curved, gram-negative rod that grows best in 5% carbon dioxide with high humidity on solid tryptic soy agar containing rabbit blood. Isolator-lysis tubes and a prolonged incubation time (up to 6 weeks) are necessary to isolate it from blood.¹¹

Treatment

Excellent clinical responses of bacillary angiomatosis to erythromycin, rifampin, doxycycline, quinolones, and gentamicin have been reported. Some strains have beta-lactamase activity.

Cat-scratch disease and bacillary angiomatosis: a common connection

Both *Afipia felis* and *Bartonella* species have been isolated in cases of cat-scratch disease. An indirect fluorescent antibody test for *B henselae*, developed at the CDC, has advanced our understanding of the epidemiology of this disease. In a recent study in Connecticut, 94% of 60 patients with cat-scratch disease had positive serologic tests, compared with 4% of age-matched, cat-owning control patients.¹⁴ In addition, *B henselae* has been isolated from the lymph nodes of patients with cat-scratch disease as well as from blood and fleas from cats suspected of transmitting it. Thus, cat-scratch disease and bacil-

lary angiomatosis appear to be different manifestations of the same infection. The causative organism in most cases appears to be *Bartonella* species. The serologic test is now commercially available.¹⁰

HANTAVIRUS PULMONARY SYNDROME

Hantavirus infection—"an old virus with a newly recognized clinical illness"—has recently been recognized to occur in the United States.¹⁵ Classically, *Hantavirus* infection, in its most severe form, causes hemorrhagic fever with renal syndrome, which is associated with hypotension and shock. A milder form, without shock and hypotension, is called nephropathia epidemica. The severe form is endemic in Eurasia and Scandinavia, and outbreaks have been associated with increased exposure to rodents, the suspected reservoir, which for prolonged periods excrete the virus in their saliva, urine, and feces.

Clinical presentation

In the recent outbreak of *Hantavirus* pulmonary syndrome in the four-corner area of the United States, (Arizona, Colorado, New Mexico, and Utah), at least 28 people died. Additional cases have now been confirmed in California, Texas, Louisiana, and New York. Unlike the European and Asian manifestations of *Hantavirus*, the US cases are characterized by shock and pulmonary involvement. Most patients presented with adult respiratory distress syndrome after a flu-like prodromal illness.

The reservoir appears to be deer mice, and transmission is presumably via aerosolization of infected droppings, although ingestion of contaminated food or a direct bite or scratch are also possible means of transmission.¹⁶ To date, there has been no evidence of person-to-person transmission.

Diagnosis

Hantaviruses are in the *Bunyaviridae* family and are about 100 nm in diameter. They have a lipid envelope, which makes them susceptible to alcohol and other lipid solvents.

The differential diagnosis of *Hantavirus* pulmonary syndrome is broad and includes all causes of the acute respiratory distress syndrome. The geographic location and the history of rodent exposure should suggest the possibility of *Hantavirus* infection. A diagnosis of *Hantavirus* pulmonary syndrome may be made from serologic studies, with an elevated IgM titer or seroconversion; a positive immunohisto-

chemical stain of formalin-fixed lung tissue; or PCR amplification of *Hantavirus* nucleotide sequences from frozen tissue.

Prevention

To prevent spread of the disease, efforts should be made to minimize exposure to rodents. For instance, campers should avoid exposure by using tents that are elevated and that can be closed with zippers.

Treatment

Ribavirin has been used to treat *Hantavirus* infection, but its efficacy is not proven.¹⁷

PRIMARY HIV INFECTION

Primary HIV infection causes significant and progressive immunologic and virologic changes in the host. Recent studies that measured the viral burden of patients who had acute HIV infections (ie, who had recently become HIV-positive) have enhanced our understanding of the natural history of HIV infection.^{18,19} Before antibodies to HIV antigens (eg, p24) develop, high levels of infectious virus are briefly detectable in the cerebrospinal fluid, peripheral blood mononuclear cells, and plasma. Thereafter, the levels of p24 core antigen and HIV rapidly and spontaneously decline, antiviral antibodies and the CD4 count increase, and symptoms resolve, all suggesting an "effective" initial immune response. However, this apparent clearance of virus and the restoration of the CD4 cell count becomes less effective over time. These phenomena were believed to be accompanied by viral latency, with little or no viral replication until late in the course of infection. However, we now know that viral replication persists throughout all phases of HIV disease.²⁰

Clinical presentation

More than half of patients with primary HIV infection have an acute symptomatic illness. Common signs and symptoms are fever, adenopathy, pharyngitis, and a rash. As many as 70% of patients with primary HIV infection experience dermatologic signs. There is commonly an erythematous, nonpruritic, macular-papular eruption on the face, neck, or upper trunk. Aphthous-like ulcers with surrounding erythema may be observed on mucous membranes.

Diagnosis

More than 80% of patients with symptomatic primary HIV infection have symptoms of mononucleosis; therefore, primary HIV infection is in the differential diagnosis of "monospot-negative mononucleosis" (along with cytomegalovirus, toxoplasmosis, Epstein-Barr virus, human herpes virus 6, and syphilis infections). A diagnosis of primary HIV infection during the period of acute infection (ie, before the development of HIV antibodies) is made by a test of serum HIV antigen p24. HIV cultures from peripheral blood mononuclear cells may also be positive.

Treatment

In view of recent reports of primary infection with zidovudine (AZT)-resistant HIV strains, it is unclear at this time when to start antiretroviral therapy for primary HIV infection.

EHRLICHIOSIS

Ehrlichia species are tick-borne rickettsial organisms that infect the leukocytes of susceptible mammals. *Ehrlichia canis* causes an illness of dogs characterized by fever, weight loss, bleeding, and pancytopenia. In 1987 the first case of human ehrlichiosis in the western hemisphere was reported: an Arkansas man presented with fever, disorientation, pancytopenia, and a history of a tick bite. Rickettsia-like organisms were observed in inclusion bodies among circulating leukocytes, and serologic study results were positive for *E canis*. Subsequently, investigators determined that *Ehrlichia chaffeensis*, closely related but not identical to *E canis*, is the sole causative agent of human ehrlichiosis in the United States. About 250 cases of human ehrlichiosis have subsequently been reported in the United States, mostly in the South Central and South Atlantic states, particularly Oklahoma, Missouri, and Georgia.^{21,22}

Of note, a novel species of *Ehrlichia* that causes human disease (*Ehrlichia phagocytophila*) has recently been described among 12 patients in the upper Midwest. This disease has been termed "human granulocytic ehrlichiosis," because unlike *E chaffeensis*, *E phagocytophila* has morulae that appear in the cytoplasm of neutrophils (granulocytes) but not in mononuclear white blood cells.²³

Clinical presentation

The most characteristic features of ehrlichiosis are high fever and headache. Other common features include malaise, nausea, and vomiting. Approximately 90% of patients have a history of a tick bite or exposure within the preceding 3 weeks. After an incubation period of 7 days, ehrlichiosis presents as a nonspecific febrile illness that resembles Rocky Mountain spotted fever. Both are diseases of the outdoors, with the highest incidence in May, June, and July. However, there are some epidemiologic differences between the two diseases. A rash develops in only approximately 20% of patients with ehrlichiosis, vs 80% of patients with Rocky Mountain spotted fever; when observed in ehrlichiosis, the rash usually does not involve the soles and the palms. Thrombocytopenia is common in both diseases, but neutropenia with an absolute lymphopenia is more common in ehrlichiosis than in Rocky Mountain spotted fever.

Diagnosis

A summertime flu-like illness following a tick bite should immediately raise one's clinical suspicion of tick-borne infections with bacteria, Rickettsiae, viruses, and protozoa.²⁴ In areas in which ehrlichiosis is known to have occurred, thrombocytopenia, lymphopenia, absence of a rash, negative serologic tests for Rocky Mountain spotted fever, and a clinical response to tetracycline suggest ehrlichiosis; a positive serologic test for ehrlichiosis confirms the diagnosis. The CDC now uses an indirect fluorescent antibody against *E. chaffeensis* for their assay. A single titer of 1:64 or a fourfold rise or fall is diagnostic. For human granulocytic ehrlichiosis, an antibody titer of 1:80 or greater for *E. phagocytophila* suggests infection.

Treatment

Most cases are self-limiting, although one fatal case of seronegative ehrlichiosis in an Arkansas woman with AIDS was recently reported.

The treatment of choice is tetracycline or chloramphenicol for 5 to 7 days.

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