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Fever of Unknown Origin Due to Zoonoses

Dennis J. Cleri, MD[a,b,*], Anthony J. Ricketti, MD[a,b], John R. Vernaleo, MD[c]

[a]Department of Medicine, St. Francis Medical Center, Room B-158,
601 Hamilton Avenue, Trenton, NJ 08629-1986, USA
[b]Seton Hall University, School of Graduate Medical Education, South Orange,
NJ 07079, USA
[c]Division of Infectious Diseases, Wyckoff Heights Medical Center,
374 Stockholm Street, Brooklyn, NY 11237, USA

When you have eliminated the impossible, whatever remains, however improbable, must be the truth.–Sherlock Holmes in the "The Adventure of the Blanched Soldier" from Sir Arthur Ignatius Conan Doyle's, "The Case-Book of Sherlock Holmes" first published in *Liberty* October 1926, and the *Strand Magazine,* London, November 1926.

There are 1407 species of human pathogens (excluding ectoparasites); more than half (816) are zoonotic, associated with 132 animal species. Of these, 73% (130) are zoonoses [1]. Having such a long list of suspects, coconspirators, and accomplices makes the diagnosis of zoonotic fever of unknown origin (FUO) a daunting task.

Approach to the patient with a possible zoonotic fever of unknown origin

Look, and you will find it –what is unsought will go undetected.
–Sophocles, Greek tragic poet (c. 496–406 BC).

Mackowiak and Durack [2] classify FUOs into four categories: (1) classic, (2) nosocomial, (3) immunodeficient, and (4) HIV-related. Adding a fifth category, zoonotic FUO, necessitates combining their categories of the "classic," "immunodeficient," and "HIV-related" with the emphasis on accurate and detailed travel, dietary, and activity history.

* Corresponding author. Department of Medicine, St. Francis Medical Center, Room B-158, 601 Hamilton Avenue, Trenton, NJ 08629-1986.
E-mail address: dcleri@stfrancismedical.org (D.J. Cleri).

Zoonotic immunodeficiency viruses: simian immunodeficiency virus

HIV infection and AIDS are the penultimate zoonotic FUOs. HIV-1 and HIV-2 are cross-species lentivirus infections. One factor facilitating cross-species transmission is the adaptability of the simian immunodeficiency virus–HIV envelope protein [3].

There are more than 40 nonhuman primate species infected with specific simian immunodeficiency viruses [4]. Sixty million years of coevolution of simian foamy virus, the oldest genus of Retroviridae, rendered the virus nonpathogenic in primates. Asymptomatic human infection has been documented in 1.8% of 231 individuals to 5.3% of 187 individuals working in primate research centers or zoos. Sources of infection were identified as chimpanzees (*Pan troglodytes*) and African green monkeys [5].

Simian immunodeficiency virus has resulted in a chronic human infection [6]. Primate handlers and those who hunt and butcher "bushmeat" (the meat of wild animals that includes chimpanzees, monkeys, and the gorilla) have detectable humoral and cell-mediated immunity to simian immunodeficiency viruses. There are at least eight documented incidents of zoonotic transfer of simian immunodeficiency viruses to humans [7].

In the proper epidemiologic setting, serologic or virologic diagnosis of simian immunodeficiency viruses should be attempted in those patients with FUO without other apparent cause. If history repeats itself, clinicians will soon appreciate a clinical syndrome associated with such transmission.

Common zoonotic coinfections with HIV

Visceral leishmaniasis and HIV infection

Visceral leishmaniasis (VL) is caused by several species of *Leishmania* [8]. These *Leishmania* spp infect more than 2 million people yearly in tropical and subtropical regions of all continents except Australia [9–11]. VL reported in troops returning from Operation Desert Storm (1990–1991) and Afghanistan (2002–2004) has made clinicians aware of the diagnosis, and prompted the consideration of the threat to the transfusion blood supply and the re-evaluation of the US military blood donor deferral policies [9,10].

VL is an important FUO in HIV-AIDS patients [12]. HIV infection increases *Leishmania* spp replication and uptake in HIV-infected macrophages [13]. At the same time, *Leishmania* is an "enhancer of the progression of AIDS" [14].

Epidemiology and pathogenesis

Leishmania donovani is the agent for disease in India and East Africa; *L donovani* and *Leishmania infantum/chagasi* cause VL in the Mediterranean basin, the Middle East, central Asia, and western China; and *L infantum/*

chagasi is the predominant agent in Central and South America. Rare cases of VL are caused by *Leishmania amazonensis,* and *Leishmania tropica*, the agents of cutaneous leishmaniasis in Latin America, and the Middle East and India, respectively [8].

Humans and other mammalian hosts (canines, jackals, and rodents) harbor the leishmania amastigotes. The female sandfly (*Lutzomyia* sp, Western Hemisphere; *Phlebotomus* sp, Old World) is the vector [8]. An outbreak of canine VL was discovered in a Dutchess County, New York, kennel among 41% of the foxhounds tested [15]. Another survey of over 12,000 foxhounds and other canines, and 185 persons in 35 states and four Canadian provinces, found no human infection, but widespread infection among foxhounds. VL seemed to be limited to dog-to-dog transmission, but human infection is possible if the parasite becomes adapted to indigenous phlebotomus [16].

Clinical presentation

In the non–HIV-infected host, most disease is asymptomatic and self-limited. Some develop mild symptoms that resolve. The minority of patients develop VL (kala-azar) characterized by fever, weight loss, hepatosplenomegaly, neutropenia, and hypergammaglobulinemia. Malnutrition, wasting, and debilitation secondary to excess cytokine production occur as the disease progresses. Patients develop ulcers around the mouth, edema, petechiae, ecchymosis, gingival bleeding, and hepatitis, which may become fulminant [8]. VL patients may present with diarrhea. Patients exhibit marked hypergammaglobulinemia, anemia, neutropenia, thrombocytopenia, elevated bilirubin, liver enzymes, circulating immune complexes, high erythrocyte sedimentation, and rheumatoid factor [8].

Clinical progression of VL is related to host genetics, cell-mediated immune response, malnutrition, and immune suppression. VL has been associated with acquired hypogammaglobulinemia secondary to carbamazepine therapy, HIV disease, transplantation, neoplastic diseases, steroid therapy, and treatment with infliximab for rheumatoid arthritis [17–20]. Incubation periods range from 10 days to months. The onset of disease may be gradual or abrupt. Clinical disease may present itself only after immune suppression [8].

In patients coinfected with HIV, most present as previously mentioned. Fever is present in only half of the patients and splenomegaly may be absent [8,11]. Patients may present with acute abdominal pain and aplastic anemia. Many organs may be infected with amastigotes (lung, pleura, pericardium, larynx, oral mucosa, bone marrow, esophagus, stomach, small intestine, and skin) [8,21–23]. Bronchoalveolar adenoma and bronchiolitis obliterans have been reported [22]. Some HIV-infected patients may be asymptomatic, whereas others infected with *Leishmania braziliensis* (the common cause of cutaneous disease) may disseminate [8,24].

Atypical disseminated leishmaniasis and VL may present with polyarthritis and unusual or disseminated skin manifestations. In HIV patients, it may be mistaken for post–kala-azar dermal disease [25,26]. Fulminant eye

disease and hypothyroidism are unusual complications [27,28]. Patients coinfected with VL and HIV may experience a chronic relapsing course not responding to VL therapy. Renal failure from secondary amyloidosis may occur [29].

Central nervous system (CNS) involvement is rare. It results from contiguous extension from the paranasal sinuses. Complications include cranial nerve dysfunction (especially the optic nerve); meningitis; ascending demyelinating disease similar to Guillain-Barré syndrome localized to the peripheral nervous system; and painful peripheral neuropathies. Amastigotes have been detected in the cerebrospinal fluid (CSF) [30].

HIV-associated immune reconstitution disease has unmasked subclinical VL. Immune reconstitution disease VL manifests itself with fever and hepatosplenomegaly within 2 weeks to the initial months of beginning highly active antiretroviral therapy (HAART) therapy. Cutaneous, mucosal, and post–kala-azar dermal leishmaniasis, leishmanial uveitis, and deterioration of cutaneous and mucosal leishmaniasis have all been reported as a consequence of immune reconstitution disease [31].

Pediatric patients (mean age, 1.7 years) not infected with HIV all presented with fever and splenomegaly. Hepatomegaly was present in 90.1%; thrombocytopenia and anemia in 70.2%; and leukopenia in 42.3% [32]. Non–HIV-infected pregnant patients present with hepatosplenomegaly. Treatment of pregnant patients with amphotericin B (five patients) resulted in no treatment failures, no congenital VL, and no congenital abnormalities [33].

Laboratory diagnosis

Most commonly, the diagnosis is confirmed by identifying the amastigotes in Wright-Giemsa biopsy touch preparations or in special parasite cultures. Bone marrow biopsy is positive in 66% of AIDS patients and 87% of patients without AIDS. A urine latex agglutination test has been developed and serologic tests are available [8,34]. Polymerase chain reaction is highly sensitive and specific for diagnosis, speciation, and estimation of parasite load [8].

Differential diagnosis

The differential diagnosis includes tropical splenomegaly from chronic malaria, hepatosplenic schistosomiasis and Katayama fever, miliary tuberculosis, histoplasmosis, brucellosis, bacterial endocarditis, infectious mononucleosis, prolonged *Salmonella* spp bacteremia and typhoid fever, amebic liver abscess, acute Chagas' disease (CD), and other bacterial and viral infections [8].

Treatment

Treatments for VL include liposomal amphotericin B (treatment of choice in the United States); pentavalent antimonies (sodium stibogluconate, meglumine antimonate), where there is no resistance; azoles (ketoconazole,

fluconazole, itraconazole); paromomycin; and miltefosine [8]. HIV protease inhibitors (indinavir and saquinavir) display antileishmanial activity [35]. Patients with uncontrolled HIV replication or poor response to HAART have frequent VL relapses [36].

Conclusion

In the proper epidemiologic setting, VL is an important consideration as a cause of FUO because of (1) the highly variable incubation period; (2) in some patients, presentation only after immune suppression; (3) both acute and gradual onset of disease; (4) highly variable clinical presentations; and (5) the absence of typical clinical findings in a significant minority of patients. HIV patients have atypical presentations, and immune reconstitution disease may unmask the disease.

Chagas' disease

Epidemiology and pathogenesis

CD infects 18 million people exclusively in North and South America [11]. CD is caused by *Trypanosoma cruzi* [37]. *T cruzi* produces lifelong infections in humans and domestic, wild, and zoo animals in endemic areas (from the southern United States to Argentina). Ten percent to 30% of human infections become symptomatic.

CD is transmitted by reduviid (kissing bugs) triatomes (*Triatoma* spp, *Rhodnius* spp, and *Panstrongylus* spp) through infected feces [37]. Transfusion, organ transplantation, laboratory accident, congenital infection, tattooing, body piercing, and ingestion of food or drink contaminated with triatome insect feces have caused infection [37,38]. One case of fatal congenital disease involving an HIV-positive mother was associated with cervical CD [39].

Trypanosoma cruzi infection, even asymptomatic reactivation, markedly increases HIV viral loads [40].

Clinical manifestations

A red and indurated lesion at the parasite's entry site heralds acute disease. Romaña's sign (unilateral painless periorbital edema) is found when the entry site is the conjunctiva. With systemic spread, patients develop fever, malaise, facial and lower limb edema, hepatosplenomegaly, and lymphadenopathy. Complications of chronic disease include cardiac (cardiomegaly, left ventricular apical aneurysm, and mural thrombi); megaesophagus; dilatation and thickening of the colon (most often the sigmoid colon); parotid enlargement; and stomach and urinary tract involvement [37]. Sudden death has been associated with cardiac focal denervation, regional asynergy, compensatory adrenergic stimulus with myotoxicity, and malignant arrhythmia [37].

Trypanosoma cruzi may have a long silent course in HIV-infected patients or may present with acute congestive heart failure, skin lesions, spontaneous

peritonitis, and acute esophageal and gastric disease [37,41,42]. Reactivation of CD (now an AIDS-defining disease) in HIV patients most commonly manifests as meningoencephalitis [43]. In immunosuppressed and HIV patients, *T cruzi* brain abscesses have occurred and may be the initial presentation of AIDS [37,44].

Whereas CNS disease is rare in CD patients, HIV-CD patients commonly exhibit CNS disease (acute fatal meningoencephalitis, mass lesions, and granulomatous encephalitis) [11,43]. Cerebral toxoplasmosis and trypanosomiasis in HIV patients may coexist [45]. Neuroimaging reveals large solitary or multiple ring-enhancing lesions with edema [44]. These may be confused with cerebral toxoplasmosis, CNS primary lymphoma, or cerebral metastases [37,46].

Parasitemia is more frequent and intense in HIV patients. Erythema nodosum, acute meningoencephalitis with parasites detectable in the CSF, and acute myocarditis have been disease presentations in HIV patients [47].

Diagnosis

Diagnosis of disease and meningoencephalitis is made by direct observation of intracellular *T cruzi* and by PCR (of blood and CSF) [46,48]. Serologic tests may assist in the diagnosis [37,40]. Xenodiagnosis is made by examining uninfected laboratory triatomes (reduviid bugs) after feeding on patients or by blood culture [11,37].

Treatment

Nifurtimox or benznidazole are the treatments of choice [37]. Treatment of non-HIV patients without heart failure and nonacute disease with benznidazole resulted in reduced progression of diseases, and increased seronegative conversion [49]. Immune reconstitution with HAART and benznidazol has resulted in long-term (3-year) survival [50].

Conclusion

Fever is a sign of dissemination in acute disease. CD is transmittable by transfusion and transplantation, and known to reactivate late in the disease in HIV-infected patients. CD becomes a serious consideration as a cause of FUO in anyone even with a distant exposure history, especially in the immunocompromised or the HIV patient.

Schistosomiasis

Epidemiology and pathogenesis

Worldwide, 200 to 300 million people are infected with schistosomiasis. Eighty-five percent of those individuals live in sub-Saharan Africa, the area with the world's highest prevalence and total number of HIV-1–infected patients [51]. The disease is a zoonoses acquired in fresh water from free-living cercarial larvae that penetrate the skin. The adults lay

eggs during their 3- to 7-year life span. The eggs migrate to venous plexuses (mesenteric venous plexus: *Schistosoma mansoni*, *Schistosoma japonicum*, *Schistosoma mekongi*, *Schistosoma intercalatum*; bladder venous plexus: *Schistosoma haematobium*) and result in liver, intestinal, kidney, and bladder disease; anemia; and growth retardation in children [51].

Human *S mansoni* infections increase the progression of AIDS by enhancing the HIV replication rates, increase immune activation, enhance selective pressure for virulent variant strains, and impair cytolytic functions of T cells and other viral-specific responses [52]. Urinary tract and genital schistosomiasis increases the risk of HIV infection in women [53].

Clinical manifestations

The three stages of schistosomal disease are (1) dermatitis caused by penetration of the cercaria (swimmers itch); (2) acute febrile and systemic disease; and (3) chronic disease. Human schistosoma (*S mansoni* and *S haematobium*) cause a pruritic rash with red papules within 24 hours of exposure. The acute febrile disease with systemic symptoms begins 4 to 8 weeks later coinciding with migration and maturation of the schistosomulae. This is followed by chronic disease and complications: periportal fibrosis; portal hypertension; pulmonary hypertension; cor pulmonale; CNS complications (especially seizures); ulcer formation in the bowel wall with chronic bleeding; and urinary complications (bladder neck obstruction, hydroureter, hydronephrosis, and hematuria) [51].

HIV can cause recrudescence of long-dormant disease [54]. Immune reconstitution after HAART has resulted in *S mansoni*–associated enteritis with fever, vomiting, diarrhea, abdominal pain, and eosinophilia [55].

Diagnosis

Diagnosis is traditionally accomplished by identification of eggs in the stool and urine. Serologic tests include indirect hemagglutination assay and ELISA [51].

In the immunosuppressed patient with CNS complications, imaging reveals solitary or multiple hyperdense lesions in the brain or spinal cord and "arborized" enhancement on MRI with surrounding edema and granuloma [56].

Treatment

Praziquantel treatment (the drug of choice) results in similar responses in HIV-positive and HIV-negative patients (86% and 85%, respectively). Cure rates based on circulating antibodies were found to be 31% and 52%, respectively [57].

Conclusion

With hundreds of millions of people infected, schistosomiasis becomes an important cause of FUO. In the otherwise normal patient, fever appears

weeks to months after the initial exposure. Recrudescence is seen in HIV-infected patients. Fever and a constellation of symptoms are seen in immune reconstitution disease.

Cryptosporidiosis

Epidemiology and pathogenesis

Cryptosporidium hominis and others are the etiologic agents for cryptosporidiosis. The protozoan infects many mammals and birds [58].

The organism's lifecycle (both sexual [sporogony] and asexual [merogony]) is completed within a single host. In the normal host, the organisms are found in the microvillus layer of the epithelial cells in the distal small intestine and proximal colon. In immunocompromised patients, it may be found throughout the gastrointestinal tract, biliary tree, and the respiratory tract. Heavy infection and chronic infection in children results in villous atrophy, crypt hyperplasia, and inflammatory cell infiltration of the mucosa [58].

The organisms have a worldwide distribution. Waterborne outbreaks have infected many individuals and the organism is the cause of chronic diarrhea in AIDS and other immunocompromised patients. After hurricanes Katrina and Rita, *Cryptosporidium* spp were detected in the canals around New Orleans [59]. Infections after contact with animals, in daycare centers, and laboratory accidents have been reported. In the United States, the number of infections peaks between July and September [58].

Clinical manifestations

Asymptomatic carriage is not uncommon. The incubation period is usually 7 days (range, 1–30 days). In developing countries, it most commonly affects 5% to 10% of children. Ten percent to 15% of infected children develop persistent diarrhea that lasts more than 14 days (mean duration, 23.2 days). Breastfeeding makes no statistical difference in infection rates [60]. In developed countries and among travelers, adults are most often infected [58].

In all groups of patients, diarrhea (mucoid or watery) is the most common presentation. In immunocompetent patients, patients exhibit nausea, vomiting, and fever. Respiratory symptoms may accompany the illness. Symptoms last 5 to 10 days and diarrhea may recur days to weeks later [58,60].

In HIV patients, cryptosporidiosis is self-limited in those with more than 150 $CD4^+$ cells/mm^3, but relapses when the cell count falls. With more severe HIV, the disease may be mild, severe, chronic, and associated with extraintestinal disease (acalculous cholecystitis, sclerosing cholangitis, or pancreatitis) [58].

Diagnosis

Diagnosis may be made by biopsy, phase-contrast microscopy of stool wet mounts, and modified Ziehl-Neelsen stain of stool. Other methods

include ELISA antigen testing of stool, PCR, and immunofluorescence staining combined with flow cytometry [58].

Treatment

Treatment should include supportive therapy, HAART for AIDS patients, and immune restoration in immunocompromised patients when possible. Nitazoxanide is the preferred treatment, although it is probably not efficacious in HIV-positive patients. Paromomycin and macrolides (azithromycin, roxithromycin, and clarithromycin) have shown some efficacy [58], although in one study, spiramycin did not [61].

Conclusion

Because cryptosporidia are ubiquitous, fever and diarrhea with or without systemic symptoms should suggest the diagnosis. Symptoms may last for many days, and diarrhea may recur. HIV-compromised patients have prolonged courses sometimes with extraintestinal complications, obfuscating the diagnosis.

Selected zoonotic viral illnesses of interest

With the proper epidemiology, the diagnosis of avian influenza and severe acute respiratory syndrome (coronavirus) can be confirmed in due course. The viral hemorrhagic fevers (Arenaviridae, Bunyaviridae [including Hantavirus genus], Filoviridae [Ebola and Marburg viruses], and Flaviviridae [dengue and yellow fever]) have been reviewed [62].

Monkeypox

Epidemiology

Monkeypox virus along with variola virus are the two Orthopoxviridae that cause systemic disease along with their vesiculopustular rash [63]. Monkeypox, a zoonoses found naturally in the Congo Basin and West Africa, was introduced into North America in 2003, with the importation of infected African rodents. The virus was transmitted to prairie dogs, and subsequently to individuals handling these animals. Human-to-human spread was also documented [64,65].

Clinical manifestations

Patients without lesions may present as a true FUO; patients with few lesions may be confused with other pustular diseases; patients with many lesions may be confused with smallpox; and hemorrhagic lesions present a broader differential diagnosis. The incubation period (7–17 days), prodrome (1–4 days for monkeypox, 2–4 days for smallpox, and 0–2 days for chickenpox), and symptomatology for the three pox diseases all overlap [66]. Fever is the most common manifestation (90%–100%). Other symptoms include chills (70%–90%); lymphadenopathy (60%–90%); sweats (60%–90%); headache

(70%); muscle pain (60%–90%); sore throat (58%–70%); cough (55%); nausea and vomiting (20%–50%); back pain (30%–60%); runny nose (20%–40%); abdominal pain (15%); wheezing (10%); diarrhea (10%); and dyspnea (10%). About half the patients have less than 25 lesions (55%); 32.5% have 26 to 100 lesions; 5% have 101 to 249 lesions; and 7.5% have more than 250 lesions [63]. Exposure to the virus involving bites or scratches shortens the incubation period and increases the severity of illness [63].

Diagnosis

Although viral culture is the gold standard, PCR and microarray assay using species-specific oligonucleotide probes have been used successfully [66]. Lesions may be tested with immunohistochemical tests for orthopoxvirus antigens. PCR remains the most important modality for definitively differentiating monkeypox from other orthopoxviridae [66].

The differential diagnosis for monkeypox is the same for smallpox [67]. In endemic areas, coinfection with varicella-zoster virus has been reported [68].

Buffalopoxvirus outbreaks have been limited to individuals with direct animal contact. In 2004 and 2005, a nosocomial outbreak was reported in Karachi, Pakistan, placing this virus higher in the differential diagnosis for those patients with the proper epidemiology [69].

Treatment

There are no licensed therapies, although the smallpox vaccine may protect or ameliorate monkeypox infection [66].

Conclusion

Now that monkeypox has been introduced into North America, it must be part of the differential diagnosis of most if not all pustular-vesicular febrile diseases. It becomes an important consideration in FUO when it presents in the paucivesicular or hemorrhagic form.

Colorado tick fever (coltiviruses)

Epidemiology and pathogenesis

The agent of Colorado tick fever is one of three (double-stranded RNA) coltiviruses of the Reoviridae family transmitted to man by a tick bite. Most common hosts are the ground squirrel and hare, and smaller and larger mammals, especially deer and porcupines. The virus infects erythropoietic cell lines in the bone marrow and peripheral blood. Transfusions are documented risks for acquiring the infection. Infection from mother to child is suspected. Viremia persists for more than 4 weeks in 50% of patients, and is independent of the severity of the disease.

Clinical manifestations

Incubation periods average 3 to 4 days (range, <1–14 or 19 days). Symptoms include a sudden onset of fever, chills, headache, myalgias,

hyperesthesia, weakness, and prostration. One fifth of patients have gastro-intestinal complaints. Physical findings include infected conjunctivae and pharynx, and an enanthem. Some patients have minimum splenomegaly and lymphadenopathy. A maculopapular or petechial rash is seen in 15% of patients, which may be confused with Rocky Mountain spotted fever.

Resolution occurs in 1 week, but 50% of patients have recurrence of fever and symptoms 2 to 3 days later. Rarely, there is a third recurrence.

Complications

Five percent to 10% of patients have aseptic meningitis or encephalitis. Almost all cases of CNS disease occur in children under 10 years of age. Fatal cases have demonstrated encephalitis; hemorrhage; purpura; petechiae; disseminated intravascular coagulopathy; swollen endothelial cells in lymph node capillaries; hyaline membranes in alveoli; and focal necrosis of the liver, myocardium, spleen, intestines, and brain.

Coinfection with other tick-borne diseases, especially Rocky Mountain spotted fever, should be included in the differential diagnosis. The differential diagnosis includes hemorrhagic fever with renal syndrome (also endemic in Colorado tick fever endemic areas); hemorrhagic scarlet fever; leptospirosis; scrub typhus; murine typhus; hemolytic-uremic syndrome (from Coxsackie viruses A4, B2, B4; parechovirus 1; and *Escherichia coli* O157:H7); and causes of disseminated intravascular coagulopathy.

Typically, there is leukopenia and thrombocytopenia. CSF in patients with CNS complications reveals elevated protein and a monocytosis.

Diagnosis

Diagnosis is made by seroconversion of neutralizing antibodies, compliment fixation, immunofluorescent antibodies, or ELISA testing.

Conclusion

The pathophysiology, persistence, recurrence after primary infection, vertical transmission, and transmission by transfusion place Colorado tick fever among the important causes of FUOs in those with the proper exposure history [70].

West Nile virus

West Nile virus (WNV) is a (RNA) flavivirus of birds, transmitted between different birds and to man by *Culex* mosquitoes. The organism first appeared in New York City in 1999, spread across the continent, and has caused nearly 900 human deaths. Horses are also infected but, like humans, do not develop a significant viremia to become an intermediate or amplifying hosts [71]. In 2006, there were 4261 cases of WNV disease reported from across the United States. Of these cases, 1491 were WNV neuroinvasive disease, which was a 14% increase from 2005. Of the patients with neuroinvasive disease,

1311 (87.9%) were hospitalized and 161 (10.8%) died. Based on past serosurveys, the Centers for Disease Control and Prevention estimates there were 41,750 cases of nonneuroinvasive WNV infections in 2006 [72].

The virus infects over 300 different bird and vertebrate species. Host die-off (especially in corvids [crows, jays, magpies] and geese) facilitates the spread of the disease, allowing infected mosquitoes to bypass immune and already infected hosts [73]. The American crow population alone has been reduced by 45%.

In nonhuman mammals, horses represent most reported infections (96.9%) [71]. Peridomestic chipmunks, eastern cottontail rabbits, and fox squirrels along with the golden hamster develop high-grade viremias, are ready meal sources for domestic mosquitoes, and are important amplifying hosts [74].

WNV represents a transfusion-transmission risk, with seven cases reported since 2003 when nucleic acid amplification testing of blood was introduced [75].

Incubation period is 2 to 6 days (range, 2–21 days). Most illnesses are mild, presenting as sudden onset of fever; chills; rash; malaise; headache; backache; arthralgia; myalgia; and eye pain (15%–20%). Febrile prodromes occur for 1 to 7 days, before onset of neurologic complications, and may be biphasic.

Meningitis, encephalitis, and acute flaccid paralysis occurs in less than 1% of patients. These patients have stiff neck, headache, weakness, gastrointestinal symptoms, disorientation, tremors, seizures, and paralysis [71,76].

Diagnosis is made by PCR or serology (ELISA). Although viral cultures are the gold-standard, isolation can be difficult [71].

WNV infection is well-established in many hosts and represents a risk in most places across North America. Those who become symptomatic primarily present with fever. The disease may be biphasic, making it an important cause of FUO.

Japanese encephalitis

JE, like WNV, is a zoonotic flavivirus exclusive to southern Asia and the Pacific Islands [71]. JE is transmitted to humans by *Culex* with amplifying vertebrate hosts (usually cattle, swine, and birds) [77]. The flying fox seems to be the natural host for JE and enterovirus (hand-foot-and-mouth disease with neurologic and systemic complications) [76]. Endemic areas report approximately 30,000 to 50,000 cases yearly with 10,000 to 15,000 deaths. Large outbreaks occurred in northern India, and it is now an emerging infection in Nepal [77]. Congenital infections have been reported in international travelers [78].

After an incubation period of 1 to 2 weeks, JE causes a mild febrile illness with aseptic meningitis. The disease is more severe in children. Presentations include stupor, seizures, local motor impairment, parkinsonian movement disorders, infrequent cranial nerve palsy, acute flaccid paralysis, and

impaired consciousness or abnormal behavior [71,77,79]. Half of all survivors have severe neuropsychiatric sequelae [77].

In children, the prodrome is short (average, 2.61 days). Findings include seizures (98.7%); hypertonia (50.6%); focal deficits (45.4%, monoparesis and hemiparesis); gastric hemorrhage (54.5%); extrapyramidal signs (31.1%); hyperpnea; thrombocytopenia; elevated liver enzymes; and elevated CSF cell counts (15.6%) [79]. Clinical cases may exceed 30% mortality [77,79]. Half of children discharged after clinical disease requiring hospitalization have neurologic sequelae (most commonly hemiparesis). Sequelae were associated with prolonged vomiting, altered sensorium, and focal neurologic deficits on admission, but 66% eventually resolved [80].

Virus is found in the lungs, liver, kidneys, myocardium, and the CNS. Viremia may last months. Fatal cases reveal neuronal necrosis, microglial nodules, perivascular inflammation, and acellular necrotic foci [71,81].

Prevention includes prevention of mosquito bites. A vaccine is available. Larvicides, insecticides, and vaccination of pigs have been unsuccessful attempts at controlling human disease. Human vaccination does not result in herd immunity [77].

Diagnosis is made by serology (IgM ELISA in serum and CSF); viral culture; and PCR. In endemic areas, JE has been confused with Nipah and Chandipura virus infections [71,77,79]. Temporal lobe involvement on MRI and CT imaging may confuse JE with herpes simplex encephalitis [82].

A single case report indicates there may be some benefit to treatment with intravenous immunoglobulin [83]. Mass vaccination campaigns in Japan, Taiwan, and Korea have reduced the incidence of disease [77].

WNV has disseminated across North America. WNV, Sindbis virus, Tahyna virus, and louping ill virus are present in Great Britain. The future spread of JE virus, along with dengue, yellow fever, Rift Valley fever, Crimean-Congo hemorrhagic fever, bluetongue, and African horse sickness, may depend on the ability to survive in changing environments in the northern latitudes as global warming progresses [84].

JE is a well-established and emerging infection in southeast and eastern Asia, and the Pacific archipelagoes. The virus disseminates, and viremia lasts for months. Large outbreaks have occurred. Presentations most frequently include fever, but additional symptoms may be mild and nonspecific or severe and variable, making it an important cause of FUO in the international traveler.

Toscana virus (Phlebovirus genus, Bunyavirdae family)

Toscana virus is an arthropod-borne virus transmitted by sand flies (*Phlebotomus periciosus* and *Phlebotomus perfiliewi*) in the Mediterranean basin, first described in 1971. In some areas of central Italy, Toscana virus is the most frequent cause of viral meningoencephalitis, and one of the most prevalent arboviruses in Spain [85].

The most common presentation is acute meningitis and encephalitis occurring in the warmer months, usually in inhabitants and travelers from central Italy, Spain, France, and other Mediterranean countries [85]. Severe headache, nuchal rigidity, and generalized malaise are typical findings. Vomiting and electroencephalogram abnormalities are less frequent, and there are no sequelae [85].

CSF reveals an elevated white blood cell count (30–900 cells/cu mm^3), with lymphocytosis (60%–90%); elevated protein (669–1840 mg/L); and CSF to serum glucose ratios of 0.61 to 0.72 [85]. Diagnosis is made by detection of IgG and IgM antibodies in the serum and CSF, and by reverse transcription-nested PCR [85].

Toscana virus is the most common cause of aseptic meningitis in southern European countries. Half of the time, the disease is accompanied by fever. As with JE in travelers to southern Asia, Toscana virus is an important cause of FUO in travelers returning from the Mediterranean basin.

Chikungunya virus

Chikungunya virus, an alphavirus (Togaviridae family), is transmitted by *Aedes albopictus* and *Aedes aegypti*. It is endemic throughout tropical Asia, Africa, and the islands of the Indian Ocean [86,87]. Peripartum mother-to-infant transmission has occurred [88].

Explosive outbreaks in 2006 on Reunion Island affecting 35% of the population (260,000 individuals over a 6-month period), and 1.4 million people in India are well documented [88]. In 2006, of the estimated 2 million cases worldwide, 1000 travelers returning to Europe and 37 cases in travelers returning to the United States were confirmed. Epidemics have been related to drought conditions and global warming [88]. *A albopictus* is now present across the United States, Central America, and parts of South America [88]. Asymptomatic viremic patients have been documented by the Centers for Disease Control and Prevention, and no doubt represent only a small number of viremic individuals [86]. To date there has been no indigenous spread of chikungunya virus in the United States, but there is always the danger of this disease becoming endemic as did WNV [86,88].

Clinical presentation

Patients initially present with abrupt onset of fever (89%); debilitating polyarthralgia (96%); conjunctivitis; and maculopapular rash (40.1%). Almost 60% of patients presenting without fever had taken antipyretics. Distal joints and lower limbs are principally affected. Joint swelling was present in 31.8% of patients, and may persist for months to a year [86,89]. Mortality is approximately 1 per 1000 [88].

Half of the patients had pruritic maculopapular rashes that rarely affected the face. Few patients developed bullous lesions. Other findings include gastrointestinal complaints (47.1%); lymphadenopathy (cervical in

most cases, 8.9%); aphthous ulcers (2.5%); and dry cough (8.9%) [89]. Bilateral macular choroiditis has been reported [90]. Hemorrhagic complications from thrombocytopenia (6.4%) and hepatic failure occur [89]. Neurologic complications (12%) include confusion (7.6%); meningoencephalitis; and rare seizures [88,89].

Diagnosis and treatment

Diagnosis is made by ELISA, plaque reduction neutralization, and viral cultures confirmed by PCR. Viral loads have exceeded 10^9 viral particles/mm^3 [88]. Treatment is supportive. Hepatic failure may have resulted from excess doses of acetaminophen [86,87].

Chikungunya virus is an important cause of FUO in patients returning from tropical Asia, Africa, and the Indian Ocean, especially those with arthritic symptoms.

Rodent-associated infections

> Rats! They fought the dogs and killed the cats, And bit the babies in the cradles, And ate the cheeses out of the vats, And licked the soup from the cooks' own ladles, Split open the kegs of salted sprats, Made nests inside men's Sunday hats, And eve.
>
> –Robert Browning

Rodent-associated infections include 10 Arenaviridae, 4 Bunyaviridae, 2 Orthopoxviridae, hepatitis E virus, 15 bacteria, 6 anaplasma and rickettsiae, 2 fungi, 3 dermatophytic fungi, 18 protozoa, microsporidia, helminths, and ectoparasites. All of the viruses, bacteria, anaplasma and rickettsiae, and the fungi (not including the dermatophytes) prominently cause fever.

The ones that first come to mind when considering the differential diagnosis of zoonotic FUO are the rat-bite fevers (*Streptobacillus moniliformis* and *Spirillum minus*); plague (*Yersinia pestis*); lymphocytic choriomeningitis virus; hantaviruses; *Francisella tularensis*; *Pasteurella multocida*; *Leptospira* sp; and all of the rickettsial species. These have been reviewed with extensive references elsewhere [91–93].

What was not included in these reviews was *Salmonella enterica* serotypes typhimurium and enteritidis. These agents are still included in rodenticides (Biorat contains 1.25% *Salmonella* and 0.02% hydroxycoumarin; Ratin contains *S enteritidis* var. Danysz). Agents containing *Salmonella* species were first used in San Francisco in 1895 during the outbreak of plague. They had no effect on the rat population and caused morbidity and mortality among those handling and producing the product.

The products were discontinued in Europe in the 1960s but are still produced in Central and South America and Asia. Both products are mixed with rice or grain, may be mistaken for human food, and accidentally ingested. They are readily available and pose a threat as bioterrorism agents [94].

Streptobacillus moniliformis

Streptobacillus moniliformis is a gram-negative pleomorphic aerobic and facultatively anaerobic bacterium that is difficult to culture. It is part of the normal oral pharynx and upper airway flora of most rodents; weasels; squirrels; dogs (especially greyhounds who have an appetite for rodents); cats; and pigs. Disease results from rat bites or ingestion of contaminated foods including milk.

Clinical presentation

Haverhill fever (erythema arthriticum epidemicum) has an incubation period from 1 to 22 days, but in most cases does not exceed 10 days. In adults, the rat bite heals and there is no lymphadenopathy. In children, the rat bites may be fresh because the disease can progress rapidly to death.

Patients experience a sudden onset of fever, chills, headache, vomiting, and migratory arthritis. A nonpruritic measles-like, petechial, maculopapular, morbilliform, vesicular, pustular, or hemorrhagic pustular rash appears over the palms, soles, and extremities, sometimes with blisters or cutaneous abscesses. The rash appears 2 to 4 days after the onset of the fever and then desquamates. Rare patients have the rash limited to macules on the fingers. Arthritis usually follows the rash days later. Half of the patients have polyarthritis and some patients develop septic arthritis with the rash. Known complications include endocarditis; myocarditis; pericardial effusion; pneumonia; hepatitis; nephritis; amnionitis; anemia; subglottic mass with bilateral parotid swelling; brain, liver, spleen, kidney, and female genital tract abscess; and meningitis.

Uncomplicated untreated patients become afebrile in 3 to 5 days and have resolution of disease within 2 weeks. Untreated patients may remain sick for months and arthritis may persist for up to 2 years. The mortality in untreated patients is 7% to 10% to 10% to 13%.

Diagnosis

Patients have periperal white blood cell count of approximately 30,000/ mm^3; false-positive serology for syphilis (25%); and elevated C-reactive protein, gamma-glutamyl transpeptidase, erythrocyte sedimentation rate, aspartate transaminase, and alanine transaminase. Organisms are seen in peripheral blood, pus, or joint fluid stained with Giemsa, Gram, or Wayson stains. Culture is definitive. ELISA and PCR also assist in the diagnosis.

The differential diagnosis includes viral infections, meningococcemia, enteric fever, drug reactions, Rocky Mountain spotted fever, and secondary syphilis. The arthritis suggests rheumatoid arthritis, Lyme disease, brucellosis, septic arthritis, and vasculitic disease.

Treatment

Recommendations for uncomplicated cases include oral amoxicillin (875 mg/100 g) twice daily for 10 to 14 days, or doxycycline, 100 mg twice

daily orally or intravenously. Endocarditis needs 4 weeks therapy with intravenous penicillin 20 million units daily. Alternate therapies include combination of rifampin and clindamycin, clarithromycin, tetracycline, and combination of ofloxacin and imipenem.

Prophylaxis with oral penicillin, amoxicillin-clavulanate, or doxycycline is recommended after rat bites.

Conclusion

The ubiquitous nature of the rodent and the inability to know whether food or drink may be contaminated places *S moniliformis* in the pantheon of causes of FUO [91].

Spirillum minus

Spirillum minus is a motile spiral-shaped probably gram-negative bacterium that is found in blood, peritoneal fluid, conjunctival fluid, muscle, tongue, and lung tissue of infected rodents [91]. It also infects wild and domestic cats and other carnivores that feed on infected rodents.

Clinical presentation

Rat-bite fever from *S minus* (Sodoku or Sokosha) has an incubation period from 5 to 30 days (usually 5–10 days). The initial bite-wound heals, but in 1 to 4 weeks becomes swollen, painful, purple, and is accompanied by lymphangitis and lymphadenitis. The wound progresses to a chancre-like ulcer. Patients develop fever, chills, headache, and malaise. There is hyperreflexia, myalgia, arthralgia, hyperesthesia, and edema. The patients' temperature rises over 3 days, remains elevated for 3 days, and returns to normal for 5 to 10 days before rising again. Untreated, recurrences occur every 3 to 9 days. A red-brown to purple macular (infrequently urticarial) rash is seen over the extremities, trunk, face, and scalp.

Uncomplicated untreated cases resolve in 1 to 2 months. Some untreated cases have been symptomatic for years. Rare complications include endocarditis, myocarditis, pleurisy, hepatitis, splenomegaly, meningitis, epididymitis, conjunctivitis, anemia, and meningoencephalitis.

Diagnosis

Half of the patients have a positive serology for syphilis. Peripheral white blood cell counts are 10,000 to 20,000/mm^3. Occasional patients have eosinophilia. Diagnosis is made by direct visualization of the organism in blood, pus, or nodes by Giemsa stain, Wright stain, or darkfield microscopy. Serology is not available, and the organisms cannot be cultured on artificial media. The organism multiples after intraperitoneal injection. The differential diagnoses include *Borrelia* spp, malaria, lymphoma, and other relapsing infections.

Treatment

High-dose intravenous penicillin G (12–24 million units daily) is the drug of choice. Uncomplicated cases are treated for 10 to 14 days. Alternate therapies include oral amoxicillin-clavulanate, 875 mg/100 mg twice daily (for 10–14 days), or oral or intravenous doxycycline, 100 mg twice daily.

Conclusion

Although untreated cases often resolve, occasional cases may remain symptomatic for years, becoming an important cause of FUO.

Infections of the land and sea

> Wouldst thou' – so the helmsman answered./Learn the secret of the sea?/
> Only those who brave its dangers/Comprehend its mystery!
> –Henry Wadsworth Longfellow

As occupations and recreation become more intimately associated with fresh and salt-water, other organisms must be considered zoonotic risks. *Flavobacterium xinjiangensis*, *Leptothrix discophora*, *Aeromonas*, *Clostridium*, *Klebsiella*, *Legionella*, *Listeria*, *Pseudomonas*, and *Vibrio* species are found in estuaries and oceans [95]. Injury from coral formations, sharks, and stingrays are a particular hazard to surfers [96]. Halophilic *Vibrio*, *Cytophaga-Flavobacterium-Bacteroides* group, and *Clostridium* spp, are all present on coral [95,96].

Because most shark attacks victims suffer relatively minor injuries (81% require simple primary suturing), infection accompanying trauma becomes a major concern [97]. Cultures from the mouth of a possibly still living 442-cm, 1227-kg adult male white shark (*Carcharodon carcharias*) revealed *Vibrio alginolyticus*, *Vibrio parahaemolyticus*, *Vibrio fluvialis*, *Pseudomonas putrefaciens*, *Staphylococcus* sp, *Psseudomonas* sp, *Citrobacter* sp, and *Micrococcus* sp [98]. Parenthetically, witnessed attacks by one or more great white sharks leave only floating lung tissue in the water or washed ashore. Because the cause of death from these attacks is massive trauma and not drowning, lungs remain buoyant, and finding one floating by should alert individuals to take immediate action to avoid shark-bite–related infections [99].

Thalassogenic infections from the consumption of filter-feeding shellfish (bivalves) is responsible for 4 million cases of hepatitis A and E causing 40,000 deaths and 40,000 cases of chronic liver disease. This figure is believed to be an underestimate with numbers approximately 50% higher [100].

Vibrio parahaemolyticus

Outbreaks of *V parahaemolyticus* have been associated with raw oyster and clam consumption. Most patients (89%) develop gastroenteritis (diarrhea, 100%; nausea, 94%; vomiting, 82%; fever, 47%; blood stools, 29%;

headache, 24%; myalgia, 24%). A small number (11%) develop sepsis and lower-extremity edema and bullae [101].

Vibrio vulnificus

Vibrio vulnificus was the leading cause of food-borne illness deaths in Florida from 1981 to 1992 [102]. It has caused wound infections, sepsis with multiorgan failure, and gastroenteritis without sepsis. One half of patients with wound infections have underlying liver disease, hematopoietic disorders, chronic renal insufficiency, are receiving immunosuppressive agents, or abusing alcohol. These at-risk individuals have often handled or cleaned shellfish, and have an associated mortality of 15%. Patients with sepsis have fever, chills, prostration, rapid onset of hypotension, and 50% mortality. The onset of sepsis is often associated with eating raw oysters within the last 24 to 48 hours. Seventy percent have bullous skin lesions, which may suggest the diagnosis. Circular necrotic lesions (ecthyma gangrenosum) are also seen [102].

Brucellosis

Brucellosis (*B abortus*, *B suis*, *B ovis*, *B melitensis*, *B canis*, *B neotomae*) is a frequently considered FUO [103]. From 0.8% to 5.2% of patients with FUO were seropositive for the disease. Males predominate and seropositivity is age-related only in males [104]. Animal handlers and consumers of fresh yogurt and goat milk have as high as a 20% seroprevalence [104]. Risk factors include laboratory handling of livestock products of conception; consumption of unpasteurized milk (especially from camels); and other unpasteurized milk products [105].

Seals, dolphins, porpoises, otters, minke whale, killer whale, and a pilot whale, including beached and stranded animals, were reported to be infected with *Brucella* sp. Thirty-three strains of *Brucella* were identified [106]. Collectively, these marine strains have been named *B maris*.

Subcutaneous lesions are present in sea mammals. The organisms were isolated from the spleen, mammary glands, uterus, testes, blood, and lymph nodes from the mandible, stomach, iliac, sublumbar, and colorectal area in these animals. The extensive nature of the infections puts animal handlers and curiosity seekers at risk for this infection [106].

In children, 70% present with arthritis, 20% with fever without localizing signs, and 10% had fever with focal signs [105]. Patients presenting with epididymo-orchitis had swollen painful testicles (unilateral or bilateral); undulant fever (96%); chills (54%); and arthralgia (23%) [107]. Fever and nonproductive cough is an unusual presentation [108]. Endocarditis is a rare complication; neuropsychiatric, adverse outcomes of pregnancy, and transplacental congenital infection have been reported [109,110].

Blood cultures are positive in only 38% of cases. Diagnosis must be made by serology or PCR [110]. With undulant fever and multiorgan

presentations, in the proper epidemiologic setting, this becomes an important cause of FUO.

Old favorites

Malaria

Malaria is easily diagnosed and only becomes an FUO when it is not suspected. Approximately 1000 to 1500 cases are reported annually in the United States, almost all imported from endemic areas. Locally acquired mosquito-transmitted malaria clusters in the United States have been documented 63 times involving 1 to 32 cases annually, for a total of 156 cases. California has reported the most cases (27%). *Plasmodium vivax* is the most common species (*Plasmodium falciparum* 11.1%, *Plasmodium malariae* 10.6%) [111].

Hyperreactive malarial splenomegaly

Hyperreactive malarial splenomegaly, or fulminant tropical splenomegaly (previously termed ''tropical splenomegaly''), may present with fever, acute hemolysis, and splenomegaly. Hyperreactive malarial splenomegaly is diagnosed when a combination of antimalarial antibodies (IgM) are higher than 2 standard deviations above the ''local mean,'' and in the presence of gross splenomegaly. Villous lymphocytes are seen in some hyperreactive malarial splenomegaly patients. It is postulated that hyperreactive malarial splenomegaly may be linked to splenic lymphoma. Malarial parasites are present on Giemsa-stained peripheral smears in the minority of patients. PCR may assist in confirming the diagnosis, although even that is not positive in all cases.

Hyperreactive malarial splenomegaly is associated with repeated attacks of malaria, and the use of chloroquine as a single agent for malarial treatment. Hyperreactive malarial splenomegaly is treated with antimalarial therapy. The differential diagnosis includes chronic kala-azar, typhoid, congenital hemolytic anemia, leukemia, and lymphoma [112,113].

Conclusion

Malaria is easily diagnosed if suspected. Malaria without the typical epidemiologic history (travel or transfusion) occurs, and must be considered as a cause of FUO. Hyperreactive malarial splenomegaly, another cause of FUO, is more difficult to diagnose because the malaria parasites are seen in a minority of peripheral smears.

Amoebae and amoebae-resistant organisms

Amoebae feed on and kill almost any bacteria [114]. Free-living amoebae are more commonly found along with their parasitizing amoeba-resistant bacteria in cooling towers and hospital water systems than natural aquatic environments [115]. These amoeba-resistant bacteria include *Legionella*

pneumophila; *Legionella anisa*; *Pseudomonas* spp; *Parachlamydia* spp (possible cause of community-acquired pneumonia, especially in immunocompromised patients, and humidifier-related fever); *Simkania negevensis* (a cause of adult pneumonia and pediatric bronchiolitis); *Mycobacterium leprae*; *Mycobacterium avium*; *Mycobacterium marinum*; *Mycobacterium ulcerans*; *Mycobacterium simiae*; and other mycobacteria. Other organisms that readily survive in amoebae are Burkholderiaceae, *Coxiella burnetti*, *F tularensis*, Enterobacteriaceae, Vibrionaceae, *Listeria monocytogenes*, *Helicobacter pylori*, and *Cryptococcus neoformans* [115].

Mimivirus, a newly described large virus that was cocultured in amoeba, caused self-limited pneumonia in a laboratory worker. Seroconversion to mimivirus was found more frequently among ventilator-associated pneumonia patients than community-acquired pneumonia patients (31.6% and 10.5%, respectively). If amoebae act as an amplifying host or ''Trojan horse,'' this agent may be added to that of zoonoses [116].

As one of the smallest members of the animal kingdom, amoeba may cause a zoonotic FUO. Approximately 85% of infections are (afebrile) amoebic keratitis in otherwise normal contact-lens wearers, granulomatous amebic encephalitis in immunocompromised patients, and disseminated acanthamebiasis [117].

The incidence of disseminated acanthamebiasis has been increasing. Six cases have been reported in solid organ transplant patients. The most recent case involved a heart transplant patient who presented with fever; skin abscesses; violaceous and ulcerated plaques; deep abscesses; and an atypical pyoderma gangrenosum (*Acanthamoeba leticulata*) [117].

Disseminated acanthamebiasis is an important although apparently unusual cause of FUO in immunocompromised patients. Amoebae as vehicles for amoebae-resistant organisms (ie, mimivirus), where amoebae act as an amplifying host, are being newly recognized.

Viceral larva migrans (Toxocara canis *and* Toxocara cati)

Visceral larva migrans is typically a disease of children with pica under the age of 5 years. It is caused by migration of the round worms and is characterized by fever, malaise, myalgia, cough, abdominal discomfort, urticaria, wheezing, and hepatomegaly. Most cases are self-limited with symptoms lasting several months. Eosinophilia and hypergammaglobulinemia are common. Occasional patients develop hypereosinophilia; liver abscesses; myocarditis; pericardial tamponade; eosinophilic pleural effusion; and eye complications (diminished acuity with or without strabismus, white pupil) [118].

Asymptomatic infection is common, and one third of adults have serologic evidence of prior exposure. A study of asymptomatic seropositive adults found that 68% had single or multiple ill-defined oval, small, low-attenuating liver lesions on CT scan. Patients with liver lesions had higher eosinophil counts [118].

Adult visceral larva migrans patients have presented with fever; fatigue; headaches; eosinophilic pneumonia; myocarditis; spinal cord swelling; and cerebral vasculitis (*Toxocara canis* and *Fasciola hepatica* co-infection). Visceral larva migrans may mimic liver tumors. Biopsies reveal nonspecific granuloma with eosinophilic infiltrate [118–122].

For systemic disease, diagnosis is made by ELISA; however, ELISA is unsatisfactory for ocular disease, which must be diagnosed by funduscopic examination. Treatments include albendazole, mebendazole, diethylcarbamazine, or ivermectin. Ocular disease is treated with laser photocoagulation or local or systemic therapy [118].

Serologic evidence of visceral larva migrans is found in a significant minority of adults. Fever and eosinophilia present in both adult and pediatric symptomatic disease, making it an important cause of FUO in this clinical setting.

Bartonella *species and cat-scratch disease*

Bartonella species cause a variety of zoonotic diseases with differing epidemiologies. *Bartonella bacilliformis* (female *Lutzomyia verrucarum* sandfly vector) causes Oroya fever, an acute septicemic disease of Peru and high South American rain forests. The same organism causes verruga peruana, which may or may not follow untreated Oroya fever. It is characterized by arthralgia, fevers, and crops of painless papules [123].

A new *Bartonella* species that causes sepsis, recurrent fever, insomnia, myalgia, nausea, headache, mild cough, and splenomegaly has been isolated. The patient had visited Peru, hiked, camped, and received multiple insect bites. The organism was cultured, and analysis suggests it is more closely related to *Bartonella clarridgeiae* than *B bacilliformis*. The patient responded to 5 days of oral levofloxacin [124].

Bartonella quintana (*Pediculus humanus corporis* louse vector) is the cause of trench fever. The disease is sometimes mild, or may be prolonged, severe, bacteremic, and complicated by endocarditis. Immunocompromised and AIDS patients have developed bacillary angiomatosis and peliosis, similar to that caused by *Bartonella henselae* [123].

Bartonella elizabethae (*Xenopsylla cheopis* oriental rat flea vector, *Rattus norvegicus* rat host) and *Bartonella vinsonii* (*Trombicula miroti* vole ear mite, *Ixodes scapularis* deer tick, and other unknown tick vectors) cause endocarditis [123,125]. Dogs are hosts for *B vinsonii* (subsp. *berkhoffii*). Importantly, dogs may be coinfected with *Ehrlichia*, *Babesia*, and *Bartonella* spp. In the Netherlands, *Ixodes ricinus* ticks are coinfected with *Borrelia burgdorferi* and *Bartonella* spp. In the United States, *Peromyscus leucopus* mice cosegregate *B burgdorferi*, *Babesia microti*, and *Bartonella* sp [125].

The common host and vector for *B henselae*, the cause of cat-scratch disease, bacillary angiomatosis, bacillary peliosis, neuroretinitis, optic neuritis, submacular exudates, serous retinal detachment of the macula, and

osteomyelitis, are the cat and cat flea (*Ctenocephalides felis*). *Afipia felis* and *B clarridgeiae* are also believed to be causes of cat-scratch disease [123]. Seroprevalence in cats in the United States is 3.7% to 54.6%, with the highest rates in warmer areas with higher flea infestations. Feral cats, opossums, zoo animals, rodents, mountain lions, bobcats, coyotes, gray foxes, elk, black-tailed deer, and wild rabbits may also host the bacteria [125].

Bartonella sp has caused FUO in several clinical situations. Culture or serologic evidence of *Bartonella* infection was found (by PCR, culture or immunofluorescence assay) in 18% of 382 patients with FUO, most of whom were HIV infected [126]. Other cases have involved liver masses 2.5 years after liver transplant; pancytopenia, rash, hepatitis with bone marrow and skin granulomas; extensive granulomas of the liver and spleen; bone pain with osteomyelitis; headache and visual disturbance with neuroretinitis; and diffuse lymphadenopathy, weight loss, splenic lesions with disseminated disease, and treatment for hepatitis C [127,128]. *B henselae* has caused FUOs in children with granulomatous hepatitis without peripheral adenopathy, and mesenteric lymphadenopathy [129].

Up to 16.1% of patients with positive serology for cat-scratch disease had no lymphadenopathy. This was associated with FUO, persistent fever, or systemic complications [130]. In another study, 21% of patients with culture-negative endocarditis were found to be infected with *Bartonella* sp [131].

Only 50% of patients with encephalopathy have fever. Seizures (46%), combative behavior (40%), lethargy, facial nerve paresis, neuroretinitis, and peripheral neuropathy were noted. Recovery from neurologic disease occurred within 1 week to 3 months in 78% of patients, and all patients recovered within 1 year [132].

Although it is common to find a papule at the inoculation site, rashes are uncommon. Papuloedematous eruptions across the upper trunk have been accompanied by lymphadenopathy, arthralgia, and fever. Other cutaneous manifestations include erythema nodosum, erythema multiforme, erythema marginatum, maculopapular, petechial, and morbilliform rashes. Most, but not all, are nonpruritic [133].

Diagnosis is made by PCR, culture, ELISA, and immunoblot analysis [123,127]. Biopsy specimens of lymph nodes show necrotizing granuloma with peripheral palisading epithelioid cells, plasma cells, and lymphocytes. Stellate necroses with microabscesses are typical of cat-scratch disease [123].

Doxycycline is the treatment of choice [123,127]. Neuroretinitis has been treated with minocycline and steroids [123].

All epidemiologic and etiologic variants of *Bartonella* species diseases (Oroya fever, verruga peruana, trench fever, bacillary angiomatosis, peliosis, and cat-scratch fever) cause fever or recurrent fever. A significant minority of HIV-infected patients have serologic evidence of infection. Its varied clinical presentations and complications make it a common consideration in the FUO diagnostic work-up.

Special populations

> All human actions have one or more of these seven causes: chance, nature,
> compulsion, habit, reason, passion, and desire.
>
> —Aristotle

Homeless patients

Homeless people are exposed to ectoparasites and mites. These individuals are at risk for trench fever (*B quintana*); epidemic typhus (*Rickettsia prowazekii*); relapsing fever *(Borrelia recurrentis)*; plague; murine typhus; cat-scratch disease; rickettsialpox (*Rickettsia akari*); and other flea-borne spotted rickettsiosis [134].

Patients with zoophilia

In a study conducted in Pakistan, of 465 men seeking care at a sexually transmitted disease clinic, 0.5% reported having sex with animals [135]. A case-control study (psychiatric inpatients versus medical inpatients and psychiatric staff) found that actual or fantasized zoophilia was expressed by 55% versus 10% and 15% in the control groups, respectively [136]. Postconviction polygraph testing of sexual offenders revealed that 36% had engaged in sex with animals [137]. Others report zoophilia associated with bouts of depression, and dopaminergic therapy for Parkinson's disease [138].

Veterinarians and their assistants are at risk for plague pneumonia, simian foamy virus, simian immunodeficiency viruses, herpesvirus simiae (B virus), brucellosis, tuberculosis from nonhuman primates, *Echinococcus multilocularis* from domestic cats, psittacosis, *C burnetii*, tularemia, cryptosporidiosis, and avian influenza [5,6,139–141]. Occupational allergies and the risk for motorneuron diseases seem to be increased in this group [142]. There seems to be no increased risk of *Toxoplasma gondii* infection [143].

Conclusion

Difficulty in obtaining an accurate history is typical when treating the homeless. Obtaining a history of zoophilia is unusual, because the question is rarely asked. At-risk (ie, prison and psychiatric) populations with FUOs should be queried as to their past and present sexual practices.

A complete history from veterinarians, their assistants, and zoo workers in direct contact with the animals is usually readily available. It is these histories that help direct the diagnostic work-up for FUO.

Peripatetic zoonotic infections

> …It is a riddle wrapped in a mystery inside an enigma: but perhaps there is
> a key.
>
> —Sir Winston Churchill (1939 radio speech commenting on Russia).

Plague (Yersinia pestis)

Clinical presentations of *Y pestis* infection include the following [93]:

1. Subclinical disease (positive serology in asymptomatic populations in endemic areas)
2. A mild febrile illness (pestis minor)
3. Bubonic plague
4. Septicemic plague (pestis siderans)
5. Primary inhalation plague pneumonia (demic plague)
6. Secondary hematogenous plague pneumonia (<50% of patients have lymphadenopathy)
7. Plague meningitis as a complication of bubonic or septicemic plague

Yersinia pestis hosts are principally 200 species of rodents. Other animals may be infected, although dogs, cats, pigs, sheep, goats, and horses are difficult to infect. Fifty-seven genera and 85 species of fleas and the *Hyalomma detritium* tick are natural vectors. Plague is endemic in the rodent population in western Canada, the western United States, and Mexico [93].

Peripatetic bubonic plague has been reported in the District of Columbia in 1990 in a mammologist who had returned from the La Paz area of Bolivia [144]. Bubonic plague was diagnosed in a husband and wife from Santa Fe County, New Mexico. They presented to a New York City emergency department with fever and unilateral inguinal adenopathy. Fleas trapped near the patients' home in New Mexico were culture positive for *Y pestis* [145].

Francisella tularensis (rabbit fever or deer fly fever)

Tularemia is an acute febrile illness often accompanied by an ulcer at the site of inoculation (skin or mucous membrane). Patients may develop pharyngitis, eye lesions, regional lymphadenopathy sepsis, and pneumonia. Diagnosis is made by culture and serology. On average, 124 cases are reported yearly (between 1990 and 2000) from 44 states. Disease is acquired from contact with infected animals (especially rabbits, prairie dogs, and muskrats); tick and deerfly bites (summer cases); or ingestion of contaminated meat [146].

Bacillus anthracis (anthrax)

Humans acquire anthrax by ingestion, contact, or inhalation of spores, causing pulmonary, cutaneous, or gastrointestinal disease. This may occur from contact with infected animals (cattle, sheep, goats, antelope, and others) or infected animal products [147].

In 2006, a resident of New York City collapsed after a 3-day history of shortness of breath, dry cough, and malaise. Radiographs revealed bilateral pneumonia and pleural effusions. The patient had become infected after

handling hard-dried animal hides for making traditional African drums he had obtained from Ivory Coast. Diagnosis was made by blood culture [147].

Anthrax spores, used as a bioterrorism weapon, were sent through the US Mail. This resulted in at least 21 cases between October 3, 2001, and October 31, 2001 [148].

Inhalation disease presents with fever, chills, severe fatigue, nonproductive cough, or cough with blood-tinged sputum. Some patients complain of abdominal pain, nausea, vomiting, chest heaviness, shortness of breath, headache, myalgias, and sore throat. Peripheral white blood cell counts were minimally elevated. Chest radiographs revealed widening mediastinum, paratracheal fullness, hilar fullness, and mediastinal lymphadenopathy [147].

Temporary petting zoos

A visit to a petting zoo is a risk for zoonotic infection. Most are temporary (67%); and although hand-washing facilities are present at most zoos, compliance is poor. Problematic behavior on the part of the public includes bringing edibles into the zoo; unsupervised animal contact with children under the age of 6 years; animal contact with very young children (including those less than 1 year of age); animal contact by pregnant women; feeding animals from ice-cream cones; feeding animals by hand; and entering animal pens not open to the public. Outbreaks of *E coli* O157:H7 associated with petting zoos were reported in North Carolina, Florida, and Arizona [149].

Zoonotic agents of bioterrorism

The zoonotic organisms that are likely candidates as agents of bioterrorism are *Bacillus anthracis*, *Burkholderia mallei*, agents of brucellosis, *Y pestis*, *C burnetii*, *F tularensis*, Venezuelan equine encephalitis virus, and agents of viral hemorrhagic fevers. Some clues suggest a deliberate spread of pathogens: (1) large epidemic in a discrete population; (2) more severe disease than expected for the pathogen; (3) unusual routes of exposure, age groups, or attack rates and populations; (4) association with zoonotic disease outbreak; (5) a single case of an unusual disease; and (6) absence of the disease's vector in the area [150]. When used as weapons they remain zoonoses except without the usual four-legged animals.

Animals that may act as sentinels for a bioterrorist attack with a zoonotic agent include sheep and cattle (anthrax, Rift Valley fever); cats (plague); horses (Venezuelan equine encephalitis and eastern equine encephalitis); and wild birds (WNV and JE virus). Increased morbidity and mortality among animals, illness in species not normally infected by the suspect agent, lack of response to normal therapy, and disease occurrence at the "wrong time" and "wrong place," all suggest a nefarious rather than a natural vector [151].

Summary

In theory there is no difference between theory and practice. In practice there is.

–Yogi Berra.

Physicians solve difficult diagnostic problems by comparing patterns of presentation. This involves (1) grouping findings into patterns; (2) ''selection of a pivotal … finding…''; (3) a list of possible etiologies; (4) selection of the most likely diagnosis and the differential diagnoses; and (5) confirmation of the diagnosis [152]. Histories, physical findings, rashes, and temperature curves overlap among different etiologies. Confirmatory laboratory tests, especially serology, are too numerous and may give false-positive information if not properly focused. The gold standard of positive cultures of fastidious organisms or viruses may be difficult to obtain even when a specific pathogen is suspected. Solving the diagnostic conundrum requires a thorough understanding of the patient's immune status and epidemiology.

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