WILDERNESS & ENVIRONMENTAL MEDICINE, **22,** 115–121 (2011)

CONCEPTS

Infectious Diseases Associated with Caves

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In recent times, caving has become increasingly popular, with almost 2 million people visiting national park caves each year in the United States. Although the 2 million tourist visits are extremely low risk, smaller numbers of sport cavers are at risk for some high risk conditions, and expedition cavers are at risk for some obscure infections. Infectious diseases like histoplasmosis, rabies, leptospirosis, and tick-borne relapsing fever may be transmitted by the underground fauna. To reduce the risk of illness or injury while caving, knowledge of potential risks before engaging in this activity is important. Caving preparation needs to be carefully planned and executed, including vaccinations, prophylactic medications, and advice regarding safe conduct and behaviors.

Key words: cave, infectious diseases, histoplasmosis, rabies

Introduction

The relationship between man and cave is as old as the history of man himself. It was in caves that man found some of his first shelters and his oldest sanctuaries. In recent times, caving has become increasingly popular, with almost 2 million people visiting national park caves each year in the United States.[1] We should make a distinction between "sport cavers" (the term used by cavers for those exploring wild caves that are nearby and known) and "expedition cavers" (those who explore previously uncharted caves). Although the 2 million tourist visits are extremely low risk, smaller numbers of sport cavers are at risk for some high risk conditions, and expedition cavers are at risk for obscure infections.

This article summarizes the health risks associated with cave exposures, particularly with regard to infectious diseases, and how they can be minimized or avoided.

Environment and Infections

The cave environment is considered one of the most peculiar and most stable in the biosphere. The rock mantle which covers and protects the cave from abrupt climatic changes like those that occur at the surface gives a series of distinct characteristics to the environment.[2] The first and principal characteristic of such an environment is the total absence of light at lower levels, increasing the chance for accidents involving constrictions, exposures, and mud that may lead to falls, contusions, abrasions, cuts, and fractures.

The absence of sunlight and the constancy of temperature are basic characteristics of the subterranean environment. The air temperature of a cave is generally the same as the annual average of the outside temperatures in each region. These differences of temperature among regions influence the composition and distribution of the cave fauna including bats, rodents, birds, reptiles, amphibians, and arthropods. Most of the infectious diseases acquired in caves are caused by agents linked to this fauna. There is an increase in popularity of caving and there are an estimated 50000 cavers in the United States.[3] General preventive measures for health risks associated with cave exposures include appropriate boots, protective clothing appropriate to the particular environment, a helmet with a 4-point attachment, and 3 sources of light. Also, tetanus toxoid should be updated in cavers. Table 1 summarizes diseases, vectors, symptoms, signs, treatment, and preventive measures of infections related to cave exposures.

Disease Vectors in the Subterranean Environment

BATS

Bats are linked to the transmission of histoplasmosis, rabies, and Marburg hemorrhagic fever (MHF).

Table 1. Diseases, vectors, symptoms, signs, treatment, and preventive measures of infections related to cave exposures

Disease	*Vector*	*Symptoms/Signs*	*Treatment/Preventive Measures*
Histoplasmosis	Bats	Asymptomatic to severe pneumonitis	Itraconazole or amphotericin B/dust-mist respirator
Rabies	Bats	Dysphagia, hydrophobia, parasthesia	Milwaukee protocol/pre-exposure vaccination
Marburg hemorrhagic fever	Bats	Hemorrhagic manifestations	No specific treatment/avoid visiting locations where an outbreak is occurring
Leptospirosis	Rodents	Fever, myalgia, headache, and jaundice	Amoxicillin or penicillin/protective clothing; doxycycline
Tick-borne relapsing fever	Ticks	Fever, headache, myalgia, arthralgia	Erythromycin, tetracyclines, or penicillins/DEET and pyrethroid-impregnated clothing; doxycycline
Other arthropod-borne diseases	Other arthropods	According to the disease	According to the disease/DEET and pyrethroid-impregnated clothing
Tetanus	No vector	Trismus and spasmus in other muscles groups	Tetanus immune globulin and penicillin/vaccine up-to-date

Histoplasmosis

Histoplasmosis (once referred to as "cave disease") is the most common cave-associated disease and it can be acquired by occupational or recreational exposure to environmental sources. Caves represent one of the foci that favor the propagation of *Histoplasma capsulatum*, the fungal causative agent of histoplasmosis, even in areas where histoplasmosis is of low endemicity.[3] The continued reporting of cave-associated outbreaks suggests that current practices among cavers continues to place them at risk for this potentially serious infection.[4] Additionally, because of increasing numbers of cavers, histoplasmosis may become more common as a recreational disease.[3]

H capsulatum is endemic to North, Central, and South America; the Caribbean; Europe; Central and Eastern Asia; Africa; and Australia. Cave-associated histoplasmosis has been reported in the Americas, Africa, and Oceania.[4]

The fungus grows in soil and its growth is thought to be enhanced by bird and bat excrement that provides a source of nitrates, which accelerate spore formation. Disruption of soil that contains bird or bat excrement is the primary means of aerosolization and exposure to spores. Bats, unlike birds, may become infected with *H capsulatum.*[5] Severity of illness and disease manifestations after primary inhalation exposure to *H capsulatum* vary, depending on the intensity of exposure and the immunity of the host. Acute exposure causes a spectrum of disease, ranging from asymptomatic infection to severe pneumonitis with respiratory compromise. In most cases, illness resolves without therapy within one month. Some patients, however, may experience protracted pulmonary complaints caused by persistent inflammation of the lung or mediastinal lymph nodes. Histoplasmosis should be considered in the differential diagnosis of febrile illness in returning travelers with a history of epidemiologic or geographic exposure.[4] Histoplasmosis can be diagnosed by identifying *H capsulatum* in clinical samples of a symptomatic person's tissues or secretions, testing the patient's serum for antibodies to the microorganism, and testing urine, serum, or other body fluids for *H capsulatum* antigen. On occasion, diagnosis may require a transbronchial biopsy.[6]

Treatment is usually unnecessary in mild-to-moderate acute pulmonary histoplasmosis. Itraconazole (200 mg, 3 times daily for 3 days and then 200 mg once or twice daily for 6–12 weeks) is recommended for patients who continue to have symptoms for more than one month. Moderately severe to severe acute pulmonary histoplasmosis should be treated with a deoxycholate formulation of amphotericin B (0.7–1.0 mg/kg daily IV for 1–2 weeks) followed by itraconazole (200 mg, 3 times daily for 3 days and then 200 mg twice daily, for a total of 12 weeks).[7]

Travelers to areas of endemic histoplasmosis who visit caves should consider using personal protective equipment to reduce their potential exposure to *H capsulatum*. They should also contact local cavers to see which caves are at high risk for histoplasmosis. Although no studies have shown that masks would prevent exposure during caving, the dust-mist respirators now recommended for use in hospitals for tuberculosis control have the capacity to filter particles of 1 to 2 microns, which is the size of *H capsulatum* spores.[3]

Although HIV-infected persons living in or visiting areas in which histoplasmosis is endemic cannot completely avoid exposure, those whose CD4+ counts are < 150 cells/μL should avoid activities known to be associated with increased risk such as exploring caves.[8]

Rabies

Rabies is a zoonotic disease caused by ribonucleic acid (RNA) viruses in the Family *Rhabdoviridae*, Genus *Lyssavirus*. Rabies is transmitted by infected animal bites or scratches, or by contamination of abrasions, open wounds, or mucous membranes by infectious material (almost always saliva). Bats are the major source of human rabies in the United States, and they are the second most common transmitters of rabies to humans in the world. Rabies among insectivorous bats occurs throughout the continental United States. Hawaii remains consistently rabies-free. Raccoons, skunks, and dogs in the developing world are additional rabies vectors.[9]

Exposures to bats deserve special assessment because bats can pose a greater risk for infecting humans under certain circumstances that might be considered inconsequential from a human perspective (ie, a minor bite or lesion). Between 1990 and 2007, a bite was documented in only 6 of the 34 US human rabies cases caused by bat-associated rabies virus variants.[9] The lone human case reported in the United States during 2005, and 2 of the 3 human rabies cases in 2006, were attributed to bat exposures, but none of these cases involved caves.[10,11] Two fatal cases of rabies in humans have been attributed to possible airborne exposures in caves containing millions of free-tailed bats.[9] The 2 infections occurred in a single cave near Uvalde, Texas. Although aerosol transmission of rabies can occur in animals in man-made situations, and there is at least one case of human rabies most likely caused by aerosol transmission in the laboratory, there are no well-documented cases of aerosol transmission of rabies in the natural environment.[12]

After entering the central nervous system, the virus causes an acute, progressive encephalomyelitis that is almost always fatal. The incubation period in humans is usually several weeks to months, but ranges from days to years.[9] Rabies should be included in the differential diagnosis of any unexplained acute, rapidly progressive encephalitis, especially in the presence of autonomic instability, dysphagia, hydrophobia, paresis, or parasthesia. The widespread availability of specific laboratory tests, coupled with compatible history and symptoms, aids the diagnosis of rabies for the astute clinician. Since the survival of a rabies patient after an experimental treatment in 2004, early diagnosis of potential rabies cases has become increasingly important if experimental treatment is to be considered. However, the benefits from any particular experimental rabies treatment regimen have not been determined. No single course of treatment for rabies in humans has been efficacious after clinical signs of rabies developed.[11] Early diagnosis of rabies is important so that protective measures for the medical staff caring for the patient can be instituted.

Pre-exposure vaccination should be considered for persons whose activities bring them into frequent contact with the rabies virus or potentially rabid bats, raccoons, skunks, cats, dogs, or other at-risk species. Although cavers seldom have direct contact with bats, they are included in a frequent-risk category by the current CDC recommendations for pre-exposure vaccination because of the potential for bite, nonbite, or aerosol exposure to the rabies virus.[9] Rabies vaccine is neither ubiquitously available nor inexpensive, and it is an out-of-pocket expense for those who choose to get pre-exposure vaccination. One study suggests that, despite longstanding guidelines for cavers to receive pre-exposure vaccination for rabies, only 20% have done so—and 14% of the cavers did not consider a bat bite a risk for rabies.[13] Three 1.0 mL injections of human diploid cell vaccine (HDCV) or purified chick embryo cell vaccine (PCECV) or Vero cell vaccine should be administered IM (deltoid area), on days 0, 7, and 21 or 28 (one injection per day).[9]

If a dead bat must be handled, gloves should minimize the risk of disease transmission via an accidental scratch from the bat's teeth or by contamination of existing scratches or abrasions on the hands. Any bare-hand contact with a bat should be considered a rabies exposure unless the bat is tested for rabies. After any potentially rabid animal exposure, immediate washing and flushing of the wound with soap and water is imperative and is probably the most effective procedure in the prevention of rabies.[10] Rabies immune globulin and rabies vaccine should be given as soon as possible after any contact with a bat that is not captured and examined for rabies.[14]

Marburg Hemorrhagic Fever

Bats and caves are also linked to the transmission of Marburg hemorrhagic fever (MHF) in Africa. Marburg hemorrhagic fever is a fatal viral hemorrhagic disease caused by a virus from the same family as the Ebola hemorrhagic fever virus. These viruses are among the most virulent pathogens known to infect humans. Both diseases are rare, but have a capacity to cause dramatic outbreaks with high fatality. Reservoir hosts of Marburg virus inhabit caves, mines, or similar habitats.[15] Greater than 80% of human cases in the Durba (Democratic Republic of Congo) MHF outbreak were linked to mining activity in a gold mine harboring large bat popula-

tions. Mining was again implicated in a 2007 outbreak of MHF in Uganda.[16] This led to the investigation of animals in and around the mines, including a large number of bats, and the eventual detection of MHF nucleic acid in liver and spleen tissues and MHF-specific IgG in serum obtained from cave-dwelling fruit bats (*Rousettus aegyptiacus*).[17] Three cases of MHF have occurred in travelers to caves harboring bats, including Kitum cave in Kenya and Python cave in Maramagambo Forest, Uganda.[18] One Dutch tourist was reportedly exposed to fruit bats during a visit to the Python cave in Uganda. This cave is thought to harbor bat species that have been found to carry filoviruses in other locations in sub-Saharan Africa. A large bat population was seen in the cave and the victim was reported to have had direct contact with one bat. The cave in the Maramagambo Forest is known to be a tourist attraction.[19]

Illness caused by Marburg virus begins abruptly, with severe headache and malaise. Many patients develop hemorrhagic manifestations between days 5 and 7, and fatal cases usually have bleeding from multiple sites. Fever coupled with rapid clinical deterioration and hemorrhaging in a patient who has returned from a suspect region should suggest viral hemorrhagic fever, especially if exposure to a possible reservoir could have occurred. Whole blood or serum may be tested for virologic (reverse transcription polymerase chain reaction [RT-PCR], antigen detection, virus isolation) and immunologic (IgM, IgG) evidence of infection. Tissue may be tested by immunohistochemistry, RT-PCR, and virus isolation. Samples should be sent for testing to a reference laboratory with biosafety level 3 and 4 capability.[18]

Presently, there are no medical interventions or vaccines approved for the treatment or prevention of filovirus infections in humans or other animals.[17] In countries with previous cases of MHF, entry into bat caves should certainly be avoided until the role of bats as reservoirs for MHF is disproved or verified. Travelers should not visit locations where an outbreak is occurring. Travel sites (eg, www.cdc.gov or www.istm.org) should be consulted to learn about potential areas of outbreak, and contact with or consumption of primates, bats, and other bushmeat should be avoided.[18]

Rodents

LEPTOSPIROSIS

Leptospirosis is a worldwide public health problem but it is a greater problem in humid tropical and subtropical areas, where most developing countries are found, than in temperate climates. Climatic and environmental conditions are the most significant factors contributing to the problem in tropical and subtropical regions, but other factors, such as local agricultural practices and poor housing and waste disposal, give rise to many sources of infection that make exposure to Leptospira more likely in these regions. In countries with temperate climates, in addition to locally acquired leptospirosis, the disease may also be acquired by those who travel abroad to tropical regions.[20]

Due to exposure to water and animal urine, caving places participants at particular risk for leptospirosis, which has been reported among cavers in Sarawak and Sabah, Malaysia.[21] Rats are a common reservoir of leptospirosis, but bats have also been found to carry leptospirosis in Southeast Asia. Some aspects of cave exploration in a tropical climate may maximize leptospirosis exposure; for example, high heat and humidity in these climates may lead to less protective clothing being worn which, in turn, exposes more skin and increases the likelihood of skin abrasions—a known portal of entry for the organism—as cavers' bodies make contact with the rocks. Underground rivers may increase exposure risk by draining multiple caves. Caves serve as multilevel habitats for bats and rats, but may drain through a single stream.[21] Cavers should be made aware of the potential risk of leptospirosis associated with environments in which animals are present.

The diagnosis of leptospirosis should be considered in any patient presenting with an abrupt onset of fever, chills, conjunctival suffusion, headache, myalgia, and jaundice. The incubation period is usually 5 to 14 days, with a range of 2 to 30 days. Its symptoms may mimic those of a number of other unrelated infections such as influenza, meningitis, hepatitis, or dengue and viral hemorrhagic fevers. For this reason, it is important to distinguish leptospirosis from dengue and viral hemorrhagic fevers in patients acquiring infections in countries where these diseases are endemic.

The disease is usually diagnosed in the laboratory by detecting antibodies, by culturing the bacteria from blood, urine or tissues, or by demonstrating the presence of bacteria in tissues using antibodies labeled with fluorescent markers. Other methods may be available in some centers (eg, polymerase chain reaction [PCR] and immunostaining).

Leptospirosis is a potentially serious but treatable disease. Treatment with effective antibiotics should be initiated as soon as the diagnosis of leptospirosis is suspected and, preferably, before the fifth day after the onset of illness.[18] Severe cases of leptospirosis should be treated with high doses of IV penicillin. Less severe cases can be treated with oral antibiotics such as amoxicillin, ampicillin, doxycycline, or erythromycin. Third-generation cephalosporins, such as ceftriaxone and cefo-

taxime, and quinolone antibiotics also appear to be effective.[20]

Transmission can be prevented by wearing protective clothing (boots, gloves, spectacles, masks); covering skin lesions with waterproof dressings; washing or showering after exposure to urine or contaminated soil or water; and washing and cleaning wounds.[20] Such preventive measures are important but may not be feasible or sufficient for cavers who are likely to have water immersion, so they should consider doxycycline prophylaxis, balancing the risk of unwanted side effects against that of acquiring leptospirosis. Usual leptospirosis prophylaxis (200 mg of doxycycline once a week) for cavers may be insufficient. Although unproven, cavers should consider augmenting daily or weekly prophylaxis by adding 200 mg of doxycycline at a time for any high-risk exposures—such as immersions, swallowing river water, or contacts with bat or rat urine.[21] When occupational, recreational, or social circumstances put people at risk, those concerned should be made aware of the symptoms of leptospirosis and, if an illness compatible with leptospirosis develops, should seek medical help without delay and inform the health care provider about the exposure.[20]

Arthropoda

The predominant *Phylum* in caves is the *Arthropoda*, represented by the *Insecta* and *Arachnida*.[2] Arthropods may cause direct trauma through envenomation (bees, wasps, spiders, and scorpions) and may also be vectors of infectious diseases (mosquitos and ticks). Bites and stings from spiders and scorpions can be painful and can result in significant morbidity and mortality.

Mosquitoes are considered to be the most important vector for "arthropod-borne diseases" (ABDs) because of the annual incidence of malaria and dengue fever, as well as their worldwide distribution, but many other types of arthropods transmit disease-causing pathogens.

Tick-borne Relapsing Fever

Tick-borne relapsing fever (TBRF), an acute febrile illness characterized by a pattern of remissions and relapses, has traditionally been called "cave fever" in Israel because of the known correlation to cave exposure.[22] The TBRF *Borrelia* species is transmitted to humans by an infected *Ornithodoros* tick bite. Human TBRF is generally contracted only in the geographic range of the tick vectors. *Boriella persica*, transmitted by *Ornithodoros tholozani* is thought to be the cause of TBRF in Israel. The *O tholozani* tick is prevalent in Middle Eastern and Central Asian countries. It is primarily found in dark, moist areas such as caves and abandoned buildings.

After an incubation period of about 7 days, TBRF typically begins abruptly with fever, chills, headache, myalgia, arthralgia, and abdominal pain. Myocarditis accompanied by arrhythmia, cerebral bleeding, and liver dysfunction are rare fatal complications. Direct visualization of Borrelia spirochetes in a blood smear is the gold standard for the diagnosis of TBRF. Polymerase chain reaction and serologic analysis have occasionally been used as additional diagnostic tools. Erythromycin, tetracyclines, chloramphenicol, or penicillins have all been shown to be effective for treating TBRF. Although duration of therapy has not been well-studied for TBRF, the current recommendation is 7 days of antibiotic therapy. Antimicrobial prophylaxis (200 mg of doxycycline in the first day, and 100 mg per day for the subsequent 4 consecutive days) for persons with tick bites or for persons who have stayed in areas (such as caves) where there is a risk of infection may prevent TBRF.[22]

Unfortunately, only a minority of ABDs have preventive vaccines, chemoprophylactic drugs, or specific therapies. Even if vaccines or drugs are available, they are not totally effective, making measures to minimize insect bites an important way—and for some ABDs the only way—to reduce the risk of acquiring ABDs. Several personal protective measures reduce the risk of acquiring ABDs, but no single measure provides complete protection; hence, the use of all measures is complementary. All travelers at risk of exposure to serious arthropod-borne infections should appropriately use insect repellent containing DEET (the preferred repellent, unless contraindicated due to allergic reaction). Icaridin (Picaridin) and *P-menthane-3,8-diol* (lemon eucalyptus oil) may be used as a second-line alternative repellent.[23] Cavers should consider wearing insecticide (permethrin)-impregnated clothing. These insecticides do not wash off, which is important in caves. Combining DEET and permethrin-impregnated clothing enhances protection against biting arthropods. Insecticide-treated (permethrin) mosquito nets have been proven effective and are advised for all travelers visiting disease endemic areas where they are at risk from biting arthropods while sleeping.[23]

If an attached tick is found, it should be removed by grasping with tweezers or fine-tipped forceps close to the skin and gently pulling with constant pressure. Folk remedies–including gasoline, kerosene, petroleum jelly, fingernail polish, or lit matches–should never be used to extract ticks. Removing the tick with bare hands should be avoided because fluids containing infectious organisms might be present in the tick's body and at the wound site. Ticks that have been removed should not be crushed between the fingers to prevent contamination, and hands

should be washed to avoid potential conjunctival inoculation. The bite wound should then be disinfected.[24]

Potentially Transmitted Diseases

Although not epidemiologically linked to cases, other diseases like histoplasmosis duboisii, cryptococcosis, and psittacosis are also potentially transmitted in caves. *H capsulatum* var. *duboisii* was isolated from soil admixed with bat guano in a cave located in Nigeria.[25] Inhalation exposure to *Cryptococcus neoformans* may be a health risk in environments containing accumulations of bat droppings or bird manure.[6] *C neoformans* uses the creatinine in avian feces as a nitrogen source. It gains a competitive advantage over other microorganisms and multiplies exceedingly well in dry bird manure accumulated in places that are not in direct sunlight. Psittacosis is caused by *Chlamydia psittaci* and most human infections result from inhalation exposures to aerosolized urine, respiratory secretions, or dried manure of infected birds.[6] In depressions and potholes of the caves in tropical environments, parakeets, parrots, macaws, and other psittaciform birds are commonly seen.[2] The use of personal protective equipment will also protect against inhalation exposures to *C neoformans*, *psittaci* and other microorganisms.[6]

Conclusion

To reduce the risk of illness or injury while caving, knowledge of potential risks before engaging in these activities is important. General recommendations are boots, appropriate clothing, a helmet, and 3 sources of light. Caving preparation needs to be carefully planned and executed, including vaccination, prophylactic medications, and advice regarding other protective measures. Expedition cavers may require more specific measures appropriate to the area to be visited.

Acknowledgement

The author verifies he has no conflicts of interest.

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