

Pharmacology Consult

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Caring for the Bite

Physical and Pharmacological Interventions for Rabies Prevention

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If it is a terrifying thought that life is at the mercy of the multiplication of these minute bodies [microbes], it is a consoling hope that science will not always remain powerless before such enemies. —Louis Pasteur (1822-1895), who developed the first rabies vaccine (<https://www.azquotes.com/quote/573085>).

Rabies cases average 1 to 2 infections per year related to near elimination of canine rabies in the United States. However, canine rabies is endemic in many areas of Asia, Africa, and South America.¹ Every 10 minutes, someone in the United States (16 000-39 000 per year) is treated for possible exposure to rabies with postexposure prophylaxis (PEP) to prevent rabies infection with approximately 5000 wildlife animals testing positive for rabies. Most fatal rabies infections are from infected bats beginning with scratch or bite smaller than the top of an eraser. Each year, the Centers for Disease Control and Prevention (CDC) responds to an average of 175 mass bat exposures, events where more than 10 persons are exposed to a possible rabid bat.²

PATHOPHYSIOLOGY OF THE BITE

After a bite or other exposure to viral shedding in saliva, the virus begins migration to the spinal cord and brain via the peripheral nervous system. The virus genome is single-stranded, antisense, nonsegmented RNA with a leader sequence of approximately 50 nucleotides, followed by N, P, M, G, and L genes. Once in the central nervous system,

preferential viral budding begins from plasma membranes. Concomitantly, the virus in the salivary glands buds primarily into the acinar lumen, which induces aggressive biting behavior in the host and maximizes the risk of viral infection in the victim. The time between the exposure and appearance of symptoms can be weeks to months to even a year based on location of the exposure site, virus type, and any existing immunity.^{3,4} Incubation is a function of the bite location; the farther the bite is from the central nervous system, the longer the incubation period. During the incubation period, the patient is without symptoms and cannot transmit rabies to others, and treatment is usually effective to stop virus progression.^{5,6}

The first symptoms of rabies infection mimic the flu: general weakness or discomfort, fever, or headache. Symptoms may last for days along with a prickling or itching sensation at the bite or scratch site. Within days, acute symptoms can include cerebral dysfunction, anxiety, confusion, and agitation. With disease progression, the person may experience delirium, abnormal behavior, hallucinations, hydrophobia or fear of water, and insomnia. This acute period typically ends after 2 to 10 days.^{3,4}

Once clinical signs of rabies are observed, rabies infection is almost always fatal, and treatment is typically supportive. Signs and symptoms progress within days to cerebral dysfunction, cranial nerve dysfunction, ataxia, weakness, paralysis, seizures, difficulty breathing, difficulty swallowing, excessive salivation, abnormal behavior, aggression, and/or self-mutilation. There are fewer than 20 cases of survival from clinical rabies infection documented in humans, with only a few survivors without pre-exposure or postexposure prophylaxis.^{3,4} Only 34 cases of human rabies were diagnosed in the United States in 2013 through 2016. However, rabies is a serious health threat in more than 150 countries, with 25 000 to 55 000 fatalities each year. Most fatalities occur in Asia and Africa, with nearly all due to a dog bite.^{5,6}

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RESPONDING TO THE BITE

Evaluation for PEP should begin as soon as possible after exposure to wildlife unless the animal is available for testing or testing of brain material is negative. The first step is always cleansing of bite wounds and/or scratches with soap and water and irrigation using a virucidal such as povidone-iodine.¹ Second, contact public health for direction when addressing the need for PEP. In most states, providers are required by law to report animal bites.^{1,7}

For the patient examination, consider the animal species, the reported behavior and appearance of the animal, if the bite was provoked, and the severity as well as location of the bite. Available dogs, cats, and ferrets without symptoms can be confined for 10 days' observation, and prophylaxis can be delayed during the monitoring period. If the animal has escaped, contact local public health officials first. Bites from skunks, raccoons, foxes, and other carnivores, as well as bats, should be treated as rabid until proven otherwise. Bites from squirrels, hamsters, guinea pigs, gerbils, chipmunks, rats, mice, livestock, small rodents, rabbits, woodchucks, or beavers rarely require postexposure treatment. However, public health officials should also be notified.^{1,7}

In summary, if the suspicion for rabies is low and the animal can be quarantined or tested, PEP may be held pending results. However, if the risk for rabies is high, or the offending animal is unavailable, PEP is generally warranted.^{5,6} With regard to bats, the CDC recommends PEP be considered "if there is any possible contact with a bat, including a bat being found in the room with a child or incapacitated or sleeping adult even if there is no visible bite."⁸ Any decisions to provide or withhold PEP should be made in collaboration with local public health department and the CDC. Remember that PEP is 100% effective if initiated in a timely manner and not effective once the patient has symptoms.^{5,6,8}

TREATING THE BITE

One percent of emergency department visits are for animal bites with healthcare costs of \$50 million.⁹ Each year, it is estimated that there are 400 000 cat bites, and 4.5 million dog bites, with the majority children bitten by a dog that is known to them.⁷ Infection rates vary from approximately 20% for dogs to as high as 50% for cat bite infections due to the puncture wound caused by the bite.^{7,10} Risk is further magnified if the wound has venous and/or lymphatic compromise or is located near a prosthetic joint, or if the person delays seeking care 12 to 24 hours after a bite to the face or 6 to 12 hours after leg or arm injury. Other risk factors include diabetes and immunosuppression.¹⁰

Bite management is a function of tetanus status, animal species, and infection risk.⁹ Wound irrigation can significantly reduce viral loads and should be a cornerstone of care.^{5,6} Assess carefully for infection: swelling, erythema,

and pain with or without drainage, which can progress to a serious systemic infection. Most animal bite wounds are polymicrobial in nature with *Pasteurella* species, the most common organism for both cat and dog bites. Cleansing and debridement, repair, and cultures are the function of the type of bite and the length of time before medical care was accessed after injury.¹⁰ Antibiotic prophylaxis should be considered, especially for puncture wounds from cat bites, which have a significant risk of infection and hand wounds, and for persons who are immunosuppressed.⁷

RABIES PREVENTION AFTER BITE

For persons with likely rabies exposure, PEP consists of wound treatment, human rabies immunoglobulin injection at the bite site, and multiple doses of intramuscular rabies vaccination as soon as possible after exposure.^{5,6} Available vaccines in the United States are human diploid-cell rabies vaccine (Imovax; Sanofi Pasteur, Bridgewater, New Jersey) or purified chick embryo cell culture rabies vaccine (RabAvert; Novartis, Emeryville, California), which contain antigens that stimulate active immunity to rabies.^{1,11,12} Prophylaxis can be discontinued if animal test results are negative. Vero cell, duck embryo, and nerve tissue vaccine (NTV) may be available outside the United States. However, NTV vaccines are grown in animal brains and should be avoided. Persons requiring rabies vaccine outside the United States should travel to another country for non-NTV vaccines.^{11,12}

Unvaccinated persons should be provided wound treatment, multiple-series rabies vaccine (4 or 5 doses), and single-dose rabies immunoglobulin (RIG). Previously vaccinated persons also require wound treatment and a booster series without RIG. For persons with immunosuppression, check prescribing information for precise dosing. The deltoid muscle is the only acceptable site for intramuscular administration for adults, adolescents, and older children. For young children, the deltoid or anterolateral thigh is recommended—never administer the vaccine in the gluteal area. Evidence of immunity is the presence of rabies antibodies in serum.^{1,11,12}

KEDRAB (Kedrion Biopharma, Ft Lee, New Jersey) or RIG provides passive, transient PEP for rabies given immediately after contact with a rabid or possibly rabid animal. KEDRAB blocks rabies virus access to the central nervous system until an immune system response to vaccine occurs. Additional doses of KEDRAB should not be administered once vaccine treatment has been initiated, because this may interfere with the immune response to the rabies vaccine. KEDRAB should not be administered to patients with a history of a complete pre-exposure or postexposure vaccination regimen and confirmed adequate rabies antibody titer. Patients at increased risk of thrombosis or thrombotic complications should be monitored for at least 24 hours after KEDRAB administration.^{13,14}

Pre-exposure rabies prophylaxis should be considered for persons at higher risk of rabies exposure and for international travelers to at-risk areas who are unlikely to have access to PEP within 24 hours of exposure.⁷ The decision for pre-exposure prophylaxis when traveling should be based on local incidence of rabies, the availability of PEP, planned activities, and duration of the visit. Pre-exposure vaccinations with boosters when indicated are recommended for children, adolescents, and adults with higher risk of exposure to the virus compared with the general population; however, PEP will still be required if exposure occurs. At-risk groups include veterinarians and staff, animal control and wildlife workers, biologists, missionaries, rabies researchers, and laboratory personnel, as well as persons in frequent contact with bats, raccoons, and skunks where exposure can be through a bite or scratch and even aerosol method.¹

BEST PREVENTION MEASURES AND RESOURCES

The evidence is simple and easy to teach and remember: Leave all wildlife alone. Wash bites or scratches with soap and water. Never touch injured wildlife. Vaccinate pets.² For state and local rabies consultation, contacts are available at <https://www.cdc.gov/rabies/resources/contacts.html>.

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