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Twelve Common Questions About Human Rabies and Its Prevention

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Rabies, described as early as the 23rd century B.C., may be one of the oldest recorded infectious diseases of mankind [1]. It is a fatal infection caused by a highly neurotropic, bullet-shaped, single-stranded RNA virus [2]. Rabies causes more than 40,000-60,000 deaths worldwide each year, primarily in countries where canine rabies is endemic and the delivery of health care is poor [3,4]. In the United States, human disease is rare: just 27 deaths have occurred since 1990 [5,6]. Nevertheless, the scarcity of human rabies does not minimize its importance to public health nor the fear it instills in individual patients who are potentially exposed.

The epidemiology of human rabies is ultimately linked to cycles of rabies virus transmission in animals. The low rate of human infection is due to animal control, animal vaccination programs, and effective application of human preexposure and postexposure prophylaxis. Combined, these efforts cost more than $300 million annually [7], and each year between 16,000 and 39,000 persons receive postexposure prophylaxis in the United States [8]. This article will address some representative scenarios and common questions about rabies and its prevention.

1. ***A graduate student, before departing for rural Latin America to study, questions whether she should receive primary rabies vaccination.*** **Who should receive the primary or preexposure vaccination?**

Preexposure prophylaxis, given by the intradermal (ID) or intramuscular (IM) route, is indicated for certain high-risk groups (see table 1)[9].

The decision to give preexposure prophylaxis to travelers is complicated by several factors: a very low incidence of rabies reported in travelers, the relatively high cost of

preexposure rabies prophylaxis (in excess of $300), and the need to begin the vaccination series at least 3 weeks before departure [10]. Nevertheless, preexposure prophylaxis should be considered for international travelers likely to come in contact with animals in areas where canine rabies is present and where immediate access to appropriate medical care, including safe and effective biologics, may be difficult. Sources of information on rabies in various geographic regions include the Centers for Disease Control and Prevention Travel Website [11].

Preexposure prophylaxis simplifies postexposure prophylaxis by eliminating the need for rabies immune globulin (RIG) and may provide a measure of protection in the event that a true exposure is not recognized. It does not eliminate the need for appropriate wound treatment and additional vaccinations in the case of a known exposure. Routine serologic testing to confirm seroconversion is not necessary except in the case of immunocompromised individuals. Chloroquine has been noted to reduce the response to the vaccine. Therefore, if preexposure prophylaxis is given ID, it must be completed prior to initiation of anti-malarial treatment. If a patient is already taking anti-malaria medications, the vaccine should be given IM [9].

2. ***A missionary traveling to Southeast Asia to do health care work wonders if the rabies vaccine is available should he need it.*** **What types of rabies biologics are available abroad?**

Cell culture vaccines are clearly the standard. They are effective and well tolerated. In the United States, human diploid cell vaccine (HDCV), rabies vaccine adsorbed (RVA) derived from fetal rhesus lung diploid cell, and purified chick embryo cell vaccine (PCEC) are available. Other cell culture vaccines used outside the United States include purified vero cell rabies vaccine (PVRV) and purified duck embryo vaccine (PDEV). In addition, many countries still

use vaccines produced from animal nerve tissue that have a high rate of adverse reactions (neuroparalytic reactions in 1 per 200 to 1 per 2000 persons vaccinated). Purified equine RIG has been used effectively in countries where human RIG is not available. Travelers should be aware that in some areas unpurified antirabies serum of equine origin immune globulin may be offered and is associated with a high rate of serious adverse reactions, including anaphylaxis [3,9].

3. ***A pet owner asks if she should obtain rabies vaccination because she thinks she got saliva on her hands while playing with her dog that had killed a rabid raccoon earlier that day.*** **What constitutes a rabies exposure?**

Rabies is transmitted when the virus is introduced into bite wounds, breaks in the skin, or onto mucous membranes. Three questions to ask are: 1) Was the person bitten?; 2) Did saliva or central nervous system material from a rabid animal contaminate an open wound or mucous membrane?; and 3) Was the animal in question a bat? (see question 4). If all can be answered no, then no exposure occurred and postexposure prophylaxis is not required. Petting a rabid animal, and contact with blood, urine, or feces of a rabid animal does not constitute an exposure and is not an indication for prophylaxis [9]. If the answer to at least one of these questions is yes, then exposure to rabies is a possibility and the likelihood that the animal has rabies must be considered (see table 2) [9].

Questions often arise regarding contact with saliva. In general, if the material containing the virus is dry it can be considered noninfectious because the rabies virus is inactivated by desiccation and ultraviolet radiation. Rabies cannot be transmitted from an animal that does not have active infection. Infectious material (saliva or neural tissue) would have to get in the mouth

or on the claw of that animal (the dog in the above scenario) and then promptly introduced through the skin or onto mucous membranes. This would be only remotely feasible in an immediate sequential exposure, and such a case has never been described. Local and state health departments can assist in deciding the likelihood that an animal has rabies and whether postexposure prophylaxis is indicated. Animals exposed to rabid animals need to be evaluated by a veterinarian and reported to the local health department immediately [12].

4. ***Parents, waking their 16-month-old son in the morning, find a bat in the corner of the room and they question if the child needs to see a doctor.*** **Why is there a concern about bats?**

Excluding dog bites that occurred outside of the country, 22 of the 31 (71%) human cases of rabies in the United States since 1980 have been associated with bat rabies virus variants. Although the histories sometimes conflict, of the 22 rabies patients, only 2 reported a bat bite, 10-12 had apparent contact with bats (many where saliva, teeth, or other contact likely occurred), and in 8-10 no exposure to bats or other source of infection was reported [6,9]. In these latter cases, an unreported or undetected bat bite remains the most plausible hypothesis. Therefore, postexposure prophylaxis should be considered when direct contact between a person and a bat might have occurred, unless the person can be certain a bite, scratch, or mucous membrane exposure did not occur; for example, consider the potential for direct contact in situations in which a sleeping person wakes to find a bat in the room or an adult witnesses a bat in the room with a previously unattended child, mentally disabled person, or intoxicated person [9]. Examination for a bite wound alone is inadequate [13]. If, as in the example above, the bat in question is available for testing, and a clear exposure has not occurred, initiation of postexposure

prophylaxis may be delayed 24-48 hours for testing of the bat. If a bite or other clear exposure occurs, postexposure prophylaxis should begin immediately and may be stopped if laboratory testing shows that the bat is not rabid [14].

5. ***Camping scouts notice several bats fluttering in the trees above them. Their adult leader wonders if they should get treatment.*** **Can rabies be caused by aerosol transmission?**

Although nonbite routes of infection are possible, they are exceedingly rare and not applicable to usual public exposures. There have been two reports of rabies transmission to laboratory workers. Both workers were exposed to concentrated aerosols of rabies virus [15]. In the 1950s, two cases of purported aerosol transmission to humans were associated with Frio Cave, Texas, which was inhabited by millions of bats. While the patients did not recall a bite before they died, complete exclusion of a bite is not possible [16]. The conditions under which aerosol transmission might occur are rare and unique, and it would be extremely unusual for them to be applicable to public exposures. Merely seeing a bat or being in the vicinity of bats does not constitute an exposure.

6. ***A nurse calls asking if she should give postexposure prophylaxis intradermally to a patient bitten by a rat.*** **How is the secondary or postexposure prophylaxis administered?**

Rabies prophylaxis in the setting of exposures to small mammals, including rodents, lagomorphs (rabbits and hares), and insectivores (e.g., shrews), is almost never required (see table 2). These animals are not reservoirs and there have been no documented cases of rabies transmission to humans by these animals [9]. If there is a question, a call to the local or state health department may be helpful.

When postexposure prophylaxis is required, all doses of vaccine are given IM in the deltoid area (anterolateral thigh is acceptable for small children). The gluteal area should not be used. For those who have had prior vaccination (with HDCV, RVA, or PCEC; or documented history of antibody response to other vaccines), only two doses are required and RIG should not be used. For those with no prior vaccination, RIG should be thoroughly infiltrated around the wound area. Any remaining should be injected IM at a site distant from the vaccine administration. If RIG was not given when vaccination was begun, it can be administered through the seventh day after vaccination was started. Beyond the seventh day it is not indicated (see table 3). Though no controlled trials have been performed, extensive experience from many parts of the world indicates that postexposure prophylaxis, consisting of local wound treatment, passive immunization (RIG), and vaccination, is effective if given in an appropriate and timely manner [9].

7. ***A student is bitten by a neighbor's dog on the way to school and presents to the emergency room for wound treatment. The emergency room providers wonder if rabies vaccination is needed at this time.*** **When can rabies prophylaxis be delayed while animals are held for quarantine and observation?**

A healthy dog, cat, or ferret that bites a person should be confined and observed for 10 days. Any illness in the animal should be reported immediately to the local health department and evaluated by a veterinarian. If the animal remains healthy, patients do not need to begin rabies prophylaxis. If the biting dog, cat, or ferret is a stray animal, it should either be observed for 10 days or be euthanized immediately and submitted for rabies examination. Management of animals other than dogs, cats, and ferrets depends on the species, the circumstances of the bite,

the epidemiology of rabies in the area, the biting animal's history and current health status, and potential for exposure to rabies. Public health and animal control officials can assist in these actions and decisions [9,12].

8. ***A physician calls the state health department inquiring if she should request rabies diagnostic tests on a comatose patient.*** **When should a diagnosis of rabies be considered and what specimens should be sent?**

Rabies should be considered in the differential diagnosis of any patient who presents with acute progressing encephalopathy of unknown cause. The lack of an exposure history should not deter pursuing the diagnosis, since most patients in the United States have no definitive exposure history [5]. Once symptoms of rabies begin, the natural history is rapid clinical deterioration and death. Patients with encephalopathy who are clinically improving generally do not need rabies testing.

If rabies is suspected, samples that should be sent for study include nuchal skin biopsy, saliva, serum, and cerebral spinal fluid. The postmortem diagnosis of rabies is made by examination of brain tissue. Because of the rarity of the disease and lack of effective treatment, antemortem brain biopsy is not indicated. However, biopsies done for other diseases (e.g., herpesvirus encephalitis), if negative, can be tested for evidence of rabies virus infection [2].

9. ***An emergency room doctor sees a patient with an infected raccoon bite 6 weeks after it occurred and questions if it is still useful to give rabies prophylaxis.*** **How long after an exposure would prophylaxis still be considered?**

Clearly, treatment with RIG and the vaccine should be given immediately if the exposure was high risk. The usual incubation period for rabies in humans is 3-8 weeks [4,17]. However, incubation periods of 6 years or longer have been documented [18]. Thus, if a true exposure has occurred, prophylaxis (including RIG) should still be given, regardless of the length of time between exposure and clinical presentation for evaluation, although no studies on the efficacy of such tactics are available.

10. ***A mother whose daughter has been scratched by a stray cat wonders what the risk of the RIG and vaccine is for her child.*** **What are the adverse reactions of the RIG and vaccine?**

With HDCV, local reactions (pain, erythema, swelling, itching) have been commonly reported (30-74%). Systemic reactions (headache, dizziness, abdominal pain, nausea, muscle aches) have been reported in 5-40% of recipients. Three cases of neurologic illness resembling Guillain-Barré syndrome that resolved without sequelae in 12 weeks have been reported. Rare reports of other nervous system disorders have been temporally associated with HDCV vaccine, but a causal relationship has not been established. There is no evidence that any viruses have ever been transmitted by commercially available RIG in the United States [9].

Of note, rabies is almost always caused by a bite. Non-bite exposures rarely cause rabies. Local or state public health officials should be contacted about the prevalence of rabies in any given area and the need to give prophylaxis for scratches or other low-risk encounters.

11. ***A patient with HIV infection wonders if his response to postexposure vaccination will be appropriate.*** **Do immunosuppressed patients require special consideration?**

Patients who are immunosuppressed should postpone preexposure vaccinations and avoid situations for which rabies preexposure prophylaxis is indicated. If this is not possible, they should be vaccinated by IM injection and have their antibody titer checked 2-4 weeks after the series. When postexposure prophylaxis is needed, it is also important that a serum sample be tested for rabies antibody to ensure that an acceptable response has developed. The minimum acceptable antibody level is complete virus neutralization at a 1:5 serum dilution by the rapid fluorescent focus inhibition test (RFFIT) [9]. No rabies postexposure failures have been attributed to HIV infection.

12. A camper has had the first two vaccine doses of the postexposure series when the state laboratory reports that the skunk that bit him tested negative. **What is the value of a negative direct fluorescent antibody (DFA) test?**

The direct fluorescent-antibody (DFA) test for detection of rabies virus antigen in brain tissue is used as the primary diagnostic test in every public health laboratory in the United States**,** and has a sensitivity approaching 100% [2]. Rabies diagnosis and prophylaxis of potential human exposures are based on the observation that the rabies virus reaches the salivary glands and is excreted in saliva only after replication in the central nervous system. Absence of rabies virus antigen in the brain of an animal by DFA examination (i.e., a negative diagnostic test result) essentially precludes the presence of virus in saliva, the risk of rabies transmission, and the need for postexposure prophylaxis. Since initiation of current testing procedures in 1958, there is no evidence that a false-negative laboratory test has ever led to rabies in a person subsequently left untreated [19].

Summary

Current public health practice has made human rabies rare in the United States. Preexposure prophylaxis is available for select high-risk groups. Potential exposures to rabies will continue to occur, and patients will often present to their physicians for guidance. A careful history of exposure and, if needed, consultation with state health departments can guide the use of postexposure prophylaxis. Appropriate wound treatment and administration of rabies vaccines and RIG prevent rabies infection in exposed individuals. Further information, including the recommendations of the Advisory Committee on Immunization Practices (ACIP), can be found at the following CDC website, www.cdc.gov/ncidod/dvrd/rabies.

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Table 1. Rabies preexposure prophylaxis guide, United States, 1999

Risk category	Nature of risk	Typical populations	Preexposure recommendations
Continuous	Virus present continuously, often in high concentrations. Specific exposures likely to go unrecognized. Bite, nonbite or aerosol exposure.	Rabies research laboratory workers;* rabies biologics production workers.	Primary course. Serologic testing every 6 months; booster vaccination if antibody titer is below acceptable level.+
Frequent	Exposure usually episodic, with source recognized, but exposure may also be unrecognized. Bite, nonbite or aerosol exposure.	Rabies diagnostic lab workers,* spelunkers, veterinarians and staff, and animal-control and wildlife workers in rabies enzootic areas.	Primary course. Serologic testing every 2 years; booster vaccination if antibody titer is below acceptable level.+
Infrequent (greater than the population at large)	Exposure nearly always episodic with source recognized. Bite, or nonbite exposure.	Veterinarians and animal-control and wildlife workers in areas of low rabies rates. Veterinary students. Travellers visiting areas where rabies is enzootic and immediate access to appropriate medical care including biologics is limited.	Primary course. No serologic testing or booster vaccination.
Rare (population at large)	Exposures always episodic with source recognized. Bite or non-bite exposure.	U.S. population at large, including persons in rabies epizootic areas.	No vaccination necessary.

* Judgment of relative risk and extra monitoring of vaccination status of laboratory workers is the responsibility of the laboratory supervisor (43).
+ Minimum acceptable antibody level is complete virus neutralization at a 1:5 serum dilution by rapid fluorescent focus inhibition test. A booster dose should be administered if the titer falls below this level.

Table 2. Rabies postexposure prophylaxis guide, United States, 1999

Animal type	Evaluation and disposition of animal	Postexposure prophylaxis recommendations
Dogs, cats, and ferrets	Healthy and available for 10 days observation	Should not begin prophylaxis unless animal develops clinical signs of rabies.*
	Rabid or suspected rabid	Immediately vaccinate.
	Unknown (e.g., escaped)	Consult public health officials.
Skunks, raccoons, foxes, and most other carnivores; bats	Regard as rabid unless animal proven negative by laboratory tests+	Consider immediate vaccination.
Livestock, small rodents, lagomorphs (rabbits and hares), large rodents (woodchucks and beavers), and other mammals	Consider individually	Consult public health officials. Bites of squirrels, hamsters, guinea pigs, gerbils, chipmunks, rats, mice, other small rodents, rabbits, and hares almost never require antirabies postexposure prophylaxis

*During the 10-day observation period, begin postexposure prophylaxis at first sign of rabies in a dog, cat, or ferret that has bitten someone. If the animal exhibits clinical signs of rabies, it should be euthanized immediately and tested.

+ The animal should be euthanized and tested as soon as possible. Holding for observation is not recommended. Discontinue vaccine if immunofluorescence test results of the animal are negative.

Table 3. Rabies postexposure prophylaxis schedule, United States, 1999

Vaccination status	Treatment	Regimen*
Not previously vaccinated	Wound cleansing	All postexposure treatment should begin with immediate thorough cleansing of all wounds with soap and water. If available, a virucidal agent such povidone-iodine solution should be used to irrigate the wounds.
	RIG	Administer 20 IU/kg body weight. If anatomically feasible, the full dose should be infiltrated around the wound(s), and any remaining volume should be administered IM at an anatomical site distant from vaccine administration. Also, RIG should not be administered in the same syringe as vaccine. Because RIG may partially suppress active production of antibody, no more than the recommended dose should be given.
	Vaccine	HDCV, RVA, or PCEC 1.0 ml, IM (deltoid area+), one each on days 0§, 3, 7, 14, and 28.
Previously vaccinated^	Wound cleansing	All postexposure treatment should begin with immediate thorough cleansing of all wounds with soap and water. If available, a virucidal agent such povidone-iodine solution should be used to irrigate the wounds.
	RIG	RIG should not be administered.
	Vaccine	HDCV, RVA, or PCEC 1.0 ml, IM (deltoid area+), one each on days 0§ and 3.

HDCV=human diploid cell vaccine; PCEC=purified chich embryo cell vaccine; RIG=rabies immune globulin; RVA=rabies vaccine adsorbed; IM, intramuscular.

* These regimens are applicable for all age groups, including children.

+ The deltoid area is the only acceptable site of vaccination for adults and older children. For younger children, the outer aspect of the thigh may be used. Vaccine should never be administered in the gluteal area.

§ Day 0 is the day the first dose of vaccine is administered.

^ Any person with a history of preexposure vaccination with HDCV, RVA, or PCEC; prior postexposure prophylaxis with HDCV, RVA, or PCEC; or previous vaccination with any other type of rabies vaccine and a documented history of antibody response to the prior vaccination.