Human Rabies: A Review

ROBERT H. BAEVSKY, MD, JOEL M. BARTFIELD, MD

Human rabies is a rarely observed but frequently prophylaxed disease in North America. Presented in this review is a typical emergency department case and a summary of the epidemiology of the rabies virus, its clinical appearances, diagnosis, and management. Emphasis is placed on issues pertinent to the emergency physician practicing in the United States. Current recommendations for the administration of both active and passive immunotherapy for preexposure and postexposure prophylaxis are discussed. A treatment algorithm to aid in the decisions faced by a practicing physician regarding proper animal management and patient therapy and future prospects for the control of rabies in wild animal populations are also included. (Am J Emerg Med 1993;11:279-286. Copyright © 1993 by W.B. Saunders Company)

CASE REPORT

A healthy 8-year-old girl living in rural upstate New York was awakened at 1:00 AM by a "scratching" sensation on her neck from under her nightgown. After frantically removing her clothing, she discovered a black furry animal about the size of a mouse and screamed for her parents. They were unable to locate any creature, but were impressed with two small scratch marks on their daughter's chest. In the morning, a small bat was found sleeping next to the dog's dish on the kitchen floor. The parents later recalled seeing a bat behind the glassed-in fireplace earlier the previous day. After capture and examination by the Department of Public Health (DPH), it was determined that the bat was in fact a carrier of the rabies virus. The little girl was sent immediately to the regional medical center for further evaluation and treatment.

On arrival at the hospital, the child was playful and in no apparent distress. Her vital signs and physical examination were remarkable only for two 1 cm faint scratch marks noted on the thorax along the left anterior axillary line. No bleeding, evidence of puncture, or infection was appreciated. It was noted that the child had showered that morning and washed the area in question thoroughly with warm soapy water. She was up to date on her tetanus vaccinations.

Because of the known intimate exposure to a rabid animal, prophylaxis was warranted and therapy was initiated. The child was given human rabies immune globulin (HRIG) 20 IU/kg one half infiltrated at the site of the scratch, and half in her right buttock. She was also begun on human diploid cell rabies vaccine (HDCV) 1.0 mL given intramuscularly (IM) in the left deltoid region. No complications developed, and she was released after 30 minutes of observation with instructions to return on days 3, 7, 14, and 28 for repeat HDCV shots. The child completed the full series of immunizations. There were no sequelae from the episode, and the patient did expectantly well.

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One hundred years ago, Louis Pasteur developed the first immunological treatment for rabies, a disease that dates back as far as 2300 BC. Since that time, our knowledge in the fields of virology and immunology have allowed us to expand treatment options greatly. However, despite large gains in technology, it remains a prevalent, worldwide killer of thousands of people every year. Rabies has remained extraordinary among infectious diseases because of its epidemiological distribution and uniformly fatal outcome after symptoms have appeared in an immunologically unprotected individual.

Presently, rabies accounts for 20,000 or more deaths reported to the World Health Organization (WHO) per year, a figure that according to other reports, may underestimate the true incidence by 50% to 100%. In the United States, with the decrease in the number of rabid dogs, there has been a corresponding drop in human cases from dozens to now less than one per year. Thirteen cases of human rabies were reported to the Centers for Disease Control (CDC) from 1980 to 1990, although only four were acquired domestically. In this country, the estimated costs of postexposure prophylaxis to more than 20,000 patients annually and vaccination of home pets (mostly canine and feline species) is more than $300 million per year. The dismal prognosis of patients with clinical disease justifies this high cost of prevention, despite the low incidence of disease.

Virology/Epidemiology

Rabies is caused by a rhabdovirus. Of the six rabies-related viruses that have been identified, only the Mokola and Duvenhage viruses are known to cause human disease. The virus causes illness primarily in animals, with human infection paralleling the animal prevalence. It is most often transmitted by saliva injection sustained by a bite wound, but other environmental exposures have been documented, including aerosolized virus, such as those in laboratories and bat caves, and viral contact with scratches, conjunctivae, or mucous membranes. There are four case reports of rabies being transmitted by corneal transplants and numerous unusual modes of transmission in anecdotal reports, such as kissing, sexual intercourse, application of human saliva to a circumcision wound, and transmission in animals by lactating mothers to suckling young.

In the United States, the striped skunk (38% of reported cases), raccoon (31%), and insectivorous bat (14%), remain the principal wildlife vectors (Table 1). Not all animals have the same susceptibility to infection from the virus. Most carnivorous wild animals are highly susceptible (foxes and wolves), whereas skunks, raccoons, bats, and bobcats are only moderately susceptible. Opossum are known to be quite resistant. Birds and rodents, such as squirrels, chipmunks, rats, mice, and rabbits, are not known to serve as natural reservoirs of the virus. Fish, snakes, turtles, and other reptiles are not known to be viral carriers.
TABLE 1. US Vectors of Animal Rabies Virus*

<table>
<thead>
<tr>
<th>High risk†</th>
<th>Low Risk‡</th>
<th>Potential Risk§</th>
<th>Noncarriers³</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bats</td>
<td>Opossum</td>
<td>Adequately vaccinated animals</td>
<td>Amphibians</td>
</tr>
<tr>
<td>Bears</td>
<td>Unvaccinated pets</td>
<td>Birds</td>
<td>Fish</td>
</tr>
<tr>
<td>Beavers</td>
<td>Unvaccinated farm animals</td>
<td>Chipmunks</td>
<td>insects</td>
</tr>
<tr>
<td>Bobcats</td>
<td>Cows</td>
<td>Humans</td>
<td>Reptiles</td>
</tr>
<tr>
<td>Foxes</td>
<td>Goats</td>
<td>Rabbits</td>
<td></td>
</tr>
<tr>
<td>Raccoons</td>
<td>Horses</td>
<td>Rats/mice</td>
<td></td>
</tr>
<tr>
<td>Skunks</td>
<td>Pigs</td>
<td>Squirrels</td>
<td></td>
</tr>
<tr>
<td>Wild dogs/cats</td>
<td>Woodchucks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wolves</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* A complete list of regional viral vectors can be obtained from the local DPH.
† Frequently reported carriers of the rabies virus.
‡ Rarely reported carriers of rabies virus, but with regional clustering of outbreaks.
§ Capable of harboring the rabies virus but species considered rabies-free.
³ Species not known to physiologically be capable of hosting the rabies virus.

In North America and Western Europe, domestic animal rabies is well controlled. In 1988, there were 550 reported cases of domestic animal rabies in the United States. Cats were the most frequently infected species (35%), and cattle (31%) and dogs (23%) accounted for a majority of the rest.4 Unimmunized farm animals (horses, mules, sheep, and swine) contributed 11% of the reported cases; properly vaccinated farm animals and exotic pets, such as skunks, raccoons and ferrets, were infrequently infected.4,6,11 In Mexico, 93% of rabies cases in 1988 were from dogs, whereas in Canada, cattle (14% of all rabid animals), cats (4%), and dogs (3%) were most commonly infected.4

Sixty countries, along with the Antarctic and Australia, presently are reported to be rabies-free, secondary to successful disease- and virus-control programs.12 Hawaii is the only state with no reported cases. Within the US, rabies vectors are regional and highly variable. For example, bats are still the principal vector in New England (despite a recent sharp increase in raccoon rabies in 1992),11 whereas skunks are the dominant vector in California.4 If a patient’s exposure is in question, the local public health department should be contacted to determine the region’s rabid animal population.

CLINICAL COURSE

The first stage of rabies, the incubation period, usually lasts from 20 to 90 days, and is defined as the time from virus contact to the onset of any symptoms. Because of viral, host, and unknown factors, a specific individual’s time course can be highly variable. The incubation period has been reported to last as briefly as only 4 days and as prolonged as 19 years.13 but 75% of those affected will have a duration of 1 to 3 months. Only 1% of cases have an incubation period of more than 1 year.14

The variable time course for incubation may be related to the age and immune status of the host, the wound’s location and severity, and the total virus inoculum implanted. Children and patients who are immunocompromised or who have received more severe and more proximal bite injuries, have been noted to have a shorter time course. Bites to the head and neck have an incubation period of 25 to 48 days compared with the more distal injury to the extremities, which have a period of 46 to 78 days.15,16

The virus is believed to first remain localized to the initial site of infection, multiplying within myocytes,17 although its exact location remains unknown. Next, while continuing reproduction, the virus begins to travel to the central nervous system via peripheral nerves, moving at a rate of 3 mm per hour, with a predilection for the limbic region. The virus then moves from the brain via efferent nerves. Most body tissues become infected, including mucus cells of the salivary glands, which are vital to the virus’s life cycle.

Other than wound healing, the patient will remain asymptomatic. Thus, without obtaining an adequate history suggestive for rabies, the treating emergency physician will likely not entertain the correct diagnosis during this period.

The second stage, the prodrome period, lasts from 2 to 10 days,18 and is marked by the onset of the early symptoms of rabies. Pruritus involving the healed wound or the entire bitten limb is the earliest symptom observed in more than 40% of those afflicted,8 and up to two-thirds of patients complain of pain, paraesthesia, or pruritus at the bite site.19 The other prodromal symptoms are very nonspecific and range from those of an upper respiratory infection (headache, fever, sore throat, chills, and malaise) to agitation, gastroenteritis (abdominal pain, nausea, vomiting, and diarrhea), and priapism.14 Rabies should be considered as a possible diagnosis in any patient with an unexplained myelitis or encephalitis. At this stage, the symptoms are nonspecific, the differential is extensive, and, therefore, misdiagnosis is common until more definitive symptoms develop.20

The third stage of rabies, the neurological period, lasts for 2 to 7 days,21 and starts when the patient first manifests clinical symptoms of central nervous system involvement. During this period, a patient’s mental status progressively deteriorates, but episodic spans of normality are observed.

This phase may be divided into two symptom complexes, the furious and the paralytic forms, although the division between them is not absolute. “Furious” rabies, may last from hours to days, and is typified by the well-known symptoms of the disease, including hyperactivity, bizarre behavior, and hallucinations. Brief periods of extreme aggression (biting, thrashing about, running, yelling, and hitting others) are interspersed with periods of calm and lucidity. Visual, tactile, or auditory stimuli may trigger the hyperagitation. In more than half of all patients, attempts at drinking liquids (hydrophobia) or blowing air onto the patient’s face (aero-
phobia) gives rise to violent, jerky contractions of the dia-
phragm, and accessory muscles of inspiration. These fits
are not usually associated with throat pain or laryngopha-
ryngeal spasm, but are considered to be an exaggerated res-
piratory tract protective reflex. Opisthotonos, hyperventi-
lation, cholinergic symptoms (hypersalivation, lacrimation,
mydriasis, and hyperpyrexia), seizures, hyperreflexia, and
muscular fasciculations may also present during this phase.

Paralytic rabies emerges if the patient has not succumbed
to cardiac or respiratory collapse during the furious stage.
Nuchal rigidity, paresis, and symmetrical or asymmetrical
paralysis, usually most pronounced in the bitten extremity,
develops. The paralysis often parallels the course of a Guil-
lain-Barré-like syndrome. Twenty percent of patients will
present with only paralytic symptomatology, although it is
most frequently observed as the exclusive manifestation af-
ter bat exposure.

Once the more typical symptoms of rabies have emerged,
a more limited differential diagnosis may be considered (Ta-
ble 2). A definitive diagnosis will still require viral isolation
or tissue testing (see Diagnosis), whereas treatment options
are limited to supportive care.

The fourth stage of rabies begins with initiation of coma. If
a person lives to this phase (2 to 10 days after the onset of
symptoms), one can expect death to occur within 7 days,
usually from respiratory arrest. With costly, intensive med-
care, the average duration of illness in the US is 25
days. Despite optimal medical therapy, without specific
antiviral preexposure or timely postexposure treatment, ra-
bies can be considered uniformly fatal.

TABLE 2. Differential Diagnosis of Rabies—Third Stage

<table>
<thead>
<tr>
<th>Major illnesses to consider</th>
<th>Presence of a serological or CSF titer in a patient indicates previous vaccination or viral exposure.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Botulism</td>
<td>Once the more typical symptoms of rabies have emerged, a more limited differential diagnosis may be considered (Table 2).</td>
</tr>
<tr>
<td>Cerebral malaria</td>
<td>A definitive diagnosis will still require viral isolation or tissue testing (see Diagnosis), whereas treatment options are limited to supportive care.</td>
</tr>
<tr>
<td>CNS hypoxia</td>
<td>The fourth stage of rabies begins with initiation of coma. If a person lives to this phase (2 to 10 days after the onset of symptoms), one can expect death to occur within 7 days, usually from respiratory arrest. With costly, intensive medical care, the average duration of illness in the US is 25 days. Despite optimal medical therapy, without specific antiviral preexposure or timely postexposure treatment, rabies can be considered uniformly fatal.</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>The potential for a long, asymptomatic incubation period for the virus, coupled with a patient’s possible inability to recall a history of contact with a known rabies vector, means that a positive titer in an unvaccinated individual warrants postexposure treatment. Except in the rare case of a patient who develops a postvaccinal allergic encephalomyelitis, CSF antibodies are not produced after vaccination.</td>
</tr>
<tr>
<td>Guillain-Barré syndrome</td>
<td>After infection, the virus is immunologically protected within its host’s cells, and antibodies are not produced until clinical symptoms have appeared. Titers are generally high enough to inactivate the virus within 2 weeks after the onset of symptoms. This unfortunately causes a significant decrease in the yield from attempted virus culturing. Thus, an early test for the detection of a true viral infection in humans is difficult. In the US, testing for the presence of the</td>
</tr>
<tr>
<td>Intracranial mass lesions</td>
<td>Serum antibodies may be demonstrated as early as 6 days after symptoms have developed, although all patients will show some antibody level by day number 13. CSF antibodies are usually demonstrable 1 week after they have become present in the serum.</td>
</tr>
<tr>
<td>Metabolic encephalopathy</td>
<td>Presence of a serological or CSF titer in a patient indicates previous vaccination or viral exposure. The rapid fluorescent focus inhibition test (RFFIT) is the standard for measuring neutralizing antibody, although other equally sensitive tests, such as the Rapid Rabies Enzyme Immuno-Diagnosis (RREID), are also being used. These tests require less than 1 day to complete and have a specificity approaching 100%, with a sensitivity of approximately 90%. Serum antibodies may be demonstrated as early as 6 days after symptoms have developed, although all patients will show some antibody level by day number 13. CSF antibodies are usually demonstrable 1 week after they have become present in the serum.</td>
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<tr>
<td>Pharmacological</td>
<td>Antibodies may be demonstrated as early as 6 days after symptoms have developed, although all patients will show some antibody level by day number 13. CSF antibodies are usually demonstrable 1 week after they have become present in the serum.</td>
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<td>Drug/alcohol withdrawal</td>
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<td>Anticholinergic/dopaminergic/atropine reactions</td>
<td>Serum antibodies may be demonstrated as early as 6 days after symptoms have developed, although all patients will show some antibody level by day number 13. CSF antibodies are usually demonstrable 1 week after they have become present in the serum.</td>
</tr>
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<td>Heroin/cocaine/LSD reactions</td>
<td>After infection, the virus is immunologically protected within its host’s cells, and antibodies are not produced until clinical symptoms have appeared. Titers are generally high enough to inactivate the virus within 2 weeks after the onset of symptoms. This unfortunately causes a significant decrease in the yield from attempted virus culturing. Thus, an early test for the detection of a true viral infection in humans is difficult. In the US, testing for the presence of the</td>
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<td>Postvaccinal encephalomyelitis</td>
<td>Antibodies may be demonstrated as early as 6 days after symptoms have developed, although all patients will show some antibody level by day number 13. CSF antibodies are usually demonstrable 1 week after they have become present in the serum.</td>
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<tr>
<td>Psychiatric</td>
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<td>Rabies hysteria</td>
<td>Serum antibodies may be demonstrated as early as 6 days after symptoms have developed, although all patients will show some antibody level by day number 13. CSF antibodies are usually demonstrable 1 week after they have become present in the serum.</td>
</tr>
<tr>
<td>Schizophrenia/mania/conversion reactions</td>
<td>After infection, the virus is immunologically protected within its host’s cells, and antibodies are not produced until clinical symptoms have appeared. Titers are generally high enough to inactivate the virus within 2 weeks after the onset of symptoms. This unfortunately causes a significant decrease in the yield from attempted virus culturing. Thus, an early test for the detection of a true viral infection in humans is difficult. In the US, testing for the presence of the</td>
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<td>Flickertail diseases</td>
<td>Serum antibodies may be demonstrated as early as 6 days after symptoms have developed, although all patients will show some antibody level by day number 13. CSF antibodies are usually demonstrable 1 week after they have become present in the serum.</td>
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<tr>
<td>Stroke</td>
<td>Serum antibodies may be demonstrated as early as 6 days after symptoms have developed, although all patients will show some antibody level by day number 13. CSF antibodies are usually demonstrable 1 week after they have become present in the serum.</td>
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<tr>
<td>Tetanus</td>
<td>Serum antibodies may be demonstrated as early as 6 days after symptoms have developed, although all patients will show some antibody level by day number 13. CSF antibodies are usually demonstrable 1 week after they have become present in the serum.</td>
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<td>Typhoid</td>
<td>Serum antibodies may be demonstrated as early as 6 days after symptoms have developed, although all patients will show some antibody level by day number 13. CSF antibodies are usually demonstrable 1 week after they have become present in the serum.</td>
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<tr>
<td>Viral Encephalitis</td>
<td>Serum antibodies may be demonstrated as early as 6 days after symptoms have developed, although all patients will show some antibody level by day number 13. CSF antibodies are usually demonstrable 1 week after they have become present in the serum.</td>
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<tr>
<td>Arbo</td>
<td>Serum antibodies may be demonstrated as early as 6 days after symptoms have developed, although all patients will show some antibody level by day number 13. CSF antibodies are usually demonstrable 1 week after they have become present in the serum.</td>
</tr>
<tr>
<td>Eastern equine</td>
<td>Serum antibodies may be demonstrated as early as 6 days after symptoms have developed, although all patients will show some antibody level by day number 13. CSF antibodies are usually demonstrable 1 week after they have become present in the serum.</td>
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<td>Herpes</td>
<td>Serum antibodies may be demonstrated as early as 6 days after symptoms have developed, although all patients will show some antibody level by day number 13. CSF antibodies are usually demonstrable 1 week after they have become present in the serum.</td>
</tr>
<tr>
<td>La crosse</td>
<td>Serum antibodies may be demonstrated as early as 6 days after symptoms have developed, although all patients will show some antibody level by day number 13. CSF antibodies are usually demonstrable 1 week after they have become present in the serum.</td>
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<td>St Louis</td>
<td>Serum antibodies may be demonstrated as early as 6 days after symptoms have developed, although all patients will show some antibody level by day number 13. CSF antibodies are usually demonstrable 1 week after they have become present in the serum.</td>
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<td>Venomzuelan equino</td>
<td>Serum antibodies may be demonstrated as early as 6 days after symptoms have developed, although all patients will show some antibody level by day number 13. CSF antibodies are usually demonstrable 1 week after they have become present in the serum.</td>
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</tbody>
</table>

Abbreviations: CNS, central nervous system; LSD, Lysergic acid diethylamide.
The rabies virus is limited to confirmation purposes only and not for the modification of treatment.

Viral recovery from saliva, brain tissue, CSF, urine, and pulmonary secretions have yielded the best results, although all body tissues are presumed infected. Some investigators advocate obtaining a 5- to 10-mm skin biopsy from the nape of the neck, just above the hair line. Isolation of the virus from blood, serum, and stool has only been reported anecdotally. The Department of Public Health should be contacted for instructions on the proper handling procedures for any tissue specimens to be obtained.

The culturing techniques for the rabies virus requires mouse inoculation of infected tissue and up to 4 weeks of observation time. If the mouse manifests symptoms, usually between 5 and 15 days, it is killed, and its brain tissue examined by direct fluorescent antibody testing. Using tissue obtained from a neck biopsy has been shown to have a specificity approaching 100%, but a sensitivity of only between 50% to 94%. Routinely blood chemistry values of infected patients will reflect premorbid metabolic abnormalities, but otherwise remain unaffected. Leukocyte counts typically range from 8,000 to 13,000/mm³, with a relatively unremarkable differential. A slowly progressive encephalitis may develop. Lumbar puncture may show an elevated pressure, and CSF analysis will be notable only for a variable leukocytosis and a mild protein elevation. Examination of brain tissue shows perivascular leukocyte infiltration, ganglionic lesions, and often cerebral edema. Eighty percent of cases will demonstrate the Negri body. These 2- to 10-µm eosinophilic structures are found in the cytoplasm of nerve cells, especially those of the hippocampus. Although thought to be pathognomonic for rabies, the Negri body has been found on postmortem examination of a child with Reyes syndrome.

TREATMENT

Even though rabies carries a high mortality, its infectivity rate is relatively low. The probability of an untreated person surviving a bite by a rabid animal is estimated to be 80% to 85%. Should clinical rabies develop, treatment is aimed at managing the multiple complications that have been reported.

Isolation and cautious management of all body fluids is essential. To best protect the health care worker from accidental transmission of the virus from an infected patient or rabid tissue, strict adherence to universal precautions must be maintained.

Patients will frequently require large doses of narcotic analgesics and sedation to help control their pain and terror. Most of the medical problems will appear during the coma phase of the illness and may involve every organ system. Death is caused by multiple-organ dysfunction, including, but not limited to, cardiac arrhythmias, congestive heart failure, acute respiratory distress syndrome (ARDS), autonomic dysfunction, and pulmonary or circulatory collapse.

Recovery from rabies has been reported only three times. In each instance, preexposure or postexposure prophylaxis had been administered, and in all cases, convalescence took a period of several months.

PREEXPOSURE MANAGEMENT

As with any vaccination series, administration of the rabies vaccine before any contact with the live virus will generate adequate antiviral antibody titers, rendering the patient immune. Preexposure immunization is recommended for those persons involved in wildlife management and treatment, veterinary medicine, rabies research, vaccine development, and spelunking. Presently, efforts have only been directed towards these high-risk populations.

Travelers going to areas for more than 30 days where dog rabies is known to be endemic, and a delay in receiving postexposure prophylaxis is likely, should also be vaccinated. The prophylaxis-injection series should be completed at least 30 days before departure. If there is less than 4 weeks time, or chloroquine (as an antimalarial agent) is to be given, then all vaccine injections should be administered via the intramuscular (IM) route.

Current recommendations in the United States are for the use of the human diploid cell vaccine (HDCV; Immovax Rabies, tel: 1-800-VAC-CINE), an inactivated-virus preparation. This should be administered IM as a 1.0 mL dose on days 0, 7, and 21 or 28. The vaccine must be given into the deltoid region because administration into the gluteal area is associated with loss of antigen to fat tissue and reported clinical failure. In very young children, the anterolateral aspect of the thigh may be used.

The World Health Organization (WHO) and CIE alternatively recommend an intradermal (ID) administration of 0.1 mL given in three doses. Although shown to be efficacious, this route of administration has recently been questioned when compared with IM administration. Although not approved for use in the US, successful alternative regimens include 2-day schedules (days 0 and 28) via subcutaneous (SC) and IM deltoid routes, and a 3-day SC regimen of 0.1 mL on days 0, 7, and 28.

A booster shot is no longer routinely recommended by the CDC when the HDCV is administered appropriately, except when the patient is immunocompromised, an incomplete series is administered, or is needed as determined by serological titers. Immunity is assumed after proper vaccination of a healthy individual. For those people at consistently high risk of exposure (ie, research workers), titers should be checked every 6 months. All other vaccinated individuals should have their titers checked every 2 years if a rabies risk persists. Presently, a titer level of =.5 IU is considered to offer satisfactory protection from the rabies virus.

Although a high margin of safety exists with the HDCV, nonfatal systemic allergic reactions (hives and angioedema) are observed in up to 20% of patients. These usually develop after administration of a booster dose. A Guillain-Barre syndrome has also been reported. Unless absolutely needed, steroids should not be used to treat allergic reactions, as this will reduce the desired antibody response. The vaccine is not contraindicated during pregnancy.

In March of 1988, Rabies Vaccine Absorbed (RVA; Biologics Products Program, Michigan Department of Health; tel: 1-517-335-8050) was licensed in the United States as an alternative vaccine for rabies. RVA should be administered only via the IM route. When given as a 1.0 mL dosage, it has
been shown to be as safe and effective for both preexposure and postexposure prophylaxis as the HDCV.36

If another vaccine, such as the suckling mouse brain vaccine (SMB), adult animal nerve tissue vaccine (NTV) or the duck embryo vaccine (DEV), is used, then serum antibody titers are recommended after administering the last dose. These vaccines are not readily available in the US because of their higher rates of inefficacy and side effects.

**POSTEXPOSURE MANAGEMENT**

There have been no case reports of individuals receiving appropriate postexposure treatment who then subsequently manifested symptoms and died from rabies. It should be stressed again, once clinical evidence of rabies has appeared, there is presently no available treatment beyond supportive care.

As with any wound, local care is important. A prompt, thorough washing of the exposed area with soap or iodine solution, has been shown to reduce the incidence of developing rabies up to 90%. Debridement should be performed when appropriate, and suturing avoided when possible. Occlusive dressings and topical nitrates should not be used. Additionally, tetanus immunization status should be addressed (Table 3).

After proper wound management is completed, the physician must decide whether or not a potential rabies exposure has occurred, thus mandating postexposure prophylaxis (Figure 1). Fifty-five percent of the more than 20,000 patients per year who receive postexposure prophylaxis in the US are reported to have had contact with dogs or cats, half of whom were not bitten.44 An encounter with a previously vaccinated animal, or simply touching a rabid animal, its blood, urine, or feces does not constitute an exposure that warrants prophylaxis. The virus does not penetrate intact skin. A bite, scratch, or lick to an open wound or mucous membrane, is considered significant.45

If a patient has come in contact with a known vector for rabies (Table 1) and a treatable exposure has occurred, concern must then be directed towards initiating proper postexposure therapy (Figure 1). If the exposure was with a dog or cat, treatment may be delayed if quarantining of the animal is done (see Animal Management). Treatment must otherwise begin immediately, although it may be terminated if laboratory testing later determines the potential vector to be nonrabid.

Specific rabies postexposure therapy is based on administering two components of treatment, passive (immunoglobulin) and active (vaccine) immunization (Table 3). If given properly, early, and before symptoms, death from rabies is preventable.

The DPH should always be notified of any suspected case of rabies to assist in proper disease control and in the locating of all possible viral contacts. They will also help in answering any questions that may arise regarding a possible exposure, treatment protocols, or on the handling of any animals (living or dead), and tissue specimens. Any further information may be obtained from the CDC’s Viral and Rickettsial Zoonosis Branch, Division of Viral and Rickettsial Diseases, National Center for Infectious Diseases (tel: 1-404-639-1075).

**TABLE 3. Postexposure Prophylaxis for Rabies**

<table>
<thead>
<tr>
<th>Unprotected exposure*</th>
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</thead>
<tbody>
<tr>
<td>Wash wound thoroughly, debridement, avoid occlusive dressings</td>
</tr>
<tr>
<td>Assess patient’s tetanus status</td>
</tr>
<tr>
<td>Administer passive immunization†</td>
</tr>
<tr>
<td>HRIG (20 IU/kg) one-half infiltrated around site of exposure; one-half IM into the gluteal region</td>
</tr>
<tr>
<td>Administer active immunization</td>
</tr>
<tr>
<td>HDCV or RVA (1.0 mL) IM into the deltoid region‡ on days 0, 3, 7, 14, 28</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Protected exposure§</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wash wound thoroughly, debridement, avoid occlusive dressings</td>
</tr>
<tr>
<td>Assess patient’s tetanus status</td>
</tr>
<tr>
<td>Administer Active Immunization:</td>
</tr>
<tr>
<td>HDCV or RVA (1.0 mL) IM into the deltoid region‡ on days: 0 and 3</td>
</tr>
</tbody>
</table>

* Patient not previously vaccinated or treated for rabies.
† Administer HRIG only within seven days after first dose of vaccine.
‡ An acceptable alternative site for young children is the anterolateral thigh.
§ Patients previously adequately vaccinated or treated for rabies.

**FIGURE 1. Algorithm for postexposure rabies management.**

1. Bite or lick to an open wound or mucous membrane; (2) regional viral vectors can be obtained from the local DPH; (3) no HRIG needs to be administered (see text); (4) both HRIG and vaccine need to be administered (see text); and (5) delay in treatment may occur pending immunofluorescent antibody testing results.
not been reported to be a vehicle for the transmission of hepatitis or the human immunodeficiency virus (HIV).19

A single 20 IU/kg dose is administered (1 mL = 150 IU of neutralizing antibody); one half is infiltrated around the site of rabies exposure and the second half is given IM in the upperouter quadrant of the buttocks or the anterolateral aspect of the thigh. The dose that is infiltrated at the wound site should be appropriately reduced if the anatomic site is small (ie, fingertip or nose). Care should be taken to prevent the inadvertent administration of the antiserum using the same syringe or at the same IM site as the vaccine injection.

Regardless of the length of time between contact and the initiation of postexposure treatment, HRIG should be administered along with the first dose of vaccine (see Vaccine). Although not available in the US, equine antirabies serum, ERIG (40 IU/kg IM dose), or a suitable alternative must be administered if HRIG is unavailable. If the vaccine series is initiated without administering passive immunization, it is recommended that HRIG be used only within the first 7 days, after which time an appropriate antibody response will have been generated.46

If a person has known preexposure prophylaxis with adequate antibody titers, or a history of previous immunization to rabies, HRIG does not need to be administered.

**Vaccine**

In the US, the human diploid cell vaccine (HDCV) and the Rabies Vaccine Absorbed (RVA) are currently recommended,36 and should be given as 1.0 mL IM doses on days 0, 3, 7, 14, and 28 in the deltoid muscle (Table 3). In children, the anterolateral aspect of the thigh is an acceptable alternative site of administration. The series should start as soon as possible after the rabies exposure, with infants and children receiving the same quantity and number of shots as the adult. As previously stated, inadvertent administration of the vaccine using the same syringe or at the same IM site as the antiserum should be avoided. Antibody titers need to be determined only in those individuals who are immunocompromised or do not complete the entire five-injection series. Although not approved for use in this country, other vaccines, regimens, and modes of administration (ie, intradermally) have been effectively demonstrated.5,47,48

As previously mentioned, there is a risk of systemic allergic reactions to the vaccine. These typically will appear between 2 to 14 days after an injection is given.49

If a person has successfully completed preexposure prophylaxis or undergone previous immunization, only two 1.0 mL injections (on days 0 and 3) need to be administered, and antiserum is not required.

**ANIMAL MANAGEMENT**

The most efficient means of controlling the rabies virus is through measures aimed at limiting its animal-population vector. Although vaccination programs of farm animals and household pets in the US have proven to be highly successful,50 not all regions have obtained rabies-free status.

A rabid animal may present clinically with bizarre or furious behavior, hypersalivation, unprovoked attacks, or the appearance during daylight hours of a nocturnal species. Alternatively, there may be no outward signs of infection on inspection of the animal.

If the suspected animal is wild and a member of a species known to carry the virus (Table 1), or is clinically rabid, immediate treatment of any person with a contact exposure, is recommended.42 The patient's vaccination series may be terminated if the animal under investigation is later found to be nonrabid.

If the animal is unwanted or clinically rabid, it should be killed, the refrigerated brain examined by direct fluorescent antibody testing, and the body properly disposed. Immunofluorescent staining for the rabies virus on fresh tissue from the limbic, cerebellar, or brain stem regions will make the definitive diagnosis and will yield the best results.51 Universal precautions should be maintained at all times to minimize potential further exposure. Notification of the DPH will help ensure proper handling procedures for any live animal or tissue specimen.

The issue becomes more complex when the unvaccinated animal is domesticated such as a dog or cat. Studies have shown that the rabies virus cannot be isolated from the saliva until 1 day before the initiation of clinical signs in cats, and until 3 days before in dogs,52,53 Given that cats have a median duration of illness for 5 days and dogs for 3 days, a 10-day period of quarantine observation is considered adequate. As mentioned previously, the human incubation period of the rabies virus is usually 20 to 90 days. Thus, in the low-risk setting of a domestic dog or cat bite, an exposed individual should wait a 10-day period to see if the quarantined pet manifests any symptoms of the disease. If the animal becomes rabid, then postexposure prophylaxis must be initiated immediately.

Finally, in species other than cats and dogs, the quarantine determination of rabies does not hold because the duration of illness and periods of virus secretion tend to be highly variable. Examination of the postmortem brain is the only way to establish a definitive diagnosis. If the suspected carrier of the virus is a rare or valuable animal, choosing not to sacrifice it should only be made by the public health authorities.

**FUTURE DIRECTIONS**

Until the rabies virus is eliminated from our environment, it will continue to remain a threat to humans. Research efforts have thus been aimed at limiting the viruses' wild animal vector population. This goal will be achieved by either one of two methods. The first is the actual reduction of a given population, which necessitates the determination and maintenance of a critical threshold population size for a given species, below which the virus is unable to survive.54 Possible methods include gassing of animal dens, anticoagulation of bats, use of strychnine bait, trapping, or directly hunting the animals. These are often impractical (both physically and economically) and ecologically irresponsible.55

The second is by inducing immunity into the vector population via vaccination. Successful oral immunization of foxes and the demonstration of the elimination of rabies once 50% to 75% of a population was vaccinated, has heavily fueled this avenue of research.56,57 Development of oral, intestinal, parenteral, and aerosolized vaccines that are effective, safe, inexpensive, labeled, and easily distributed throughout a given region, are presently underway.58 Promising results have been obtained recently with a vaccinia-
rabies glycoprotein (V-RG) for oral vaccination of raccoons and with field testing of various other raccoon and skunk bait vaccines.

The current high costs of immunization programs are generally considered prohibitive in developing countries. Research efforts are being directed towards lowering the high costs of both preexposure and postexposure prophylaxis regimens while maintaining the immunogenicity, availability, and efficacy of the treatment. Less expensive, equally efficacious vaccines such as the cell culture Vero rabies vaccine or the FBKC vaccine, or a combination incorporating already administered vaccines (ie, diphtheria and tetanus) are being investigated.

Regarding vaccine administration, modifications in the site and methods, including revised intramuscular and subcutaneous routes, as well as changes of dosing schedules that require fewer doses and associated clinic visits, are also being actively pursued. To date, a regimen of administering the HDCV bilaterally IM on day 0, with additional single doses on days 7 and 21 (a 2-1-1 schedule), has been proven efficacious in more than 300 patients. Research using interferon or interferon-inducers, with the hopes of modifying present treatment protocols, have hinted at promising results.

Education remains the most cost-effective means of controlling rabies. There needs to be continued instruction on avoiding wild animals, not leaving garbage (food) in accessible areas, seeking prompt medical attention for any potential rabies contact, and receiving proper preexposure vaccination for those at high risk. Emphasis must also be placed on vaccinating all domestic dogs, cats, and farm animals.

**SUMMARY**

We have presented a case in which a child was clearly exposed to a high-risk vector of the rabies virus that warranted postexposure prophylaxis. The parents should have obtained medical attention for their child before waiting for any laboratory results. If testing of the bat later proved negative for rabies, then the initiated treatment series could have been terminated. Proper wound management, along with the administration of active and passive immunotherapy, were appropriately applied. The expected results of no clinical sequelae, for this preventable disease, were observed.

This review has emphasized the issues of rabies pertinent to the physician practicing in the US. We have discussed the epidemiology of the rabies virus, its clinical course, diagnosis, and treatment. Preexposure and postexposure prophylaxis regimens were outlined, as well as the presentation of a treatment algorithm.

Rabies continues to remain a threat to both humans and animals. Although present domestic animal management and prophylaxis measures make this disease very rare within the US, research efforts are continuing to develop better wild animal vaccines and control measures. Future development of human vaccines and immunoglobulins that are less expensive and administered via more efficient protocols, will help to lower present costs, particularly in less affluent countries.

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