

REVIEWS OF THERAPEUTICS

Overview, Prevention, and Treatment of Rabies

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Each year, approximately 55,000 individuals worldwide die from an infection due to the rabies virus. Rabies is a life-threatening disease caused by an RNA virus that is usually transmitted to humans through bites from rabid animals. More recently, reports of transmission by means of organ transplantation have been reported. Since human rabies is nearly 100% fatal if prophylactic measures are not followed, an increased awareness of who should receive prophylaxis and when prophylaxis should be administered is necessary. Preexposure prophylaxis entails the administration of the rabies vaccine to individuals at high risk for exposure to rabies viruses (e.g., laboratory workers who handle infected specimens, diagnosticians, veterinarians, animal control workers, rabies researchers, cave explorers). Preexposure prophylaxis involves a three-dose series of the rabies vaccine that may confer some protection from the virus while simplifying postexposure prophylaxis regimens. Postexposure prophylaxis consists of a multimodal approach to decrease an individual's likelihood of developing clinical rabies after a possible exposure to the virus. Regimens depend on the vaccination status of the victim and involve a combination of wound cleansing, administration of the rabies vaccine, and administration of human rabies immune globulin. If used in a timely and accurate fashion, postexposure prophylaxis is nearly 100% effective. Once clinical manifestations of rabies have developed, however, treatment options for rabies are limited, and to date, only seven individuals have survived rabies virus infection. Treatment of clinical rabies consists of medical support in an intensive care unit, using a multifaceted approach that includes supportive care, heavy sedation, analgesics, anticonvulsants, and antivirals. The recently developed Milwaukee Protocol added induction of therapeutic coma to supportive care measures and antivirals; however, its use has shown inconsistent outcomes.

Key Words: rabies virus, human rabies, rabies vaccine, human rabies immune globulin, HRIG, antivirals, immunizations, Milwaukee Protocol.
(*Pharmacotherapy* 2009;29(10):1182–1195)

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Human rabies is a life-threatening infection that is associated with a mortality rate of nearly 100% when appropriate prophylactic measures

are not followed before or shortly after an exposure. The incidence of human rabies remains high worldwide with an estimated death toll of 55,000 annually, despite the existence of effective prophylaxis.¹ In the United States, the average number of deaths due to the rabies virus has decreased from more than 100/year in the early 20th century to approximately 2–3/year.² To date, only seven individuals have survived rabies virus infection after the onset of clinical symptoms of the disease, and all except one received some form of prophylaxis against rabies.^{3–5}

Rabies Virus

Human rabies is caused by nonsegmented, antisense, single-stranded RNA viruses of the family Rhabdoviridae and genus *Lyssavirus*,⁶ with seven recognized genotypes.⁷ The genotypes responsible for causing human rabies are types 1 and 3–7, although genotype 3 is rare (only two human cases have been reported, both in Africa) and causes atypical rabies symptoms such as fatigue, confusion, and convulsions.³ The rabies virus genome is approximately 12 kilobase pairs in length and encodes five viral proteins: nucleoprotein, phosphoprotein, matrix protein, glycoprotein, and polymerase.² The viruses are not viable outside of hosts and are inactivated by sunlight, heat, and desiccation. Within the host, the rabies viruses are highly neurotropic and replicate slowly within muscle cells.⁸

Transmission

Although all mammals are susceptible to and capable of transmitting the rabies virus, those considered reservoirs of the virus include carnivorous mammals and bats.⁶ Reservoirs of the rabies virus are responsible for the long-term existence and persistence of the virus, and samples from various reservoirs have revealed genetically distinct variants.⁹ Canines are considered the primary vectors of the virus worldwide and are responsible for the majority of human rabies cases in Africa, Asia, Central America, Eastern Europe, Russia, and South

America.³ In more developed regions, including the United States, where the prevalence of domestic animal vaccination is high, bats are responsible for the majority of human rabies cases. In South America, vampire bats are a well-recognized source of human rabies transmission, whereas in the United States the silver-haired bat (*Lasiurus noctivagans*) and eastern pipistrelle (*Pipistrellus subflavus*) are the usual suspects. Both bats are insectivorous and are rarely seen near human dwellings. The silver-haired bat is found in the majority of the continental United States except for Florida and southern California, whereas the eastern pipistrelle concentrates in the eastern and Midwestern states.⁹ In addition to bats, raccoons, skunks, coyotes, and foxes are among the common reservoirs for rabies in North America (Figure 1).^{2,3}

Human transmission of the rabies virus occurs primarily through rabid animal bites, where infected saliva penetrates the skin.⁶ The virus can also be transmitted by exposure of an open wound or mucous membrane to the saliva of a rabid animal, although this occurs less frequently. A remote potential of rabies infection occurs through aerosol inhalation of the virus, although this may only be possible in a few caves located within the United States where bat density is high, and high temperatures, extreme humidity, and little ventilation exist.⁹

Infrequently, human-to-human transmission has been reported. In 2004, the rabies virus was transmitted to four transplant recipients from an infected organ donor in Texas and three transplant recipients from an infected donor in Germany, all resulting in death for the organ recipients.^{10,11}

Clinical Manifestations

In humans, rabies typically manifests in five stages: incubation period, prodrome, acute neurologic phase, coma, and death (or in rare instances, recovery). The duration of the incubation period ranges from a few days to several years, but typically is 1–2 months.^{7,8} Rabies viruses bind to nicotinic receptors on the surface of muscle fibers, replicate slowly within muscle, and travel into nerve tissue through neuromuscular junctions.^{7,8,11} The variation in incubation periods may be associated with the time required to replicate within muscle tissue and transverse into neuronal axons. Deep lacerations or bites occurring on the head and neck in which the virus is directly inoculated

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into nerve tissue are generally associated with shorter incubation periods.

Once the virus attaches to the axons of nerves, it travels in a retrograde fashion to the central nervous system (CNS), where rapid replication occurs. The prodromal stage of rabies begins once the virus has traveled to the dorsal root ganglia and CNS, when nonspecific symptoms such as fever, headache, malaise, irritability, nausea, and vomiting, may occur.³ Paresthesias, pain, and pruritus may arise locally at the site of viral entry.^{7,8} The prodrome generally lasts a few days to 2 weeks. Progression from the prodromal stage to the acute neurologic phase is characterized by neurologic dysfunction. At this point the virus begins invasive replication within the CNS, where it travels from neuron to neuron through synaptic junctions.³ From the CNS, the virus moves into other organs, glands, and tissues and is copiously secreted in the saliva.

The acute neurologic phase can manifest as encephalitic (furious) or paralytic (dumb) rabies. Approximately 80% of patients present with the encephalitic form, whereas the remainder suffer from paralytic rabies.¹² Encephalitic rabies symptoms include hyperexcitability, hyperactivity, hallucinations, excessive salivation, hydrophobia (fear of water), and aerophobia (fear of air).^{3,7} Hydrophobia and aerophobia may result from painful laryngeal and pharyngeal spasms.⁸ Once the encephalitic form of rabies presents, the patient usually dies within 5 days.⁷ Patients with the paralytic form of rabies frequently present with limp paralysis of the limb initially exposed to the virus. Paralysis may progress to quadriplegia symmetrically or asymmetrically and ultimately results in urinary and fecal

incontinence. Death results after the onset of diaphragmatic and bulbar paralysis within a few weeks.⁸ Coma occurs in the late stages of clinical progression and is associated with multiorgan failure regardless of the form of presentation. In addition, hematemesis occurs in approximately 30–60% of patients during the last few hours of life.⁷ Cardiac arrhythmias occur in almost all cases, with the cause of death related to cardiac and circulatory insufficiency.⁸

Diagnosis

The diagnosis of rabies involves the consideration of a combination of clinical and laboratory findings. Magnetic resonance imaging may indicate rabies when abnormal hypersignaling is present in the brainstem, hippocampus, or hypothalamus regions.⁷ The degree of abnormality may vary widely depending on the stage of progression, and gadolinium enhancement only occurs in late stages. Although clinical findings should be a strong indication of rabies, a number of other conditions have similar presentations. Conditions mimicking the paralytic presentation of rabies include Guillain Barré syndrome, Japanese encephalitis, cerebral malaria, and the West Nile virus.^{7,8} Included in the differential diagnosis for the encephalitic presentation are tetanus (which may be caused by animal bites), diphtheria, botulism, substance abuse, and alcohol withdrawal with delirium tremens. Although the distinguishing symptoms of hydrophobia and aerophobia only occur in rabies, a definitive diagnosis requires laboratory findings.

Laboratory test sensitivities have extreme

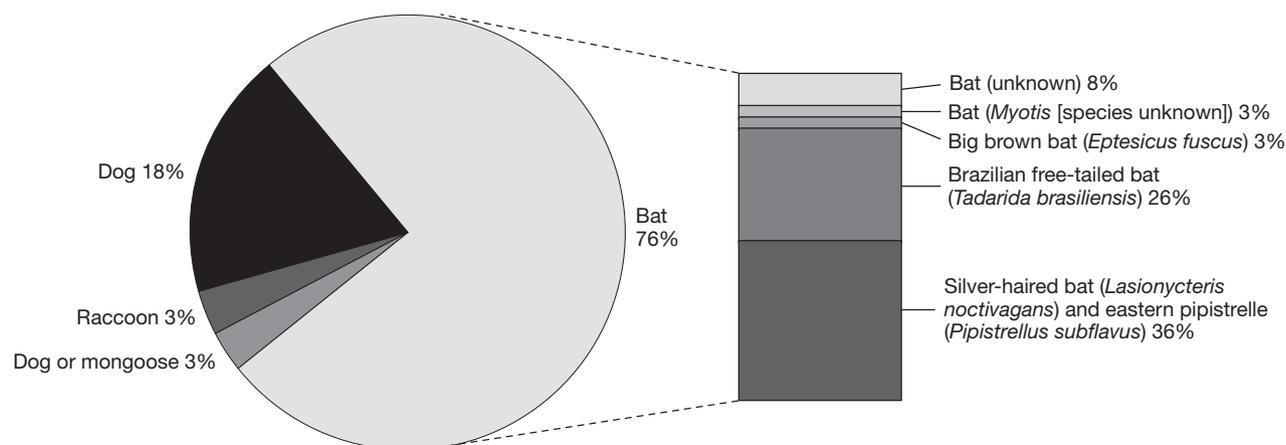


Figure 1. Causes of human rabies infections in 38 cases in the United States from 1995–2008. (From reference 2.)

variability for the diagnosis of rabies; results may vary depending on the stage of clinical progression, the individual's antibody status, the technique being performed, the technical skill of the laboratory staff, and the intermittent nature of viral shedding into bodily fluids and tissues.^{7,8} The isolation of rabies viral RNA from saliva samples or full-thickness skin biopsies obtained from nuchal regions with reverse transcriptase polymerase chain reaction confirms a diagnosis of rabies. Isolation of the rabies virus from saliva or other biological fluids (serum and cerebral spinal fluid [CSF]) would also be indicative of a rabies infection. Since the virus is not continuously shed by infected individuals, isolation of the virus or viral RNA may not be possible. Individuals with a greater extent of antibody production are less likely to have the rabies virus isolated from bodily fluids. The detection of rabies virus antibodies from the serum of unvaccinated individuals through the direct fluorescent antibody test is also diagnostic of a rabies infection. Production of antibodies to the rabies virus generally occurs 7–10 days after onset of clinical symptoms, although isolation of antibodies from sera of infected individuals may not always occur. Isolation of rabies virus antibodies from the CSF through the direct fluorescent antibody test is also diagnostic regardless of previous vaccination status, since antibodies are too large to penetrate the blood-brain barrier. Antibody appearance in the CSF occurs later in the disease progression than that in serum. To assist in rabies testing, the Center for Disease Control and Prevention or state health officials should be contacted, as testing may be performed in a number of locations depending on geographic locale.

Rabies Vaccines

Three rabies vaccines are licensed for human use in the United States: Imovax Rabies (Sanofi Pasteur, Swiftwater, PA), RabAvert (Novartis Vaccines and Diagnostics, Marburg, Germany), and rabies vaccine adsorbed (RVA; BioPort Corp., Lansing, MI).¹³ However, only Imovax Rabies and RabAvert are manufactured for use and are available in the United States. Imovax Rabies is a human diploid cell vaccine prepared with the Pitman-Moore rabies strain grown on a human diploid cell culture. The vaccine is available in single-dose vials with the accompanying diluent in a prepackaged syringe.¹⁴ The current availability of Imovax is limited due to the

renovation of the Sanofi Pasteur production facility in France to maintain compliance with U.S. Food and Drug Administration requirements.¹⁵ The renovated facility should be operational by mid- to late 2009. Until that time, Imovax is available only for postexposure prophylaxis.

RabAvert, a purified chick embryo cell vaccine, has been available in the United States since 1997.¹⁶ It is prepared from the fixed rabies virus strain Flury low egg passage grown in cultures of chick fibroblasts. RabAvert is also available in a single-dose vial with accompanying diluent. After the start of the renovation of the Sanofi Pasteur facility, Novartis was not able to meet the market demand for RabAvert. Thus, from October 2008–April 2009, RabAvert was available only for postexposure prophylaxis. Since April 2009, however, RabAvert has been available for both pre- and postexposure prophylaxis, without limitations for its use.¹⁵

Both vaccines available in the United States are preservative free and should be administered immediately after reconstitution. For both vaccines, the total volume of one dose is 1 ml (regardless of indication) and should be administered intramuscularly into the deltoid region. In young children and infants, the vaccines may be injected into the anterolateral area of the thigh. Gluteal administration is not recommended as this may result in lower neutralizing antibody titers and may damage the sciatic nerve.^{14, 17} The potency of each dose is equal to or greater than the World Health Organization's recommended standard of 2.5 IU/ml.¹³ The dosage regimen for the rabies vaccines depends on the indication, and these regimens are delineated in their respective sections below. Because both Imovax and RabAvert are inactivated virus vaccines, no cytotoxic T-cell response is elicited, which may be important for viral clearance. It may take 7–10 days for the active production of viral neutralizing antibodies to occur, although the antibodies generally persist for several years. The cost of one dose of either rabies vaccine is approximately \$200.¹⁸

Common adverse effects associated with the use of either rabies vaccine include local injection-site reactions such as erythema, itching, swelling, and induration, and systemic reactions such as headache, nausea, abdominal pain, muscle aches, dizziness, and fever. The occurrence of adverse effects should not interrupt the vaccination schedule, as no deaths have been reported following the use of either vaccine.

RabAvert should be avoided in patients with severe egg allergies since the vaccine is prepared with chick embryos and may contain a small amount of egg protein. Both vaccines are safe for use during pregnancy.^{13, 19}

Human Rabies Immune Globulin

Two human rabies immune globulin (HRIG) products are available in the United States: HyperRAB S/D (Talecris Biotherapeutics, Research Triangle Park, SC) and Imogam Rabies HT (Aventis Pasteur, Lyon, France).¹³ Human rabies immune globulin provides activity against rabies viruses by providing passive immunization through neutralizing viral antibodies.^{20, 21} Both products are preservative-free immunoglobulin G preparations obtained from pooled plasma of human donors hyperimmunized with the rabies vaccine. HyperRAB S/D and Imogam Rabies HT are supplied as sterile solutions of antirabies immune globulin for intramuscular administration. The minimal potency of each is 150 IU/ml, and both products are available in 2-ml (300 IU) and 10-ml (1500 IU) vials that should be stored under refrigeration (2–8°C). The recommended dose for HRIG is 20 IU/kg. After intramuscular injection, antibodies are present in the serum within 24 hours. The antibody level peaks in 2–13 days and persists for approximately 24 days. Human rabies immune globulin should only be used as postexposure prophylaxis in patients who have not previously been vaccinated with a rabies vaccine.

Human rabies immune globulin should be administered as soon as possible after recognition of a potential exposure to rabies. The entire dose of HRIG should be injected directly into and around the bite wound if feasible and if a wound is evident; the remainder of the dose should be given intramuscularly in the upper arm, lateral thigh, or gluteal muscle.^{20, 21} Human rabies immune globulin should not be administered more than 7 days after the rabies vaccine, as it may interfere with active immune response and antibody production. Because HRIG may interfere with the response to live vaccines, live vaccines such as measles, mumps, polio, or rubella should not be given within 3 months of HRIG administration. Adverse effects of HRIG include local injection site reactions such as tenderness, pain, and soreness; headache; malaise; fever; skin rash; angioneurotic edema; nephrotic syndrome; and anaphylactic shock. Since the HRIG products are obtained from

human donors, they have the potential to contain other viruses, although, to our knowledge, no transmissions have been documented. The approximate cost of one dose of HRIG for a 70-kg individual is \$1500.¹⁸

Prevention of Human Rabies

Exposure Prevention

Due to the high mortality rate associated with human rabies, adequate measures to ensure prevention of transmission should be followed. Individuals, including children, should be educated to avoid contact with unfamiliar animals, especially bats, in the United States. To prevent bats from entering homes, churches, schools, or other locations where potential human contact may occur, openings larger than one-quarter inch by one-half inch in buildings should be repaired. The best times of the year to repair bat entry sites are the fall and winter, as young bats may be unable to fly during the summer months and may become trapped inside living quarters.²² If bats are found dead or alive within living quarters, the local animal control or public health agency should be contacted to facilitate removal, and the animal should be tested to determine whether medical attention should be sought, especially if it is unknown whether a bite may have occurred. Individuals should also be responsible pet owners, by maintaining current rabies vaccinations for all pets and preventing pets from coming into contact with wild animals by keeping them from roaming free.⁹

Health care workers involved in the direct care of patients who have had known or suspected exposure to the rabies virus should take precautions to ensure that they do not contract the virus from patients. Contact precautions, including barrier methods such as gloves, goggles, masks, and gowns, should be used to avoid contact with patients' bodily substances, mucous membranes, or open wounds, which could theoretically lead to exposure. Although no cases of patient-to-health care worker transmission have been reported to date, proper prevention of exposure is warranted.⁶

Preexposure Prophylaxis

The purpose of preexposure prophylaxis is to simplify the management of patients if an exposure to rabies occurs and to offer some protection to individuals who may incur an

Table 1. Pre- and Postexposure Prophylaxis Regimens

Type of Prophylaxis	Product	Regimen
Preexposure prophylaxis	Rabies vaccine ^a	1 ml on days 0, 7, and 21 or 28
Postexposure prophylaxis	Rabies vaccine ^a	1 ml on days 0, 3, 7, and 14 ^b
Patients not previously vaccinated, were vaccinated > 2 yrs earlier, or whose titers have decreased below 0.5 IU/ml	Human rabies immune globulin ^c	20 IU/kg (0.133 ml/kg) on days 0–7 ^d
Patients vaccinated within previous 2 yrs	Rabies vaccine ^a	1 ml on days 0 and 3

^aImovax or RabAvert.

^bFour-dose regimen recommended by the Advisory Committee for Immunization Practices in July 2009. Immunosuppressed individuals should also receive a fifth dose on day 28.

^cHyperRAB S/D or Imogam Rabies HT.

^dDay 0 refers to the day of first rabies vaccine administration; earlier administration may be more efficacious.

unrecognized exposure.⁶ The use of proper preexposure prophylaxis decreases the number of rabies vaccine doses needed and eliminates the need for HRIG administration in the case of a possible exposure. For individuals in areas where the safety of rabies biologics may not be as inherent as in more developed areas, preexposure prophylaxis reduces their exposure to potentially harmful products and lessens their risk for adverse effects. Preexposure prophylaxis entails the administration of the rabies vaccine to individuals at high risk for exposure to rabies viruses. Those individuals include laboratory workers who handle infected specimens, diagnosticians, veterinarians, animal control workers, rabies researchers, and cave explorers in areas where the virus is common.¹³ Other individuals who may frequently come into contact with possibly rabid animals should consider vaccination. In addition, travelers to areas where rabies is prevalent who engage in wilderness activities such as camping and hiking may benefit from the vaccine, especially if the availability of postexposure prophylaxis at the travel destination is limited, nonexistent, or its administration may be delayed.⁶

Individuals undergoing primary vaccination should receive three 1-ml intramuscular injections of either the purified chick embryo cell vaccine (RabAvert) or the human diploid cell vaccine (Imovax) product on days 0, 7, and 21 or 28 (Table 1).¹³ Minor deviations to this vaccination schedule should not have an impact on efficacy. If major deviations occur, titers should be evaluated or the series should be reinitiated. Previous studies have demonstrated sufficient antibody response to rabies in healthy individuals after primary vaccination with the three-dose regimen administered appropriately¹³; therefore, assessing antibody levels after

preexposure prophylaxis to evaluate seroconversion is not warranted unless an individual is immunosuppressed. Immunocompromised patients should forgo preexposure prophylaxis and take all precautionary measures previously mentioned to avoid rabies exposure. If avoidance is not feasible, the Center for Disease Control and Prevention recommends assessing titers 1–2 weeks after completion of the three-dose series. Titers obtained should completely neutralize the virus at a 1:5 serum dilution or they should exceed a level of 0.5 IU/ml. In the event a patient fails to seroconvert, public health officials should be consulted.

Rabies virus neutralizing antibody levels have not been correlated to an individual's susceptibility to the rabies virus although levels do indicate the immune status to rabies. Based on the Advisory Committee for Immunization Practices (ACIP) recommendations, periodic measuring of rabies virus neutralizing antibody levels should be performed based on an individual's risk for exposure. Individuals at a continuous risk, including rabies researchers and biologic producers, should undergo titer testing every 6 months. Animal control and wildlife workers, bat handlers, rabies diagnostic laboratory workers, veterinarians and their staff, and cave explorers fall into the frequent-risk category for rabies exposure and should have their titers measured every 2 years. Those considered at infrequent risk, including veterinarians, veterinary students, and animal control workers in areas where rabies is uncommon; and travelers, and those at rare risk for exposure to rabies such as the general population are not recommended to undergo serologic testing or to receive booster doses. A booster dose of the vaccine should be given to individuals in the continuous-risk and frequent-

risk categories when their titer levels are < 0.5 IU/ml or if their titer fails to completely neutralize virus at a 1:5 serum dilution.

Due to limited investigation into the interchangeability of the two vaccine products, current recommendations suggest using the same vaccine product for the duration of the vaccination series; however, if an intolerable adverse reaction occurs after the use of one product, the other vaccine may be used.⁶ If different products are used within the same series, having titers assessed 1–2 weeks after completion of the series may be useful to ensure adequate immune status.

Postexposure Prophylaxis

Postexposure prophylaxis consists of a multimodal approach to decrease an individual's likelihood of developing clinical rabies after a possible exposure to the virus. Wound cleansing and administration of the rabies vaccine and HRIG are the primary components of rabies postexposure prophylaxis. Since the likelihood of a rabies infection depends on the type and extent of the exposure, thorough assessment of a patient's risk of infection should be undertaken before initiation of postexposure prophylaxis

(Figure 2). Before administration of postexposure prophylaxis, the individual's risk factors for exposure to rabies should be assessed. The decision to initiate postexposure prophylaxis should occur in a timely fashion, as delays may increase an individual's risk for developing clinical rabies. When used appropriately, postexposure prophylaxis is nearly 100% effective.²³

When individuals in the United States present with nonbite exposures to bats, raccoons, foxes, skunks, or coyotes, only those in which saliva, blood, or other possible infectious substances from the animal come into contact with open wounds or mucous membranes warrant initiation of postexposure prophylaxis. All bite exposures to these animals require prophylaxis, as the rabies virus concentrates in saliva. Under circumstances where a bat bite may have occurred in an individual unable to communicate or unaware of the incident (e.g., bat found in room of young infants, deep sleepers, or mentally incapacitated individuals), postexposure prophylaxis should be initiated even if a bite wound is not evident. Whether the exposure involved a bite or nonbite contact, the animal to which the exposure occurred should be captured if possible and undergo testing for rabies.

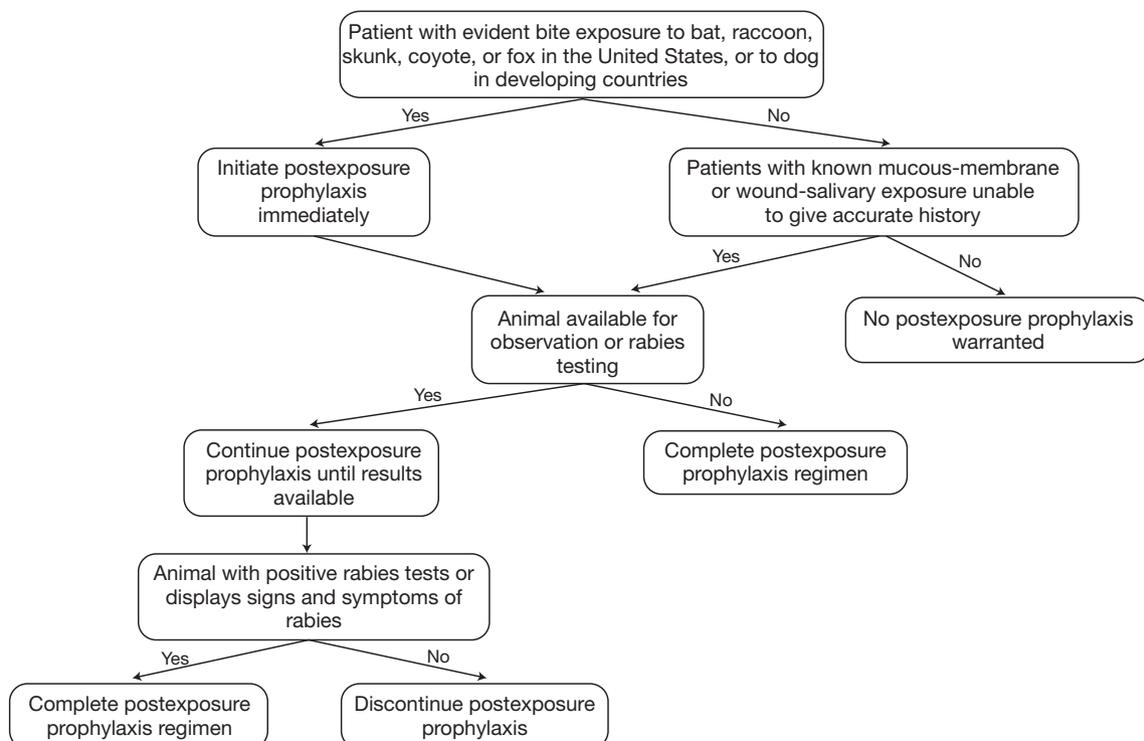


Figure 2. Decision tree for starting and continuing rabies postexposure prophylaxis.

Postexposure prophylaxis should be discontinued if the animal in question is found to have a negative rabies test. Household pets involved in potential human exposures should be observed for 10 days for the presence of rabies. If rabies symptoms do not present in the animal under observation, postexposure prophylaxis for the victim should be discontinued.

When a bite wound is evident or an open wound is exposed to infectious substances, the wound should be promptly and thoroughly cleansed with soap and water for a minimum duration of 15 minutes.²⁴ The use of virucidal antiseptics such as povidone iodine and ethanol is advocated for initial wound treatment. Topical antibiotics may also be considered depending on wound severity. In addition, closure of bite or scratch wounds should be avoided.²⁵

Following wound cleansing, postexposure prophylaxis regimens differ depending on the rabies immunization status of the individual exposed. For individuals who have not received preexposure prophylaxis in the preceding 2 years, HRIG should be administered immediately.^{6, 8, 13} A dose of 20 IU/kg (0.133 ml/kg) of either HRIG product (HyperRAB S/D or Imogam Rabies HT) should be administered directly into the wound and the area surrounding the wound (Table 1). If it is not feasible to administer the entire dose near the wound or a wound is not apparent, any remaining volume should be given intramuscularly in the upper arm or lateral thigh muscle.

In addition, patients who have not been previously vaccinated, were vaccinated more than 2 years earlier, or whose titers have dropped below the recommended level of 0.5 IU/ml should receive four 1-ml doses of either rabies vaccine.^{6, 13, 26} The first dose should be administered as soon as possible (day 0) at a site distant to the administration site of HRIG, as HRIG can interfere with the immune action of the rabies vaccine. The vaccine and HRIG should not be mixed in the same syringe. The remaining three doses of vaccine should be given on days 3, 7, and 14 after the first dose (Table 1).^{6, 13, 27} In July 2009, the ACIP recommendations were amended, decreasing the number of rabies vaccine doses required for postexposure prophylaxis from five to four based on current evidence.²⁶ However, patients who are immunosuppressed should still receive a five-dose series of the vaccine on days 0, 3, 7, 14, and 28. If HRIG was not administered in conjunction with the first vaccine dose, it can be given up to and including day 7 of the vaccination series. After day 7 of the vaccination

series, an immune response should have occurred, so the use of HRIG is no longer warranted.

For patients who have received recent (≤ 2 years) preexposure prophylaxis, two 1-ml intramuscular doses of the rabies vaccine should be administered (Table 1). The first dose should be given immediately and the second dose 3 days later. No HRIG is warranted, as passive antibody administration may interfere with innate antibody production.

Deviations from HRIG administration recommendations and postexposure vaccination schedules should be minimized as much as possible. If a minor lapse in vaccination schedule occurs, it should be resumed by maintaining the same time interval(s) between subsequent scheduled doses. For example, if a patient misses the vaccine due on day 3 and presents on day 4 for a dose, subsequent doses should be given on days 8, 15 and 29 (vs days 7, 14, and 28) after the first dose. The impact of large deviations from both pre- and postexposure vaccination schedules is unknown; therefore, deviations are not recommended.¹³

Management of Clinical Rabies

To date, only seven individuals have survived rabies, and all except one received some form of pre- or postexposure prophylaxis before the onset of clinical symptoms.^{4, 5} Patients who may have contracted rabies should undergo postexposure prophylaxis as soon as possible to improve their chances of survival, although administration of HRIG should be avoided after the onset of symptoms. Human rabies immune globulin may interfere with the innate immune response to an active rabies infection and does not penetrate the blood-brain barrier. Aside from preventing the development of rabies with the use of pre- and postexposure prophylaxis, no single treatment regimen has consistently proven effective for the management of human rabies.

A diagnosis of rabies should be confirmed by the Centers for Disease Control and Prevention before initiating therapy. Before aggressive management of patients with a diagnosis of human rabies is initiated, the patient, provider, and family must recognize and understand that the chances of survival are low. If the patient survives medical management of human rabies, they must also be aware of the high likelihood of a poor neurologic outcome. Only two of six rabies survivors recovered without serious

Table 2. Summary of the Milwaukee Protocol for Treatment of Patients with Clinical Rabies³¹

Treatment	Agents	Rationale
Supportive care	Nutrition (preferably enteral), fluids (usually crystalloid)	Provides the patient with support necessary to allow the immune system to mount a response to the virus
	Vitamin, mineral, and cofactor supplements (tetrahydrobiopterin, [BH ₄], coenzyme Q ₁₀ , vitamin C highly recommended)	Corrects deficiencies associated with the virus
	Antipyretics (if body temperature > 38.9°C); anticoagulants (s.c. heparin for prophylaxis or i.v. heparin infusion if thromboembolic treatment is warranted) ^a	Provides prophylaxis for complications that commonly occur in critical illness
Therapeutic coma	Benzodiazepines	Decreases metabolic demands of cerebral tissue
	Ketamine	Decreases autonomic hyperactivity
	Adjunct agents if needed to maintain partial burst suppression (barbiturates, propofol)	Reduces seizure activity, possibly decreases excitotoxicity associated with rabies virus
Antivirals	Amantadine, ketamine ^b	Decreases viral load while immune system response develops
Agents to avoid if possible	Barbiturates	Inhibits T-cell activation necessary for immune response against the virus
	Propofol	Associated with flat electroencephalogram in two cases
	Rabies vaccine	No apparent benefit; may slow natural immune response to virus
	Human rabies immune globulin	No apparent benefit; may not penetrate blood-brain barrier
	Ribavirin	No in vivo evidence to support its use; may cause pancreatitis, mitochondrial toxicity, and hemolysis; suppresses humoral immune response; depletes BH ₄ ; does not penetrate blood-brain barrier well

^aHeparin is easily reversible in the event complications arise or if surgical procedures are warranted.

^bOnly in vitro data exist to support the antiviral activity of ketamine.

neurologic sequelae; however, the neurologic outcome of a Brazilian boy who recently survived has yet to be determined.^{4,5} Factors that may be associated with better outcomes include younger age of patient, relatively few or no concomitant medical conditions, vaccination before the onset of symptoms, and early presentation at the time of treatment initiation.²⁸

The treatment of rabies involves a multifaceted approach including supportive care, heavy sedation, analgesics, anticonvulsants, and antivirals.^{1, 28–30} The treatment of rabies entails medical support in an intensive care unit with personnel trained in the management of multisystem organ failure, as this often occurs in the later stages of clinical rabies.

The Milwaukee Protocol

A variety of approaches have been used in the treatment of human rabies, and a recent protocol was developed by the Medical College of Wisconsin—the Milwaukee Protocol—after the survival of a young patient from Wisconsin diagnosed with rabies (Table 2).³¹ In the case of

this survivor, induction of a therapeutic coma in addition to supportive care measures and antivirals were used with success. A number of agents were used to induce a therapeutic coma to decrease the metabolic demands of the CNS, theoretically reduce possible excitotoxicity of rabies, and diminish autonomic hyperactivity associated with progressing clinical rabies.²⁹ After the success of the Milwaukee Protocol for the young Wisconsin patient, several others have employed similar treatment regimens with minimal beneficial outcomes.^{30, 32}

Supportive Care

Supportive care for patients with rabies consists of several approaches to enable a patient to recover without directly attempting to cure the patient. Immobile patients should receive general prophylactic measures for the prevention of venous thromboembolism, stress ulcers, and pressure ulcers. Vitamin, mineral and cofactor supplementation is recommended, as profound deficiencies may result due to critical illness and medical management.²⁹ The metabolic demands of

individuals significantly increase when under the physical stresses associated with critical illness. When hypermetabolic states are maintained for significant periods of time, which is likely in the case of human rabies, body stores of essential nutrients are diminished. Recommended oral supplementation includes creatine 3 g/day, coenzyme Q₁₀ (adults 1200–2400 mg/day, pediatrics 30–60 mg/kg/day), L-carnitine (adults 1.3 g every 8 hrs, pediatrics 100 mg/kg every 8 hrs), vitamin C (adults 500 mg/day, pediatrics 35–100 mg/day), vitamin E (200 IU/day), and zinc sulfate (adults 2.5–5 mg/day, pediatrics 100–300 µg/kg/day) if patients are noted to be deficient.³¹ Since tetrahydrobiopterin (BH₄ [BioMarin Pharmaceutical Inc., Novato, CA], a cofactor necessary for the production of catecholamine and serotonergic neurotransmitters) deficiency has been noted in the CSF of patients with clinical manifestations of rabies, its supplementation with 800 mg enterally every 8 hours (pediatrics 2 mg/kg every 8 hrs) is recommended by the Milwaukee Protocol to prevent deficiency from occurring. Antipyretics may be used to assist in defervescence, although the Wisconsin survivor exhibited no response to acetaminophen, ibuprofen, or ketorolac. Airway protection with intubation and mechanical ventilation may be necessary for patients with excessive salivation and pharyngeal and laryngeal spasm or uncontrollable swallow reflexes.^{29, 30} The use of vasopressors may also be warranted to facilitate adequate blood pressure in severe cases. Supportive care is not limited to these options and should also include seizure prophylaxis and treatment, pain management, and optimal nutrition (including correction of fluid and electrolyte imbalances) based on the patient's clinical status.

Therapeutic Coma

The agents employed to induce a therapeutic coma in the case of the Wisconsin patient included ketamine, benzodiazepines, and barbiturates.²⁹ Propofol has also been used in the management of other human rabies cases. The rationale behind instituting a therapeutic coma relates to decreasing the metabolic demands of cerebral tissue, reducing autonomic hyperactivity and possible seizure activity that may occur in later stages of the disease, and inhibiting the possible excitotoxicity that may occur in rabies. If therapeutic coma induction is employed, patients must be mechanically ventilated.

Sedation should be titrated to achieve and maintain partial burst suppression on electroencephalographic (EEG) monitoring; therefore all patients should undergo continuous EEG monitoring.

Ketamine, a dissociative anesthetic derivative of phencyclidine, was used in the Wisconsin patient at an infusion rate of 2 mg/kg/hour.²⁹ Ketamine exhibits both anesthetic and analgesic properties and acts by noncompetitive inhibition of the excitatory effects of glutamate at the *N*-methyl-D-aspartate (NMDA) receptor.^{33, 34} Extensive research has demonstrated that drugs with high affinity for the phencyclidine binding site on the NMDA receptor possess antiviral activity *in vitro*.³³ The researchers concluded that ketamine inhibits transcription of the rabies virus genome *in vitro*. *In vivo* antiviral effects of ketamine are yet to be determined, although its use in the management of rabies may be beneficial from a sedation and antiviral standpoint. Ketamine is associated with emergence reactions, which may include vivid dreams, nightmares, and hallucinations. Ketamine may also cause an increase in salivation, so vigilance is warranted to avoid aspiration (which should not be a concern if the patient is adequately intubated) and dehydration.³¹ On discontinuation of a therapeutic coma, ketamine may be rapidly tapered by halving the infusion rate every 12 hours until a rate of 0.5 mg/kg/hour is attained.

Benzodiazepines have been used in a number of cases to aid in the maintenance of a therapeutic coma. The most common agents used include midazolam, lorazepam, diazepam, and alprazolam. Benzodiazepines exert their sedative and anticonvulsant effects by potentiating the action of γ -aminobutyric acid (GABA) at the GABA_A receptor. The use of benzodiazepines may also help alleviate emergence reactions that may occur with the use of ketamine. Prolonged high-dose continuous infusions of preservative-containing midazolam may result in metabolic acidosis, which occurred in the Wisconsin patient, due to the benzyl alcohol content.²⁹ Similarly, and likely to a greater extent, the propylene glycol and benzyl alcohol content of the intravenous lorazepam formulation may contribute to lactic acidosis and renal failure. If prolonged high-dose continuous infusions are anticipated, preservative-free midazolam should be used to minimize these adverse effects. Diazepam or alprazolam may be employed if intermittent intravenous or oral sedation is sufficient.

If sufficient sedation is not achieved with

ketamine in combination with a benzodiazepine, a barbiturate may be added as adjunct therapy. In the Wisconsin patient, phenobarbital was added to the patient's medical therapy to maintain burst suppression. In the treatment of other patients with rabies, thiopental sodium and pentobarbital have been used.²⁵ The barbiturates have a mechanism of action similar to that of the benzodiazepines, although they bind to a different site on the GABA_A receptor. They also have the ability to inhibit glutamate and may have the potential to directly activate the GABA receptor chloride channels. Due to the lack of specificity in the mechanism and sites of action of barbiturates, the drug class has a greater toxicity potential and lower margin of safety.³⁴ Barbiturate use in treatment of human rabies should be limited to allow the host to mount an immune response to the infection, as these agents are thought to display immunosuppressant effects through inhibition of T-cell activation.³⁵ This inhibition is dose dependent (loading doses should be avoided) and occurs to a greater extent with the use of thiopental and pentobarbital.

Propofol has also been used in maintaining a therapeutic coma for rabies cases.²⁵ Like benzodiazepines and barbiturates, propofol potentiates the inhibitory function of GABA at the GABA_A receptor.³⁶ It is highly lipophilic, with a rapid onset similar to that of barbiturates and a very short duration. Propofol is rapidly metabolized in the liver and may undergo extrahepatic metabolism as well.^{34, 37} Propofol is only available as an intravenous lipid formulation, so patients should have serum triglyceride levels monitored in the setting of prolonged infusions. Long-term and/or high-dose propofol infusions may also lead to propofol infusion syndrome, characterized by metabolic acidosis, rhabdomyolysis, cardiac failure, and renal failure, which may be of particular concern in the pediatric population. Propofol also has more pronounced cardiovascular effects compared with the aforementioned agents. Propofol may cause profound hypotension due to vasodilation and a decrease in cardiac contractility.³⁴ These actions may warrant discontinuation of the infusion in patients who are unable to maintain adequate pressures, especially during the later stages of clinical rabies when cardiac complications may ensue. Two patients with rabies who had been previously treated with propofol had no EEG activity after initiation of propofol.³¹ Due to the adverse effects and limitations associated with the use of propofol in patients with rabies, its use

is not recommended by the Milwaukee Protocol.

The duration of maintaining a therapeutic coma may vary from patient to patient. As recommended by the Milwaukee protocol, discontinuation of sedation and analgesia should occur when patients have mounted an adequate immune response by evidence of anti-rabies titers in the CSF exceeding 1:1024 by indirect immunofluorescence assay or 1:40 by rapid fluorescent focus inhibition test.³¹ Conversely, sedation may be discontinued if the patient has progressed to denervation of cardiac tissue, indicated by a lack of heart rate or blood pressure variability over a 24-hour period. At this point, the rabies virus has caused significant neuronal dysfunction and continuation of care may be considered futile.

Antiviral Therapy

A number of antiviral agents have been employed in the treatment of human rabies. In combination with a therapeutic coma, antivirals should aid in viral clearance and allow the patient to recover. These agents include ribavirin, amantadine, interferon alfa, and acyclovir.^{29, 38} As previously mentioned, no one treatment regimen has been consistently successful in eliminating the rabies virus in humans. Current literature strongly advises against the use of antiviral monotherapy in the aggressive management of rabies due to concerns of resistance and ineffectiveness; therefore, at least two antiviral agents should be used.²⁸

Ribavirin is a purine nucleoside analog that inhibits viral messenger RNA production and contributes to RNA mutations. Ribavirin is commercially available only as an inhalation powder for solution (reconstituted for nebulization) and as an oral formulation with a bioavailability of approximately 50%. Oral absorption of ribavirin is increased when taken with high-fat meals. In several rabies cases, including the Wisconsin survivor, ribavirin was administered intravenously as an investigational drug.^{28, 29} Ribavirin may cause hemolysis, mitochondrial toxicity, and pancreatitis, all of which occurred in the Wisconsin patient.²⁹ In the Wisconsin patient, ribavirin was initiated with a loading dose of 33 mg/kg followed by a maintenance dose of 16 mg/kg every 6 hours. Due to toxicity, the dose was reduced to 8 mg/kg for nine doses before discontinuation. The efficacy of ribavirin in the treatment of rabies has yet to be proven. In a study of mice infected with rabies, ribavirin

did not demonstrate any antiviral activity.³⁹ A study conducted in four human patients with rabies in Bangkok, Thailand, found the use of both intravenous and intrathecal ribavirin to be of no benefit.⁴⁰ In a review of the 32 U.S. rabies cases reported from 1980–1996, antiviral therapy, including ribavirin, interferon alfa, and acyclovir, did not change the duration of illness before death.³⁸ Due to a lack of evidence supporting its efficacy, the use of ribavirin is not recommended for the treatment of rabies.³¹

Amantadine is an antiviral agent that exerts its actions by preventing viral uncoating through the inhibition of the viral M2 protein. In vitro, amantadine displays inhibitory effects against rabies infection.⁴¹ However, to our knowledge, no human studies have been conducted with the use of amantadine for the treatment of rabies. Of five patients who underwent the Milwaukee Protocol or modifications of the protocol in 2006 and 2007, all received amantadine without success.²⁵ Because amantadine may also exhibit neuroprotective effects through NMDA antagonism, as indicated by its use in the treatment of Parkinson's disease, enterally administered amantadine 2.5 mg/kg every 12 hours or 100 mg every 12 hours (if > 40 kg) is recommended by the Milwaukee Protocol.³¹ The use of interferon alfa and acyclovir are not recommended for the treatment of rabies. No evidence exists to support the use of either agent in the treatment of rabies, and interferon alfa may possess neurotoxic effects.²⁹

Considerations for Use of the Milwaukee Protocol

Although the use of a therapeutic coma in combination with antiviral agents may have contributed to the beneficial outcomes in the case of the young Wisconsin patient, her survival may have been confounded by the possibility of infection with a less virulent rabies strain. The possibility of a very low inoculum also exists since the virus was likely transmitted when she sustained a 5-mm bat bite wound at a distal site on her left index finger.²⁹ Eighteen other reported cases since the Wisconsin survivor have attempted the Milwaukee Protocol, or slight deviations of it, with limited success.^{5, 25} Although the rabies virus or antigen was never isolated from any of the previous rabies survivors, serum and CSF samples all contained rabies antibodies. The presence of antibodies in CSF is not consistent with previous vaccination, confirming the diagnosis of rabies in these

patients. Recently, a 15-year-old Brazilian male was the first survivor to have the rabies virus isolated before initiation of the Milwaukee Protocol.

The survival of a limited number of rabies victims, only one of whom had the rabies virus detected, may indicate the presence of an unidentified viral strain that may not possess the virulence to completely evade the human immune system. These findings may also indicate a genetic variation in the host immune system that enables the host to more readily clear the rabies virus. Conversely, these findings could be related to the effectiveness of postexposure prophylaxis in five of the seven survivors and the Milwaukee Protocol in the case of the two recent survivors. The explanation for failure of the Milwaukee Protocol in 16 patients may be due to a combination of the time interval between inoculation with the virus and protocol initiation, or deviations from the protocol. In the five cases published before 2008 that used the Milwaukee Protocol, more than 8 weeks lapsed between inoculation with the virus and initiation of the protocol in four patients (the original survivor began treatment at 4 wks).²⁵ The fifth patient began treatment with the Milwaukee Protocol 4 weeks after viral exposure; however HRIG was given, which may have interfered with the host's immune response to the virus. Details of the exact regimens used in the remaining 13 cases have yet to be published, so speculation regarding treatment failure cannot be made.

Based on the beneficial outcomes of the Milwaukee Protocol in the Wisconsin and Brazilian patients and the lack of successful alternatives, the implementation of the Milwaukee Protocol may be appropriate in certain cases. Rabies victims in whom the protocol may be effective include those who are healthy, immune competent and of young age, as was the case for both the Wisconsin and Brazilian survivors. Due to the high rate of mortality associated with the rabies virus regardless of treatment, patients and families must be aware of the likelihood of negative neurologic outcomes and treatment failure that may result.

Conclusion

The most common mode of rabies transmission in the United States is the silver-haired bat or the eastern pipistrelle, and the incidence of rabies in these bat populations is on the rise. Individuals at high or continuous risk for exposure should

undergo preexposure prophylaxis. If an exposure to the rabies virus is suspected, individuals should undergo assessment for postexposure prophylaxis at a local emergency department as soon as possible. Once an individual develops clinical signs of rabies, effective treatment options are limited, and the disease is nearly 100% fatal. Both clinicians and the public need to be cognizant of the disease and its transmission, the clinical manifestations of rabies, proper exposure prevention measures, preexposure prophylaxis regimens in individuals at high risk for exposure to rabies, and prompt initiation of postexposure prophylaxis regimens after possible exposure to the virus. Resources for additional information on human rabies are provided in Appendix 1.

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Appendix 1. Resources for Information on Human Rabies

Sponsor	Web Site	Telephone Number
Sanofi Pasteur	www.sanofipasteur.com	(800) 822-2463
Centers for Disease Control and Prevention	www.cdc.gov/rabies	(404) 639-1050
Novartis Vaccines and Diagnostics	www.novartis-vaccines.com	(510) 655-8730
State Rabies Consultation Contacts	www.cdc.gov/rabies/staterabiespoclist.html	Telephone numbers for each state may be found at Web site
Talecris Biopharmaceuticals	www.talecris.com	(919) 316-6300