Rabies is a viral infection of animals that can be transmitted to humans. This viral disease affects the central nervous system (CNS) and eventually the brain.

The genus Lyssavirus which is the causative agent contains more than 80 viruses. Classic rabies is the prototypical human Lyssavirus pathogen. There are 10 viruses in the rabies serogroup, most of which only rarely cause human disease. The genus Lyssavirus, rabies serogroup, includes the classic rabies virus, Mokola virus, Duvenhage virus, Obodhiang virus, Kotonkan virus, Rochambeau virus, European bat Lyssavirus types 1 and 2, and Australian bat Lyssavirus.

The rabies virus is a bullet-shaped virion with a single-stranded ribonucleic acid (RNA) nucleocapsid core and lipoprotein envelope. Its nucleocapsid material consists of Negri bodies, which are observed in the cytoplasm of infected neurons.

The virus is transmitted in saliva or in aerosolized secretions from infected animals, typically via a bite. The virus is not hardy and is quickly inactivated by drying, ultraviolet rays, x-rays, trypsin, detergents, and ether.

**ETIOLOGY**

Rabies is a highly neurotropic virus that evades immune surveillance by its sequestration in the nervous system. Upon inoculation, it enters the peripheral nerves. A prolonged incubation follows, the length of which depends on the size of the inoculum and its proximity to the CNS. Amplification occurs until bare nucleocapsids spill into the myoneural junction and enter motor and sensory axons. At this point, prophylactic therapy becomes futile, and rabies can be expected to follow its fatal course, with a mortality rate of 100%. Death occurs from global neurologic and organ dysfunction. The virion acts in the synaptic space, where homology in amino acid sequences between neurotransmitter receptors for acetylcholine, GABA, and glycine may afford a mechanism for viral binding of these receptors. Thus, its action is neurotoxic, rather than direct damage.

The rabies virus travels along these axons at a rate of 12-24 mm/d to enter the spinal ganglion. Its multiplication in the ganglion is heralded by the onset of pain or paresthesia at the site of the inoculum, which is the first clinical symptom and a hallmark finding. From here, the rabies virus spreads quickly, at a rate of 200-400 mm/d, into the CNS, and spread is marked by rapidly progressive encephalitis. Thereafter, the virus spreads to the periphery and salivary glands.
RESERVOIRS

International

Rabies is more prevalent in the developing world than in industrialized countries. The World Health Organization (WHO) estimates that rabies is responsible for 35,000-50,000 deaths annually worldwide and that gross underreporting is likely. An estimated 10 million people receive post-exposure prophylaxis each year after being exposed to animals with suspected rabies. Unvaccinated dogs are the major reservoir for rabies.

Global reservoirs of rabies virus are as follows:

- Europe - Foxes, bats
- Middle East - Wolves, dogs
- Asia - Dogs
- Africa - Dogs, mongooses, antelopes
- North America - Foxes, skunks, raccoons, insectivoros bats
- South America - Dogs, vampire bats

TRANSMISSION

Transmission of rabies virus usually begins when infected saliva of a host is passed to an uninfected animal. The most common mode of rabies virus transmission is through the bite and virus-containing saliva of an infected host. Though transmission has been rarely documented via other routes such as contamination of mucous membranes (i.e., eyes, nose, mouth), aerosol transmission, and corneal and organ transplantations.

DIAGNOSTIC/ CONFIRMATORY EXAMS

Diagnosis in animals

A diagnosis of rabies can be made after detection of rabies virus from any part of the affected brain, but in order to rule out rabies, the test must include tissue from at least two locations in the brain, preferably the brain stem and cerebellum.

The test requires that the animal be euthanized. The test itself takes about 2 hours, but it takes time to remove the brain samples from an animal suspected of having rabies and to ship these samples to a state public health or veterinary diagnostic laboratory for diagnosis.
Based on routine public health surveillance and pathogenesis studies, we have learned that it is not necessary to euthanize and test all animals that bite or otherwise potentially expose a person to rabies. For animals with a low probability of rabies such as dogs, cats, and ferrets, observation periods (10 days) may be appropriate to rule out the risk of potential human rabies exposure.

Consultation with a local or state health official following a potential exposure can help determine the best course of action based on current public health recommendations.

In animals, rabies is diagnosed using the direct fluorescent antibody (DFA) test, which looks for the presence of rabies virus antigens in brain tissue.

**Diagnosis in humans**

Several tests are necessary to diagnose rabies ante-mortem (before death) in humans; no single test is sufficient. Tests are performed on samples of saliva, serum, spinal fluid, and skin biopsies of hair follicles at the nape of the neck. Saliva can be tested by virus isolation or reverse transcription followed by polymerase chain reaction (RT-PCR). Serum and spinal fluid are tested for antibodies to rabies virus. Skin biopsy specimens are examined for rabies antigen in the cutaneous nerves at the base of hair follicles.

**Direct fluorescent antibody test**

The dFA test is based on the observation that animals infected by rabies virus have rabies virus proteins (antigen) present in their tissues. Because rabies is present in nervous tissue (and not blood like many other viruses), the ideal tissue to test for rabies antigen is brain.

**Incubation Period**

The infected individual remains asymptomatic during this period. The average duration of incubation is 20-90 days. Rarely, incubation has been reported up to 7-19 years. In more than 90% of cases, incubation is less than 1 year. Patients may not recall exposure because of the prolonged incubation period.

The incubation period is less than 50 days if the patient is bitten on the head or neck or if a heavy inoculum is transferred through multiple bites, deep wounds, or large wounds. A person with a scratch on the hand may take longer to develop symptoms of rabies than a person who receives a bite to the head.

The rabies virus is segregated from the immune system during this period, and no antibody response is observed.
**Prodromal Period**

The virus enters the CNS. The duration of this period is 2-10 days. Nonspecific symptoms and signs develop. Paresthesia, pain, or intense itching at the inoculation site is pathognomonic for rabies and occurs in 50% of cases during this phase; this may be the individual’s only presenting sign. Symptoms may include the following: Malaise, Anorexia, Headaches, Fever, Chills, Pharyngitis, Nausea, Emesis, Diarrhea, Anxiety, Agitation, Insomnia and Depression.

**Acute Neurologic Period**

This period is associated with objective signs of developing CNS disease. The duration is 2-7 days. Symptoms include muscle fasciculations, priapism, and focal or generalized convulsions. Patients may die immediately or may progress to paralysis, which may be present only in the bitten limb at first but usually becomes diffuse.

The form of rabies known as furious rabies may develop during this period. Patients develop agitation, hyperactivity, restlessness, thrashing, biting, confusion, or hallucinations. After several hours to days, this becomes episodic and interspersed with calm, cooperative, lucid periods. Furious episodes last less than 5 minutes. Episodes may be triggered by visual, auditory, or tactile stimuli or may be spontaneous. Seizures may occur. This phase may end in cardiorespiratory arrest or may progress to paralysis.

Another form of rabies, paralytic rabies, is also known as dumb rabies or apathetic rabies, because the patient is relatively quiet compared with a person with the furious form. Twenty percent of patients do not develop the furious form. Paralysis occurs from the outset, and fever and headache are prominent.

**Neurologic Period**

With furious rabies, patients present with episodic delirium, psychosis, restlessness, thrashing, muscular fasciculations, seizures, and aphasia. Hydrophobia and aerophobia are pathognomonic for rabies and occur in 50% of patients. Attempting to drink or having air blown in the face produces severe laryngeal or diaphragmatic spasms and a sensation of asphyxia. This may be related to a violent response of the airway irritant mechanisms. Even the suggestion of drinking may induce hydrophobic spasm.

Autonomic instability is observed with furious rabies, with symptoms that include the following: Fever, Tachycardia, Hypertension, Hyperventilation, Anisocoria - fixed pupillary dilation (“blown pupil”), optic neuritis (may falsely suggest brain death), Facial palsy, Mydriasis, Lacrimation, Excessive salivation, Perspiration, Postural Hypotension.
In patients with paralytic rabies, fever and nuchal rigidity may occur. Paralysis is symmetrical and may be either generalized or ascending and may be mistaken for Guillain-Barré syndrome. The sensory system is usually spared. Calm clarity gradually progresses to delirium, stupor, and then coma.

Coma

Respiratory failure occurs within 1 week of neurologic symptoms. Hypoventilation and metabolic acidosis predominate. Acute respiratory distress syndrome is common. Wide variations in blood pressure, cardiac arrhythmias, and hypothermia ensue. Bradycardia and cardiac arrest occur. With intensive support, life may be extended for 3 or 4 months; however, death is usually the outcome.

Death

It is important to determine brain death by brain biopsy or absence of cerebral arterial flow, because some of the neurologic signs may falsely suggest brain death.

TREATMENT AND MEDICATIONS

Wound Care

Regardless of the risk of rabies, bite wounds can cause serious injury such as nerve or tendon laceration and local and system infection. Your doctor will determine the best way to care for your wound, and will also consider how to treat the wound for the best possible cosmetic results.

For many types of bite wounds, immediate gentle irrigation with water or a dilute water povidone-iodine solution has been shown to markedly decrease the risk of bacterial infection.

Wound cleansing is especially important in rabies prevention since, in animal studies, thorough wound cleansing alone without other post-exposure prophylaxis has been shown to markedly reduce the likelihood of rabies.

You should receive a tetanus shot if you have not been immunized in ten years. Decisions regarding the use of antibiotics, and primary wound closure should be decided together with your doctor.

Rabies Post-exposure Vaccinations

For people who have never been vaccinated against rabies previously, postexposure anti-rabies vaccination should always include administration of both passive antibody and vaccine.
The combination of **human rabies immune globulin (HRIG)** and **vaccine** is recommended for both bite and nonbite exposures, regardless of the interval between exposure and initiation of treatment.

People who have been previously vaccinated or are receiving pre-exposure vaccination for rabies should receive only vaccine.

Adverse reactions to rabies vaccine and immune globulin are not common. Newer vaccines in use today cause fewer adverse reactions than previously available vaccines. Mild, local reactions to the rabies vaccine, such as pain, redness, swelling, or itching at the injection site, have been reported. Rarely, symptoms such as headache, nausea, abdominal pain, muscle aches, and dizziness have been reported. Local pain and low-grade fever may follow injection of rabies immune globulin.

The vaccine should be given at recommended intervals for best results. Talk to your with your doctor or state or local public health officials if you will not be able to have shot at the recommended interval. Rabies prevention is a serious matter and changes should not be made in the schedule of doses.

People cannot transmit rabies to other people unless they themselves are sick with rabies. The prophylaxis you are receiving will protect you from developing rabies, and therefore you cannot expose other people to rabies. You should continue to participate in your normal activities.

**Postexposure Vaccinations - Programs for uninsured and underinsured patients**

Rabies postexposure vaccinations consists of a dose of human rabies immune globulin and **four doses of rabies vaccine given on the day of the exposure, and then again on days 3, 7, and 14.** The vaccine is given in a muscle, usually in the upper arm. This set of vaccinations is highly effective at preventing rabies if given as soon as possible following an exposure.

If a person has previously received postexposure vaccinations or received preexposure vaccinations, only **two doses of vaccine (on the day of exposure and then 3 days later)** are needed. Human rabies immune globulin is not required. Your doctor and local health department will be able to guide you through the process.

<table>
<thead>
<tr>
<th>Type</th>
<th>Name</th>
<th>Route</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human Diploid Cell Vaccine (HDCV)</td>
<td>Imovax®</td>
<td>Intramuscular</td>
<td>Preexposure or Postexposure</td>
</tr>
<tr>
<td></td>
<td>Rabies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Purified Chick Embryo Cell Vaccine (PCEC)</td>
<td>RabAvert®</td>
<td>Intramuscular</td>
<td>Preexposure or Postexposure</td>
</tr>
</tbody>
</table>
### Human Rabies Immune Globulin

<table>
<thead>
<tr>
<th>Imogam® Rabies-HT</th>
<th>Local infusion at wound site, with additional amount intramuscular at site distant from vaccine</th>
<th>Postexposure</th>
</tr>
</thead>
</table>

| HyperRab TM S/D   | Local infusion at wound site, with additional amount intramuscular at site distant from vaccine | Postexposure |

---

### Postexposure Prophylaxis for Non-immunized Individuals

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wound cleansing</td>
<td>All postexposure prophylaxis should begin with immediate thorough cleansing of all wounds with soap and water. If available, a virucidal agent such as povidine-iodine solution should be used to irrigate the wounds.</td>
</tr>
<tr>
<td>RIG</td>
<td>If possible, the full dose should be infiltrated around any wound(s) and any remaining volume should be administered IM at an anatomical site distant from vaccine administration. Also, RIG should not be administered in the same syringe as vaccine. Because RIG might partially suppress active production of antibody, no more than the recommended dose should be given.</td>
</tr>
<tr>
<td>Vaccine</td>
<td>HDCV or PCECV 1.0 mL, IM (deltoid area), one each on days 0, 3, 7, and 14.</td>
</tr>
</tbody>
</table>

### Postexposure Prophylaxis for Previously Immunized Individuals

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wound cleansing</td>
<td>All postexposure prophylaxis should begin with immediate thorough cleansing of all wounds with soap and water. If available, a virucidal agent such as povidine-iodine solution should be used to irrigate the wounds.</td>
</tr>
<tr>
<td>RIG</td>
<td>RIG should not be administered.</td>
</tr>
<tr>
<td>Vaccine</td>
<td>HDCV or PCECV 1.0 mL, IM (deltoid area), one each on days 0 and 3.</td>
</tr>
</tbody>
</table>

### Rabies Preexposure Prophylaxis Guide

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Nature of Risk</th>
<th>Typical Population</th>
<th>Preexposure Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuous</td>
<td>Virus present continuously, often in high concentrations. Specific exposures likely to go unrecognized. Bite, nonbite, or aerosol exposure.</td>
<td>Rabies research laboratory workers; rabies biologics production workers.</td>
<td>Primary course. Serologic testing every 6 months; booster vaccination if antibody titer is below acceptable level.</td>
</tr>
<tr>
<td>Frequent</td>
<td>Exposure usually episodic, with source recognized, but exposure also might be unrecognized. Bite, nonbite, or aerosol exposure.</td>
<td>Rabies diagnostic lab workers, spelunkers, veterinarians and staff, and animal-control and wildlife workers in rabies-enzootic areas. All persons who frequently handle bats.</td>
<td>Primary course. Serologic testing every 2 years; booster vaccination if antibody titer is below acceptable level.</td>
</tr>
<tr>
<td>Infrequent</td>
<td>Exposure nearly always episodic with source</td>
<td>Veterinarians and terrestrial animal-control workers in areas where rabies</td>
<td>Primary course. No serologic testing or booster</td>
</tr>
<tr>
<td>Rare (population at large)</td>
<td>Exposure always episodic with source recognized. Bite or nonbite exposure.</td>
<td>U.S. population at large, including persons in rabies-epizootic areas.</td>
<td>No vaccination necessary.</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>--------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------</td>
<td>-------------------------</td>
</tr>
</tbody>
</table>

**Primary vaccination**

Three 1.0-mL injections of HDCV or PCEC vaccine should be administered intramuscularly (deltoid area) -- one injection per day on days 0, 7, and 21 or 28.

**Booster doses-Continuous risk**

People who work with rabies virus in research laboratories or vaccine production facilities are at the highest risk for unapparent exposures. Such persons should have a serum sample tested for rabies antibody every six months. Intramuscular booster doses of vaccine should be administered to maintain a serum titer corresponding to at least complete neutralization at a 1:5 serum dilution by the RFFIT.

**Frequent risk**

This group includes other laboratory workers such as those performing rabies diagnostic testing, spelunkers, veterinarians and staff, and animal-control and wildlife officers in areas where animal rabies is enzootic. The frequent-risk category also includes persons who frequently handle bats. Persons in the frequent risk group should have a serum sample tested for rabies antibody every 2 years; if the titer is less than complete neutralization at a 1:5 serum dilution by the RFFIT, the person also should receive a single booster dose of vaccine.

**Infrequent risk**

Veterinarians, veterinary students, and terrestrial animal-control and wildlife officers working in areas where rabies is uncommon to rare (infrequent exposure group) and at-risk international travelers fall into this category and do not routine preexposure booster doses of vaccine after completion of primary preexposure vaccination.

**MEDICAL TREATMENT AFTER SYMPTOM**

Inpatient care

Symptomatic rabies cannot be managed in the outpatient setting. Intensive cardiopulmonary supportive care is the only treatment available for patients with symptomatic rabies. Rabies vaccination and administration of HRIG (HUMAN RABIES IMMUNOGLOBULIN) is ineffective at this point. In animal studies, rabies immunoglobulin has been associated with “early death”; it has been suggested that HRIG may also pose a risk of early death in humans and should be avoided.
Regardless of treatment, symptomatic rabies is almost invariably fatal, with autonomic dysfunction leading to cardiac arrhythmia and hypotension. Some role for combination treatments including ribavirin, interferon, ketamine, and immunomodulatory therapies has been proposed and may be considered in future cases under investigational protocols.

Immunomodulatory therapies such as rabies immunoglobulin, rabies vaccine, and interferon have not altered outcomes in trials.

**Steroids,** which are usually indicated in the treatment of local vaccine reactions or cerebral edema, are **contraindicated** because of increased mortality noted in animal studies and because they reduce the response to the vaccine.

Transfer

For a patient with an illness consistent with rabies, timely diagnostic workup is essential. Transfer to a tertiary care center with high-level intensive care support and clinicians knowledgeable in managing rabies is optimal whenever feasible.

MEDICATION SUMMARY

Before the onset of rabies symptoms, passive and active immunizations are effective in preventing progression to full-blown rabies.

If the patient has had no prior rabies vaccination, if he or she is of unknown status, or if more than 5 years have passed since his or her last vaccination, rabies vaccine and immunoglobulin should be administered as follows:

**Rabies vaccine IM (deltoid) - 1 mL on days on days 0, 3, 7, and 14 (if immunocompromised, add an additional dose: 1 mL IM deltoid on days 0, 3, 7, 14, and 28)**

HRIG is administered only once, at the beginning of post-exposure prophylaxis. If anatomically feasible, the full dose of HRIG should be thoroughly infiltrated in the area around and into the wounds. Any remaining volume should be injected intramuscularly (IM) at a site distant from rabies vaccine administration. The gluteal muscle is **NOT an acceptable site for HRIG.** HRIG should never be administered in the same syringe or in the same anatomical site as the first vaccine dose. Human Rabies immunoglobulin (HRIG) - 20 IU/kg infiltrated as much as feasible around and under the bite wound; if any left over, give IM (gluteus)
*If HRIG is not given on day 0, it may be administered up to seven days after the first rabies vaccine.

If the patient has had prior rabies vaccination, vaccine should be administered as follows:

**Rabies vaccine IM (deltoid) 1 mL on days on days 0 and 3.**

*The gluteal muscle should NOT be used for rabies vaccine injections. Administration in this area can result in a decreased antibody response. Doses of rabies vaccine administered in the gluteal site should not be counted as valid doses and should be repeated. HRIG and vaccine MUST be given in different sites on the body.

**SITES FOR INJECTION:**

**Deltoid Muscle (Upper Arm)**

> Client may be positioned sitting, standing, supine, or prone.
> Locate site by measuring 2 - 3 fingerbreadths below the acromion process on the lateral midline of the arm.
**Anterolateral Thigh (Vastus Lateralis)**

> This is the preferred site for infants and children < 7 mo.
> Position client in supine or sitting position.
> Locate by identifying the greater trochanter and lateral femoral condyle. Injection site is the middle third and anterior lateral aspect of the thigh.

**DETERRENCE AND PREVENTION IN THE COMMUNITY**

Rabies in humans is 100% preventable through prompt and appropriate medical care. Rabies post-exposure prophylaxis (PEP) consists of a dose of Human Rabies Immune Globulin (HRIG) and a series of rabies vaccine shots

**Patient education**

The need for adherence to local public health recommendations regarding the control and vaccination of domestic animals and the vaccination of individuals who may be exposed to rabies in their occupation cannot be stressed enough.
Counsel patients regarding the subjective nature of provocative behavior toward animals. Especially stress avoiding contact with unfamiliar or wild animals. Wild animals seen in areas or at times of day that seem unusual are reason to suspect rabid behavior. Wild animals that are rabid may seem unusually docile or fearless. **Hypersalivation, or “foaming at the mouth,” is pathognomonic** for rabies but is often absent.

Prompt, vigorous cleansing of any injury or bite from any animal is critical and may reduce the risk of rabies transmission. Provide extensive reassurance after any injury that may be related to rabies transmission. Fear of rabies is primal and is known to induce hysterical reactions that mimic the disease manifestations.

Promote educational efforts at home and at schools teaching children about safety procedures and precautions regarding pets and wild animals. Many communities have programs through camps, schools, and public libraries, as well as information through local health department Web sites. Veterinarians and public health officials are excellent resources for concerns regarding animal rabies prevention.

In addition, the public should be advised to do the following:

1) Teach children at an early age not to handle stray animals or wildlife, especially bats found on the ground
2) Report any animals that are sick or acting strange to local public health authorities
3) Consult public health authorities if a bat is seen in the home at night, even if a bite is not suspected
4) Keep pets indoors at night and fenced in or on a leash when outdoors
5) Keep pet food and water dishes indoors
6) Have professional animal trappers remove bat colonies from homes and barns
7) Handle sick or dead animals with heavy gloves and shovels
8) Keep trash container lids tight and maintain compost piles away from dwellings
9) Wash hands with soap and water after contact with wildlife

If an animal scratch or bite occurs, especially if due to a bat, fox, raccoon, skunk, or unvaccinated dog or cat:

1) immediately wash the areas vigorously with soap and water and
2) immediately seek the care of a physician.

Aside from rabies, bites may become infected, and preventive care is available if sought. Mass control and mandatory vaccination of domesticated dogs and cats are effective in controlling rabies; however, developing some nations have found cost to be a barrier to such campaigns.

**Consultations**

Consultation with infectious disease specialists, neurologists, and neurosurgeons may be necessary to assist in diagnosis and management of patients with rabies or patients exposed to rabies.
Consultation with public health authorities is appropriate to assist in management of bite wound prophylaxis and animal epidemiology. Also, consult with animal control officers and veterinarians for the management, disposal, and testing of animals that have attacked and injured a human.