

Rabies

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Opinion statement

Human rabies is a fatal disease, except in rare patients who received rabies immunization before the onset of their disease. Attempts to treat rabies have otherwise been futile. Rabies is always preventable after an exposure if current recommendations are followed. Details about the contact, animal, and local epidemiologic situation are important when deciding whether to initiate postexposure prophylaxis after a potential rabies exposure. Rabies postexposure prophylaxis includes thorough local wound cleansing and active and passive immunization. Five doses of rabies vaccine should be administered intramuscularly in the deltoid muscle on days 0, 3, 7, 14, and 28 in individuals not previously immunized against rabies virus. Human rabies immune globulin should be administered into and around the wounds on day 0, with the remaining volume given intramuscularly at a site distant from the vaccine. Certain individuals at high risk of rabies exposure are candidates for pre-exposure rabies prophylaxis with three doses of rabies vaccine. Booster doses should be given as required.

Introduction

Worldwide rabies remains an important public health problem, and has a long history that dates back to antiquity [1]. Rabies is an acute encephalomyelitis caused by rabies virus, which is transmitted usually through a bite of a rabid animal. Beginning in the 1990s, there has been a re-emergence of human rabies in the United States, with zero to six reported cases of human rabies annually [2,3•]. The majority of these cases have involved indigenously acquired transmissions by insect-eating bats to patients without a history of a known exposure, although some have a history of contact with bats. Imported cases have been reported in travelers to or immigrants from developing countries with endemic canine rabies.

Typically, there is an incubation period in rabies that lasts approximately 1 to 3 months and, rarely, more than 1 year [4]. Much of what is known about the pathogenesis of rabies has been learned from experimental work in animal models [5•]. The long incubation period in rabies is likely the result of a delay in movement of the virus at the site of the bite. Experimental models have demonstrated infection of muscle fibers [6], which may be an important pathogenetic step. Rabies virus binds to nicotinic acetylcholine receptors at the motor endplate [7]. The virus travels centripetally along peripheral nerves within axons by retrograde fast axonal transport at a rate of approxi-

mately 50 to 100 mm daily [8]. Neurons in the spinal cord become infected, followed by rapid intra-axonal spread of the virus throughout the central nervous system along neuroanatomic pathways. Subsequently, there is centrifugal spread of the virus along nerves to multiple organs in animals and humans [9], including the salivary glands in rabies vectors.

Rabies is diagnosed on the basis of the clinical picture [10••] and confirmatory laboratory investigations [11•]. Rabies is a fatal disease. All attempts at therapy after the onset of the neurologic disease have been unsuccessful, with the exception of four patients who were fully immunized before developing the clinical features of rabies [12–16]; only one of these patients made a good neurologic recovery [12]. Therapy of rabies with antiviral agents, including an open trial with intravenous ribavirin or interferon- α (combined intravenous and intrathecal administration), was unsuccessful [17,18]. Antirabies virus hyperimmune serum of human or equine origin has been administered without clear beneficial effect [19–21]. Therapy of rabies is supportive. Adequate sedation and analgesia are very important for palliation. Aggressive care in an intensive care setting may prolong survival for up to a few weeks.

Although human-to-human transmission of rabies virus is unlikely, it is important that a diagnosis of

rabies be considered so that appropriate body substance precautions are initiated. After a diagnosis of rabies is made in the United States, it is common that rabies PEP is recommended for a given number of health care workers, primarily because of their potential contact with the saliva of an infected patient before the initiation of appropriate body substance precautions.

Because the therapy of patients with rabies not previously immunized has proven futile, the therapeutic emphasis is on prevention of the disease. PEP is successful uniformly after rabies exposure when current recommendations are followed. However, even minor deviations from the recommendations have resulted in treatment failures, leading to the development of rabies [22,23]. The Centers for Disease Control and Prevention periodically updates current recommendations of the Advisory Committee on Immunization Practices in the *Morbidity and Mortality Weekly Report*. The most recent recommendations were published in January 1999 [24••], and are available on the Internet at <http://www.cdc.gov/mmwr>.

Physicians can prevent rabies transmission by initiating appropriate treatment after potential rabies exposure. A decision must be made about whether PEP should be initiated after a bite or nonbite (eg, contamination of open wounds, abrasions, mucous membranes, or scratches with saliva or neural tissue) exposure to an animal. The species of the animal, the animal's availability for observation or laboratory testing, and the local epidemiologic situation are important factors in deciding whether to initiate rabies PEP. After an exposure to a dog, cat, or ferret, a healthy animal may be captured, confined, and observed for a period of 10 days and then examined by a veterinarian before it is released. If the animal is unwanted or has or develops signs of rabies during the observation period, it should be killed. The head should be transported properly to a laboratory for determination of rabies virus infection, which includes detection of rabies virus antigen with the direct fluorescent antibody technique [11•]. In other animal species, the time period of infectious rabies virus secretion in the saliva is unknown before the onset of clinical disease; therefore, these animals should be killed

immediately and a laboratory examination should be performed on brain tissues to determine whether the animal had rabies. If the laboratory examination is negative, one may reasonably conclude that the saliva of the animal did not contain rabies virus. If an animal escapes after an exposure, it should be considered rabid and PEP should be initiated unless information from public health officials indicates that PEP is unnecessary.

In recent cases of indigenously acquired human rabies in the United States, many patients did not have a history of a rabies exposure [2]. Molecular studies have shown that transmission of rabies virus occurred from variants associated with insect-eating bats, primarily silver-haired bats or Eastern pipistrelle bats [25•]. Most of these individuals were unaware that they were bitten by bats. Bite wounds from these bats may be small [26•], and therefore may go unrecognized unless the bites are witnessed. Current recommendations suggest that individuals receive rabies PEP when there is a reasonable probability that an exposure from a bat may have occurred. The presence of a potentially rabid bat (*ie*, rabies not excluded by a laboratory examination) in a room with an unattended small child, mentally disabled person, or intoxicated person are situations in which rabies PEP should be considered. Unfortunately, it has become common practice to initiate PEP in highly theoretical potential exposure situations in which human infections have never been described [27].

Rabies PEP includes local wound cleansing and active and passive immunization. Inactivated cell culture rabies vaccines are used for active immunization. Human rabies immune globulin (RIG) is used for passive immunization. Pre-exposure prophylaxis with three doses of rabies vaccine on days 0, 7, and 21 or 28 are recommended for individuals at high risk of having rabies exposures, including certain travelers to rabies-endemic areas where modern rabies biologics may not be available. Booster doses should be given as required based on serologic monitoring. If previously immunized individuals have a rabies exposure, they should be given two doses of rabies vaccine on days 0 and 3, and should not receive RIG.

Treatment

Pharmacologic treatment

- Five doses of rabies vaccine plus RIG should be administered as soon as possible after rabies exposure to patients not previously immunized.
- Two doses of rabies vaccine without RIG should be administered to previously immunized patients after rabies exposure.

Rabies vaccine

Standard dosage Five doses of 1.0 mL purified chick embryo cell (PCEC) vaccine (RabAvert; Chiron Behring GmbH, Marburg, Germany), human diploid cell vaccine (HDCV) (Imovax Rabies; Aventis Pasteur, Lyon, France), or rabies vaccine adsorbed (RVA) are

administered in the deltoid muscle on days 0, 3, 7, 14, and 28. In infants and small children, the anterolateral aspect of the thigh is the preferred site. There have been reports of vaccine failure after administration of rabies vaccine into the gluteal area [22]. Vaccine should be administered as soon as possible after an exposure, and should be given regardless of the length of a delay that may be due to failure to recognize an exposure. Rabies vaccine must never be given at the same site or in the same syringe as RIG. After an exposure, persons who have previously received rabies immunization should receive two doses of vaccine on days 0 and 3, and should not receive RIG.

- Contraindications** None for postexposure treatment because of the fatal outcome of rabies. Rabies vaccine should be given with caution in persons known to be sensitive to vaccine constituents, including processed bovine gelatin, chicken protein, neomycin, chlortetracycline, and amphotericin B for PCEC vaccine and neomycin and phenol red for HDCV. Neomycin is not a constituent of RVA. Pregnancy is not a contraindication for the administration of rabies vaccine.
- Main drug interactions** None. However, corticosteroids, other immunosuppressive drugs, and antimalarial drugs may interfere with the antibody response to rabies vaccines.
- Main side effects** Anaphylaxis and acute hypersensitivity reactions have occurred, but these reactions are uncommon. Type 1 immediate hypersensitivity reactions occurred in approximately one in 10,000 persons administered HDCV [28]. When there is a history of hypersensitivity, antihistamines may be given, epinephrine (1:1000) should be readily available, and the patient should be observed closely. Mild systemic reactions, including fever, headache, dizziness, myalgias, nausea, and abdominal pain, occur in approximately 20% of recipients. Local reactions, including pain, erythema, edema, and pruritus, occur in approximately 25% of recipients. These reactions can be treated with anti-inflammatory medications and antipyretics, and immunization should not be interrupted or discontinued because of mild systemic or local reactions. Rarely, Guillain-Barré syndrome and transient paralytic disorders have been associated with these rabies vaccines. Type III hypersensitivity reactions (*eg*, immune complex-like disease) occur in approximately 6% of persons receiving booster doses of HDCV [29], but they have not been reported with PCEC vaccine. These reactions are associated with the development of immunoglobulin E antibodies to β -propiolactone-altered human serum albumin in the vaccine (β -propiolactone is used to inactivate infectious rabies virus, albumin is used as a stabilizer in HDCV).
- Special points** Freeze-dried PCEC vaccine and HDCV should be stored under refrigeration at 36° to 46°F and used immediately after reconstitution. Any unused portion should be discarded because the vaccine contains no preservative.
- Cost effectiveness** Rabies vaccines are expensive and highly effective. The wholesale cost of the five doses of vaccine required for PEP is \$735.60.

Human rabies immune globulin

- Standard dosage** Administration of 20 IU/kg body weight of RIG at the time of the first rabies vaccine dose. RIG is packaged in 2-mL and 10-mL vials containing 150 IU/mL. Administration of RIG should never be delayed beyond the seventh day after the first dose of the vaccine is given. If anatomically feasible, the full dose should be infiltrated into and around the wounds, and any remaining volume administered IM (5 mL or less per inoculation) at a site distant from vaccine administration (gluteal area or lateral thigh muscles). If a large volume is needed for infiltration of large or multiple wounds, then RIG may be diluted twofold or threefold in a solution of 0.9% sodium chloride [23]. Infiltration of wounds in certain anatomic sites (*eg*, fingertips) should be performed in a manner that avoids increased pressure in the tissue compartment. RIG must never be administered in the same syringe as vaccine. A higher dose of RIG than the recommended dose or repeated doses of RIG should not be given because there may be interference with the development of active immunity.
- Contraindications** None known, with the exception that patients who have previously received rabies immunization should not receive RIG. Should be administered with caution in patients with a history of prior systemic allergic reactions after the administration

of human immunoglobulin preparations. People with specific immunoglobulin (Ig)A deficiency have an increased potential for developing antibodies to IgA. In addition, they could have anaphylactic reactions to subsequent administrations of blood products containing IgA. Pregnancy is not a contraindication for the administration of RIG.

- Main drug interactions** None. Live virus vaccines should not be given for a period of 4 months after the administration of RIG because of possible interference with the immune response to the vaccine.
- Main side effects** Local soreness may occur at the site of inoculation and there may be mild fever. Urticaria, angioedema, and anaphylactic shock are rare, although it is unclear if there is a causal relationship. Because RIG is made from human plasma, it may contain unknown infectious agents, even though donors are screened, purification and inactivation (heat treatment) procedures are used, and testing is performed for certain viral infections. As a result of intramuscular administration, bleeding complications may occur in patients with thrombocytopenia or bleeding disorders.
- Special points** RIG should be stored at 36° to 46°F and should not be used if the solution has been frozen.
- Cost effectiveness** RIG is expensive and highly effective, with a wholesale cost of \$706.25 for a 75-kg patient requiring 10 mL (1500 IU).

Other treatments

- All patients with potential rabies exposure should receive immediate and thorough local wound cleansing.

Local wound cleansing

- Standard procedure** Immediate and thorough washing of all bite wounds and scratches with soap and water is recommended to inactivate infectious rabies virus at the site of the wounds. Administration of a virucidal agent (*eg*, povidone-iodine solution) is also recommended, particularly with deep wounds. Studies performed in animal models have shown that thorough wound cleansing alone greatly reduces the likelihood of developing rabies [30,31]. Suturing of wounds should be avoided whenever possible [23], but cosmetic factors and the potential for the development of bacterial infections must be considered.
- Contraindications** None.
- Complications** None significant.
- Cost effectiveness** Inexpensive and highly effective.

Lifestyle factors and prevention

- Persons at risk for potential occupational or recreational rabies exposures (*eg*, spelunkers) and travelers to areas with endemic dog rabies should consider pre-exposure rabies immunization (three doses of rabies vaccine and booster doses as required).
- Wild animals that are rabies vectors should not be kept as pets.
- Potential rabies exposures should be avoided as much as possible, particularly in developing countries where dog rabies is endemic.

Emerging therapies

- A worldwide shortage of human RIG should stimulate exploration of alternative products for passive immunization, including human neutralizing monoclonal antibodies [32•].
- Experimental protocols should be developed to treat patients with rabies.

Infection control

- Because of a theoretical risk of transmission, patients with suspected rabies should be isolated and body substance precautions should be used; health care workers should wear gloves, masks, and eye protection, especially in the critical care setting.

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