18 Rabies

NOTIFIABLE

In some circumstances, advice in these guidelines may differ from that in the Summary of Product Characteristics of the vaccines. When this occurs, the recommendations in these guidelines, which are based on current expert advice from NIAC, should be followed.

This chapter has been updated as follows:

- changes in definition of types of exposure
- clarification of the groups who should receive rabies pre-exposure immunisation
- reduction in the number of vaccine doses for post-exposure prophylaxis of immunocompetent individuals to 4.

Introduction

Rabies is an acute viral encephalomyelitis caused by a lyssavirus. Infection usually results from the bite or scratch of a rabid animal.

The virus attacks the central nervous system, causing progressive paralysis, encephalitis and coma. Once symptoms are present, rabies is invariably fatal.

Rabies is usually caused by rabies virus genotype 1 (classical rabies), less commonly by rabies-related lyssaviruses. European bat lyssavirus (EBLV1 and 2) infects insectivorous bats in Europe. Since 1977, four human cases of EBLV infection have been reported across Europe.

Epidemiology

Any warm-blooded animal may be infected with rabies virus, including dogs, cats, foxes, bats, skunks, racoons and monkeys. Worldwide 40-70,000 cases of human rabies occur annually, over 90% from dog bites in low-resource countries. In these countries, 60% of animal bites occur in or around the home, increasing the risks for

those visiting friends and relatives (VFRs). Almost 50% of deaths occur in children, who are more vulnerable than adults to attack by animals.

No indigenous rabies cases have been reported in Ireland since 1923. Very few cases of rabies in humans are reported in the EU.

Some countries (e.g. the UK, Australia) that are declared rabies-free have rabies-related lyssaviruses in their bat populations.

Any bite, lick or scratch from a warm-blooded animal in an endemic area must be considered as high risk and specialist advice should be sought as soon as possible.

Transmission
Infection is usually transmitted by the bite or scratch of a rabid animal. The virus may also be passed when infected saliva comes in contact with broken skin, mucous membranes or the cornea. Laboratory workers in contact with specimens containing the virus are at risk of occupational contact. Aerosol transmission is possible and may be important in rabies-infected bat caverns. Human-to-human transmission is extremely rare, the only documented cases involved corneal and solid organ transplantation from infected patients who died prior to diagnosis.

Effects of rabies

The incubation period of rabies is generally between 2 and 12 weeks but may range from 4 days to many years. In over 90% of cases the disease presents within 1 year. Factors that tend to shorten the incubation period include younger age, inoculation near well-innervated parts of the body, inoculation near the head and neck, and more extensive wounds.

Untreated rabies is almost invariably fatal; the rare cases of survival after symptoms have developed had some pre- or post-exposure treatment.

Initial viral replication takes place in the tissues at the point of entry, persisting for between 48 and 72 hours. The virus moves along the axonal sheaths in peripheral nerves towards the central nervous system. Viral spread then occurs to the peripheral nerves; there is no antibody response until the onset of clinical symptoms.

Symptoms are variable. Early symptoms are non-specific and include pain and paraesthesia at the inoculation site. Low-grade fever, malaise, anorexia, headache, nausea and vomiting are common. The patient may be excitable or irritable, with more classical hypoglossal spasm associated with water contact (hydrophobia) or blowing in the face (aerophobia). Rising intracranial pressure leads to decreased level of consciousness and convulsions. Central and peripheral nerve impairment leads to progressive respiratory distress. A wide variety of cardiac dysrhythmias can occur. Other causes of acute encephalitis, Guillain-Barré syndrome, tetanus, poliomyelitis, and neurological adverse reactions to drugs and poisons are among the differential diagnoses.

Rabies vaccines

Rabies vaccines are used for pre-and post-exposure prophylaxis. Vaccines available in Ireland are either Human Diploid Cell vaccines (HDCV) or inactivated, produced on purified chick embryo cells.

Currently licenced vaccines are

- Rabies vaccine BP (1ml/dose).
- Rabipur (1ml/dose)
- Verorab (0.5ml/dose).

Not all are currently marketed.

They can be used interchangeably.

They are available through the National Cold Chain Service or from Cherry Orchard Hospital (Tel. 076 695 5000)

An up to date list of licensed vaccines can be accessed on the HPRA website www.hpra.ie

Rabies vaccines should be stored at +2^{o}C to +8^{o}C.

Dose and route of administration for pre-exposure prophylaxis (PREP)
The dose is ≥2.5 IU on days 0, 7 and 21 or 28 administered by IM injection into the deltoid region.

When time does not permit, an accelerated schedule at 0, 3 and 7 days will give sufficient short-term protection, but a booster at one year is required to complete the course.

A complete primary or pre-exposure course is considered to give lifelong protection if completed as days 0, 7 and 21-28, or days 0, 3, 7, and 365.

NOTE: One IM dose (≥2.5 IU) is the entire content of the vial.
For instructions on reconstitution of the vaccine before administration, see the SmPC.

For those in high-risk occupations, see below.

The intramuscular route is preferred. Although approved by the WHO, a two-site two-dose intradermal vaccine course is not recommended by NIAC for routine use. Suitably qualified and experienced healthcare professionals may give the vaccine via the intradermal route for pre-exposure prophylaxis.

All travellers to areas of risk should be advised to seek immediate medical aid if an animal bite or scratch is sustained, and should be given advice on wound toilet

Indications

PRE-EXPOSURE PROPHYLAXIS FOR THOSE AT HIGH RISK

Those who are at continuous or frequent risk of exposure should be offered pre-exposure vaccine. Groups in these risk categories include:

- Laboratory workers handling or potentially handling the virus
- Those likely to be in direct contact with rabies-prone animals. This includes:
    - Staff at animal quarantine centres
    - Staff at zoos
    - Staff at research and acclimatisation centres where rabies-prone animals are housed
    - 'At-risk' staff at ports and airports, e.g. Department of Agriculture and Food Inspection staff
    - Dog wardens
    - Animal workers who regularly travel to rabies enzootic areas
    - Authorised carrying agents for imported Rabies-prone animals
    - Selected National Parks and Wildlife staff who may handle bats, based on risk assessment
    - Workers in enzootic areas at special risk (e.g. veterinary staff, zoologists)
- Health-care workers who have or may come into close contact with a patient (or their clinical specimens) with probable or confirmed rabies
- Adults and children living or travelling to rabies-endemic areas (particularly children, who may be more at risk or who may not report an exposure)

Immunocompromised persons may have a sub-optimal immune response to the vaccine.

Post vaccination serological testing

Post vaccination serology is recommended for

i. those at continuous or frequent risk, to determine the need for a booster dose.

ii. those who had a severe reaction to a previous dose of rabies vaccine, to determine if a course should be completed.

Most travellers are at infrequent risk and do not require serological testing.

When indicated, antibody assay should be performed 2 – 4 weeks after the last dose. An additional dose should be considered if the antibody titre is less than 0.5 IU/ml.

Booster doses

Booster doses are recommended for:

a. Those at regular and continuous risk.

- A booster dose is recommended one year after the primary course, and then 3 to 5 yearly
- Antibody titres are advised 6 monthly for those who work with live rabies virus; they may be given booster doses if their titre is below 0.5IU/ml.

b. Those with frequent episodic exposure, e.g. rabies diagnostic workers, veterinary surgeons and staff, and wildlife rangers conducting bat research.

Antibody titres should be checked every 3 years and boosters administered as necessary.

Those at increased but infrequent risk of episodic exposure who are fully vaccinated do not require further booster doses.

Boosters should not be administered more frequently than every 3 years to minimise the possibility of localised reactions to the vaccine.

Contraindications

Anaphylaxis to any of the vaccine constituents

However, as rabies infection is generally fatal, there are no contraindications to post-exposure vaccination. Consider using an alternative Rabies vaccine.

Precautions

Acute severe febrile illness – defer until recovery, unless used for post-exposure management.

Pregnancy. Pre-exposure vaccine should only be given to pregnant women if the risk of exposure to rabies is high and rapid access to post exposure prophylaxis will be limited. Post exposure treatment should be given when indicated.

Adverse reactions

Local: redness, swelling or pain at the site of injection within 24-48 hours of administration.

General: Headaches, nausea, diarrhoea, myalgia, fever, muscle aches, vomiting and urticarial rashes are common.

Adverse reactions to the vaccine may be more severe with repeated doses.

POST- EXPOSURE TREATMENT

Treatment must be started as soon as possible after exposure.

Moreover, treatment should be considered, *irrespective of the period between exposure and presentation*, unless the individual is fully vaccinated and rabies antibodies can be detected. Anyone with a possible exposure to rabies virus should seek immediate medical attention.

Treatment after possible exposure depends upon the circumstances of the exposure.

1. As soon as possible

- The wound should be washed thoroughly with soap or detergent and water and rinsed completely. It is important not to mix disinfectant with soap during washing, as detergents can negate the effects of disinfectant.
- The wound or site of exposure (e.g. mucous membrane) should be held under a running tap for at least 10 minutes.
- Human Rabies Immunoglobulin (HRIG) should be infiltrated into the depth of the wound and around the wound (see Rabies-specific immunoglobulin section).
- Primary suturing should be avoided or postponed, as it may increase the risk of introduction of rabies virus into nerves.
- Tetanus prophylaxis and measures to control bacterial infection should be administered as indicated.

2. Risk assessment

Risk assessment of each case of possible exposure should include the following:

- *Country of exposure (or the country of origin of the animal):* Up-to- date information on rabies by country can be found at http://www.who-rabies-bulletin.org/ or http://www.cdc.gov/rabies
- *Type, severity and site of the wound*: Highest risk wounds are those with broken skin, or where mucus membranes are contaminated with the animal's saliva or body fluids. Proximal bites, such as the face represent a greater risk than distal wounds.
- *Circumstances of bite:* Unprovoked bites carry a much higher risk than provoked bites.
- *Animal involved:* Bat rabies may be suspected if the bat is sick, grounded without injury or if an uninjured bat is found dead. If the bat is available, urgent testing is required.
- *Vaccination status of the animal (if known):* Regularly vaccinated animals are much less likely to be infected with rabies.
- *Immune status of the individual involved:* Fatal rabies encephalomyelitis is extremely unlikely in a fully immunised individual and is virtually certain to be prevented by an appropriate course of post-exposure treatment, if given sufficiently early.

3. Post exposure prophylaxis (PEP)

Specialist advice from Cherry Orchard Hospital or the HPSC should be sought when post-exposure immunisation and immunoglobulin seem indicated. Management depends on the type of contact with the rabid animal.

Types of contact are:
Category I – touching or feeding animals, licks on intact skin.

Category II - nibbling of uncovered skin, minor scratches or abrasions without bleeding.

Category III – single or multiple transdermal bites or scratches, contamination of mucous membrane or broken skin with saliva from licks, exposure due to direct contact with bats.

All category II and III exposures assessed as carrying a risk of developing rabies require PEP. The risk is increased if:

- the biting mammal is a known rabies reservoir or vector species
- the exposure occurs in a geographical area where rabies is still endemic
- the animal looks sick or displays abnormal behaviour
- a wound or mucous membrane was contaminated by the animal's saliva
- the bite was unprovoked
- the animal has not been vaccinated.

All immunosuppressed subjects should be given Human Rabies immunoglobulin (HRIG) following Category ll or lll exposure.

In the event of a Category ll or lll exposure, persons who have previously been immunised should receive 2 further doses of rabies vaccine on days 0 and 3.

Rabies-specific immunoglobulin

The mainstay of post exposure prophylaxis is rabies vaccine. Human rabies immunoglobulin (HRIG) may provide short term immunity in the first 7 days after the commencement of active immunisation. After 7 days the antibody level induced by active immunisation (vaccine) is many orders of magnitude greater that can be provided by passive immunisation with HRIG.

After thorough wound cleansing, HRIG should be infiltrated into the depth of the wound and around the wound as much as anatomically feasible. Any remainder should be injected at an intramuscular site distant from that of the vaccine, e.g. anterolateral thigh or deltoid.

Dose
The dose is 20 IU/kg.

Indications
Post-exposure prophylaxis of rabies infection in persons after exposure to scratches, bites or other injuries including mucous membrane contamination with infectious tissue, such as saliva, caused by a suspected rabid animal. (See Table 18.1)

HRIG is not indicated if more than seven days have elapsed since commencement of active immunisation.

HRIG must only be used in combination with rabies vaccine.

Adverse reactions
Local: Very common: injection site pain, erythema, induration, pruritus.
General: Very common or common: headache, nausea, diarrhoea, myalgia, arthralgia, lymphadenopathy, abdominal pain, vomiting, urticaria, pruritus, dyspnoea, wheezing, dizziness.

Contraindications
Because of the life-threatening risk due to rabies, there are no contraindications to the administration of HRIG.

Precautions for use
HRIG must not administered into a blood vessel, because of the risk of shock.

HRIG contains a small quantity of IgA. Individuals who are deficient in IgA have the potential for developing IgA antibodies and may develop anaphylaxis after administration of blood components containing IgA.

Vaccine and HRIG suppliers
Both the vaccine and HRIG are available from Cherry Orchard Hospital (Tel. 076 695 5000).
Table 18.1 provides guidance on the post-exposure administration of rabies vaccine and HRIG following risk assessment

Table 18.1 Post-exposure treatment following risk assessment

Rabies risk (any age)	Unimmunised	Previously immunised
Category I exposure	Wash exposed skin No PEP required.	Wash exposed skin No PEP required.
Category II exposure	Wound washing and immediate vaccination: 1 dose IM on days 0, 3, 7 and day 14–28 (four doses) **HRIG is NOT indicated**	Wound washing and immediate vaccination: 1 dose IM days 0 and 3 (two doses) **HRIG is NOT indicated**
Category III exposure	Wound washing and immediate vaccination: 1 dose IM on days 0, 3, 7 and day 14–28 (four doses) **HRIG is recommended**	Wound washing and immediate vaccination: 1 dose days 0 and 3 (2 doses) **HRIG is NOT indicated.**

Further information on rabies vaccine and post-exposure treatment is available from the Health Products Regulatory Authority (https://www.hpra.ie/), Cherry Orchard Hospital (Tel. 076 695 5000), and the Health Protection Surveillance Centre (https://www.hpsc.ie/)

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