

3.2 AUSTRALIAN BAT LYSSAVIRUS INFECTION AND RABIES

Virology

Australian bat lyssavirus (ABL) and rabies virus are members of the family Rhabdoviridae, genus *Lyssavirus*. There are 7 known genotypes within the genus *Lyssavirus*; ABL (genotype 7) is more closely related to rabies virus (genotype 1) than any of the other 6 genotypes.

Clinical features

Based on the two recognised human cases of ABL infection, it has to be assumed that ABL has the same clinical features as rabies. Typically, in the prodromal phase of rabies, which lasts up to 10 days, the patient may experience non-specific symptoms such as anorexia, cough, fever, headache, myalgia, nausea, sore throat, tiredness and vomiting.¹ Paraesthesiae and/or fasciculations at or near the site of the wound may be present at this stage. Anxiety, agitation and apprehension may also occur.

Most rabies patients present with the furious or encephalitic form.¹ In the encephalitic phase, objective signs of nervous system involvement include aerophobia, hydrophobia, bizarre behaviour, disorientation and hyperactivity. Signs of autonomic instability such as hypersalivation, hyperthermia and hyperventilation may occur.¹ The neurological status of the patient deteriorates over a period of up to 12 days, and the patient either dies abruptly from cardiac or respiratory arrest, or lapses into a coma. Rabies is almost invariably fatal.

Epidemiology

Rabies is endemic throughout much of Africa, Asia, the Americas and Europe, where the virus is maintained in certain species of mammals.¹ Australia, New Zealand and Papua New Guinea are free of endemic rabies. Human rabies characteristically follows a bite from a rabid animal, most frequently a dog, but in some parts of the world other animals, such as jackals and bats, are important sources of exposure. In countries where rabies vaccination of domestic animals is widespread (North America and Europe), wild animals such as raccoons and foxes are important reservoirs.¹

Cases of rabies after animal scratches or the licking of open wounds are extremely rare. Cases have been recorded after exposure to aerosols in a laboratory and in caves infested with rabid bats, and cases have been reported following corneal transplants from donors who died with undiagnosed rabies.¹

In Australia, 2 cases of a fatal rabies-like illness caused by ABL have been reported, one in 1996 and the other in 1998.² Both patients had been bitten by bats. Evidence of ABL infection has since been identified in all 4 species of Australian fruit bats (flying foxes) and in at least 3 species of Australian insectivorous bats. It should therefore be assumed that all Australian bats have the potential to be infected with ABL.

Rabies vaccine

- Mériieux Inactivated Rabies Vaccine – Aventis Pasteur. Each 1.0 mL dose contains at least 2.5 IU viral antigens, neomycin 100-150 µg, and up to 70 mg of human serum albumin. Presentation is a 1.0 mL single dose vial of lyophilised vaccine with 1.0 mL distilled water as diluent.

The vaccine is a lyophilised, stabilised suspension of inactivated Wistar rabies virus (strain PM/W1381503-3M) that has been cultured on human diploid cells and then inactivated by beta-propiolactone. The dry vaccine is coloured off-white, but after reconstitution with the diluent it turns a pinkish colour due to the presence of phenol red. The vaccine does not contain a preservative.

Rabies immunoglobulin

- Imogam Rabies – Aventis Pasteur (Human rabies immunoglobulin). Each 1.0 mL contains IgG class human rabies antibodies with a minimum titre of 150 IU, glycine 22.5 mg and sodium chloride 1 mg.

Human rabies immunoglobulin (HRIG) is prepared by cold ethanol fractionation from the plasma of hyperimmunised human donors. It is supplied in 2 mL and 10 mL vials.

Transport, storage and handling

The vaccine, diluent and HRIG should be transported and stored at 2°C to 8°C. They must not be frozen; do not use either the vaccine or HRIG if either has been exposed to a temperature of less than 0°C. Do not freeze or store either the vaccine or HRIG in direct contact with ice packs. The reconstituted vaccine should be used immediately after reconstituting; the HRIG should be used immediately once the vial is opened.

Dosage and administration

(i) Pre-exposure prophylaxis

The dose of rabies vaccine for pre-exposure prophylaxis is 1.0 mL by IM or SC injection, on days 0, 7 and 28.

(ii) Post-exposure treatment

The dose of rabies vaccine for post-exposure treatment is 1.0 mL by IM or deep SC injection on days 0, 3, 7, 14 and 30. Also administer HRIG (human rabies immunoglobulin) 20 IU/kg body mass, by infiltration around wounds (may give remainder of dose by IM injection).

Recommendations

(i) Pre-exposure prophylaxis for Australian bat lyssavirus infection and rabies

Rabies vaccine is effective and safe when used for pre-exposure prophylaxis for either ABL³ or rabies¹ (*level IV evidence*). The rationale for pre-exposure prophylaxis is that: (i) vaccination may provide protection to people with inapparent exposure to either ABL infection or rabies; (ii) it may protect people whose post-exposure treatment may be delayed or inadequate; and (iii) it simplifies post-exposure treatment. Patients should be advised that the main reason for pre-exposure

prophylaxis is to prime the immune system for a secondary response, and that if a possible ABL or rabies exposure occurs, booster doses of vaccine may still be required.

Pre-exposure prophylaxis with rabies vaccine is strongly recommended for people in Australia liable to receive bites or scratches from bats (this includes bat handlers, veterinarians, wildlife officers and others who come into direct contact with bats).

Pre-exposure prophylaxis is strongly recommended for expatriates and travellers who will be spending prolonged periods (ie. more than a month) in rural parts of rabies endemic areas.⁴ The World Health Organization (WHO) maintains data on rabies infected countries, the most recent of which can be accessed at the following web site – <http://www.who.int/emc/diseases/zoo/rabies.html>

Pre-exposure prophylaxis for both ABL infection and rabies, for all ages, consists of a total of 3 IM or deep SC injections of 1 mL of rabies vaccine, the second given 7 days after the first, and the third given 28 days after the first. For pre-exposure prophylaxis, the vaccine can be obtained from CSL Vaccines. Costs of pre-exposure prophylaxis have to be met by the individual or the employer.

Inadvertent prolongation of the intervals does not impair the response. Doses should be given in the deltoid area, as rabies neutralising antibody titres may be reduced after administration in other sites. In particular, vaccine should never be given in the buttock, as failure of pre-exposure prophylaxis has been reported when given by this route.

Because the antibody response is reported as satisfactory after the pre-exposure prophylaxis regimen, routine serological testing to confirm seroconversion is not necessary. However, immunosuppressed people who are at risk of exposure to ABL or rabies should have their antibody titres determined 2 to 3 weeks after the third dose of vaccine.

Booster doses of rabies vaccine should be considered for immunised people who have ongoing exposure to either ABL or rabies. People who work with live lyssaviruses in research laboratories are at risk of inapparent exposures, and should have rabies antibody titres measured every 6 months. If the titre is reported as inadequate, they should have a booster dose. Other laboratory workers who perform ABL or rabies diagnostic tests, those with occupational exposures to bats in Australia, and those who are likely to be exposed to potentially rabid animals in endemic countries should have rabies antibody titres measured every 2 years. If the titre is reported as inadequate, they should have a booster dose. Alternatively a booster dose may be offered every 2 years without determining the antibody titre.

Intradermal pre-exposure prophylaxis: There are no data on the protection provided by intradermal rabies vaccination for ABL exposures. Therefore *intradermal pre-exposure administration of rabies vaccine should not be used for pre-exposure prophylaxis of ABL.*

Antibody titres are lower after intradermal compared to either IM or SC administration of rabies vaccine,¹ and there may be an impaired anamnestic response following exposure to rabies virus in those given intradermal rabies vaccine.^{5,6} For these two reasons *it is strongly recommended that either the IM or SC route be used for pre-exposure prophylaxis for potential future exposures to rabies virus.*

However, the cost of either IM or SC rabies vaccination may be prohibitive for some travellers. In this circumstance intradermal rabies vaccination, using a dose of 0.1 mL on days 0, 7 and 28, may be considered provided that:

- it is given by those with not only expertise in, but also regular practice of, the intradermal technique (because intradermal vaccination is reliable only if the whole of the 0.1 mL dose is properly given into the dermis);
- it must not be administered to anyone known to be immunocompromised in any way;
- it must not be administered to those taking either chloroquine or other antimalarials structurally related to chloroquine (eg. mefloquine) at either the time of, or within a month following vaccination;
- any remaining vaccine is discarded at the end of the session during which the vial is opened; and
- the rabies antibody level should be checked 2 to 3 weeks following completion of the pre-exposure course of intradermal vaccine.¹

The use of the intradermal route for rabies vaccination is the practitioner's own responsibility as the vaccine is not licensed for use via this route in Australia. The intradermal route should never be used to administer rabies vaccine by practitioners who only occasionally provide travel medicine services.

(ii) Post-exposure treatment for Australian bat lyssavirus and rabies exposures

Rabies vaccine and HRIG are effective and safe when used for post-exposure treatment following either ABL³ or rabies exposures¹ (*level IV evidence*). The essential components of post-exposure treatment for either ABL or rabies exposures are prompt local wound management and, for people who have not previously been vaccinated, administration of HRIG and rabies vaccine. Both HRIG and rabies vaccine are available for post-exposure treatment, without charge, from the relevant State/Territory health authorities (see Appendix 1 for contact phone numbers).

Post-exposure treatment should be considered whenever a bite, scratch or mucous membrane exposure to saliva from any Australian bat has occurred, regardless of:

- the extent of the bite or scratch – even very minor bites overseas have been known to transmit rabies;¹
- the time lapsed since the bite or scratch – although treatment should begin as soon as practicable after a bite or scratch, incubation periods of several years have been recorded for both ABL and rabies;¹
- the species of bat – ABL has been detected in all 4 species of flying fox, and in at least 3 species of Australian insectivorous bats; and
- the bat being apparently normal in appearance and behaviour – although ABL is more likely to be found in bats that either appear unwell or are behaving abnormally⁷ it has to be assumed that any bat is potentially infected with ABL.

However, exposure to bat blood, urine or faeces, or to a bat that has been dead for more than 4 hours does not warrant post-exposure treatment.

Where post-exposure treatment for a potential exposure to ABL is indicated the bat should, if possible without placing other persons at risk of exposure, be kept and arrangements made immediately for testing by the relevant State/Territory veterinary or health authority. Following the wound management, the administration of HRIG

and rabies vaccine can be withheld if the result (concerning the bat's ABL status) will be available within 48 hours of the exposure; if the result will not be available within 48 hours full post-exposure treatment should be commenced immediately.

An assessment must be made of the potential risk of transmission of rabies as soon as possible after exposure to a possibly infected animal. Dogs and monkeys comprise the usual exposures in Asia, Africa and Central and South America, but exposures to other animals must also be assessed for potential rabies transmission. Advice should be sought from the relevant State/Territory health authority before advising against rabies post-exposure treatment.

Post-exposure treatment of a patient presenting after possible rabies exposure should be commenced as soon as possible; treatment should not be withheld even if there has been a considerable delay in recognising the exposure. Unless the animal has been tested and found to be negative for rabies, the course should be completed irrespective of the clinical outcome in the animal.

Immediate and thorough washing of all bite wounds and scratches with soap and water, and the application of a virucidal preparation such as povidone-iodine solution after the washing, is an important measure in the prevention of ABL infection and rabies.¹ Consideration should be given at this stage of wound management to the possibility of tetanus and other wound infections, and appropriate measures taken. Primary suture of a bite from a potentially rabid animal should be avoided. Bites should be cleaned, debrided and well infiltrated with HRIG (see below). Secondary suture, if necessary, should be performed after 1 to 2 weeks, when it can be assumed that the patient has circulating neutralising antibodies.

The treatment subsequent to the wound management is the same for both ABL and rabies exposures, except that consideration may be given to omitting the HRIG if it is more than one year after an exposure to ABL. This is because the risk of infection at this time is considered to be low. Advice should be sought from the relevant State/Territory health authorities.

a) Use of rabies vaccine in post-exposure treatment

Following the local wound management, the subsequent post-exposure treatment for either ABL or rabies exposures consists of: (i) a total of 5 doses of 1.0 mL of rabies vaccine given by IM or SC injection; and (ii) HRIG (see below). The volume of vaccine administered to infants and children is the same as that given to adults (ie. 1.0 mL). The first dose of vaccine is given immediately (day 0), and subsequent doses are given on days 3, 7, 14 and 30. In adults and children the vaccine should be administered into the deltoid area, as administration in other sites may result in reduced neutralising antibody titres. In infants less than 12 months of age, administration into the anterolateral aspect of the thigh is recommended.

Serological testing to measure response is unnecessary except in unusual circumstances, such as when the patient is known to be immunocompromised. In such cases, the antibody titre should be measured 2 to 3 weeks after the dose given at 28 days and a further dose given if the titre is reported as inadequate.

b) Use of rabies immunoglobulin in post-exposure treatment

Rabies has occurred in people who have received post-exposure rabies vaccine without rabies immunoglobulin being infiltrated in and around the wound.^{8,9} Therefore *post-exposure treatment should always include the infiltration of HRIG in and around wounds at the same time as the first dose of rabies vaccine*, the only

exceptions being people with documented evidence of either completion of the pre-exposure prophylaxis regimen or adequate rabies antibody titres. These people should receive vaccine only.

A single dose of HRIG is given to provide localised anti-rabies antibody protection while the patient responds to the rabies vaccine. It should be given at the same time as the first post-exposure dose of vaccine (day 0). If not given with the first vaccine dose, it may be given up to day 7, but should not be given any later in the course of the vaccination program. From day 8 onwards, an antibody response to rabies vaccine is presumed to have occurred.

The dose of HRIG for all age groups is 20 IU per kg body mass. HRIG should be infiltrated in and around all wounds using as much of the calculated dose as possible, and the remainder administered intramuscularly at a site away from the injection site of rabies vaccine. Although the value of administering the remaining HRIG intramuscularly is uncertain,¹⁰ it must not be omitted. Rather, it must be emphasised that as much as possible of the HRIG be infiltrated in and around the wounds, so that as little HRIG as possible needs to be given intramuscularly.

If the wound has healed, the HRIG should be administered in the vicinity of the healed wound (eg. around a scar). If the wounds are severe and the calculated volume of HRIG is inadequate for complete infiltration (eg. extensive dog bites in a young child), the HRIG should be diluted in saline to make up an adequate volume for the careful infiltration of all wounds.

However, many bat bites occur as small puncture wounds on the fingers;¹¹ such exposures are probably high-risk exposures because of the extensive nerve supply to the fingers and hand.¹ Therefore, although infiltration of HRIG into finger wounds is likely not only to be technically difficult but also to be painful for the recipient, it must be undertaken. As much of the calculated dose of HRIG as possible should be infiltrated into finger and hand wounds using either a 25 or a 26-gauge needle. To avoid the development of a compartment syndrome, the HRIG should be infiltrated very gently, and should not cause the adjacent finger tissue to go frankly pale or white. If necessary a ring-block using a local anaesthetic may be required.

There is a theoretical risk that HRIG may suppress the patient's response to rabies vaccine, and no more than the recommended dose should be given.

Summary of Australian bat lyssavirus and rabies post-exposure treatment for non-immune individuals

Treatment	Immediate (Day 0)	Follow-up
Local treatment	Wound cleansing is vital	
Rabies vaccine	1.0 mL	1.0 mL on days 3, 7, 14, 30
Human rabies immunoglobulin (150 IU / mL)	20 IU/kg – no later than 7 days after rabies vaccine started	Do not give later than 7 days after rabies vaccine started

c) Post-exposure treatment of previously vaccinated people

People who have either completed a recommended course of pre-exposure prophylaxis, or previous post-exposure treatment, or who have documented adequate rabies neutralising antibodies, require a modified post-exposure treatment regimen if potentially exposed to either rabies virus or ABL. Local wound

management as described above must be carried out, and a total of 2 doses of rabies vaccine (1.0 mL each) should be given by IM injection on day 0 and day 3. HRIG is not necessary in these cases.

In cases where the vaccination status is uncertain because the documentation of a full course of rabies vaccine is not available, the standard post-exposure treatment regimen (HRIG plus 5 doses of rabies vaccine) should be administered.

d) Post-exposure treatment commenced overseas

Australians who are exposed to a potentially rabid animal while travelling abroad may be given post-exposure treatment whilst abroad with vaccines that are not available in Australia.

The Thai Red Cross Rabies Committee considers that the following 'first' and 'second' generation tissue culture vaccines are interchangeable:¹²

- human diploid cell vaccines (eg. Imovax Rabies),
- purified chick embryo cell vaccines (eg. Rabipur),
- purified Vero cell vaccine (Verorab),
- purified duck embryo vaccine (Lyssavac N), and
- rhesus lung cell vaccine (Rabies Vaccine Adsorbed).

Therefore, if a person has received one of the above vaccines abroad, the standard post-exposure treatment regimen should be continued in Australia with the locally available human diploid cell rabies vaccine. If the post-exposure treatment was started overseas with one of the above vaccines but HRIG was not given, and the person presents in Australia within 7 days of commencing post-exposure treatment, HRIG should be given immediately. If the person presents in Australia after 8 days then HRIG should be withheld.

If post-exposure treatment was started abroad using either a primary hamster kidney cell culture vaccine (in widespread use in China) or a nerve tissue vaccine (eg. sheep brain vaccine), the standard post-exposure treatment regimen (HRIG plus 5 doses of human diploid cell rabies vaccine) should be commenced in Australia as soon as possible. The full regimen of 5 doses of vaccine should be administered, regardless of how many doses of the (suboptimal) hamster kidney or nerve tissue vaccines were received overseas.

Adverse events and precautions

In a large (1770 volunteers) study the following adverse events were reported after administration of human diploid cell culture rabies vaccines: sore arm (15 to 25%), headache (5 to 8%), malaise, nausea or both (2 to 5%); and allergic oedema (0.1%).¹ In another study of post-exposure vaccination, 21% had local reactions, 3.6% had fever, 7% had headache and 5% had nausea. These reactions are not more frequent in children.¹

Anaphylactic reactions are rare (approximately 1 per 10 000 vaccinations) following administration of human diploid cell culture rabies vaccines. However, allergic reactions occur in approximately 6% of people receiving booster doses of some of the human diploid cell vaccines.¹ The reactions typically occur 2 to 21 days after a booster dose, and are characterised by generalised urticaria, sometimes with arthralgia, arthritis, oedema, nausea, vomiting, fever and malaise. These reactions are

not life-threatening; they have been attributed to the presence of beta-propiolactone-altered human albumin in the implicated vaccines.¹ NB: Mérieux Inactivated Rabies Vaccine contains human albumin.

Management of adverse events

Once initiated, rabies prophylaxis should not be interrupted or discontinued because of local reactions or mild systemic reactions. Such reactions can usually be managed with either aspirin or paracetamol.

Because ABL infection and rabies are lethal diseases, the recommended vaccination regimens, in particular the post-exposure treatment regimen, should be continued even if a significant allergic reaction occurs following a dose of rabies vaccine. Antihistamines can be administered in an attempt to ameliorate any subsequent reactions. A patient's risk of developing either ABL infection or rabies must be carefully considered before deciding to discontinue vaccination.

Contraindications

There are no contraindications to post-exposure treatment in a person with a presumed exposure to either ABL or rabies.

Use of steroids and immunosuppressive agents

Corticosteroids and immunosuppressive agents can interfere with the development of active immunity, and therefore if possible should not be administered during post-exposure treatment. A person who either has an immunosuppressing illness or is taking immunosuppressant medications should have his/her rabies antibody titres checked 2 to 4 weeks after completion of the vaccination regimen (see above).

Pregnancy

Pregnancy is never a contraindication to rabies vaccination. Follow-up of 202 Thai women vaccinated during pregnancy did not indicate either increased medical complications or birth defects.¹³

Conflicts with product information

The product information does not mention that the rabies vaccine should be used for both pre-exposure prophylaxis and post-exposure treatment for ABL exposures.

The product information recommends a routine sixth dose at 90 days in the post-exposure treatment regimen. This dose is not considered necessary on a routine basis but should be offered to an immunosuppressed person without adequate antibodies following the standard regimen. It also recommends a pre-exposure booster after a year; boosters are usually recommended in Australia after 2 years (see above).

The product information for rabies vaccine recommends administration by 'deep subcutaneous injection, preferably into the infraspinous fossa'. However, NHMRC recommends that it be given by either IM or SC injection into the usual sites. The vaccine is not licensed for administration by the intradermal route in Australia.

Rabies-free countries

The WHO maintains data on rabies-infected countries, the most recent of which can be accessed at the following web site: <http://www.who.int/emc/diseases/zoo/rabies.html>.

As of March 2003 the Department of Agriculture, Fisheries & Forestry – Australia advised that Bali continued to be rabies free. Furthermore, no cases of Bali-acquired rabies have ever been reported in the medical literature despite many people being bitten and scratched by animals in Bali every year. Although post-exposure treatment following animal bites sustained in Bali is therefore not warranted, it must be emphasised that this situation could change at any time.

However, rabies still exists in other parts of Indonesia including the islands of Flores, Sulawesi, Sumatra and parts of Java and Kalimantan. Post-exposure treatment is necessary for any animal bite sustained in any of these locations. Any doubts or concerns about the need for post-exposure treatment following animal bites in any part of Indonesia should be discussed with the State/Territory public health authority.

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