Introduction

Rabies is an acute encephalomyelitis caused by a rhabdo virus. It is primarily an infection of mammals, spread mainly through bites of infected animals. Rabies in dogs is the source of nearly 97% of human infections and poses a potential threat to > 3.3 billion people, primarily in Asia and Africa.

In Sri Lanka, rabies has been detected also in cats, mongoose, cattle, goats, bandicoots, jackals, pole cats, rock squirrels, monkeys, horses and elephants. Domestic rats have not been implicated in the transmission of rabies in Sri Lanka. Human to human transmission also has not been documented.

Virology

Rabies virus is a RNA virus which belongs to the genus *Lyassa* virus of the *Rhabdoviridae* family. Currently this genus comprises of 7 geno types.

Mode of transmission

The virus can penetrate through broken skin or intact mucous membranes. Human infection usually occurs following a transdermal bite or scratch by an infected animal. Transmission may also occur when infectious material, usually saliva, comes in contact with the victim's mucosa, or with fresh abraded skin lesions or by drinking raw milk from a rabid cow or goat.

The virus has been isolated in an animal's saliva even up to 14 days before it exhibits the first signs of rabies. Intermittent excretion of the virus in the saliva continues throughout the illness.

Clinical Features

In human cases, the incubation period is typically several weeks to several months (average 1-3 months), but may vary from less than a week to more than a year. Once the clinical symptoms have occurred, rabies is almost invariably fatal. The initial symptoms of rabies are often mild fever and pain or paraesthesia at the wound site. As the virus spreads in the central nervous system, progressive encephalitis develops characterized by hydrophobia or aerophobia, hyperactivity and fluctuating consciousness, dysphagia, generalized convulsions and within a few days cardio-respiratory arrest. These symptoms are generally seen in the furious form of the disease in about 70% of patients.

Paralytic rabies, which may represent as much as 20% of the total number of human cases, runs a less dramatic, although ultimately fatal, course.

Epidemiology

Global Situation

The estimated 55,000 deaths in the world per year may be an underestimate. In India alone, 20,000 deaths are estimated to occur annually. Although all age groups are susceptible, rabies is most common in children aged below 15 years.

Situation in Sri Lanka

Human rabies is a notifiable disease in Sri Lanka. In Sri Lanka. Human deaths due to rabies reported in years 2008, 2009, 2010 and 2011 were 52, 58, 49 and 41 respectively

Vaccines against human rabies

Prevention of rabies in humans depends on a combination of interventions, including provision of post-exposure prophylaxis to potentially exposed patients, pre-exposure immunization of people who are at frequent risk of exposure, control of infection in animal reservoirs and control of stray dog populations.

Following inactivated anti rabies cell culture vaccines are available.

- Human diploid cell vaccine (HDCV)
- *Purified vero cell rabies vaccine (PVRV)
- *Purified chick embryo cell vaccine (PCEC)

**Vaccines available in Sri Lanka at present*

Pre exposure immunization

This form of therapy is indicated for persons who are at a higher risk of exposure to rabies virus i.e. laboratory staff handling live rabies virus, veterinarians, rabies control staff (vaccinators), wild life officers, employees of animal quarantine premises and zoological establishments.

The recommended schedule is IM- ARV :- 1 dose each on D0, D7 and D28.
A booster dose is given 1 year after the first dose. Additional booster doses are given once every five years even if they do not have a definitive exposure. Any person in this category should seek expert advice if exposed to a suspected rabid animal.

Administration of rabies immunoglobulin is contraindicated in persons on pre-exposure therapy.
They should only be given additional doses of IM-ARV 1 dose each on D0 and D3 as boosters even in a case of major exposure to a suspected rabid animal.

Post exposure immunization (PET)

Choice of therapy depends on the screening of the person exposed, the animal involved in the incident and the type of exposure.

Anti rabies PET when indicated:-

All patients in the major category should be given rabies immunoglobulin (equine or human) followed by a course of anti rabies vaccine (ARV).

Patients in the minor exposure category should be given only a course of ARV.

Type of exposure

- **Major exposures**

  a. Single or multiple bites with bleeding on head, neck, face, chest, upper arms, palms, tips of fingers and toes and genitalia.
  b. Multiple deep scratches with bleeding on the head, neck and face.
  c. Multiple or single deep bites on any part of the body.
  d. Contamination of mucous membranes with saliva.
  e. Bites of wild animals with bleeding.

- **Minor exposures**

  a. Single, superficial bite or scratch with bleeding on the lower limbs (excluding tips of toes), upper limbs (excluding upper arms, palms and tips of fingers), abdomen and back.
  b. Nibbling of uncovered skin.
  c. Contamination of open wounds with saliva.
  d. Single or multiple bites or scratches without bleeding on any part of the body
  e. Drinking of raw milk of rabid cow or goat.

The following are **not considered** as exposures:-
Contamination of intact skin with saliva of suspected rabid animal
Petting, bathing or coming in contact with utensils of a suspected rabid animal

Screening the animal

In case of major exposure to dogs and cats:

- If the animal is apparently healthy, observable and has had a minimum of 2 rabies vaccinations given not more than 2 years apart, with the

last vaccination given within 1 year of the incident, PET can be delayed while observing the animal for 14 days.

- When the animal is suspicious to have rabies or is sick, but observable, initiate PET while observing the animal. Discontinue treatment if the animal is apparently healthy after 14 days.

- If the animal is having rabies (confirmed by laboratory diagnosis) or unobservable (animal dead, missing or stray animal) initiate PET and continue the full course.

In case of minor exposure to dogs and cats:

- If the animal is apparently healthy, observable and has had a minimum of 1 rabies vaccination:
    - within 1 year of the incident,
    - at an age above 3 months,
    - incident occurring at least 1 month after the vaccination.

PET can be delayed while observing the animal for 14 days.

- When the animal is suspected to have rabies or is sick, but observable, initiate PET while observing the animal. Discontinue PET if the ani mal is healthy after 14 days.

- If the animal is having rabies (confirmed by laboratory diagnosis) or unobservable (animal dead, killed, missing or stray animal) initiate PET and continue the full course.

The patient must be clearly advised that the animal should be put in a cage or leashed during the observation period. If the animal dies, becomes sick or develop any abnormal behaviour, the patient should be advised to report to the hospital immediately. In case of death of the animal patient should be encouraged to send the head of the animal for laboratory confirmation of rabies.

Rabies immunoglobulin(RIG)

- Equine rabies immunoglobulin(ERIG)
- Human rabies immunoglobulin(HRIG)

RIG should be given immediately after the incident. It is essential to test for sensitivity before administering ERIG. HRIG does not require sensitivity testing prior to its administration. If the patient reports late, RIG could be given up to 3 months after exposure, if the patient has not taken the anti rabies vaccine.

Dosage and administration of RIG

HRIG - 20 IU/Kg body wt
ERIG - 40 IU/Kg body wt

Part of the dose (as much as possible depending on the site) should be infiltrated in and around all wounds. After infiltration if there is any remaining RIG, it should be given deep subcutaneously (SC) or intramuscularly (IM) on the thighs. Deltoids should be spared for ARV when giving RIG. Vaccine should be administered preferably on the same day after RIG, but at a different site. In small children with multiple bites, if the volume is not sufficient for infiltration of all wounds , dilute RIG with sterile N saline up to double or 3 times.

Anti rabies vaccine (ARV)- Intramuscular schedule

Patients with **major exposures** should be given RIG and ARV IM or deep SC according to the following schedule.

One dose to be given in the deltoid on days 0, 3, 7, 14 and 30

Recommended IM dose is either 0.5mL (PVRV) or 1mL (PCEC)

Patients with **minor exposures** should be given 4 doses of ARV IM or deep SC on the following days.

Day 0:	2 doses to be given IM or SC, one on each deltoid
Day 7:	1 dose IM or SC
Day 21:	1 dose IM or SC

Intradermal (ID) inoculation of ARV

Intradermal (ID) vaccination schedule has been recommended by the WHO to be used in developing countries where cost is a major limiting factor.

Recommended ID dose is 0.1ml per site for both PCEC and PVRV.

2 site ID schedule

One dose (0.1ml) is given ID at each of 2 sites in the deltoids on days 0, 3, 7 and 30.

2 site schedule is routinely used in all patients irrespective of the use of RIG.

The modified 4 site ID schedule

One dose of (0.1ml) given ID at each of 4 sites on day 0, (deltoids and lateral thighs) one dose given ID at each of 2 sites on days 3,7 and 30.

The 4 site schedule is helpful in patients with a minor exposure who come late for treatment. It gives an early antibody response than the 2 site schedule.

The 4 site ARV is not recommended as an alternative for RIG in major exposures on a routine basis.

All ID injections should be **administered only by trained staff** under supervision of a medical officer. Once the vaccine is reconstituted the contents should be used as soon as possible (preferably within 8 hours stored at 2°-8°C). Separate disposable syringes and needles should be used for each patient to prevent contamination.

Efficacy

In both pre and post-exposure prophylaxis settings, they induce an antibody response in >99% of vaccinees. Prompt post-exposure use of modern vaccines combined with proper wound care and RIG is nearly 100% effective in preventing rabies, even following high-risk exposure. However, delays in starting or failure in completing correct prophylaxis, especially with severe lesions on the head, neck, hands or multiple wounds, may result in death.

Management of patients following a full course of rabies PET Previously

For both major and minor exposures: If the animal is apparently healthy and observable, PET could be delayed while observing the animal for 14 days.

If the animal is **proven rabid, suspected of rabies or unobservable:**

- Up to 6 months from the last dose of ARV – PET is not indicated.
- From 6 months - 5 years from the last dose of ARV – 2 site ID ARV 2 doses each or IM ARV one dose each should be given on days 0 and 3. As an alternative to this regimen, the patient may be offered a single visit 4 site ID regimen on day 0, consisting of 4 injections of 0.1 mL, equally distributed over left and right deltoids or prescapular areas.
- Up to 5 years from the last dose of ARV, RIG is not indicated.

- After 5 years, a full course of ARV with or without RIG (depending on the category of exposure and animal screening) is recommended.

Storage

Both ARV vaccine and immunoglobulin should be stored at +2 °C to +8 °C. Following reconstitution with the accompanying sterile diluents, the vaccines should be used immediately, or within a maximum of 6 hours when kept at +2 °C to +8 °C.

Cautions and contraindications

In view of the gravity of the disease, all contraindications are secondary in cases of exposure to a suspected rabid animal. This also pertains to post-exposure rabies prophylaxis in infancy and pregnancy.

For pre-exposure immunization, previous severe reaction to any of the vaccine components is a contraindication for further use of the same vaccine.

In immunocompromised individuals, including patients with HIV/AIDS, comprehensive wound management and local infiltration with RIG, in combination with a complete CCV series, are of utmost importance for the successful prevention of rabies.

Adverse Events

Modern CCVs are considered to be safe and well tolerated. Adverse events

following rabies vaccination include:

- Local reactions - pain, tenderness and erythema at the site of injection,
- Mild systemic reactions - malaise, headache, nausea, mild fever and uticaria,
- Severe systemic hypersensitivity reactions following booster injections reported in 6% of vaccinees, but are less common following primary immunization.

Sources

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