*Rabies Lecture - 2016*
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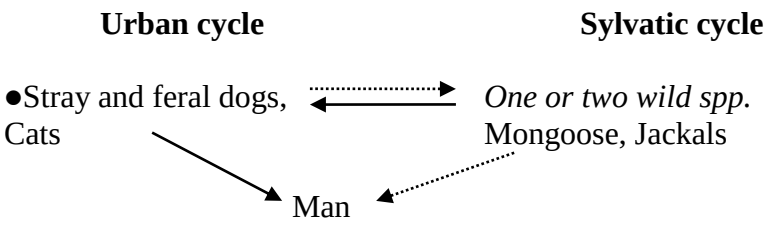
## Rabies *(Rhabdoviridae)*

An "old" ancient disease
A fearful **zoonotic viral disease** still prevailing in many countries of the world
"The most severe of all communicable diseases"

Rabies & rabies-like viruses of Genus Lyssavirus
*Rabies virus* is not one virus rather a set of different genotypes
Each transmitted within a separate reservoir host niche
( i.e."Raccoons-bite-raccoons-bite-raccoons" ⟶ Virus becomes a distinct genotype)

**Sri Lanka** the nature of sylvatic rabies virus is not known

**Natural history of rabies virus**
●Rabies is maintained in two not necessarily inter-related cycles




# Family: Rhabdovoridae

More widely distributed in nature than other virus families (> 100 rhabdoviruses infecting plants, arthropods, fish, reptiles & mammals.

There are 5 genera: 3 infect animals, 2 infect plants.

**Animal Rhabdoviruses:**
1. Genus: Vesiculovirus
**2. Genus: Lyssavirus**
3. Genus: Ephemerovirus

**Mammalian Rhabdoviruses**
Rhabdoviruses infecting mammals including humans classfied into 2 genera.
1. Genus: Vesiculovirus (i.e. vescicular stomatitis virus)
2. Genus: Lyssavirus (i.e., rabies & rabies-like viruses)
All have wide host range.

**Lyssavirus genus**

Only one serogroup has been established within the genus. Placement within the genus is determined by serological cross reactions with antigenic sites of N- protein as recognised by FAT.

Placement of virus as rabies or rabies-like viruses depend on antigenic sites of G protein as recognised by neutralization test.

Virus species assigned to Lyssavirus genus

(Lyssavirus serogroup is sub divided into serotypes based on neutralisation & cross protection studies).

According to pylogenetic relationships divided into genotypes:

| genotype | Host |
|---|---|
| 1. rabies (RAB) | Warm blooded animals |
| 2. lagos bat (LB) | bat, cat |
| 3. Mokola (MOK) | shrew, dog, cat, man, rodent |
| 4. Duvenhage (DUV) | bat |
| 5. Europian bat virus type 1 (EB-1) | bat |
| 6. Europian bat virus type 2 (EB-2) | bat |
| 7. Australian bat lyssavirus | bat |

## Rabies virus

Rabies virus is the type species of genus Lyssavirus.

Refer to Rabies virus EM picture

**Virion & genome structure**

Negative sense ssRNA
70-80nm size, bullet shaped,
Enveloped & helical nucleocapsid

Important virus proteins:

**1. G – protein (glycoprotein):**

located in envelop spikes. Only antigen capable of inducing & reacting with virus neutralising Abs. Induce CTL (CD8) responses

**2. N protein (nucleoprotein):**

Located in ribonucleocapsid core. Major target antigen for Th cells that cross react with other lyssaviruses. Induce CD4 T cell responses.

History of rabies :

6th July 1885: Milestone in the history of rabies.
Joseph Meister 9 year old boy bitten 14 sites by a rabid dog received 1st post exposure treatment with the pasture vaccine & he survived.
Louise Pasteur developed & tested the 1st rabies vaccine

Rabies virus replicate in all warm blooded animals and excrete in saliva of rabid animals & their other secretions ( tears, respiratory)

**Transmission to man:**
via broken skin & intact mucous membranes.

- Animal bites & salivary contamination (broken skin, mucous membranes)
- Inhalation (rare)
- Person to person (rare)

**Epidemiology**
Rabies is a zoonosis.
Endemic in every continent except Antarctica.
In Sri Lanka endemic in all provinces
Main zoonotic vector in SL is the dog
Other animals in SL: cats, mongooses, jackals, civet cats

**Immunology**
*After infection:*
Virus **evade host immune response** by traveling through nerve tracts, absence of viraemia (therefore not expose to immune cells) & by suppression of IFN induction

Neutralizing antibody (NA)in serum appears on 7 day following onset of encephalitis.
NA appears in serum 7-14 days post vaccination.
G- protein induce Neutralising ab, Th & Tc lymphocyte responses.
N- protein induce Th responsible for cross protection from rabies strains & rabies-like viruses.

**Virus pathogenesis**
**Initial replication in muscle** at site of bite
Virus attaches to acetyl choline (Ach) receptor at NuroMuscular junctions & enter to nerves.
Virus can directly infect adjacent sensory nerve endings via salivary contamination of mucous membranes.
Virus may establish a latent phase at the site of entry.
Ascending infection occurs via both sensory and motor nerve pathways
Spread of virus within spinal cord & brain coincides with onset of symptoms.
From CNS virus spread centrifugally via peripheral nerves to many body tissues; skin, skeletal muscles, **salivary glands**

**Clinical features**
Incubation period: 20-90 days in more than 60% cases, ranged from 4 days to 19 years.

*Prodromal signs & symptoms:*

- Non specific flu-like illness
- An earliest but inconsistent signs is tingling sensation at the site of bite (>50% patients) is pathgnomonic

In Furious (encephalytic) form of rabies most consistent but later sign is nervous hydrophobia is pathognomonic (30-50% patients).
Generalized convulsions, coma, paralysis & death

In Paralytic form of rabies (less commonly occurs)
Patients develop flascid paralysis of the bitten limb & then ascend. Hydrophobia is not seen until terminal stages.

**Diagnosis**
Clinical diagnosis in the rabid animal: observe the suspected rabid animal for 10 -14 days for signs & symptoms.

**Laboratory diagnosis**:
*Methods of transporting the specimen:*
Best is sent to whole head ( within 2 hrs) in a sealed container
If a delay anticipated double bag the container with ice

PM diagnosis in dogs:
Sellers' stain for Negri bodies but –ve result should be confirmed by FAT.
Detection of Ag in brain smears is the most rapid and sensitive test and it is used as the confirmatory test.

Intravitam diagnosis in humans:
1st few days, antigen detection from saliva, CSF, tears, respiratory secretions, nuchal skin biopsies, and corneal impression smears.
At 7-10 days of illness NA abs in CSF or serum is possible.

Differential diagnosis in dogs:
Apparently healthy animal may excrete virus in saliva before it show signs.
Animals with other neurological diseases can bite ( i.e. distemper)

Human rabies
can be suspected from any mammalian bite in an endemic area.

Intense itching at site of biting wound is pathognomonic

Rabies should be differentiated in humans from poliomeylitis, tetanus, other encephalitides, post vaccinal encephalomyelitis.

**Prevention of rabies**

Rabies vaccines for human use

**Post exposure treatment**

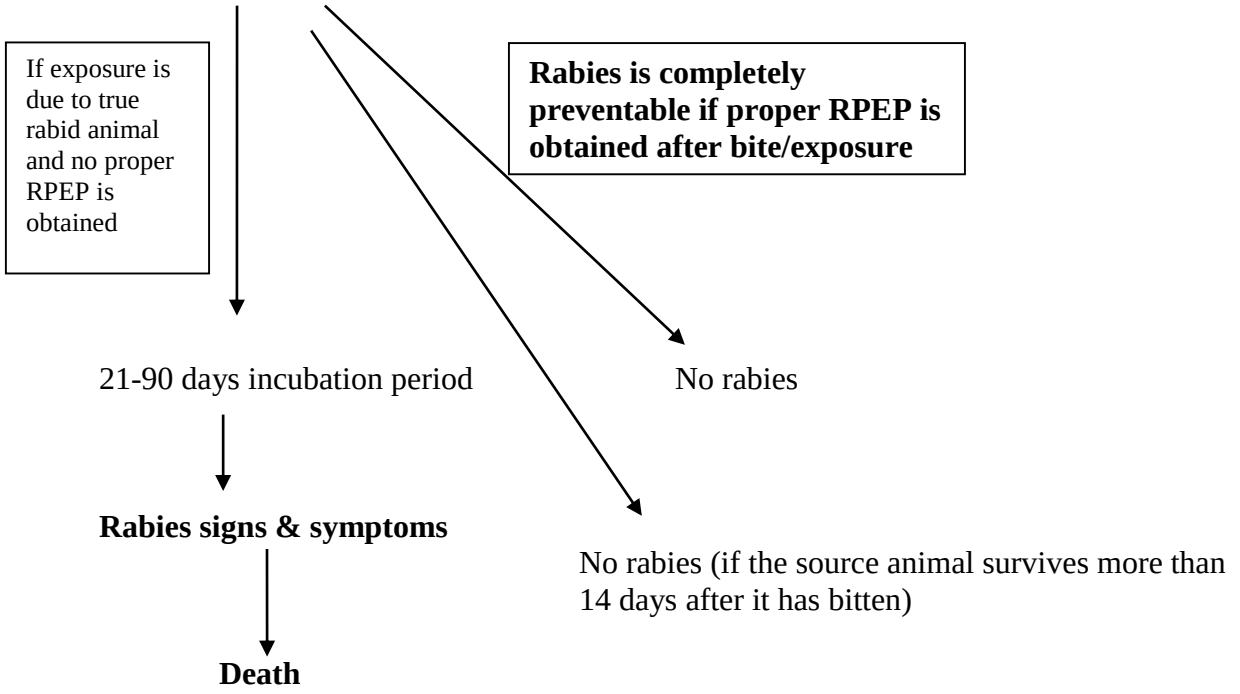
Prompt local treatment of bite wounds (First Aid)

General considerations determine the type of PEP
Administration of ARIg
Vaccine administration

**pre-exposure immunization for persons at risk**

**Rabies virus infection & prevention**

Suspected rabid animal bite /exposure to suspected source of rabies
(Dogs, cats & wild carnivores)




(Rabies is almost always fatal and acute viral disease of the CNS in humans)

***Indications & guidelines for anti-rabies treatment***

**(A). Post exposure anti-rabies treatment**

1.1.Assessment of the type of exposure and the risk level of the situation.

Choice of therapy depend on

(a). the nature and extent of exposure (bite)

(b). Level of risk associated with the infecting animal.

1.1.1. **Exposure categories:**

(A). ***Severe exposure*** *(if one or more of the following are present)*

Bite on the head, face or neck

Bite on the front or back of the chest

Bite on the tips of toes or genitalia

Licks on the mucous membranes (eyes, nose, lips)

Multiple bites

A single deep bite anywhere on the body

(B). ***Minor exposure*** *(if one or more of the following are present)*

Single superficial bite or scratches with a skin break by cats or dogs over areas of body that are not highly innervated e.g.: legs, arms, trunk

Nibbling (without break in skin) and licks on a wound

Drinking of raw milk from a rabid cow or goat

**1.1.2. Risk category:**

(A). **High Risk** *(if one or more of the following are present)*

Wild animal bite (those relevant to Sri Lanka include jackals, bandicoots, mongoose, pole cats, monkeys, rock squirrels and civet cats)

Animal cannot be identified or observed (e.g: stray dog)

Non-immune animal

Animal showing a change in its behavior pattern within the previous 2 weeks.

Several people bitten without provocation

Animal dies or appears unwell within 14 days following the bite and brain is not available for examination.

(B). **Low Risk** *(if one or more of the following are present)*

Domestic healthy non-immune animal that can be observed

Bite due to provocation of a healthy animal
Known fierce animal

Animal immunized within the preceding year but appears unwell at the time of bite

**1.2. Choice of Regimen:**

1.2.1 With severe exposure & high risk category of animal:

*RIG + ARV*

1.2.2 With severe exposure & low risk category of animal:

*RIG+ARV* (treatment can be discontinued if animal is healthy 14 days after bite)

1.2.3. With minor exposure & high risk category of animal:

*ARV only* ( except with wild animal bites. All wild animal bites require RIG+ARV)

1.2.4. With minor exposure & low risk category of animal:

(a). *No specific treatment immediately* (except where raw milk from a rabid animal has been consumed needs ARV only).

(b). observe the animal for 14 days following the bite and start ARV if the animal falls sick or dies within observation period.

(c ). Send the head of the animal to the MRI or other recognized diagnostic laboratory ( in a polythene bag with ice and saw dust outside, in a leak proof container with full name and address of sender. If head can reach the lab within 10 hrs of death of the animal packing in ice is not needed)

(d). Discontinue treatment if brain is FAT negative for rabies. If positive complete the ARV treatment schedule.

## 2. Treatment schedules:

### 2.1.RIG+ARV

***(a). First aid for wounds immediately & tetanus prophylaxis only if indicated***

Wash well with soap and water
Clean the wound thoroughly with surgical sprit or iodine antiseptic
( This measure reduces the average risk with a rabid dog bite from 20% to 5%.)

***(b). RIG immediately***

***(c ). ARV***

**(i).** ***Intramuscular (IM) schedule –*** one dose given IM into the deltoid muscle on days 0, 3, 7, 14, and 30.

(ii). Intradermal (ID) schedule – each ID dose is $1/5^{th}$ of IM dose.

Two site schedule:
On days 0, 3 and 7 one dose given ID at each of 2 sites (into the deltoids of both arms).
On days 30 and 90 one dose at one site into the deltoid.

Eight site schedule ( this schedule is indicated as the option only if the patient is sensitive to ERIG or when RIG is not available in the country) :

One dose given ID at each of 8 sites on day 0 &
One dose given ID at each of 4 sites on day 7 &
One dose given Id at one site on days 30 and 90.

### 2.2.ARV alone:

(a). First aid for wounds immediately and tetanus prophylaxis only if indicated.
ARV

(i). Intramuscular (IM) schedule - 4 doses (2:1:1) Schedule of tissue culture ARV

Day 0 - 2 doses IM. One into each of deltoid
Day 7 - 1dose IM into the deltoid
Day 21 - 1dose IM into the deltoid

(ii). Intradermal (ID) schedule – each ID dose is 1/5 of the IM dose.

On days 0, 3, 7 one dose given ID at each of two sites into the deltoid of both arms.

On days 30 and 90 one dose one dose at one site into the deltoid.

**The use of specific Rabies Immunoglobulins:**

1. ERIG (available in Govt. hospitals): dosage 40 IU/Kg body weight
2. HRIG (Much more expensive but less reactogenic): dosage 20 IU/Kg body weight

**Rabies Immunoglobulins** should be infiltrated into and around the bite wound as much as possible. Rest given IM to the upper outer quadrant of a buttock.

When the volume is not adequate for infiltration of all wounds, **Immunoglobulins can be diluted 2 or 3 fold with sterile normal saline**.

Sensitivity test should be performed before ERIG is administered.

**(B). Pre-exposure rabies prophylaxis:**

Indications: Veterinary Staff
Dog handlers
Employees in animal quarantine premises
Zoological establishments
Laboratory staff handling rabies virus

Vaccine: Tissue Culture grown anti-rabies vaccine (TC ARV) is used

Vaccination Schedule:
Three doses of vaccine should be given on day 0, 7, and 28 by deep subcutaneous or intramuscular injection.

A reinforcing dose is given at 12 months.

Additional reinforcing doses are given once every 1-3 years, depending on the risk of exposure.

**Management of re-exposure:**

After a course of anti-rabies therapy a person who has taken a full course of TC ARV and who has been exposed to rabid animal:

- Up to 8 months after the last dose of the vaccine: Need not be given anti-rabies post exposure therapy

- Between 8 months and 1 1/2 years after the last dose of the vaccine : one dose of TC ARV is indicated

- Between 1 1/2 and 2 years after the last dose of the vaccine : 2 doses of TC ARV on day 0 and day 3

- Between 2 and 3 years after the last dose of the vaccine : 3 doses of TC ARV on days 0, 3 and 7
- Over 3 years after the last dose of the vaccine:

  A full TC ARV course has to be given

  **Up to 5 years no RIG should be given**

  If exposure to a low risk category, TC ARV can be delayed while observing the animal.

Refer:

●Booklet issued by College of General Practitioners on guidelines for rabies prophylaxis
●Protocol for anti-rabies post exposure therapy (PET), Ministry of Health 31.07.2004