Rabies: Recent Advances

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Fatal encephalitis
Rabies in India: Facts & Figures

- Highest global burden (20,000 deaths annually)
- >95% of human cases canine mediated; 60% victims children
- Endemic in all states except Andaman, Nicobar & Lakshadweeep islands
- Estimated stray dogs: 25-30 million
- 17.4 million animal bites annually; PEP ~4 million
- A dog bites a human every 2 seconds and every 30 minutes a human dies of rabies
- Not a notifiable disease
Animals transmitting Rabies (India)

- Dogs (95% cases)
- Cats, monkeys, mongooses, wild animals
- Cattle, buffalo, horses, donkeys, pigs

- Not transmitted by
  - House rats/mice, rabbits, birds, squirrels, bats
Human rabies: Clinical course

Exposure
- 20-90 days
- Prodrome (1-2 days)
- Incubation
- Paralytic

Furious
- Hyperactivity, confusion and agitation
- First symptom
- Fever, pruritus and paraesthesia
- Clinical expression

Paralytic
- Fever, pruritus and paraesthesia
- Acute phase
- Quadriplegia, dysarthria, dysphagia, hypersalivation, inspiratory spasms, respiratory failure and hydrophobia or aerophobia (in ~50% of cases)
- Drowsiness

Need for Lab Diagnosis

- Early diagnosis helps avoid unnecessary tests and treatment
- Distinguish from GB syndrome/other mimics in paralytic/atypical rabies
- Patient management/Barrier Nursing
- Case closure and grief counseling
- Prophylactic vaccination to close contacts
- Characterization of causative agent
- Surveillance and estimation of disease burden
Clinical Mimics

- Guillain-Barre syndrome
- Anti-NMDA receptor encephalitis
- Psychiatric disorders
- Post-vaccinal encephalitis
- Scorpion and snake envenomation
- Cerebral malaria, herpes simplex encephalitis
- Illicit drug use
- Organophosphate poisoning
**ANTEMORTEM**

**Viral RNA detection (RT-PCR)**
- Saliva
- Nuchal Skin/ Hair follicles
- CSF
  - Negative in all samples
  - Positive in single or multiple samples
    - Rabies cannot be ruled out
    - Confirmed Rabies

**Anti-Rabies antibodies RFFIT/FAVN/ELISA**
- CSF
  - Positive
  - Negative
    - Rabies cannot be ruled out
    - Test another sample after 7-10 days
      - Positive
        - Confirmed Rabies
      - Negative
    - Diagnostic of Rabies if NEVER vaccinated
    - If previously vaccinated look for rise in titres
    - Unlikely to be Rabies; but cannot be ruled out
- Serum
  - Positive

POSTMORTEM

Brain Tissue

Available

Fluorescent Antibody Test (FAT) (or PCR)

Positive

Confirmed Rabies

Negative

Confirmed Rabies

Not Available

Viral RNA detection (RT-PCR)

Nuchal skin

Single or both samples POSITIVE

Confirmed Rabies

Both samples NEGATIVE

Rabies cannot be ruled out

CSF

Both samples NEGATIVE

Confirmed Rabies

Obtained by craniotomy or by sub-occipital cisternal puncture, retro-orbital or a trans-nasal route.
Diagnostic Challenges

- ‘Gold standard’-Antigen detection by DFA in brain tissue (post-mortem)
- Obtaining consent for autopsy is a challenge
- Lab facilities for antemortem diagnosis few
- Sensitivity of antemortem diagnosis low—multiple tests on several/serial clinical samples required to confirm diagnosis
- Antemortem tests can ‘rule in’ Rabies but cannot ‘rule out’ Rabies
Human rabies: ante-mortem diagnosis
(NIMHANS 2012-2017; 267 cases)

<table>
<thead>
<tr>
<th>Test</th>
<th>Sample</th>
<th>No of cases Tested</th>
<th>Number Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Real Time PCR</td>
<td>CSF</td>
<td>169</td>
<td>14 (8.2%)</td>
</tr>
<tr>
<td></td>
<td>Nuchal Skin</td>
<td>87</td>
<td>16 (18.4%)</td>
</tr>
<tr>
<td></td>
<td>Saliva</td>
<td>140</td>
<td>28 (20%)</td>
</tr>
<tr>
<td>RFFIT (Antibodies)</td>
<td>CSF</td>
<td>189</td>
<td>61 (32%)</td>
</tr>
</tbody>
</table>

Antemortem Diagnosis in 115/267 (43%)
Approach to Rabies Post-exposure Prophylaxis (PEP)

- WOUND MANAGEMENT
- PASSIVE IMMUNIZATION (RIG)
- ACTIVE IMMUNIZATION (ARV)
### Category of Exposure & PEP

<table>
<thead>
<tr>
<th>Category</th>
<th>Type of contact with a suspect or confirmed rabid domestic or wild animal, or animal unavailable for testing</th>
<th>Type of exposure</th>
<th>Recommended post-exposure prophylaxis (PEP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Touching or feeding of animals • Licks on intact skin</td>
<td>None</td>
<td>None, if reliable case history available</td>
</tr>
<tr>
<td>II</td>
<td>Nibbling of uncovered skin • Minor scratches or abrasions without bleeding</td>
<td>Minor</td>
<td>Administer vaccine immediately.</td>
</tr>
<tr>
<td>III</td>
<td>Single or multiple transdermal bites, scratches or licks on broken skin • Contamination of mucus membranes with saliva (licks) • Exposure due to direct contact with bats</td>
<td>Severe</td>
<td>Administer rabies immunoglobulin and vaccine immediately.</td>
</tr>
</tbody>
</table>
Immediate wound care following an exposure to rabies

Often a neglected step; when done appropriately reduces the risk (50–70%) of developing rabies

- Immediate washing and flushing with water alone or by using soap and water (running water; 10-15 minutes)
- Disinfection of the wound using povidone iodine
- AVOID covering the wound with dressings or bandages
- Suturing of the wound is usually avoided/postponed; where suturing is necessary ensure that RIG has already been applied locally
- Antimicrobials and tetanus toxoid can be administered if needed
Intradermal rabies vaccination in India
A paradigm shift

- Administering minute doses (0.1mL) of vaccine into the layers of skin
- Rational and Scientific; Highly Immunogenic, Safe and Efficacious
- Reduction in volume and costs (60-80%)
- Approved by WHO since 1992
- Used in Thailand, Philippines and Sri Lanka since 1993
- Approved by DCGI since 2006 (India)
- Implemented successfully in several states (public sector)

**Use I/D schedule to improve availability, accessibility and affordability of rabies vaccine!**
# Post-exposure Propylaxis (PEP)

## Intradermal (ID)

<table>
<thead>
<tr>
<th>Route</th>
<th>Regimen</th>
<th>Days</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>ID</td>
<td>Updated Thai Red Cross</td>
<td>![Injection Images]</td>
</tr>
</tbody>
</table>

One ID dose = 0.1 mL
### Post-exposure Propylaxis (PEP)

**Intramuscular (IM)**

<table>
<thead>
<tr>
<th>Route</th>
<th>Regimen</th>
<th>Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>IM</td>
<td>Essen</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>14</td>
</tr>
<tr>
<td></td>
<td></td>
<td>28</td>
</tr>
</tbody>
</table>

One IM dose = entire vial (0.5 or 1 mL)
Passive Immunization

- Necessary in **all category III exposures** (and Cat II exposures in immunocompromised individuals)
- Many PEP failures due to lack of RIG administration
- RIG administered only **ONCE**, preferably within 24 hrs of exposure; Can be given within 7 days of first vaccine dose
- The maximum dose is **20 IU (hRIG)** and **40 IU (eRIG)** per kg body weight. There is no minimum dose
- Local infiltration
Rabies monoclonal antibodies

First mAb licensed for clinical use: Serum Institute of India
Will help fill critical health gaps

- Concentrated product;
- Small volume (3.33 IU/kg body wt)
- rDNA technology - Less prone to availability/purity/safety issues
- Cheaper than hRIG
- No skin sensitivity testing
PEP for close contacts of patients
## Pre-exposure Propylaxis (PrEP)

<table>
<thead>
<tr>
<th>Route</th>
<th>Regimen</th>
<th>Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>IM/ID</td>
<td>One-site</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>14</td>
</tr>
<tr>
<td></td>
<td></td>
<td>21/28</td>
</tr>
</tbody>
</table>
Advantages of PrEP?

- Fewer Injections!
- NO RIG
- Only 2 boosters (Day 0,3) on any re-exposure
## Rabies PEP Regimens

*In previously immunized*

<table>
<thead>
<tr>
<th>Route/Regimen</th>
<th>Days</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>1-site ID or IM</td>
<td>[Red Syringe]</td>
</tr>
</tbody>
</table>
Day 0 is the day when the **first dose of vaccine** is administered.

**Deltoid** area is the only acceptable site of IM vaccination in adults.

In children, **anterolateral aspect of thigh** can be used.

Vaccines should **never** be administered in the **gluteal region**.

No contra-indications for rabies PEP
Management

Proposed algorithm to guide management of cases of confirmed or suspected human rabies

Rabies (confirmed or clinically suspected?)
  - Aggressive management
    - Physician decides with family; explains consequences
  - Palliative care with at least WHO essential medicine
    - Everywhere

Critical care in selected hospitals

Rabies-specific treatment
  - Antiviral agents? If so, which?
  - Immunotherapy? (controversial)
  - Neuroprotective agents?
    - Combination?
      * Approval could be obtained in advance for certain therapy, in keeping with scientific and ethical standards.*

In-hospital (isolation)
  - Sedatives (diazepam/ midazolam)
  - Analgesics (morphine?)
  - Haloperidol?
  - Rehydration?
    - Route?

Home care (culturally sensitive)
  - Sedatives (diazepam/ midazolam)
  - Analgesics (morphine?)
  - Rehydration? (nasogastric tube?)
    - Subcutaneous, intrarectal (oral, usually not possible)

WHO 2018
Rabies Survivors?
<table>
<thead>
<tr>
<th>Country and year of disease onset</th>
<th>Sex and age (years) of the patient and disease outcome</th>
<th>Mode and site of exposure</th>
<th>PEP type and doses; type of RIG</th>
<th>Incubation period</th>
<th>Antibodies in CSF and serum (highest titres or concentrations recorded)</th>
<th>Type of antibody and method of testing</th>
<th>Viral material detected (sample tested)</th>
</tr>
</thead>
<tbody>
<tr>
<td>India, 2014</td>
<td>Male, 6, severe sequelae</td>
<td>Dog bite; neck and back</td>
<td>PECV, 4; ERIG</td>
<td>~22 days</td>
<td>CSF (8,192); serum (&gt;200,000)</td>
<td>RVNA; RFFIT</td>
<td>None (saliva, nuchal skin and CSF)</td>
</tr>
<tr>
<td>India, 2014</td>
<td>Male, 13, severe sequelae</td>
<td>Dog bite; right hand</td>
<td>PECV, 3; none</td>
<td>~2 weeks</td>
<td>CSF (&gt;64,000); serum (&gt;64,000)</td>
<td>RVNA; RFFIT</td>
<td>Antigen (nuchal skin)</td>
</tr>
<tr>
<td>South Africa, 2012</td>
<td>Male, 4, severe sequelae</td>
<td>Dog bite on left ankle and scratch on forehead</td>
<td>Type NA; 3; none</td>
<td>~3–7 weeks (multiple exposures to dogs)</td>
<td>CSF (&gt;13.975 IU/ml); serum &gt;13.975 IU/ml</td>
<td>RVNA; RFFIT</td>
<td>None (saliva and nuchal skin)</td>
</tr>
<tr>
<td>USA, 2011</td>
<td>Female, 8, complete recovery</td>
<td>Scratches from free-roaming, unvaccinated cats (probable source); site NA</td>
<td>None; none</td>
<td>Unknown</td>
<td>CSF (8); serum (160)</td>
<td>IgM antibody; IFA</td>
<td>None (saliva and nuchal skin)</td>
</tr>
<tr>
<td>India, 2010</td>
<td>Male, 17, severe sequelae</td>
<td>Dog bite; left calf</td>
<td>PECV, 4; HRIG</td>
<td>~2 weeks</td>
<td>CSF (&gt;8,000); serum (&gt;16,000)</td>
<td>RVNA; RFFIT</td>
<td>None (corneal smear and nuchal skin)</td>
</tr>
<tr>
<td>India, 2011</td>
<td>Male, 4, severe sequelae</td>
<td>Dog bite; face</td>
<td>PECV, 4; HRIG</td>
<td>25 days</td>
<td>CSF (512); serum (12,784)</td>
<td>RVNA; RFFIT</td>
<td>Antigen (nuchal skin) and RNA (nuchal skin and saliva)</td>
</tr>
<tr>
<td>Turkey, 2008</td>
<td>Male, 17, complete recovery</td>
<td>Dog bites; left forearm and right shoulder</td>
<td>VCV, 1; none</td>
<td>~3 weeks</td>
<td>CSF (NA); serum (3,788)</td>
<td>RVNA; RFFIT</td>
<td>Antigen (corneal smear) and RNA (CSF and saliva)</td>
</tr>
<tr>
<td>Brazil, 2008</td>
<td>Male, 15, moderate sequelae</td>
<td>Vampire bat bite; site NA</td>
<td>Type NA; 4; none</td>
<td>~29 days</td>
<td>CSF (&gt;100 IU/ml); serum (&gt;100 IU/ml)</td>
<td>RVNA; RFFIT</td>
<td>RNA (nuchal skin hair follicles)</td>
</tr>
<tr>
<td>USA, 2004</td>
<td>Female, 15, mild sequelae</td>
<td>Bat bite; left index finger</td>
<td>None; none</td>
<td>1 month</td>
<td>CSF (1,300); serum (1,604)</td>
<td>RVNA; RFFIT</td>
<td>None (nuchal skin and nuchal skin)</td>
</tr>
<tr>
<td>India, 2000</td>
<td>Female, 6, severe sequelae</td>
<td>Dog bites; face and hands</td>
<td>PECV, 3; none</td>
<td>20 days</td>
<td>CSF (312,000); serum (182,000)</td>
<td>RVNA; MNT</td>
<td>None (CSF, nuchal skin and corneal smear)</td>
</tr>
<tr>
<td>Mexico, 1992</td>
<td>Male, 9, severe sequelae</td>
<td>Dog bite; face</td>
<td>VCV, 3 and HDCV, 1; none</td>
<td>18 days</td>
<td>CSF (78,125); serum (134,800)</td>
<td>RVNA; RFFIT</td>
<td>None (saliva, nuchal skin and corneal smear)</td>
</tr>
<tr>
<td>USA, 1977</td>
<td>Male, 32, severe sequelae</td>
<td>Laboratory exposure to virus (aerosol)</td>
<td>None; none</td>
<td>~2 weeks (probable)</td>
<td>CSF (16,225); serum (175,000)</td>
<td>RVNA; RFFIT</td>
<td>None (nuchal skin and corneal smear)</td>
</tr>
<tr>
<td>Argentina, 1972</td>
<td>Female, 45, nearly complete recovery</td>
<td>Dog bite; left arm</td>
<td>SMBV, 14 and 2 boosters; none</td>
<td>21 days</td>
<td>CSF (150,000); serum (640,000)</td>
<td>RVNA; MNT</td>
<td>None (saliva, nuchal skin and corneal smear)</td>
</tr>
<tr>
<td>USA, 1970</td>
<td>Male, 6, complete recovery</td>
<td>Bat bite; left thumb</td>
<td>DEV, 14; none</td>
<td>20 days</td>
<td>CSF (3,200); serum (63,000)</td>
<td>RVNA; MNT</td>
<td>None (saliva, CSF, brain biopsy, corneal smear)</td>
</tr>
</tbody>
</table>

Survival from rabies: Case series from India (2015-2017)
American Journal of Tropical Medicine & Hygiene (November 2018)

8 Survivors
Maharashtra (4), Karnataka (1), Andhra Pradesh (1), Telangana (1), Sikkim (1)

Clinical Profile-Laboratory confirmed cases
2012-2017; n=115

- Encephalitic: 38.50%
- Paralytic/Atypical: 61.50%
Duration of Survival (n=63)

- >6 months, 20.60%
- 1-6 months, 28.50%
- 7-15 days, 15.80%
- <7 days, 17.40%
- 15 days-1 month, 17.40%

n=31
Access to advanced medical facilities: Excellent ICU care
All had received at least partial vaccination
‘Survival’ not synonymous with ‘Recovery’
All rabies survivors in India: severe sequelae
Long-term emotional, social and economic repercussions
Need to explore newer therapeutic strategies
‘Prevention’ should remain primary focus

PEP - The Alarming Statistics

**NIMHANS (2015-2017):** 65% of the patients with lab-confirmed rabies had received ARV (partial/complete with/without RIG)

**Isolation hospital, Rajasthan (2016-2018):** 42 cases of hydrophobia; No PEP (26%), partial ARV (48%), partial ARV and RIG (26%)

**ID hospital, Delhi (10 years):** 783 cases of hydrophobia; 32% had received ARV (with or without RIG)
Rabies despite vaccination?

Deviations in PEP protocols
- Incorrect advice/regimen
- Wound care Inadequate/Not done
- Suturing of wounds without RIG
- Delay in initiating PEP
- Inadequate dosage of vaccine
- Unsuitable site of vaccine administration
- Inappropriate administration of RIG (only IM)
- Omission of RIG even in category III exposures

Counterfeit vaccines/ Cold-chain lapses

Vaccine/PEP failures lead to rabies and survivors (with poor functional outcomes)
“But alas, oh ye doctors, though skilful are ye, This potsherd of earth still a potsherd must be Not yet hydrophobia your nostrums can cure, His dread of the water he still must endure....”

*John Edwards*

*(written in 1821)*