Tetanus, Rabies, Botulinum

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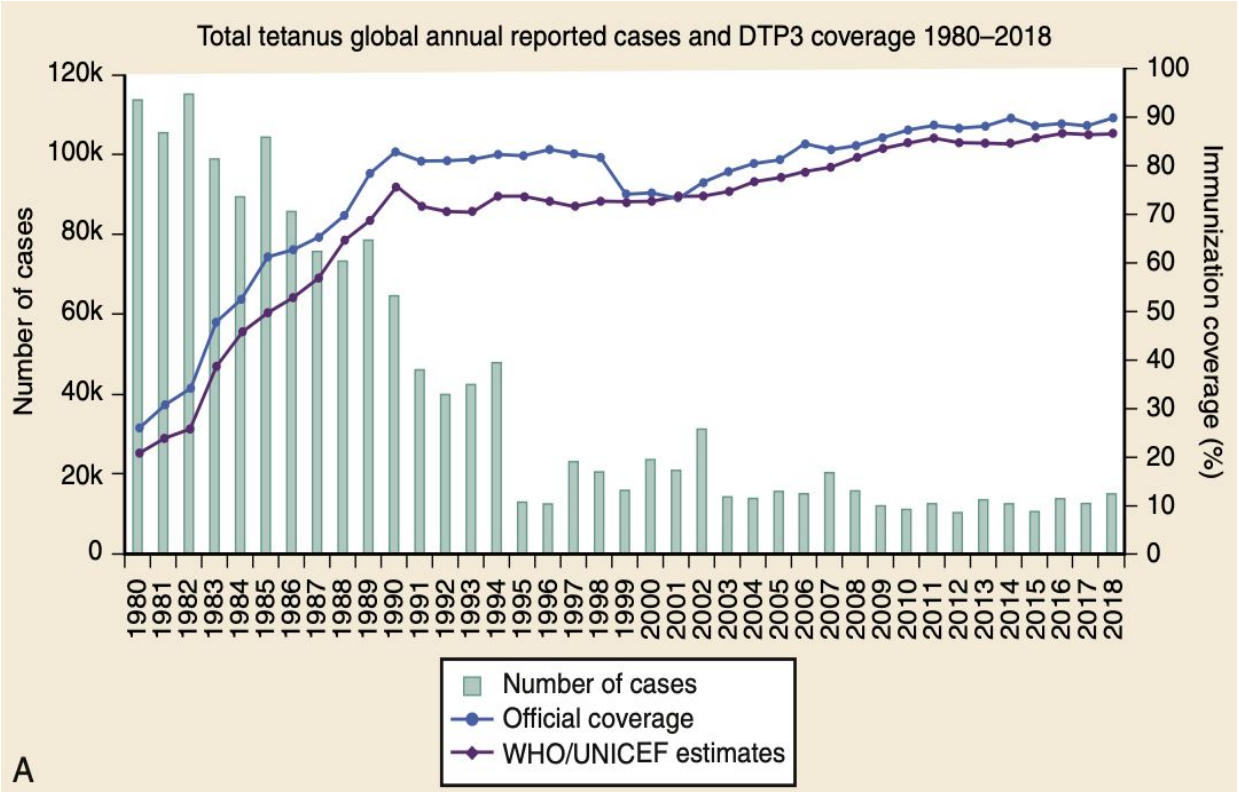
Tetanus

Introduction

- Tetanus is a nervous system disease caused by the toxin tetanospasmin produced by Clostridium tetani.
- Vaccination for tetanus has been widely available since the 1940s.

Epidemiology



Global annual reported cases of tetanus compared with percentage of immunization coverage. WHO

At St. Mary's Hospital, Lacor

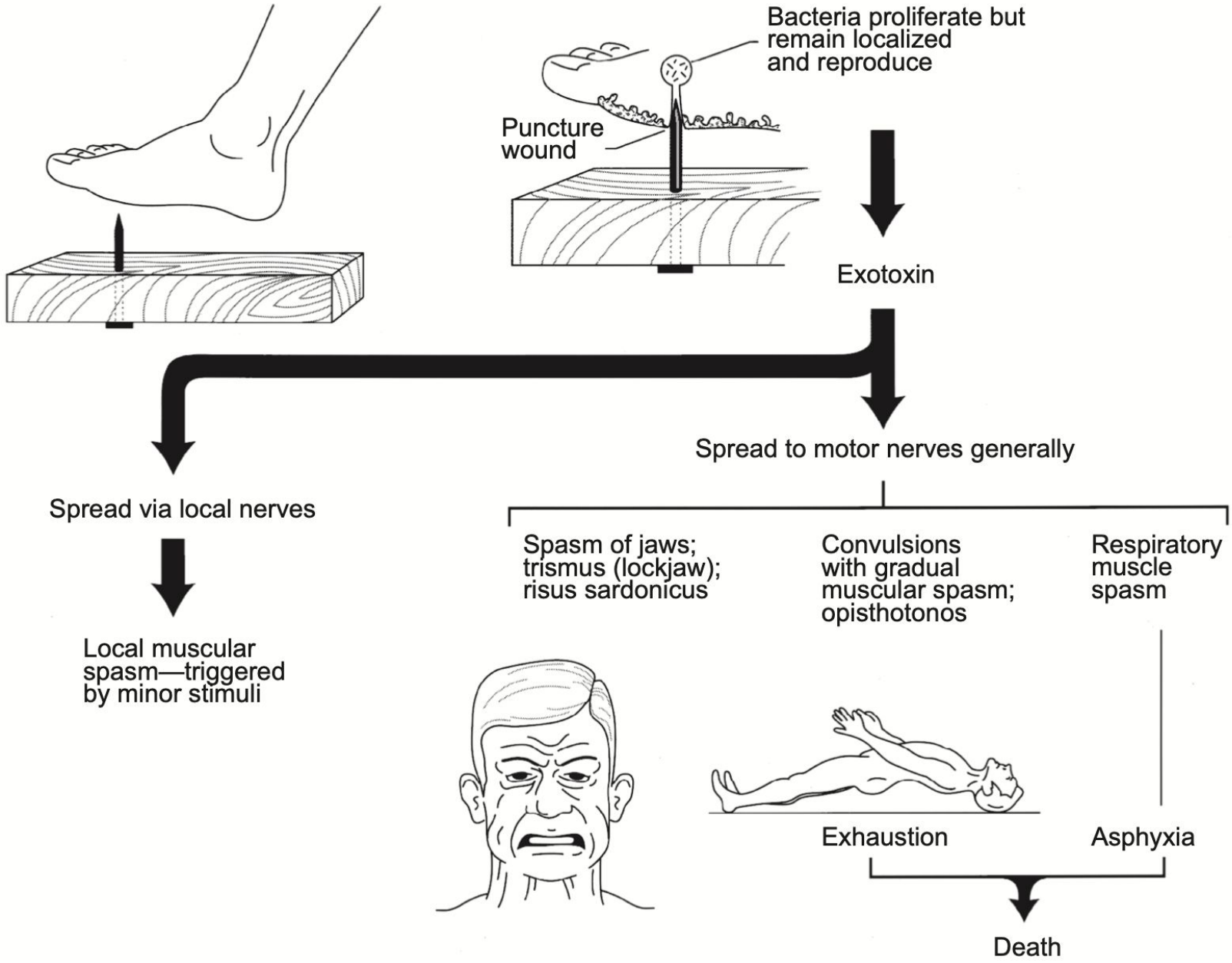
- 2022 to 2023 December
- 7 patients, Median age of 40 years, 2 females and 5 males
- 4 patients died (3patients with DM and 80yrs/F)
- Oldest was 80 years old female
- 4 were diabetic patients which was poorly controlled
- 2 cases of neonatal tetanus 2-3 wks old babies. One of which was born from home and the other, no risk factors identified.
- They were all discharged following treatment

Pathogenesis

- C. tetani is an obligately anaerobic bacillus that produces two toxins:
  - ❖ Tetanospasmin and tetanolysin.

- ○ Tetanospasmin enters the NS through the LMNs and is carried to the brain and spinal cord via retrograde transport.

  - ✔ Tetanospasmin prevents release of neurotransmitters from inhibitory cells leading to increased muscle tone and a hyper-sympathetic state.



The cycle of tetanus infection: Bacteria enter a wound and produce a toxin that spreads through the body, often causing death.

Clinical Manifestations

- Tetanus is divided into four clinical types:
  - Generalized, localized, cephalic, and neonatal.
- Hallmarks of generalized tetanus include:
  - Trismus (lockjaw, or masseter rigidity)
  - Risus sardonicus (increased tone in the orbicularis oris)
  - Difficulty swallowing, muscle rigidity, and spasms.
- Complications include;
  - Laryngospasm, fractures, hypertension, nosocomial infections, and death.

Differential Diagnosis of Tetanus

Acute abdomen
Black widow spider bite
Dental abscess/infection
Dislocated mandible
Dystonic reaction
Encephalitis
Head trauma
Hyperventilation syndrome
Subarachnoid hemorrhage
Temporomandibular joint syndrome
Hypocalcemia
Meningitis
Peritonsillar abscess
Progressive fluctuating muscle rigidity (stiff-man syndrome)
Psychogenic
Rabies
Sepsis
Status epilepticus
Strychnine poisoning

Management of Tetanus

The management priorities:

1. Secure the airway,
2. Administer anti-toxin immune globulins,
3. Debride potentially infected wounds.
4. Administer tetanus toxoid

Spasms control

- Benzodiazepines
- Magnesium sulfate infusions to help control spasms

Control of autonomic dysfunction.

"Suffering from Tetanus does not confer immunity: vaccinate all survivors." Dr. Oriba Dan Langoya

Summary of Management of Tetanus

Respiratory management	Sedation and neuromuscular blockade with succinylcholine or vecuronium for intubation and ongoing mechanical ventilation
Immunotherapy	Tetanus immunoglobulin, 3000–6000 units IM opposite side of the body from tetanus toxoid, with at least a portion around the wound site *and* Tetanus toxoid (DTaP or Td/Tdap depending on age), 0.5 mL IM at presentation, and 6 wk and 6 mo after presentation
Wound care	Wound debridement
Antibiotic therapy	Metronidazole, 500 milligrams IV every 6 h. **Penicillin can theoretically potentiate the effects of tetanospasm.**
Muscle relaxation	Diazepam preferred
Management of autonomic dysfunction	Magnesium sulfate, 40 milligrams/kg IV loading, then 2 grams/h (1.5 grams/h if ≤45 kg) continuous infusion to maintain blood level of 2.0–4.0 mmol/L *or* Labetalol, 0.25–1.0 milligram/min continuous IV infusion Morphine sulfate, 0.5–1.0 milligram/kg/h Clonidine, 300 micrograms every 8 h by nasogastric tube

Pediatric Doses of Metronidazole Based on Age and Weight

Weight and Age	Dosage
Neonates <1200 g and 0 to 7 days	7.5 mg/kg IV or orally every 24 hours
Neonates <1200 g and 8 to 28 days	7.5 mg/kg IV or orally every 12 hours
Neonates >1200 g and 0 to 7 days	7.5 mg/kg IV or orally every 12 hours
Neonates >1200 g and 8 to 28 days	25 to 30 mg/kg/day IV or orally every 12 hours
Infants and children	30 mg/kg/day IV divided every 6 hours, maximum 4 g/day

Routine Diphtheria, Tetanus, and Pertussis Vaccination Schedule for Children and Adults

Dose	Customary Age	Age/Interval	Product
Primary 1	2 months old	6 weeks or older	DTaP
Primary 2	4 months old	4 to 8 weeks after first dose[b]	DTaP
Primary 3	6 months old	4 to 8 weeks after second dose[b]	DTaP
Primary 4	15 to 18 months old	6 to 12 months after third dose[b]	DTaP
Booster	4 to 6 years old, not needed if fourth vaccination administered after birthday[a]		DTaP
Additional booster	11 to 18 years old		Tdap
Adult booster	>18 years old All pregnant women	Every 10 years	Tdap or Td[c]

[a]If primary immunizations are started after the age of 6 years, the series should begin and continue with Tdap.
[b]Prolonging the interval does not require restarting of the series.
[c]Td should be given to adult patients who have previously received Tdap. Tdap can be given regardless of interval since Td.
DTaP, Diphtheria, tetanus, and acellular pertussis; *Td,* diphtheria-tetanus; *Tdap,* tetanus, diphtheria, activated pertussis.

http://www.cdc.gov/vaccines/schedules/hcp/imz/child-adolescent.html

Rabies

Rabies

Definition

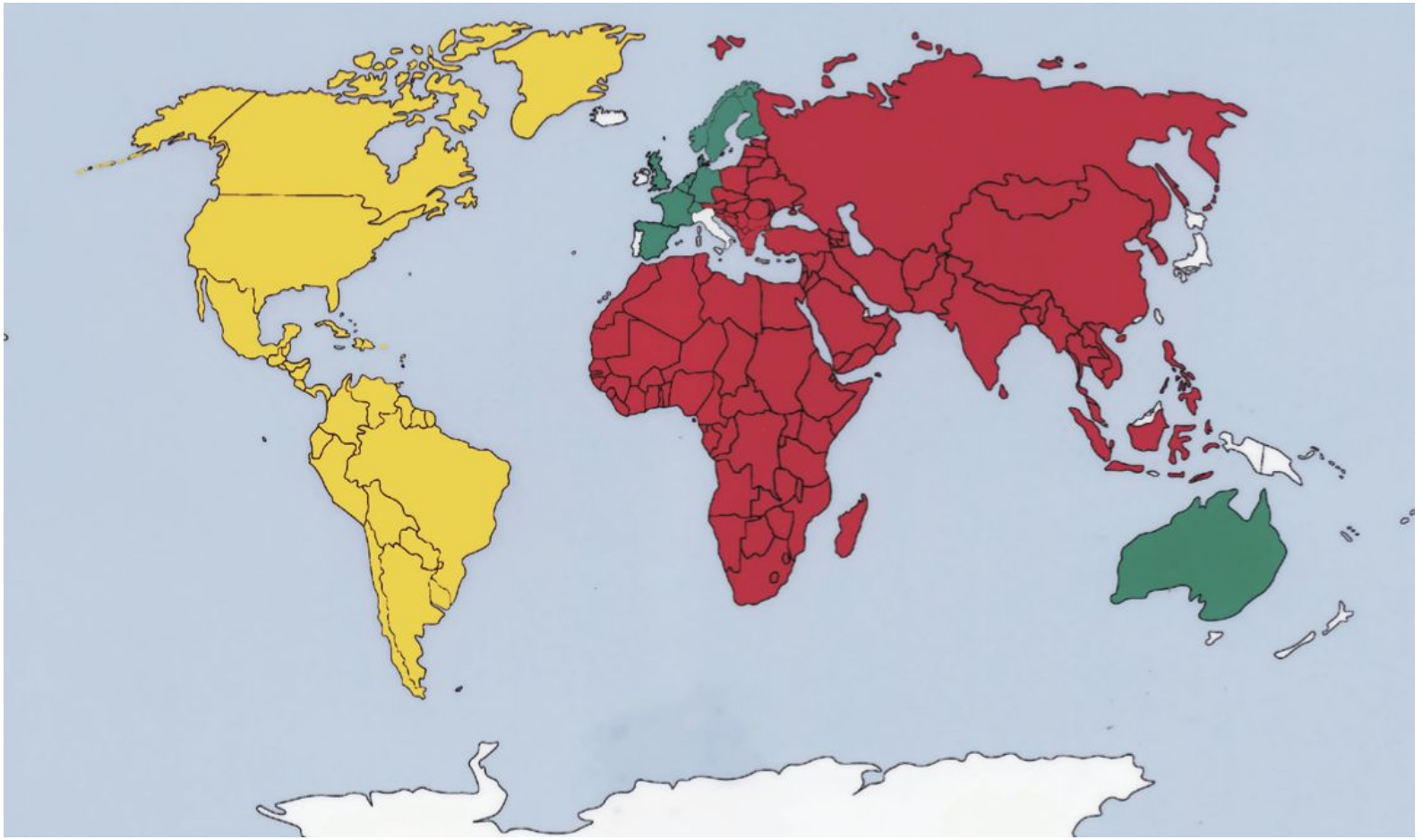
- Rabies is a zoonotic encephalitis caused by different species of neurotropic viruses
  - Lyssavirus genus, Rhabdoviridae family.

Epidemiology

- Rabies is one of the oldest human diseases, with the highest case-fatality rate.
- Approximately 3.3 billion people live in regions where rabies is enzootic.[1]
- An estimated 25,000 to 159,000 people die from rabies each year.[1]

1- World Health Organization. Rabies vaccines: WHO position paper. *Wkly Epidemiol Rec*. 2007;82:425– 436.

Global distribution of rabies and rabies- related lyssaviruses which infect humans.



Red: Rabies in terrestrial mammal species (Lyssavirus classic rabies) and bat infections by other lyssavirus species.
Yellow: Terrestrial and bat rabies are all the classical species. Green: Bat lyssaviruses, Australian bat lyssavirus European bat lyssaviruses and Irkut, only. White: No lyssaviruses reported.

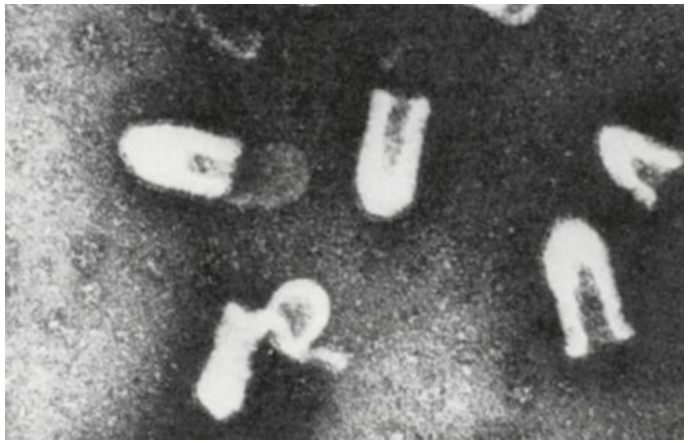
Rabies Fact Sheet

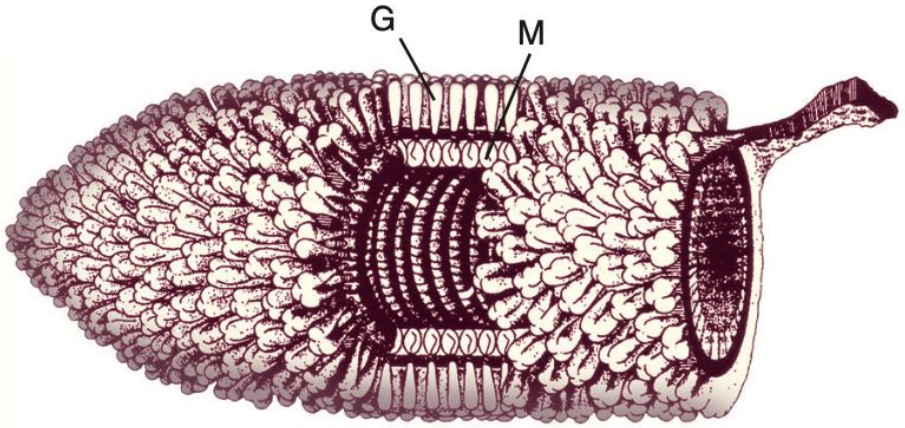
- Rabies occurs in more than 150 countries and territories.
- Worldwide, more than 55,000 people die of rabies infection each year.
- Forty percent of persons who are bitten by suspect rabid animals are children younger than age fifteen years.
- Dogs are the source of 99 percent of human rabies deaths.
- Wound cleansing and immunization within a few hours after contact with a suspect rabid animal can prevent the onset of rabies, and possible death.
- Every year, more than 15 million people worldwide receive a postexposure treatment regimen to avert the disease; this is estimated to prevent 327,000 rabies deaths annually.

Source: World Health Organization.

Microbiology

- Lyssaviruses are bullet-shaped, single-stranded RNA viruses of the order.
- Mononegavirales, family Rhabdoviridae, and genus Lyssavirus.
- Rabies virus is the type species of the Lyssavirus genus.





Dietzschold B, Rupprecht CE, Fu ZF, Koprowski H. Rhabdoviruses. In: Fields BN, Knipe DM, Howley PM, et al, eds. Fields Virology. *3rd ed. Philadelphia: Lippincott Raven; 1996:1137–1159.)*

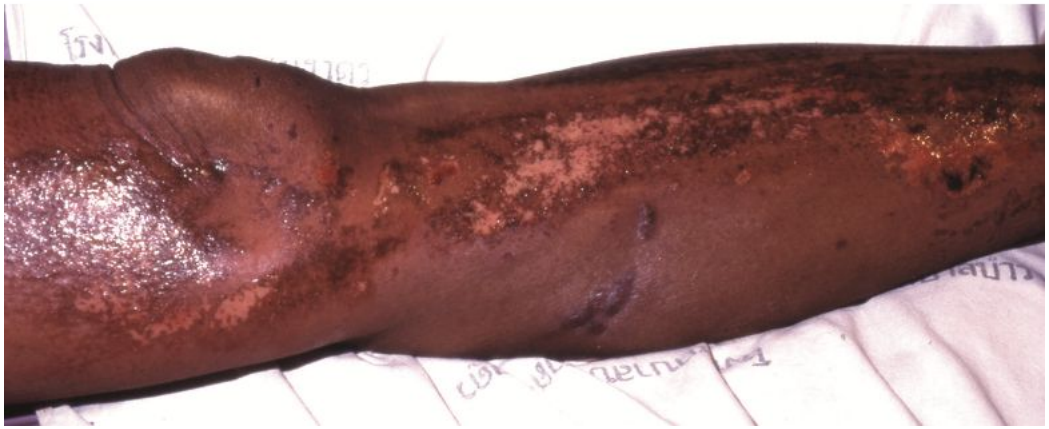
Pathogenesis

- Rabies virus replicates slowly following inoculation in skin and muscle.
- The virus then enters the peripheral motor nerve, utilizing the nicotinic acetylcholine receptor.
  - The virus travels by fast axonal transport, crossing synapses roughly every 12 hr.
  - Rapid dissemination occurs throughout the brain and spinal cord before symptoms appear.
- Infection of the dorsal root ganglia is apparently futile
  - Despite severe neurologic dysfunction with rabies, histopathology reveals limited damage, inflammation, or apoptosis.

Clinical features in humans

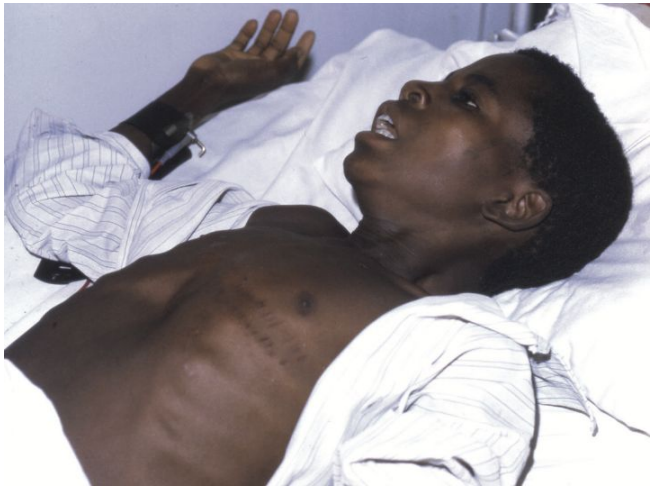
- Prodromal symptoms
  - First symptom is itching, pain, or paraesthesia at the site of the healed bite wound
- Non specific prodromal symptoms include:
  - Fever, chills, malaise, weakness, tiredness, headache, photophobia, myalgia, anxiety, depression, irritability, and symptoms URTI & Gastrointestinal Infections
- Subsequently, either furious or paralytic rabies develop;
  - *Depends on whether the spinal cord or brain are predominantly infected.*

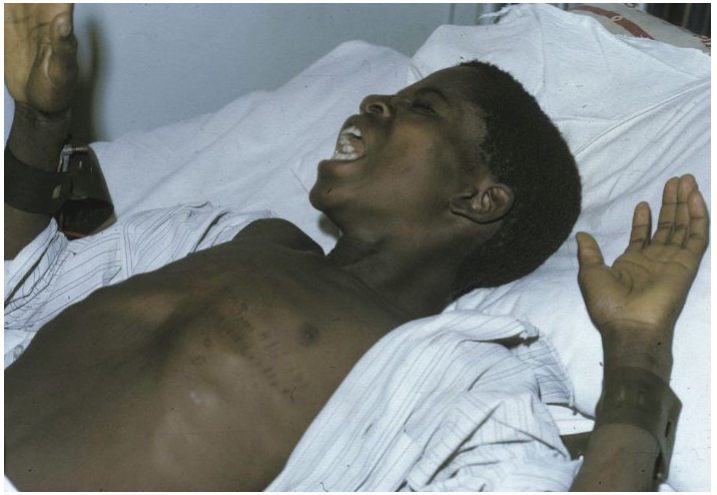
Prodromal symptoms



- This man developed intense itching in the right leg, provoking scratching and excoriation, 8 weeks after being bitten in that limb by a rabid dog.
- He died with furious rabies a few days later.

Hydrophobic spasms





14- year- old boy with furious rabies. Note the violent contraction of inspiratory muscles (sternomastoid and diaphragm) depressing the xiphisternum

I have never seen such a complex interplay of pathophysiological derangements caused by any disease worst than rabies
Dr. Oriba Dan Langoya

Clinical presentation

- Classically encephalitic rabies presents with:
  - Fever, hydrophobia, pharyngeal spasms, and hyperactivity subsiding to paralysis, coma and death.
  - Aerophobia is also pathognomonic of rabies but less frequent.
  - Facial grimace, opisthotonos
  - Autonomic instability with:
    - Hypersalivation, lacrimation, sweating (goose flesh), dilated pupils, hyperthermia/hypothermia
  - Dysarthria, dysphagia, diplopia/vertigo
  - Agitation, combativeness & hyperexcitability

Sumarised from UPTODATE

Durations of Different Stages

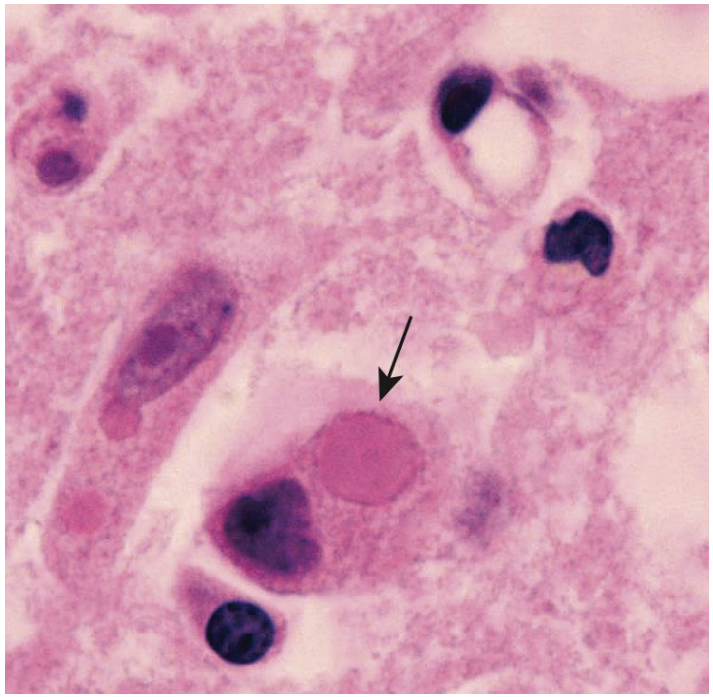
Stage	DURATION (% OF CASES)	ASSOCIATED FINDINGS
Incubation period	<30 days (25%) 30–90 days (50%) 90 days to 1 year (20%) >1 year (5%)	None
Prodrome and early symptoms	2–10 days	Paresthesias or pain at the wound site; fever; malaise; anorexia; nausea and vomiting
Acute neurologic disease; furious rabies (80% of cases)	2–7 days	Hallucinations; bizarre behavior; anxiety; agitation; biting; hydrophobia; autonomic dysfunction; syndrome of inappropriate antidiuretic hormone (SIADH)
Paralytic rabies (20% of cases)	2–7 days	Ascending flaccid paralysis
Coma, death[a]	0–14 days	—

Data modified from Fishbein DB. Rabies in humans. In: Baer GM, ed. The Natural History of Rabies. *2nd ed. Boca Raton, FL: CRC Press; 1991:519–549.*

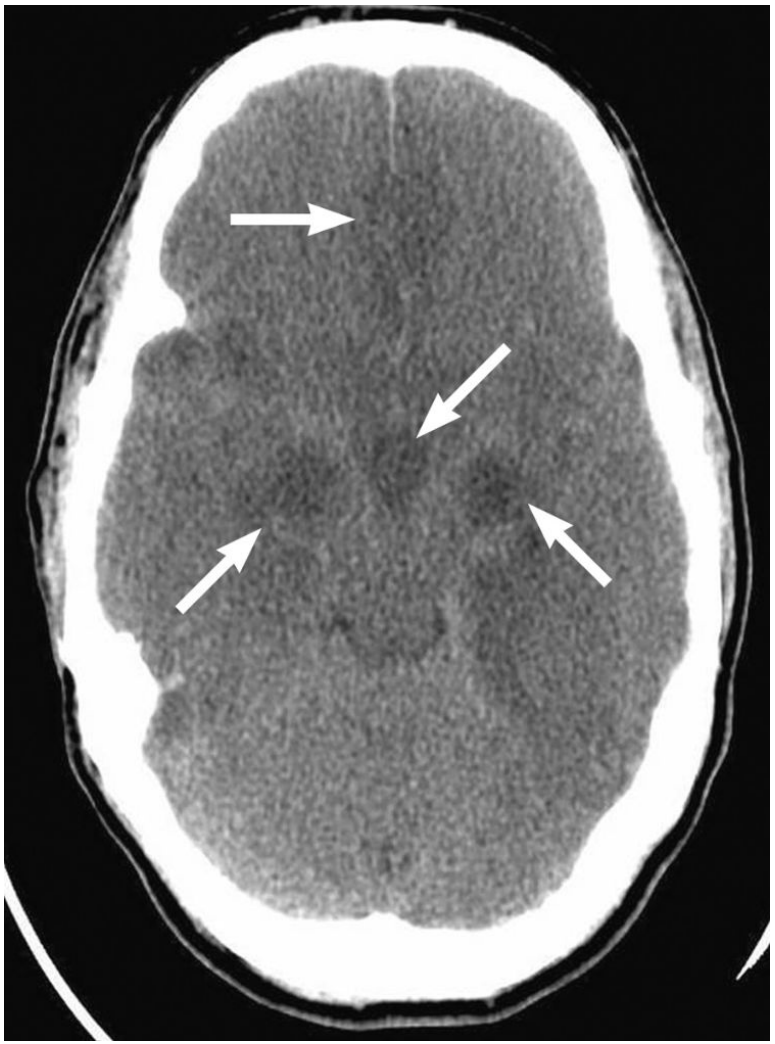
Diagnosis

- Immunofluorescence of punch biopsy specimens of skin taken from a hairy area.
- PCR to detect rabies in saliva and skin biopsy material.
- In our setting, diagnosis relies on recognition of hydrophobic spasms and other clinical features of furious rabies.
- Paralytic disease is rarely identified.
- Rabies has been misdiagnosed as cerebral malaria, or even drug abuse.

Diagnosis

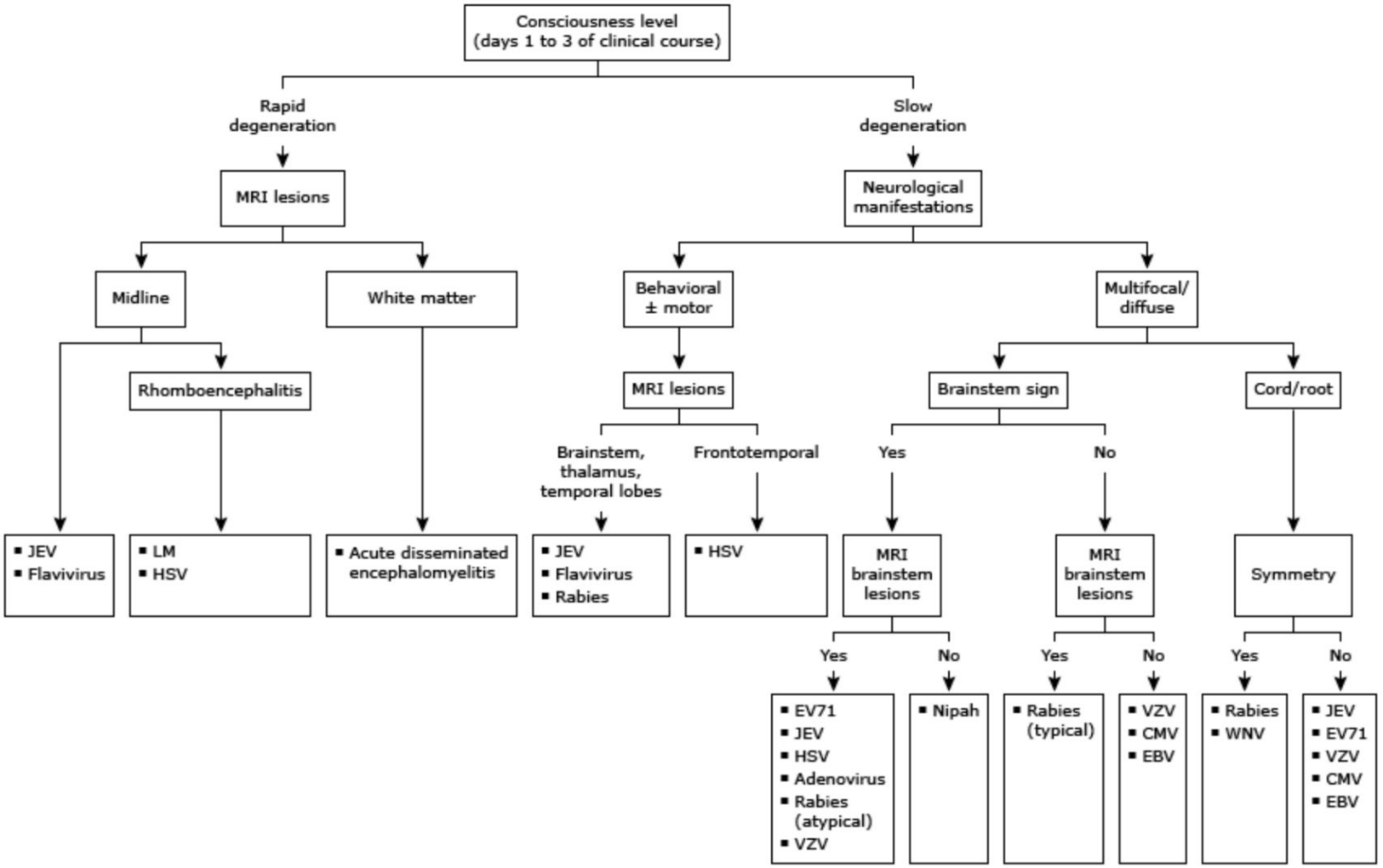


Negri body *(arrow).* ×400.
*(*Courtesy Maria-Beatriz Lopes, MD, Division of Neuropathology, University of Virginia.)



Non-contrast CT scan showing areas of both severe cerebral edema *(arrows)* and more widespread swelling.

Algorithm for the differential diagnosis of Rabies



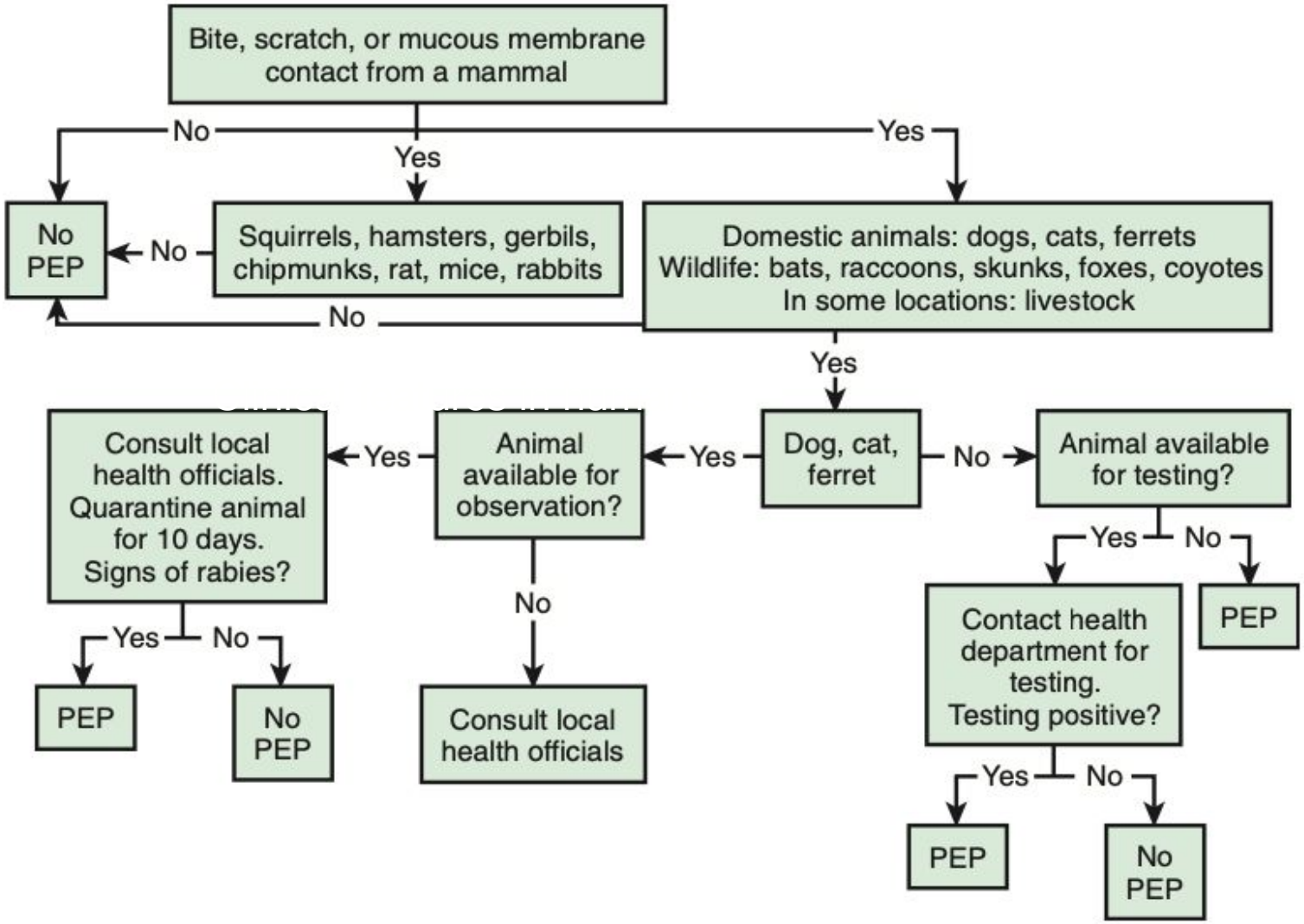
MRI: magnetic resonance imaging; JEV: Japanese encephalitis virus; LM: *Listeria monocytogenes*; HSV: herpes simplex virus; EV71: enterovirus 71; VZV: varicella zoster virus; CMV: cytomegalovirus; EBV: Epstein-Barr virus; WNV: West Nile virus.

Treatment and prevention

- Generally, rabies cannot be effectively treated, so most efforts must be focused on prevention

Pre- exposure vaccination is the most effective form of rabies prevention.
No rabies deaths have been reported in anyone who had had pre- exposure vaccine and then postexposure booster doses.

Algorithm for evaluating for rabies postexposure prophylaxis.



This and any other algorithm should be used in concert with local epidemiologic information regarding the incidence of animal rabies in any given location.

Specific postexposure prophylaxis for use in a rabies endemic area

Minor exposure (including minor scratches, or abrasions without bleeding)

- Start vaccine immediately
- Stop treatment if animal remains healthy for 10 days
- Stop treatment if animal's brain proves negative for rabies by appropriate laboratory tests

Major exposure (including licks of broken skin or mucosa, minor bites on arms, trunk or legs, or major severe bites, i.e. multiple or on face, head, fingers, or neck)

- Immediate rabies immune globulin and vaccine
- Stop treatment if domestic cat or dog remains healthy for 10 days
- Stop treatment if animal's brain proves negative for rabies by appropriate laboratory tests

[a] This scheme is a simplification of the recommendations of the World Health Organization Expert Consultation on Rabies (2018).

Prevention & Challenges

- Control of rabies in domestic dogs;
  - 99% of human rabies deaths could be prevented by controlling the transmission of dog rabies.
  - Education and resources are lacking.
- Pre-exposure prophylaxis;
  - A 2 or 3-dose course of rabies vaccine is recommended for travellers and indigenous people in dog rabies endemic areas.
  - The cost is often prohibitive.
- Postexposure prophylaxis; at the time of a bite, correct cleaning of the wound & optimum PEP immunization virtually eliminate the risk of rabies.
  - Effective prophylaxis demands urgent wound cleaning with copious amounts of soap and water, followed by vaccine and rabies immunoglobulin

Botulism

Introduction:

- Botulism is a rare life-threatening paralytic illness
- Caused by potent neurotoxins produced by *Clostridium botulinum*.
- 5 forms have been recognized
  - Food-borne botulism, infant botulism, wound botulism, unclassified botulism, and inadvertent botulism.
- The potential exists for botulinum toxin to be used as a biologic weapon. It is highly potent and easy to produce.

botulism comes from the Latin *botulus,* meaning "sausage,"

Pathogenesis

- The spores of *C. botulinum* are highly resistant.
- Under appropriate conditions, they germinate to release vegetative organisms that produce neurotoxin.
- After absorption and hematogenous dissemination.
    - Botulinum toxin exerts its effects at the presynaptic terminals of cholinergic nerve junctions by blocking neurotransmitter release.

Clinical presentation

- Typically presents with bilateral cranial nerve palsies
  - Followed by symmetric descending flaccid paralysis & occasional progression to respiratory muscle weakness.
- Botulism should be suspected in any adult with acute-onset GI, autonomic, and cranial nerve dysfunction.
- The four “Ds” are the key clues:
  - Dysphonia
  - Dysphagia
  - Dysarthria
  - Descending paralysis.

Pediatric considerations

- Constipation is usually the first manifestation of infant botulism.
- Over 1 to 2 weeks neurologic features develop, leading to presentations with;
  - A weakened cry,
  - Diminished feeding
  - Increasingly “floppy” infant as descending paresis occurs.
- Examination reveals;
  - Hypotonia, loss of facial expression, extraocular muscle weakness, and dilated pupils.
- 70% require mechanical ventilatory support.

Differential diagnosis

Important differential diagnoses to consider when botulism is suspected include

- Alcohol or drug misuse,
- Guillain–Barré syndrome (GBS),
- Myasthenia gravis,
- Stroke syndromes,
- Eaton–Lambert syndrome
- Tick paralysis

Management

Entails

- Early administration of antitoxin
- Prompt recognition of respiratory compromise
    - To allow for the timely implementation of ventilatory support
- These strategies are key to optimizing outcome.

QUESTIONS & DISCUSSIONS