ECHO Summary,10/MAY/2024
Session Title: Rabies, Tetanus, and Botulism Part 2

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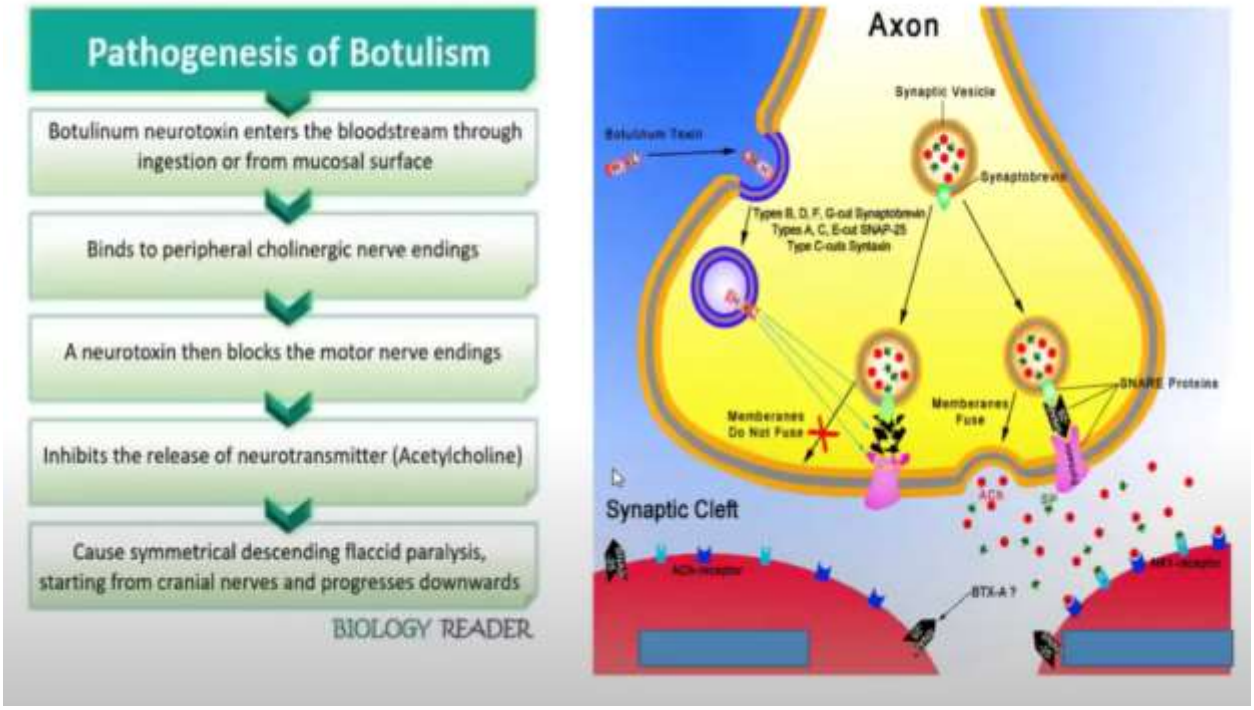
Epidemiology/Pathophysiology

- Rabies
    - Causes 60,000 deaths/year globally
    - 40% of those sustaining a bite from a rabid animal are children < 15 years
    - Huge global cost burden
    - After inoculation with rabies virus from saliva/bite of an infected animal, the virus replicates in local tissue, enters the peripheral nervous system (PNS) via the motor end plate, and then is hidden from the immune system
        - Migrates from there to the central nervous system (CNS)
        - Symptoms of encephalitis start once the virus starts replicating in the CNS[1]
- Tetanus
    - More common in warm, damp climates with rich soil
    - Deaths have been declining since the 1940s due to improved food storage[2]
    - Disease caused by exotoxin of *Clostridium tetani*
    - The incubation period is from few days to weeks (average 7-10 days)
    - Common sources of infection include deep penetrating skin wounds, the umbilical cord of the newborn, ear infections, or wounds produced during delivery and septic abortions[3]
- Botulism
    - Rare in all settings (high-income and low/middle-income)[4]
    - *Clostridium botulinum* is an anaerobic gram-positive bacteria
    - Bacteria live in the soil in the form of spores
    - Can be transmitted via aerosolization of dirt or via food contamination
    - When conditions are favorable, spores can germinate into live bacteria which form toxins
        - There are numerous strains, but A and B are most toxic to humans
    - In adults, exposure to the toxin is necessary
    - In infants, lower gastric acidity allows the spores to actually germinate after ingestion (which doesn't happen in adults).[5] Because of less robust gut flora, the bacteria colonizes the intestine and the toxin is subsequently released[6]



Risk Factors

- Rabies
    - Bite by an unvaccinated domestic animal or a wild animal[1]
    - In Uganda, the most common sources include dogs, jackals, and livestock[7]
- Tetanus
    - Wounds that have not been properly cleaned
    - Intravenous (IV) drug use, particularly in patients who re-use needles or do not clean their skin prior to injection
    - Lack of full immunization
    - Older age[2]
- Botulism
    - Food contamination
        - Improperly canned foods
        - Contaminated milk or honey
            - *Infants are at particularly high risk - in fact, infant botulism is the most common type of botulism
    - Dirt inhalation (i.e. construction sites)
    - Wound contamination with spores
    - Laboratory work with botulism

Clinical features

- Rabies

    - **AIRWAY/BREATHING:** Copious secretions. If there is ascending paralysis, the patient may eventually develop paralysis of the respiratory muscles or coma that compromise airway/breathing
    - **CIRCULATION:** In patients with paralytic rabies, they may suffer from neurogenic shock, similar to tetanus and botulism patients
    - **DISABILITY:**
        - Hydrophobia
        - Aerophobia
        - Altered mental status, including hallucinations and aggressive behavior
        - Muscle twitching
        - Seizures
        - In the paralytic form, may have ascending paralysis
    - **EXPOSURE:** Autonomic instability can cause temperature dysregulation
- Tetanus
    - **AIRWAY:** May be compromised secondary to glottal spasms/"lockjaw" (i.e. trismus)
    - **BREATHING:** May be compromised secondary to paralysis of respiratory musculature
    - **CIRCULATION:** Usually normal, though neurogenic shock can occur due to autonomic dysfunction
    - **DISABILITY:**
        - Generalized spasms induced by sounds and/or strong light, characterized by grimace (risus sardonicus)
        - Arching of the back (opisthotonus)[3]
    - **EXPOSURE:** Autonomic instability can cause temperature dysregulation/fever
- Botulism
    - **AIRWAY**: May be compromised secondary to paralysis of oropharyngeal musculature
    - **BREATHING**: May be compromised secondary to paralysis of respiratory musculature
    - **CIRCULATION**: Usually normal, though hypovolemic shock secondary to GI losses through vomiting/diarrhea can occur. Rarely, neurogenic shock can occur due to autonomic dysfunction
    - **DISABILITY:**
        - Symmetric descending flaccid paralysis
        - May have vision issues secondary to cranial nerve deficits leading to diplopia, dysconjugate gaze, vertigo
        - Dry eyes, dry mouth, and sore throat secondary to drying of secretions may occur
        - Infantile botulism: constipation followed by floppiness/poor feeding[5]
    - **EXPOSURE**: There may be prodromal gastrointestinal (GI) symptoms in patients with botulism secondary to contaminated food sources. In patients with wound botulism, they may have a prodrome of fever but should NOT have GI symptoms

Diagnostics

- *Diagnosis of all three of these conditions is primarily clinical, based on classic clinical presentations and exposures*
- Rabies
    - Pre-mortem diagnosis
        - Reverse transcription polymerase chain reaction (RT-PCR) - sources may include multiple repeated saliva, cerebrospinal fluid, urine, hair follicle, or skin biopsy (if available)
        - Magnetic resonance imaging (MRI) may help distinguish rabies encephalitis from other viral encephalitis (if available)[1]
    - Post-mortem diagnosis can be confirmed via brain biopsy from the patient or the infected animal they were exposed to (if these services are made available by animal control in your region)
- Tetanus
    - Wound culture
    - Spatula test
        - Touch the oropharynx with a tongue depressor
            - Positive test: patient has masseter muscle spasm and bites the spatula
            - Negative test: patient gags[2]
- Botulism
    - Toxin detection in serum/stool or via testing of the contaminated food source
    - Bacterial culture can be quite challenging and may not be available depending on the setting

Treatment

- Rabies
    - Pre-exposure prophylaxis (2-3 doses of rabies vaccine) is recommended for:
        - Travelers to/individuals who live in rabies-endemic areas
        - Laboratory staff working with rabies virus
        - Veterinarians, zoologists, animal handlers
        - Cost can be a barrier
        - Regimen:
            - Day 0: One dose intramuscular (IM) or intradermal (ID)
            - Day 7: One dose IM or ID
            - Day 28: One dose IM or ID[3]
    - Post-exposure prophylaxis is indicated in the setting of significant exposure
        - The most important aspect of post-exposure prophylaxis is proper wound cleansing, which involves copious soap and water
        - Wound care
            - Wash with soap and water immediately
            - Do not suture the wound

- Immunoglobulin (IG) and vaccination - see Table 1 for administration recommendations and Table 2 for dosing recommendations[3]

Table 1. Recommendations for Rabies Vaccination/Serum. Adapted from: The Republic of Uganda Ministry of Health. *Uganda Clinical Guidelines 2023: National Guidelines for Management of Common Health Conditions*.; 2023. Accessed May 11, 2024. chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://www.health.go.ug/wp-content/uploads/2023/11/UCG-2023-Publication-Final-PDF-Version-1.pdf

Nature of Exposure	Condition of Animal		Recommended Action
	At time of exposure	10 days after exposure	
Saliva in contact with skin but no skin lesion	Healthy Healthy	Healthy	Do not vaccinate
		Rabid	Vaccinate
	Rabid or unknown		Vaccinate
Saliva in contact with skin that has lesions, minor bites on trunk or proximal limbs	Healthy	Healthy	Do not vaccinate
		Rabid	Vaccinate
	Suspect/unknown	Healthy	Vaccinate; but stop course if animal healthy after 10 days
		Rabid or unknown	Vaccinate
Saliva in contact with mucosae, serious bites (face, head, fingers or multiple bites)	Rabid or unknown		Vaccinate and give antirabies IG but stop course if the animal is healthy after 10 days

Table 2. Dosing Guidelines for Rabies Vaccination/Serum. Adapted from: The Republic of Uganda Ministry of Health. *Uganda Clinical Guidelines 2023: National Guidelines for Management of Common Health Conditions*.; 2023. Accessed May 11, 2024. chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://www.health.go.ug/wp-content/uploads/2023/11/UCG-2023-Publication-Final-PDF-Version-1.pdf

Vaccination Status	Regimen	First-Line	Alternative

Unvaccinated	Vaccination, no IG	2-1-1 IM regimen ● Day 0: One dose (0.5 ml) in right arm + one dose in left arm ● Day 7: One dose ● Day 21: One dose	2-site ID regimen* ● Day 0: one dose of 0.1 ml in each arm (deltoid) ● Day 3: one dose of 0.1 ml in each arm ● Day 7: one dose of 0.1 ml in each arm ● Day 28: one dose of 0.1 ml in each arm
	Vaccination, plus IG	2-1-1 IM regimen PLUS HRIG 20 IU/kg**	

HRIG = human rabies immunoglobulin, ID = intradermal, IM = intramuscular.
*This uses PVRV intradermal (ID) doses of 0.1 ml (i.e. one fifth of the 0.5 ml IM dose of PVRV). This method is much cheaper as it requires less vaccine but requires special staff training in ID technique using 1 ml syringes and short needles. Compliance with the Day 28 is vital but may be difficult to achieve. Patients must be followed up for at least 6-18 months to confirm the outcome of treatment. If patients are on malaria chemoprophylaxis, this method is contraindicated
*Infiltrate as much as possible of this dose around the wound/s (if multiple wounds and insufficient quantity, dilute it 2 to 3 fold with normal saline) and give the remainder IM into gluteal muscle. The first dose of vaccine should be given at the same time as the immunoglobulin, but at a site as far away as possible from the site where the vaccine was injected. If the bite is at or near the upper arm, do not infiltrate the wound with the immunoglobulin unless the vaccine will not be injected in the deltoid muscle of that arm. If the wound near the deltoid is infiltrated with the immunoglobulin, use the deltoid muscle of the opposite arm for the vaccine

        - For patients with active signs and symptoms of rabies, this is unfortunately fatal. Treatment involves supportive care and isolation in an intensive care setting to prevent spread of disease via transfer of saliva to other humans or animals
            - Personal protective equipment for healthcare workers: gown, gloves, face mask, eye protection
            - Wash hands before and after patient contact
            - Keep the room quiet and dark to avoid agitation
            - Manage airway compromise as needed
                - Secretions may be copious
            - Provide continuous cardiac/respiratory monitoring
            - Administer sedatives and analgesics as needed
            - Provide emotional/spiritual support to the family
- Tetanus
    - Treatment is largely supportive for patients with active infection
        - **AIRWAY/BREATHING:** High risk for compromise given the neuroparalytic effects of tetanus toxin. Consider early airway stabilization and respiratory support if critical care/intensive care is available at your facility. If there is airway compromise but there is no availability of

prolonged ventilator use at your facility, the patient should be transitioned to comfort care

- If the patient needs to be intubated, do NOT use succinylcholine - this can cause life-threatening hyperkalemia[2]
- If the patient is on the ventilator, they may be on it for weeks. Consider the following:
  - Preventing ventilator-associated pneumonia
    - Elevate the head of the bed
    - Sedation holidays
    - Spontaneous breathing trials
    - Peptic ulcer prophylaxis with a proton pump inhibitor (PPI)
    - Oral care
  - Venous thromboembolism (VTE) prophylaxis

- **CIRCULATION:**
  - Provide IVF as needed for hypotension if the patient has signs or symptoms of hypovolemia/dehydration secondary to GI losses
  - Treat septic shock as one would otherwise, with IVF resuscitation and rapid administration of IV antibiotics
  - If the patient has autonomic instability with hypertension and tachycardia, consider blockade of adrenergic response with dual alpha and beta blockade (i.e. labetalol 0.25 to 1 mg/minute)[2]
- **DISABILITY:**
  - Pain control
    - Paracetamol
    - Opioids
  - Spasm control - critical for avoiding rhabdomyolysis and fractures!
    - First-line: diazepam
    - Second-line: magnesium sulfate or chlorpromazine[3]
  - Many patients will develop neurogenic bladder - consider in-and-out catheterization on a scheduled basis vs. indwelling catheter placement (though the latter places the patient at higher risk for urinary tract infection)
  - May have neurogenic bowel; consider bowel regimen
- **EXPOSURE:**
  - Ensure normothermia
  - Antibiotics - see Table 3

Table 3. Antibiotic therapy for tetanus infection. Source: The Republic of Uganda Ministry of Health. *Uganda Clinical Guidelines 2023: National Guidelines for Management of Common Health Conditions*.; 2023. Accessed May 11, 2024. chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://www.health.go.ug/wp-content/uploads/2023/11/UCG-2023-Publication-Final-PDF-Version-1.pdf

Antibiotic Regimen	Adult	Pediatric
First-Line	Metronidazole 500 mg every 8 hours IV or by mouth for 7 days	Metronidazole 7.5 mg/kg every 8 hours by mouth for 7 days
Alternative	Benzylpenicillin 2.5 MU every 6 hours for 10 days	Benzylpenicillin 50,000-100,000 IU/kg per dose every 6 hours for 10 days

- Tetanus IG
  - 150 IU/kg (adults and children). Give the dose in at least 2 different sites IM, different from the tetanus toxoid site[3]
- Administer a full course of age-appropriate tetanus vaccination
- Wound care and debridement
- For patients with wound tetanus in particular, ensure proper nutrition to aid in wound healing
  - Proper nutrition will help all patients with tetanus infection, as recovery from this condition places substantial demands on the body
  - Patients with respiratory compromise will likely need a nasogastric (NG) tube for feeding
  - Monitor fluid status and electrolytes
- Frequent turning to prevent bed sores

- Prevention
  - Tetanus vaccination lasts for 10 years
  - Proper wound cleaning

- Botulism
  - There is no vaccine for botulism at this time[8]
  - Treatment is largely supportive for patients with active infection
    - **AIRWAY/BREATHING:** High risk for compromise given the neuroparalytic effects of botulinum toxin. Consider early airway stabilization and respiratory support if critical care/an intensive care unit (ICU) is available at your facility. If there is airway compromise but there is no availability of prolonged ventilator use at your facility, the patient should be transitioned to comfort care
      - Monitoring for respiratory compromise: consider serial incentive spirometry, blood gases, pulse oximetry
      - If the patient is on the ventilator, they may be on it for weeks. Consider the following:
        - Preventing ventilator-associated pneumonia
          - Elevate the head of the bed
          - Sedation holidays
          - Spontaneous breathing trials

        - Peptic ulcer prophylaxis with a PPI
        - Oral care
      - VTE prophylaxis
  - **CIRCULATION:**
    - Provide IV fluids (IVF) as needed for hypotension if the patient has signs or symptoms of hypovolemia/dehydration secondary to GI losses
    - Botulism can cause septic shock; in this situation, provide rapid administration of IV antibiotics and fluid resuscitation[9]
  - **DISABILITY:**
    - Pain and spasm control
    - Many patients will develop neurogenic bladder - consider in-and-out catheterization on a scheduled basis vs. indwelling catheter placement (though the latter places the patient at higher risk for urinary tract infection)
    - May have neurogenic bowel; consider bowel regimen
  - **EXPOSURE:**
    - Ensure normothermia
    - Antitoxin if available in your setting (this is expensive and rarely available)
    - Antibiotics
      - Penicillin G and metronidazole are recommended if the cause is a wound infection
      - No indication for their use in infantile botulism[6]
    - For patients with wound botulism in particular, ensure proper nutrition to aid in wound healing
      - Proper nutrition will help all patients with botulism infection, as recovery from this condition places substantial demands on the body
      - Patients with respiratory compromise will likely need a nasogastric (NG) tube for feeding
      - Monitor fluid status and electrolytes
    - Frequent turning to prevent bed sores
- Prevention
  - Proper food storage and cooking
  - Avoid giving honey to infants less than 1 year of age
  - Clean wounds contaminated with soil thoroughly and avoid delays to cleansing

Complications

- Rabies infection can cause multiorgan failure[1]
- Severe muscular spasms in patients with tetanus can lead to rhabdomyolysis

- Creatine kinase (CK) and creatinine levels should be monitored closely. If the patient has an elevated CK or myoglobinuria, consider aggressive IVF resuscitation
- If renal failure results from this, patients may require dialysis (if available)

Disposition

- Home for patients with possible rabies exposure
- Admission to ICU for all patients with rabies, tetanus, or botulism infections

Special Notes

- Remember that some snake envenomations can also cause flaccid descending paralysis and symptoms very similar to botulism, so taking a thorough exposure history (including obtaining collateral history from witnesses/friends/family) is essential

Collaborating Partners

1. Ministry of Health of the Republic of Uganda
2. Seed Global Health
3. Techies Without Borders

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