Clostridium tetani and *Clostridium botulinum*

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Dr. Sulaiman Mahmoud Bani Abdel-Rahman

MBBS, Mutah unisversity

MSC Medical Microbiology – University of Manchester

PhD Medical Virology - University of Manchester

Clostridial Family Overview

Shared Characteristics:

- Gram-positive, spore-forming, anaerobic bacilli
- **Environmental ubiquity:** Found in soil, dust, and animal GI tract
- **Spore resistance:** Survive harsh conditions for decades
- **Toxin-mediated disease:** Potent neurotoxins cause clinical manifestations

Clostridial Family Overview (cont.)

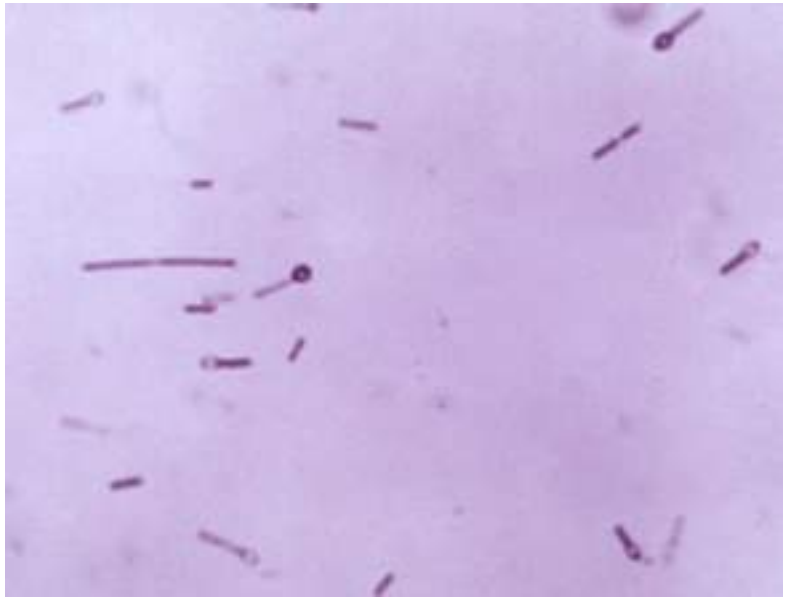
Important Family Members:

- *Clostridium tetani* → Tetanus
- *Clostridium botulinum* → Botulism
- *Clostridium perfringens* → Gas gangrene
- *Clostridium difficile* → Pseudomembranous colitis

Clostridium tetani

Morphological Characteristics:

- Gram-positive rods with terminal spores ("drumstick" appearance)
- Motile (peritrichous flagella in vegetative form)
- Strict anaerobe - dies in presence of oxygen
- Ubiquitous (especially animal feces and soil)
- Difficult to culture
- Produces neurotoxins tetanospasmin and tetanolysin



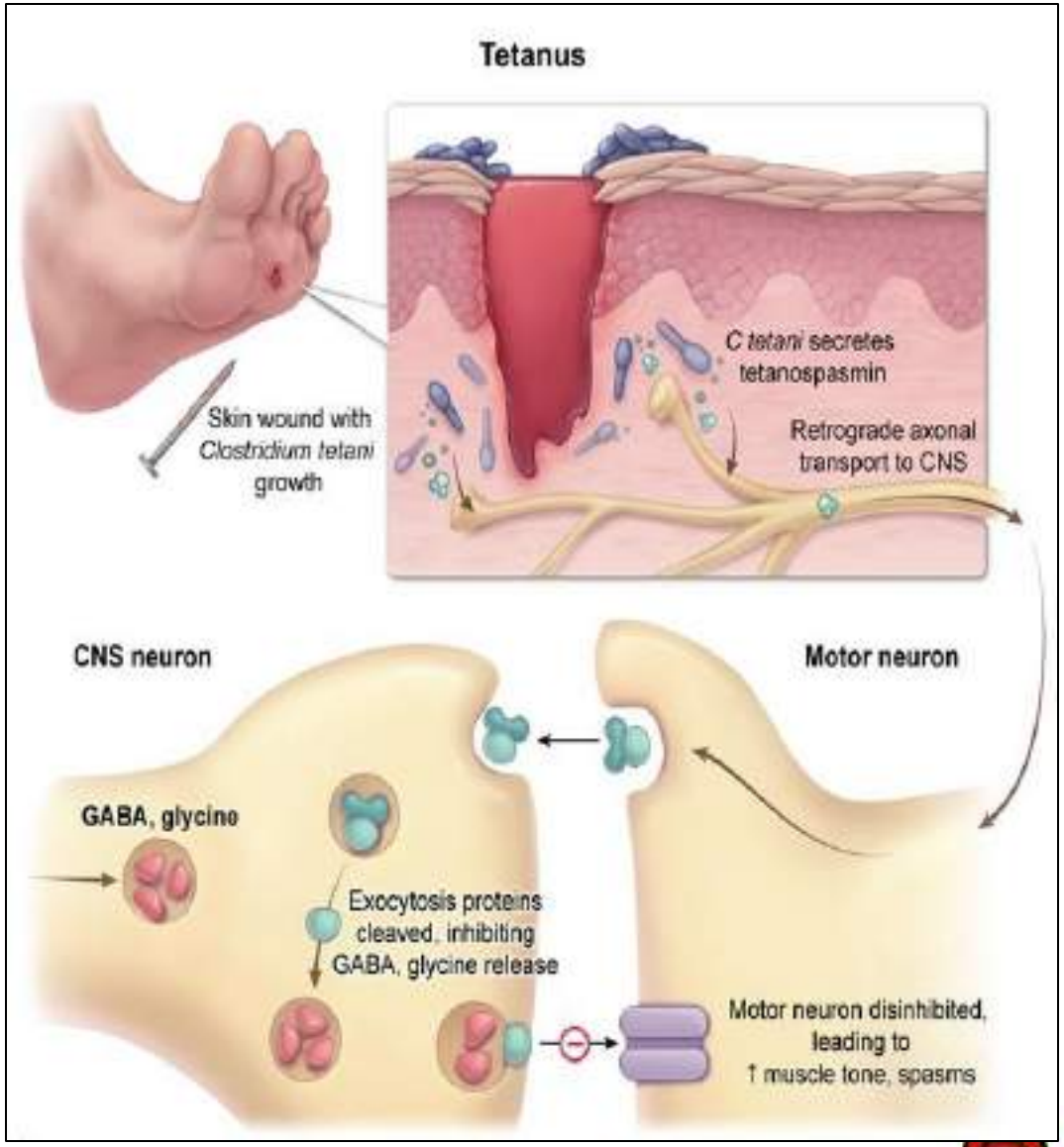
Clostridium tetani
Route of infection

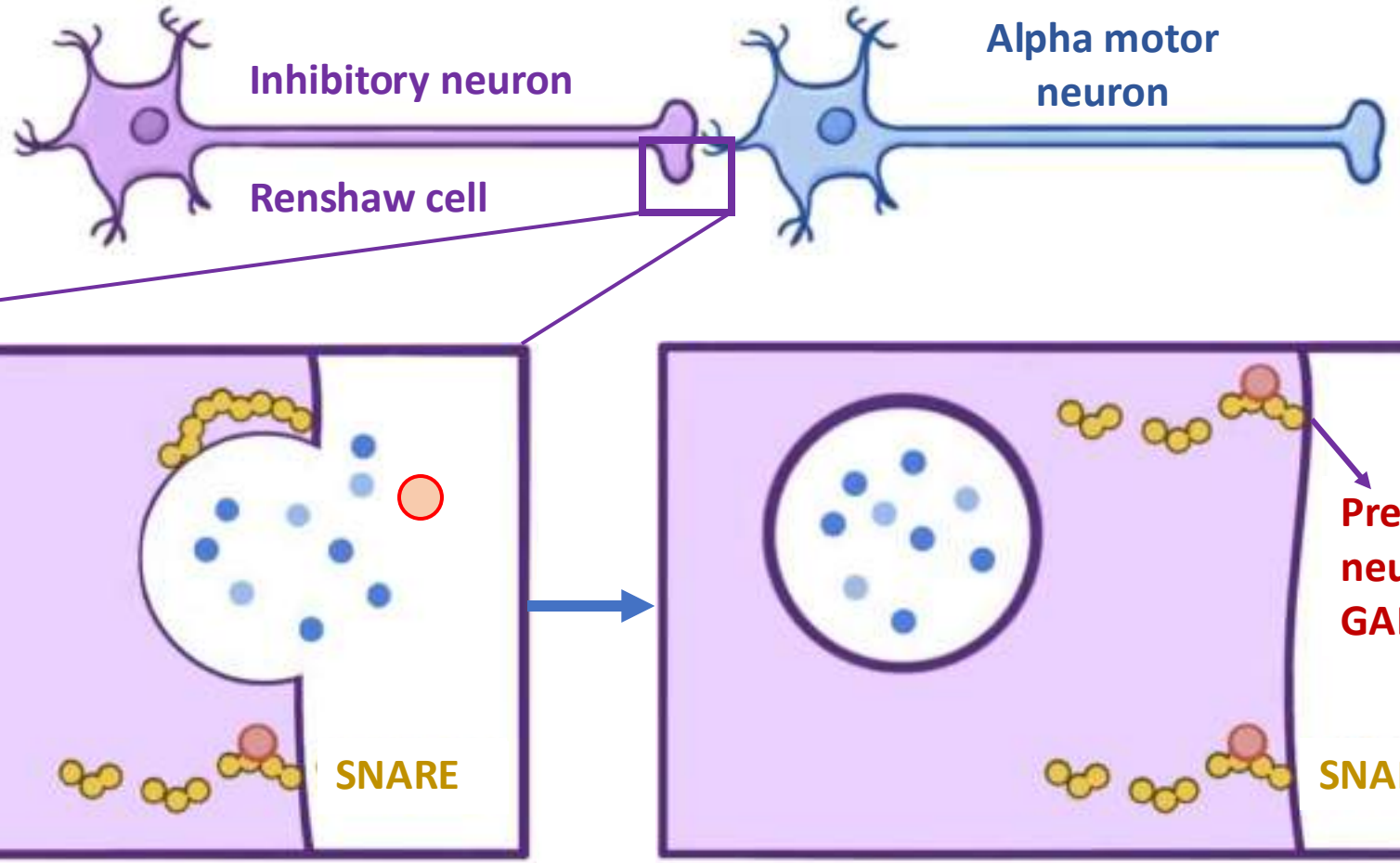
- Clostridial spores contaminate a wound (e.g., through dirt, saliva, feces).
- Localized ischemia, necrosis, foreign bodies and/or coinfection with other bacteria predispose to infection.
- Wounds with compromised blood supply create anaerobic conditions that are required for the germination and multiplication of C. tetani.
  - Deep, penetrating wounds (e.g., knife, gunshot, animal bites)
  - Open fractures
  - Surgical procedures (e.g., bowel, biliary tract, or dental surgery)

Clostridium tetani
Pathophysiology

- ***Clostridium tetani*** is a spore-forming, gram-positive anaerobic bacteria normally found in soil.
- The disease develops when spores enter the body through a break in the skin. The **spores** germinate in anaerobic conditions (like that of a puncture wound) and subsequently produce a potent metalloprotease exotoxin (tetanospasmin).
- Using retrograde axonal transport, the toxin migrates through lower motor neurons to inhibitory interneurons in the CNS at the level of the spinal cord and brainstem; there, it acts on the anterior horn cells, blocking the release of inhibitory neurotransmitters (glycine, GABA).
- This action leads to uncontrolled firing of alpha motor neurons and subsequent tonic muscle contraction.

- Ubiquitous *C. tetani* spores contaminate a wound → bacterial reproduction under anaerobic conditions → production of the neurotoxins tetanospasmin and tetanolysin
- Tetanospasmin: reaches the CNS through retrograde axonal transport
  - Toxin binds to receptors of peripheral nerves and is then transported to interneurons (Renshaw cells) in the CNS via vesicles.
  - Acts as protease that cleaves synaptobrevin, a SNARE protein → prevention of inhibitory neurotransmitters (i.e., GABA and glycine) release from Renshaw cells in the spinal cord → uninhibited activation of alpha motor neurons → muscle spasms, rigidity, and autonomic instability




Inhibitory neuron
Alpha motor neuron
Renshaw cell
SNARE
SNARE
Prevents the release of inhibitory neurotransmitters (Glycine and GABA)

Clostridium tetani
Clinical Spectrum of Tetanus

Generalized Tetanus (Most Common):

- **Incubation**: 7-10 days (range: 3-21 days)
- **Progression**: Trismus → generalized rigidity → spasms
- **Complications**: Respiratory failure, autonomic dysfunction

Localized Tetanus (Rare):

- **Muscle contraction** isolated near wound site
- **May progress** to generalized form
- **Better prognosis**

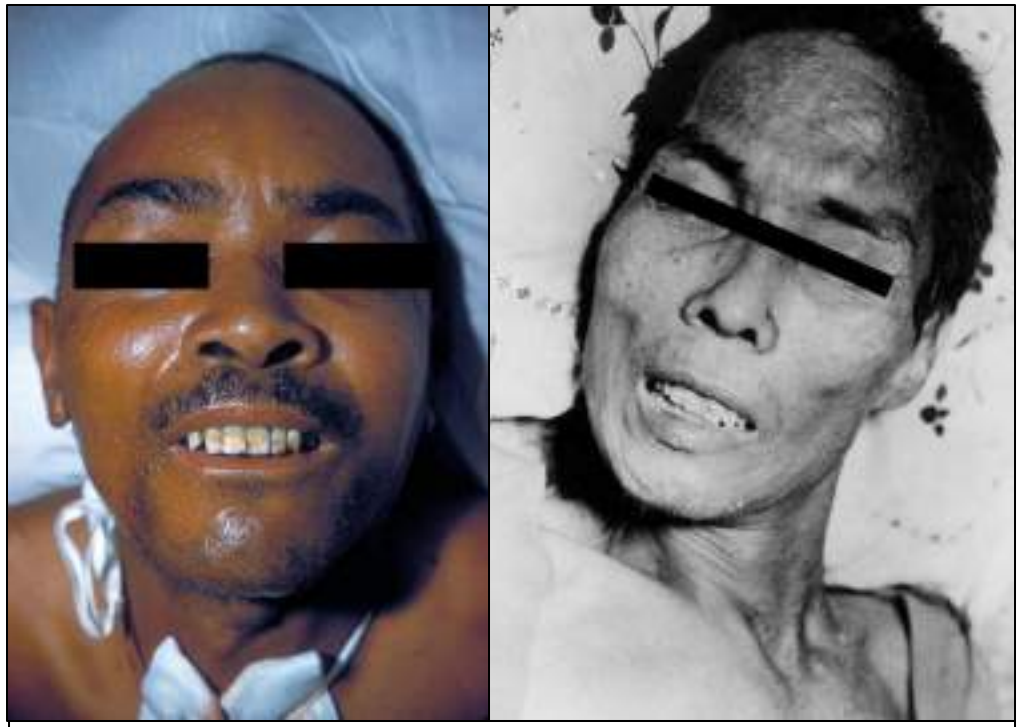
Cephalic Tetanus (Rare):

- **Head wound** involvement
- **Cranial nerve dysfunction**
- **Usually progresses** to generalized

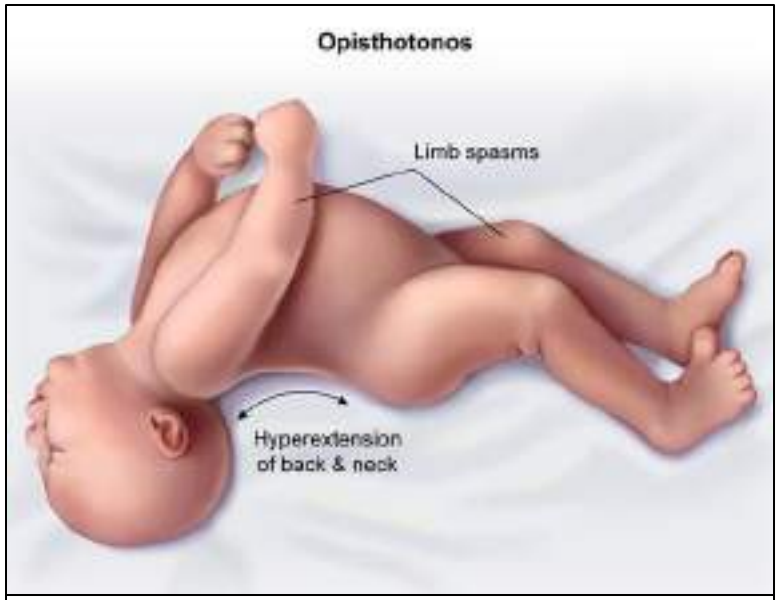
Neonatal Tetanus:

- **Onset**: 5-7 days after birth
- **Umbilical stump infection** in non-sterile conditions
- **Rapid progression** due to shorter neuron length

Jaw stiffness due to masseter muscle spasm (**trismus/lockjaw**); frequently the first manifestation of tetanus



Facial muscles spasm, producing a bizarre "smiling" appearance (risus sardonicus)



Spasm of the back and neck muscles causing extension and arching of the back (**opisthotonos**); occurs in about half of patients

Clostridium tetani
Diagnosis

- Tetanus is a clinical diagnosis based on muscle spasms and rigidity associated with an entry point for bacteria and inadequate immunization.
- Wound culture and serology may confirm the diagnosis but have low sensitivity and specificity.

Clostridium tetani
Management

- **Tetanus prophylaxis**
  - Following a wound, the decision to administer tetanus prophylaxis (ie, tetanus toxoid–containing vaccine ± tetanus immune globulin) is based on the severity of the wound and the immunization status of the patient:
    - For patients who have received ≥3 tetanus toxoid doses, a booster dose of tetanus toxoid is indicated only if their last tetanus dose was ≥10 years ago for clean or minor wounds or ≥5 years ago for dirty (eg, dirt, feces, saliva) or severe (eg, punctures, avulsions, crush injuries, burns, frostbite) wounds.
    - Patients who have received <3 tetanus toxoid doses (ie, incompletely immunized) or whose vaccine status is uncertain should receive a tetanus toxoid booster. If such patients have dirty or severe wounds, they should also receive tetanus immunoglobulin. Tetanus immunoglobulin primes the immune system but does not confer long-term immunity (only immediate, temporary immunity).
  - Patients with a clean or minor wound who have had >3 tetanus vaccinations and a booster within the past 10 years do not require an additional vaccine booster.

Clostridium tetani
Management (cont.)

- **Active tetanus infection**
  - For those who become ill from tetanus, intensive care is often required for a few weeks. Patients with respiratory or laryngeal muscle spasms often require intubation and mechanical ventilation. Limited sensory stimulation is recommended to prevent spasms from occurring (eg, dark, quiet room). Muscle relaxants, such as benzodiazepines and neuromuscular blocking agents, can be used to treat muscle spasms.
  - If present, an infected wound should be debrided and antibiotics should be started. Metronidazole or penicillin G are the preferred antibiotics, usually for 7-10 days. **Human tetanus immunoglobulin** can bind residual circulating toxin to prevent further neurological progression and should be administered; however, it cannot reverse the effects of already-bound toxin.

Tetanus prophylaxis		
	Clean/minor wound	**Dirty/severe wound**
≥3 tetanus toxoid doses	• Tetanus toxoid–containing vaccine* only if last dose ≥10 years ago • **No** TIG	• Tetanus toxoid–containing vaccine* only if last dose ≥5 years ago • **No** TIG
Unimmunized, uncertain, or <3 tetanus toxoid doses	• Tetanus toxoid–containing vaccine* only • **No** TIG	• Tetanus toxoid–containing vaccine* **PLUS** • TIG
*Booster given as tetanus/diphtheria (Td) toxoids adsorbed or tetanus toxoid/reduced diphtheria toxoid/acellular pertussis (Tdap). **TIG** = tetanus immune globulin.		

Summary

Tetanus	
Cause	• *Clostridium tetani* spores inoculate skin wound → germinate → produce tetanus toxin → retrograde axonal transport to CNS → blocks inhibitory interneurons • Risk: incomplete childhood vaccines or lack of 10-year booster shot
Symptoms	• Trismus (lockjaw) & difficulty swallowing • Intermittent intense muscular spasms • Opisthotonos (extremely arched back) • Risus sardonicus (facial muscle spasm while smiling)
Prevention	• Tetanus toxoid vaccination

Clostridium botulinum
Introduction

- **Bacterial Characteristics:**
  - **Gram-positive, anaerobic, spore-forming bacillus** (Botulus = Latin for sausage)
  - Synthesizes botulinum toxin, a highly potent toxin that can be lethal in small quantities
  - **Eight toxin serotypes**: A, B, C_1, C_2, D, E, F, G
  - **Human disease**: Types A, B, E, F

  - **Environmental distribution**: Soil, marine sediments, dust

Clostridium botulinum
Introduction (cont.)

- **Botulinum Toxin Properties:**
  - **Most potent biological toxin** known to humans
  - **Heat-labile**: Destroyed by cooking (120°C for 5 min)
  - **Mechanism**: Destruction of SNARE proteins
  - **Target**: Presynaptic nerve terminals

- The anaerobic environment within certain foods that are fermented, preserved, or canned at home (where improper processing can lead to contamination by viable *C botulinum* spores) allows for germination and growth of the organism.

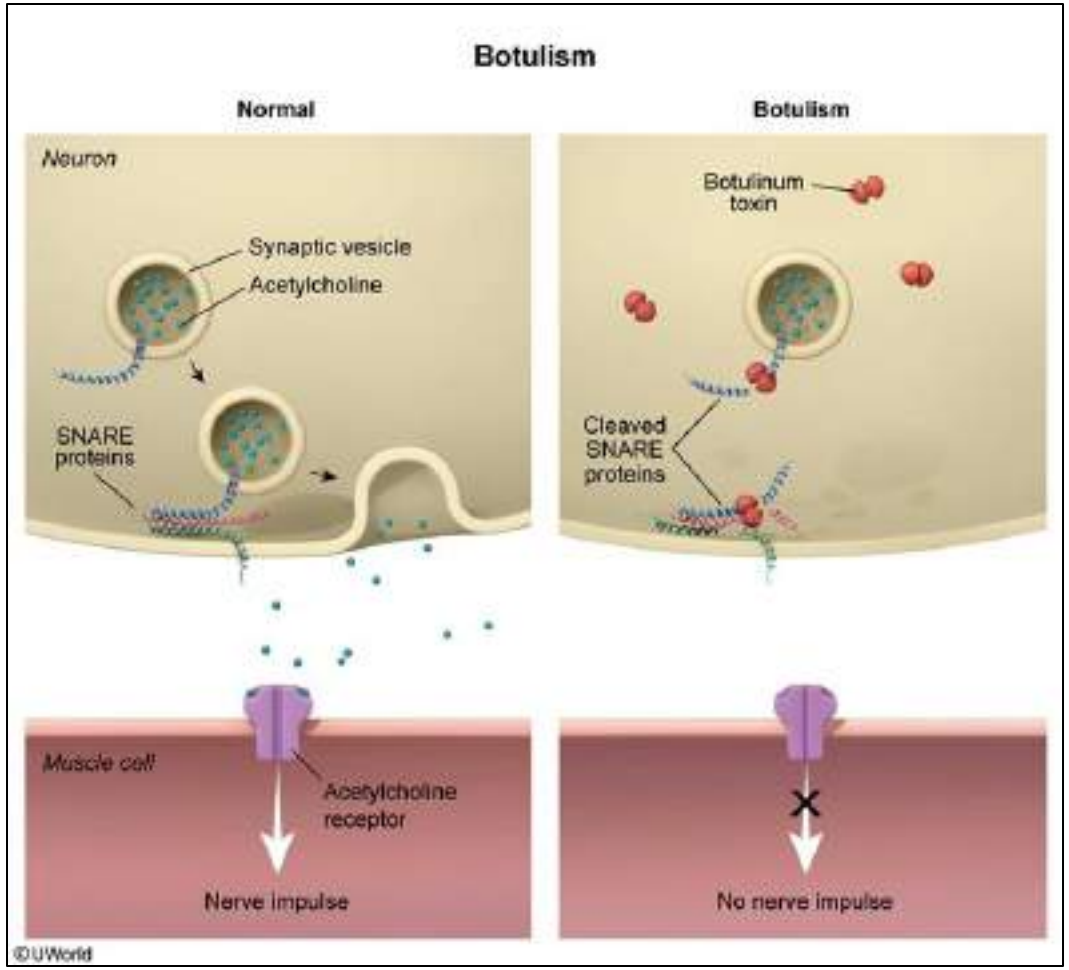
Clostridium botulinum
Botulinum Toxin

Normal vs. Botulism:

- **Normal:** Ca^{2+} influx → SNARE protein fusion → ACh vesicle release
- **Botulism:** Toxin cleaves SNARE proteins → blocks vesicle fusion

Clinical Result:

- **Complete blockade** of acetylcholine release
- **Affects both:** Nicotinic (skeletal muscle) and muscarinic (autonomic) receptors



Clostridium botulinum
Common types of botulism

- **Infant botulism**: most common type, accounting for 75% of cases. Although it has classically been associated with the ingestion of raw honey, most cases occur from the ingestion of dust/soil. Infants have an immature digestive system that allows for spore germination, which causes *C botulinum* to colonize the gastrointestinal tract and produce **botulinum toxin in situ**.
- **Foodborne botulism**: This type occurs due to ingestion of contaminated food that has **preformed botulinum toxin** in it. It usually occurs through the consumption of fermented/aged foods (particularly seafood) or foods canned at home.
- **Wound botulism**: *C botulinum* can infect wounds (typically deep puncture wounds. The bacteria can replicate within the wound, which may provide an ideal anaerobic environment, and subsequently **release the toxin**.

Clostridium botulinum
General presentation

- Bilateral cranial nerve deficits leading to oculobulbar weakness, including oculomotor (CN III), trochlear (CN IV), and abducens (CN VI) nerves, causing ophthalmoplegia, ptosis, or mydriasis; facial nerve (CN VII), causing facial weakness; and/or glossopharyngeal (CN IX) and vagus (CN X), causing dysphagia or suppressed gag
- Symmetric descending weakness with progression from the upper extremities to the lower extremities
- Autonomic dysfunction (eg, constipation, urinary retention, and/or dry mouth)
- Respiratory compromise from involvement of the diaphragm, sometimes requiring mechanical ventilation

Infant botulism	
Pathogenesis	• Ingestion of *Clostridium botulinum* spores (eg, environmental dust/soil, honey) • Spores colonize the immature gastrointestinal tract & produce toxin • Toxin inhibits presynaptic acetylcholine release
Clinical presentation	• Age <12 months • Constipation, poor feeding, hypotonia ("Floppy baby syndrome") • Oculobulbar palsies (eg, absent gag reflex, ptosis) • Symmetric descending paralysis: Upper → lower extremities • Autonomic dysfunction (eg, decreased salivation, fluctuating HR/BP)
Diagnosis	• Clinical; supported by abnormal EMG findings (eg, ↓ CMAP) • Confirmation by stool *C botulinum* spores or toxins
Treatment	• Antitoxin therapy (botulism immunoglobulin)
BP = blood pressure; **CMAP** = compound muscle action potential; **EMG** = electromyography; **HR** = heart rate.	

Foodborne botulism	
Pathogenesis	*Clostridium botulinum* toxin inhibits presynaptic acetylcholine release at neuromuscular junction
Sources	• Improperly canned foods (eg, fruits, vegetables) • Aged seafood (eg, cured fish)

Clinical features	Acute onset within 36 hr of ingestion
	• Bilateral cranial neuropathies
	  • Blurred vision, diplopia
	  • Facial weakness, dysarthria, dysphagia
	• Symmetric descending muscle weakness
	• Diaphragmatic weakness with respiratory failure

Diagnosis	Serum analysis for toxin
Treatment	Equine serum heptavalent botulinum antitoxin

Clostridium botulinum
Diagnosis

- The diagnosis can be difficult due to the rarity of the disease and its similarities to other neurologic conditions such as myasthenia gravis.
- Diagnosis is primarily clinical, based on history and physical examination findings
- CSF analysis and neuroimaging are obtained in many patients to rule out other disorders
- Electromyography may show a decrease in the compound muscle action potential (or electrical response of the muscle)
- Identification of spores or toxins from serum, stool, gastric aspirate, a suspected food source, or a wound is confirmatory.

Clostridium botulinum
Management

- Hospital admission in an intensive care setting with cardiopulmonary monitoring for respiratory failure
- Immediate intubation is required in patients with clinical or laboratory signs of impending respiratory failure
- The primary treatment for botulism is **antitoxin therapy**
  - Either botulism immunoglobulin for infant botulism or horse (equine) serum botulinum antitoxin for all other cases
  - Should be administered as soon as the diagnosis is suspected

Clostridium botulinum
Prognosis

- The prognosis for botulism varies depending on the severity of the disease.
- A full recovery is typical with early administration of botulism antitoxin.
- The antitoxin binds circulating neurotoxin and limits the progression of neurologic symptoms **but cannot reverse paralysis**.
- Because of the prolonged duration of action of botulinum toxin, hospitalization is often required for weeks to months as the initial weakness and paralysis slowly improve.

Clostridium botulinum
Prevention

- Botulism that occurs from contaminated food can be prevented by proper food handling and avoiding canned foods that show signs of damage.
- The spores can be destroyed at very high temperatures (120 C for 5 minutes), so disease can be prevented by thoroughly heating home canned food prior to consumption.
- Honey should also be avoided in children age <12 months to help prevent the occurrence of infant botulism.

Feature	Tetanus	Botulism
Causative organism	*Clostridium tetani*	*Clostridium botulinum*
Source of toxin	Toxin produced **in vivo** at the wound site	Toxin may be **preformed in food** (foodborne) or produced **in vivo** (infant/wound botulism)
Mode of acquisition	Contaminated wounds (soil, feces, saliva)	Ingestion (foodborne, infant) or wound contamination
Primary toxin	**Tetanospasmin**	**Botulinum toxin**
Toxin transport	Retrograde axonal transport to CNS	Acts **peripherally** at neuromuscular junction
Mechanism of action	Blocks release of **inhibitory neurotransmitters (GABA, glycine)** by cleaving synaptobrevin	Blocks release of **acetylcholine** by cleaving SNARE proteins
Effect on motor neurons	**Disinhibition → excessive firing**	**Complete inhibition → failure of transmission**
Type of paralysis	**Spastic paralysis**	**Flaccid paralysis**
Pattern of weakness	Muscle rigidity and painful spasms	**Symmetric descending weakness**
Early hallmark sign	**Trismus (lockjaw)**	**Cranial nerve palsies** (ptosis, diplopia, dysphagia)
Autonomic involvement	Common (labile BP, HR)	Common (dry mouth, constipation, urinary retention)
Diagnosis	Clinical	Clinical ± toxin/spore detection
Treatment	TIG + antibiotics + muscle relaxants + ICU care	Antitoxin + respiratory support
Prevention	**Vaccination (tetanus toxoid)**	Safe food handling; **avoid honey in infants**

Thank You