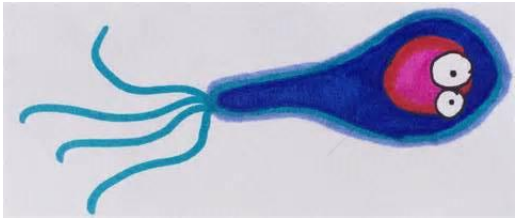
Clostredium tetani

Dr. Eman Albataineh

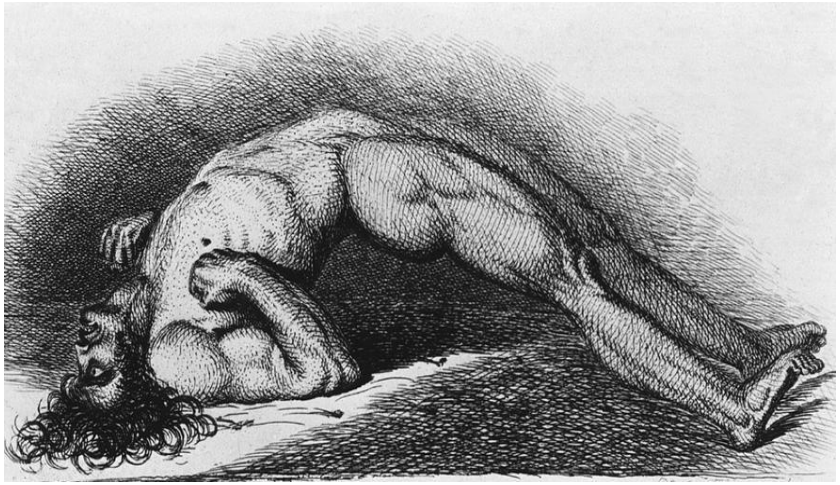
Mutah university

Faculty of Medicine



Introduction

- Tetanus: It is a serious infectious disease of the nervous system in which toxin causes severe prolonged contraction of skeletal muscle fibers



- "tetanus" comes from the Greek word meaning taut which means to stretch

- It is also called lockjaw

Introduction

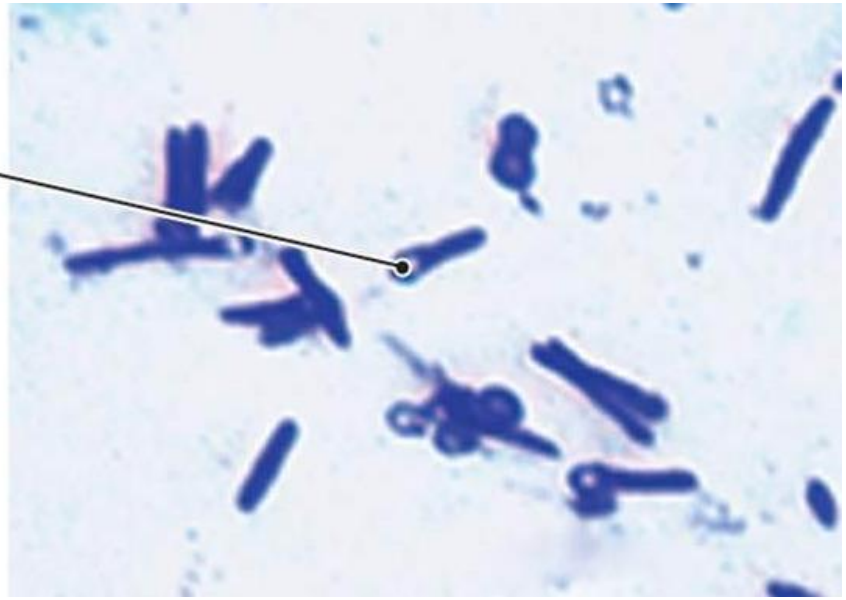
History of tetanus

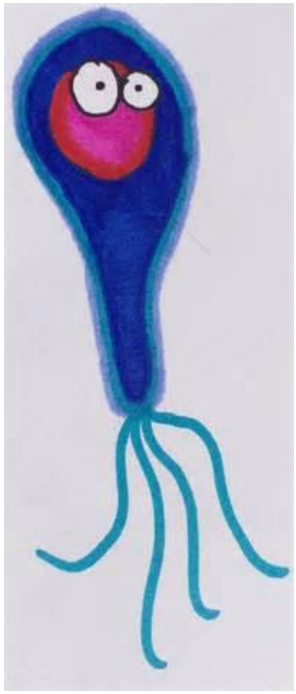
- Etiology: discovered in 1884 by Carle and Rattone
- In 1889, Kitasato isolated the organism from a human victim, showed that it produced disease when injected into animals, and reported that the toxin could be neutralized by specific antibodies
- Passive immunization used for treatment and prophylaxis during World War I
- Tetanus toxoid first widely used during World War II

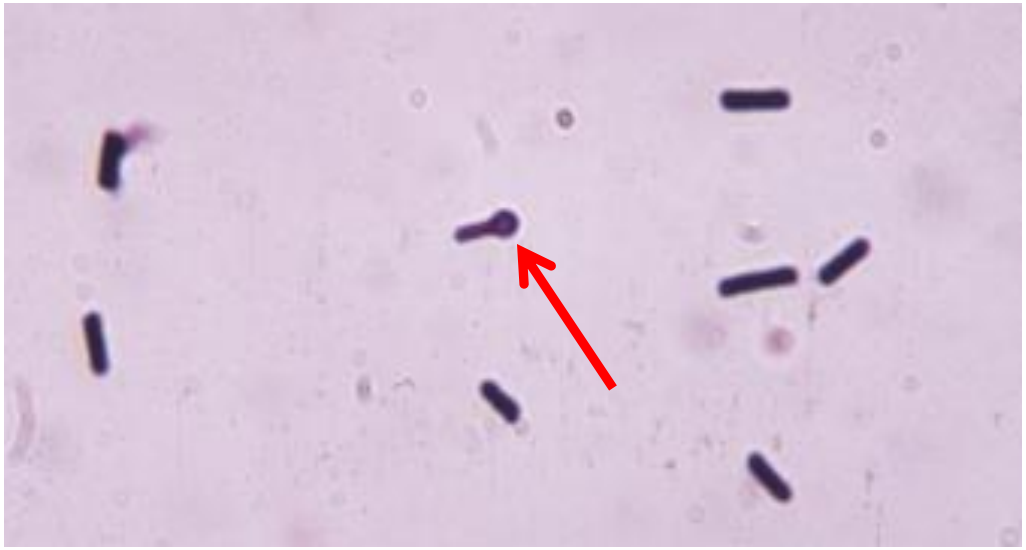
Giorgio Rattone

Kitasato

Microbiology of Clostridium tetani







Microbiology of Clostridium tetani

- *C. tetani* is a slender, gram-positive, anaerobic rod
- Develop a terminal spore, giving it a drumstick appearance.
- The organism is sensitive to heat and cannot survive in the presence of oxygen.
- The spores are very resistant to heat and the usual antiseptics. The spores are also relatively resistant to phenol and other chemical agents.
- The spores are widely distributed in soil and in the intestines and feces of horses, sheep, cattle, dogs, cats, rats, guinea pigs, and chickens. Manure-treated soil may contain large numbers of spores. In agricultural areas, a significant number of human adults may harbor the organism.

Epidemiology

Communicability

- Tetanus is not contagious from person to person.
- It is the only vaccine-preventable disease that is infectious but not contagious

Mode of Transmission

- Transmission is primarily by contaminated wounds
- The wound may be major or minor.
- Tetanus may follow elective surgery, burns, deep puncture wounds, crush wounds, otitis media (ear infections), dental infection, animal bites, and abortion

Toxins

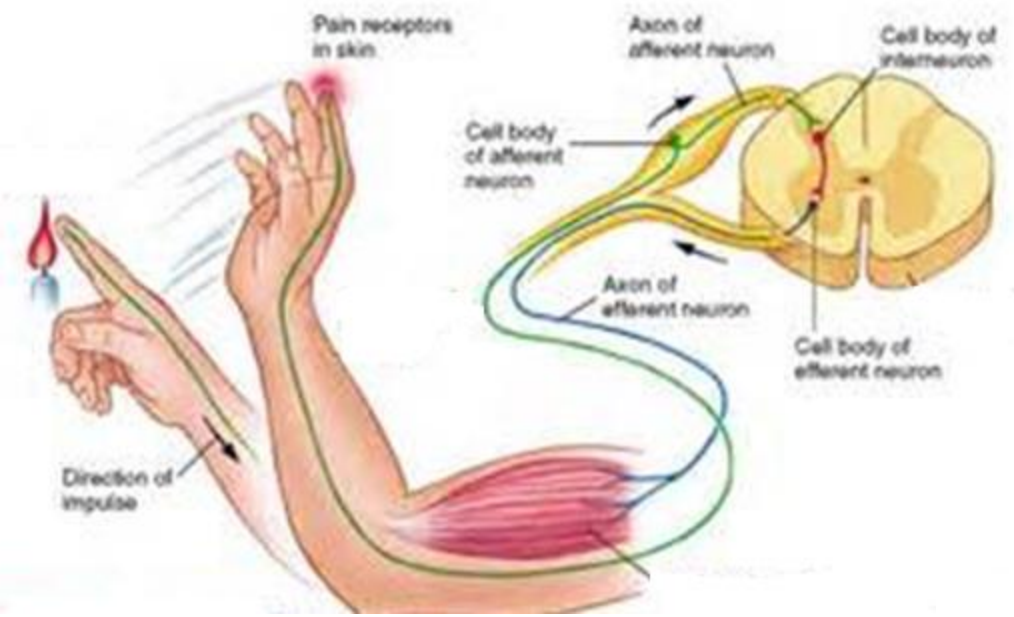
C. tetani produces two exotoxins:

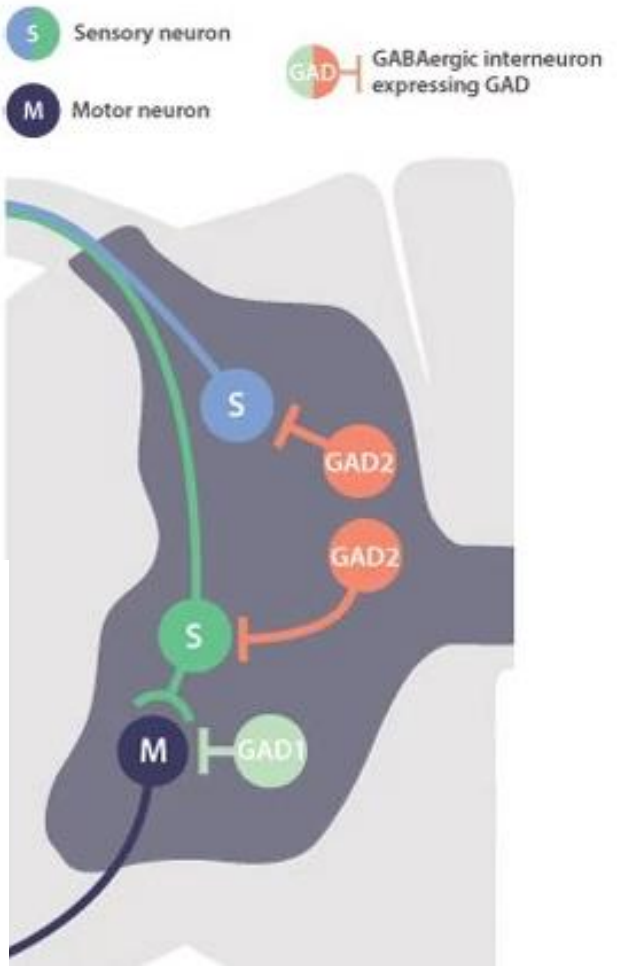
1. Tetanolysin: the function of tetanolysin is not known with certainty
2. Tetano- spasmin:
   - Is a neurotoxin and causes the clinical manifestations of tetanus.
   - It is one of the most potent toxins known.
   - The estimated minimum human lethal dose is 2.5 ng/ kilogram of body weight, or 175 ng for a 70-kg human

Pathogenesis

1. *C. tetani* usually enters the body through a wound.
2. In the presence of anaerobic (low oxygen) conditions, the spores germinate.
3. Toxins are produced and disseminated via blood and lymphatics.
4. Toxin is transported by intra-axonal transport to motor nuclei of the cranial nerves or ventral horns of the spinal cord
5. The toxin reaches the inhibitory interneurons which finally inhibits the release of inhibitory neurotransmitters
6. This leads to unopposed muscle contraction and spasm.

Pathogenesis



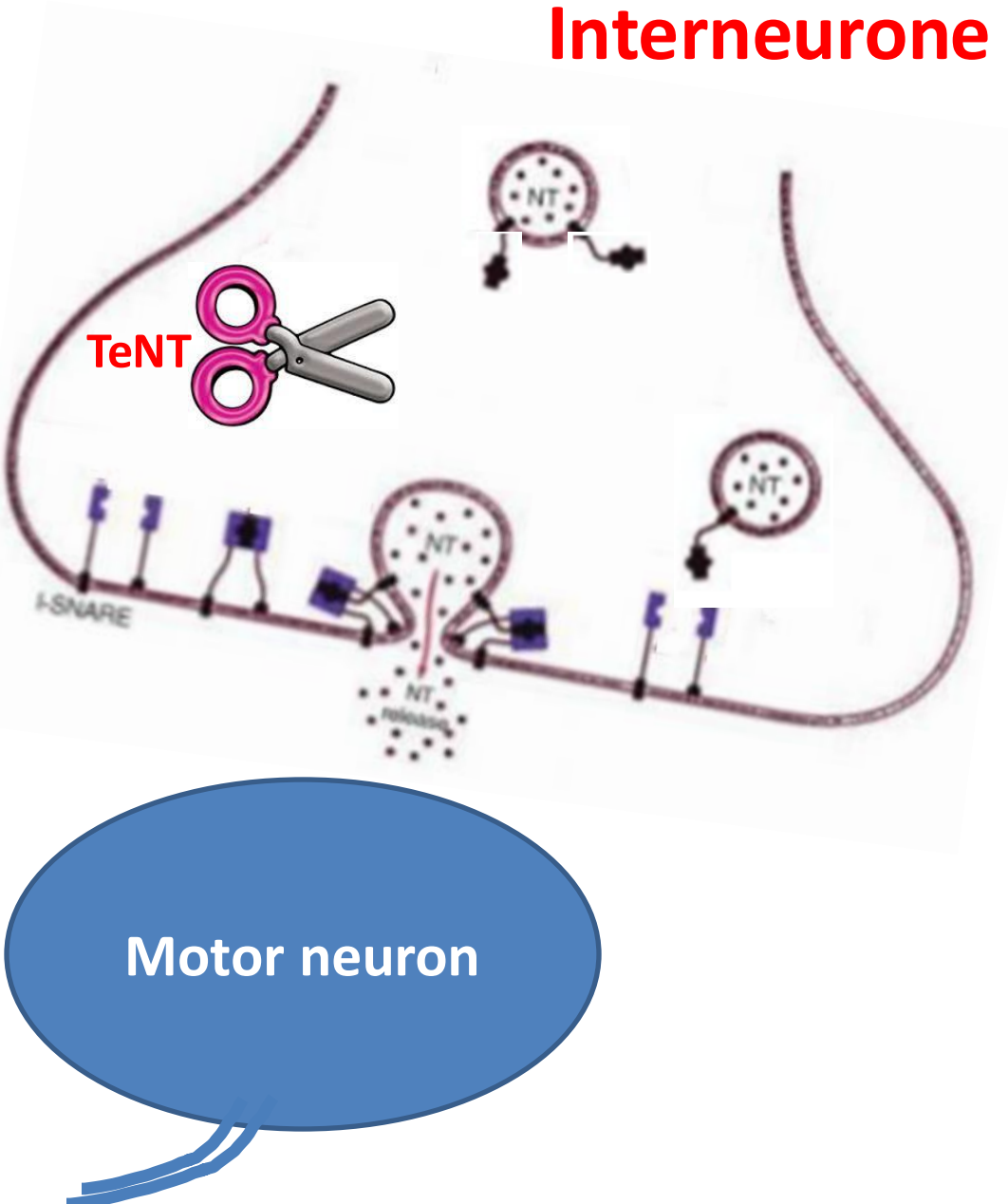


Muscle response to a stimulus: Contraction and relaxation
- inhibitory neurons release the neurotransmitter GABA, Most often, inhibitory neurons are also called GABAergic neurons for that reason, GABA release is inhibited by toxins

Pathogenesis

Once the toxin reaches the interneuron cytosole it will start Cleavaing of synaptobrevin. Synaptobrevin is a necessary for vesicle fusion to membranes

The cleavage of synaptobrevin is the final target of TeNT and even in low doses the tetanus toxin will inhibit neurotransmitter exocytosis in the inhibitory interneurons. The blockage of these neurotransmitters is what causes the physiological effects that accompany TeNT.



Pathogenesis

Tetanus toxin acts on inhibitory interneurons

- ✓ The CNS contains diverse classes of specialized inhibitory interneurons.
- ✓ Inhibitory interneurons have **Glutamic acid decarboxylase** (GAD2) enzyme which is a gamma amino butyric acid (GABA) synthesizing enzyme.

Pathogenesis

GABA mode of action

- GABA acts at inhibitory synapses in the brain by binding to specific transmembrane receptors in the plasma membrane of both pre- and postsynaptic neuronal processes

- This binding causes the opening of ion channels to allow the flow of either negatively charged chloride ions into the cell or positively charged potassium ions out of the cell.

- This action results in a negative change in the transmembrane potential, usually causing hyperpolarization **making it harder for the neuron to reach the threshold to fire an action potential, thereby causing 'inhibition'**

Clinical Features

The incubation period:

- Ranges from 3 to 21 days, usually about 8 days
- In neonatal tetanus, symptoms usually appear from 4 to 14 days after birth, averaging about 7 days

Tetanus has tow different forms based on the clinical findings:

1. Local (including cephalic).
2. Generalized (including neonatal).

Forms of tetanus

Local tetanus:

- Is an uncommon form of the disease, in which patients have persistent contraction of muscles in the same anatomic area (at the sit of injury)
- These contractions may persist for many weeks before gradually subsiding.
- Local tetanus may precede the onset of generalized tetanus.
- Only about 1% of cases are fatal.

Forms of tetanus

Cephalic tetanus:

- Is a rare form of the disease
- Occasionally occurring with otitis media (ear infections or following injuries to the head
- There is involvement of the cranial nerves, especially in the facial area.
- If the cranial nerves are involved in localized cephalic tetanus, the phargyngeal or laryngeal muscles may spasm, with consequent aspiration or airway obstruction, and the prognosis may be poor.

Forms of tetanus

Generalized tetanus

- The most common type (about 80% of reported tetanus)
- The first sign is trismus or lockjaw, followed by stiffness of the neck, difficulty in swallowing, and rigidity of abdominal muscles.
- Other symptoms include elevated temperature, sweating, elevated blood pressure, and episodic rapid heart rate.
- Spasms may occur frequently and last for several minutes. Complete recovery may take months.

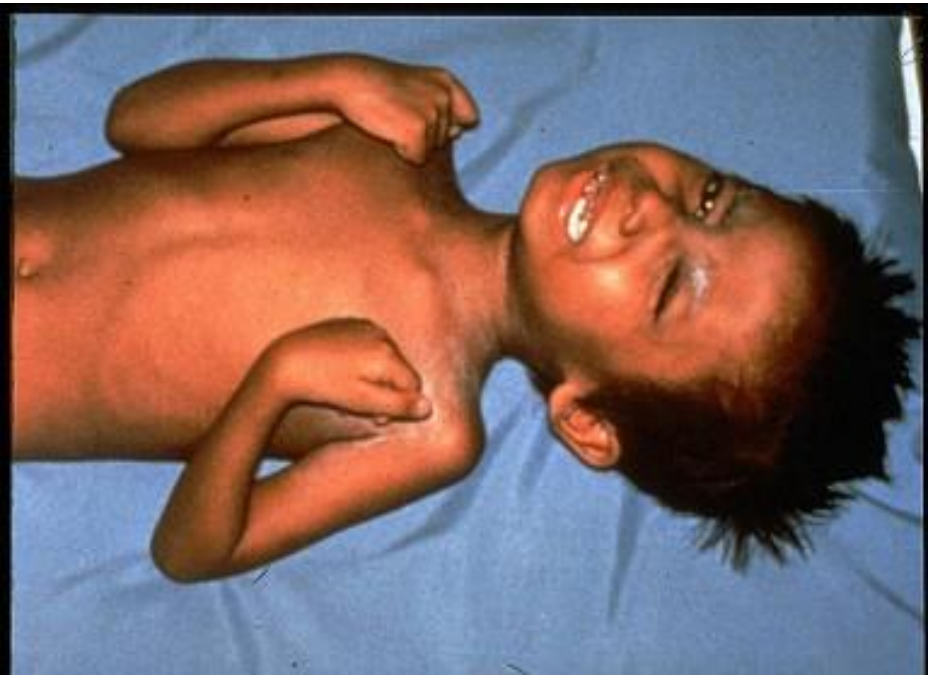
Forms of tetanus

Neonatal tetanus (NT)

- Is a form of generalized tetanus that occurs in newborn infants.
- Neonatal tetanus occurs in infants born without protective passive immunity, because the mother is not immune
- It usually occurs through infection of the unhealed umbilical stump, particularly when the stump is cut with an unsterile instrument
- Neonatal tetanus is common in some developing countries but very rare in the United States.

Clinical Features

Generalized tetanus



Neonatal tetanus (NT)

Complications

- Laryngospasm (spasm of the vocal cords) and/or spasm of the muscles of respiration leads to interference with breathing.
- Fractures of the spine or long bones may result from sustained contractions and convulsions.
- Hyperactivity of the autonomic nervous system may lead to hypertension and/or an abnormal heart rhythm.
- Cases most likely to be fatal are those occurring in persons 60 years of age and older (18%), and unvaccinated persons (22%).

Diagnosis

The diagnosis of generalized tetanus is usually made by observing the clinical presentation and a combination of the following:

- History of a recent injury resulting in skin breakage (only 70% of cases have an identified injury)
- Incomplete tetanus immunizations
- Progressive muscle spasms (starting in the facial region, especially lockjaw and progressing outward from the face to include all muscles of the body)
- Fever
- Changes in blood pressure (especially high blood pressure)
- Irregular heartbeat

Diagnosis

- Neonates show signs of being generally irritable, muscle spasms, and poor ability to take in liquids (poor sucking response), usually seen in neonates about 7-10 days old.
- Laboratory tests are rarely used to diagnose tetanus.

Medical treatment of tetanus

Medical treatment has two aims:

1. limit growth and eventually kill the infecting *C. tetani* and thus eliminate toxin production
2. To neutralize any toxin that is formed.

If the toxin has already affected the patient, the two aims are still important, but supportive measures will be needed for the patient.

Treatment of tetanus

A. Antibiotics for example, metronidazole, penicillin G or doxycycline to kill the bacteria

B. Antitoxin (termed tetanus immune globulin or TIG) to neutralize the toxin

Medical treatment of tetanus

C. Wound cleansing to remove any obvious bacteria collections (abscesses) or foreign bodies; if the patient is exhibiting any toxin-related problems, TIG is usually administered first and wound care is delayed for a few hours while the TIG neutralizes toxin because infected wounds, when manipulated, may release more toxin

D. Supportive measures

E. Pain medicine as needed

F. sedative such as diazepam (Valium) to control muscle spasms and muscle relaxants

G. Ventilator support to help with breathing in the event of spasms of the vocal cords or the respiratory muscles

H. IV rehydration because, as muscles spasm constantly, increased metabolic demands are placed on the body

Medical Management

Tetanus immune globulin (TIG)

Dosage and Administration

A. Adults prophylactic dose:

- IM 250 units. Give 500 units if wounds are severe or treatment is delayed. Dosage may be increased to 1,000 to 2,000 units.

B. For therapy of tetanus:

- give 3,000 or 6,000 units.
- Give deep IM, preferably in upper outer quadrant of gluteal muscle.

- **Children** IM Dose is calculated on basis of body weight (4 units/kg); however, it may be advisable to administer 250 units regardless of the size of the child.

Tetanus toxoid

Tetanus toxoid is available combined with diphtheria toxoid as

1. Pediatric diphtheria-tetanus toxoid (DT) or
2. Adult tetanus-diphtheria (Td),
3. And with both diphtheria toxoid and acellular pertussis vaccine as DTaP.

Tetanus toxoid

- Pediatric formulations (DT and DTaP) contain a similar amount of tetanus toxoid as adult Td, but contain 3 to 4 times as much diphtheria toxoid.

- Children younger than 7 years of age should receive either DTaP or pediatric DT. Persons 7 years of age or older should receive the adult formulation (adult Td), even if they have not completed a series of DTaP or pediatric DT.

When to Seek Medical Care

When to go to the nearest hospital's emergency department immediately

- If the wound is large, contains crushed tissues, or is heavily contaminated
- If individuals have a recent injury and are starting to experience muscle cramps or spasms at or near the injury
- If individuals have trouble swallowing or have muscle spasms in the facial muscles

Tetanus Prognosis

- Overall, about 25%-50% of people with generalized tetanus will die.
- Older people and very young children tend to have more severe cases; those over 65 years are more likely to die from the infection.
- Intensive medical care improves the prognosis in severe cases.
- Death is usually due to respiratory failure or disturbance of heart rhythm.

Case Study

- A 4-year-old boy presented to hospital with a one-week history of general malaise, indolence, and progressive anorexia.
- Three days prior to presentation at the hospital he had started to refuse all food and fluids, accompanied by a progressive dysphagia, sore throat and sialorrhoea.
- Subsequently, the boy demonstrated increased difficulties with opening his mouth and experienced a progressive dehydration. Due to the parents' concern about the refusal of fluids and dehydration, a pediatrician was consulted.

History

- The history revealed that the boy had recently injured his left big toe. This had resulted in a small local hematoma and loose toenail.
- There were no recorded insect or animal bites

On physical examination

- The paediatrician saw an afebrile, irritable and anxious boy gently playing at the table, with trismus and mild dehydration.
- After being asked to walk, he showed muscle spasms of the back and thighs evidently worsening during examination.
- There was no cervical lymphadenopathy and the ear and nose examination was unremarkable.
- Inspection of the oropharynx was not possible due to trismus.

Case Study

- Tendon reflexes were normal, there was no meningeal irritation.The heart rate was slightly increased, the blood pressure was normal and further clinical examination was unremarkable

Diagnosis

- Based on normal complete blood cell count and chemistry profiles, immunization status and the presence of generalized muscle spasms and a possible portal of entry, the working diagnosis 'generalized tetanus' was established.

Treatment

- Treatment was initiated immediately with the administration of anti-tetanus immunoglobulins (3000 IU i.m.) and amoxicillin (100 mg/kg i.v.).
- In order to prevent respiratory failure, the boy was intubated and mechanical ventilation was started. Thereafter the boy was transferred to the pediatric intensive care unit (PICU) for further treatment
- On the second day of admittance, surgical debridement of the left toenail was performed.
- Active immunization against diphteria, tetanus and polio (DTP) was started after one week

Clostridium botulinium

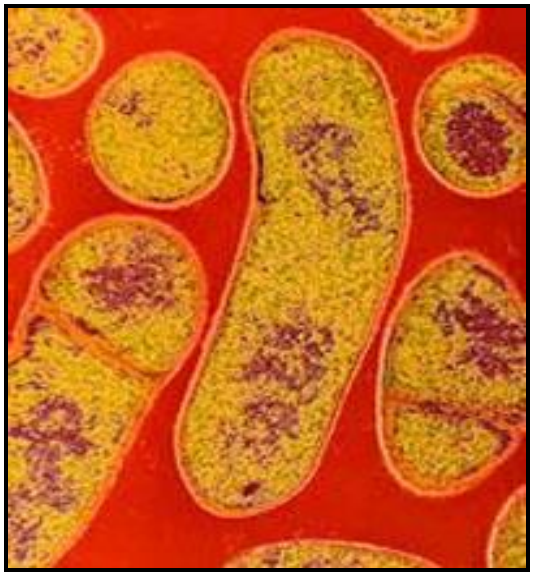
Dr. Eman Albataineh

Mutah university

Faculty of Medicine

Clostridium botulinium

Introduction



Special identification features

- Rod-shaped, Gram positive, obligate anaerobic,
- Spore-forming. (Botulus = Latin for sausage)

Distribution

- Ubiquitous
- Commonly found in soil and marine sediments throughout the world
- Since it is found in the soil, it may contaminate vegetables

Specific conditions for germination

- An anaerobic atmosphere
- Mild alkalinity (provided by vegetables as green beans, and mushroom)
- Low salt and sugar concentrations

Clostridium botulinium

Botulinium toxins

- Seven different types of neurotoxins: A to G
- Four of these (types A, B, E and rarely F) cause human botulism. Types C, D and E cause illness in other mammals, birds and fish.
- All cause flaccid paralysis
- Only a few nanograms can cause illness
- The most lethal known toxin
- Destroyed by boiling

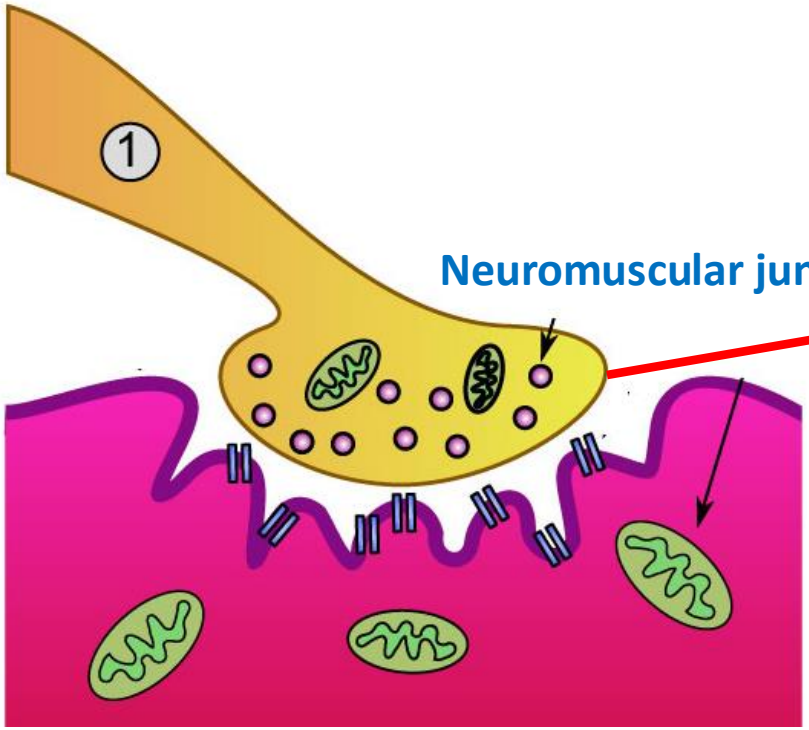
Mode of action

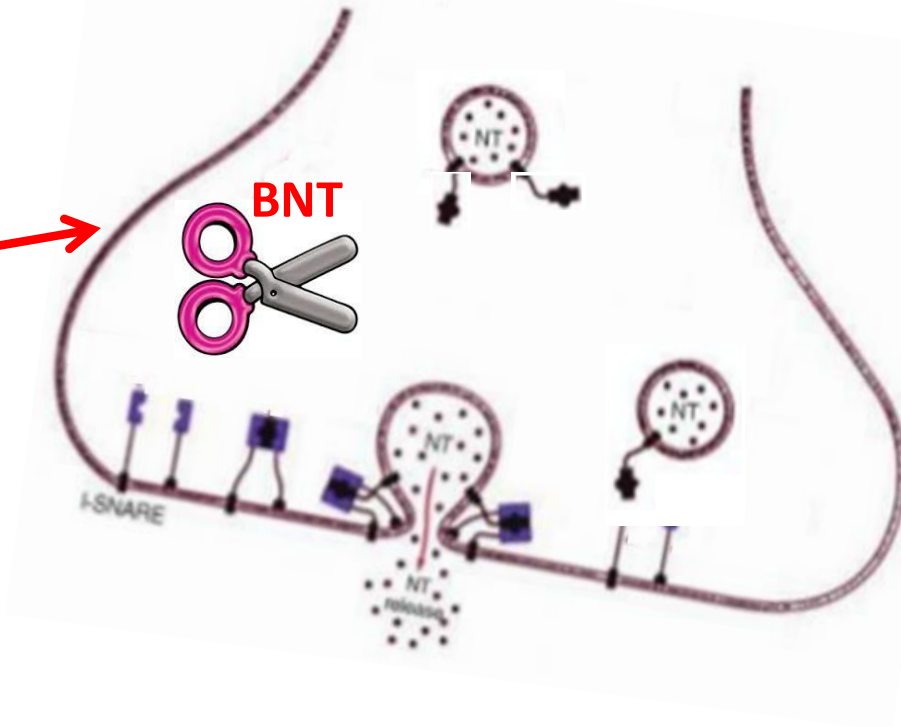
Neurotoxin production > stomach absorption > circulation > Neuromuscular junction (NMJ) > inhibition of acetylcholine release at the neuromuscular junction > flaccid descending motor paralysis

Clostridium botulinium

Mode of action

to peripheral cholinergic nerve terminals,





Whether ingested, inhaled, or produced in the intestine or a wound, botulinum neurotoxin enters the vascular system and is transported to peripheral cholinergic nerve terminals, including neuromuscular junctions, postganglionic parasympathetic nerve endings, and peripheral ganglia. The central nervous system probably is not involved

Syndromes of Botulism

Botulism occurs naturally as four syndromes:

1. food-borne botulism due to ingestion of toxin in contaminated food
2. Infant botulism due to colonization of the infant intestine by toxigenic clostridia with in situ toxin production
3. Wound botulism due to wound colonization by toxigenic clostridia with in situ toxin production
4. Adult intestinal toxemia botulism, a rare form of colonization with similarities to infant botulism.

Syndromes of Botulism

Botulinum toxin is the most toxic substance known. Botulism occurs naturally as four syndromes:

1. food-borne botulism due to ingestion of toxin in contaminated food:

- Foodborne botulism occurs when *C. botulinum* grows and produces toxins in food prior to consumption
- Most common from Home-canned foods with a low acid content, improperly canned commercial foods, fermented fish, herb-infused oils, foods held warm for extended periods of time

Food-borne Botulism

Signs and Symptoms

- Onset : 18 to 36 hours after exposure (range, 6 hours to 8 days)
- Early: nausea, vomiting, weakness, dizziness but no fever
- Late: double vision, difficulty in swallowing and speaking
- In severe cases, death due to respiratory muscle paralysis

Prevention

- Inspect canned food for
  - Bulging
  - Loose lids
  - Mold
  - Odor
- Proper home canning procedures:
  - Hygiene
  - Time schedule,
  - Proper processing method
  - Equipment
- Avoiding home canning or cheaply produced commercial food

Syndromes of Botulism

2- Infant botulism

- Infant botulism results from absorption of toxin produced in situ by toxigenic clostridia colonizing the intestine of Infants < 1 year old (94% < 6 months old)
- Colonization is believed to occur because the normal bowel flora is not yet fully established; this theory is supported by studies in animals
- Spores from varied sources (Honey, food, dust, corn syrup)
- Germinate then toxin released
- Death if not treated

Infant Botulism

Signs and Symptoms

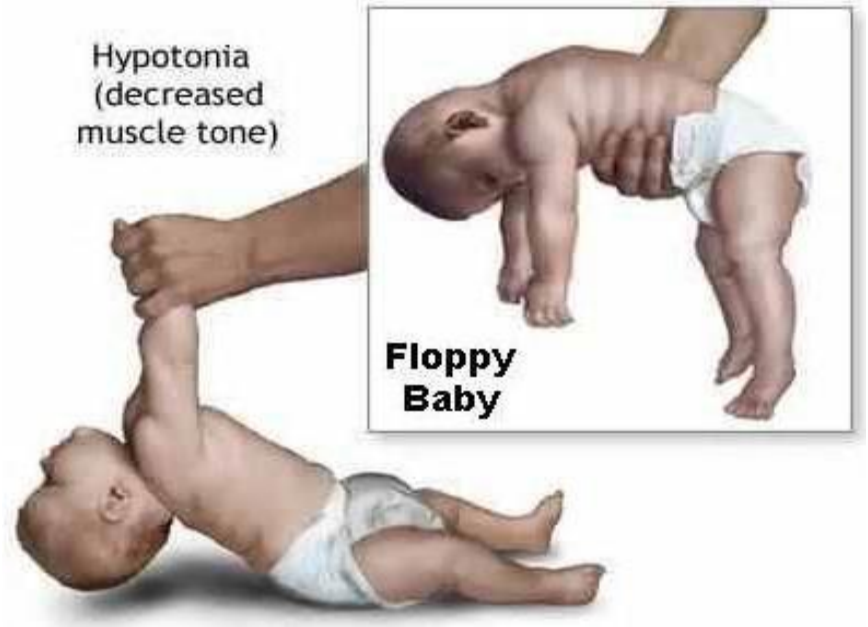
- The first clinical sign is usually constipation
- No fever
- Poor feeding (weak sucking)
- Weak cry
- Decreased movement
- Appearing lethargic
- Trouble swallowing
- Excessive drooling
- Muscle weakness
- Breathing problems
- Ptosis (Drooping eyelids)
- Poor head control
- Decreased anal sphincter tone
- Decreased deep tendon reflexes

Treatment and Recovery

- With early detection, proper treatment, no long term effects observed
- New drug: BabyBIG®, Botulism Immune Globulin Intravenous (Human) (BIG-IV)
- IV feeding and hospital stay

Syndromes of Botulism

Infant botulism



Syndromes of Botulism

3. Wound botulism

- Wound botulism is rare
- Caused by contamination of wounds with C. botulinum spores, subsequent spore germination, and toxin production in an abscess.
- The symptoms are similar to the foodborne botulism, but may take up to 2 weeks to appear.
- This form of the disease has been associated with substance abuse, particularly when injecting black tar heroin.

Syndromes of Botulism

4. Adult intestinal toxemia botulism:

- Results from absorption of toxin produced in situ after rarely occurring intestinal colonization with toxigenic clostridia.
- Why?

  Typically, patients have some anatomic or functional bowel abnormality or have recently used antibiotics that may help normally fastidious Clostridium species to compete the bowel flora.
- Despite antitoxin treatment, prolonged symptoms or relapse due to ongoing intraluminal production of toxin may be observed.

Diagnosis

- **The initial diagnosis should be made on the basis of history and physical findings**
- **Diagnosis of the different types of botulism:**

1- In suspected food-borne botulism:

- A 3- to 5-day food history should be obtained, with specific questions about home-canned, exotic, and unusual foods.
- The names of contacts who may have shared foods should be obtained early in case the patient's illness progresses to respiratory failure.

Diagnosis

2- In wound botulism:

- Material from abscesses should be collected in anaerobic culture tubes for testing at public health laboratories, and serum samples should be collected

3- Diagnosis of adult intestinal toxemia botulism:

- Requires the demonstration of excreted organisms and toxin in the stool

Diagnosis

- **Differential diagnosis**

1. Guillain-Barré syndrome (GBS)
2. Myasthenia gravis
3. Stroke syndromes
4. Eaton-Lambert syndrome
5. Tick paralysis.
6. Less likely are poisoning by shellfish and antimicrobial drug–associated paralysis.

Treatment

- The cornerstones of treatment for botulism are thorough intensive care and immediate administration of botulinum antitoxin.
- In wound botulism, suspect wounds and abscesses should be cleaned, debrided, and drained promptly.
- *C. botulinum* is susceptible to penicillins and various other antimicrobial agents.

Clostridium botulinium

✓ Treatment:

- Gastric wash
- Antitoxin (A, B, E)
- Supportive: ICU and respiratory support, wound cleaning and debridement

✓ Prevention:

- Proper cooking and heating of food
- Avoid suspicious canned food
- Proper processing, preservation and canning of food
- Vaccine

Case Study: Botulism

Case Presentation

- Sarah, a twenty-one year old student at a University and had spent a day with here grandparents . During her drive back to campus on Friday morning her vision became blurry, and she was forced to pull over to the side of the road. As she sat in her car, her vision worsened. She opened the car hood in hope of attracting aid and tried to relax. In a short time, a highway patrol officer pulled over and approached Sarah. By this time, Sarah was having trouble swallowing and speaking clearly. The officer helped Sarah to his car and rushed her to the emergency room at a nearby hospital.

Case Study: Botulism

- In the ER, Sarah was able to describe her symptoms to a physician. The physician made note of what Sarah had eaten during the last 24 hours and was especially interested in the fact that Sarah's grandmother canned all of her own vegetables. The physician observed that Sarah's breathing was becoming labored. She ordered Sarah's blood sampled, her gastrointestinal tract pumped, and a mechanical respirator prepared for use. Fearing that Sarah suffered from a case of botulism, she asked that Sarah's grandparents be contacted and samples of the meal retained, if possible, and sent to a local clinic for analysis.