CNS II
Microbiology Lecture VI

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Infections of the peripheral nervous system

- Poliovirus infection
- Tetanus
- Botulism
- Tick paralysis
- Leprosy (Hansen's Disease)
- Guillain-Barre syndrome

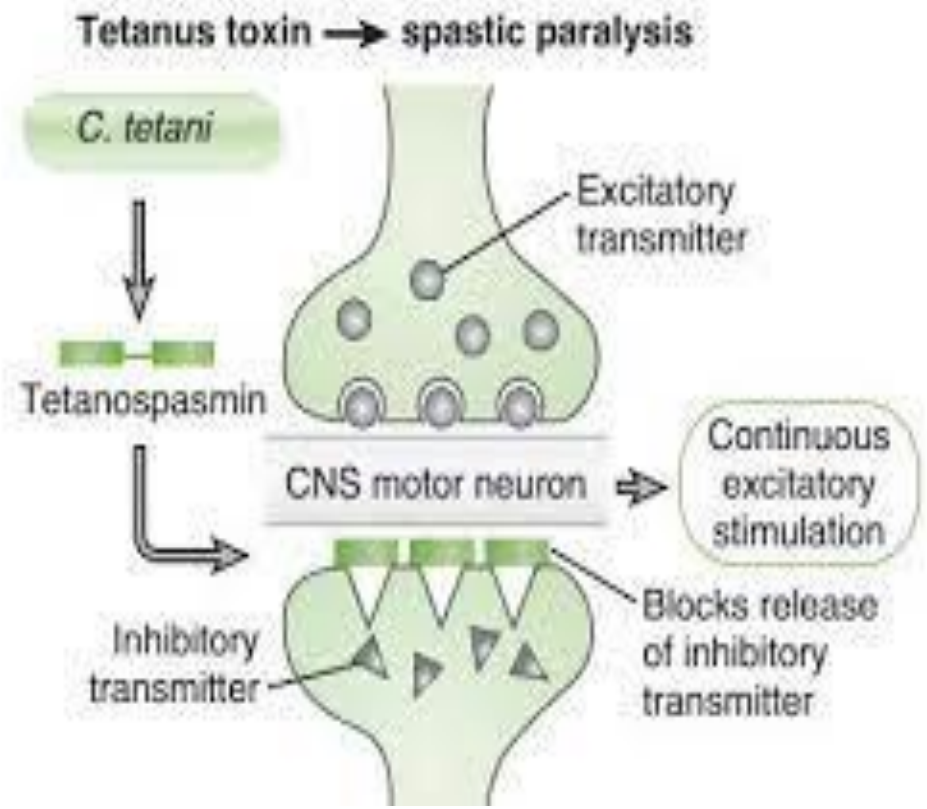
Tetanus

- Tetanus is an infection characterized by an acute onset of hypertonia, painful muscular contractions (usually of the muscles of the jaw and neck), and generalized muscle spasms without other apparent medical causes.
- *Tetanus is caused by Clostridium tetani*. *C. tetani* is an obligate, **anaerobic**, motile, gram-positive bacillus. It is nonencapsulated and forms spores that are resistant to heat, desiccation, and disinfectants. These spores are found in soil, house dust, animal intestines, and human feces and can persist in normal tissue for years.

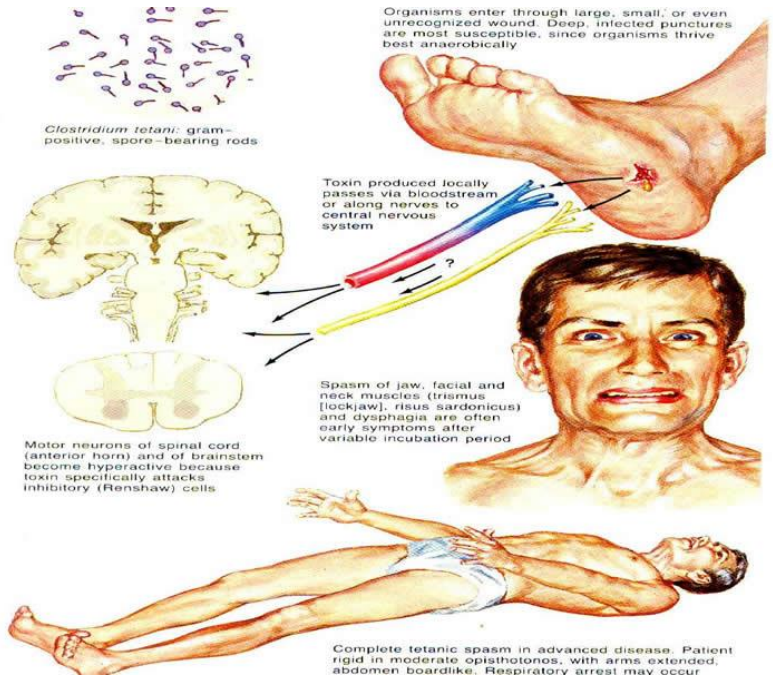
Pathogenesis

- *C. tetani* produce tetanus toxin (tetanospasmin) that is responsible for all the clinical manifestations of tetanus. Tetanospasmin is one of the most potent toxins known.
- The source of infection:
  - Wound (65% of cases) from wood or metal splinters or thorns.
  - Chronic skin ulcers (5% of cases)
  - In the remainder of cases, no obvious source can be identified.

- Tetanospasmin is elaborated at the site of infection and enters the presynaptic terminals of lower motor neurons, reaching the central nervous system (CNS) mainly by exploiting the retrograde axonal transport system in the nerves.
- When the toxin reaches the spinal cord, it enters central inhibitory neurons. Tetanus toxin degrades a protein required for neurotransmitter release from vesicles at the appropriate site on presynaptic membranes. As a result, gamma-aminobutyric acid (GABA) and glycine containing vesicles are **not** released, and there is a loss of inhibitory action on motor and autonomic neurons.



- The diagnosis is clinical; neither culture nor toxin testing is useful.
- The masseter muscles are often the first to be affected, resulting in inability to open the mouth properly (**trismus**); this effect accounts for the term lock-jaw. As other muscles become affected, intermittent spasms can become generalized to include muscles of respiration and swallowing.
- In extreme cases, massive contractions of the back muscles (**opisthotonos**) develop



Prognosis

- Untreated patients with tetanus retain consciousness, however, any small stimulus can trigger massive contractions.
- In fatal cases, death results from exhaustion and respiratory failure.
- Untreated, the mortality rate caused by the generalized disease varies from 15% to more than 60%, according to the lesion, incubation period, and age of the patient.
- Mortality is highest in neonates and in elderly patients.

Treatment

- Passive immunization with human **tetanus immunoglobulin** (TIG) shortens the course of tetanus and may lessen its severity.
- Other treatment measures include ventilatory support, nutritional support, and pharmacologic agents that treat reflex muscle spasms, rigidity, tetanic seizures and infections.
- Patients usually survive tetanus and return to their pre-disease state of health. However, recovery is slow and usually occurs over 2-4 months.

Prevention

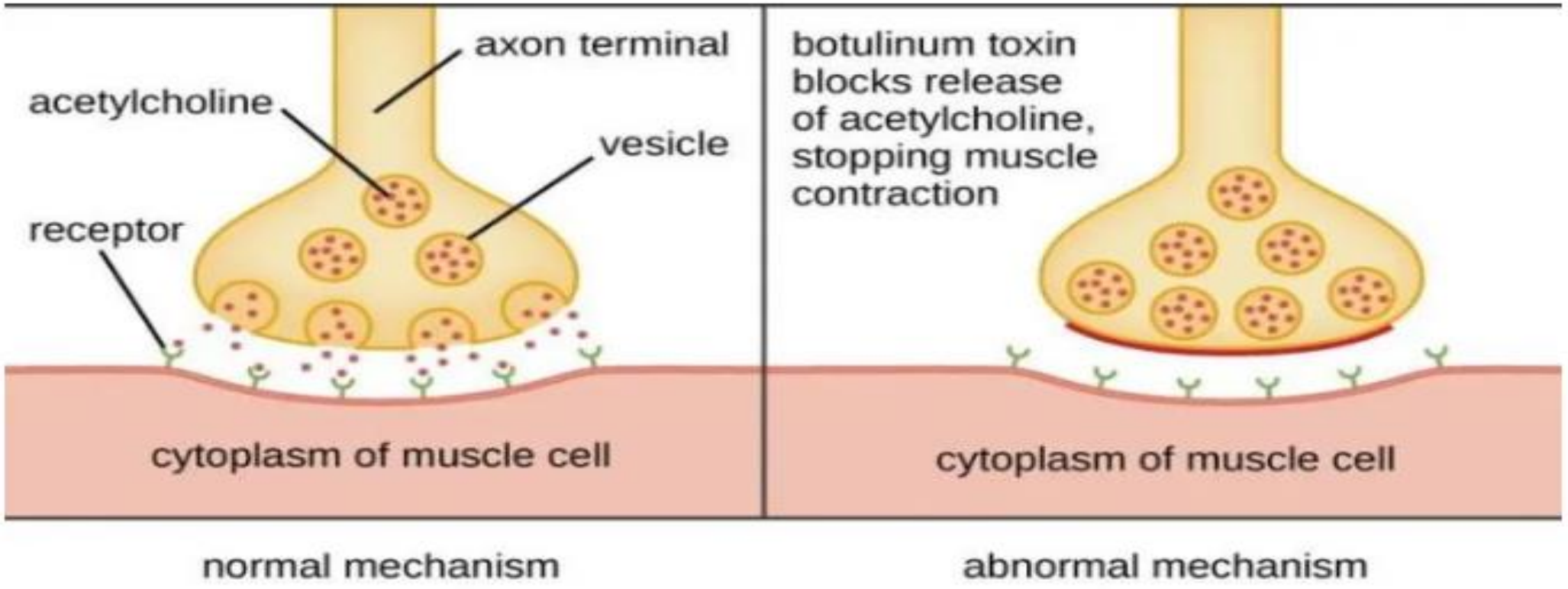
- Prevention of tetanus is accomplished through vaccination with **DTP** at the ages of 2 months, 4 months, 6 months, 12-18 months, and 4-6 years.
- Secondary prevention of tetanus is accomplished after exposure through appropriate wound cleansing and debridement and the administration of tetanus toxoid (vaccine) and TIG (as prophylaxis), when indicated.
- The toxin is heat-labile, antigenic, readily neutralized by antitoxin, and rapidly destroyed by intestinal proteases. Treatment with formaldehyde yields a nontoxic product or toxoid that retains the antigenicity of toxin and thus stimulates the production of antitoxin.

Botulism

- Botulism is an acute neurologic disorder that causes potentially life-threatening neuroparalysis due to a **neurotoxin** (**botulinum toxin**) produced by *Clostridium botulinum*.
- Botulism begins with cranial nerve palsies and develops into descending symmetric motor paralysis, which may involve the respiratory muscles. No fever or other signs of infection occur.
- The time course of the disease depends on the amount of toxin present and whether it was ingested preformed in food or produced endogenously in the intestinal tract or a wound.
- The 3 main clinical presentations of botulism are as follows:
  - Infant botulism
  - Foodborne botulism
  - Wound botulism

Pathogenesis

- Foodborne botulism most often occurs after ingestion of contaminated home-canned products that have not been heated to temperatures sufficient to inactivate ***C. botulinum*** **toxin**. Because the botulinum toxin is heat-labile, in order to produce disease, the food must be ingested uncooked or after insufficient cooking.
- Wound and infant botulism result when the botulinum toxin is produced endogenously from **the spores**. The spores enter the body through contaminated wounds or that are ingested in "difficult to sterilize" foods (honey).



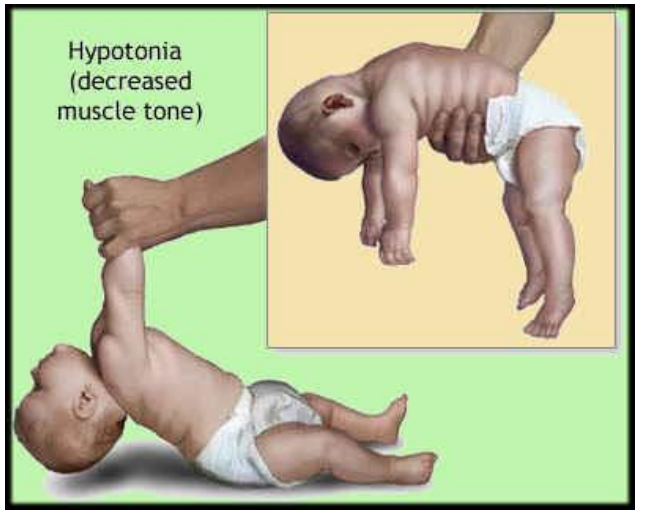
Mechanism of Botulinum toxin
(Image source: lumenlearning.com)

Foodborne botulism

- Foodborne botulism is an intoxication, not an infection.
- It starts 12 to 36 hours after ingestion of the toxin.
- The ingested **preformed** toxin is absorbed in the intestinal tract and reaches its neuromuscular junction target via the bloodstream. Once bound there, its **inhibition of acetylcholine release** causes paralysis due to lack of neuromuscular transmission.
- The first signs are nausea, dry mouth, and, in some cases, diarrhea. Cranial nerve signs, including blurred vision, pupillary dilatation, and nystagmus, occur later. Symmetric paralysis begins with the ocular, laryngeal, and respiratory muscles and spreads to the trunk and extremities (**descending**). The most serious finding is complete respiratory paralysis.
- Mortality is 10% to 20%.

Infant Botulism

- A syndrome associated with *C. botulinum* that occurs in infants between the ages of 3 weeks and 8 months and is now the most commonly diagnosed form of botulism.
- The organism is apparently introduced on weaning or with dietary supplements, especially honey, which is virtually impossible to sterilize.
- Ingested spores yield vegetative bacteria, which multiply and produce small amounts of toxin in the infant's colon.
- The infant shows constipation, poor muscle tone, lethargy, and feeding problems and may have ophthalmic and other paralyses similar to those in foodborne botulism.



Diagnosis

- The diagnosis is basically clinical, with history of eating uncooked canned foods, contaminated/unsterilized wound or a baby with history of honey ingestion.
- The toxin can be demonstrated in blood, intestinal contents, or remaining food, but these tests are available only in reference laboratories.
- Clostridium botulinum may also be isolated from stool or from foodstuffs suspected of responsibility for botulism.

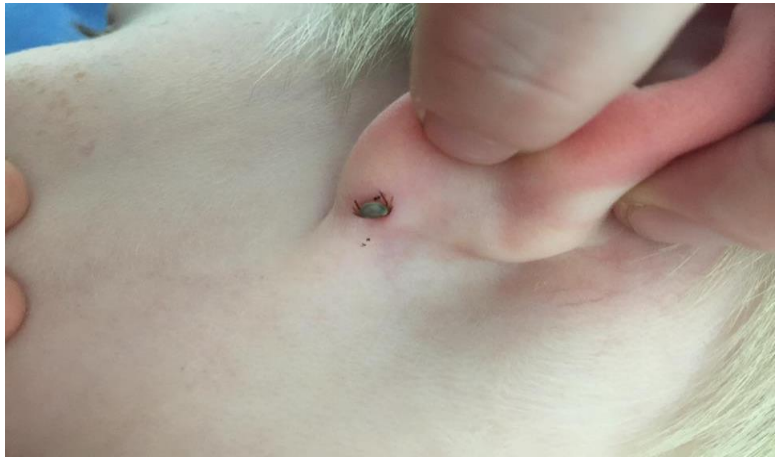
Treatment and prevention

- The availability of intensive supportive measures, particularly mechanical ventilation, is the single most important determinant of clinical outcome. With proper ventilatory support, mortality rate should be less than 10%.
- The administration of large doses of horse C botulinum antitoxin is thought to be useful in neutralizing free toxin.
- Antimicrobial agents are given only to patients with wound botulism.
- Adequate pressure cooking or autoclaving in the canning process kills spores, and heating food at 100°C for 10 minutes before eating destroys the toxin.
- Food from damaged cans or those that present evidence of positive inside pressure should not even be tasted because of the extreme toxicity of the C botulinum toxin.

- In an interesting twist, botulinum toxin as Botox has itself become a therapeutic agent. Originally licensed as a treatment of spasmotic neuromuscular conditions by direct injection into muscle, it has found a far larger use for cosmetic applications. For those that can afford it, a temporary respite from the wrinkles of aging can be gained from Botox injections administered by dermatologists and plastic surgeons.

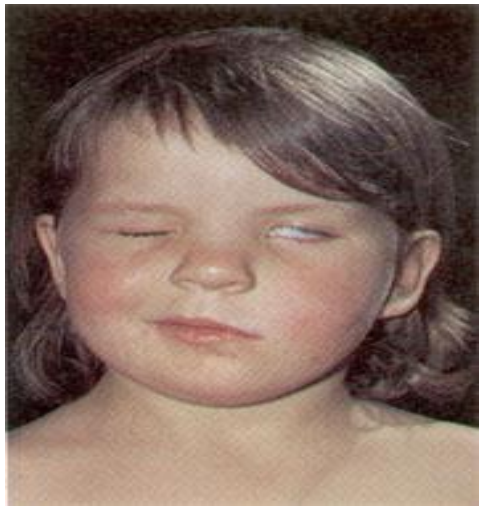
Tick paralysis

- Tick paralysis is a **flaccid ascending** paralysis caused by the bite of certain female ticks namely, *Dermacentor and Amblyomma species*.
- Paralysis is more common in children than adults.
- The head and neck are the most common sites of tick attachment, although any part of the body may be involved. Proximity of the site of attachment to the brain appears to influence the severity of the disease.



Pathogenesis and presentation

- Following attachment to the host by a female tick, a salivary neurotoxin is secreted.
- The toxin acts by inhibiting acetylcholine release at the neuromuscular junction, including neurons of the spinal cord and brainstem.
- The disease starts with a day-long prodrome of irritability, lassitude, or generalized weakness. Over the next day or two a symmetrical flaccid paralysis develops in the legs and ascends to the arms and then the neck, pharyngeal, and respiratory muscles.
- death occurs in 10% to 12% of patients, almost always children.



Diagnosis and Treatment

- Diagnosis hinges on finding and removing a tick, found on the head or neck in 60% to 70% of the cases. The tick should be removed by steady traction.
- The course of tick paralysis depends on the interval between identification and removal of the tick.
- Once the tick is completely removed, improvement usually is rapid, but paralysis can progress for up to 2 days after tick removal.
- If removal occurs before bulbar symptoms begin complete recovery occurs by 1 week. If bulbar symptoms have appeared, patients usually die despite intensive treatment.

Leprosy

- Leprosy is a chronic infection caused by the acid-fast, rod-shaped bacillus *Mycobacterium leprae*.
- Leprosy has traditionally been classified into two major types:
  - Tuberculoid: limited disease and relatively few bacteria in the skin and nerves
  - Lepromatous: widespread disease and large numbers of bacteria
- The disease can affect the skin, mucous membranes, and eyes and some of the peripheral nerves; primarily the nerves of the hands and feet.

Presentation

- The symptoms of nerve involvement include diminished sensation or feeling in the affected areas (anesthesia) and, sometimes, burning and tingling sensations (paresthesias). In more advanced cases, there may be weakness, paralysis, atrophy of muscles in the hands or feet and even blindness.
- Persons with **tuberculoid leprosy** have limited disease with relatively few skin lesions and only a few affected nerves. However, early in the course of the disease, they may have significant sensory loss and muscle weakness, even though only one hand or foot is involved.
- Persons with **lepromatous leprosy** may have minimal loss of sensation at the onset; however, if untreated, they will develop extensive involvement of the skin and nerves. The complications that may occur include eye involvement and deformities of the face, nasal septum, hands, and feet. Deformities of the hands and feet may result from muscle paralysis and repeated trauma that is not felt due to sensory loss

- The most serious complication of leprosy is the nerve damage that may occur sometimes even after treatment is begun.
- Much of the nerve damage occurs during a type of immunologic problem that occurs in 25 to 50% of patients during treatment and is commonly the patient's own immune system reacting against the dead bacteria that are still in the skin and nerves. During this process, **nerve damage can occur.**
- During reactions and at times without any signs of reaction, there may be damage to the nerves of the face resulting in weakness of closure of the eyelids and loss of feeling in the cornea (corneal anesthesia). This can result in corneal dryness and scarring and lead to blindness.

Diagnosis and Management

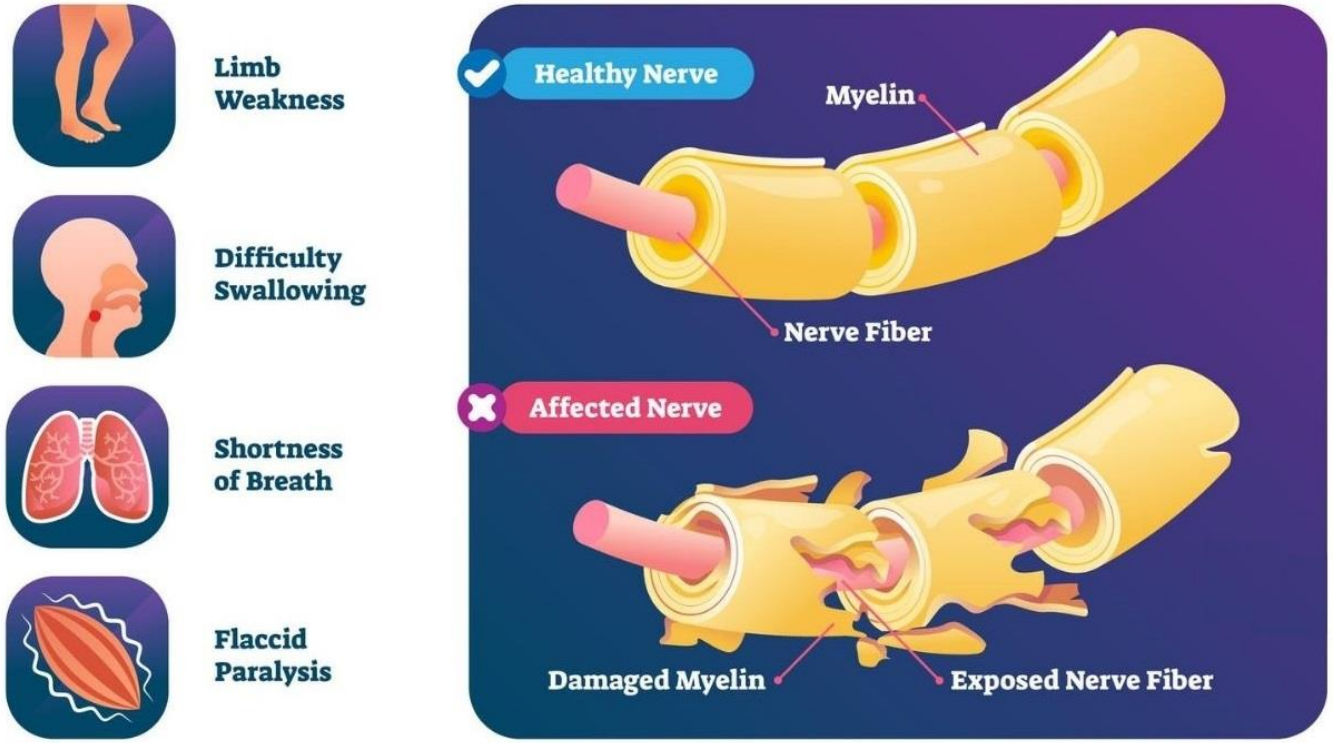
- *Mycobacterium leprae* cannot be grown in vitro.
- Disease is diagnosed via skin biopsy or tissue PCR.
- The currently available drugs are very effective. The major drugs are dapsone, rifampin, and clofazimine.

Guillain-Barre Syndrome

- **Definitions:**
  - Polyneuropathy: pathology damaging the peripheral nerves
  - Polyradiculopathy: pathology damaging the nerve roots
- **Guillain-Barré syndrome** (GBS): manifests as an **acute** inflammatory polyneuropathy with resultant weakness and diminished reflexes. GBS is considered an important cause of acute flaccid paralysis.

Pathogenesis

- GBS is considered to be a **postinfectious**, immune-mediated disease targeting peripheral nerves. Up to two thirds of patients report an antecedent bacterial or viral illness prior to the onset of neurologic symptoms.
- Respiratory infections are most frequently reported, followed by gastrointestinal infections.
- Mechanism: an **autoimmune** condition that destroys Schwann cells via inflammation and demyelination of motor fibers, sensory fibers and cranial nerves. Likely facilitated by molecular **mimicry** and triggered by inoculations or stress.


Limb Weakness
Difficulty Swallowing
Shortness of Breath
Flaccid Paralysis
Healthy Nerve
Myelin
Nerve Fiber
Affected Nerve
Damaged Myelin
Exposed Nerve Fiber

Presentation

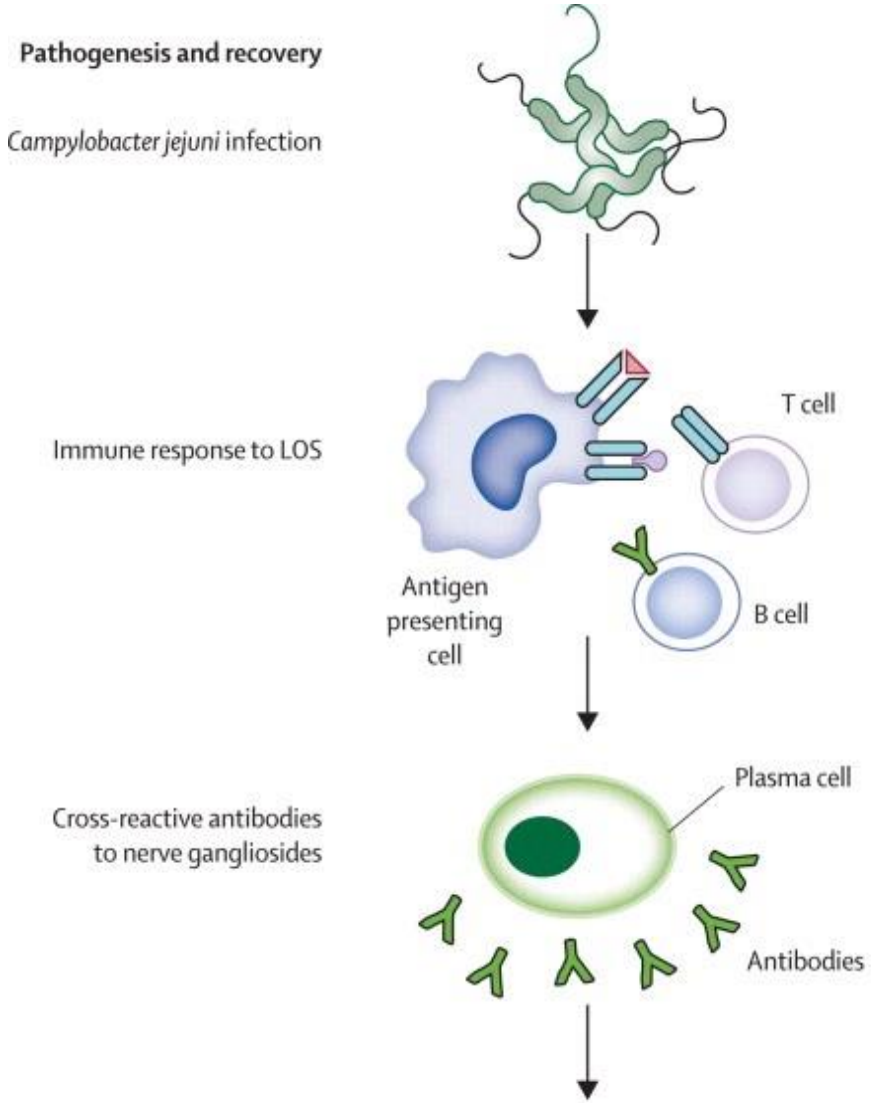
- GBS presents 2-4 weeks following a relatively benign respiratory or gastrointestinal illness with complaints of finger dysesthesias and proximal muscle weakness of the lower extremities. The weakness may progress over hours to days to involve the arms, truncal muscles, cranial nerves, and muscles of respiration
- The weakness is initially mild however, symptoms can progress rapidly over just a few days. Continued progression may result in a neuromuscular emergency with profound paralysis, ventilatory failure with required respiratory support occurs in up to one third of patients at some time during the course of their disease, and/or autonomic dysfunction with cardiovascular complications.
- Most patients complain of paresthesias, numbness, pain or similar sensory changes. Paresthesias generally begin in the toes and fingertips, progressing upward (ascending) but generally not extending beyond the wrists or ankles.

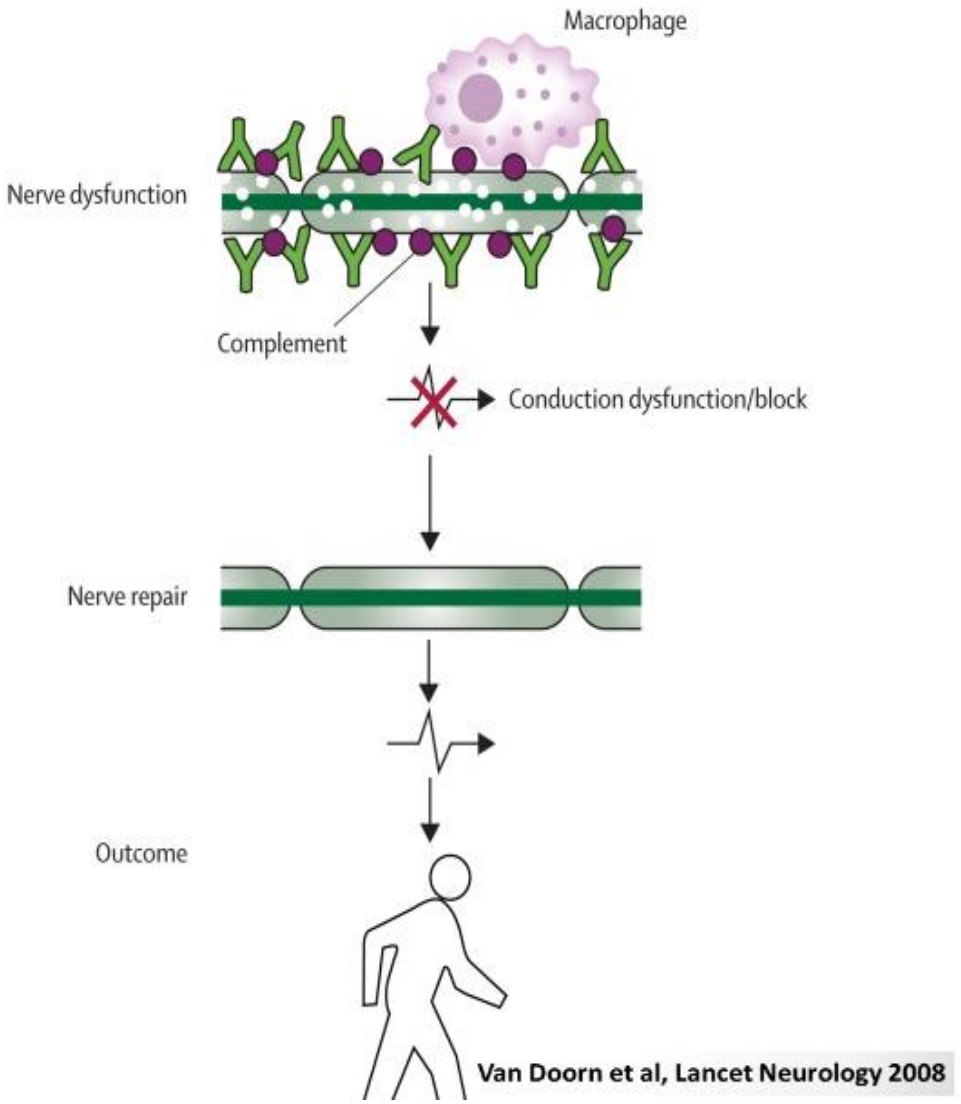
Etiology

- Despite association with certain infections, there is no definitive causal link to any pathogen.
- Implicated infections:
  - ***Campylobacter jejuni*** was the most commonly isolated pathogen in GBS.
  - **Cytomegalovirus** (CMV) infections are the second most commonly reported infections preceding GBS, with CMV being the most common viral trigger of GBS.
  - Other significant, although less frequently identified, infectious agents in GBS patients include Epstein-Barr virus (EBV), *Mycoplasma pneumoniae*, human immunodeficiency virus (HIV) and varicella-zoster virus.

- **Zika virus** has been implicated as a possible cause of GBS.
  - Zika virus is a flavivirus-arbovirus that is transmitted by *Aedes* mosquito bite. Infection is mostly asymptomatic. It is considered significant due to its congenital manifestations during pregnancy, since infants born to mothers who have acquired Zika virus during pregnancy have microcephaly.

- Evidence exists that coronavirus disease 2019 (**COVID-19**) is linked to the development of neurologic complications, including GBS. By April 20, 2020, one case of GBS in a patient with COVID-19 had been reported out of China and five such cases had been reported out of Italy. In June 2020, the first US case report of a patient with GBS associated with COVID-19 was published.


Pathogenesis and recovery
Campylobacter jejuni infection
Immune response to LOS
T cell
Antigen presenting cell
B cell
Cross-reactive antibodies to nerve gangliosides
Plasma cell
Antibodies


Macrophage
Nerve dysfunction
Complement
Conduction dysfunction/block
Nerve repair
Outcome
Van Doorn et al, Lancet Neurology 2008

Prognosis

- Disease progression stops by the third week of the illness and then improves after a variable period of stability.
- About 60-80% of patients attain full recovery of motor strength by 1 year.
- Recovery in approximately 5-10% of patients with GBS is prolonged, with several months of ventilator dependency and a very delayed, incomplete recovery.

Treatment

- Patients who are diagnosed with GBS should be admitted to a hospital for close monitoring until it has been determined that the course of the disease has reached a plateau or undergone reversal. Respiratory support is critical until recovery.
- Immunomodulatory treatment has been used to hasten recovery. Intravenous immunoglobulin (IVIG) and plasma exchange have proved equally effective.
- Corticosteroids (oral and intravenous) have not been found to have a clinical benefit in GBS.

Thank you ☺