Chapter 17

Anaerobic Gram positive bacilli

Clostridium

-- All clostridia are **Gram positive, anaerobic, spore forming rods**.

-- There are **four** medically important species:

1. ***Cl. tetani***
2. ***Cl. botulinum***
3. ***Cl. perfringens***
4. ***Cl. difficile***

Clostridium tetani

-- ***Clostridium tetani*** causes **tetanus**.

-- Transmission is through **spores** which are widespread in **soil**.

-- Portal of entry is usually a **wound**.

-- Spores germination is helped by **poor blood supply** and presence of **necrotic tissue**.

-- **Neonatal tetanus** occurs when organism enters through a **contaminated umbilicus** or **circumcision wound**.

-- The organism produces **terminal spores** within a swollen sporangium giving it a **distinctive drumstick or tennis racket** like appearance.

-- Although the bacterium has a typical **Gram-positive** cell wall, it may stain Gram-negative or Gram-variable, especially in older cells.

Clostridium tetani Gram Stain

NOTE: **Round terminal spores give cells a "drumstick" or "tennis racket" appearance.**

Pathogenesis

-- Growing vegetative cells produce a potent neurotoxin (**tetanus toxin** or **tetanospasmin**).

-- Tetanus toxin is **one of the three most poisonous substances** known, the other two being the toxins of **botulism** and **diphtheria**.

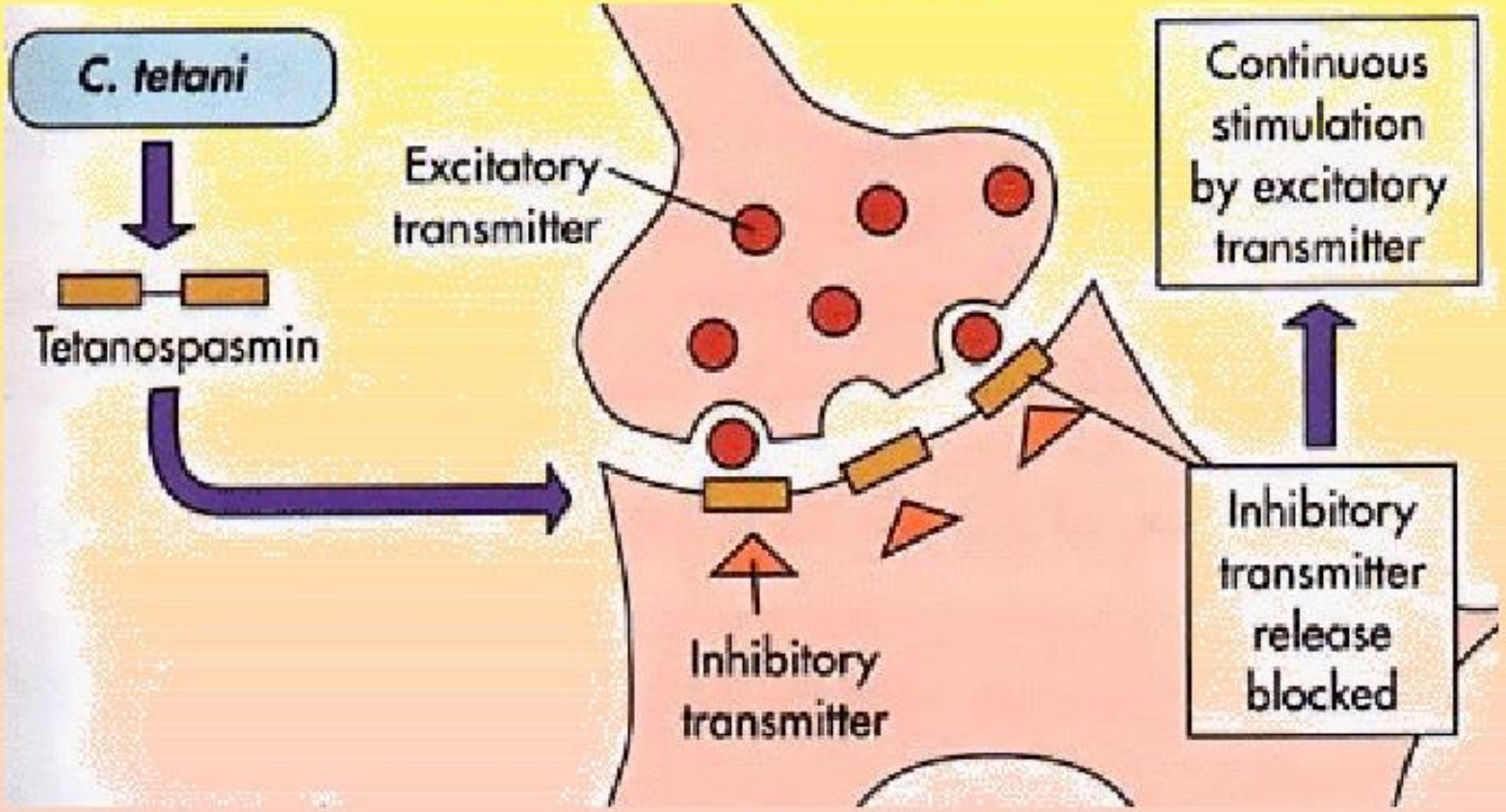
-- The organism **multiplies locally** and symptoms appear **remote from the infection site.**

-- **Tetanus toxin** migrates along **neural paths** from a local wound to sites of action in the **CNS** (retrograde) where it binds to **ganglioside receptors**.

-- **It blocks release of inhibitory mediators** (e.g., **glycine** and **GABA**, i.e., gamma-amino butyric acid) at **spinal synapses**.

-- It is a **protease** and cleaves proteins involved in **mediator release**.

Mechanism of Action of Tetanus Toxin



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-- There are **11 strains** of ***C. tetani*** distinguished primarily on the basis of **flagellar antigens**.

-- They **differ in their ability to produce tetanus toxin**, but all strains produce **same toxin** which is identical in its immunological and pharmacological properties.

-- So there is **only one type** of toxoid in vaccine.

-- **Tetanospasmin is encoded on a plasmid** which is present in **all** toxigenic strains.

Clinical findings

-- Tetanus is characterized by strong **muscle spasm** (spastic paralysis, tetany).

-- Specific clinical features include **lockjaw** (**trismus**) due to rigid contraction of jaw muscles.

-- **Opisthotonos**, a pronounced arching of the back due to spasm of strong extensor muscles of the back, is often seen.

-- **Respiratory failure** follows and there is high mortality rate.

-- **Spastic paralysis** occurs in tetanus in contrast to **flaccid paralysis** seen in botulism.

Laboratory diagnosis

-- There is **no microbiological or serological diagnosis**. Organisms are rarely isolated from wound site.

Treatment

-- **Tetanus antitoxin (Ig) is used to neutralize the toxin**.

-- Role of antibiotics is uncertain. If used, **metronidazole** or **penicillin G** are given.

-- An **adequate airway** must be maintained and **respiratory support** given.

-- **Diazepam (Valium)** should be given to prevent spasms.

Prevention

-- **Immunization is done with tetanus toxoid in childhood and every 10 years thereafter.**

-- In children, **tetanus toxoid** is usually given **in combination** with **diphtheria toxoid** and the **acellular pertussis vaccine** (**DTaP**).

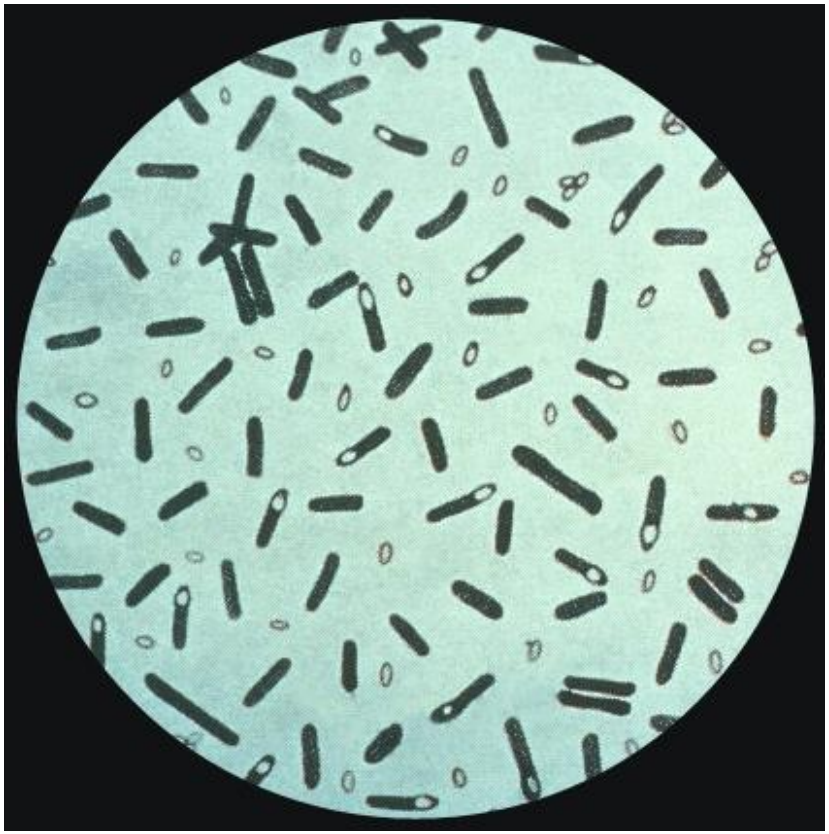
-- In case of injury, **wound should be cleaned** and a **booster dose** should be given.

-- If wound is **grossly contaminated**, tetanus antitoxin and penicillin should also be administered (**passive-active immunity**).

-- Tetanus antitoxin produced in humans is preferable to that produced in horses to avoid **serum sickness**.

Clostridium botulinum

C. botulinum is a **large anaerobic bacillus** that forms **subterminal endospores**.



-- ***C. botulinum*** causes **botulism**.

-- Transmission is **from soil** through **contamination of vegetables and meat.**

-- In **canned or vacuum packed foods**, spores may survive and germinate in **anaerobic environment**. Toxin is produced and ingested **preformed**.

-- Highest risk foods are green beans, mushrooms, and smoked fish.

-- The **toxin is inactivated by boiling** for several minutes.

Pathogenesis

-- **Botulinum toxin** after absorption from gut is carried to **peripheral nerve synapses** via blood where it **blocks release of acetylcholine** by cleaving the related proteins.

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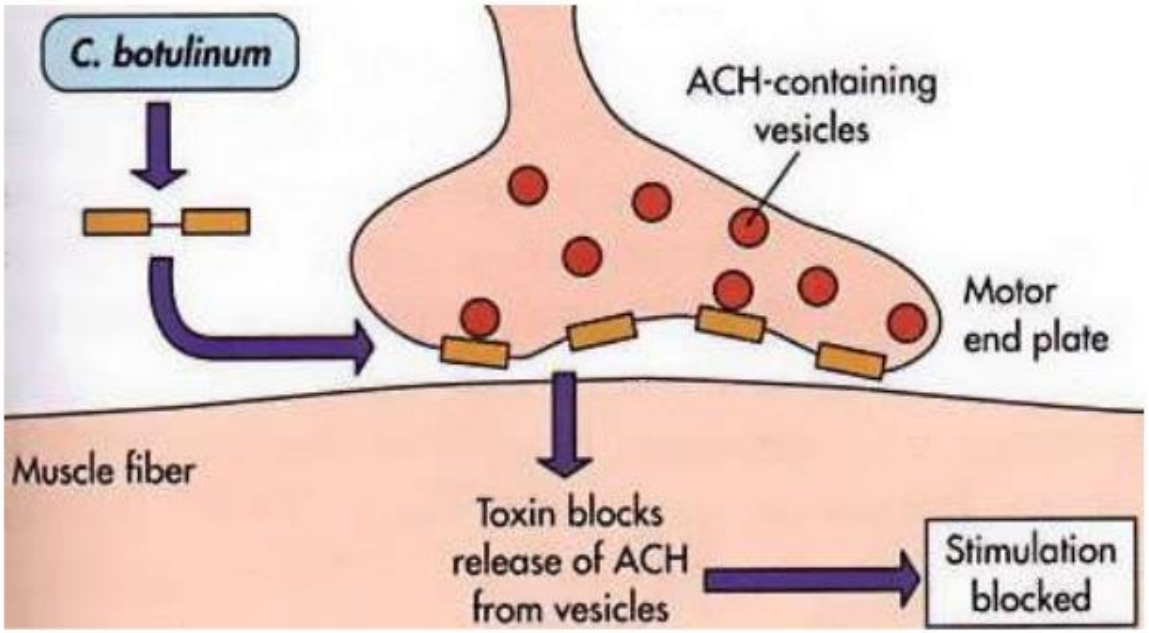
Mechanism of Action of Botulinum Toxin



-- **It is the most toxic substance known**.

-- There are 8 immunological types: **types A, B, and E** are most common.

Clinical findings

Descending weakness and **paralysis** including **diplopia, dysphagia,** and **respiratory muscle failure** are seen. There is **no fever**.

There are two special clinical forms:

1. **Wound botulism** in which spores **contaminate a wound**, germinate and produce toxin at the site.

2. **Infant botulism** in which the **organisms grow in the gut** and produce the toxin there. Ingestion of honey containing the organisms is implicated.

   Affected infants develop **weakness** and **paralysis** and may need respiratory support but usually recover spontaneously.

Laboratory diagnosis

-- The organism is usually **not cultured.**

-- Toxin is demonstrable in **uneaten food** and the **patient's serum** by **mouse protection tests**.

-- Inoculated mice die unless protected by antitoxin.

Treatment

-- **Trivalent antitoxin** (types A, B, and E) is given along with **respiratory support.**

-- Antitoxin is made in horses and **serum sickness** occurs in about 15% cases.

Prevention

-- Proper sterilization of all **canned and vacuum-packed** food is essential.

-- Food must be **adequately cooked** to inactivate the toxin.

-- **Swollen cans** must be discarded (clostridial proteolytic enzymes form gas).

Clostridium perfringens

-- It causes two main diseases **gas gangrene** and **food poisoning**.

-- Gas gangrene may also be caused by other ***Clostridial*** species.

-- **Gas gangrene** is associated with **war wounds, automobile accidents** and **septic abortions** (endometritis).

-- Spores are located in **soil**.

-- **Vegetative cells** are members of **normal flora** of the colon and vagina.

Gas gangrene

Pathogenesis

-- Organism grows in **traumatized tissue** (esp. muscle) and produce toxins.

-- The most important is **alpha toxin (lecithinase)** which **damages cell membranes**, including those of RBCs resulting in hemolysis.

-- **Degradative enzymes** produce **gas** in tissues.

Clinical findings

-- **Pain, edema, cellulitis and gangrene (necrosis) occur in the wound area.**

-- **Crepitation** indicates presence of gas in tissue.

-- **Hemolysis** and **jaundice** is common as are blood – tinged exudates.

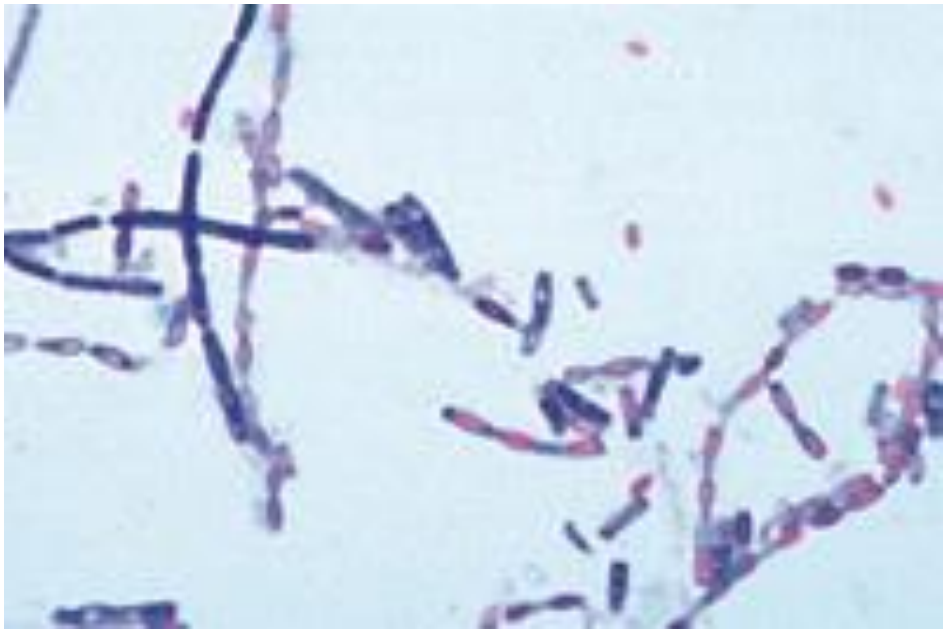
-- **Shock** and **death** can occur.

-- **Mortality rates are high.**

Laboratory diagnosis

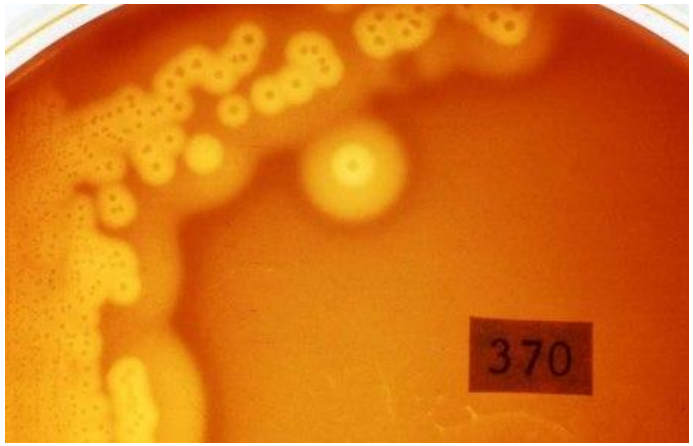
-- Smears of tissue and exudates show **large Gram positive rods**.

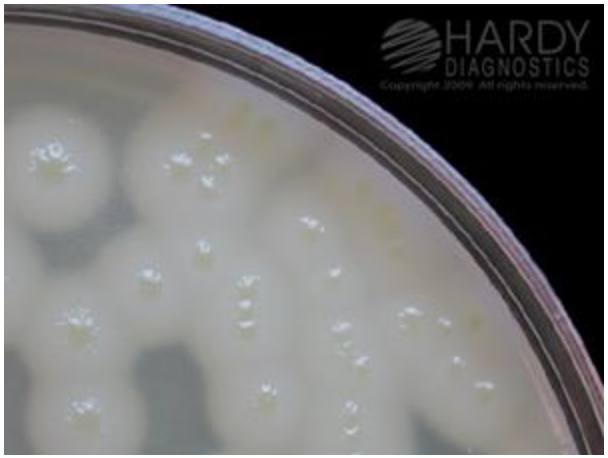
-- **Spores are usually not seen**.



-- **After anaerobic culture, identification is made by sugar fermentation reactions.**

The colonies are surrounded by a **double zone of hemolysis** on blood agar.





Egg yolk agar is used to demonstrate the presence of **lecithinase.**

Serological tests are not useful.

Treatment

-- **Penicillin G** is the antibiotic of choice.

-- Wounds should be **debrided**.

Prevention

-- There is **no vaccine**.

Food poisoning

-- Heat resistant spores **survive cooking** and germinate.

-- The organisms **grow to large numbers in reheated foods**, esp. meat dishes.

Pathogenesis

-- The organism is member of **normal flora in the colon** but not in the small bowel where exotoxins cause diarrhea.

-- **Mode of action is same as Staphylococcal enterotoxin**.

Clinical findings

-- There is an **incubation period of 8-16** hours characterized by **watery diarrhea with cramps** and **little vomiting**.

-- It resolves in 24 hours.

Laboratory diagnosis

-- **It is usually not required. There is no assay for toxin.**

-- Organisms can be isolated from **uneaten food**.

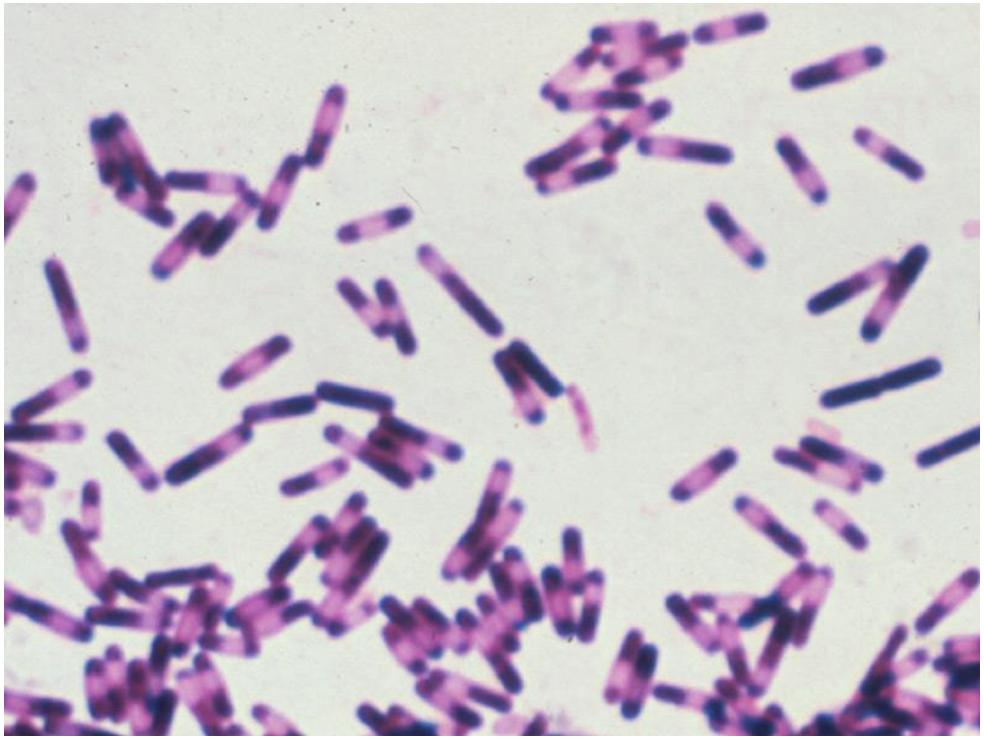
Treatment

-- **Symptomatic treatment** is given.

-- No antimicrobials are needed.

Clostridium difficile

Cl. difficile are **Gram positive rods** with **subterminal non bulging spores**.



-- They cause antibiotic associated **pseudomembranous colitis**.

-- They are also the **most common nosocomial cause of diarrhea**.

-- They are carried in GIT of **3% of general population** and **30%** of **hospitalized** patients.

-- They are transmitted by **feco-oral route** and **hands** of **hospital personnel** who are important intermediaries.

Pathogenesis

-- Antibiotic use suppress normal flora allowing ***Cl. difficile*** to multiply and produce **exotoxins A and B**.

-- Both exotoxins are **glucosyl transferases**.

-- These toxins, particularly **exotoxin B destroy actin** resulting in loss of cytoskeletal integrity, apoptosis and death of the enterocytes.

Pathogenesis

-- **Clindamycin**, **cephalosporins** and **fluoroquinolones** are generally responsible for **suppressing normal flora** and thus leading to **pseudomembranous colitis**.

-- **Cancer therapy** can also be a cause.

-- Intestinal mucosa is **rarely** invaded.

Laboratory Diagnosis

-- **Detection of exotoxins in the filtrate of patient's stool is the basis of diagnosis.**

-- **Culture is of little value** unless the isolate is shown to produce toxins and it takes rather long time.

-- The **exotoxins in filtrate** can be detected by **ELISA** or **cytotoxicity test.**

-- **PCR to detect toxic related genes is rapid and very helpful.**

Treatment

-- **The causative antibiotic should be withdrawn**.

-- Oral **metronidazole** or **vancomycin** should be given (esp. in life threatening situation) and fluids should be replaced.

-- To **avoid carriers** and recurrence **Fidaxomycin (Dificid)** is preferred.

-- High success with **fecal bacteriotherapy** involving introduction of bowel flora of a normal person has been claimed but the procedure has limited acceptance due to safety issues.


Thank You!