***Clostridium tetani***

* Its gram positive, anaerobic , spore forming bacilli , it causes the disease tetanus by the production of toxins (tetanus toxins)
* another name for tetanus is "locked jaw"
* Motile (peritrichous flagella) and they have terminal spores (at the end of the bacilli)
* It causes tetanus by virtue of producing a potent, heat labile, neurotoxin (tetanospasmin) that is produced during the stationary phase of growth and released when cell lyses occurs. so toxin **production starts** during **stationary phase** and **released** during **death phase (cell lyses)**
* Toxin is composed of two chains, light and heavy (A and B), and it is cleaved into the subunits by **protease** when it is released from the cell. The two chains are held together by an S-S bond.
* The **heavy chain** **binds** to gangliosides (GT1) on **neuronal membranes**.
* The **light chain** is then internalized and **release the toxins** which cause the disease
* Tetanospasmin (neurotoxin) released in the wound, absorbed into the circulation and reaches the ends of motor neurons all over the body. The toxin acts at several sites within the [central nervous system](http://en.wikipedia.org/wiki/Central_nervous_system), including [nerve](http://en.wikipedia.org/wiki/Nerve) terminals, the [spinal cord](http://en.wikipedia.org/wiki/Spinal_cord), and [brain](http://en.wikipedia.org/wiki/Brain), and within the [sympathetic nervous system](http://en.wikipedia.org/wiki/Sympathetic_nervous_system). By binding to peripheral motor neuron terminals, the toxin enters the nerve axons, and is transported across [synaptic junctions](http://en.wikipedia.org/wiki/Synapse) to the nerve-cell body in the brain stem and spinal cord by [**retrograde** **intraneuronal transport**](http://en.wikipedia.org/wiki/Retrograde_transport), until it reaches the central nervous system, where it rapidly binds to [gangliosides](http://en.wikipedia.org/wiki/Ganglioside) at the presynaptic membrane of inhibitory motor nerve endings.

\*\*\* then **they will interfere with the inhibitory neurons** (Once they gain access to **inhibitory neurons** they will block the release of the neurotransmitters **glycine** **and** gamma- aminobutyric acid (**GABA**)) and they will inhibit the inhibitory stimuli so there is no control on the excitation of the neuron which will lead to contraction of **both** extensors and flexors, This permits simultaneous **spasms** of both agonist and antagonist muscles producing muscle **rigidity and convulsions**.

\*\*\* **Retrograde (they go backward) >>>>** they are released from the postsynaptic dendrites, cross the synaptic cleft, and are localized within vesicles in the presynaptic nerve terminals and

**Toxin Effect**

* It enters through neuromuscular junction of α motor neurons and it involves three components of the nervous system

 1) Central motor control

 2) Neuromuscular junction of the peripheral nerves (defective release of Acetylcholine)

 3) Autonomic function

* tetanus can be either periphero (localized\ascending) or centero (generalized\descending )
* periphero >>>> is concerned with the site of infection , there is twitching and spasm around the origin of infection (e.g. : puncture wound)

\*\*\*I googled generalized and localized tetanus and this is what I found, and this is for further explanation (**Generalized Tetanus)**

Is the most common form, accounting for more than 80% of cases. Neonatal tetanus usually occurs because of umbilical stump infections. The most common initial sign is spasm of the muscles of the jaw or "lockjaw". This may be followed by painful spasms in other muscle groups in the neck, trunk, and extremities and by generalized, seizure-like activity or convulsions in severe cases. Generalized tetanus can be accompanied by nervous system abnormalities, as well as a variety of complications related to severe spasm and prolonged hospitalization. The clinical course of generalized tetanus is variable and depends on the degree of prior immunity, the amount of toxin present, and the age and general health of the patient. Even with modern intensive care, generalized tetanus is associated with death rates of 10%–20%.

**Localized Tetanus**

Localized tetanus is an unusual form of the disease consisting of muscle spasms in a confined area close to the site of the injury. Although localized tetanus often occurs in people with partial immunity and is usually mild, progression to generalized tetanus can occur.)

* In **generalized** (descending) tetanus, it is **not** possible to absorb all of the toxin by local nerve endings, therefore, it passes into the blood and lymph with subsequent absorption by motor nerves. and it is the **most** **common** form seen
* In **Localized** tetanus (ascending), toxins travel along the neural route causing a disease confined to the extremities.

**Pathogenesis**

* - The organism is **not** invasive and remains confined to the necrotic tissue where the vegetative cells elaborate the lethal toxin.

\*\*\* I also googled the pathogenesis of the disease but it's **required** because the Dr. mentioned it throughout the lecture and it's like a revision (**Clostridium tetani (C. tetani); spores usually enters the body through a wound or breach in the skin. In the presence of anaerobic (low oxygen) conditions, the spores germinate. Toxins are produced and disseminated via** **blood stream** **and lymphatic system**. **Toxins act at several sites within the central nervous system, including peripheral motor** end plates, **spinal cord, and brain, and in the sympathetic nervous system**. **The typical clinical manifestations of tetanus are caused when tetanus toxin interferes with release of neurotransmitters, blocking inhibitor impulses. This leads to unopposed muscle contraction and spasm. Seizures may occur, and the autonomic nervous system may also be affected)**

* The **first symptom and the most common** is usually **trismus (lock jaw)** with masseter muscle spasms descending from the neck to the trunk and limbs. ( they can't talk )



* As the disease progresses, the spasm increases in severity becoming very painful and exhausting.

**Clinical Syndromes**

* The initial symptom is cramping and twitching of muscles around the wound.
* Spasm with head and hands are bent backward and the body bowed forward is common.
* Complications include fractures, muscle ruptures, hematomas and organ failure due to extensive contraction

Variable things can happen:

1. Involvement of the masseter muscles (trismus or lock-Jaw) is the presenting sign in the majority of patients.
2. The sardonic smile characteristic of sustained trismus is known as "risus Sardonicus" ((الضحكة التهكمية (spasm in muscles of facial expression )



1. Other early signs include drooling, sweating associated with the autonomic nervous system
2. persistent back spasms >>> which will result in arching in the back because extensor muscles are stronger than flexor muscles in the spinal cord and that will lead to extension of the back



1. respiratory muscles system can be involved
* More severe disease is seen with involvement of the autonomic nervous system with cardiac arrhythmias, fluctuation in blood pressure, profound sweating, and dehydration >>>> contribute with death
* many people can actually die either from generalized tetanus or from localized tetanus when the condition is improved

\*\*tetanus can start as localized and improve to become generalized

\*\* It's more serious condition to have both localized and generalized

* A variant of localized tetanus is cephalic tetanus in which the primary site of infection is the head (very poor prognosis).
* if the infection was in the cranium (localized near the head)then it's **both** generalized and localized because it's close to the CNS and it spreads very fast >>>>> very serious condition

**Treatment**

\*\*\* Once the symptoms appear we can't do so much about it

But:

1. We can start by giving the patient **human** anti serum to neutralize the **available** toxins

2. We give him antibiotics (penicillin) to kill the bacteria

3. **Most** **importantly** is supportive treatment which is the life savior (e.g.: muscle relaxant, sedative)

* mortality is high 50-60 % ( there is a chance that they may survive )

\*\*\* If the disease was in the peripheral can the immune system eliminate the toxin?

No, once the toxins reaches the nerves it can't be eliminated, the antibodies neutralize the toxins before it reaches the nerves

**Neonatal tetanus**



 - In newborns of susceptible mothers where the umbilical stump is contaminated. (In poor countries sometimes when a mother delivers a baby they cut the umbilical cord with a stone, then the cord will be contaminated with spores of tetanus ..... after we cut the cord it will become necrotic and black which provide a perfect anaerobic medium for the bacteria to grow)

 - 90% fatal Vs 40% for adults.

- It happens due to unhygienic practices

 - It can spread to the heart

- More fatal in newborns than adults

* Prevention

 - Proper care of wounds >>> any wound has to be cleaned properly and we have to remove dead tissues because they provide anaerobic environment

 - Anti toxin >>>> if you suspect that the person hasn't been vaccinated in the past then we give prophylactic anti serum (anti toxin)

 - Vaccination (Toxoid)

* Treatment (antitoxin)

No immunity following infection......

\*\*\* Clostridium tetanus is mainly found in water, soil and feces of animals (horses, cows)

\*\*\* Any wound contaminated with soil can lead to tetanus, that's why the wounds have to be cleaned especially if it has been contaminated

\*\*\* We can get tetanus by a sting of a flower thorn or a needle puncture

***Clostridium botulinum***

* The etiological agent of botulism.
* Four group's I-IV and they produce different toxins of which....
* Toxin is composed of two subunits A (neurotoxin) which does the job and B the nontoxic subunit which protects the neurotoxin from inactivation by stomach acids.

\*\*\* That indicates that the patients are going to suffer from the disease through the GI tract so it's really a food poisoning

\*\*\* The toxins normally are not produced in the body, they are produced in the food where there are anaerobic conditions specially canned food (if you have a can that has a bulge in it or a hole it's better to discard it

\*\*\* In the old days, they used to produce canned food at home that is why they were more likely to get botulism.

**Pathogenesis**

* Three forms of botulism have been identified, **classical (or food** **borne)** which is the **most common**, infant (babies under 6 months), and wound botulism (not common).

\*\*\* After eating the infected food, the body absorbs the toxins, the toxins will reach the nerves, and they can affect any nerves in the body because they effect Ach

\*\*\*Botulism is very specific for cholinergic nerves mainly it will effect motor neurons

* The toxin blocks neurotransmission at peripheral cholinergic synapses by preventing release of acetylcholine resulting in **flaccid paralysis.**

**\*\*\*its common sense if we don't have Ach we will have paralysis**

**(Tetanus >>>> spasm , botulism >>>> paralysis)**

- Toxin binds to neuromuscular junctions of **parasympathetic** nerves.

 - Cranial nerves are affected first followed by motor nerves.

\*\*\* The patient is almost motionless and weak

-and this is so serious when the muscles of respiration are affected, death occurs because of respiratory failure

-autonomic nervous improvements ( in the parasympathetic nervous system) : your eyes will be dilated , pupils will be dilated , patients can't focus , blurred vision , interference with the heart rate, tachycardia , and cardiac arrythmatics ,hearing and speech can be affected as well , because of the interference with acetylcholine

- How does the bacteria reduce acetylcholine?

destroys the synapses , and that's why full recovery takes a long time and even if the patient recovered and he didn't die because of this it will take you a long time because these synapses have to regenerate

**- Food-borne Botulism**

-1-4 days after consumption of contaminated food the patient develops weakness and dizziness

-symptoms are caused mainly because of paralysis of muscles or blockage of parasympathetic autonomic nervous system

- Complete recovery in patients who survive this initial period frequently requires a very long time, many months to years until the affected nerve endings regrow.

- Treatment:

Antitoxin and supportive care (in their breathing, they can't swallow so you have to feed the patient, their urination because they have problems in the urinary bladder

- Mortality can be treated in this case, it can be reduced to 10% (it was 70%) with better supportive care.

**Infant botulism**

-not very serious disease , not as serious as intoxification or food poisoning and it's associated with eating honey that is contaminated by spores of C.botulinum and that's why infants under six months or even one year shouldn't eat honey (they can acquire the disease).

-not that honey is bad but sometimes when it's contaminated with spores of C.botulinum (which is widely distributed in the nature and exist in spores that bud and produce bacteria that produces toxins in anaerobic conditions)

-if you ingest honey that is contaminated with spores they go to GIT and in babies who haven't established normal flora and there they find enough anaerobic conditions to grow and produce toxins. Those toxins are produced in small amounts (that's why it's not really a serious disease)

- In adults: they have a well developed normal flora so the spores will have no chance to grow or produce a toxin

- The baby will have a very low mortality (1-2%), they might die and they won't grow properly like normal babies

**Wound botulism**

- A rare disease resulting from contaminated wounds like cutting umbilical cord using a rock (but this disease is less likely to happen, the greater possibility is for other disease to occur)

- So if you have a wound and anaerobic conditions and it's contaminated by C.botulinum, the toxin will be produced and you will have botulism

-wound botulism is relatively less common than food poisoning. But be careful this doesn't mean that food poisoning is common, actually you may spend your entire life as a doctor and don't examine such patients

Clostridium difficile

-they are widely spread in the nature, quite often developing from normal flora of GIT and this is how they produce disease. So there is no wound infection or anything like this

-so when you have broad range antibiotics that kill normal flora of GIT this will give a chance for clostridium difficile to actually overgrow and produce toxins . Those toxins are really toxic to the mucosa of the large intestine

-so as a conclusion, C.difficile are actually part of normal flora. They are there but they are suppressed by the normal flora which is not really pathogenic

- C.difficile associated with:

1-broad range antibiotics

2-hospitals (they can be hospital acquired)

3-sometimes they can be ingested from environment, but usually if its community acquired the bacteria is already in GIT and when you take broad range antibiotic elimination of normal flora will occur allowing C.difficile to grow and produce toxins that injures mucosa of the large intestine

- manifestation vary from mild disease when you have a little bit of diarrhea to sever , fatal bleeding and necrosis of the lining of the large intestine and pseudo membrane formation and this is known as : pseudo membranous colitis ( inflammation of colon and production of a membrane)

- you should be careful when you take broad range antibiotic : if you start having diarrhea when the course is almost done it's okay, but if you have severe diarrhea with blood and so on you should stop immediately ( in this case it's pseudo membranous colitis)

-after you stop the antibiotic, you should take another antibiotic to kill the bacteria in the large intestine: vancomycin or metronidazole

***Anaerobic Non Spore-forming
Gram-Positive Bacilli
 Actinomyces***

-they are gram positive , anaerobic but they don't produce spores and they are known as actinomyces because they grow like fungi in filaments so they are connected to each other and that's why we name them ***ray fungus***

-don't be confused they are really bacillus bacteria (they are not fungi)



-They are facultative anaerobes or strict anaerobes, not acid fast and are nonmotile

-These lesions discharge pus containing the organisms in firm yellowish granules called sulfur granules.

-they are not violent and they can be part of your normal flora in the mouth, GIT, respiratory tract or genital tract

-the problem here is that you really need to have some injury to the tissue so that organisms can produce a chronic infection ( granuoloma or abscess) these granuolomas open up on the surface of skin or mucus membrane and drain and when you have this it will be known as (sinus or duct) and those are very characteristic to C.difficile

-very slow chronic infection , produces sinuses and sometimes the abscesses are very numerous that they can intercalate with one another and they have discharging yellow material known as sulfur granules

-they can involve mouth, GIT, or respiratory tract involving skin or mucus membranes from the inside

- Example for you to understand the concept: on the respiratory tract bacteria can drain inside bronchi or they may be in the pleura get into chest wall and then drain to the outside. As a conclusion it can involve chest wall or lungs

-the source is always endogenous, actinomyces are part of the normal flora in GIT or respiratory tract

-majority of cases involve: cervicofacial, thoracic and abdominal.

***Gram Negative Cocci:
the Neisseria***

***-***species are: ***Neisseria gonorrhea***and***Neisseria meningitidis***

***-*** Aerobic, Gram-negative cocci and usually are intracellular

-they grow in pairs (diplococci), they occur in tubes but they look like coffee beans (one side is convex and the other is concave)

- **Oxidase positive**, Most of them are **catalase positive**

**-**nonmotile and they don't have flagella

-flagella doesn't exist in cocci since they are too small, so flagella only exists in bacilli if they are necessary present but they have fimbria which is very important for attachment ( pathogenicity factor)

-they are gram negative having outer membrane that contains LPS.But, here LPS is slightly different: it's smaller so we call it oligo lippolysaccharide

-remember that normally LPS have three parts: lipid A, core polysaccharide, O polysaccharide

-but here the LPS don't have side chain of carbohydrates (O antigens)

-nevertheless, they are considered as a pathogenisity factor

- don't forget to refer to slides

-done by : Razan Lahham & Sarah Momani