Chlamydia and Rickettsia

Intro
There are 3 groups of bacteria that have a tiny genome: chlamydia, rickettsia and spirochetes (1/3 the number of genes of e. coli)

Chlamydia

- Chlamydia are bimorphic which is a fancy way of saying that they come in 2 stages: the elementary body and the reticular body.
- They have either no or a very small amount of peptidoglycan. This is why they are not susceptible to peptidoglycan inhibiting drugs such as penicillin.

The Life Cycle

- The elementary body is the form of chlamydia in the invasive stage and the reticular body is the form in the dividing stage.
- When a chlamydia infected cell lyses, elementary bodies are released and make contact with epithelial cells at an unknown site that is thought to require sialic acid.
- After binding, the elementary body induces its own phagocytosis at which point the body resides in a phagosome.
- Conditions within the phagosome are reducing and acidic and lead to the destruction of the outer membrane of the elementary body (which is well woven together due to the disulfide bonding of the outer membrane proteins).
- The phagosome environment leads to the formation of the reticular body which divides and forms elementary bodies.
- The phagosome with the chlamydia inside is known as an inclusion body. The disease was once known as inclusion body disease.
- Chlamydia has a preference for epithelial tissue, particularly the outer layers of the lining of the vagina, the outside of the penis, the soft tissue of the mouth, the perianal region and the inside of the anus. STDs do not only occur in the genitals.
- Chlamydia is an obligate intracellular organisms – however, the elementary body can exist outside of a cell, but it cannot grow.
- One could conceivably contract conjunctivitis by swimming in a pool which has chlamydia in it.

Clinical Chlamydia trachomatis

- Chlamydia trachomatis is one of three species but there are many serotypes that can be distinguished at the level of PCR but not by morphology or antigenically.
- Serotypes A through C cause trachoma which is not common in the U.S. but is the major cause of blindness in the world. It infects the conjunctiva of the eye and the cornea can become infected and opaque if not treated and can also be the site of secondary bacterial infection.
- Serotypes D thru K cause the STD chlamydia which is the #1 STD in the U.S., though probably the mildest as well.
- Chlamydia is easier to detect in males than females.
- In males the most common symptom is non-gonococcal urethritis with a purulent discharge from the penis and pain in the pelvic region.
- In females there is purulent cervical discharge (not always apparent) and fallopian tube inflammation which equals ye olde pelvic inflammatory disease (also seen in gonorrhea and syphilis). If untreated in females it can lead to infertility.
- It is important to educate the male to advise any unsuspecting female partners because the female will not be aware as quickly.
- STDs travel in pairs (chlamydia and gonorrhea). Gonorrhea is the more clinically apparent and is usually treated first (with penicillin). Those of you who have been paying attention know that penicillin doesn’t work for chlamydia – though it does suppress the disease a little which can give the patient the feeling that they are better only to return later with a chlamydia infection.
- Chlamydia can also be spread by the genital-ocular route causing inclusion body conjunctivitis which results from rubbing your eyes after scratching an “infected area”.
- In the infant, inclusion conjunctivitis is picked up in the birth canal during birth. Babies are given silver nitrate drops immediately which may take care of it. Infants can also get chlamydia trachomatis pneumonia which is also acquired in the birth canal.
- Serotypes L1, L2 and L3 cause lymphogranuloma venerium which is an infiltration of neutrophils in the lymph nodes. The nodes become swollen and can protrude through the skin. This is not common in the U.S.

**Chlamydia psittaci**

- Chlamydia psittaci infections will give you a nasty case of psittacosis which can be caught from parrots. This is an occupational disease seen mostly in poultry workers and in pet shops (in fact, this is what killed the Pet Shop Boys). This infection will cause a pneumonia treated with tetracycline (a protein synthesis inhibitor) which would not be the drug of choice for other bacterial pneumonias.

**Chlamydia pneumoniae**

- Chlamydia pneumoniae is new (10 years old) and is the major cause of pneumonia in adolescents. This is known as atypical bacterial pneumonia which looks like viral pneumonia.
- This pneumonia is not that virulent and responds to protein synthesis inhibitors.
- There is growing evidence of an association between chlamydia pneumonia and atherosclerotic plaques.

**Rickettsia**

**The Evil Tick**

- Rocky Mountain Spotted Fever (Rickettsia rickettsii) and Borrelia burgdorferi (Lyme Disease) both have the honor of being transmitted by ticks.
- The tick has a serrated organ called a hypostome which is driven by the tick into the skin - some species secrete a cement that holds the organ in place.
- A tick is not an insect it is an arachnid (a likely test question).
- Its sole source of food is blood.
- The male dies quickly after mating and the female spits out 4,000 eggs which turn into larvae which feed on rodents.
- They eventually molt to become nymphs.
- Ticks feed 3 times in their life cycle, larvae, nymph and adult.
- Rocky Mountain Spotted Fever (RMSF) is carried by the dog tick and Lyme is carried by the deer tick. The incidence of Lyme is much greater because the nymph (very small and hard to find and remove) transmits Lyme disease while RMSF is transmitted by the female dog tick, which is only slightly smaller than a fully blossomed chia pet, making it easier to see and remove.
- When a tick engorges it increases to 10 times its normal size (another testable morsel).
Rickettsia

- This bugger is tough to cure with a mortality rate of 10%.
- It is a very small, pleomorphic organism which divides by binary fission and has a very thin cell wall.
- It does have a peptidoglycan but does not respond well to penicillin – protein synthesis inhibitors are much better.
- Rickettsia has many similarities to Chlamydia.
  1) Both are obligate intracellular organisms.
  2) Both are covered in this lecture
  3) Their life cycles do have some differences –
     a) Rickettsia has no inclusion bodies
     b) Rickettsia is taken up by endothelial cells and once inside, they break the phagosome down and inhabit the cytoplasm (RMSF inhabits the nucleus).
     c) They both rely on the cell’s machinery and leave the infected cell by lysis.

Rocky Mountain Spotted Fever (and the Boogie Woogie Flu)

- Unlike the other Rickettsias, RMSF does not lyse the endothelial cells, they are excreted in streams of cytoplasm and eventually damage the cell beyond repair.
- Howard Ricketts discovered the organism and, making up in scientific prowess what he lacked in creativity, named it Rickettsia rickettsii. He also described the disease and named it after his best friend, Charlie Rocky Mountain Spotted.
- Ricketts described RMSF and figured out it was transmitted by a tick. He infected himself to prove to a doubting world how smart he really was and, of course, promptly died (apparently he only had book smarts)
- RMSF is actually more common on the east coast (100 to 1) and occurs 10 days after the bite of the dog tick.
- The symptoms are a very bad headache, abrupt onset fever and peculiar edema of the face. The rash (spotted) sometimes doesn’t occur for another 5 days and sometimes not at all.
- The rash is a mixture of flat and raised and occurs most often on the soles of the feet and palms of the hand – tell tale signs.
- RMSF does its damage by increasing the permeability in blood vessels which causes necrotizing vasculitis. A blood sample will show the patient to be low in platelets because so many are in use.
- Platelets aggregate at the sites of endothelial damage causing disseminated intra-vascular coagulation (DIC).
- DIC causes clots which effect and damage a wide array of organs.
- An LPS is associated with this disease and is very toxic to mice and seems to be associated with the severity of the disease and is the source of the serological cross reaction (diagnosis).
- Occurs April – June

Q – fever

Is a disease caused by the rickettsia Coxiella burnetii, which is propagated in sheep and cattle, where it produces no symptoms; human infections occur as a result of contact not only with such animals but also with other infected humans, air and dust, wild reservoir hosts, and other sources. Syn: nine mile fever.

This disease does occur in the US, and can be transmitted by ticks. Since the transmission is aerosol in nature, a severe sequela is pneumonia. This disease [causing microorganism] can be[come] systemic and therefore possibly very severe.
Spirochetes

These organisms look like telephone cords. [You know, the coiled cords, not the type that the boyz have on their kitchen phone that automatically winds itself up.]

There are three of 'em: leptospira, treponema, an borrelia. In the following definitions, I have tried to highlight (actually bold) the points he stressed.

Leptospira

A genus of aerobic bacteria (order Spirochaetales) containing thin, tightly coiled organisms 6 to 20 4m in length. They possess an axial filament, and one or both ends may be bent into a semicircular hook. They stain with difficulty except with Giemsa's stain or silver impregnation [dark-field microscopy]. Associated with icterohemorrhagic fever. The type species is Leptospira interrogans.

The disease associated with leptospira is occupational in nature (large animal handlers, such as cows and such). This illness is biphasic, meaning that it has a period of intense clinical activity followed by a period of low clinical activity, and back to intense clinical activity. Thus, the patient gets worse then better then worse then better then worse then better then worse then better then worse then better.....get the idea yet? This biphasic illness is important in diagnosis.

Treponema

A genus of anaerobic bacteria (order Spirochaetales) consisting of cells, 3 to 8 4m in length, with acute, regular, or irregular spirals and no obvious protoplasmic structure. A terminal filament may be present. They stain with difficulty except with Giemsa's stain or silver impregnation. Some species are pathogenic and parasitic for humans and other animals, generally producing local lesions in tissues. The type species is Treponema pallidum.

Syphilis is [from the dictionary, so just simply “read” this paragraph, other points will be brought up in the next lecture] an acute and chronic infectious disease caused by Treponema pallidum and transmitted by direct contact, usually through sexual intercourse. After an incubation period of 12 to 30 days, the first symptom is a chancre, followed by slight fever and other constitutional symptoms (primary syphilis), followed by a skin eruption of various appearances with mucous patches and generalized lymphadenopathy (secondary syphilis), and subsequently by the formation of gummas, cellular infiltration, and functional abnormalities usually resulting from cardiovascular and central nervous system lesions (tertiary syphilis). Syn: lues venerea, malum venereum.

Borrelia

A genus of bacteria (family Treponemataceae) containing cells 8 to 16 4m in length, with coarse, shallow, irregular spirals [coils are loose] and tapered, finely filamented ends. These organisms are parasitic on many forms of animal life, are generally hematophytic, or are found on mucous membranes. Some borreliae are transmitted by the bites of arthropods. The type species is Borrelia anserina.

Causes Lyme disease, which is important in this very geographical location since, for example, there were 2,000 to 3,000 cases in this county [last year?].

Let's talk about spirochetes in general. They are very thin, ~ 0.2 micrometers in diameter, and 15 micrometers in length. Only microbacteria have more lipid per organism than spirochetes.

He showed a slide, a cross-sectional electron micrograph [kinda like a CT scan, but different] of a spirochete. It looked something like this:
By the way, this, and Chlamydia and rickettsia are Gram negative.

LYME DISEASE

There is a list of sequelae from Lyme disease, of which do not occur in any particular order. Furthermore, there may be any sequence of these signs/symptoms between which there are usually remission periods. These are:

Cutaneous lesions – erythema migrans, which is erythematous circinate macules, often bounded peripherally by a white band, as a result of atrophy of the filiform papillae; with time the lesions resolve, coalesce, and change in distribution. Can be macular or papular, or both. Can be diagnosed on black/dark skinned individuals. Can be circular, triangular, and can cover extremely large portions of the body. Sunburn may help mask the morphology of this lesion. Furthermore, the morphology is extremely variable. Treated with oral antibiotics (b-lactam antibiotics, and protein synthesis inhibitors). Twenty or so percent of patient do not have erythema migrans. Sometimes multiple erythema migrans are present, and thus the patients are thought to have disseminated Lyme disease. Some docs choose to treat this condition with intravenous antibiotics.

Neurological manifestations – neuroborreliosis. Approximately 20 - 30% of patients have central or peripheral nervous system involvement.

Cardiac manifestations – in about 8% of patients.

Lyme arthritis – hallmark of this disease!! This is usually restricted to large joints (mmmm…..I could go for one of those right now) such as the knees or elbows, and is a late manifestation.

Twenty percent of patients do not have erythema migrans, and contrastedly, sometimes patients present with multiple lesions (indicative of systemic disease).

Borrelia genetics

Borrelia have a linear chromosome as well as plasmids. These plasmids contain approximately 430 open reading frames, and have a G/C content of about 23-32% (which, is low). This means that there is a high A/T content, consequently a favoring for poly-lysine, and therefore the entire isoelectric point of the Borrelia organism is cationic (basic), and helps it bind and colonize in such a wide variety of tissues, simply on the basis of charge. Only 16% of these genes have predicted biological roles (thus we don’t know that much about the genes) and we also know that the genes are highly redundant. Borrelia also have linear plasmids, which are more abundant. However, the circular plasmids (which contain a lot of garbage DNA) are stronger and contain much more information than the linear plasmids. Borrelia can have a raised (papular) or flat (macular) lesion.

Lyme neuroborreliosis

Is divided into two stages……

Early Neuroborreliosis is characterized (and is within months after onset) by:
- lymphocytic meningitis (inflammatory cells are usually lymphocytes)
- cranial neuropathy – Bell’s palsy is the most frequent early manifestation of neuroborreliosis
- radiculoneuritis
- lymphocytic meningoradiculitis (Bannwarth’s syndrome)

Late Neuroborreliosis – (months to years after onset)
- ACA [I have no idea, and he never said what “ACA” stood for] associated peripheral neuropathy
- Chronic encephalomyelitis
- Mild chronic encephalopathy

Lyme Arthritis – the hallmark of Lyme disease

Large joints preferentially are affected, occurs months to years after onset of disease. Swelling will go away without treatment, but will eventually come back (see all about the biphasic cycle of this disease above).

One of the biggest things that he said, and stressed a few times, was that there is no sequence of events to lyme disease manifestations.
Culturing spirochetes

Extremely fastidious, leptospira grow best, Borrelia grow grudgingly, and treponema has never grown in vitro. Cultures are never of any diagnostic use.

Syphilis

Some years, syphilis is important, and others unimportant. This year syphilis is unimportant (then why are we studying it this year?). Transmitted sexually, incubation period is approx. 3 weeks, organisms multiply locally, and disseminate through the blood stream. Can also be in the ANAL area or MOUTH area. Secondary syphilis can affect any organ in the body….the liver, joints, kidneys, brain, you name it. There is also a maculo-papular rash in secondary syphilis that looks very much like that found in Rocky Mountain spotted fever (RMSF) rash. History of the patient will help you differentiate the two. Secondary syphilis would most likely be in an adult, whereas children may have RMSF. RMSF patients look sicker.

- The patient will feel that they are getting better, but this is not true. Untreated, will go into latent syphilis
- Cutaneous lesions appear:
  - condylomata lata occur in the genital area. Do not confuse these with genial warts. They can be internal or external.
  - A petechial rash may develop. These occur following macular-papular rashes.
  - Dissemination to various organs, prominent rash, invasion of major organs (hepatitis, carditis), resolves spontaneously within weeks to months

Latent syphilis:
- A period where there is serologic reactivity but no clinical symptoms. Early latent syphilis is subject to relapses. Late latent syphilis has few, if any episodic relapses.
- Many times it is asymptomatic

Tertiary syphilis:
- Rarely seen in United States
- Lesions in skin called gummas. A gumma is basically a huge granuloma seen in various organs, e.g. skin, bones, testis.
- Progressive inflammatory disease, produce disabling lesions of the cardiovascular and central nervous systems.
- Endarteritis – T. pallidum attacks the endothelium leading to irregular, peeling intima layer reminiscent of a peeling onion. May lead to coronary occlusion and then aneurysm.
- Tabes dorsais – involvement of the posterior columns and dorsal roots of the spinal cord resulting in a strange gait.
- Neurosyphylis which can lead to insanity

Syphilis is truly a systemic disease. Can be treated at any stage, but treatment is always parenteral. Spirochetes do not replicate quickly, so you need a drug that will persist systemically for a long time.

- b-lactams
- protein synthesis inhibitors