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BACTERIOLOGY - CHAPTER FOURTEEN

SPIROCHETES AND NEISSERIA

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SPIROCHETES

The most important genera of spirochetes are *Treponema*, *Borrelia* and *Leptospira*. These are Gram negative bacteria that are long, thin, helical and motile. Axial filaments (a form of flagella) found between the peptidoglycan layer and outer membrane and running parallel to them, are the locomotory organelles.

Syphilis

Treponema pallidum pallidum

T. pallidum is the causative agent of syphilis, a common sexually-transmitted disease found world-wide (figure 1a). It is generally transmitted by genital/genital contact. Transmission *in utero* or during birth can also occur (figure 1b). Syphilis, chronic and slowly progressive, is the third most common sexually transmitted disease. After initial infection, a primary chancre (an area of ulceration/inflammation) is seen in genital areas (figure 4 and 6) or elsewhere (figure 3) within 10 to 60 days. The organism, meantime, has penetrated and systemically spread. The patient has flu-like symptoms with secondary lesions particularly affecting the skin (figure 5). These occur 2 to 10 weeks later. The final stage (if untreated) is tertiary syphilis (several years later). In primary and secondary syphilis organisms are often present in large numbers. However, as the disease progresses immunity controls bacterial replication and fewer organisms are seen. It is extremely difficult to detect spirochetes in tertiary syphilis. The systemic lesions of skin, central nervous system and elsewhere are suggestive of a delayed hypersensitivity reaction.

The organism cannot be cultured from clinical specimens. Thus, experimentally, syphilis is commonly studied in animal models. Also microscopic and serological methods are the only means of clinical diagnosis.

In primary syphilis (before immunity develops), the organisms are often present in sufficient numbers in exudates to be detected by dark field microscopy. In conventional light microscopy, the light shines through the sample and thin treponemes cannot be visualized. In dark field microscopy, the light shines at an angle and when reflected from the organism will enter the objective lens. The actively motile organisms appears brightly lit against the dark backdrop. Alternatively fluorescent antibody staining is used.

In secondary and tertiary syphilis, serological methods are usually used to detect syphilis. Screening methods are based on detecting serum antibodies to **cardiolipin** in patients (including VDRL test). The antibodies result from tissue

injury, with autoimmunity developing to self components. Thus, there are many other diseases that result in anti-cardiolipin antibodies and false positives are common. However, these are cheap screening tests. More definitive diagnosis is achieved by detecting the presence of "specific" serum antibodies against treponemal antigens. These tests are more expensive and usually performed (as a definitive diagnosis) on sera previously shown to be positive after first detecting antibodies to cardiolipin.

Primary and secondary syphilis occur within a year of infection and are sometimes referred to as "early syphilis". Patients with early syphilis are highly infectious..

Summary of Symptoms

Primary syphilis

- Usually a single firm, round sore (but there may be more). Usually on the genitals but can be elsewhere
- No pain at the site of the sore

The sore will heal without intervention

Secondary syphilis

- Rough red skin rash, often on the back (figure 6d) but can be elsewhere. The rash does not usually itch
- Sores on mucous membranes (seen in mouth, anus, vagina)
- Red spots (known as syphilids) on palms of hands and soles of feet (figure 6a, b and c)
- Fever
- Lymphadenopathy (swollen lymph glands)
- Sore throat
- Hair loss
- Headache
- Weight loss
- General malaise

Symptoms will resolve with or without treatment and the infection becomes latent.

Tertiary Syphilis

The disease, when untreated, can remain latent for years (even two to three decades) and most infected people do not develop further symptoms; however, if disease does reappear it can be very serious and sometimes fatal. The symptoms include:

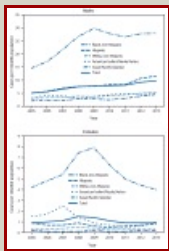
- Failure to coordinate muscle movements
- Paralysis
- Numbness
- Blindness
- Dementia
- Organ failure

Epidemiology

From 2005 to 2013, the number of primary and secondary syphilis cases

KEY WORDS

Spirochete
Axial filament
Treponema pallidum
Syphilis
Chancre
Primary Lesion
Darkfield microscopy
Secondary Lesion
Tertiary Lesion
Anti-cardiolipin antibodies
Borrelia burgdorferi
Lyme disease
Relapsing fever
Leptospira
(leptospirosis)
Neisseria
Thayer Martin agar
Oxidase test
N. gonorrhoeae
Gonorrhoea
N. meningitidis
Meningitis



Figure

1a. Annual rate of primary and secondary syphilis cases among males and females, by race/ethnicity — National Notifiable Diseases Surveillance System, United States, 2005–2013. CDC



Figure 1b

Umbilicus of an infant, which displayed an inflamed lesion that under a darkfield examination revealed the presence of *Treponema pallidum* spirochetes, and hence, a diagnosis of congenital syphilis. CDC



Figure 1c
The interior oral cavity of an elderly African-American male patient, revealing a perforated hard palate due to what was a congenital syphilis infection. At the time of this photograph, the patient was being treated for both active syphilis, and gonorrhea infections. CDC



Figure 2
Histopathology showing *Treponema pallidum* spirochetes in testis of experimentally infected rabbit. Modified Steiner silver stain. CDC/Dr. Edwin P. Ewing, Jr. epe1@cdc.gov

reported each year in the United States nearly doubled, from 8,724 to 16,663; the annual rate increased from 2.9 to 5.3 cases per 100,000 population. Most of these cases were in men (91.1% of all primary and secondary syphilis cases in 2013) and mostly in men who have sex with men. The rate per 100,000 among men increased from 5.1 in 2005 to 9.8 in 2013.

Treatment

No vaccine exists, but antibiotic therapy (usually penicillin G) is usually highly effective, including treatment of congenital syphilis.

Bejel

Treponema pallidum endemicum

This disease is rare (in the US) and is caused by organisms related to *T. pallidum*. *T. pallidum endemicum* is morphologically and serologically indistinguishable from *Treponema pallidum pallidum*.

Bejel, also known as endemic syphilis, is not transmitted sexually but via contact, for example hands to broken skin and mouth to mouth. The disease can also be spread by sharing eating utensils. It is a disease of low income groups with poor hygiene and often begins in childhood.

Depending on the route of transmission, skin or mucous membranes are the first to be infected but the bacterium can spread deeper to the bones. Thus, one sees sores in the mouth, throat and the nasal passages and the infected lesions can penetrate deep into the tissue causing major malformations of the face and limbs. This results in severe bone pain and there is also swelling of the lymph nodes. The *T. pallidum* organisms can be found in swabs of the sores.

Treatment

Treatment of bejel, which can be completely curative, is similar to syphilis, that is penicillin G or tetracycline.

Epidemiology

Bejel is found in the Middle-East, Africa, Australia and central Asia. It is also known as sahel disease in West Africa.

Pinta

Treponema carateum

Pinta is another non-venereal, treponematous disease which is caused by *T. carateum*. It occurs in the New World, particularly the Caribbean, central America and northern South America. Pinta is the Spanish for "painted". Again, it is a disease of poor regions with sub-standard hygiene and is spread by personal contact through cuts in the skin. This results in scaly red lesions (hence the name) which form a lump at the site of the primary infection. Small satellite lesions form around the primary lesion and lymph node swelling is also seen. Some months after the primary infection, the patient experiences more scaly red lesions that are now flat and tend to itch. These are the pintids and occur around or distant from the site of the primary infection. The color of the pintids changes to blue black with time and then can lose pigmentation. Unlike bejel, the disease does not spread deep into the tissues and bones. Detection is via serology or direct examination of lesion specimens under the light microscope.

Treatment

Treatment of pinta is again curative and can be accomplished by a single injection of penicillin G.

Yaws

Treponema pertenue

Yaws (figure 7) is another chronic treponematous disease of poor hygiene. It can be very disfiguring. It strikes mainly children in Africa, south Asia and northern South America. The causative agent is *T. pertenue*. As with pinta and bejel, spread is via direct contact through skin lesions. About a month after the infection, a papule forms at the infection site which transforms into a crusted ulcer that takes months to heal. Painful swelling of the lymph nodes occurs. Later, soft growths appear on the face, buttocks and limbs. They can also occur in the bottoms of the feet causing the infected person to have a very characteristic walk which gives rise to the name of "crab yaws". Further formation of tumors and ulcers on the face can cause bone malformation and can be disfiguring. Microscopy (of samples from the lymph nodes) is diagnostic and there are various serological tests.

Treatment of yaws is also a single penicillin G injection which can be completely curative



Figure 4 Primary syphilis. Primary chancre on the glans The University of Texas Medical Branch

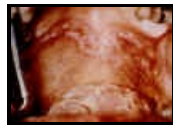


Figure 5 Secondary syphilis - mouth mucosa Bristol Biomedical Archive © University of Bristol. Used with permission



Figure 6 Primary syphilis. A vulvar chancre and condylomata acuminata The University of Texas Medical Branch



Figure 6a. Secondary syphilis: Soles of both feet of a syphilis patient revealing the presence of secondary syphilitic lesions consisting of erosive dermal regions of the toes, mainly involving the intertriginous spaces between the toes. CDC



Figure 6b. Secondary syphilis: Soles of feet of a syphilis-infected patient (plantar syphilids) in a secondary syphilitic infection. CDC



Figure 6c. Secondary syphilis: Palms of hands showing palmar syphilids, due to secondary syphilis. Rash may include forearms. CDC



Figure 6d. Secondary syphilis: Upper back and neck of patient with a maculopapulosquamous outbreak of nodular syphilids. CDC



Figure 7a. Yaws is a crippling and disfiguring disease affecting some 50 million people in the world © WHO



Figure 7b. Discolored areas indicative of pinta. Pathologic changes accompanying this discoloration include thickening of the epidermis, followed by scaliness and drying of the skin, known as acanthosis. CDC



Figure 3 Primary Syphilis Bristol Biomedical Archive © University of Bristol. Used with permission

Lyme disease

Borrelia burgdorferi

Lyme disease is caused by *Borrelia burgdorferi* (figure 8a,b and 13) and is a relatively newly recognized disease. It is found widely in the United States (figure 9) but is most concentrated in the north east and mid west. The number of cases peaked in 2009 (figure 10a).

Although clinically first described in 1975, the role of a tick-borne spirochete was not proven until 1983. These ticks (figure 12) infect a large array of wild life. A tick bite leads to transmission of *B. burgdorferi* causing an erythematous skin rash (figure 11) in a few days along with a transient bacteremia leading to (weeks or months later) severe neurologic symptoms or polyarthritis. Cardiac problems may occur in a minority of cases (figure 10c). Cases of Lyme disease occur primarily in the summer months in the United States because of increased outdoor activities leading to increased likelihood of picking up a tick.

If antibiotic therapy is initiated early, a cure is usually achieved. However, late antibiotic administration (penicillin or tetracycline) is often ineffective.

The life cycle of Lyme disease ticks is shown in figure 14a.

WEB RESOURCES
Some facts about Syphilis
CDC

Some facts about Lyme
disease
CDC



Figure 8a

Histopathology showing *Borrelia burgdorferi* spirochetes in Lyme disease. Dieterle silver stain. CDC/Dr. Edwin P. Ewing, Jr. epe1@cdc.gov



Figure 8b

Under a high magnification, this digitally-colored scanning electron micrograph depicts three Gram-negative, anaerobic, *Borrelia burgdorferi* bacteria, which had been derived from a pure culture.



Figure 9

Incidence of Lyme disease by county in the United States 2012. CDC

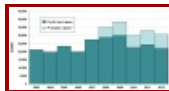


Figure 10a

The number of reported cases of Lyme disease from 2003 through 2012. The number of confirmed cases ranged from a low of 19,804 in 2004 to high of 29,959 in 2009. CDC

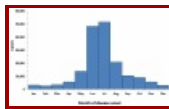


Figure 10b

Lyme disease patients are most likely to have illness onset in June, July, or August and less likely to have illness onset from December through March. CDC

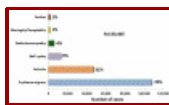


Figure 10c

Breakdown of reported Lyme disease cases from 2001 to 2010 by disease manifestation. The majority of cases are the EM rash. Other manifestations are less common, some patients have more than one presentation. CDC



Figure 11a

Left anterior chest and shoulder region of a patient who'd presented with the erythema migrans (EM) rash characteristic of what was diagnosed as Lyme disease, caused by the bacterium, *Borrelia burgdorferi*. CDC



Figure 11b Lyme disease rash CDC



Figure 12 *Ixodes scapularis* (deer tick), tick vector for Lyme disease. Its abdomen is engorged with a host blood meal, this image shows a lateral view of a female. CDC

Diagnosis

B. burgdorferi is highly fastidious, growing extremely slowly in tissue culture (not bacteriological) media. The vast majority of body fluid or tissue samples from patients with Lyme disease do not yield spirochetes on culture. Lyme disease is thus usually diagnosed by detection of serum antibodies to *B. burgdorferi*. However, acutely antibodies may not occur in detectable titer, making early diagnosis difficult. However, late diagnosis may lead to ineffective treatment. Many patients are unaware of having had a tick bite or a rash.

Etiology

The chronic arthritis clinically resembles rheumatoid arthritis. Live agent is almost never cultivated from the joint (in common with other forms of reactive arthritis such as Reiter's syndrome and rheumatic fever). However, small numbers of persistent spirochetes and borrelial antigens have been detected histologically in human tissues. Whether the organism persists in a viable form or not remains to be determined. Thus, there is no clear explanation for the immunopathologic stimulus for chronic tissue injury in Lyme arthritis.



Figure 13 Morphology of *Borrelia burgdorferi*. Dark field image © Jeffrey Nelson, Rush University, Chicago, Illinois and The MicrobeLibrary

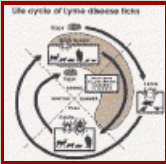


Figure 14a Life cycle of Lyme disease ticks CDC



Figure 14b Tick borne relapsing fever. During the years 1990-2011, 483 cases of TBRF were reported in the western U.S., with infections being transmitted most frequently in California, Washington, and Colorado. CDC

Relapsing fever

Borrelia hermsii and *Borrelia recurrentis*

There are two types of relapsing fever:

- Tick-borne relapsing fever (TBRF)
- Louse-borne relapsing fever (LBRF)

Tick-borne relapsing fever occurs in the western United States and is usually linked to sleeping in rustic, rodent-infested cabins in mountainous areas. Louse-borne relapsing fever is transmitted by the human body louse and is generally restricted to refugee settings in developing regions of the world.

There are fewer than 100 cases of relapsing fever per year in US. During the years 1990-2011, 483 cases of TBRF were reported in the western United States.

Relapsing fever (with associated bacteremia) is caused by species of *Borrelia* that are transmitted by tick (*Borrelia hermsii*, rodent host) and lice (*B. recurrentis*, human host) bites. The term relapsing fever is derived from the following repeating cycle. As an immune response develops the disease relapses. However, the antigens expressed change and the disease reappears.

The organism is extremely difficult to culture and there is no serological test. The organism is generally detected by blood smear.

Leptospirosis

There are fewer than 100 cases of leptospirosis per year in US. This flu-like or severe systemic disease is a zoonotic infection. *Leptospira* (figure 15) are transmitted in water contaminated with infected urine from wild animals (including rodents) and farm animals and can be taken in through broken skin (e.g. bathing). *Leptospira* particularly infect the kidney (figure 16), brain and eye. They are the most readily culturable of the pathogenic spirochetes; but this is not routine and diagnosis is usually by serology.

Treatment

Leptospirosis is treated with antibiotics, such as doxycycline or penicillin, which



Figure 15 Scanning electron micrograph of *Leptospira interrogans* strain RGA. Two spirochetes bound to a 0.2 μm filter. Strain RGA was isolated in 1915 by Uhlenhuth and Fromme from the blood of a soldier in Belgium. CDC/NCID/Rob Weyant rsw2@cdc.gov

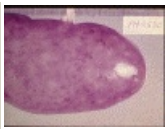


Figure 16

Leptospirosis in the kidney Bristol Biomedical Archive © University of Bristol. Used with permission

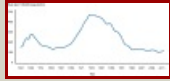


Figure 17a

Gonorrhea — Rates by Year, United States, 1941 – 2012. CDC



Figure 17b

Gonorrhea—Rates by Age and Sex, United States, 2012. CDC



Figure 17c

Gonorrhea — Rates by Sex, United States, 1992 – 2012. CDC



Figure 17d

Gonorrhea — Rates by County, United States, 2012. CDC

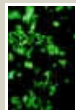


Figure 17e

Positive FA test for *Neisseria gonorrhoeae*. This strain was penicillin-resistant. CDC

WEB RESOURCES

[Some facts about gonorrhea](#)
CDC

[Diagnosis of Neisseria gonorrhoeae](#)
CDC Division of AIDS, STD, and TB Laboratory Research

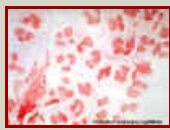


Figure 18

Neisseria gonorrhoeae Gram stained urethral discharge. The image shows many polymorphonuclear leukocytes (PMNs) and gram-negative extra- and intra-cellular diplococci. (1,000X oil) © J. Michael Miller
Centers for Disease Control and Prevention Atlanta, Georgia and The

should be given early in the course of the disease. Intravenous antibiotics may be required for persons with more severe symptoms. Persons with symptoms suggestive of leptospirosis should contact a health care provider.

NEISSERIA

Neisseria are Gram negative diplococci (pairs of cocci). These bacteria grow best on chocolate agar (so-called because it contains heated blood, brown in color); a modified (selective) chocolate agar commonly used is Thayer Martin. The colonies are oxidase positive (i.e. produce cytochrome oxidase) which is demonstrated by flooding the plate with a dye which on oxidation changes color.

N. gonorrhoeae (the "gonococcus")

N. gonorrhoeae (figure 20 and 21), found only in man, is the causative agent of gonorrhea, the second most common venereal disease. Gonorrhea has recently declined after a peak in 1976 (figure 17a). The disease particularly occurs in younger adults (figure 17b) and is found equally in males and females (figure 17c). Highest rates in the United States are in the southeast (figure 17d).

N. gonorrhoeae often causes an effusion of polymorphonuclear cells. A smear (figure 18, 19) may show the presence of Gram negative cocci present in cells. However, culture is essential for definitive diagnosis. There is a fluorescent antibody test (figure 17e).

A common feature of disseminated gonococcal disease is arthritis. Although commonly considered a form of septic arthritis, in many cases gonococci cannot be isolated from the joint (i.e. they are "reactive" in nature). Dermatitis is also common.

Penicillin therapy is still usually effective. However, resistant strains producing beta lactamases are sufficiently common that alternatives are recommended for all gonococcal infections; this includes ceftriaxone (a beta lactamase-resistant cephalosporin).

Because of increasing antibiotic resistance, new therapies to treat gonorrhea have been sought. Two new antibiotic regimens using existing drugs - injectable gentamicin in combination with oral azithromycin and oral gemifloxacin in combination with oral azithromycin - successfully treated gonorrhea infections in a clinical trial. The injectable gentamicin/oral azithromycin combination appears to be 100% effective in curing genital gonorrhea infections, and while the oral gemifloxacin/oral azithromycin combination was 99.5% effective.

There is no vaccine since strains are highly variable in their external antigens (both outer membrane and pili). Both are involved in the initial adhesion of the organism to genital epithelium.

IgA proteases (also produced by *N. meningitidis*) are involved in successful colonization. As for many other bacterial infections, a role for both the lipopolysaccharide and peptidoglycan in tissue injury have been suggested. Exotoxins are not believed to be of importance in pathogenesis.

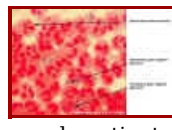


Figure 19 Gram Stain from *Neisseria gonorrhoeae* Infection Urethral discharge from a male patient. Stain shows gram-negative diplococci both intracellular and extracellular to a polymorphonuclear leukocyte or puss cell. In a symptomatic male patient, this Gram stain finding is considered diagnostic of the sexually transmitted disease caused by *Neisseria gonorrhoeae*. In female patients, one cannot use this type of finding as diagnostic of *N. gonorrhoeae* infection because the female genital tract may contain commensal *Neisseria* species. © Gloria J. Delisle and Lewis Tomalty, Queens University, Kingston, Ontario Canada and The MicrobeLibrary



Figure 20 Scanning electron micrograph of *Neisseria gonorrhoeae* © Margaret Ketterer, University of Iowa, Iowa City, Iowa USA and The MicrobeLibrary



Figure 21 *Neisseria gonorrhoeae* - coccoid prokaryote (dividing); causes gonorrhoea (SEM x 40,000) © Dennis Kunkel Microscopy, Inc. Used with permission



Figure 22
Neisseria meningitidis, group C, in spinal fluid. CDC/Dr. M.S. Mitchell



Figure 23
Neisseria meningitidis - coccoid prokaryote (dividing); causes meningitis and Waterhouse-Friderichson syndrome (a fulminating meningococcal infection occurring mainly in children under ten years old) © Dennis Kunkel Microscopy, Inc. Used with permission

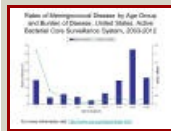


Figure 24
Rates of meningococcal disease in the United States by age group. CDC

***Neisseria meningitidis* (the "meningococcus")**

This organism (figure 22 and 23) resides only in man. The majority of cases are sporadic cases most commonly seen among young children (figure 24). Outbreaks occur usually among adults living in confined and crowded conditions (e.g. university dorms, army barracks, prisons). Initial infection of the upper respiratory tract (involving binding by pili) leads to invasion into the bloodstream and from there to the brain. Indeed, it is the second most common cause of meningitis (pneumococcus is the most common). *Neisseria meningitidis* is usually fatal if untreated but responds well to antibiotic therapy. Thus, rapid diagnosis is important. The organism is often detectable in spinal fluid (Gram negative diplococci within polymorphonuclear cells) or antigenically. Culture on Thayer Martin (or similar) agar is essential for definitive diagnosis. Penicillin is the drug of choice.

Meningococci vary antigenically and can be serogrouped with anti-capsular antibodies. The capsule is an important pathogenesis factor allowing inhibition of phagocytosis.

There are effective meningococcal vaccines that protect against most types of meningococcal disease, although they do not prevent all cases. There are two vaccines against *Neisseria meningitidis* available in the United States: meningococcal polysaccharide vaccine (Menomune) and meningococcal conjugate vaccine (Menactra, Menveo and MenHibrix). In the United States, vaccines are approved and routinely used against serogroups C and Y (in addition to A and W, which circulate globally), but not B. A serogroup B meningococcal vaccine that is licensed for use in Europe, Canada, and Australia has been used in the United States to help control 2 outbreaks of this disease in universities.

Non-pathogenic species morphologically resembling *Neisseria* are found in the normal flora of the oropharynx but can be differentiated from the pathogenic *Neisseria* readily. These occasionally cause opportunistic human disease (including pneumonia).



Return to the Bacteriology Section of Microbiology and Immunology On-line