Sexually Transmitted Infections

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The terms STIs (sexually transmitted infections) and STDs (sexually transmitted diseases) are interchangeable. However, more authors now favor using STI because not all "infections" are manifest as "disease" – that is they are not clinically evident or symptomatic.

A note on terminology. One preventative method that applies to all STIs discussed here is "safer sex" which refers to risk-reduction methods that persons can take to reduce the chances of acquiring or transmitting an STI. While risk-reduction will be different for each person's circumstance, in general, this refers to: use of barrier methods (condoms – male, female, oral), sharing of sexual health history between new partners, avoiding intoxication with drugs/alcohol, avoid douching after sex for females, regular self-exam and STI screens, and exploring sexual activities other than vaginal, anal, and oral sex that do not involve exchange of body fluids.

Definition of Sexually Transmitted Infections

STIs are Infections transmitted through (typically) sexual acts involving contact of skin/mucosal surfaces of the penis, vagina, rectum and oropharynx or exchange of body fluids at these sites.

STI Syndromes and Associated Pathogens

SYNDROME	ORGANISM
GENITAL ULCERS	
Genital herpes	Herpes simplex
Syphilis	*Treponema pallidum*
Chancroid	*Haemophilus ducreyi*
Lymphogranuloma venereum	*Chlamydia trachomatis* serovar L1-L3
Granuloma inguinale (Donovanosis)	*Klebsiella granulomatis*
EPITHELIAL CELL INFECTIONS	
Genital warts	Human papillomavirus
Cervical neoplasia	Human papillomavirus types 16 and 18
URETHRITIS	
Gonococcal	*Neisseria gonorrhoeae*
Nongonococcal	*Chlamydia trachomatis*
	Trichomonas vaginalis
	Herpes simplex (primary infection)
FEMALE GENITAL DISCHARGE	
Cervicitis	*Neisseria gonorrhoeae*
	Chlamydia trachomatis
	Trichomonas vaginalis
	Herpes simplex
Bacterial vaginosis	*Gardnerella vaginalis*, anaerobes
Vaginitis	*Trichomonas vaginalis*
	Candida albicans

Modified from Table 269-1. Swygard H, Cohen MS. Approach to the Patient with a Sexually Transmitted Infection. In: Goldman L, Schafer AI, eds. Goldman-Cecil Medicine. 26th ed. Philadelphia, PA: Elsevier; 2020. pp. 1841-1845.e2

STIs caused by ectoparasites that are not covered in the large group teaching sessions are: genital scabies and pubic lice.

Genital Herpes – Herpes Simplex Virus: HSV-2, HSV-1 – see session on Herpes Viruses in FMS502 for review here

Table: HSV-1 and HSV-2

Designation	Common Name	Transmission	Primary Infection Site	Disease	Latent Infection Site
HHV-1	Herpes simplex virus 1 (HSV-1)	Close contact	Mucoepithelial cells	Oral (fever blisters), ocular lesions; encephalitis	Nerve ganglia
HHV-2	Herpes simplex virus 2 (HSV-2)	Close contact Sexual transmission	Mucoepithelial cells	Genital, anal lesions; severe neonatal infections; meningitis	Nerve ganglia

Modified from Table 14.1. Herpesvirus. Ryan. Sherris Medical Microbiology, 7e

Overview

8 HHVs divided into 3 genera of herpesviruses with HSV being in the α group.

Epidemiology

Genital herpes most frequently due to HSV-2 where HSV-1 is more frequently associated with facial herpes – but this is not absolute – depending on the nature of the transmission (which mucosal parts are in contact), either subtype can cause either syndrome.

Asymptomatic shedding accounts for transmission from a partner who has no active genital lesions and often no history of genital herpes and is an important part of transmission *and* facilitated transmission of other STIs.

Prevalence is higher in: female gender, women using hormonal contraception, high number of lifetime sex partners, higher prevalence in black americans. Transmission is greater from males to females;

Microbiology and Pathogenesis (review)

ds-DNA - icosahedral – enveloped virus

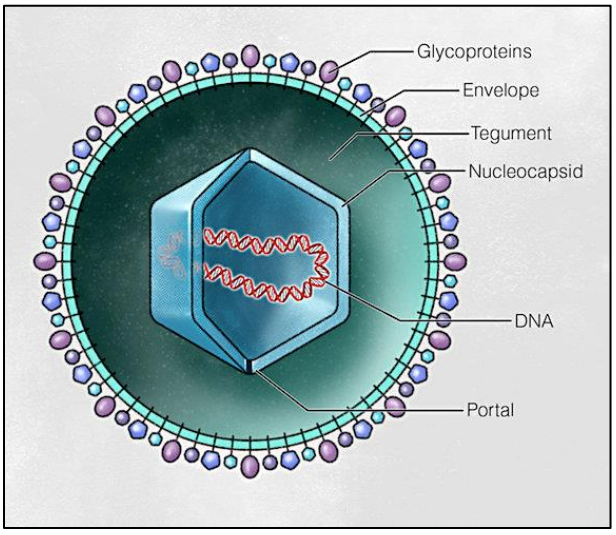


Fig. 5 Herpes simplex virus STD Module, National STD Curriculum
https://www.std.uw.edu/go/pathogen-based/hsv/core-concept/all#page-title

Following entry, capsid migrates to nucleus where genome extruded into it, circularizes and expresses its genes through a series of mRNA transcriptions to encode proteins. Thymidine kinase and DNA polymerase, distinct from host cell enzymes, are the targets of antiviral chemotherapy.

Herpesviruses assemble in the nuclei. Envelope acquired from the nuclear membrane, budding occurs and virions transported through the endoplasmic reticulum and Golgi. De-envelopment through the cytoplasmic membrane with release of virions. Host cell protein shut off occurs for α- and γ-herpesviruses (but not β-herpesviruses: CMV, HHV-6 and HHV-&) causing cell death.

Latent infection for the life of the host occurs for all Herpesviruses. While there is an initial lytic phase eventually controlled by the host immune system, lifelong latency is also established. During latency, the genome of the virus is present in cells, but infectious virus is not recovered. The viral DNA is maintained as an episome in the nucleus with minimal gene expression until and if reactivation occurs.

Multinucleated giant cells, focal necrosis, eosinophilic nuclear inclusions, inflammation with initial inf PMNs and then mononuclear cell infiltrate.

Spreads to local sensory neurons and then retrograde to sensory ganglia (face - trigeminal ganglia, genital - dorsal root or sacral ganglia).

Because latent infection does not require synthesis of early or late viral polypeptides, antiviral drugs directed at the thymidine kinase enzymes or viral DNA polymerase do not eradicate the virus in its latent state.

Initial disease is often more severe than recurrent infection. Recurrent infection is kept in check by the host immune system.

Clinical Findings

Primary Disease
Incubation 5 days
Symptoms can be relatively severe in primary infection – fever, malaise, myalgias
Grouped painful vesicles that pustulate and leave shallow ulcers that can coalesce and *heal without scarring.*
Duration 2-3 weeks
Bilateral tender inguinal nodes can persist for weeks to months
Primary disease more likely has complication of aseptic meningitis
Since this primary disease, patients have not yet developed antibodies to HSV

Recurrent/Reactivation Disease
Prodromal paresthesias 12-24 hours before lesions
Milder pain compared to primary and itching is common
Usually lasts 3 days
Shedding without evident disease is common (especially with HSV-2)
Symptomatic reactivation frequency

- HSV-2: 1st year of infection median 4-5x / year then 3-4x / year
- HSV-1: 1st year median 1x / year then none in subsequent years

Unrecognized and Asymptomatic Infection
~80% of people seropositive for HSV-2 have not received a diagnosis of genital herpes
Of these patients:

- 1/4 are truly asymptomatic (or have unobserved or unseen lesions such as on the cervix)
- 3/4 symptoms are very mild, or it has been misdiagnosed

Complications of Genital HSV Infection
Aseptic meningitis (about 10% of aseptic meningitis cases due to HSV)
Uncommon: radicular pain, transverse myelitis, hepatitis
Genital HSV facilitates both acquisition and transmission of HIV

Neonatal Herpes (one of the TORCH infections)

Defined as HSV in neonate within 4 weeks of birth
Most likely from mothers with primary genital herpes and thus lack of transplacental type-specific HSV-2 antibodies
Risk 10-30x greater with primary disease than if mother shedding HSV during a recurrent HSV infection
Skin lesions, and disseminated disease may involve multiple organ systems, including the liver, lungs and CNS

Diagnosis

The diagnosis can be presumptively made in setting of classic presentation, but should be confirmed with virologic testing and typing. Virologic testing is particularly important for patients with atypical symptoms.

- *Virologic testing*
  - Preferred: Skin swab/scraping of the base of lesion for NAAT/PCR or cell culture
- Older version: Tzanck smear (Giemsa or PAP smear) less sensitive but quick – rarely performed due to lack of point of care microscopy

In the absence of a lesion, *serologic* testing can provide some utility, especially for: patients with recurrent or atypical genital symptoms with negative HSV cultures, and *screening* of asymptomatic persons in select instances (e.g. determining susceptibility to HSV in individual with sex partner who has HSV, asymptomatic pregnant women, etc). Serologic tests do not distinguish Type-2 very well and cannot determine whether the history is oral or genital herpes.

Treatment

General Principles and Pharmacology

- Episodic therapy:
  - Used to treat first clinical and recurrent episodes at onset of symptoms. 7-10days
- Suppressive Therapy:
  - Used daily to prevent recurrences or transmission
  - Reduces frequency of recurrences by 75% and transmission to discordant susceptible partner
  - No evidence that therapy leads to drug resistance
  - Suppressive therapy is recommended for persons with HIV infection, and those at risk for HIV as herpes activity increases risk for HIV
- Antiviral therapy does not eradicate HSV, nor impact the risk, frequency, or severity of recurrences after the medication is discontinued
- Acyclovir (and its prodrugs valacyclovir, famciclovir):
  - MOA: Nucleoside analog converted by viral thymidine kinase to a form used by viral polymerase in trying to form replicating viral genomes but prevented from doing so because of the lack of hydroxyl group resulting in chain termination.

Prevention

Safer sexual practices
Suppressive therapy for those with discordant partner
Suppressive therapy for pregnant women starting at 36 weeks if any lesions occurred during pregnancy
C-section for mothers with active lesions during labor to prevent (but not totally eliminate) neonatal herpes

Syphilis: *Treponema pallidum*

Overview

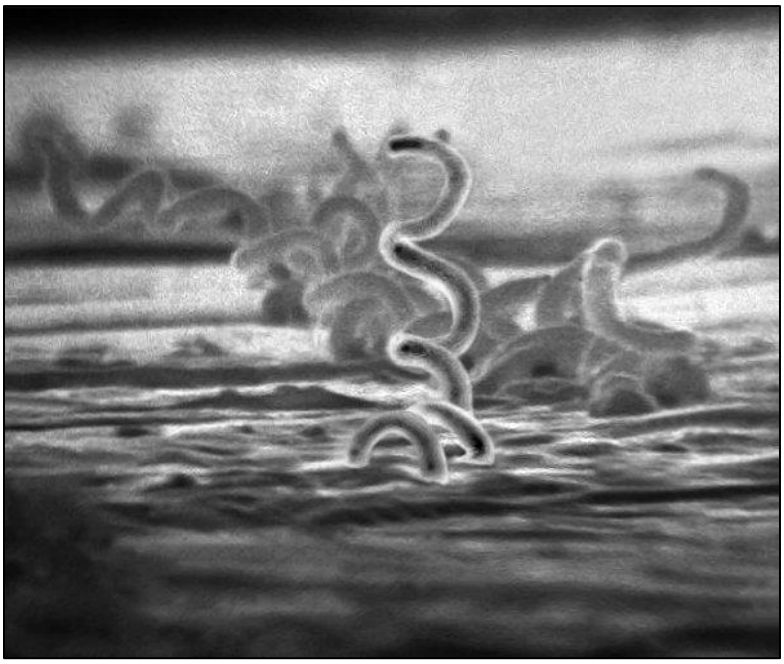
Syphilis is an exclusively human microbe. It is a spirochete which causes a variety of clinical manifestations depending on the stage of infection. It is called the "great imitator" because of the wide variety of clinical manifestations and complications. Sir William Osler felt that if you knew syphilis, you would know medicine. In an address to the New York Academy of Medicine in 1897, he stated: *"Know syphilis in all its manifestations and relations, and all other things will be added unto you."*
And according to Dr. Breems, "Syphilis is *always* on the differential!"

Epidemiology

Highest prevalence (US): MSM, persons living with HIV, commercial sex worker, persons with substance abuse disorders (esp. illicit drugs)
After significant decline, incidence of primary and secondary syphilis has now risen since 2001 with cases in men >> women

Transmission: sexual (through breaks in skin or mucosa), human bites, vertical from mother to fetus, blood transfusion (rare)

Microbiology and Pathogenesis (review prior session in FMS 503 on spirochetes here)



SEM photomicrograph Treponema pallidum rabbit epithelial cell culture CDC PHIL
https://phil.cdc.gov/Details.aspx?pid=1977

Highly motile corkscrew-shaped microaerophilic spirochete with minimal proteins, no LPS
Wound axial filaments are thought to cause a spinning and bowing motility

Too thin to be seen by routine stains or by light microscopy
Visualization requires dark-field microscopy (uncommon in commercial labs) or in fixed specimens by silver stain or fluorescent antibody methods (preferred method for pathology specimens/biopsy)
Historically unable to culture syphilis – recent advances in cultivation in mammalian cell culture, but limited to research so far.
Fragile - killed quickly by heating, drying, disinfectants

Reaches subepithelial tissues through microscopic or macroscopic breaks in skin
In submucosa, multiplies slowly (division time 30 minutes) inducing little tissue reaction (probably due to paucity of surface antigens
As lesion progresses, basic pathologic finding is an endarteritis
    Small arteriole endothelial cells proliferate reducing lumen causing ischemic necrosis
    Dense granulomatous cuffs of lymphocytes, monocytes and plasma cells surround vessels
Primary lesion heals spontaneously
However, spirochetes spread from primary site to bloodstream within minutes and are established in distant tissues within hours
Activated macrophages and T-lymphocytes play a major role in the clearance of T pallidum from early syphilitic lesions

Clinical Findings

Forms of Syphilis:

- Acquired (sexually transmitted)
    - Stages: Primary, Secondary, Latent, Tertiary
    - Locations: Neurosyphilis, Ocular syphilis

Two Important Facts

Before clinical signs or symptoms appear, *T. pallidum* invades the circulatory system, lymphatic system and regional lymph nodes.
Neurosyphilis and ocular syphilis can occur at any stage of infection.

Natural Course of Syphilis

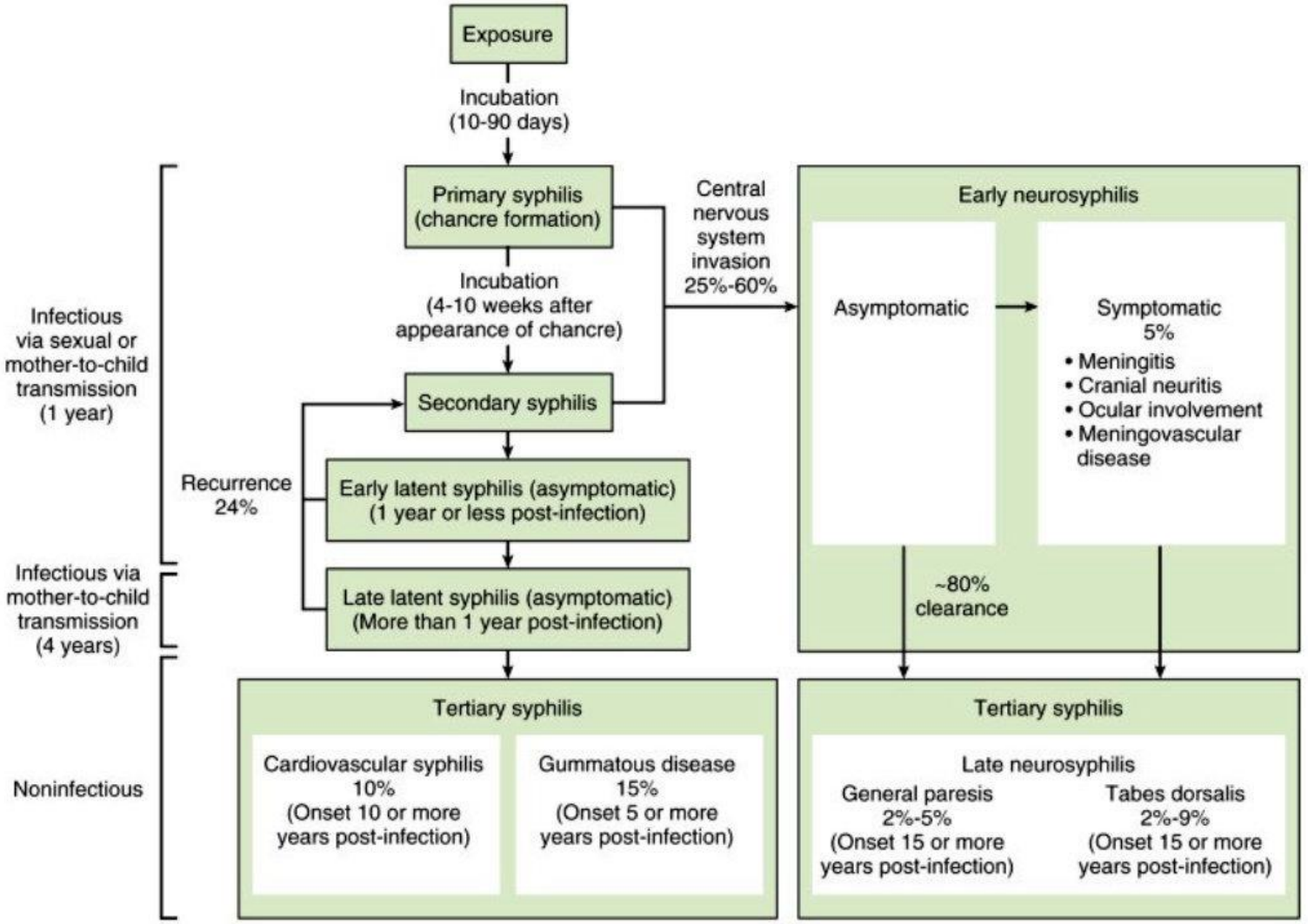


Fig 237.5 from Radolf JD et al. Syphilis (*Treponema pallidum*). In: Bennett JE, Dolin R, Blaser MJ, eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 9th ed. Philadelphia, PA: Elsevier; 2020. Chapter 237, pp. 2865-2892.

Primary syphilis (Chancre stage)
Incubation after entry ~3 weeks (range 10-90 days)
*Painless, 1-2 cm chancre with indurated edges (*Chancres teeming with spirochetes, highly infectious!)
Regional firm, nontender adenopathy, usually bilateral
Heals spontaneously in 1-6 weeks
Untreated patients go on to develop later manifestations

Secondary Syphilis (if you don't want it… don't touch it)
Incubation 4-10 weeks after onset of chancre (therefore, primary and secondary may overlap in some)
Rash

- 75-100% of patients
- Macular, papular, squamous or combination
- Chest, back, *palms and soles*
- Teeming with spirochetes - wear gloves
- NOTE: ANY new onset macular, papular, squamous rash -- consider testing for secondary syphilis

Lymphadenopathy (50-86% of patients)
Systemic symptoms: Malaise, fevers
Mucous patches: Flat patches in oropharynx or genital areas (6-30% of patients)
Condyloma Lata

- 10-20%of patients
- Moist, heaped up, wart-like papules in perineal or perianal areas

- Teeming with spirochetes - wear gloves!

Alopecia
Visceral organs: liver, kidney, lungs, GI tract, spleen
Neurosyphilis: See below
If untreated, relapses of secondary symptoms may occur in 25% of untreated patients, usually within first year of infection

Latent Syphilis
Persistence of *T. pallidum* without any signs or symptoms
Early latent syphilis (infection < 1 year)
Late latent syphilis (infection > 1 year, or unknown duration)

Tertiary Syphilis (Other Than Neurosyphilis)
Historically ~30% of patients with untreated syphilis progress to this stage – overall pretty rare
Destructive gummas that resemble carcinoma involving skeleton, eyes or viscera on average 10-15 years after infection
Cardiovascular syphilis involving aortic vasa vasorum causing ascending and/or transverse aortic aneurysm, aortic insufficiency or coronary ostial stenosis appearing about 20-30 years after infection

Neurosyphilis – involvement of the CNS at any stage. 
Early Neurosyphilis

- Usually within a few months to a few years of initial infection
- Acute meningitis
- Acute basilar meningitis involving CN III, VI, VII, VIII
- Meningovascular syphilis - endarteritis causing stroke

Late Neurosyphilis

- Decades after infection
- Generalized paresis due to cortical degeneration (mnemonic: personality, affect, reflexes, eyes, sensorium, intellect, speech)
- Tabes dorsalis due to demyelination of the posterior columns resulting in loss of proprioception manifesting as wide-based ataxic, slapping gait; positive Romberg test
- Argyll Robertson pupil: “accommodating but not reactive”

Ocular Syphilis
Can develop at any stage
Any part of the eye: uveitis, vitritis, interstitial keratitis, retinal detachment 
Primary optic atrophy is unique to late syphilis (with tabes dorsalis)

Congenital Syphilis (part of TORCH)
Transmitted from pregnant woman with syphilis to fetus is virtually 100%
Can occur during any stage of of syphilis but risk higher with primary or secondary syphilis
Can lead to stillbirth, neonatal death or infant disorders
Classified as either early or late disease
Characterized by a vasculitis with progression to necrosis and scarring

Early Congenital Syphilis (child < 2 y/o)
Snuffles: bloody rhinitis
Mucocutaneous rash

- Erythematous maculopapular or vesiculobullous lesions followed by desquamation
- Involvement of hands and feet common
- Mucous patches
- Condylomata

Bone involvement, osteochondritis (frontal bossing, saddle nose)
Alopecia, lymphadenopathy, meningitis
Nephritis
Hepatosplenomegaly

Thrombocytopenia, anemia

Late Congenital Syphilis (child > 2 y/o)
Scarring at sites of persistent infection and inflammation
Bone lesions: frontal bossing, shortened maxilla, high palatal arch
Saber shins
Perforation of hard palate
Hutchinson triad

- CN VIII deafness
- interstitial keratitis
- Hutchinson teeth

Diagnosis – requires combination of clinical findings and serologic combination testing

Direct Detection of T. pallidum (rarely used)
A. Dark-Field Microscopy
Definitive method for diagnosing early syphilis by examining exudate or tissue
Rarely used in clinical practice because lack of access, inexperience

B. Direct Fluorescent Antibody Test
Identify T. pallidum antigens in oral or rectal lesions that may have background non-pathogenic spirochetes

Nontreponemal Serologic Test
VDRL, RPR measure IgM and IgG antibody to cardiolipin (beef heart lipid complex)
Not specific for T. pallidum
False positives with a variety of autoimmune diseases or in diseases involving substantial tissue or liver destruction, such as lupus erythematosus, viral hepatitis, infectious mononucleosis, and malaria
4-fold change in titer (two dilutions) considered significant change when monitoring for treatment response (decrease in titer) or reinfection (increase)
Valuable for monitoring treatment because the height of the antibody titer is directly related to activity of disease
False negative reactions can occur with the "prozone effect": Very high serum antibody amounts supersaturate antigens preventing cross-linking lattice formation needed to see the flocculation reaction

Treponemal Serologic Tests (antibodies specific to T. pallidum)
TP-PA, FTA-ABS, EIA, CIA
Most often remain *reactive for life* - cannot be used to assess treatment response

Standard (Traditional) Screening Algorithm
Initial nontreponemal test with follow up with a treponemal test if positive

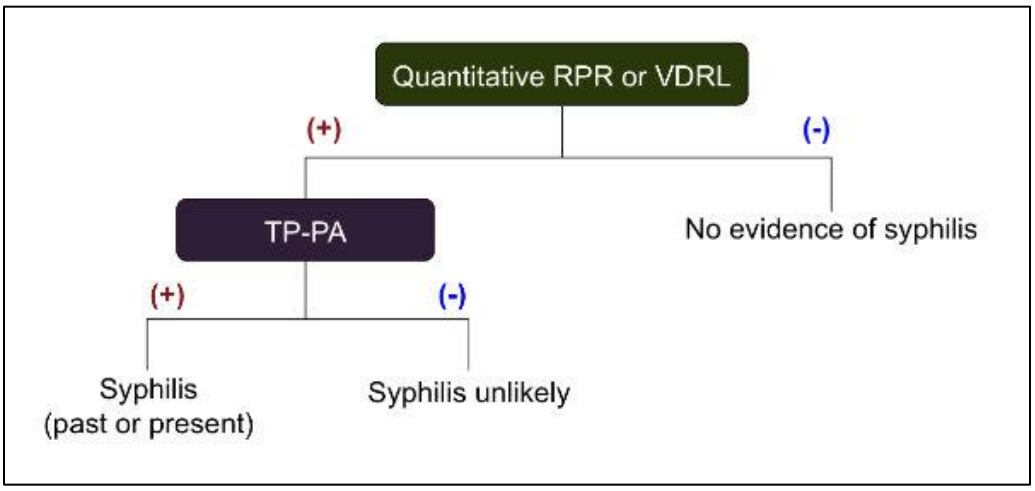


Fig. 25 Syphilis STD Module, National STD Curriculum
https://www.std.uw.edu/go/pathogen-based/syphilis/core-concept/all#laboratory-diagnosis

Reverse Sequence Screening Algorithm (increasingly more common)
Advances in the speed and economy of automated and point-of-care tests have led to this approach
Positive EIA or CIA test followed by nontreponemal test
In case the nontreponemal test is negative, a second but different treponemal test is done
Advantages of the reverse sequence algorithm include improved detection of early primary and treated infection, low cost, and reduced laboratory time and effort

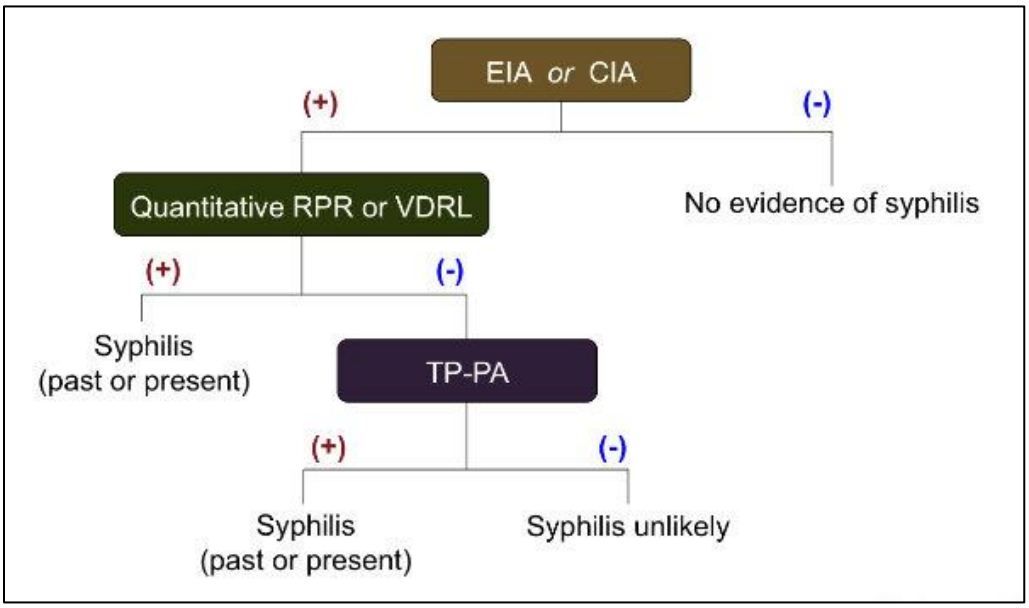


Fig. 26 Syphilis STD Module, National STD Curriculum
https://www.std.uw.edu/go/pathogen-based/syphilis/core-concept/all#laboratory-diagnosis

Treatment

Primary and secondary syphilis	Benzathine penicillin G 2.4 million U IM one dose
Early latent syphilis	Benzathine penicillin G 2.4 million U IM one dose
Late latent syphilis	Benzathine penicillin G 2.4 million U IM one dose per week x 3
Tertiary syphilis	Benzathine penicillin G 2.4 million U IM one dose per week x 3
Neurosyphilis or ocular syphilis	Aqueous penicillin 3-4 million U IV q4h x 10-14 days

Jarisch-Herxheimer Reaction
System reaction associated when starting antibiotics (especially penicillin) to treat spirochetal infections
Common with secondary syphilis (when bacteria counts are higher) but can occur at any stage
Due to creation of a cytokine storm caused by the abrupt release of lipoproteins and other PAMPs (pathogen associated molecular proteins such as LPS) from lysed spirochetes
Fever, chills malaise, myalgias, headache, nausea, vomiting, tachycardia, flushing, and hypotension
Occurs within hours of starting antibiotics and resolves within 24 hours
NOT an allergic reaction
Managed with antipyretics, fluids
Patient should be warned and watched while initiating antibiotics

Prevention

Mandatory reporting and contact tracing
Safer sex practices
Screening of all pregnant women at 1st prenatal visit (and 28 weeks plus at-delivery if at high risk)

Chancroid: *Haemophilus ducreyi*

Overview

Epidemiology

Very few cases in the U.S
Africa, Caribbean, South Pacific

Microbiology and Pathogenesis

Fastidious, gram-negative coccobacillus
Microscopic appearance and nutritional requirement for hemin makes it a *Haemophilus*
Not closely related to other members of the genus so will likely be reclassified in the future
Strict human pathogen
Inoculation through skin breaks
Evades phagocytosis by PMNs
Ulcers contain predominantly T cells with low numbers of B cells
Natural infection does not confer protective immunity

Clinical Findings

Painful ulcers begin as a papule
"Soft chancres" with ragged, less indurated undermined edges with necrotic exudate in base of ulcer
Ulceration may resolve before adenopathy
Expansive, tender buboes (unilateral or bilateral)
Central fluctuance if untreated spontaneously ruptures

Diagnosis

Clinical criteria
Special supplemented media culture of lesion or node aspiration but not readily available
PCR if available

Treatment

Azithromycin, ceftriaxone or erythromycin

Prevention

Mandatory reporting and contact tracing
Safer sex practices

Lymphogranuloma venereum (LGV): *Chlamydia trachomatis* serovar L1-L3

Overview

LGV is uncommon in the U.S. It is caused by *Chlamydia trachomatis* serovar L1-L3. The much more common STI in the U.S. is nongonococcal urethritis (NGU) caused by *Chlamydia trachomatis* serovar D-K. For that reason, the **in-depth microbiology of Chlamydia is detailed in Novan Notes - Urethritis Cervicitis Vaginitis.docx**

As background, C*hlamydia* has three species with characteristics and pathogenicity outlined in the following table:

SPECIES	SEROVAR	DISEASE	TRANSMISSION	DIAGNOSIS	TREATMENT
C. trachomatis	A–C	Trachoma	Fomites, eye-seeking flies	Clinical findings NAAT	Azithromycin
	D–K	**NGU, cervicitis, proctitis, epididymitis, PID**	**Sexual contact**	**Clinical findings NAAT**	Azithromycin

	D–K	Inclusion conjunctivitis, infant pneumonia	Perinatal contact	DFA NAAT	Azithromycin
	L1–L3	**LGV**	**Sexual contact**	**NAAT plus OmpA typing**	Doxycycline
C. pneumoniae	One	URIs, atypical pneumonia, asthma exacerbations	Respiratory droplet	Serology or culture/PCR	Doxycycline Azithromycin
C. psittaci	Multiple	Psittacosis, atypical pneumonia, febrile illness	Aerosolized bird secretions, dust	Serology	Doxycycline

2 biovars of C. trachomatis

- Trachoma: eye, urogenital (NGU, cervicitis) and neonatal infections
- LGV: lymphogranuloma venereum

Epidemiology

Primarily in the tropics and subtropics
Sporadic in U.S. but outbreaks in MSM who are usually HIV-positive

Microbiology and Pathogenesis

For review of Chlamydia microbiology and life cycle, see Chlamydia section in *Novan Notes – Urethritis Cervicitis Vaginitis*

Clinical Findings

Asymptomatic small papule or rarely a HSV-like ulcer that usually resolves before recognition
Comes to medical attention with tender inguinal lymphadenopathy as the primary process of concern
Expansive, tender unilateral or bilateral buboes
Central fluctuance if untreated spontaneously ruptures
Fibrosis, fistula formation

Diagnosis

Clinical criteria
NAAT of bubo drainage

Treatment

Azithromycin, doxycycline x 3 weeks or longer

Prevention

Mandatory reporting and contact tracing
Safer sex practices

Granuloma inguinale (Donovanosis): *Klebsiella granulomatis*

Overview

Donovanosis is a chronic, progressive ulcerative disease of the skin and subcutaneous tissues.
Commonly referred to as granuloma inguinale, but because this term can easily be confused with LGV, many experts now recommend using “donovanosis”.

Microbiology and Pathogenesis

Klebsiella granulomatis

Encapsulated intracellular pleomorphic gram-negative bacillus resides in cytoplasmic vacuoles of large mononuclear cells.
Bacteria are described as having bipolar densities when stained (Donovan bodies).
Multiply intracellularly and are subsequently released on rupture of mature intracytoplasmic vacuoles'
Capsule, no flagella, small surface projections resembling pili or fimbriae'

Epidemiology

Uncommon in developed, nontropical settings.
Sporadically reported from Papua New Guinea, South Africa, India, Brazil, and Australia.

Clinical Findings

Incubation ~20 days
Firm subcutaneous painless nodule or papule ulcerates to form a painless, beefy red ulcer with rolled edges that bleeds
Multiple lesions may coalesce
Slow-growing
Extends into subcutaneous tissues becoming progressively more destructive
Slow, extended local tissue destruction if not treated but surprisingly painless
Subcutaneous inguinal spread leads to pseudobuboes (NO lymph node involvement)

Complications

Scarring, lymphedema, genital elephantiasis
Rarely bone or joint involvement

Diagnosis

Clinical findings lead to presumptive diagnosis
Giemsa or Wright stain of biopsy or crush prep smears of tissues taken from edges of active lesion looking typical bipolar staining, intracellular Donovan bodies

Treatment

Prompt therapy may slow progression and limit further tissue destruction
Azithromycin for 4-6 weeks

Prevention

Safer sex practices

Clinical Summary of Genital Ulcers

Syndrome	Pathogen	Appearance of Ulcer	Pain	Adenopathy	Diagnosis	Treatment
Genital herpes	HSV-2 more common than HSV-1	Multiple, small vesicles and ulcers with an erythematous base	Painful	Tender lymphadenopathy	Scraping for HSV DNA by PCR or for cell culture Tzanck prep (Giemsa or PAP smear) less sensitive but quick	Acyclovir, famciclovir, valacyclovir
Syphilis	*Treponema pallidum*	Single (usually) indurated ulcer with a clean base; self-resolves and	Painless	Painless, regional lymphadenopathy; Lymph nodes feel "rubbery"	Dark field microscopy if possible DFA	Benzathine penicillin G

		may not be observed			Serologies both non-treponemal (VDRL or RPR) and treponemal (FTA-ABS)	
Chancroid	*Haemophilus ducreyi*	Multiple, nonindurated ulcers with a gray or yellow exudate at the base	Very painful	Tender, lymphadenopathy; buboes	Clinical criteria Special culture not readily available PCR if available	Azithromycin
Lymphogranuloma venereum	*Chlamydia trachomatis* serovars L1–3	Small, shallow ulcers that self-resolve and are not usually observed	Painless	Characteristic appearance of lymph nodes is key feature; may be bilateral, large, and painful; presents with fluctuant "buboes" and sinus tracts	Clinical criteria NAAT of bubo drainage	Doxycycline x 3 weeks
Granuloma inguinale (donovanosis)	*Klebsiella granulomatis*	Marked, beefy red, vascular ulcer with granulomatous appearance and rolled edges	Painless	Not a major feature; subcutaneous granulomas, "pseudobuboes" may occur	Clinical findings Giemsa stain of biopsy for Donovan bodies	Azithromycin x 3 weeks or healed

Modified from Table 74-1, Chapter 74. Pelvic infections. Levinson. Review of Medical Microbiology & Immunology, 15e.

Human Papillomavirus (HPV)

Overview

VIRUS SIZE	HUMAN SUBTYPES	TRANSMISSION	DISEASE	TREATMENT	PREVENTION
Papillomavirus 55 nm	HPV-1-4, 7, 10	Close skin-to-skin contact, occupational exposure, public shower/swimming pool	Skin warts Common warts Plantar warts Flat cutaneous warts Meat/fish handler warts	Topical cytotoxins or surgical removal	
Papillomavirus 55 nm	HPV-6, 11	Close contact, sexual contact	Oral, laryngeal papillomatosis Genital warts (condylomata accuminata)	Treatment of laryngeal lesions is complex, varied	Vaccine
Papillomavirus 55 nm	HPV-16, 18 and 31, 33, 45, 52, and 58	Sexual (anal, vaginal, oral)	Cervical, oropharyngeal, other neoplasias	May be removed by electrocautery	Vaccine

Modified from Table 19-1. Chapter 19: Papilloma and Polyoma virus. Ryan. Sherris Medical Microbiology, 7e

Genital HPV divided into two groups based on whether they cause cancer

- Non-oncogenic types cause genital warts and benign or low-grade cervical changes

- Oncogenic types that cause cervical cancer mainly but also cancers of vulva, anus, penis and oropharynx

Epidemiology

Estimated that most sexually active men and women will acquire genital HPV at some point

- 90% will be clinically silent
- 90% clear infection within 2 years

HPV infection is the most common sexually transmitted infection in the United States
Highest prevalence in 20-24 years-old
Sexual transmission through anal and/or vaginal, oral sex

- Transmission does not require a visible lesion
- Condom use reduces risk of disease but not entirely

Type 16 associated with 60% and type 18 with 10% to 15% cervical cancers and CIN

- Develops decades after initial infection
- Persistent infection is essential for oncogenesis

Microbiology and Pathogenesis

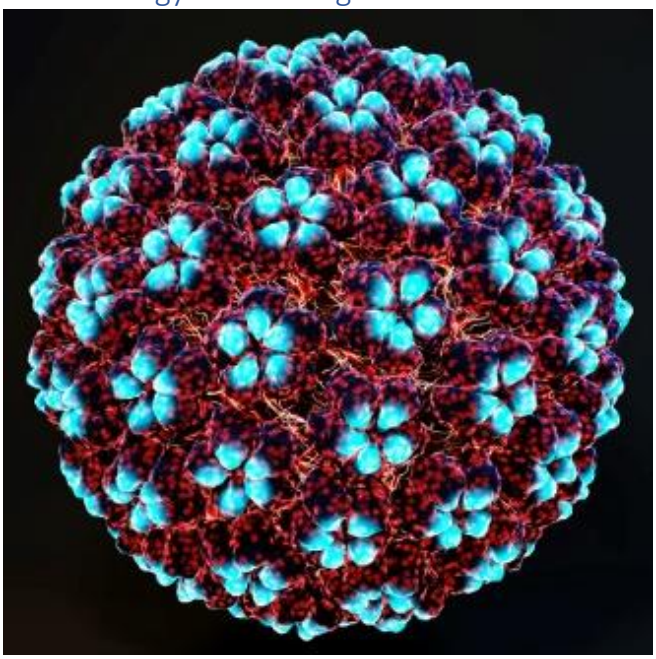


Fig 4. HPV type 16 graphic Natl STD Curriculum
https://www.std.uw.edu/go/pathogen-based/hpv/core-concept/all

Naked (no envelope) icosahedral capsid; double-stranded, circular DNA virus
Genome with eight early genes (E1-E8) and two late genes (L1 and L2)

- Early genes involved in synthesis of viral mRNA and replication of the progeny DNA genomes
- Late genes encode the structural proteins of the progeny virions

E6 and E7 genes transform host cells to increase cell division and potentially oncogenesis

- Encode enzymes that inactivate proteins encoded by host tumor suppressor genes (p53 gene and the retinoblastoma [RB] gene)
- E6 and E7 proteins of HPV-16 and HPV-18 bind more strongly to p53 and RB proteins than the E6 and E7 proteins of low risk strains
- E6 accelerates the degradation of p53, a tumor suppressor protein, and reduces its stability
- E7 interacts with pRB, retinoblastoma protein, to preventing cell cycle regulation
- Basically, E6 and E7 gene create proteins that degrade the growth-inhibitory effects of host p53 and pRB tumor suppressor genes leading to carcinogenesis

Immunity

- Hampered due to location of initial infection in basal epithelial cells
- Immune cells can detect viral proteins when the virus replication moves to suprabasal keratinocytes, leading to a strong localized cell-mediated immunity

- Effective localized cell-mediated immunity eliminates infection, whereas depressed immunity allows persistence

Summary of Replicative Cycle in Epithelial Cells

- HPV infects and initially replicates in the basal layer of the epidermis ->
- Attachment and uncoating -> Genome DNA moves to the nucleus -> Initial progeny genomes maintained as episomes in the nucleus -> Synthesis of progeny viral DNA occurs in conjunction with cellular DNA synthesis during S phase -> Vegetative DNA replication and viral assembly in terminally differentiated epithelial cells (keratinocytes) -> Latent viral DNA maintained in the basal layer of epithelium
- HPV is devoid of viral RNA or DNA polymerase so uses host RNA and DNA polymerase

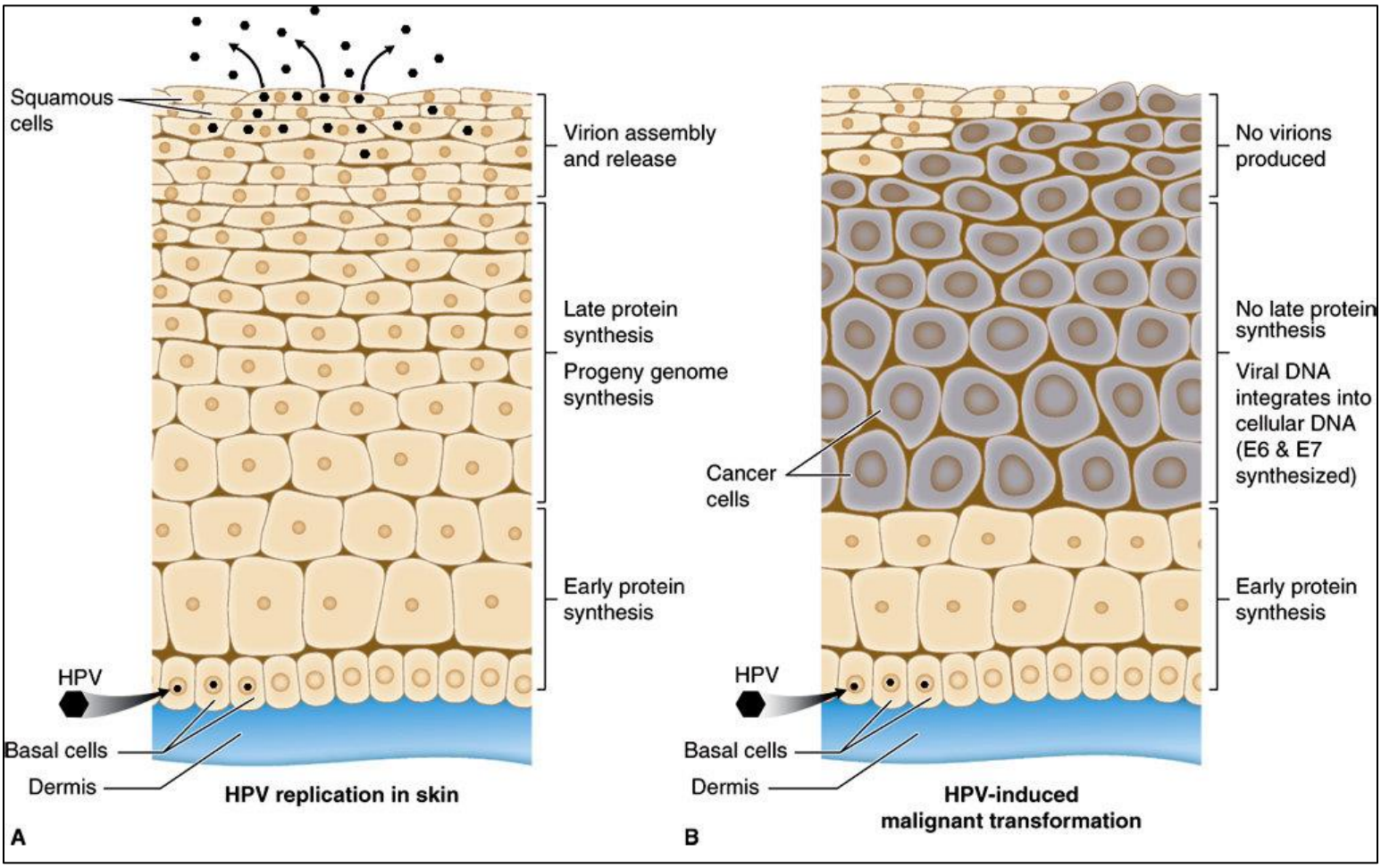


Fig. 37-12. Herpesviruses, Poxviruses, & Human Papilloma Virus. Levinson et al. Review of Medical Microbiology & Immunology: A Guide to Clinical Infectious Diseases, 15e

A. Benign warts

- In human tissues, infectious virus particles are found in the terminal differentiated squamous cells
- HPV initially infects the cells of the basal layer in the skin BUT no virus is produced by the basal cells
- Infectious virions are produced by squamous cells on the surface ensuring more efficient transmission of virus

B. Cancer

- In malignant cells, viral DNA is integrated into host cell DNA in the vicinity of cellular proto-oncogenes
- E6 and E7 are overexpressed and inactivate tumor suppressor proteins p53 and RB
- However, in latently infected, nonmalignant cells, the viral DNA is episomal, and E6 and E7 are not overexpressed
- E2 gene controls E6 and E7 expression
- E2 gene is functional when the viral DNA is episomal but is inactivated when it is integrated
    - No late viral proteins and no progeny virions are produced

Clinical Findings

Most HPV infections are transient, asymptomatic, or subclinical, and have no clinical consequences.

Most common clinically significant manifestations associated with HPV infection are:

- Anogenital warts
- Cervical cellular abnormalities (or lesions that are detected by Pap test or colposcopy}
- Anal cancer in MSM
- Minority of women with cervical cellular abnormalities will subsequently progress to cervical cancer

Anogenital Warts

Types

- Condyloma accuminata (cauliflower-like appearance – distinguish from condyloma lata of syphilis)
- Papules
- Keratotic lesions

Sites

- Areas of coital friction
- Perianal wars may be due to autoinoculation or spread from other areas

Symptoms

- Most often minimal symptoms
- Vulvar warts may cause dyspareunia, pruritus, burning
- Penile warts may cause pruritus, hematuria or impaired urinary stream if urethra involved
- Perianal or intra-anal warts can cause pain, bleeding on defecation

Dysplasia and Malignancy

Carcinomas of the uterine cervix, the penis, and the anus, as well as premalignant lesions called intraepithelial neoplasia
Oropharyngeal carcinoma
Can be detected by Pap test or colposcopy

Laboratory Diagnosis

Most cases of anogenital warts are diagnosed clinically
Confirmation by biopsy may be needed in the following situations

- Uncertain diagnosis
- Immunocompromised patient
- Pigmented, indurated or fixed warts
- Lesions unresponsive to therapy
- Persistent ulceration or bleeding

High-risk HVP type NAAT is not used for routine screening

Treatment

Because of possibility of spontaneous remissions, some patients choose to see if it occurs
Even with successful treatment, 20-50% chance of recurrence
Selection of specific therapies is based on lesion location, provider experience, availability, and patient preference
Patient applied therapy

- Imiquod 3.75% or 5% cream
- Sinechatechins 15% ointment

Provider administered therapy

- Cryotherapy with liquid nitrogen
- Surgery (scissor or shave)
- Tricholoracetic acid (TCA) or Bichloroacetic acid (BCA)

In pregnant women, do not use cytotoxic agents
C-section not indicated

Prevention

HPV vaccine very effective in preventing carcinoma of the cervix, anal carcinoma, and genital warts
HPV vaccines have no effect on existing papillomas
IN US -- Gardasil 9: Recombinant vaccine against nine types of HPV

- Immunization against types 6 and 11, which cause genital warts, and types 16 and 18, which are the two most common causes of cervical, penile, and anal carcinoma
- Also against five more types (31, 33, 45, 52, and 58) that are less common causes of these cancers
- Recommended for both males and females, between the ages of 9 and 26 years

Outside of US – Gardasil 4 (6,11,16, and 18) and Cervarix – HPV types 16 and 18
Safer sex practices

Nongonococcal Urethritis (NGU): *Chlamydia trachomatis*, serovar D-K

Epidemiology

Most common reportable *bacterial* STI in U.S.
Prevalence highest in sexually active females, ages 15-24
Disproportionate burden/higher incidence in African-Americans

Microbiology and Pathogenesis

Obligate intracellular bacterium with a cell wall and ribosomes like those of gram-negative organisms
Obligate because it relies on the host cell for key amino acids and energy generating ATP
Cell wall contains outer lipopolysaccharide membrane but lacks peptidoglycan (not stainable by Gram stain and β-lactam antibiotics ineffective)
Outer membrane includes immunogenic outer membrane protein (OMPa) also known as major outer membrane protein (MOMP)

The life cycle is interesting. It involves transitioning from inert but infectious elementary bodies (EB) entering cells and transforming to actively dividing but non-infectious reticulate bodies (RB) within a vacuole in the host cell. Once numbers are high enough, one more transformation yields EBs and cell death with release of EBs to continue infection.

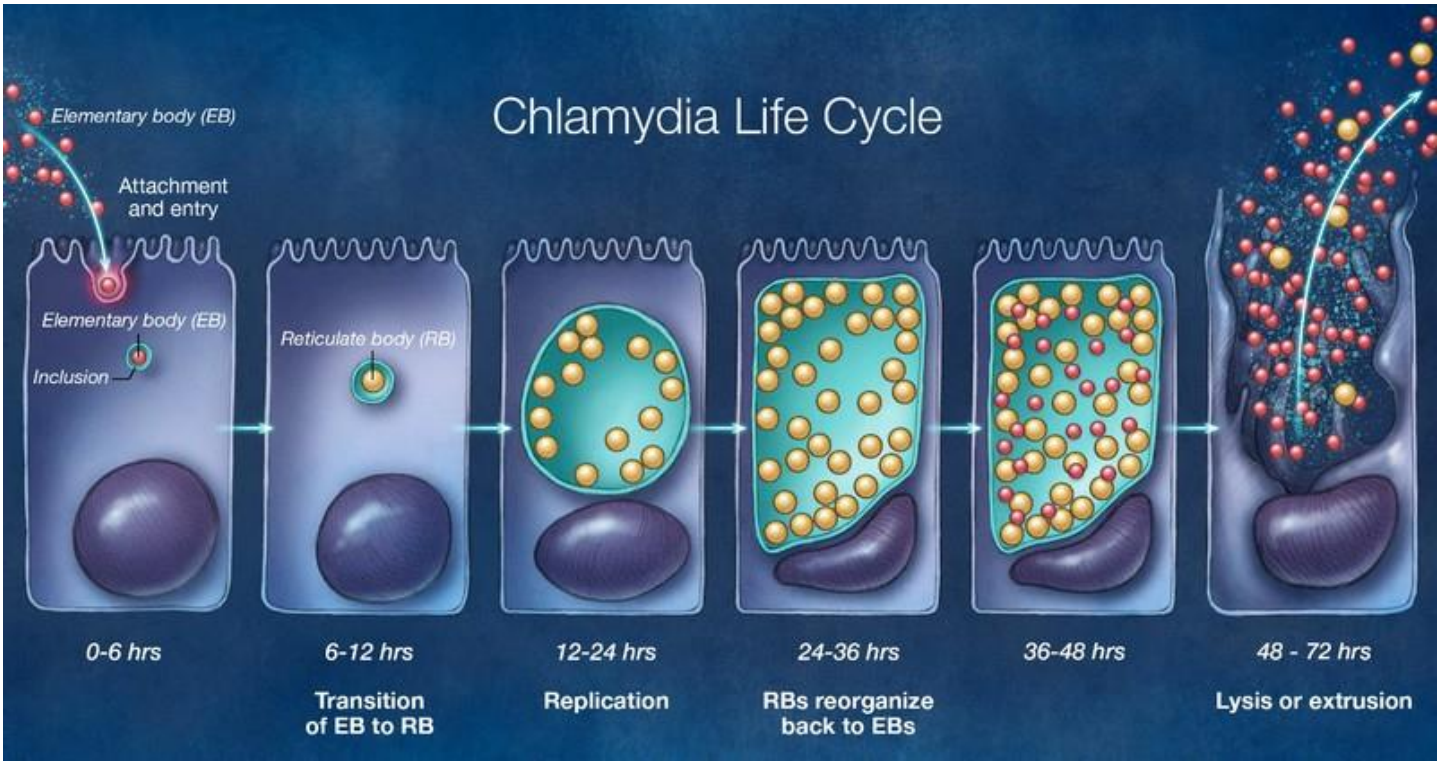


Fig. 8 Chlamydia STD Module National STD Curriculum
https://www.std.uw.edu/go/pathogen-based/chlamydia/core-concept/all

1. The elementary body attaches to and enters a host cell. The contact with the host cell membrane causes the elementary body to induce its own endocytosis.
2. Within eight hours, the now-intracellular elementary body interacts with glycogen and transforms into a reticulate body, which begins to multiply within an isolated intracellular structure referred to as an inclusion
3. Within 48 hours, some of the reticulate bodies begin to reorganize back to elementary bodies.
4. Within 72 hours, most of reticulate bodies have transitioned back to elementary bodies and the inclusion either undergoes lysis at the host cell wall or the intact inclusion is released into the extracellular space.
5. The elementary bodies are released to infect adjacent cells or to be transmitted to and infect another person.

A variant in the overall replicative cycle is called the persistent state in which the EBs and RBs become dormant but are still able to resume multiplication. This state can be induced by some cytokines (IFN-γ) and nutrient restriction.

Pathogenesis
Initial attachment is probably mediated by MOMP.
Primary injury is due to inflammation secondary to the release of proinflammatory cytokines such as interleukin-8 by infected epithelial cells.
Tissue infiltration by polymorphonuclear leukocytes, later followed by lymphocytes, macrophages, plasma cells, and eosinophils.
Aggregates of lymphocytes and macrophages may form in the submucosa.
Can progress to necrosis, followed by fibrosis and scarring.
When the slow immune response develops, it is T-helper 1 cells that are the most important.

Transmission of *C. trachomatis* can occur from mother-to-infant via the genital tract during birth

Clinical Findings

Majority of infections in both men and women are asymptomatic
Incubation period of 1-3 weeks
Dysuria
Thin, mucoid or mucopurulent urethral discharge in men
Additional spectrum of clinical manifestations from *local extenstion*

- Men: epididymitis, prostatitis
- Women: cervicitis, salpingitis, PID, infertility from scarring of Fallopian tubes, PID (pelvic inflammatory disease), Fitz-Hugh-Curtis syndrome (perihepatitis due to leakage of inflammatory fluids out of Fallopian tubes)
- Men or women: conjunctivitis from autoinoculation, oropharyngeal infection*, proctitis, reactive arthritis (see following description)

*Clinical relevance of oropharyngeal chlamydia is unclear, but as it can be spread to genital sites, treatment is recommended

Reactive arthritis in HLA-B27 individuals

- "Can't see, can't pee, can't climb a tree"
- Autoimmune reaction to preceding bacterial infections (*Chlamydia trachomatis* urethritis is not the most common preceding infection. It is more commonly from bacteria that cause gastroenteritis or dysentery)
- Manifestations include conjunctivitis, uveitis, nonbacterial urethritis, enthesitis (inflammation of tendon insertion sites classically the heels), arthritis typically of the knees, sacroiliitis, ankylosing spondylitis, keratoderma blennorrhagicum, circinate balanitis
- Occurs predominantly in males

Infections in infants and children as result of vertical transmission

- Inclusion conjunctivitis (most common of the vertically transmitted infections)
- Pneumonia that can occur 1-3 months post delivery
- Urogenital infection can persist for 2-3 years so it can be the result of vertical transmission

Diagnosis

> 2 PMNs per oil immersion field on microscopy is a marker of urethritis
*Preferred: NAAT
Culture or DFA reserved for pharyngeal and rectal specimens for which NAATs might generate false positives.

Treatment

Doxycycline 100 mg b.i.d. x 7 days (preferred)
Azithromycin 1 gm PO (alternative)

CDC does not recommend test of cure with follow-up NAAT but DOES recommend it at 3 months to check for reinfection

Treatment of ophthalmia neonatorum

- Erythromycin base or ethylsuccinate 50 mg/kg/day orally divided into 4 doses daily for 14 days

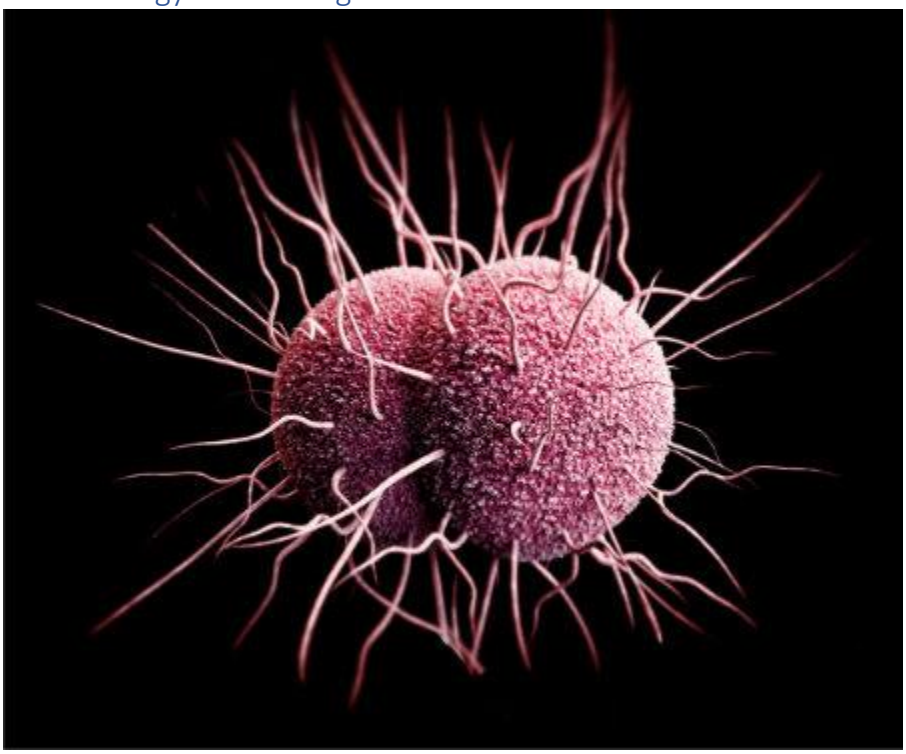
Prevention
Mandatory reporting and contact tracing
Safer sex practices

Gonorrhea: *Neisseria gonorrhoeae* (Gonococcus)

Epidemiology
Probably underreported
Highest rates in women ages 15-19 and men ages 20-24
95% of men are symptomatic
50% of women are symptomatic
Major reservoir for transmission is asymptomatic patients
Lack of immunity means repeat infections are the rule

Transmissions rates: male to female 50-70% and female to male 20% per sexual intercourse episode

Gonococcal antibiotic resistance has increased and is a worldwide problem.

Microbiology and Pathogenesis

Neisseria gonorrhoeae SEM reproduction CDC PHIL
https://phil.cdc.gov/Details.aspx?pid=16874

Gram-negative, kidney bean-shaped diplococci
Cell wall typical of Gram-negative bacteria (peptidoglycan)
Unlike meningococcus, no capsule
Grows well on chocolate agar
More fastidious than meningococcus

N. gonorrhoeae Pathogenic Factors (see following graphic)
Panel A
- Pili: attachment, twitching motion that allows bacteria to embed themselves into non-ciliated epithelial cells
- Opa: opacity protein that is an adhesin

- Por: porin that acts as sieve for certain solutes
- LOS: lipooligosaccharide that is analogous to LPS in Gram-negative rods; endotoxin

Panel B

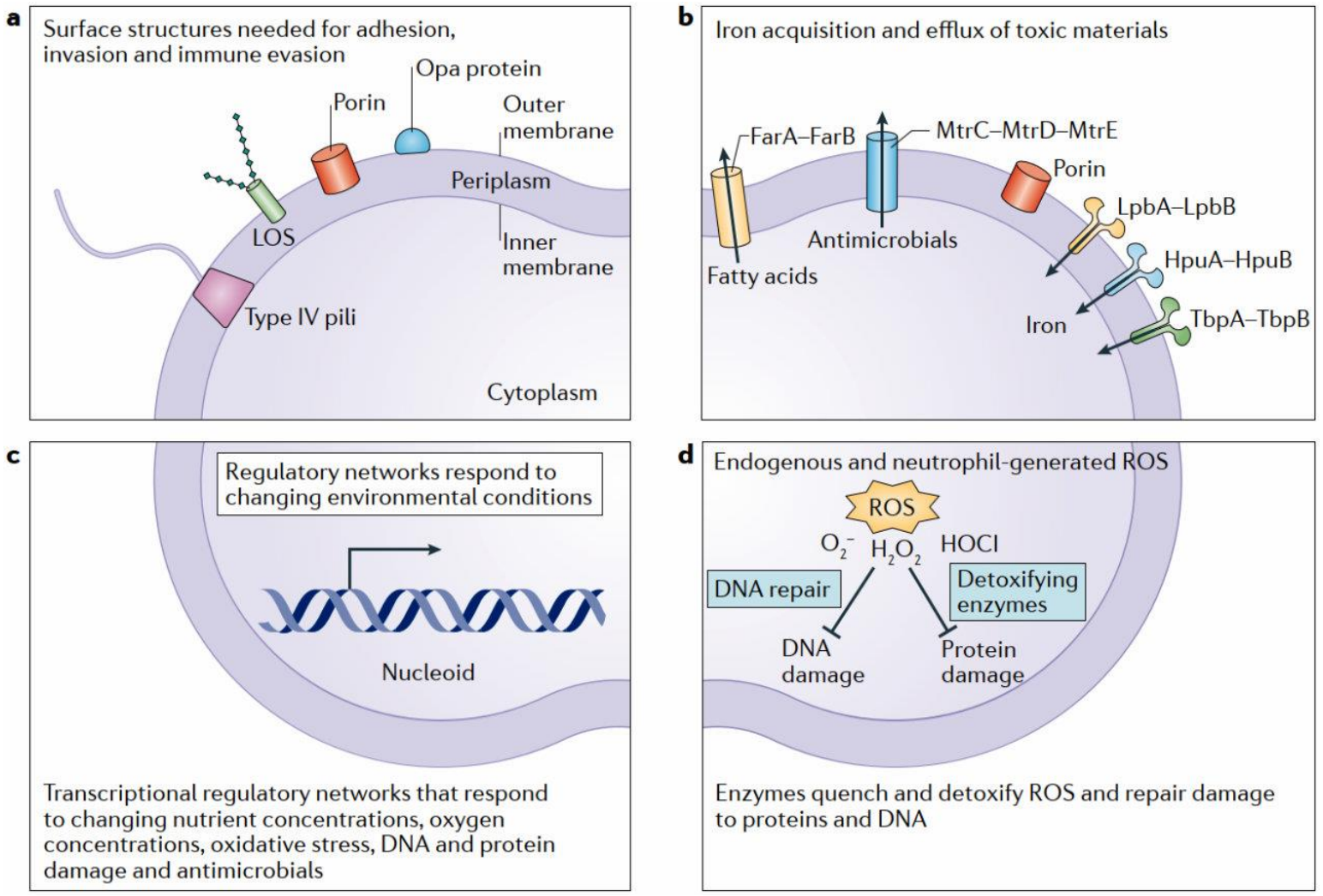
- Efflux pumps: protection from antimicrobials and fatty acids
- Membrane transporters: co-opt nutrients from the environment

Panel C

- Regulons: set of transcriptional regulators allow bacteria to respond and survive changing environment during infection

Panel D

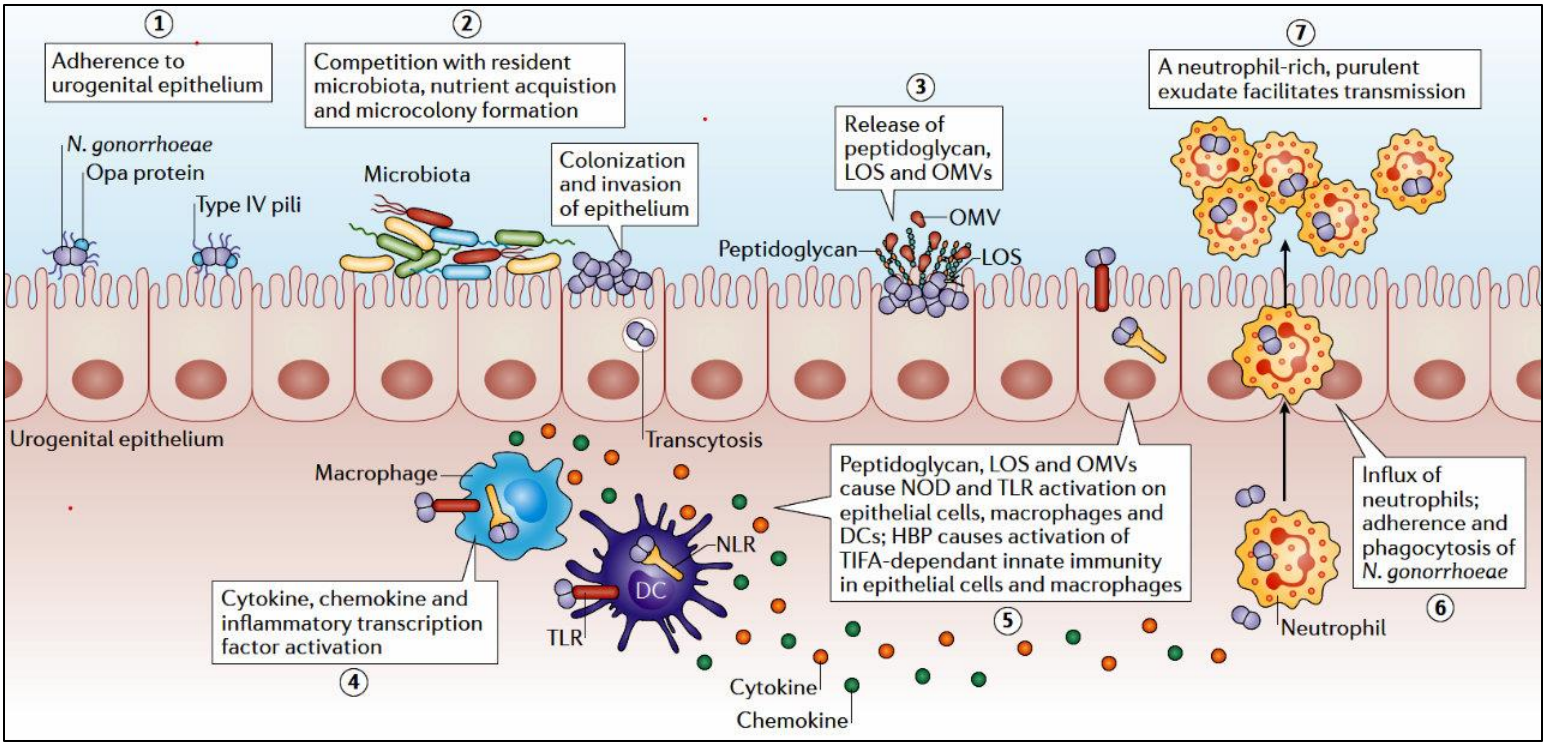
- Protective enzymes: i.e. catalase that detoxifies reactive oxygen species (ROS)



Quillin SJ, Seifert HS. *Neisseria gonorrhoeae* host adaptation and pathogenesis. Nature Rev Microbiol. 2018 Apr;16(4):226–40.

Antigenic variations in surface structures (pili, OMPs, LOS) in response to environmental pressures allow the gonococcus to survive as a "new version" of itself to escape from immune surveillance and to create functioning binders to receptors. The immune system that is mounted now finds a changed pathogen and it is no longer effective until the immune system too changes. It is also why effective vaccines have yet to be created.

Overview of Pathogenesis of *Neisseria gonorrhoeae* infection



Quillin SJ, Seifert HS. *Neisseria gonorrhoeae* host adaptation and pathogenesis. Nature Rev Microbiol. 2018 Apr;16(4):226-40.

How *Neisseria gonorrhoeae* Infection Occurs

1. Bacteria adhere to non-ciliated epithelial cells through type IV pili and Opa proteins (adherence proteins)
2. Microcolonies form and compete with resident flora then invade by transcytosis (vesicle transport across cell membrane)
3. Fragments of peptidoglycan, lipooligosaccharide (LOS) and outer membrane vesicles / proteins (OMV or OMP) activate inflammation signaling in epithelial cells and macrophages
4. Release of cytokines and chemokines
5. Activation of innate immunity in epithelial cells and macrophages
6. Cytokines and chemokines also recruit PMNs (neutrophils) to site of infection
7. PMNs phagocytose *N. gonorrhoeae* yielding pus that facilitates transmission

Clinical Findings

Genital infection in men

Urethritis: Purulent or mucopurulent discharge, dysuria usually 2-5 days after exposure
Small percentage are asymptomatic
Anorectal infection for MSM resulting in proctitis: painless muocpurulent discharge, painful defecation, tenesmus, bleeding
Epididymitis
Prostatitis
Local abscess

Genital infection in women

Cervicitis and/or urethritis
Anorectal infection from perineal contamination
Complications

- Accessory glans (Bartholin's or Skene's) infection -> abscess
- PID, tubal scarring, infertility, ectopic pregnancy
- Fitz-Hugh-Curtis syndrome (perihepatitis due to leakage from Fallopian tubes)

Additional syndromes in men and women

- Pharyngitis
- Conjunctivitis from autoinoculation: marked purulent discharge which if untreated can corneal perforation and blindness
- Disseminated gonococcal infection (DGI) results from bacteremia and includes necrotic skin lesions, tenosynovitis, oligoarthritis of larger joints (with or without purulence) and rarely, endocarditis.

Perinatal (during childbirth) infection
Conjunctivitis (ophthalmia neonatorum) which can be prevented with ocular antimicrobial prophylaxis
Pharynx, respiratory tract, anal canal can be infected

Diagnosis

Nucleic acid detection tests

- * Preferred: NAATs – most sensitive tests to detect N. gonorrhoeae infection
- PCR

Gram's stain

- Presumptive diagnosis in men with urethral discharge (rarely done: painful and NAAT on urine equally diagnostic)
- Gram-negative diplococci
- 95% sensitivity and >99% specificity
- Not to be used for endocervical, pharyngeal or rectal specimens

Culture

- Historic standard
- Can be used for a variety of specimen sources
- Not as sensitive as a NAAT
- *Used more now for antimicrobial resistance surveillance*

Treatment

Principles of treatment: Ceftriaxone (at sufficiently high dose)
Treatment recommendations were updated in 2021 due to rising antimicrobial resistance. Prior to this, dual therapy with Ceftriaxone and Azithromycin was recommended. The update dropped Azithromycin as a recommended treatment and increased the dose of ceftriaxone recommended.

Regimens

Urethra, cervix, rectum or pharynx	Ceftriaxone 500 mg IM
Conjunctiva	Ceftriaxone 1 gm IM x 1 dose
DGI	Ceftriaxone 1 gm IM or 1V q 24 hours x 7 days
DGI with endocarditis or meningitis	Ceftriaxone 1-2 gm IV q12-24 hours x 10-14 days

Follow-Up of Treatment
Test-of-cure is not recommended for patients who have uncomplicated gonorrhea
Culture and sensitivities for persistent symptoms to check for resistance

Prevention

Safer sex practices including condoms
Mandatory reporting and contact tracing
Newborn ocular erythromycin ointment

CDC recommendations for screening

- Annual for sexually active women age < 25
- Annual for sexually active women > 25 if at increased risk
- Pregnant women
    - First prenatal visit
    - Third trimester for women with continued risk
- Annual for men who have sex with men (MSM)
- Annual (at least) for persons with HIV

Vaginal Discharges | Vaginitis

Background

Vagina contains a normal resident microbial flora
Physiologic vaginal fluid is clear, white, odorless with a high viscosity
Lactobacilli dominate the resident microflora and keep pathogens in check by

- Converting glycogen to lactic acid maintaining the normal pH acidic between 3.8 and 4.5
- Production of hydrogen peroxide that kills pathogenic bacteria and viruses

The three most common causes of vaginitis presenting in primary care settings:
Bacterial vaginosis (BV): 25-50% of cases
Vulvovaginal candidiasis: 17-39% of cases
Trichomoniasis: 4-35% of cases

Diagnostic Approach

Visual inspection of vaginal discharge, vagina and cervix – important to visualize cervix to check if discharge is due to cervicitis
Most of the diagnostic evaluation initially is not organism specific

1. Saline wet mount looking for clue cells and motile trichomonads
2. 10% KOH wet mount and whiff test
    a. Whiff test: strong amine "fishy" odor positive for BV
    Fishy odor caused by metabolism of vaginal peptides into volatile and malodorous amines
    b. KOH destroys most cells and bacteria making it easier to see yeast, pseudohyphae and hyphae
3. pH Litmus paper looking for pH > 4.5 found with BV
4. Gram's stain
    a. Not used much anymore
    b. Looking for replacement of abundant Gram-positive rods with abundant Gram-negative bacteria
    c. Can show yeast or pseudohyphae but wet mount preferred
5. Point-of-Care Organism Specific Tests
    a. OSOM Trichomonas Rapid Test (detects T. vaginalis)
    b. BD Affirm VPIII Microbial Identification Test (detects T. vaginalis, C. albicans, and Gardnerella vaginalis)
    c. Sensitivity, specificity, and clinical utility of these tests are higher than wet mount, but lower than culture
    d. Neither the OSOM nor Affirm tests are approved for testing in men
6. Culture
    a. Fungal culture not necessary for vulvovaginal candidiasis, but when needed, it is the gold standard
    b. For *T. vaginalis* (using modified Diamond's medium) is more sensitive than wet mount, but less sensitive than NAAT
7. Nucleic Acid Amplification Tests (NAAT)
    a. Trichomonas APTIMA test (Gen-Probe) now the preferred test for the diagnosis of trichomoniasis
    b. Polymerase Chain Reaction: BD MAX Vaginal Panel test, a molecular test that detects bacterial vaginosis, trichomoniasis, and vulvovaginal candidiasis

Bacterial Vaginosis (BV): *Gardnerella vaginalis,* anaerobes

Epidemiology

Gardnerella can be isolated in 50% of asymptomatic women
Not technically a sexually transmitted disease however:

- Positive association between BV and multiple sexual partners
- Negative association between BV and condom usage

Microbiology and Pathogenesis

Definitive explanation of the pathogenesis of bacterial vaginosis remains elusive
Displacement of the normal lactobacilli in the vagina by *Gardnerella vaginalis* and anaerobic bacteria, which leads to a subsequent pro-inflammatory response and clinical syndrome

One proposed model of bacterial vaginosis:

- *G. vaginalis* adheres to host epithelium and creates a biofilm bacterial community that facilitates subsequent epithelial accumulation of other pathogens
- Sexual transmission of anaerobic bacteria may play a role in the development of bacterial vaginosis

Clinical Findings

Homogeneous, nonviscous, milky-white discharge adherent to the vaginal walls
No signs of inflammation

Diagnosis

pH > 4.5
Saline wet mount reveals at least 20% of vaginal epithelial cells being "clue cells"

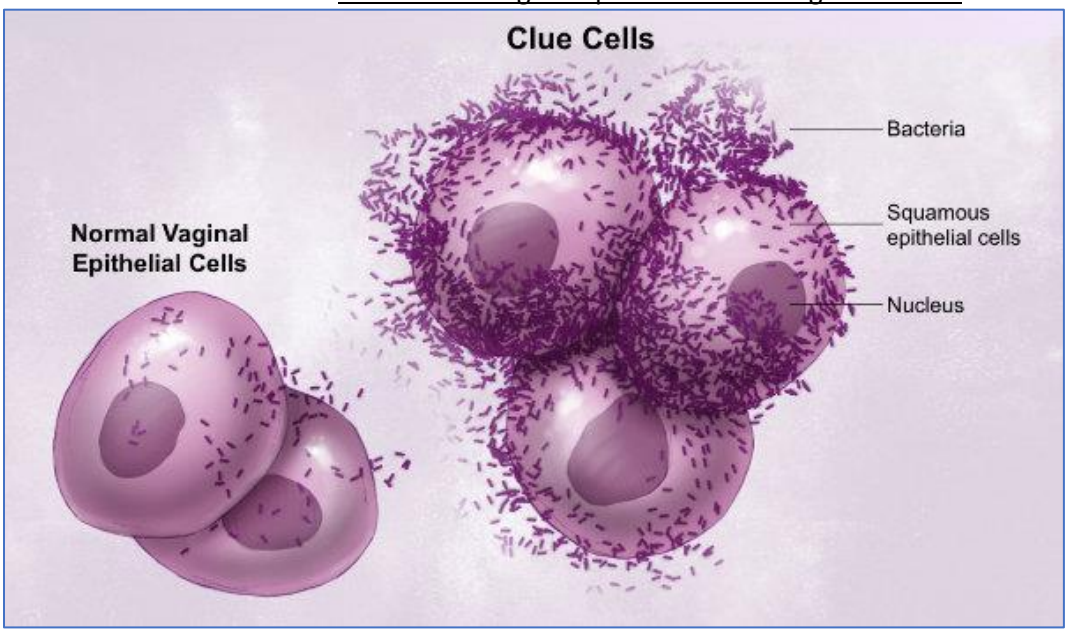


Fig. 1. National STD Curriculum: Vaginitis
https://www.std.uw.edu/go/syndrome-based/vaginal-discharge/core-concept/all

Whiff test positive – more pronounced with 10% KOH

Treatment

Recommended treatment is metronidazole 2gm PO as a single dose
Tinidazole PO (contraindicated in pregnancy due to risk of fetal harm)
Pregnant women treated with metronidazole
Avoid drinking alcohol with metronidazole or tinidazole because of risk of disulfiram (Antabuse)reaction

- Buildup of blood acetaldehyde levels → headache, nausea, flushing, hypotension, chest pain

Screening

Not recommended for asymptomatic women is not recommended in general
Considered prior to a surgical abortion or hysterectomy to decrease rates of post-op infections by treating with metronidazole
Cost-comparison studies have found that adding metronidazole to standard surgical prophylaxis, rather than a screen-and-treat approach, is more cost effective

Vaginal Candidiasis: *Candida albicans*

Overview

Besides vulvovaginitis, candidiasis can cause diaper rash, oral thrush, urinary tract infections, pneumonia and bloodstream infection.

Epidemiology

Infections are often from endogenous flora
75% of women will have at least one episode of vulvovaginitis in their life
Candida albicans responsible for 85 to 95% of cases of vulvovaginal candidiasis in U.S., remainder due to non-albicans species, most commonly *C. glabrata*

Microbiology and Pathogenesis

Budding round or oval yeast
During infection, forms hyphae or pseudohyphae

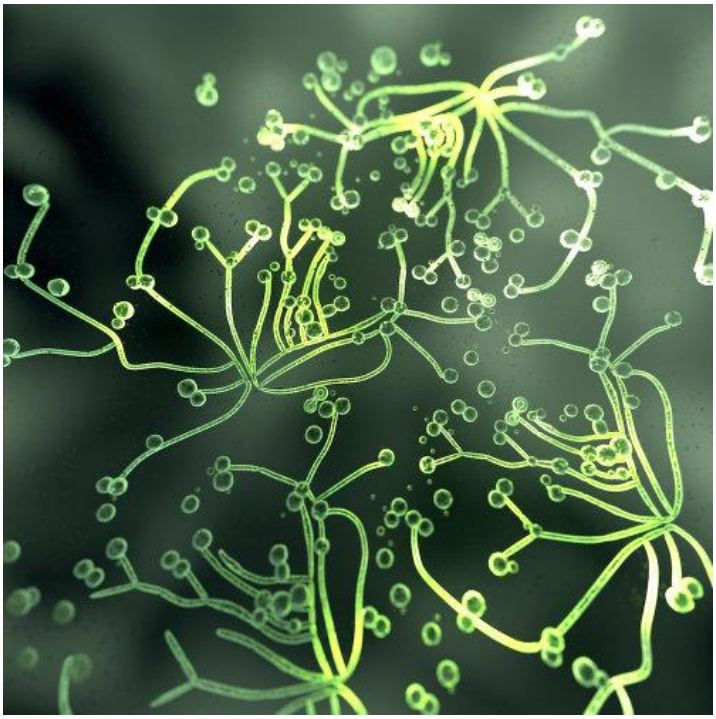


Fig. 10 National STD Curriculum: Vaginitis
https://www.std.uw.edu/go/syndrome-based/vaginal-discharge/core-concept/all

Grow easily on blood agar as 2-4 mm smooth, white colonies
Production of germ tubes differentiates *C. albicans* from other species of *Candida*
Cell wall includes surface mannoproteins

Candida albicans Infection Attachment and Invasion

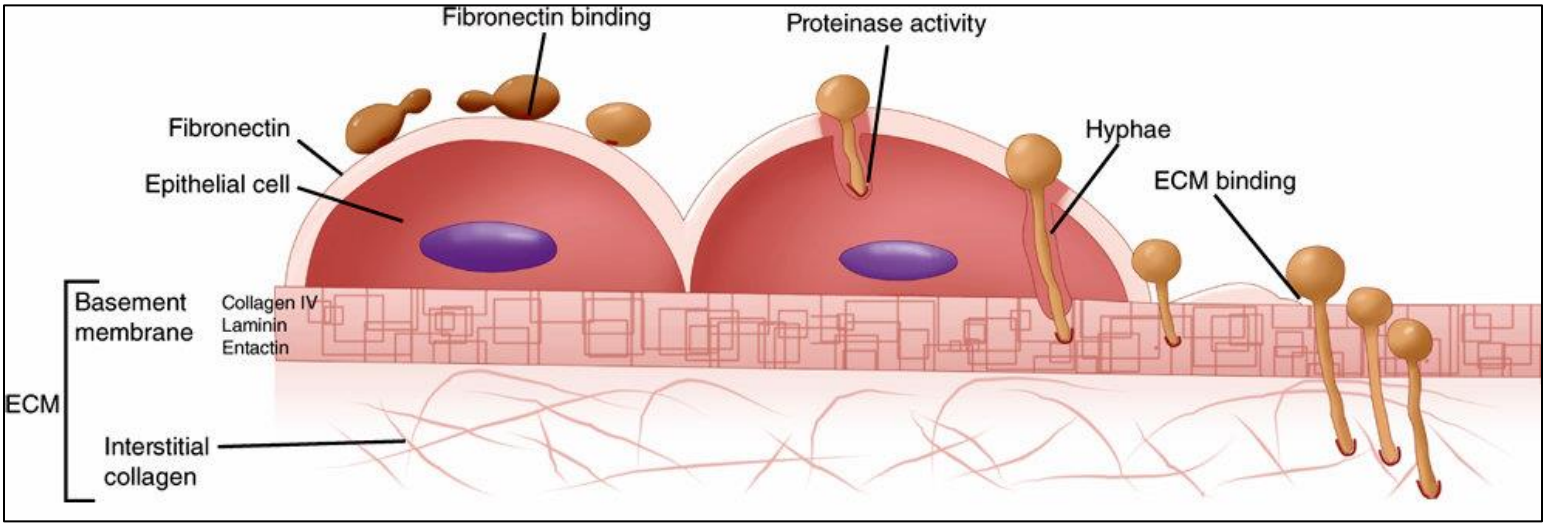


Fig 46-1. The opportunistic fungi: *Candida*, *Aspergillus*, the zygomycetes, and *Pneumocystis*. In: Ryan KJ, ed. Sherris Medical Microbiology, 7e. New York, NY: McGraw-Hill; 2018.

1. Yeast surface glucomannan receptors bind to fibronectin of epithelial cell or ECM (extracellular matrix)
2. Invasion with formation of hyphae and production of proteinases that digest tissues

Forms adherent biofilms to components of the ECM (as well as to plastics i.e. catheters)
Surface proteins resemble complement receptors confusing phagocytes
Promoting factors

- Antibacterial antibiotics reduce host microflora increasing the relative abundance of **Candida**
- High glucose concentrations promote greater production of surface mannoproteins
- Immune system defects

Immunity depends on functioning PMNs, antibodies and T-cells

Clinical Findings

Itching of the vulva, dyspareunia
Thick, white, "cottage cheese" discharge without odor that is loosely adherent to the mucosal surface
Less often, thin discharge
Mucosal inflammation

Complicated vulvovaginal candidiasis defined as infection

1. moderate to severe
2. associated with pregnancy or other concomitant conditions (i.e. immunosuppression, diabetes mellitus)
3. recurs more than four times per year in immunocompetent women

Diagnosis

pH < 4.5
Saline or KOH wet mount of discharge shows yeast and hyphae
Readily isolated from culture

Treatment

Fluconazole PO
Miconazole suppository

Trichomoniasis: *Trichomonas vaginalis*

Overview

Classic exogenous sexually transmitted infection

Epidemiology

Prevalence difficult to ascertain because it is not reportable
~ 4 million people in U.S. have trichomoniasis with 1.1 million new cases per year
Prevalence 3% among reproductive age women but 4x higher in non-Hispanic black women (highest risk group)
25% of sexually active women become infected at some point in their lives
~70% of their male sexual partners transiently parasitized

Microbiology and Pathogenesis

Single celled protozoan that exists only in the trophozoite stage
Pear-shape, 4 flagella anteriorly, one flagellum undulating membrane
A microtubule containing a supporting rod (an axostyle) bisects the trophozoite longitudinally with its pointed tip thought to mediate attachment

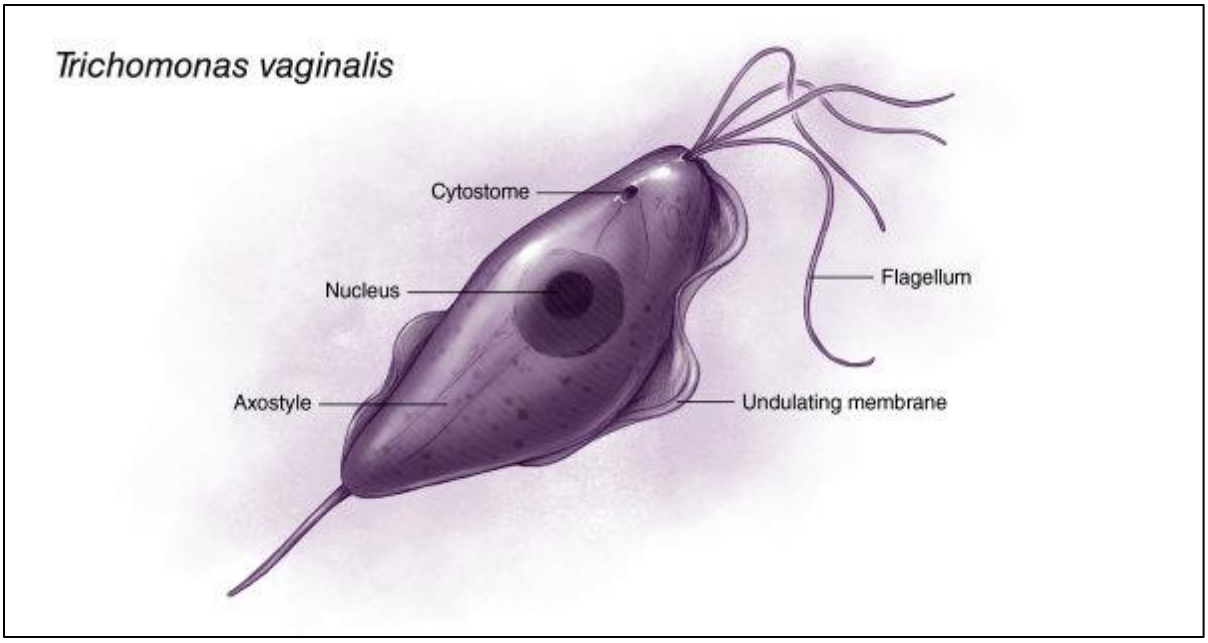


Fig. 4 National STD Curriculum: Vaginitis
https://www.std.uw.edu/go/syndrome-based/vaginal-discharge/core-concept/all

Pathogenesis
Attachment
Secretion of proteinases resulting in cytolysis (destruction of epithelial cells)
PMN inflammatory reaction and petechial hemorrhages
Humoral and cellular immune not clinically significant
Inflammation increase risk of acquisition of other pathogens such as HIV

Clinical Findings

Vulvar itching, dyspareunia, dysuria
Green-yellow, thin, frothy
Mucosal inflammation
"Strawberry" cervix
Chronic vaginitis that might last for months

In men, urethral infection usually asymptomatic

Infection in pregnancy associated with premature rupture of membranes and preterm labor

Relationship of trichomoniasis and HIV
2-3-fold increase risk of acquiring HIV
HIV does not make a woman more likely to have persistent or recurrent trichomoniasis

Diagnosis

Saline wet mount shows PMNs and parasites (cheap, rapid, and can be done at point-of-care, but low sensitivity 44-68%)
pH < 4.5
NAAT more sensitive (95-100%) and can be performed on clinician-collected swabs, or patient-collected urine
Rapid antigen test available (sensitivity 82-95% compared to wet mount)

Treatment

Metronidazole 2 grams orally in a single dose or tinidazole 2 grams orally in a single dose
Metronidazole but not tinidazole in pregnancy because of risk of fetal damage
Alternative regimen is metronidazole 500 mg orally twice daily for 7 day

Prevention

Not a reportable disease
Safer sex practices