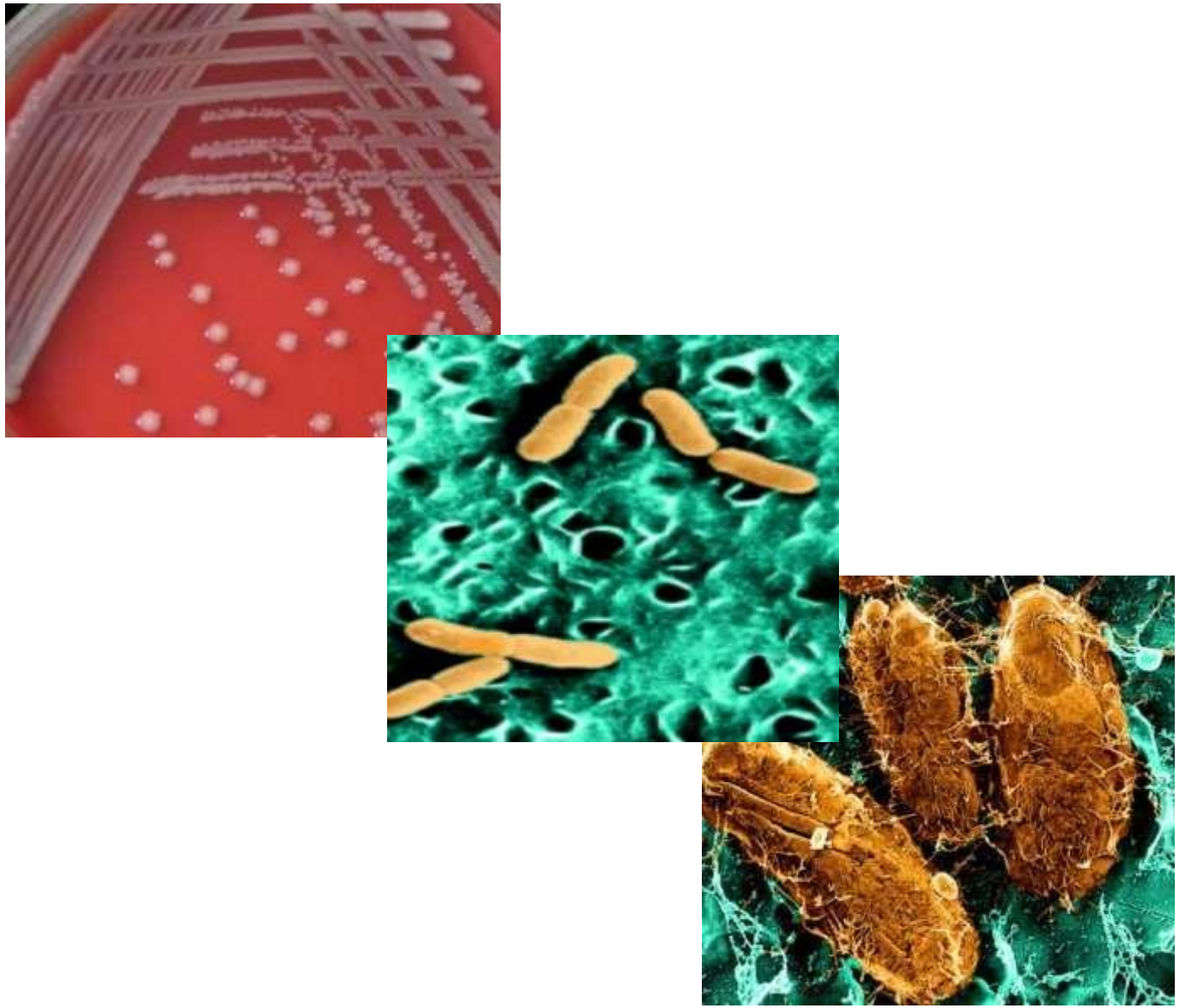
Microbiology of Urogenital system



Anas Abu-Humaidan
M.D. Ph.D.

B.B

Lecture 6

Sexually transmitted diseases

In this slide we'll cover ulcerative genital lesions, genital warts and pelvic inflammatory disease.

Things that'll be covered:

- **Chancroid**
- **Syphilis**
- **Genital herpes**

- **Genital warts**

Note: anything bolded, highlighted or added in green is what the doctor emphasized, added or focused on.

SEXUALLY TRANSMITTED AND SEXUALLY TRANSMISSIBLE MICROORGANISMS

BACTERIA	VIRUSES	OTHER[a]
Transmitted in Adults Predominantly by Sexual Intercourse		
Neisseria gonorrhoeae	HIV (types 1 and 2)	Trichomonas vaginalis
Chlamydia trachomatis	Human T cell lymphotropic virus type 1	Pthirus pubis
Treponema pallidum	Herpes simplex virus type 2	
Haemophilus ducreyi	Human papillomavirus (multiple genital genotypes)	
Klebsiella (Calymmatobacterium) granulomatis	Hepatitis B virus[b]	
Ureaplasma urealyticum	Molluscum contagiosum virus	
Mycoplasma genitalium		

Ulcerative genital infections

- **Genital ulceration** reflects a set of important STIs, most of these ulcers sharply increase the risk of sexual acquisition and shedding of HIV.

- PCR testing of ulcer specimens demonstrated **herpes simplex virus HSV** in 62% of patients, **Treponema pallidum** (the cause of **syphilis chancers**) in 13%, and **Haemophilus ducreyi** (the cause of **chancroid**) in 12–20%.

✓ major cause of ulcers is **HSV2** followed by **T. pallidum** (syphilitic chancers) followed by **H. ducreyi** (chancroids)

- In Asia and Africa (developing countries), **chancroid** was once considered the most common type of genital ulcer, PCR testing of genital ulcers now clearly implicates **genital herpes** was by far the most common cause of genital ulceration.

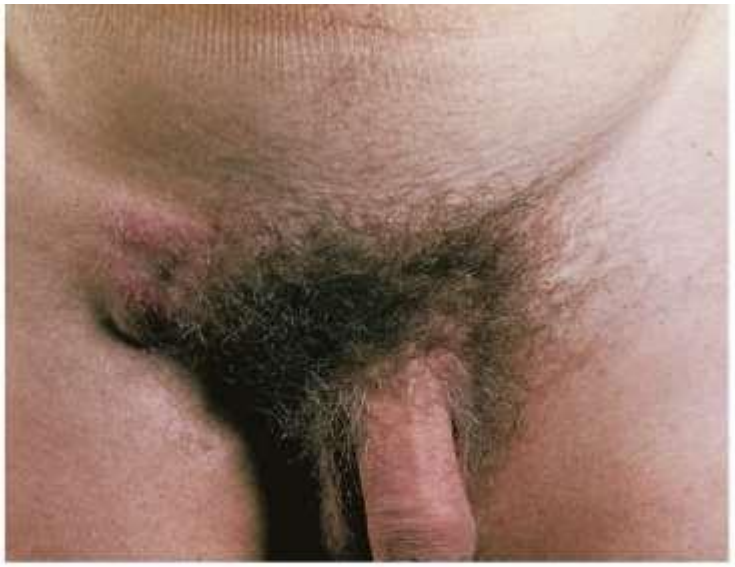


FIGURE 35-7
Lymphogranuloma venereum (LGV): striking tender lymphadenopathy occurring at the femoral and inguinal lymph nodes, separated by a groove made by Poupart's ligament. This "sign-of-the-groove" is not considered specific for LGV; for example, lymphomas may present with this sign.

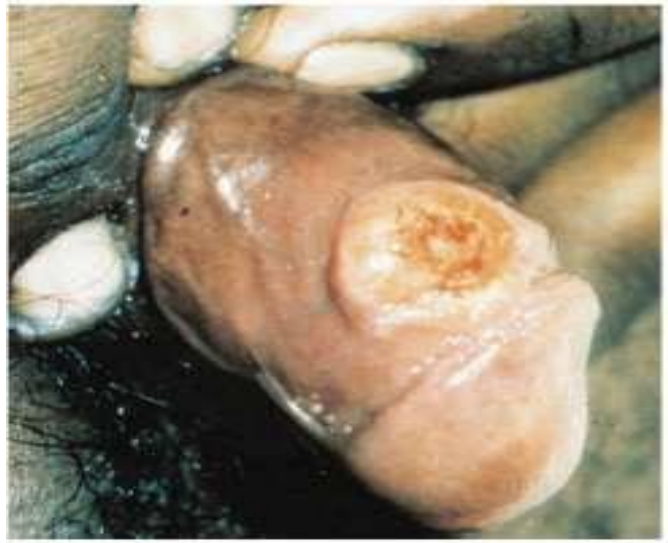


FIGURE 78-2
Primary syphilis with a firm, nontender chancre.

Lympho granuloma venereum:

It's caused by serotypes L1,L2,L3 of chlamydia. Other than the non-ghonococcal urethritis caused by chlamydia, **some serotypes can cause LGV,**

which starts first as an ulcer that goes unnoticed most of the time, then the ulcer disappears and the lymph nodes enlarge (inguinal and femoral LNs)

Notice how the enlargement is grooved by a tendon

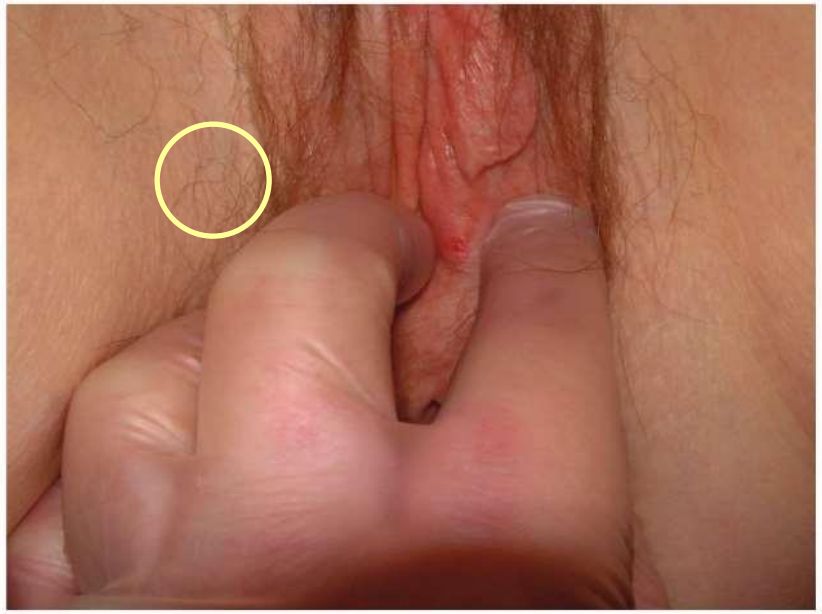


FIGURE 35-6
Genital herpes. A relatively mild, superficial ulcer is typically seen in episodic outbreaks. (Courtesy of Michael Remington, University of Washington Virology Research Clinic.)

The most common cause of ulcerations in the genitals (HSV)

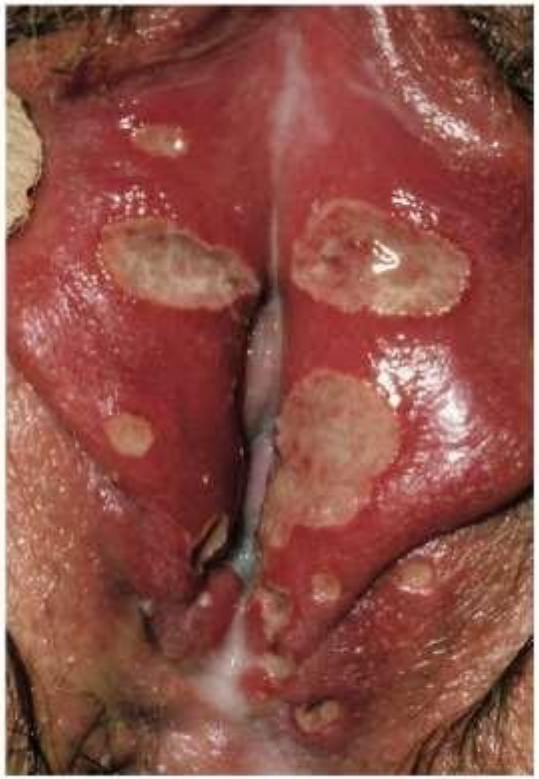


FIGURE 35-5
Chancroid: multiple, painful, punched-out ulcers with undermined borders on the labia occurring after autoinoculation.

Chancroids present as multiples painful ulcers

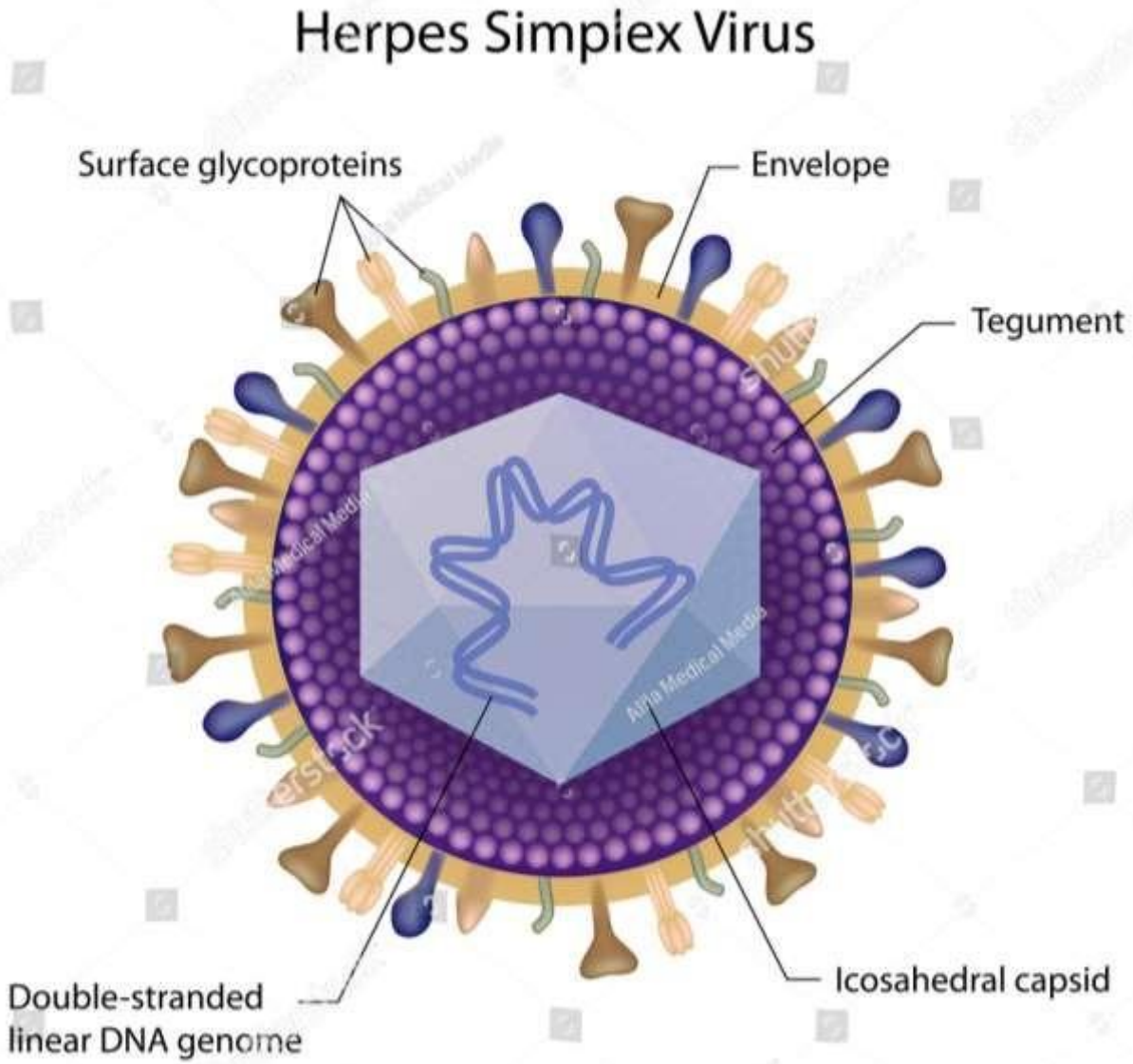
- **Genital herpes** is a common sexually transmitted disease, affecting **more than 400 million persons worldwide**

- In the United States, nearly **one in five adults** (approximately 50 million persons) has **HSV-2** infection, with 1 million new infections occurring each year.

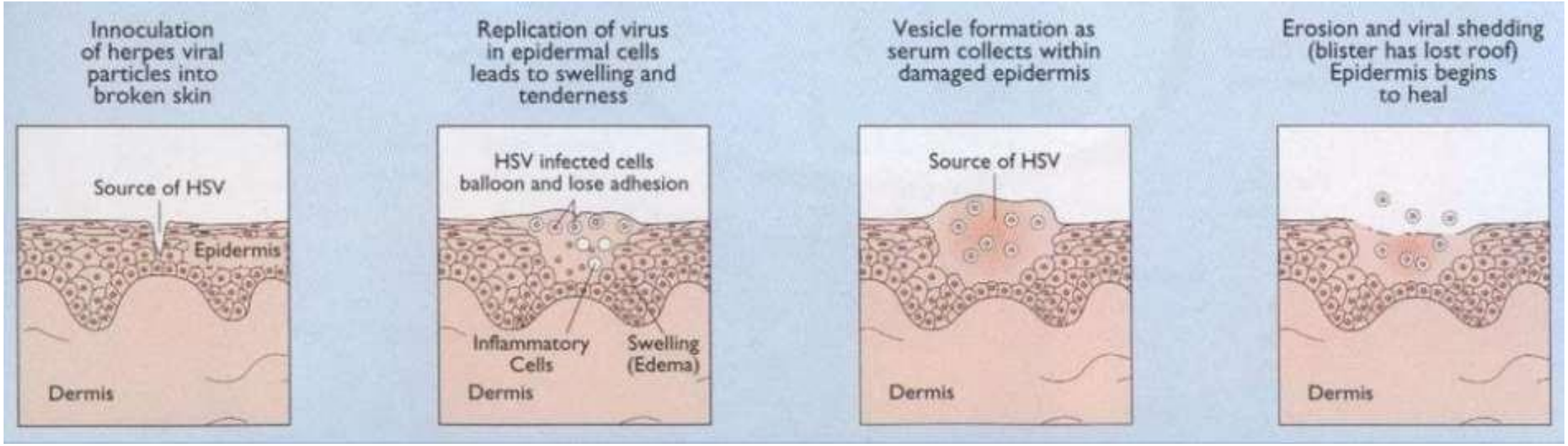
✓ HSV-2 is the most common cause of genital herpes (but type one can cause it too!)

✓ HSV has a double stranded linear DNA genome, these viruses are usually characterized by:

- **Lifelong** infection and periodic **reactivation**



Ulcerative genital infections / Genital herpes / **pathophysiology**



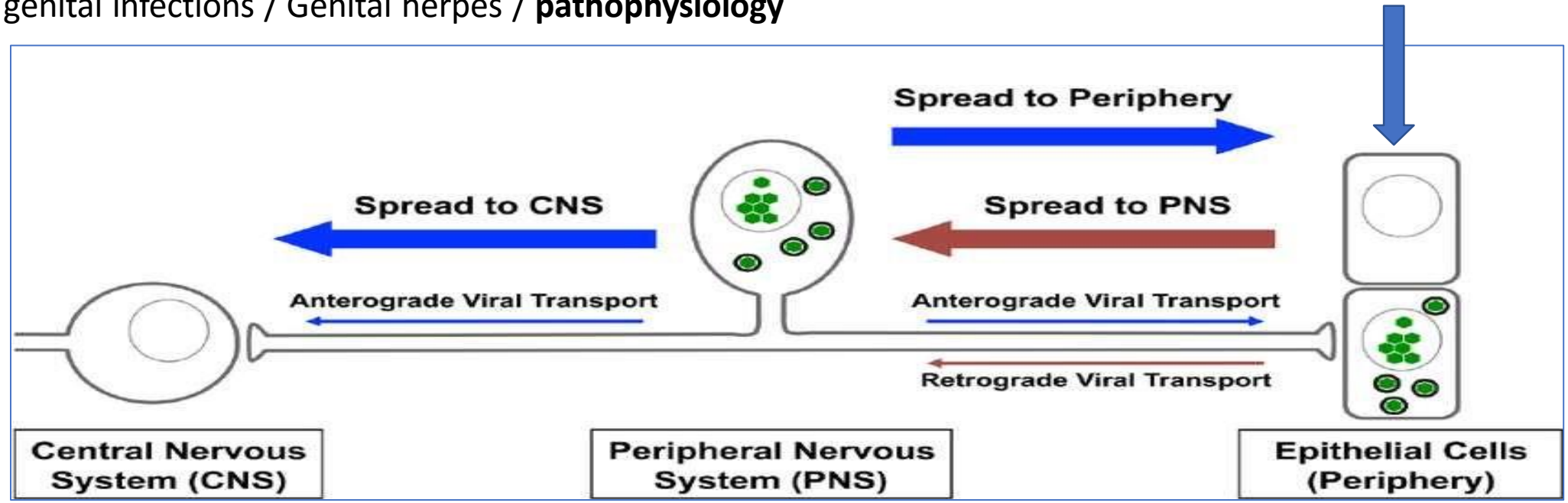
HSV manages to find a break in the skin (even micro-abrasions) during sexual contact and it gets inoculated into the epidermis.

It starts its cytopathic effects by causing swelling and apoptosis in epidermal cells, this draws in inflammatory cells.

Inflammation then ensues to cause blisters within the skin.

later on the blisters rupture and lead to release of viruses, forming an ulcer behind which would heal with time. However, The story doesn't end here …

Ulcerative genital infections / Genital herpes / **pathophysiology**



The virus would then move from the epithelial cells in the periphery (skin) through the peripheral nervous system to lay dormant within the dorsal ganglia neurons, So after causing the initial pathology within the epithelial layers, the virus would sit dormant in the peripheral NS.

Very rarely, HSV can spread to the CNS causing meningitis or encephalitis.

But the more common route is reactivation every once in a while within the epithelial cells and causing the same pathological presentation

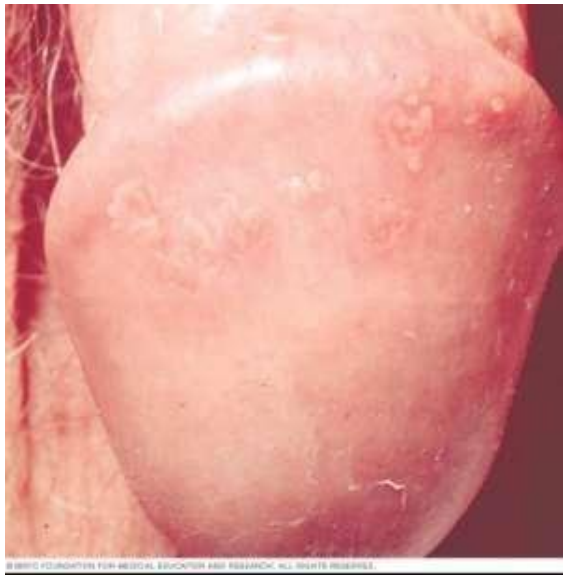
It's been noted that reactivation is usually less symptomatic than the primary infection

Ulcerative genital infections / Genital herpes/ **signs and symptoms**

- A visible outbreak consists of **single or clustered vesicles** (a cluster of blisters) on the genitalia that **rupture and ulcerate before resolving.**

✓ This is the effect of epithelial damage

✓ If a genital ulcer is preceded by a blister: suspect herpes

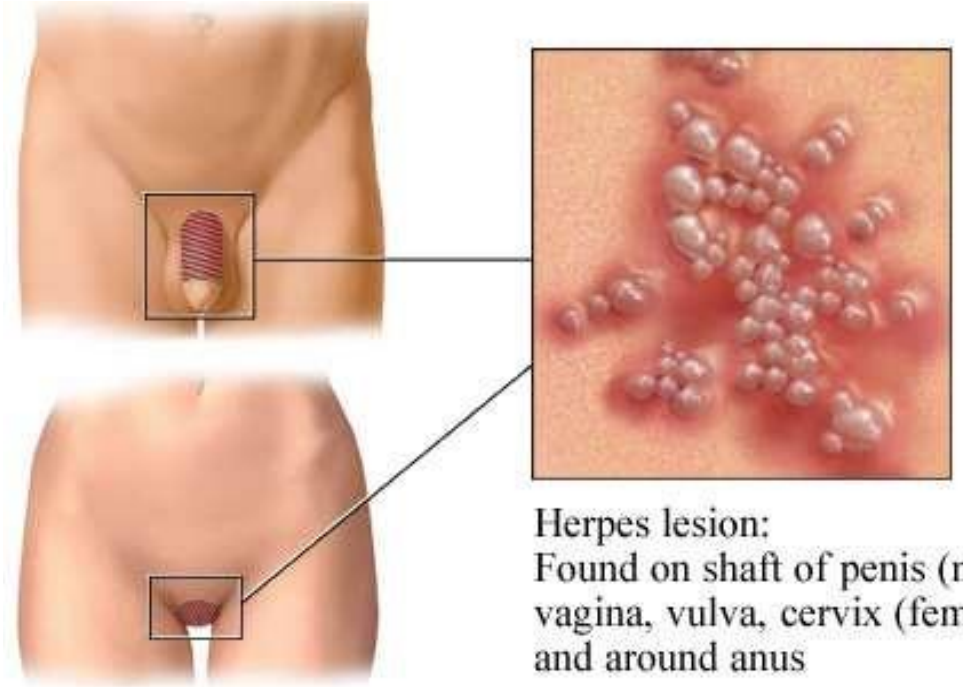


- Primary infections may cause malaise, fever, or localized adenopathy, **Subsequent outbreaks are usually milder** and are caused by reactivation of latent virus.

- Patients with HSV-1 infection average zero to one recurrence per year, whereas **HSV-2 recurs four to five times annually**

- **Asymptomatic viral shedding** is common, occurring on 10% to 20% of all days, and facilitates viral transmission.

✓ Even if the patient doesn't have blisters or ulcers they can still be spreading it.



Herpes lesion:
Found on shaft of penis (male), vagina, vulva, cervix (female), and around anus

Ulcerative genital infections / Genital herpes/ **Diagnosis and treatment**

✓ We previously mentioned that clinically it can be diagnosed by the presence of an ulcer preceded by a blister with a history of recurrence.

- **Viral culture** from vesicular fluid and ulcerated lesions are useful for definitive diagnosis

- **PCR- based viral detection** (the gold standard) is rapid and specific. And so is **Viral antigen detection**.

✓ The infection is lifelong, it reactivates and can't be eradicated but:

- **Systemic antiviral drugs** especially **acyclovir, valacyclovir, and famciclovir** can partially control the signs and symptoms of genital herpes when used to treat first clinical and recurrent episodes or when used as daily suppressive therapy.

  ➲ These drugs **do not eradicate latent virus** nor affect/reduce the risk, frequency, or severity of recurrences after the drug is **discontinued**.

- **Symptomatic treatment**— saline bathing, analgesia, and topical local anaesthetic agents (e.g. 5% lidocaine) ointment especially for painful micturition.

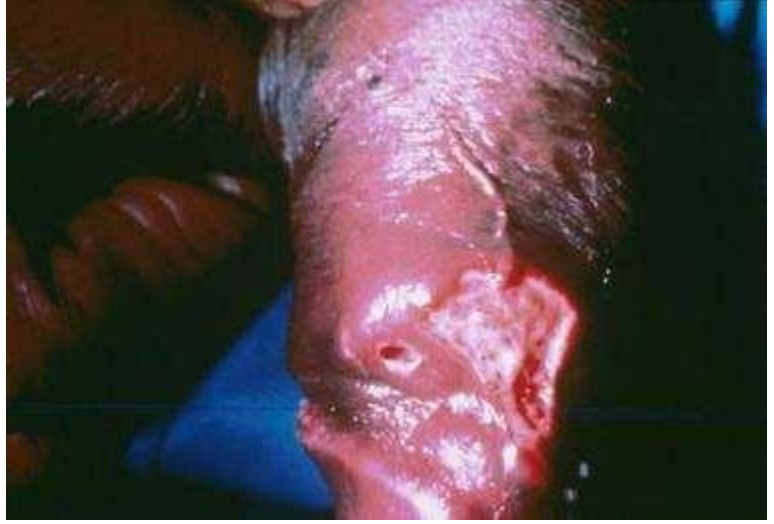
Ulcerative genital infections / **Chancroid**

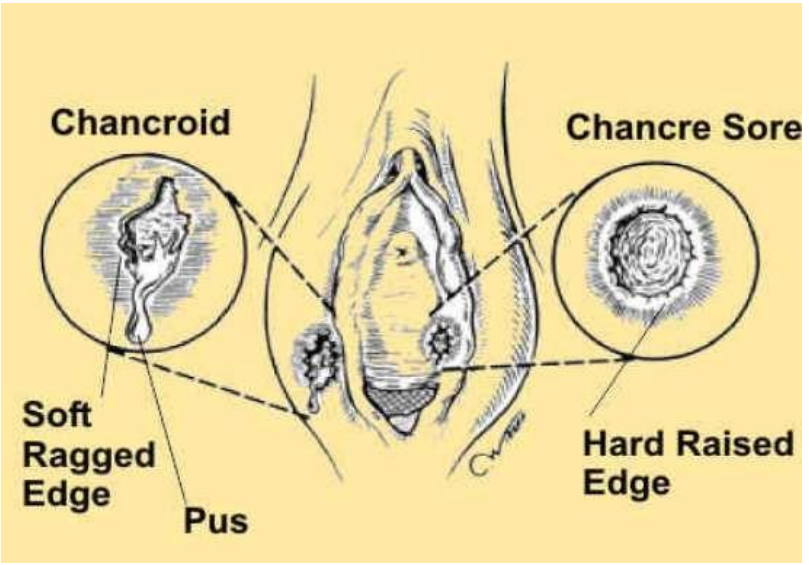
- Chancroid is a sexually transmitted disease (STD) caused by the Gram negative bacterium **Haemophilus ducreyi** and is characterised by **necrotising genital ulceration**

✓ H. Ducreyi is still a leading cause of genital ulceration in developing countries

- Painful, erythematous papules develop on the external genitalia then advance into pustules, and then erode into **sloughy**, **non- indurated haemorrhagic ulcers**

- To treat chancroids, Single oral dose of **azithromycin** or **ciprofloxacin** and intramuscular **ceftriaxone** regimens offer advantages in terms of improved patient compliance.





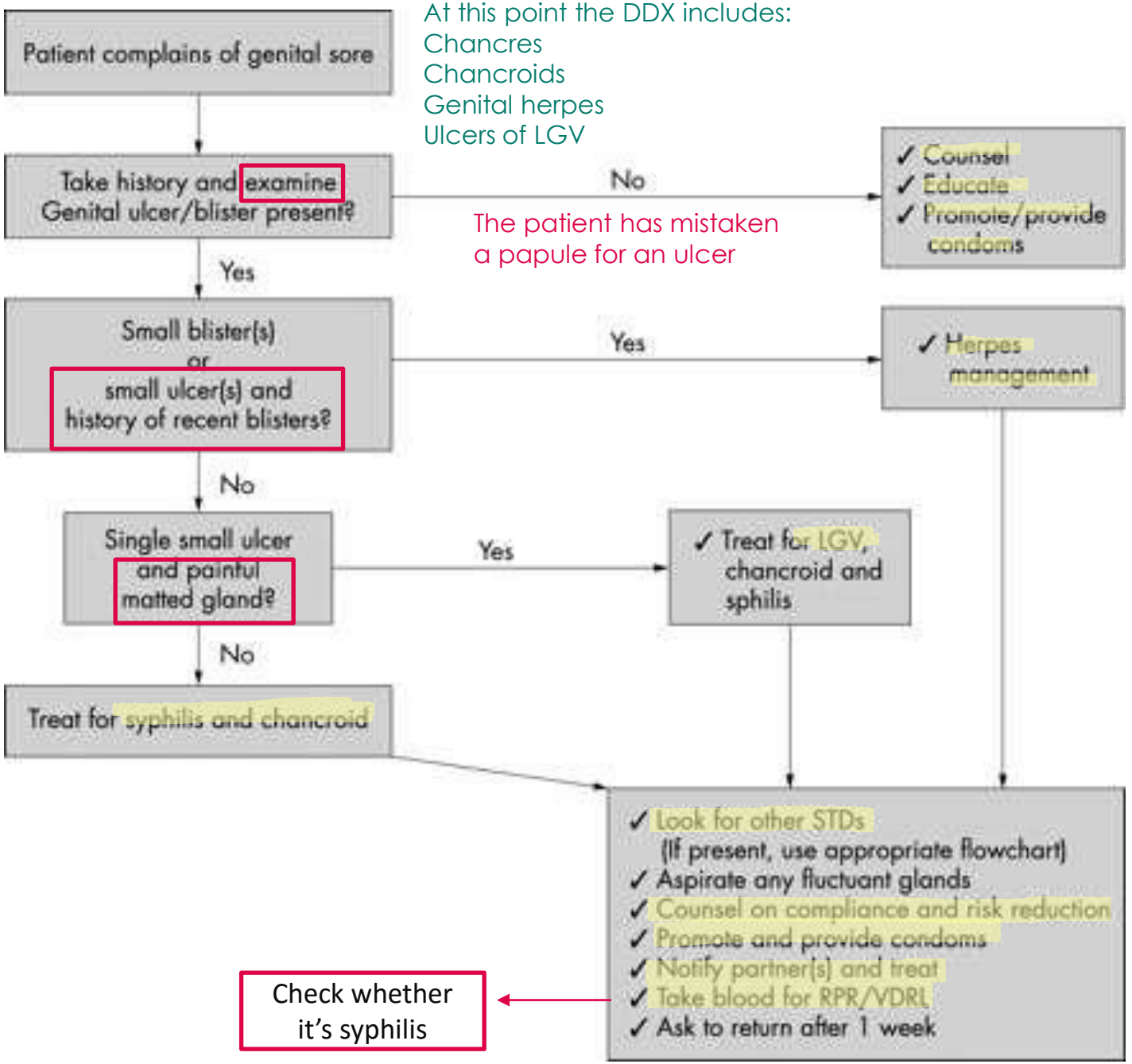
✓ Chancroids are similar to chancres (syphilitic ulcers), but they can be differentiated by some characteristics:

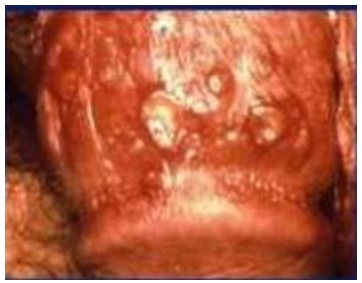
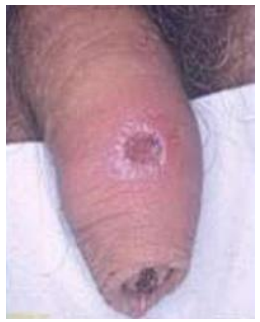
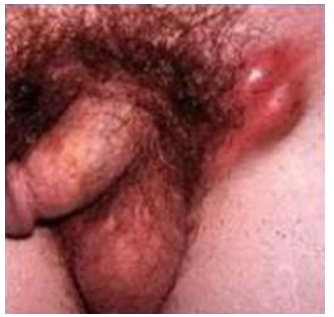
✓ Chancroids are painful and they have a ragged edge whereas chancres have raised, circular edges and are painless.

You start here by taking the complaint

At this point the DDX includes:
Chancres
Chancroids
Genital herpes
Ulcers of LGV

- WHO recommended syndromic management for genital ulceration includes therapy for both chancroid and syphilis.



	Genital herpes	Primary syphilis	Chancroid	LGV
				
Diagnostic clue	Painful vesicular lesions → multi-superficial ulcer	Painless indurated border	Extremely painful deep ulceration, ragged edges	Painless ulcer, heals within few days ‘ Groove sign’
Treatment	Acyclovir	Benzathine pen G Alternatives Doxycycline Tetracycline Eryhtomycin	Ceftriaxone Ciprofloxacin Erythromycin azithromycin	Doxycycline Erythromycin

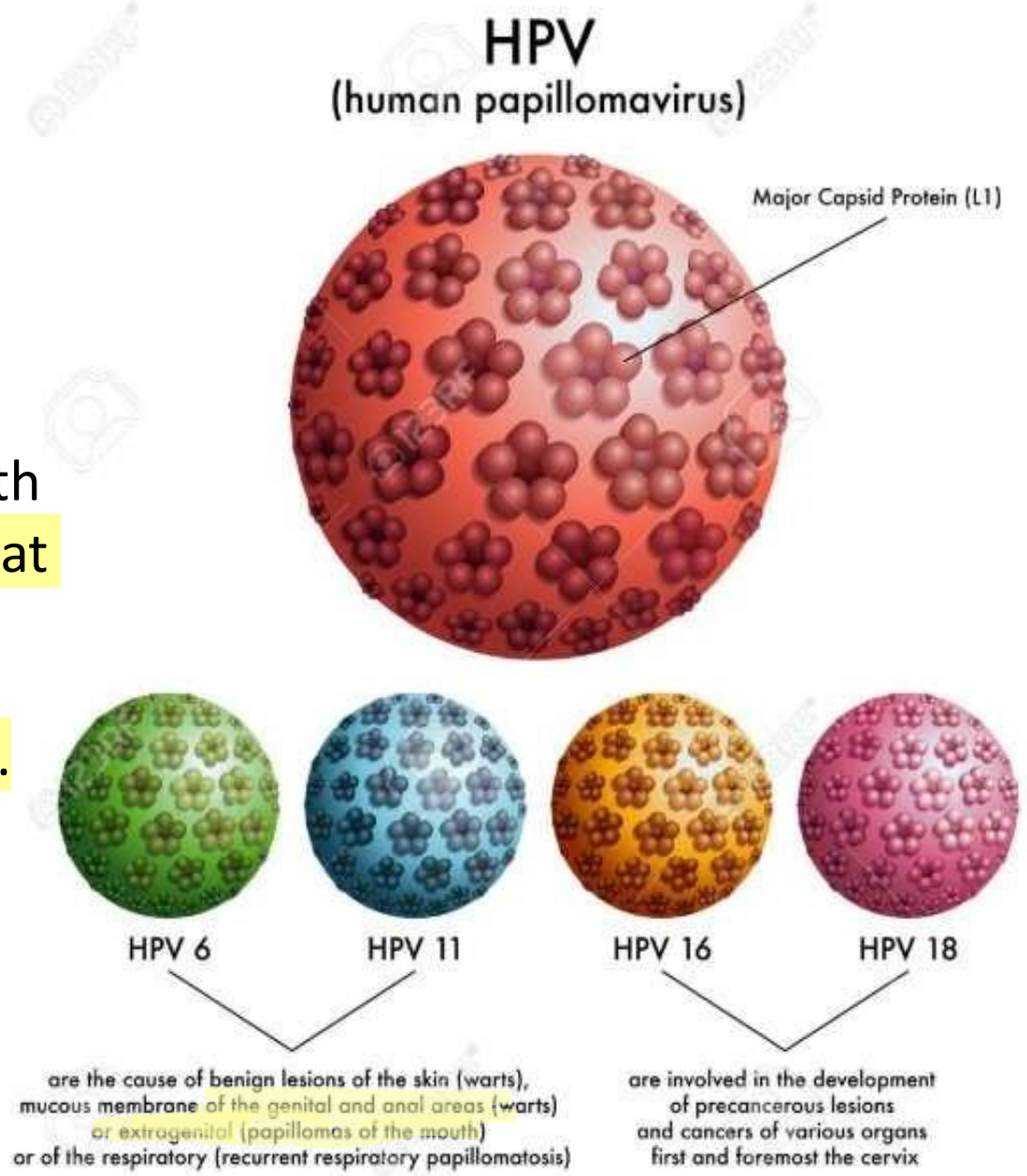
Genital warts/ etiology and epidemiology

- Genital warts are a **sexually transmitted infection** caused by certain types of **human papillomavirus** (HPV)

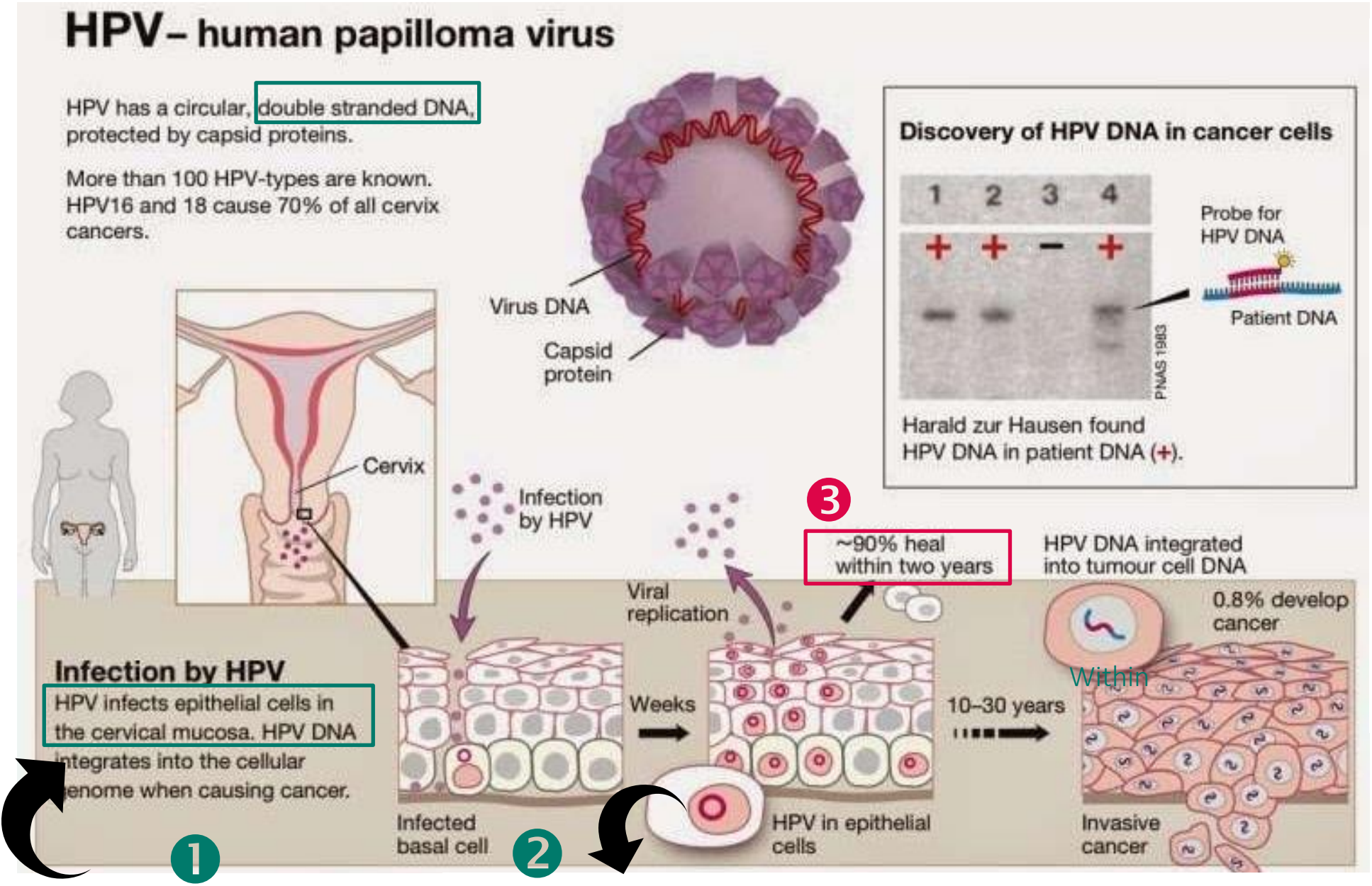
- Genital warts are a common cause of morbidity, with estimates of up to 50% of the population (US) HPV at some point in their lifetime
  - ✓ In some cases HPV can manage to cause life long infections
- **90% of cases** are related to **HPV subtypes 6 and 11**.

- **HPV Subtypes 16 and 18** are associated with **squamous cell carcinoma**.
  - ✓ Especially in the cervix

- **Women** tend to be affected **more than men** in most settings.



Genital warts/ **pathophysiology**



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The wart goes away and the epithelial physiology is restored. However, in types associated with cancer, the virus would insert its DNA within the genome of the epithelial cells, this takes a long period of time (10-30 years) in the case of warts there's no DNA insertion.

We try to screen early for any changes within the epithelium of the cervix, and if the changes look malignant we should worry about cancerous transformation in the future

During sexual contact

The virus replicates and causes the upper layers of the epithelium to keep dividing (we know that normally there's no division as cells go to the surface). It's a mitogenic virus.

Histopathologically, the hallmark of an HPV-infected cell is the development of morphologically atypical keratinocytes known as koilocytes. These are enlarged cells with eccentric, pyknotic nuclei that are often surrounded by a perinuclear halo I forgot to add this (however, the doctor didn't read it)

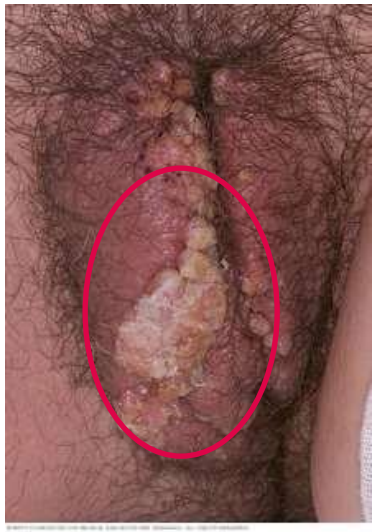
Appreciation:

The clinician that discovered the HPV genome within cervical cancer patients (the association between HPV and cervical cancer) was awarded the noble prize in 2008

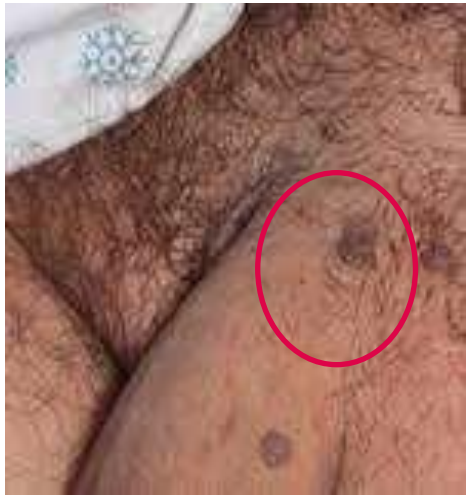
Hopefully in 20 years, medical students would be appreciating YOU for some grand discovery.

Genital warts/ **Signs and symptoms**

- On average, physical symptoms begin approximately 2 to 3 months after initial contact, Many studies estimate the rate of **subclinical** HPV infection to be as high as **40%**
- **Within few weeks of the initial contact we can start seeing those fleshy outgrowths, around the genitals or anus**



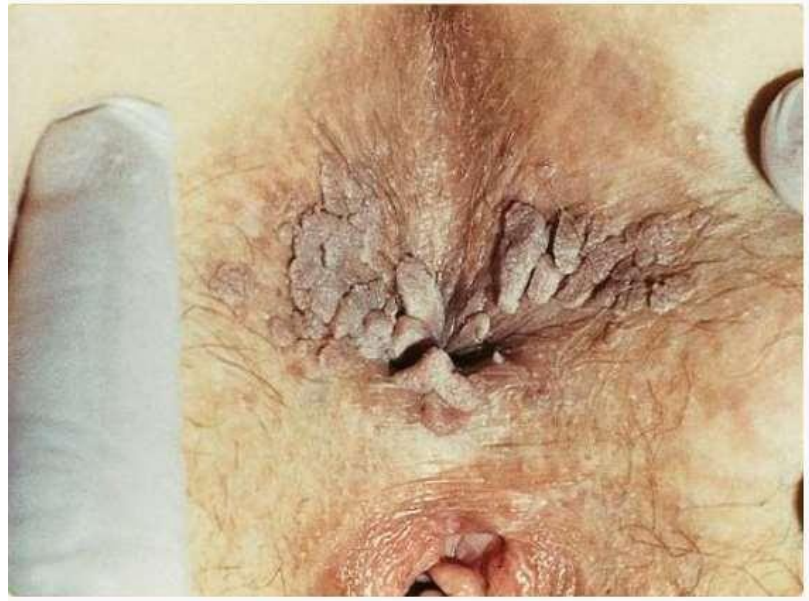
Female genital warts



- Approximately 30 percent of all warts will regress within the first four months of infection.

- Significant risk factors for long-term wart **persistence** include host **immunosuppression**, infection with **high-risk HPV subtypes**, and an **older patient age**

- Lesions are **rarely** considered to be **painful**; however, they are **often** associated with severe **discomfort**, **burning**, and **pruritis and they may bleed.**



Severe case of genital warts around the anus of a female

Genital warts/ **diagnosis and prevention**

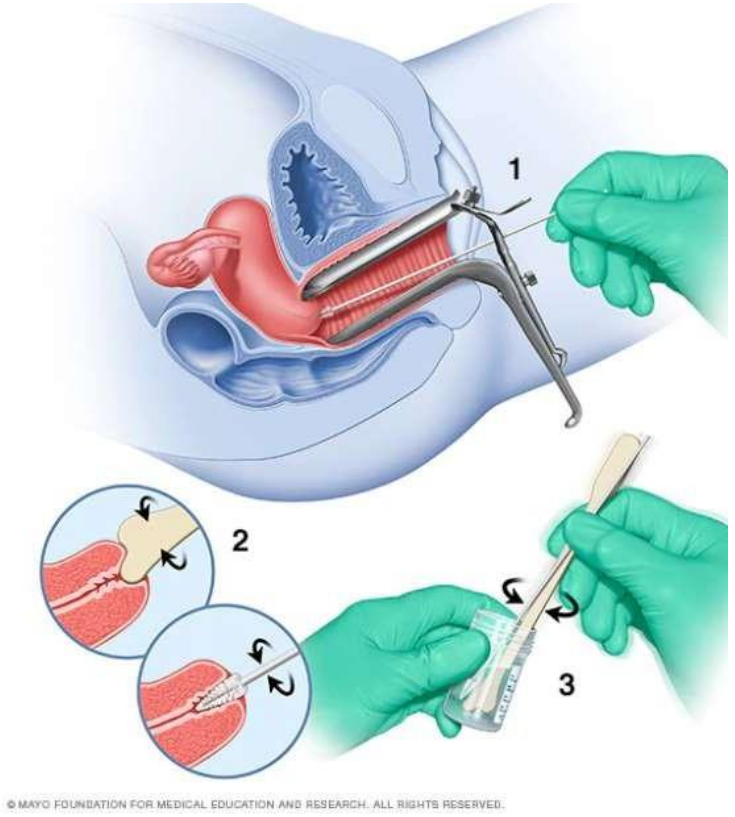
- **Diagnosis** is mostly made through clinical examination or through PCR of DNA or antigens tests to determine the type of HPV.

- A **vaccine** known as Gardasil protects against four strains of HPV that cause cancer, and is used to prevent genital warts (against HPV 6,11,16,18)

- These vaccines are most effective if given to children **before they become sexually active**

- **Pap tests**, can help **detect vaginal and cervical changes** caused by genital warts or the early signs of cervical cancer, some advocate that it should be performed annually after the age of 21, or after one's sexually active.

✓ A pap test is performed by opening up of the vagina, taking specimens from the cervix and examining them under the microscope to see if there're changes within the epithelial layers.

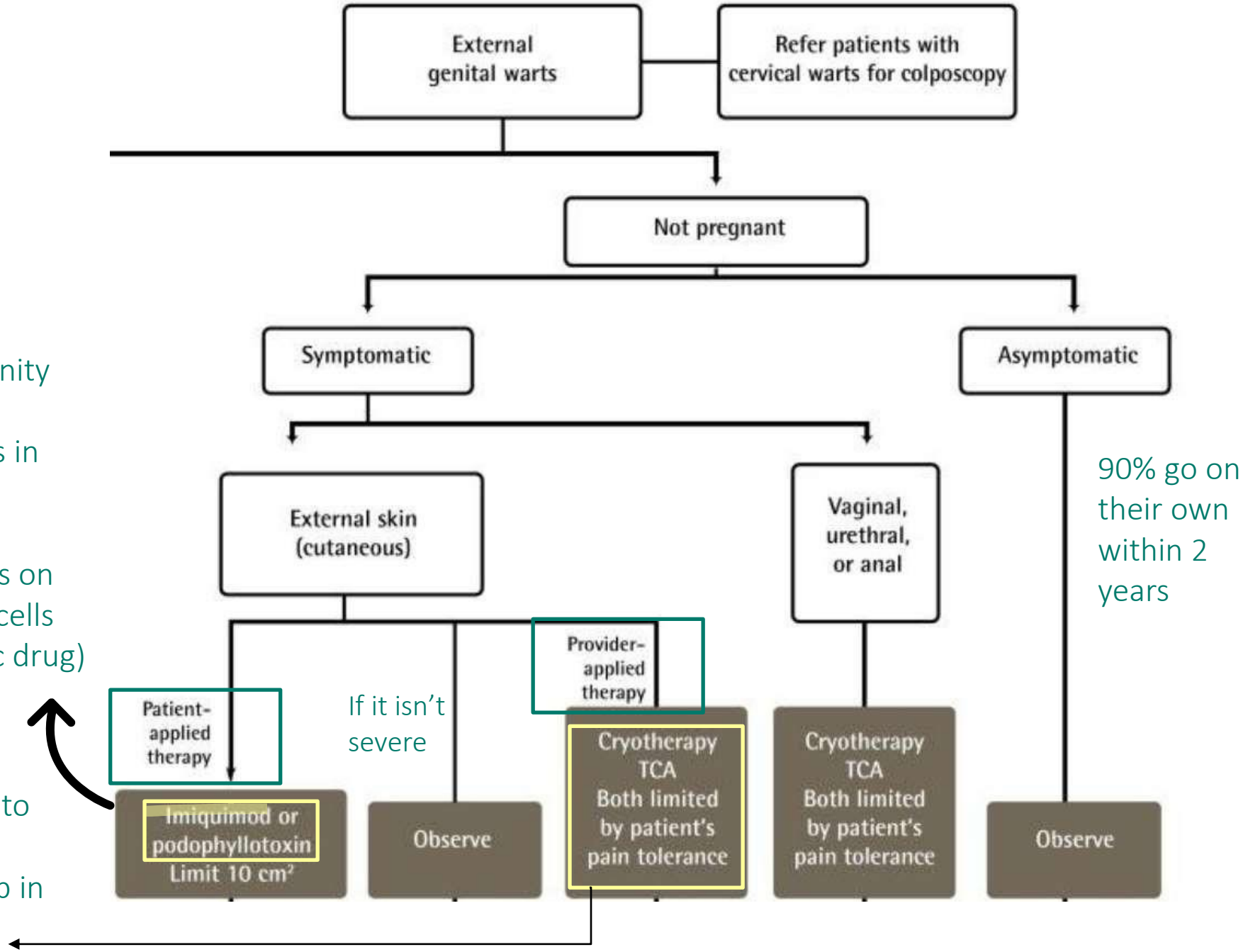


Pap test

Genital warts/ **treatment**

- ✓ **Imiquimod** is a newer modality of therapy, it activates innate immunity by activating toll like receptor 7 and it helps in activation of adaptive immunity.
- ✓ **podophyllotoxin**, works on continuously dividing cells or viruses, (antimitotic drug)

- ✓ **Cryotherapy:** application of liquid nitrogen to the warts to help in eliminating them
- ✓ **Trichloroacetic acid:** can help in "melting" the warts



90% go on their own within 2 years

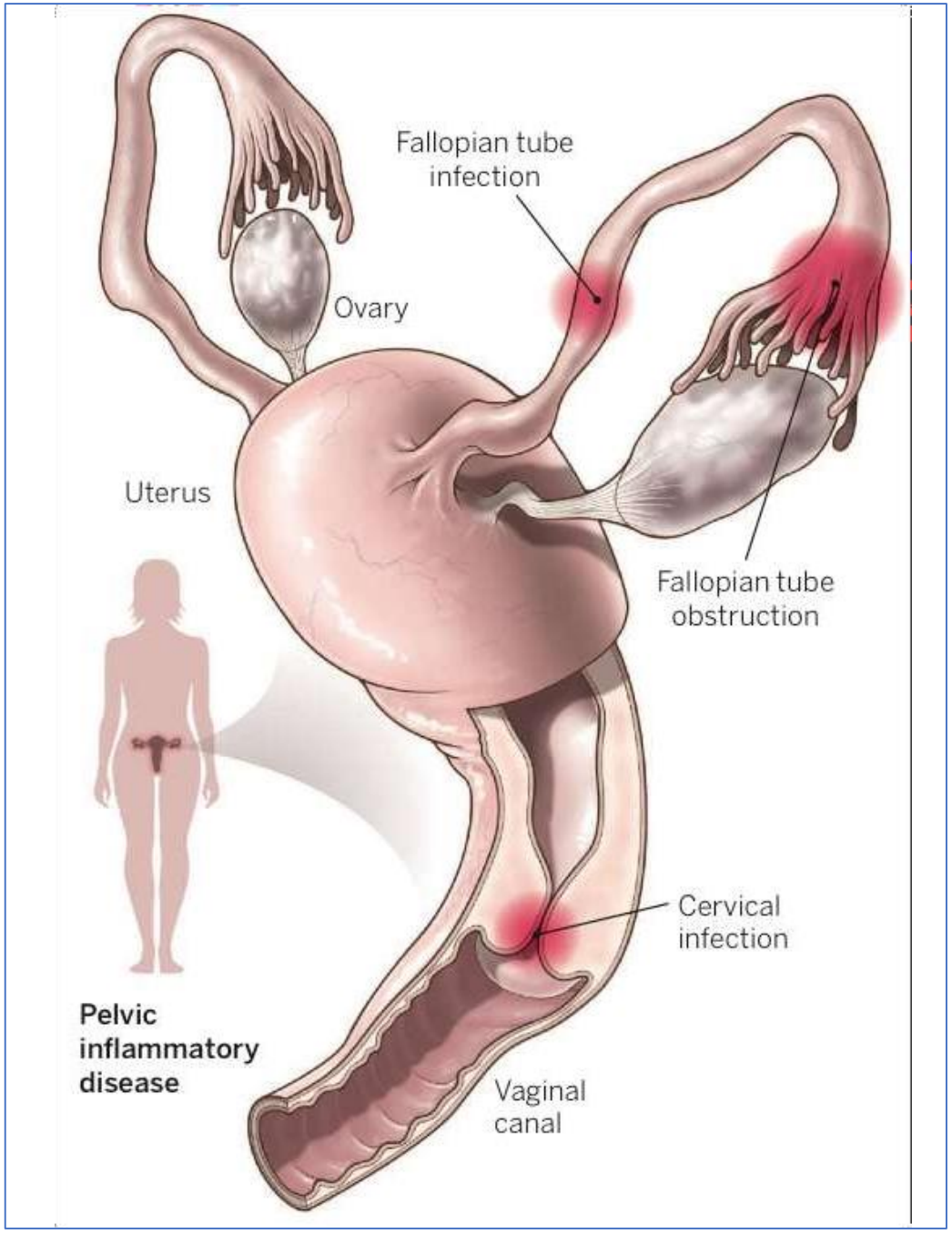
Pelvic inflammatory disease (PID)

- The term pelvic inflammatory disease usually refers to **infection** that ascends from the cervix or vagina to involve the **endometrium** and/ or **fallopian tubes** and **ovaries**.
- Infection can extend beyond the reproductive tract to cause **peritonitis** or **pelvic abscesses**.

✓ Most of the time it's caused by an STI like chlamydia or gonorrhea because they're commonly asymptomatic in females and they remain in the vagina for awhile then ascend upwards to cause PID, but it can result from infections other than STIs like **bacterial vaginosis**.

- Other than primary infections from STDs, infection can also be **secondary** to invasive **intrauterine surgical procedures** (e.g. termination of pregnancy).

Rarely, infection is not related to specific sexually transmitted pathogens, and originates from **another focus of infection.** (the infection can originate **from the peritoneum** then extend to the reproductive organs)



Pelvic inflammatory disease (PID)

Table 1. Clinical Classification of Pelvic Inflammatory Disease and Likely Microbial Causes.

Clinical Syndrome	Causes
Acute pelvic inflammatory disease (≤30 days' duration)	Cervical pathogens (*Neisseria gonorrhoeae*, *Chlamydia trachomatis*, and *Mycoplasma genitalium*) Suspect STIs
	Bacterial vaginosis pathogens (peptostreptococcus species, bacteroides species, atopobium species, leptotrichia species, *M. hominis*, *Ureaplasma urealyticum*, and clostridia species)
Introduction of foreign pathogens, Iatrogenic infection.	Respiratory pathogens (*Haemophilus influenzae*, *Streptococcus pneumoniae*, group A streptococci, and *Staphylococcus aureus*)
	Enteric pathogens (*Escherichia coli*, *Bacteroides fragilis*, group B streptococci, and campylobacter species)
Subclinical pelvic inflammatory disease	*C. trachomatis* and *N. gonorrhoeae*
Chronic pelvic inflammatory disease (>30 days' duration)	*Mycobacterium tuberculosis* and actinomyces species Slow development → suspect villains that grow slowly

Pelvic inflammatory disease/ **Signs and symptoms**

- The hallmark of the diagnosis is **pelvic tenderness** (cervical motion tenderness, adnexal tenderness, or uterine compression tenderness) combined with **inflammation of the lower genital tract**; women with pelvic inflammatory disease often have **very subtle** symptoms and signs

- **Fever** can occur, but systemic manifestations are **not a prominent feature** of PID.

- The abrupt **onset** of severe lower abdominal pain **during or shortly after menses** has been the classic symptom used to identify acute PID.

- Clinical diagnosis is **often imprecise** and more tests are needed to confirm diagnosis.

Pelvic inflammatory disease/ **Diagnosis**

- Although **laparoscopy** has been considered the standard for the diagnosis of pelvic inflammatory disease, it has high interobserver variability and is invasive.

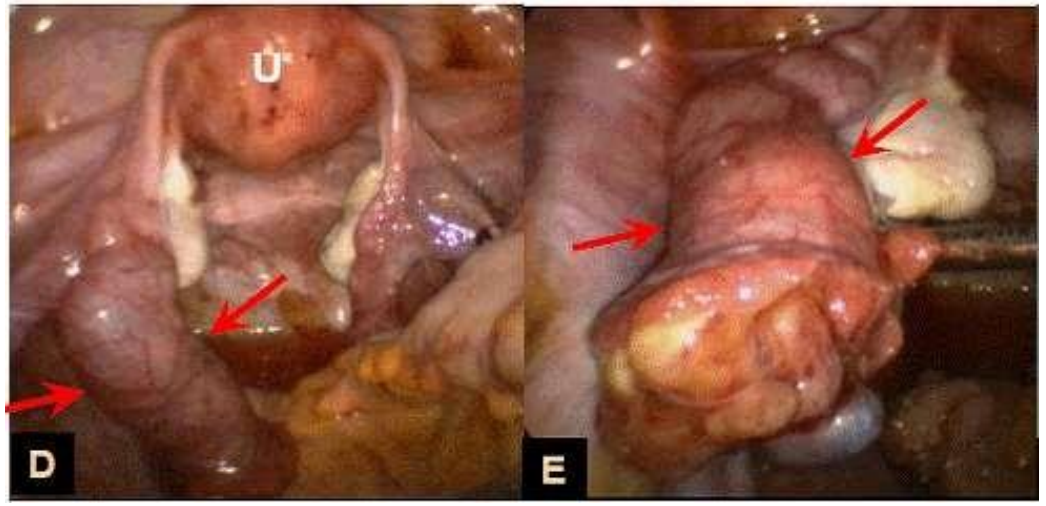
✓ Diagnostic differences among doctors observing such cases

- Transcervical endometrial aspiration with **histopathological findings** of increased WBCs is more commonly used to confirm the diagnosis of pelvic inflammatory disease.

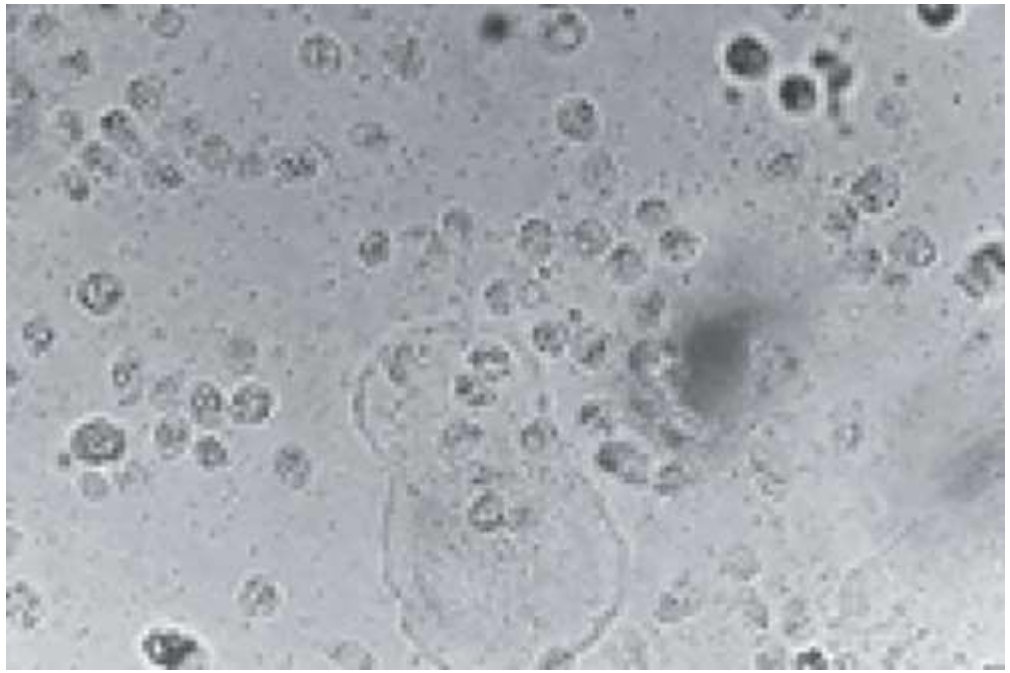
- Imaging: **MRI** has high sensitivity, reveals thickened, fluid-filled tubes.

- All patients with suspected PID should undergo cervical or vaginal **NAATs** for *N. gonorrhoeae* and *C. trachomatis* infection

Nucleic acid amplification test



Laparoscopy image and close-up image of same patient show sausage-shape dilated right fallopian tube (arrow)

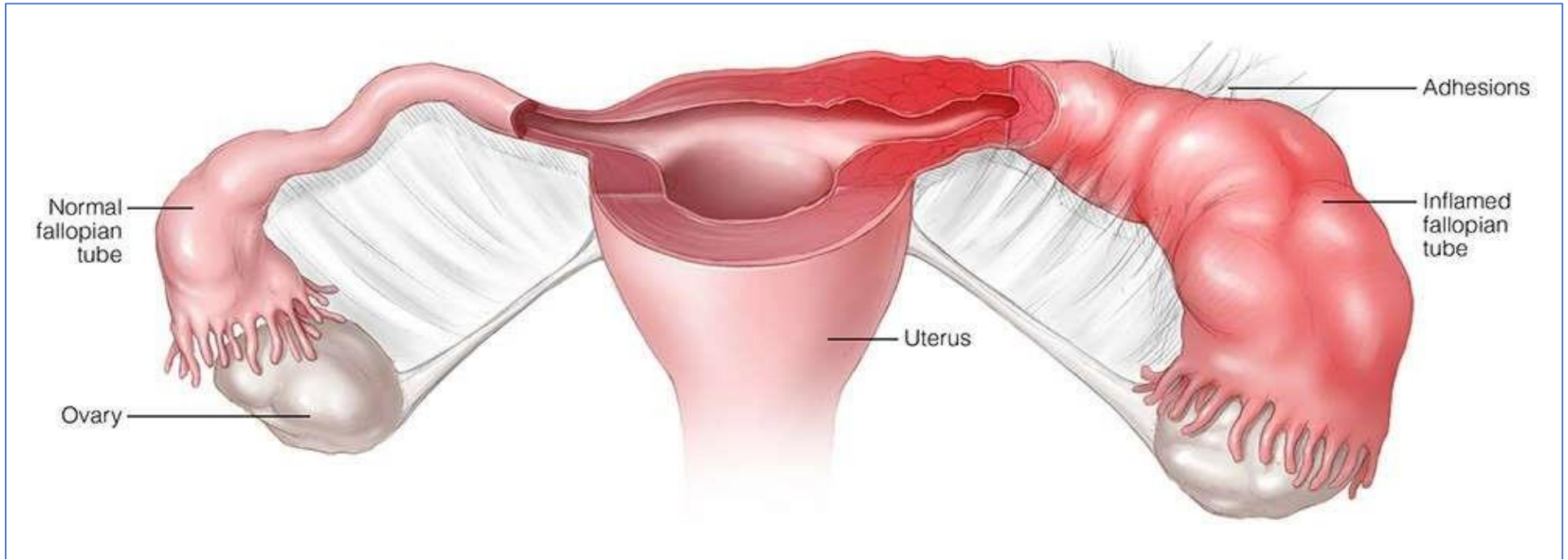


increased numbers of white cells (≥1 per vaginal epithelial cell)

Pelvic inflammatory disease/ **Sequalae**

- Infection results in **fibrinous** or suppurative **inflammatory damage** along the epithelial surface of the fallopian tubes and the peritoneal surface of the fallopian tubes and ovaries, which leads to **scarring**, **adhesions** with surrounding organs, and possibly partial or total **obstruction of the fallopian tubes**

- This can result in long-term reproductive disability, including **infertility**, **ectopic pregnancy**, and **chronic pelvic pain**.



Pelvic inflammatory disease/ Treatment

✓ Treatment depends mainly on eradication of the primary causative agent

- The treatment of pelvic inflammatory disease is **empirical** and involves the use of **broad-spectrum combination** regimens of antimicrobial agents to cover likely pathogens.

To cover chlamydia we give **doxycycline,** **Metronidazole** to cover trichomoniasis or Bacteroides that cause bacterial vaginosis, **ceftriaxone** and other **third generation cephalosporins** to cover Neisseria gonorrhoea. And hopefully with antimicrobial treatment the inflammation subsides.

Table 2. First-Line Antimicrobial Treatment Recommended by the Centers for Disease Control and Prevention (CDC) for Pelvic Inflammatory Disease.*

Outpatient regimen for mild-to-moderate pelvic inflammatory disease
Doxycycline (100 mg orally twice daily for 2 wk) with or without metronidazole (500 mg orally twice daily for 2 wk), plus one of the following:
Ceftriaxone (250 mg intramuscularly in a single dose)
Cefoxitin (2 g intramuscularly) with probenicid (1 g orally) concurrently in a single dose
Other parenteral third-generation cephalosporin (cefotaxime or ceftizoxime)
Inpatient regimen for moderate-to-severe pelvic inflammatory disease with or without tubo-ovarian abscess†
One of the following:
Cefotetan (2 g intravenously every 12 hr) plus doxycycline (100 mg orally or intravenously every 12 hr)
Cefoxitin (2 g intravenously every 6 hr) plus doxycycline (100 mg orally or intravenously every 12 hr)
Clindamycin (900 mg intravenously every 8 hr) plus gentamicin (3 to 5 mg per kilogram of body weight intravenously once daily)

* Complete treatment information, including alternative regimens and additional considerations, is available at the CDC website.[33]

† Transition to oral therapy can usually be initiated within 24 to 48 hours after clinical improvement, and oral therapy should be continued to complete 2 weeks of therapy.

Further reading:

- Oxford handbook of infectious diseases and microbiology-
Part4: Clinical syndroms
Chapter 18: Sexually transmitted infections

- Harrison's Infectious Diseases 3rd Edition
SECTION III Infections in organ systems
Chapter 35