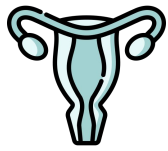


TEAM 443  
MICROBIOLOGY

# L2- Syphilis + Gonorrhoea & chlamydia

- Dr.Khalifa Bin Khamis & Dr.Hanan





# OBJECTIVES

- 1** Recall the causative agents of syphilis, gonorrhoea and Chlamydia infections.  
Describe the pathogenesis of syphilis, gonorrhoea and Chlamydia infection.
- 2** Describe the clinical features of Chlamydial infections  
Describe the laboratory diagnosis of Chlamydia
- 3** Recall the different genera, species and serotypes of the family Chlamydia
- 4** Describe the clinical features of gonorrhoea that affect only men, only women and those ones which affect both sexes.
- 5** Describe the different laboratory tests for the diagnosis of gonorrhoea
- 6** Describe the clinical feature of the primary, secondary tertiary syphilis and complications.
- 7** Recall the different diagnostic methods for the different stages of syphilis.  
Recall the treatment regimens of syphilis, gonorrhoea and Chlamydia infections
- 8** Recall that there are no effective vaccines against all these three diseases.



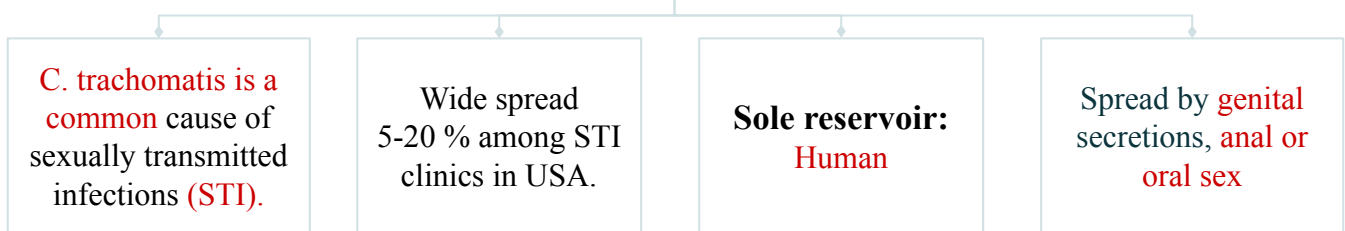
# Chlamydia (1)

## Introduction

An **obligate intracellular** bacteria with elements of bacteria but **no rigid cell wall**.

- ❖ Fail to grow on artificial media.
- ❖ Uses host cell metabolism for growth and replication.

## Epidemiology



## Chlamydia species

Chlamydia serotype	Disease
<b>C. trachomatis</b>	<ul style="list-style-type: none"> <li>❖ A common cause of sexually transmitted disease (STD).</li> <li>❖ 1/3 of male sexual contacts of women with C.trachomatis cervicitis develop urethritis <b>after 2 - 6 weeks incubation period (IP)</b></li> </ul>
	<ul style="list-style-type: none"> <li>❖ (A,B,C)               <ul style="list-style-type: none"> <li>- <b>Trachoma</b> (type of eye infection, seen in some African countries aka: الرممد)</li> </ul> </li> <li>❖ (D - K)               <ul style="list-style-type: none"> <li>- <b>Inclusion conjunctivitis</b> (appears in newborns after one week of being born to an infected mother) , <b>genital infection</b>.</li> </ul> </li> </ul>
	<ul style="list-style-type: none"> <li>❖ (L1, L2, L3)               <ul style="list-style-type: none"> <li>- <b>Lymphogranuloma venereum (LGV)</b>: common in South America &amp; Africa. (STD but its presentation is different from chlamydia)</li> </ul> </li> </ul>
<b>C. psittaci</b>	Psittacosis
<b>C. pneumoniae</b>	Respiratory infections

## Pathogenesis

- ❖ 1- Chlamydia **have tropism for epithelial cells** of:
  - Both sexes: urethra - rectum - conjunctiva.
  - Women: endocervix & upper genital tract
- ❖ 2- **LGV can enter through skin or mucosal breaks.**
- ❖ 3- Release of pro-inflammatory cytokines → tissue infiltration by inflammatory cells → necrosis, fibrosis & scarring.



# Chlamydia con...

## Genital Infections Caused by C.trachomatis (local spread)

<p><b>In Men</b></p>	<ul style="list-style-type: none"> <li>❖ Urethritis (Non gonococcal urethritis (NGU))</li> <li>❖ Epididymitis</li> <li>❖ Proctitis</li> <li>❖ Urethritis present as dysuria &amp; thin urethral discharge in 50 % of men.</li> </ul>
<p><b>In Women</b></p>	<ul style="list-style-type: none"> <li>❖ Cervicitis (mainly): uterine cervix infection</li> <li>❖ Salpingitis</li> <li>❖ Urethral syndrome</li> <li>❖ Endometritis</li> <li>❖ Proctitis</li> </ul> <p>Complications:</p> <ul style="list-style-type: none"> <li>❖ Salpingitis &amp; Pelvic inflammatory disease can cause → sterility &amp; ectopic pregnancy.</li> <li>❖ LGV -+ papule and inguinal lymphadenopathy (not common).</li> <li>❖ Chronic infection - abscesses (not common), strictures and fistulas.</li> <li>❖ Uterine cervix infection may produce vaginal discharge but is <u>asymptomatic</u> in 50 - 70% of women.</li> </ul>
<p><b>In Infants</b></p>	<ul style="list-style-type: none"> <li>❖ 50% of infants born to mothers excreting C. trachomatis during labor show evidence of infection during the first year of life. <ul style="list-style-type: none"> <li>- Inclusion conjunctivitis (eye) (mostly)</li> <li>- Infant pneumonia syndrome (lung) (5-10%)</li> </ul> </li> </ul>



## Diagnosis

### 1. Isolation on Tissue Culture (McCoy Cell Line)

- C. trachomatis inclusions can be seen by iodine or Giemsa stained smear.
- Rarely done since it can be false negative.  
(mainly for research)

### 2. Polymerase Chain Reaction (PCR) (main diagnostic)

- Most sensitive diagnostic method.
- Performed on vaginal, cervical, urethral swabs, or urine.
- Gold standard



## Treatment & Prevention

<p><b>Treatment</b></p>	<ul style="list-style-type: none"> <li>❖ <b>Azithromycin or Doxycycline</b></li> <li>❖ <b>Pregnant: Azithromycin</b></li> <li>❖ <b>LGV: Doxycycline (contraindicated in pregnancy).</b></li> </ul>
<p><b>Prevention</b></p>	<ul style="list-style-type: none"> <li>❖ Early detection of asymptomatic cases.</li> <li>❖ Screening women under 25 years → reduce transmission to sexual partner.</li> </ul>



# Gonorrhoea (السيلان) (6)

## Introduction

Gonorrhoea: STI disease acquired by direct genital contact. (never is normal flora)

- ❖ Localized to mucosal surfaces with infrequent spread to blood or deep tissues.
- ❖ Caused by: *N. gonorrhoeae*.

## Epidemiology

Rates among adolescents are high, about 10% increase per year in USA.

Major reservoir: asymptomatic cases → continued spread.

Marital intercourse




Inability to detect asymptomatic cases (women & patient fail to seek medical care) hampers control. (5)

Non-sexual transmission is rare.



## Clinical aspect

- ❖ Incubation period (IP): 2 - 5 days (Gonorrhoea in days; Chlamydia in weeks).
- ❖ Symptoms are similar to Chlamydia infection
- ❖ Pharyngitis, dysuria & eye discharge may occur.

 <b>In women</b> (3)	<ul style="list-style-type: none"> <li>❖ <b>Mucopurulent cervicitis</b></li> <li>❖ Pelvic inflammatory disease (PID)</li> <li>❖ Gonococcal urethritis with discharge</li> <li>❖ Proctitis</li> </ul>
 <b>In men</b>	<ul style="list-style-type: none"> <li>❖ Gonococcal <b>urethritis</b>: acute urethritis with acute profuse <b>purulent</b> (2) urethral discharge</li> <li>❖ Proctitis</li> </ul>
 <b>In neonates</b>	- <b>Conjunctivitis</b> (4) by vertical transmission (vaginal tract)

Pelvic Inflammatory Disease (PID)	Disseminated Gonococcal Infection (DGI)
<ul style="list-style-type: none"> <li>❖ 10 - 20% of cases.</li> <li>❖ Symptoms: <ul style="list-style-type: none"> <li>-Fever</li> <li>-Lower abdominal pain</li> <li>-Adnexal tenderness</li> <li>-Leukocytosis with or without signs of local infection.</li> </ul> </li> <li>❖ Salpingitis &amp; pelvic peritonitis → <b>scarring &amp; infertility</b>.</li> <li>❖ Spread to bloodstream → DGI.</li> </ul>	<ul style="list-style-type: none"> <li>❖ Due to spread of bacteria to bloodstream.</li> <li>❖ Symptoms: <ul style="list-style-type: none"> <li>-Fever</li> <li>-Migratory</li> <li>-<b>Arthralgia &amp; arthritis</b></li> <li>-<b>Purulent arthritis of large joints</b></li> <li>- Petechial &amp; maculopapular rash.</li> </ul> </li> <li>❖ <b>Metastatic infections</b>: (endocarditis - meningitis &amp; perihepatitis may develop)</li> </ul>



# Neisseria gonorrhoeae

## Features of N. gonorrhoeae

- 1 **Gram negative diplococci.**
- 2 Never considered as a normal flora.
- 3 **Grows on chocolate agar & selective enriched media & CO<sub>2</sub> required. (7)**

## Pathogenesis of N. gonorrhoeae

- ❖ Localized infection of epithelium → intense inflammation.
- ❖ **Pili & outer membrane proteins** → mediate attachment to non-ciliated epithelium.



## Diagnosis (molecular options) (11)

Transport media required unless transfer to the lab. is immediate.

1. Direct Smear for Gram Stain of Urethral Specimens (9)	- <b>Gram negative diplococci within a neutrophil/pus (intracellular).</b>
2. Culture	- <b>Thayer-Martin (8)</b> or other <b>selective</b> medium.
3. Confirmation	- <b>Fermentation of glucose only</b> (doesn't ferment maltose or sucrose). - <b>Coagglutination test.</b>
4. Nucleic Acid Amplification Tests (PCR) (10)	- Is an <b>option for diagnosing</b> genital infections.



## Treatment

- ❖ Guided by local resistance pattern & susceptibility testing.
- ❖ Partner should be treated as well.
- ❖ **[Drug of choice]: IM \*Ceftriaxone (or oral Cefixime) + \*Azithromycin combination** is recommended to cover chlamydia as well & to increase success rates & decrease resistance emergence, one drug is not enough to treat it.
- ❖ **Alternatives:**
  - Ciprofloxacin or Ofloxacin
  - Azithromycin, Doxycycline (orally for 7 days) both cover C.trachomatis infection.
- ❖ Counseling



# Syphilis (12)

## Introduction

- ❖ Syphilis: **chronic** systemic infection, sexually transmitted, **caused by** a spiral organism called **Treponema pallidum subsp.pallidum**.  
Syphilis is a chronic infection unlike chlamydia + Gonorrhea Which are Acute infections
- ❖ Grow on cultured **mammalian cells only**.
- ❖ NOT stained by Gram stain . (because they're very thin spirals)
- ❖ Readily seen only by **immunofluorescence (IF)**, dark field microscopy or silver impregnation histology technique.



## Epidemiology of Syphilis

<b>Host</b>	Exclusively human pathogen.
<b>Transmission</b>	<ul style="list-style-type: none"> <li>❖ <b>Common</b> <ul style="list-style-type: none"> <li>-Contact with mucosal surfaces</li> <li>-Blood</li> </ul> </li> <li>❖ <b>Less common</b> <ul style="list-style-type: none"> <li>-Non-genital contacts with a lesion.</li> <li>-Sharing needles by IV drug users.</li> <li>-Transplacental transmission to fetus.</li> </ul> </li> </ul>
<b>Infectivity</b>	<ul style="list-style-type: none"> <li>-Early disease is infectious.</li> <li>-Late disease is not infectious</li> </ul>
<b>Pathogenesis</b>	<ol style="list-style-type: none"> <li>1- <b>Access of bacteria:</b> inapparent skin or mucosal breaks.</li> <li>2- Slow multiplication.</li> <li>3- <b>Endarteritis &amp; granulomas.</b></li> <li>4- Ulcer heals but Spirochete disseminate.</li> <li>5- Surface binding of host components → latent periods.</li> <li>6- Delayed hypersensitivity response to spirochetes → Injury</li> </ol>



# Syphilis

## Primary Syphilis

- **Start:** after IP  $\approx$  2 - 6 weeks.
- **Clinical Presentation:**
  1. **Chancre:** **painless**, indurated ulcer with firm base & raised margins on external genitalia or cervix, anal or oral site.
  2. Enlarged inguinal **lymph nodes** may persist for months.
- **Infectivity:** lesion most **infectious**. (main problem in primary syphilis)
- **Healing:** lesion **spontaneously heals** after 4 - 6 weeks.

## Secondary Syphilis

- **Start:** 2 - 8 weeks **after primary** lesion healed.
- **Clinical Presentation:**
  1. **Symmetric** mucocutaneous rash.
  2. **Mouth lesions** (snail track ulcers).
  3. Generalized non-tender lymph nodes enlargement (full of spirochete)
  4. **Bacteremia** (fever - malaise) and other systemic manifestations. (acute)
  5. **Skin lesions** on trunk & extremities (palms - soles - face).
  6. **Condylomata Lata:** painless mucosal warty erosions on genital area and perineum in 1/3 of patients.
- **Infectivity:** infectious lesion.
- **Healing:** few days to many weeks but disease continue in 1/3 of patients, disease enter into a latent state

## Latent Syphilis

- **No clinical manifestations.**
- Infection evident by **serological tests**. (positive)
- **Relapse** cease.
- **Infectivity:** **risk of blood-borne transmission** from relapsing infection or from mother to fetus continue

## Tertiary Syphilis

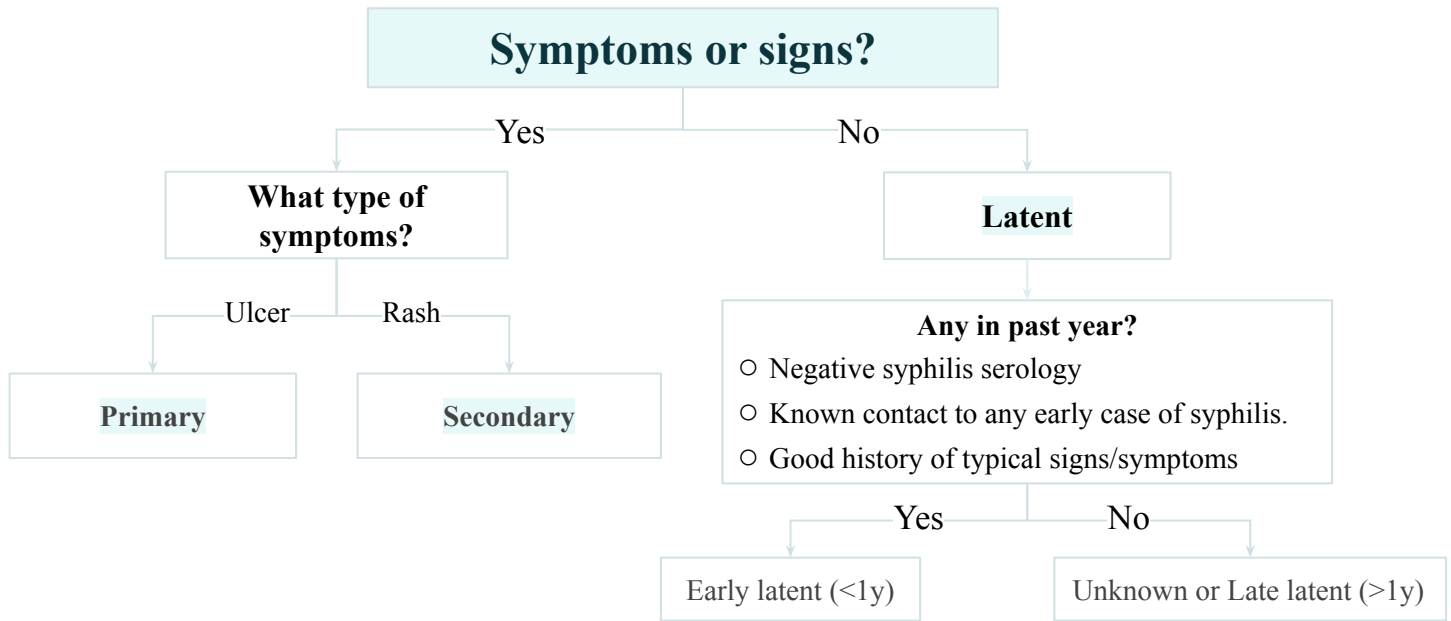
- **Start:** occurs in 1/3 of untreated cases, **manifestations may appear after 15-20 years**
- May be **asymptomatic** but **serological tests positive**.
- **Clinical Manifestation:**
  1. **Neurosyphilis**
    - **Chronic meningitis** with  $\uparrow$  cells & protein in CSF  $\rightarrow$  degenerative changes & psychosis.
    - Demyelination  $\rightarrow$  peripheral neuropathies .
    - Advanced cases: effect on brain parenchyma & posterior columns of spinal cord & dorsal roots  $\rightarrow$  **paresis** (personality - affect - reflexes - eyes - sensorium - intellect - speech).
  2. **Cardiovascular Syphilis**
    - Due to arteritis  $\rightarrow$  aneurysm of aorta & aortic valve ring.
    - **Gumma** (large lesion) (localized **granulomatous** reaction) on skin, bones, joints or other organs  $\rightarrow$  local destruction. :
- **Infectivity:** not infectious at the stage.



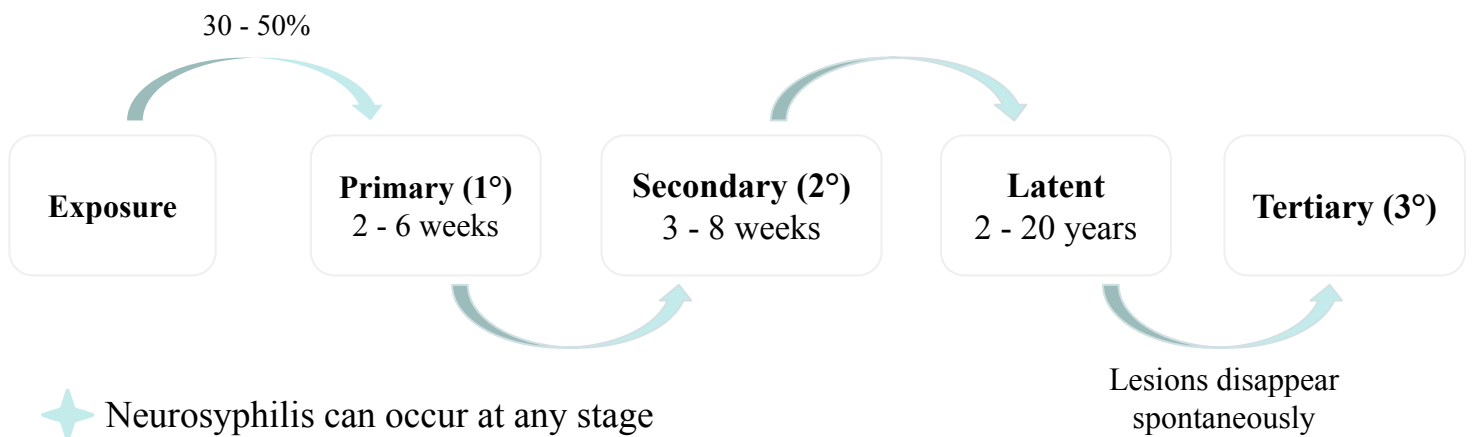


# Syphilis

## Syphilis Staging Flow Chart



## Syphilis Natural History



✦ Neurosyphilis can occur at any stage

## Congenital Syphilis (13)

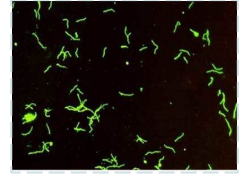
<b>Pathogenesis</b>	Develop if the <b>mother was not treated</b> from syphilis, <b>after the fourth month of gestation</b> → fetal loss or congenital syphilis.
<b>Symptoms</b>	○ Rhinitis ○ Rash ○ Bone changes (saddle nose - saber shine) ○ Anemia ○ Thrombocytopenia ○ Liver failure
<b>Reverse Sequence Syphilis Serology</b>	<b>IgM antibody</b>



# Syphilis Diagnosis

## Direct Microscopic Examination

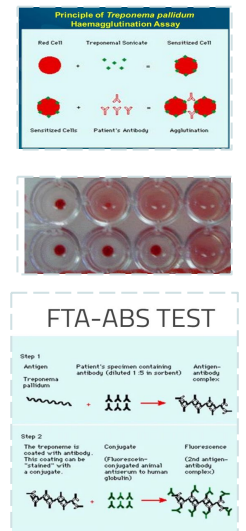
- Smear from 1° / 2° lesions using dark field microscopy.
- Positive → diagnosis confirmed.
- Has many limitations → rarely used. (14)



## Serologic Tests (Common)

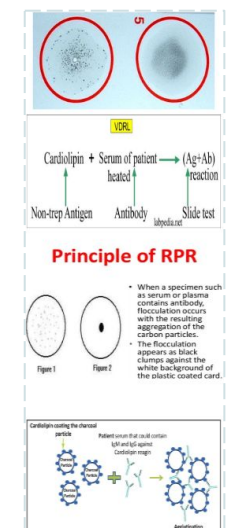
### Specific Treponemal Tests (target Syphilis antigen)

- ❖ **Specific to treponemal antigens.**
- ❖ Detect **IgG & IgM** directed against treponema membrane lipoproteins.
- ❖ 1. Positive: after 3 weeks after infection:
  - Fluorescent Treponemal Antibody-Absorption (**FTA-ABS**).
  - T.palladium particle Agglutination (**TP-PA**).
  - Enzyme Immunoassay (EIA).
- ❖ 2. Remain positive: even after effective therapy.
  - Used for: used initially for **diagnosis & confirmation of RPR & VDRL**



### Non-specific Treponemal Tests

- **Nonspecific, directed against lipoidal antigens** released as a result of cell damage.
- 1. Positive: 6 weeks after infection:
  - ❖ -Rapid Plasma Reagin (**RPR**).
  - ❖ - Venereal Disease Research Laboratory (**VDRL**).
- 2. **Positive: during 1° stage** (possible exception: HIV).
- 3. Antibody peak: 2° syphilis.
- 4. Negative: following effective therapy.
- **Used for: screening, staging the disease & follow up therapy.** (screening pregnant women as well)



## Treatment & Prevention

<b>Treatment</b>	<ul style="list-style-type: none"> <li>❖ Treponema is sensitive to <b>Penicillin</b> (17) (Gold Standard).</li> <li>❖ <b>Hypersensitive patient:</b> Tetracycline - Erythromycin - Cephalosporins.</li> </ul>
<b>Prevention</b>	<ul style="list-style-type: none"> <li>❖ Counseling.</li> </ul>



# Syphilis

## Interpretation of Serological test

Possible explanation	Treponemal Tests (TPPA/FTA-ADS) (15)	Non-Treponemal Tests (RPR/VDRL) (16)
- Syphilis recent or previous - Yaws or Pinta	+	+
- No syphilis (false positive)	-	+
- Consistent with Previously treated or untreated late syphilis - Yaws - Pinta - Bejel	+	-
- No syphilis - Syphilis in Incubation Period	-	-

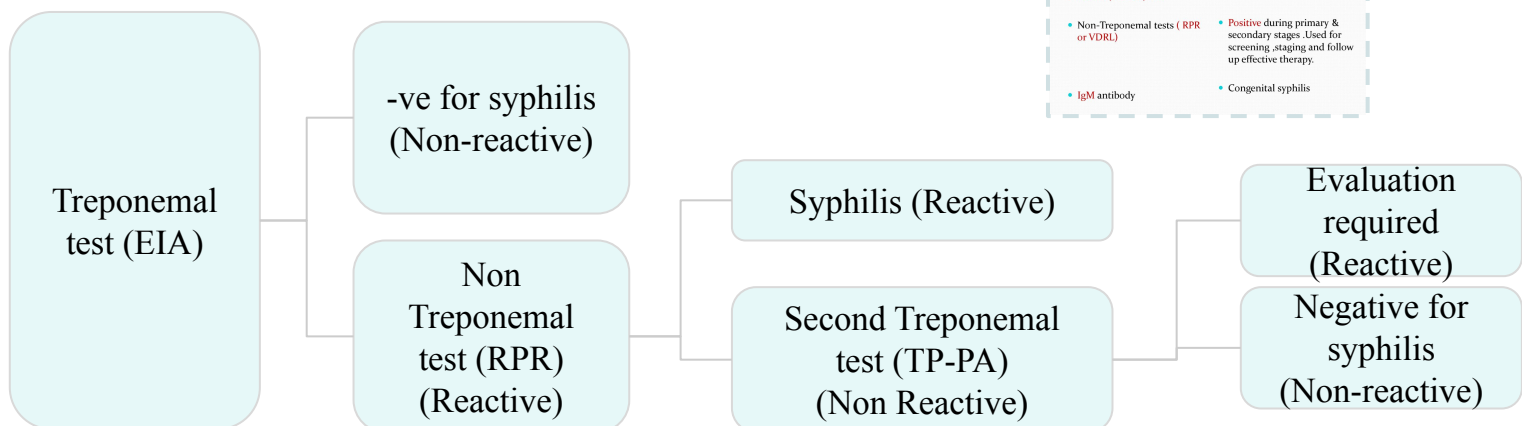
❖ To help with understanding:

- Both positive = **Syphilis**
- Nontreponemal positive + treponemal negative = **No syphilis (false positive)**
- Nontreponemal negative + treponemal positive = **previously treated** / late latent stage
- Both negative = **no syphilis** / in Incubation Period

## Manifestations



## Reverse Algorithm



**Summary of Syphilis Serology**  
Reverse Sequence Syphilis Serology

<p><b>Test</b></p> <ul style="list-style-type: none"> <li>• Treponemal tests FTA-ABS, TP PA, EIA</li> <li>• Non-Treponemal tests ( RPR or VDRL)</li> <li>• IgM antibody</li> </ul>	<p><b>Stage</b></p> <ul style="list-style-type: none"> <li>• Positive in all stages, confirms RPR &amp; VDRL</li> <li>• Positive during primary &amp; secondary stages. Used for screening, staging and follow up effective therapy.</li> <li>• Congenital syphilis</li> </ul>
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# Dr's notes

- 1- Chlamydia is non gram stain, it is bacteria but similar to virus.
- 2- the difference between Gonorrhoea and chlamydia in discharge, in Gonorrhoea it is purulent discharge while chlamydia is not.
- 3- we see vaginitis in Gonorrhoea more than in chlamydia.
- 4- the Gonorrhoea cause only conjunctivitis in neonate, while chlamydia cause conjunctivitis and pneumonia.
- 5- in asymptomatic situation the disease can spread because the patient doesn't know he is affected.
- 6- less common than chlamydia but more problematic, and it similar to chlamydia but the difference in affecting on neonate and discharge and present of arthritis or not:

—	Affecting neonate	Discharge	Arthritis
<b>Chlamydia</b>	-Conjunctivitis. -pneumonia.	<b>-in men:</b> no purulent. <b>-in women:</b> no mucopurulent.	Absence
<b>Gonorrhoea</b>	-Conjunctivitis only.	<b>-in men:</b> purulent. <b>-in women:</b> mucopurulent.	Present

- 7- and catalase positive, oxidase positive.
- 8- Thayer-Martin is composed of chocolate agar and antibiotic.
- 9- it is diagnostic in male but not diagnostic in female.
- 10- PCR is first line diagnosis because it is more sensitive, but culture less sensitive because it depend in many factors.
- 11- we doing the molecular tests or gram stain or both for diagnosis (based in case).
- 12- the Syphilis and Herpes both is genital ulcers but the Syphilis is painless ulcers while the herpes is painful ulcers.
- 13- Congenital syphilis transmitted by placenta, and the risk difference (based on when syphilis come the mother and which stage), show this table:

Late stage during pregnancy	Primary stage during pregnancy
The possibility of infection is low	The possibility of infection is high

- 14- Rarely used because of limitations which means it is needs specific type of microscope.
- 15-Positive in all stages (acute or latent or previous infection).
- 16- Indicate the state of disease if it acute (high) or treated (low).
- 17- The dose difference based on stage of disease and also administration difference, some cases IM and others IV, but in primary usually high dose intramuscular (IM).

The clinical manifestations of Gonorrhoea and chlamydia similar to each other but in come as SAQs or MCQs we will give you a hint to differentiated between them like gram -ve diplococci or any other difference (you can see it in the above table in note number 6) and asks about treatment of them.



# MCQs - SAQ

**Q1 -Genital infection caused by which serotype of Chlamydia trichomonas**

- |               |               |               |               |
|---------------|---------------|---------------|---------------|
| A) serotype A | B) serotype B | C) serotype c | D) serotype D |
|---------------|---------------|---------------|---------------|

**Q2 - The most sensitive diagnostic method of Chlamydia?**

- |                  |        |                   |                 |
|------------------|--------|-------------------|-----------------|
| A) Gram staining | B) PCR | C) tissue culture | D) none of them |
|------------------|--------|-------------------|-----------------|

**Q3 -Patient with dysuria reported having an extramarital sexual relationship, the gram stain revealed gram negative diplococci. Which one of the following is the causative agent?**

- |                         |        |        |                          |
|-------------------------|--------|--------|--------------------------|
| A) Neisseria gonorrhoea | B) HSV | C) HPV | D) Chlamydia trachomatis |
|-------------------------|--------|--------|--------------------------|

**Q4 - Which antibiotic is effective in both gonorrhoea and chlamydia?**

- |                |                 |                  |               |
|----------------|-----------------|------------------|---------------|
| A) Ceftriaxone | B) Azithromycin | C) ciprofloxacin | D) Ampicillin |
|----------------|-----------------|------------------|---------------|

**Q5 - Syphilis is usually non-infectious with which one of the following manifestations of it ?**

- |            |                     |          |                       |
|------------|---------------------|----------|-----------------------|
| A) Chancre | B) Condylomata lata | C) Gumma | D) mucocutaneous rash |
|------------|---------------------|----------|-----------------------|

- 1-D  
2-B  
3-A  
4-B  
5-C

1

A 30 years old recently returned from travel, presented to ER with urethral discharge and dysuria. Has history of unprotected sexual intercourse with different partners. Urine culture and urethral swab both taken and came negative.

Q1: What is the most likely diagnosis?

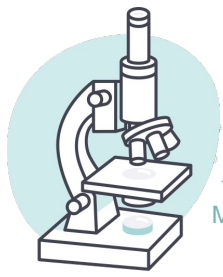
- Non gonococcal urethritis most likely chlamydia trachomatis

2

A 32 years old recently returned from travel, presented to ER with septic arthritis in his knee. Has history of unprotected sexual intercourse with different partners.

Q1: What is the most likely causative organism?

-Neisseria gonorrhoeae



TEAM 443  
MICROBIOLOGY

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