

Chlamydia, Gonorrhoea & Syphilis

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Objectives

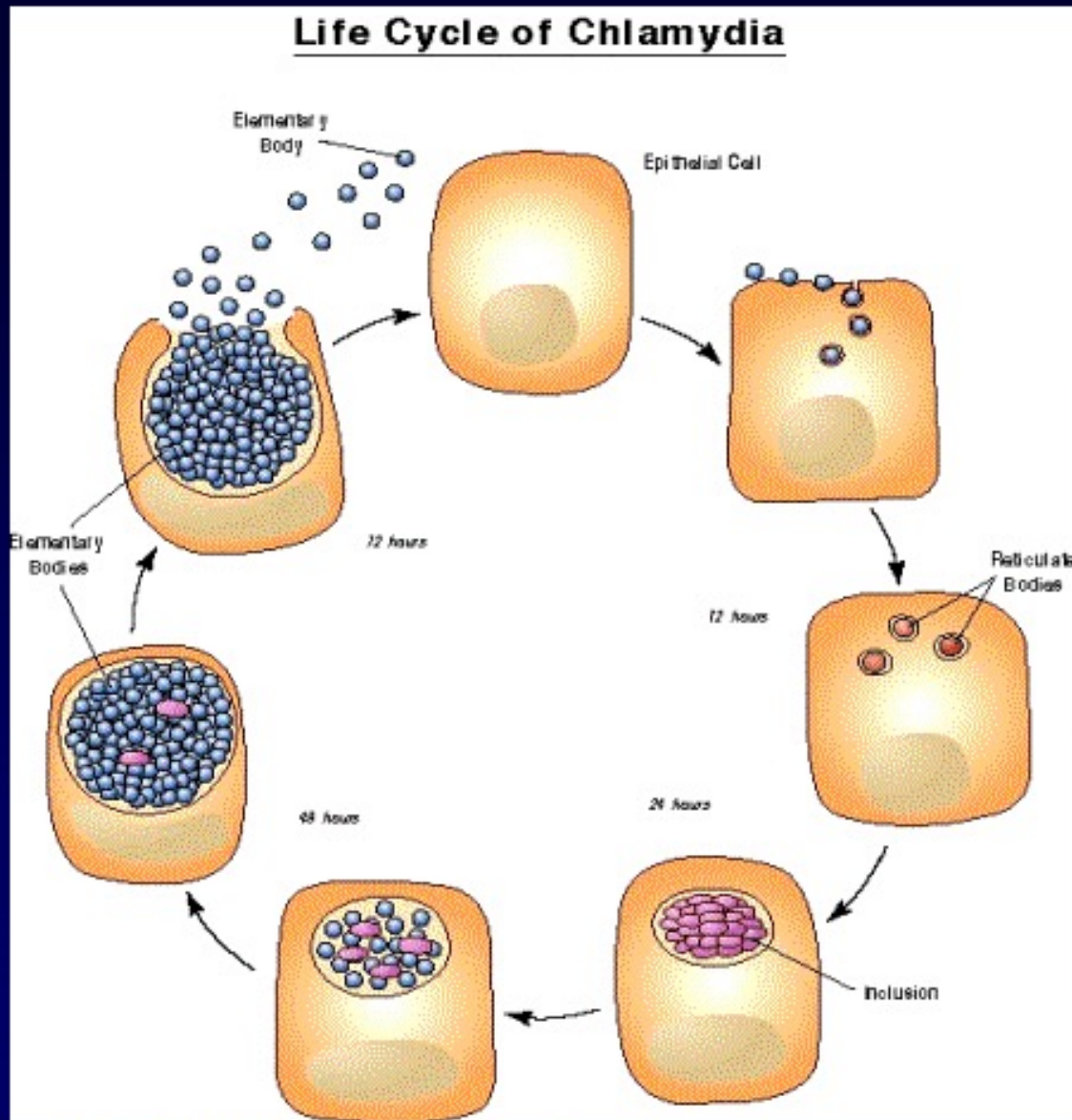
Recall	Recall the causative agents of syphilis, gonorrhea and Chlamydia infections.
Describe	Describe the pathogenesis of syphilis, gonorrhea and Chlamydia infection.
Describe	Describe the clinical features of Chlamydial infections
Recall	Recall the different genera, species and serotypes of the family Chlamydia.
Describe	Describe the laboratory diagnosis of Chlamydia
Describe	Describe the clinical features of gonorrhea that affect only men, only women and those ones which affect both sexes.

Objectives

Describe	Describe the different laboratory tests for the diagnosis of gonorrhea
Describe	Describe the clinical feature of the primary, secondary tertiary syphilis and complications.
Recall	Recall the different diagnostic methods for the different stages of syphilis.
Recall	Recall the treatment regimens of syphilis, gonorrhea and Chlamydia infections.
Recall	Recall that there are no effective vaccines against all these three diseases.

Chlamydia

- 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.



Source: California STD/HIV Prevention Training Center

Chlamydia species

Chlamydia serotypes

- *C. trachomatis*

A,B,C

D - K

L₁, L₂, L₃

- *C. psittaci*
- *C. pneumoniae*

Disease

- Trachoma
 - Inclusion conjunctivitis,
genital infection
- Lymphogranuloma venerum
(LGV)

Psittacosis

Respiratory infections

Epidemiology

- ***C.trachomatis* is a common cause of sexually transmitted disease (STD).**
- **Spread by genital secretions , anal or oral sex.**
- **Wide spread, 5-20 % among STD clinic in USA.**
- **Human are the sole reservoir .**
- **1/3 of male sexual contacts of women with *C.trachomatis* cervicitis develop urethritis after 2-6 weeks incubation period.**

Pathogenesis of Chlamydia

- *Chlamydia* have tropism for epithelial cells of endocervix and upper genital tract of women, urethra, rectum and conjunctiva of both sexes.
- **LGV can enter through skin or mucosal breaks**
- Release of pro-inflammatory cytokines, lead to tissue infiltration by inflammatory cells, progress to necrosis, fibrosis then scarring.

Genital infections caused by *C.trachomatis*

- **In men**: urethritis (non gonococcal urethritis (NGU)) , epididymitis & proctitis.
- **In women**: cervicitis, salpingitis, urethral syndrome, endometritis & proctitis.
- Urethritis presents as dysuria and **thin** urethral discharge in 50 % of men.

Uterine cervix infection may produce vaginal discharge but is asymptomatic in 50-70% of women.

Salpingitis and pelvic inflammatory disease can cause sterility and ectopic pregnancy.

- 50% of infants born to mothers excreting *C.trachomatis* during labor show evidence of infection during the first year of life. Most develop **inclusion conjunctivitis**, 5-10% develop infant pneumonia syndrome.
- **LGV caused by *C.trachomatis* strains L₁,L₂,L₃**
LGV is common in South America and Africa.
Papule and inguinal lymphadenopathy.
Chronic infection leads to abscesses, strictures and fistulas.

Diagnosis of *Chlamydia* genital infections

- **Polymerase chain reaction (PCR) :**

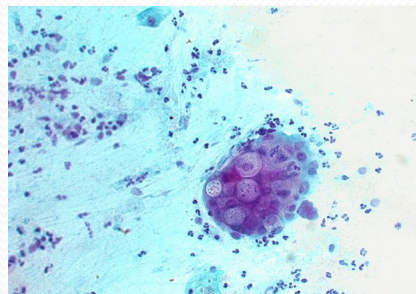
the most sensitive methods of diagnosis.

Performed on vaginal ,cervical , urethral swabs, or urine .

- Isolation on tissue culture (McCoy cell line) :

C.trachomatis inclusions can be seen by iodine or Giemsa stained smear.

Rarely done



Treatment & Prevention

- **Azithromycin** : single dose for non- LGV infection.
- **Erythromycin** : for pregnant women.
- **Doxycycline** : for LGV.
- **Prevention** and control through early detection of asymptomatic cases , screening women under 25 years to reduce transmission to the sexual partner.

Gonorrhoea: Clinical Aspects

- A STD disease acquired by direct genital contact. It is localized to mucosal surfaces with infrequent spread to blood or deep tissues. Caused by *N.gonorrhoeae*.
- **Clinical manifestations: 2-5 days IP .**

Men: acute urethritis and acute profuse **purulent** urethral discharge.

Women: **mucopurulent** cervicitis, urethritis with discharge.

In both sexes: urethritis & proctitis.

Symptoms are similar to *Chlamydia* infection.

Pharyngitis may occur.

Pelvic inflammatory disease (PID) in women.

Conjunctivitis in neonates born to infected mothers

Pelvic Inflammatory Disease (PID)

- PID occurs in 10-20% of cases, include fever, lower abdominal pain, adnexal tenderness, leukocytosis with or without signs of local infection.
- Salpingitis and pelvic peritonitis cause **scarring** and **infertility**.
- Disseminated Gonococcal Infection (DGI) due to spread to the bloodstream.

Disseminated Gonococcal Infection (DGI)

- Due to spread of the bacteria to the blood stream.
- Clinically : Fever, migratory arthralgia and arthritis. Purulent arthritis involving large joints. Petechial and maculopapular rash.
- Metastatic infections such as Endocarditis , Meningitis & Perihepatitis may develop.

Epidemiology of Gonorrhoea

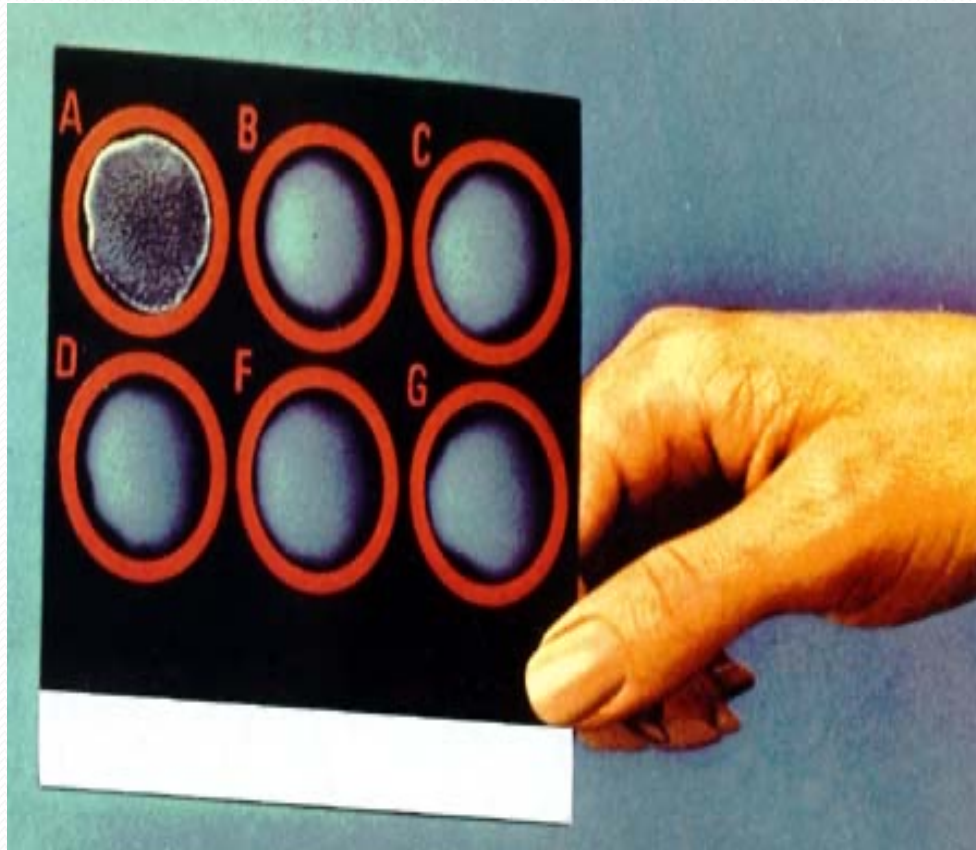
- Rates among adolescents are high, about 10% increase per year in USA .
- **Inability to detect asymptomatic cases such as women and patient fail to seek medical care hampers control .**
- Major reservoir for continued spread are asymptomatic cases.
- Non-sexual transmission is rare.

Neisseria gonorrhoeae

- A Gram negative diplococci grows on chocolate agar and on selective enriched media and CO₂ required. Not a normal flora.
- **Pathogenesis:** mainly a localized infection of epithelium ,leads to intense inflammation.
- Posses pili and outer membrane proteins that mediate attachment to non-ciliated epithelium.

Diagnosis of Gonorrhoea

- Transport media required unless transfer to the lab. is immediate.
- Direct smear for Gram stain of urethral specimens : **Gram negative diplococci within a neutrophil (intracellular)** .
- Culture on **Thayer-Martin** or other selective medium.
- Confirmation : fermentation of **glucose** only (*does not ferment maltose or sucrose*) or **Co-agglutination test**.
- Nucleic acid amplification tests (**PCR**) is an option for diagnosing genital infections.



Treatment of Gonorrhoea

- Guided by local resistance pattern and susceptibility testing. Partner should be treated as well.
- **Ceftriaxone IM** (or oral **Cefixime**) recommended.
 - Combination with Azithromycin recommended
- **Alternatives:**
 - **Ciprofloxacin** or **Ofloxacin**
 - **Azithromycin, Doxycycline** (orally for 7 days) both cover *C.trachomatis* infection as well .
- Counseling.

Syphilis



- A **chronic** systemic infection , sexually transmitted , caused by a spiral organism called *Treponema pallidum* subsp.*pallidum* .
- The organism grow on cultured mammalian cells **only** , **NOT** stained by Gram stain but readily seen only by immunofluorescence (IF), **dark field microscopy** or **silver impregnation histology technique**.



Epidemiology of Syphilis



- An exclusively human pathogen.
- Transmission by **contact with mucosal surfaces or blood**, less commonly by non-genital contacts with a lesion, sharing needles by IV drug users, or **transplacental transmission** to fetus.
- **Early disease is infectious.**
- Late disease is not infectious .

Pathogenesis

- Bacteria access through inapparent skin or mucosal breaks.
- Slow multiplication , **endarteritis & granulomas.**
- **Ulcer heals but spirochete disseminate.**
- Latent periods may be due to surface binding of host components.
- Injury is due to delayed hypersensitivity responses to the persistence of the spirochetes.

Clinical Manifestations: Stages of Syphilis

- **Primary syphilis:** chancre is a painless, indurated ulcer with firm base and raised margins on external genitalia or cervix ,anal or oral site, appear after an IP of about 2-6 weeks .
- Enlarged inguinal lymph nodes may persist for months.
- Lesion is infectious
- Lesion heals spontaneously after 4-6 weeks.

•Secondary Syphilis

- Develops 2-8 weeks after primary lesion healed.
- Characterized by symmetric mucocutaneous rash , mouth lesions (snail track ulcers) and generalized non-tender lymph nodes enlargement (*full of spirochete*) with bacteremia causing fever, malaise and other systemic manifestations.
- Skin lesion distributed on trunk and extremities often palms, soles and face.
- 1/3 develop **Condylomata Lata**: which are painless mucosal warty erosions on genital area and perineum.

Secondary lesions resolve after few days to many weeks but disease continues in 1/3 of patients. Disease enters into a latent state.

Lesions are infectious.

- **Latent syphilis**: a stage where there are no clinical manifestations but infection is evident by **serological tests**. Relapses cease.

Risk of blood-borne transmission from relapsing infection or from mother to fetus continues.

• Tertiary syphilis

Occurs in 1/3 of untreated cases. Manifestations may appear after 15-20 years or may be asymptomatic but serological tests positive.

Neurosyphilis: chronic meningitis, with increased cells and protein in CSF, leads to degenerative changes and psychosis. Demyelination causes peripheral neuropathies. Most advanced cases result in **paresis** (*p*ersonality, *a*ffect, *r*eflexes, *e*yes, *s*enorium, *i*ntellect, *s*peech) due to the effect on the brain parenchyma and posterior columns of spinal cord and dorsal roots.

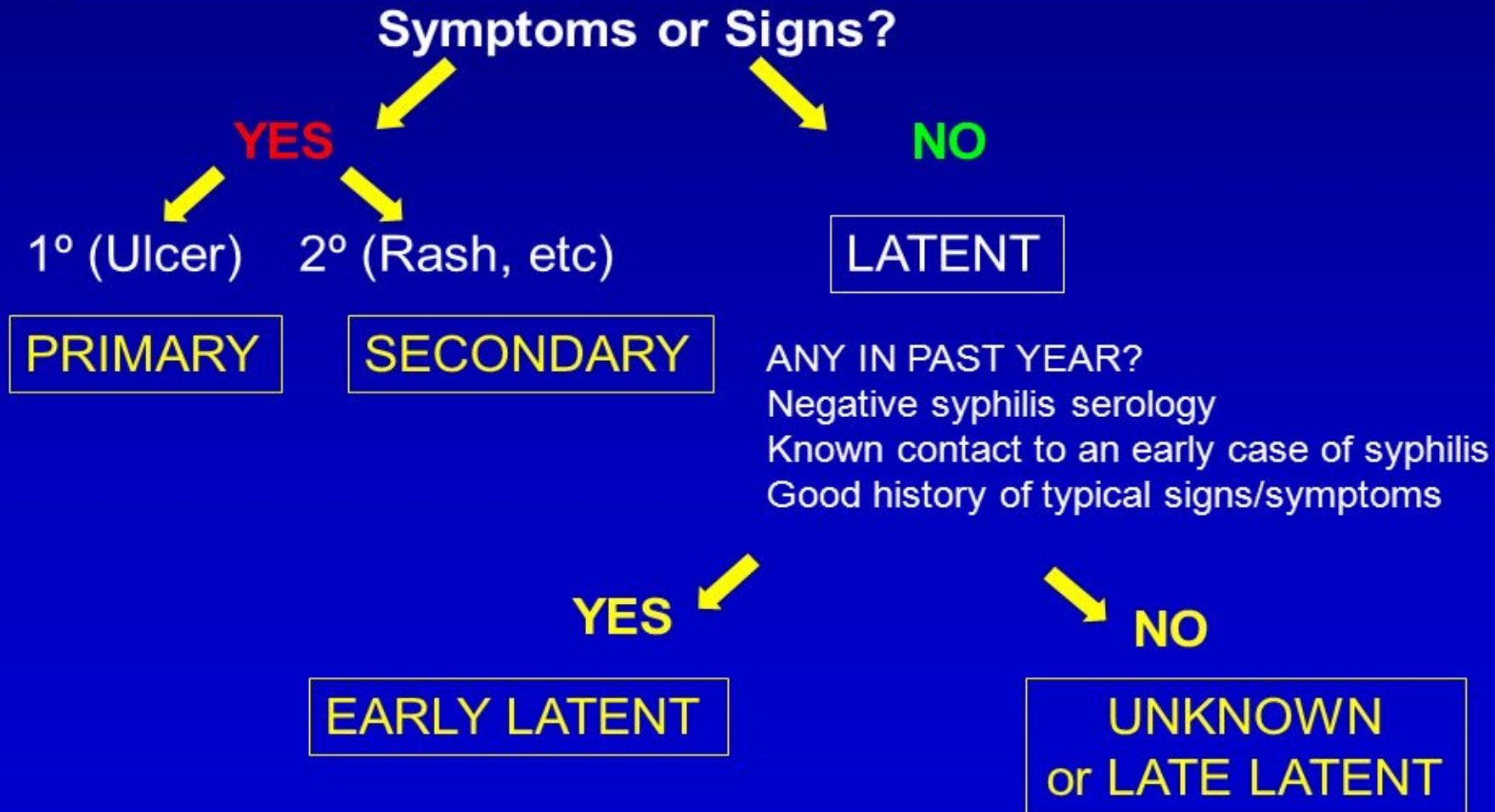
Cardiovascular Syphilis

- Due to **arteritis**, leads to aneurysm of aorta and aortic valve ring.

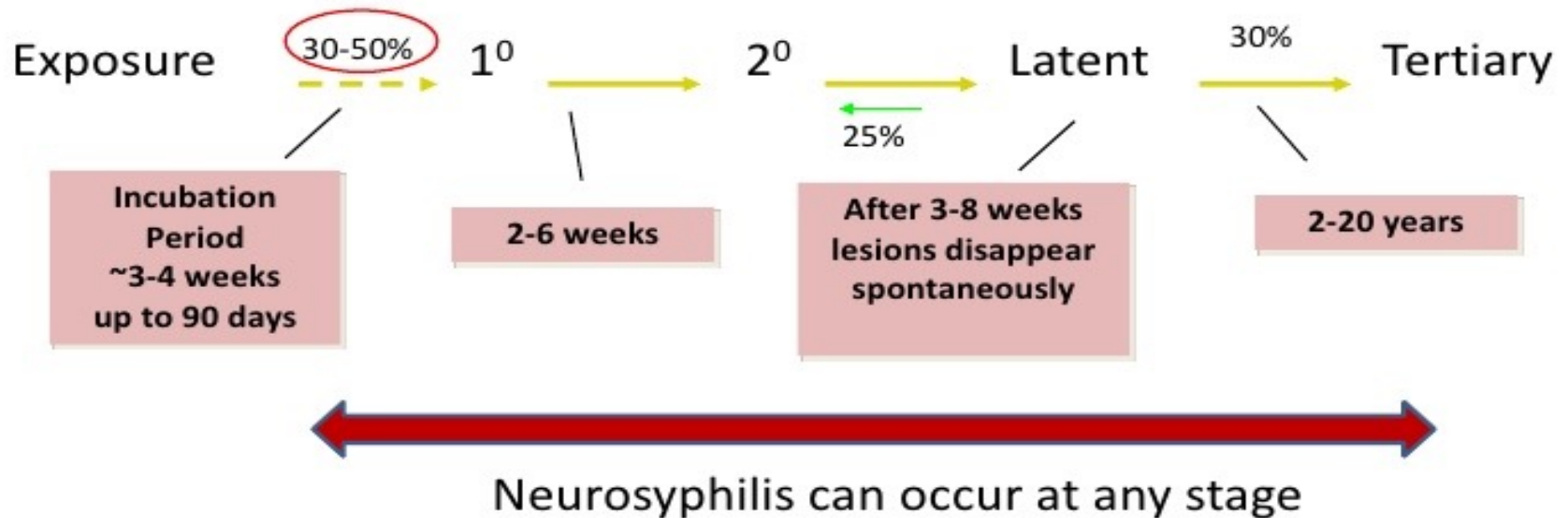
Localized granulomatous reaction called **gumma** on skin, bones, joints or other organs leads to local destruction .

- **Congenital syphilis** :develop if the mother not treated ,fetus susceptible **after 4th month** of gestation. Fetal loss or congenital syphilis result. Rhinitis ,rash and bone changes (*saddle nose, saber shine*) anemia ,thrombocytopenia, and liver failure.

Syphilis Staging Flowchart



Syphilis Natural History



Courtesy: Susan Philip, SF DPH & UCSF

Laboratory Diagnosis of Syphilis

- **Direct microscopic examination** of a smear of a smear from primary or secondary lesions using dark field microscopy **rarely used**. Has many limitations. *If positive , confirms the diagnosis.*
- **Serologic tests** commonly used:
 - **Specific Treponemal tests**: used initially for diagnosis and for confirmation.
 - **Nonspecific Treponemal tests** : used for screening and follow up of therapy.

Syphilis Serology

Nontreponemal tests: Nonspecific ,directed against lipoidal antigens released as a result of cell damage .Becomes positive 6 weeks after infection:

❖ Rapid Plasma Reagin (**RPR**)

❖ Venereal Disease Research Laboratory (**VDRL**).

Becomes positive during the primary stage (*possible exception HIV*) ,antibody peak in secondary syphilis. Negative following effective therapy .

Used for screening , staging the disease & follow up therapy.

Syphilis Serology

- **Treponemal tests :**

Specific to treponemal antigens . Detect IgG and IgM directed against treponema membrane lipoproteins.

Becomes positive after 3 weeks after infection. **Used for confirmation of RPR & VDRL.** Remain positive even after effective therapy .Commonly used tests are:

- ❖ **FTA-ABS** (Fluorescent Treponemal Antibody-Absorption)
- ❖ **TP -PA**(T. palladium Particle Agglutination)
- ❖ **EIA** (Enzyme Immunoassay)

VDRL

Cardiolipin + Serum of patient \longrightarrow (Ag+Ab)
heated \uparrow reaction
 \uparrow
Non-trep Antigen Antibody Slide test

Principle of RPR



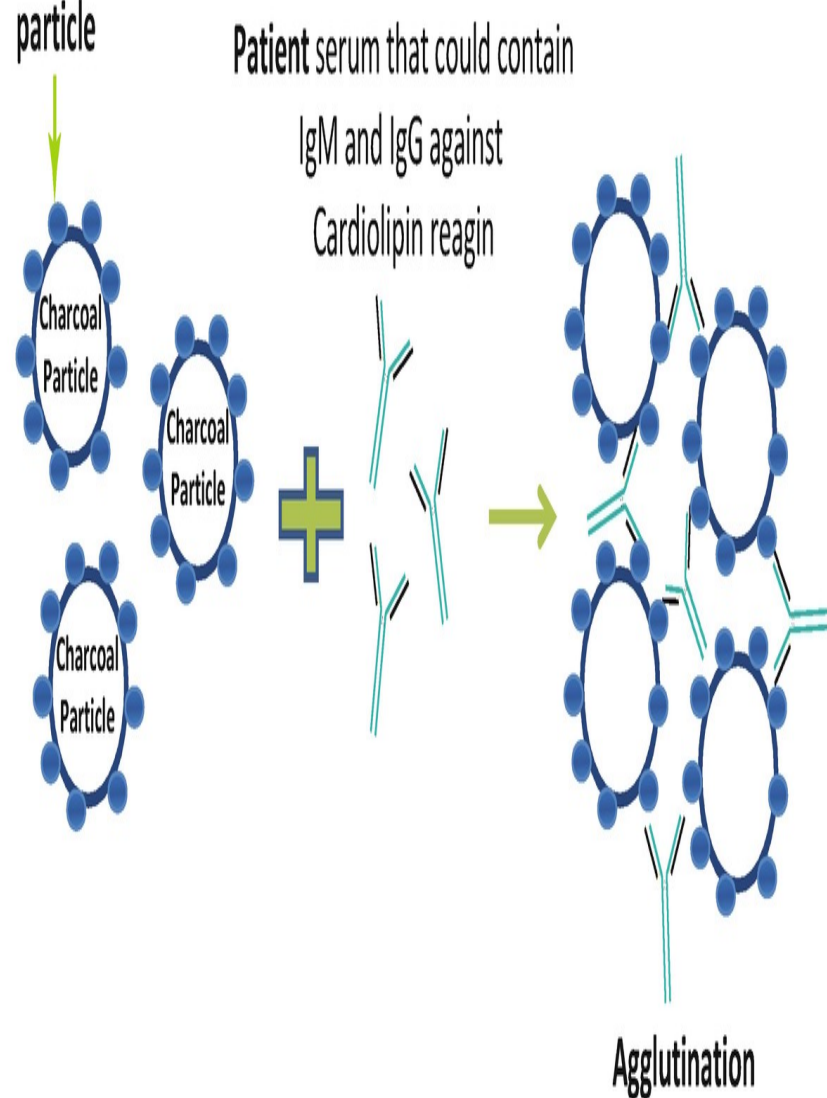
Figure 1



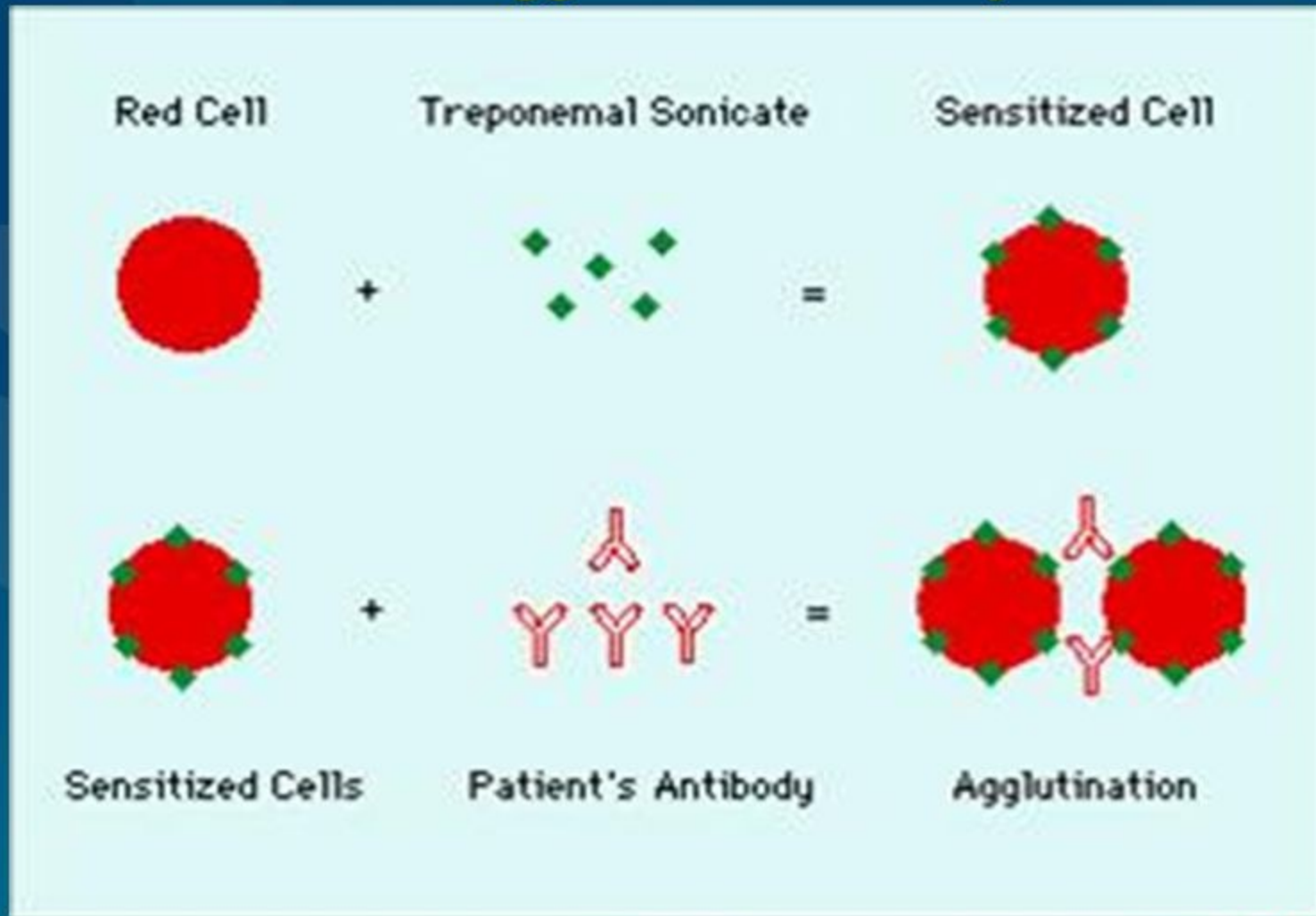
Figure 2

- When a specimen such as serum or plasma contains antibody, flocculation occurs with the resulting aggregation of the carbon particles.
- The flocculation appears as black clumps against the white background of the plastic coated card.

Cardiolipin coating the charcoal



Principle of *Treponema pallidum* Haemagglutination Assay



Syphilis serology

Reactive



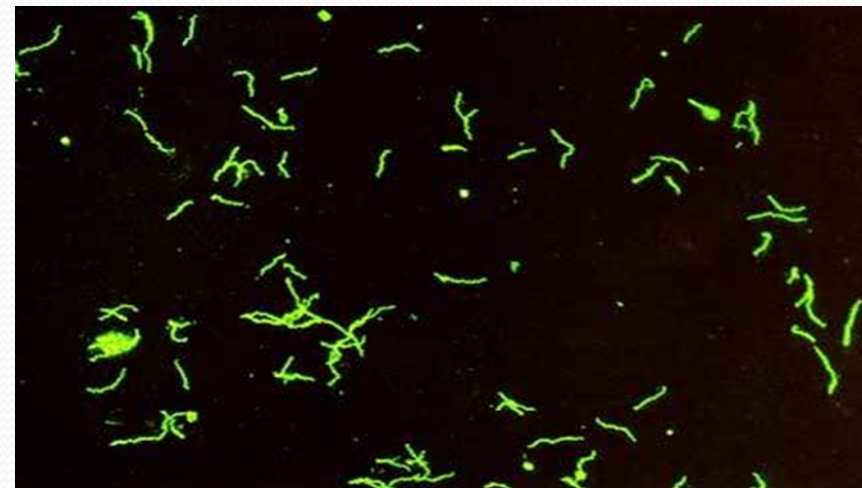
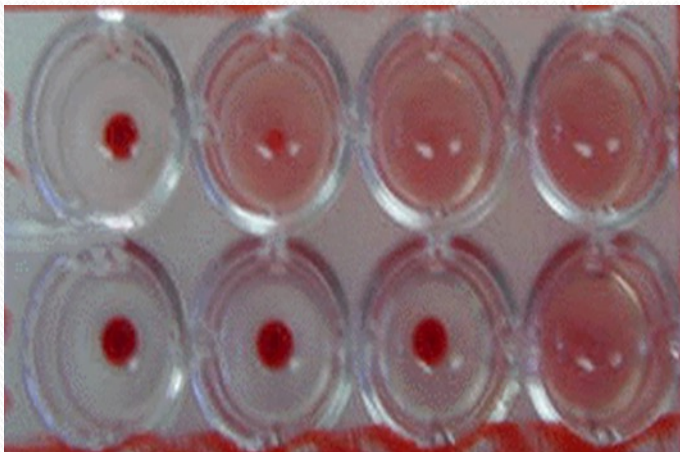
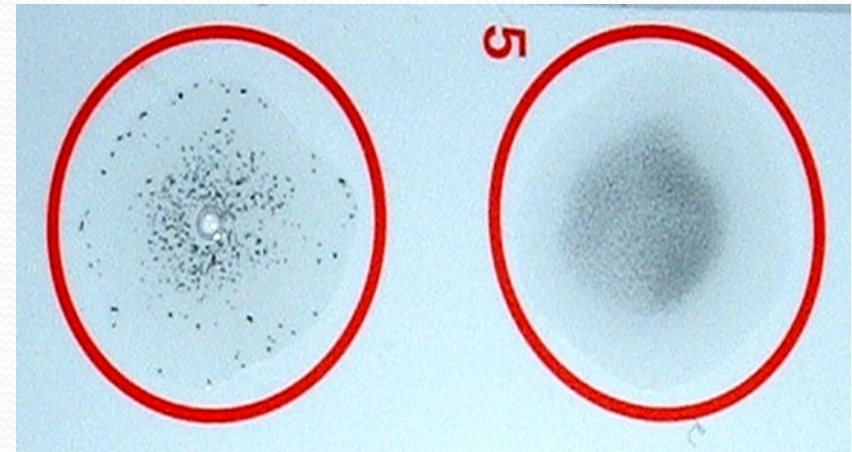
Weak Reactive



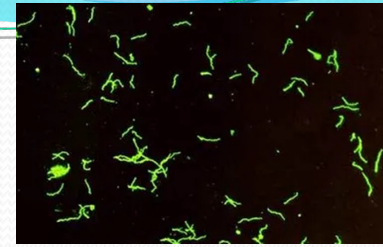
**Weak Reactive
(Minimally)**



Nonreactive



FTA-ABS TEST



Step 1

Antigen

Treponema
pallidum



Patient's specimen containing
antibody (diluted 1 :5 in sorbent)

+



Antigen-
antibody
complex



Step 2

The treponeme is
coated with antibody.
This coating can be
"stained" with
a conjugate.



+

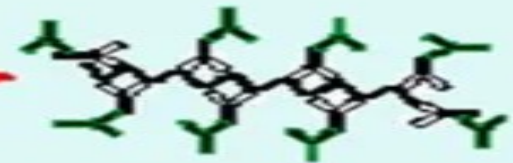
Conjugate

(Fluorescein-
conjugated animal
antiserum to human
globulin)



Fluorescence

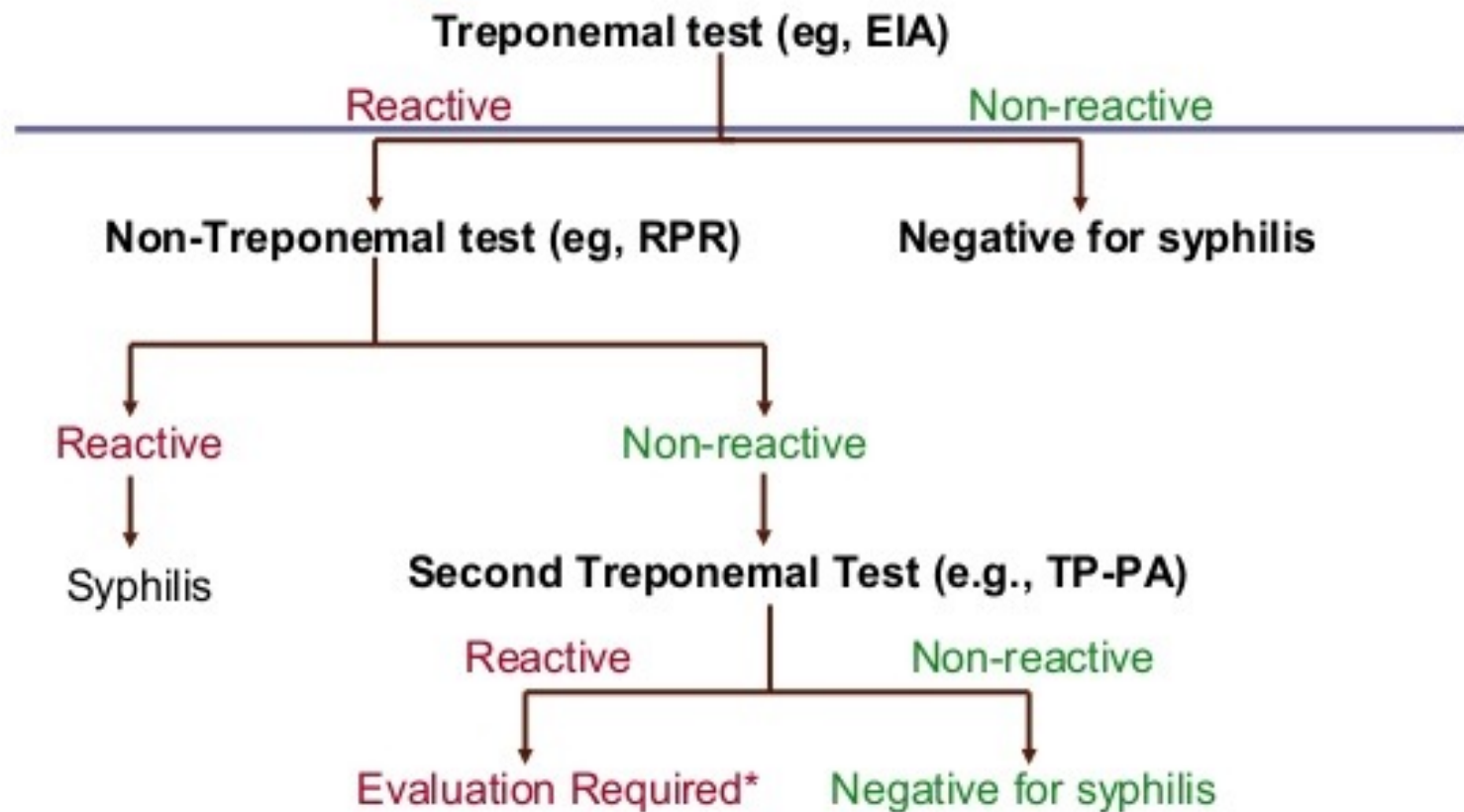
(2nd antigen-
antibody
complex)

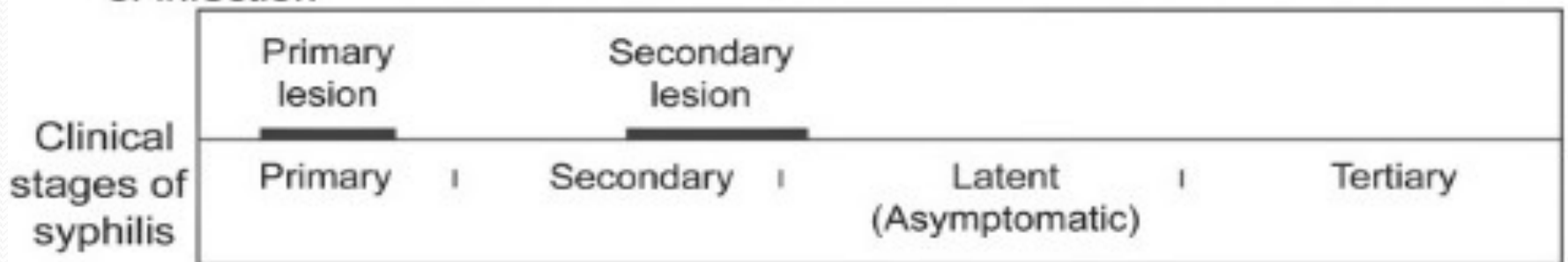
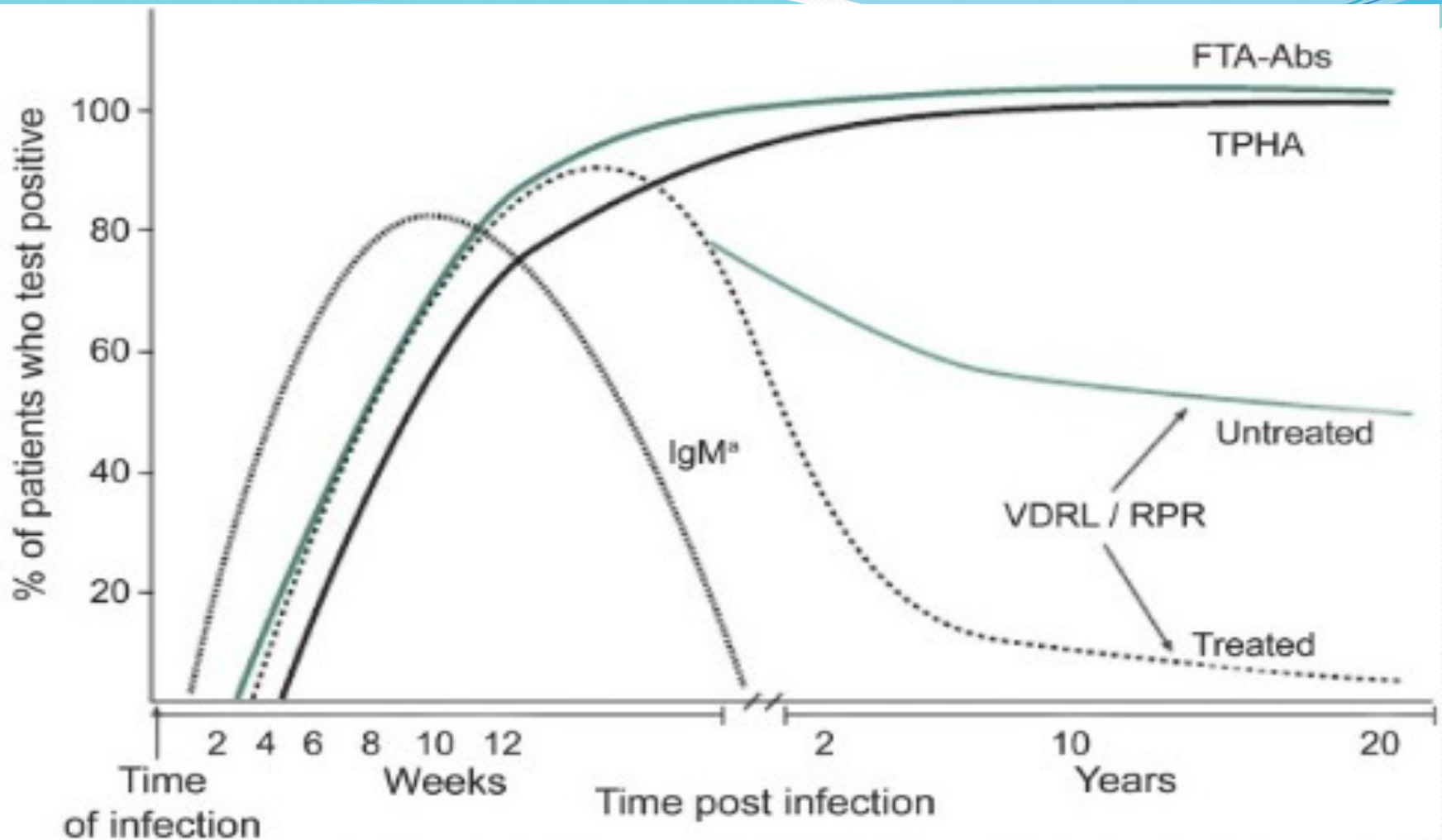


INTERPRETATION OF SEROLOGICAL TESTS FOR SYPHILIS

Non-Treponemal tests (RPR/ VDRL)	Treponemal Tests (TP-PA/ FTA-ADS)	Possible Explanation
+	+	Syphilis - recent or previous Yaws or pinta
+	-	No syphilis False positive
-	+	Consistent with previously treated or untreated Syphilis Yaws, Pinta, Bejel
-	-	No syphilis Syphilis in incubation period

Reverse Algorithm





Syphilis manifestations



Summary of Syphilis Serology

Reverse Sequence Syphilis Serology

Test

- Treponemal tests
FTA-ABS , MP PA , EIA
- Non-Treponemal tests (RPR
or VDRL)
- IgM antibody

Stage

- **Positive** in all stages ,
confirms RPR & VDRL
- **Positive** during primary &
secondary stages .Used for
screening ,staging and follow
up effective therapy.
- Congenital syphilis

Treatment and Prevention

- *Treponema* is sensitive to **Penicillin**.
- Hypersensitive patients treated with Tetracycline, Erythromycin or Cephalosporins
- **Prevention:** counseling.

Take Home Message

- Syphilis, Chlamydia and Gonorrhoea are main STDs ,caused by delicate organisms ,cannot survive outside the body.
- Infection may not be localized.
- Clinical presentation may be similar (urethral or genital discharge, ulcers).
- One or more organisms (Bacteria, virus, parasite) may be transmitted by sexual contact.
- Screening for HIV required .
- If not treated early may end in serious complications .

Reference book

Ryan, Kenneth J. Sherris Medical Microbiology.
Latest edition. Mc Graw –Hill education

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