MINISTRY OF HEALTH
OF AZERBAIJAN REPUBLIC

AZERBAIJAN
MEDICAL UNIVERSITY

Farid Mahmudov

VENEREOLOGY

Textbook

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VENEREOLOGY

"Dermatovenereology II"

Textbook

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Chapter "AIDS" is assembled in cooperation with the Anti AIDS center against (chief -Esmira A Almammadova).The photos have been presented by the Anti AIDS Centre against .

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CONTENTS

List of abreviations

STIs	Sexually Transmitted Infections
GI	Gonococcal infection
DFM	Dark Field Microscopy
PCR	Polymerase Chain Reaction
RW	Wasserman Reaction
NTT	Nontreponemal Tests
TT	Treponemal Tests
RMP	Reaction Microprecipitation
RPR	Rapid Plasma Reagins
VDRL	Venereal Disease Research Laboratory test
TPI	Treponema Pallidum Immobilization test
FTI	Fluorescent Treponemal Antibody
TPHA	Treponema Pallidum Haemagglutination Assay
ELISA	Enzyme-Linked Immunosorbent Assay
IB	Immuniblotimg
IgM	Immunoglobulin M
IgG	Immunoglobulin G
PID	Pelvic Inflammatory Disease
HPV	Human Papillomavirus
LGV	Lymphogranuloma Venereum
IB	Immunoblotting

Devoted to the memory of prominent professors: Rasim H. Haciyev, Mina M. Davatdarova

"Venereal diseases" as a part of " Dermatovenereology" is included in teaching program for students at high and secondary institutions.

Literature related with venereal diseases was published in Azerbaijan language and included in the course books given below; M.M. Jeltakov " Skin venereal diseases", 1975 (translated by H.A.Huseynzade, R.H.Hajiyev); R.H.Hajiyev, M.M.Davatdarova " Venereal diseases", 1978.

These resources were written in Cyrillic, but later, in 1992, they were rewritten in Latin.

During past years the essence of the questions regarding pathogenesis of venereal diseases was changed: its scheme of therapy was improved and laboratory diagnostic methods and new medications, used in treatment of these diseases, were testing.

Moreover, some names of venereal diseases were changed due to International classification of diseases.

The term "Sexually Transmitted Infections (STI) replaced the term "venereal infections". Taking into consideration all changes "Venereal infections" course book was compiled. It was illustrated by 180 colourful photos that made this textbook easy to understand. In (AMU) Azerbaijan Medical University "Venereal diseases" was accepted a course book for students, residents and dermatologists.

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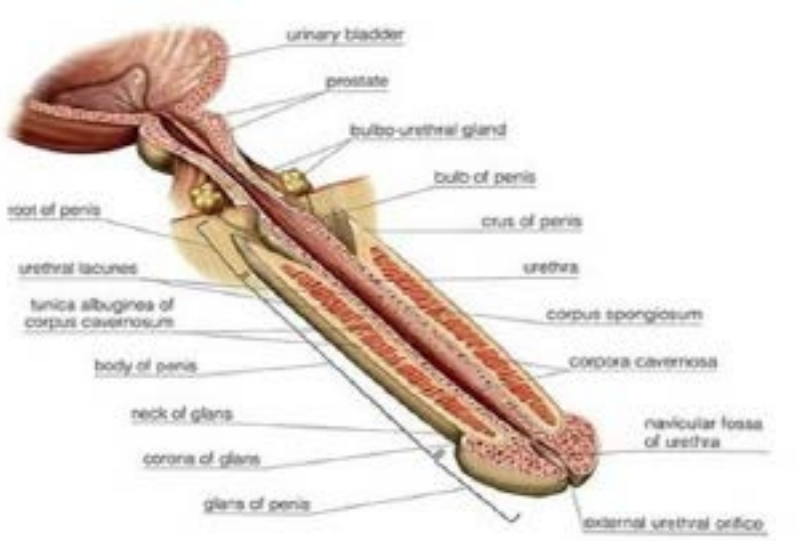
External Genitalia

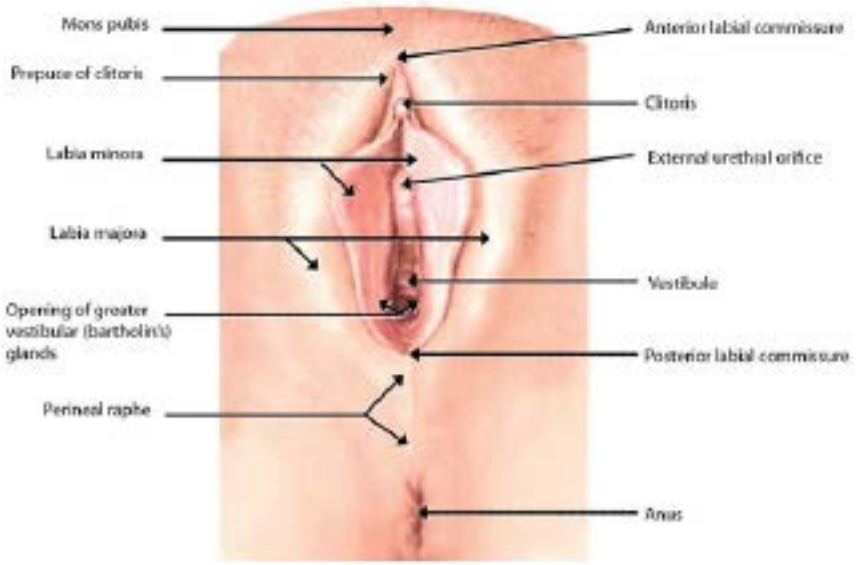
Male external genitalia : genital region with scrotum, penis shaft and external surface of foreskin consisting of a keratinized , multilayered epidermal surface with appendages (including apocrine sweat glands) : internal surface , glans and urinary track opening , a non-keratinized , multilayered epithelium without mucous glands at the mucocutaneous junction. The mucosa of the urethra consists of a multilayered , cylindrical epithelial surface with glands(Littre's and Cowper's). A peculiarity of the vascular system is the cavernous blood passages of the erectile tissue , which are enclosed by fascia and connective tissues (corpus cavernosum ,corpus spongiosum) . (Pic 1)



Pic 1

Female external genitalia : genital region with vulva ; external labia majora of the vulva possessing a keratinized , multilayered epidermal surface with appendages (including apocrine sweat glands); internal labia of the vulva , i.e., the labia minora of the vagina , which is a non-(or only slightly) keratinized, multilayered epithelial surface without mucous glands at the mucocutaneous junction .

The epithelial ducts of skene's glands open in the vestibule , as do many small and large mucous glands (vestibular glands). The mucosa of the female urethra consists , at the opening , of non-keratinized , multilayered epithelium which then becomes cylindrical. it possesses mucous glands (urethral glands).(Pic 2)



Pic 2

The skin of the external male and female genitalia contains numerous melanocytes and sensory nerve fibers.

INTRODUCTİON AND CLASSİFİCATİON

STIs (Infections transmitted primarily through sexual contact).

Sexually transmitted venereal diseases were known since ancient times. The term "venereal disease" (after the name goddess of love Venus - Latin Venus, Veneris) was proposed in 1527 by the French scientist J. de Betancourt. For a long time, all sexually transmitted diseases were considered as one, the same disease.

At the end of the XIX – beginning of the XX century, thanks to the numerous discoveries of the causative agents of infectious diseases, sexually transmitted illnesses were separated as independent group of diseases. Nowadays the term "venereal diseases" is replaced by the term "sexually transmitted infections" - **STIs.**

STIs- being different according to their etymology and clinical manifestation, infectious diseases are combined into one group by the method of infection — mainly through sexual contact.

Due to ICD-10 (International Classification of X Diseases) the group of STIs consists of;

A50 – A53	syphilis
A54	gonococcal infection
A56; A74.0	chlamydial infection
A59	urogenital trichomoniasis
A60	herpes genitalis
A63.0	anogenital carbuncles
A57	soft chancre (Chancroid)
A58	ulcerating (venereal) granuloma (donovanosis)
A55	limphogranuloma venereum
A63.8	urogenital diseases, caused by Ureaplasma spp., Mycoplasma spp.

Note: Urogenital candidosis and bacterial vaginosis are not related to STIs but due to the fact that they are often found in patients with STIs, they are studied in this section.

SYPHILIS

Comparing with other STIs, syphilis is highly severe illness because of its polysystemicity of disease manifestation.

A. GENERAL INFORMATION

1. Historical reference

Syphilis has 146 names (Spanish, Italian, French, Gallic disease, etc.). The name "syphilis" is associated with the name of the shepherd Syphilous, the hero of the poem "Syphilis, or About the Gallic disease" (author- the Italian doctor and poet Girolamo (Jeronimo) Fracastoro, XVI century, Verona, Renaissance epoch). According that poem, Syphilous was punished by the Gods by disease of genital organs for "friendship with a pig" (from Greek. "sys"- pig + "philos" - friend). According to another version –he was punished for "the insolent reproaches that he addressed to the Gods."

There are three theories of the syphilis origin (genesis):

- Americanistic theory. According to this theory syphilis was brought in Europe by the sailors of H. Columbus after he discovered America in 1492. The infection of the sailors came from local residents who practiced bestiality (zooerastia) and as a result were infected by llamas. Spirochetosis in llamas was known and proved from olden times. After returning of H.Columbus' expedition to his homeland in 1493. That period there were some cases of syphilis disease in seaports of Spain. In Europe, this infection was spread by mercenaries of the French king Charles VIII, who conquered Napoli in 1497. There also were Spanish soldiers among them. Charles VIII had to raise a siege of Napoli, to dissolve the soldiers who caught a disease and spread in other European countries.

- Europeanist theory proves the existence of syphilis on the Eurasian continent since prehistoric times. This fact is proved by the results of archaeological excavations in Europe, Asia and the Middle East.
- Africanist theory - supporters of this theory consider Africa as motherland of syphilis. According to the theory of T. Cockburn (1961) and E. Hudson (1963), the infectious agents of tropical treponematoses (T.pertenue - the infectious agent of phrambesia, T.carateum - the infectious agent of the pinta, T. bejel / T. pallidum - the infectious agent of the bagel), were widely spread in Africa, and the infectious agent of venereal syphilis are variants of the same, single treponema. To T. Cockburn and E. Hudson's mind, the evolution of tropical treponematoses is closely connected with the evolution of human society. While cities were growing and civilization was expanding the direct way of transmission of treponema by household way was significantly limited and trepanematosis transformed into venereal syphilis

Thus, the question - whether syphilis arose initially in Central America, or in the Eurasian continent or in Africa is still open. Most likely, syphilis appeared on the Earth simultaneously with human.

In the history of syphilidology there were many significant discoveries and observations which were connected with the exploits of researchers and their self-sacrifice. However, the history of syphilology also knows samples of mistakes, errors, unethical behavior of researchers who conducted experiments on people, endangering their life and health. There were two points of view on the essence of syphilitic infection According to the one point syphilis and gonococcal infection were considered as a single infection with various manifestations. Due to the other mind, they are two different infections. Supporters of the first point of view were called unitarists, the second - dualists.

The English scientist J. Hunter decided to stop this debate around these points. For this purpose in 1767 J. Hunter injected pus from a

patient with gonorrhea into his own urethra. After a few days, he had discharge, and after a few weeks - a solid chancre appeared. In this case, a fatal mistake took place: the material was taken from a patient who had simultaneously both syphilis and gonorrhea. That self-sacrificing experiment conducted by the famous scientist made a great public impression and postponed the correct decision of the problem for a long time (60-70 years).

A proper interpretation of J. Hunter's experiment was given only in 1838. During 1831-1837 the French scientist F. Ricord infected 700 prisoners with syphilis sentenced to death and 677 prisoners infected with gonorrhea. It was made by inoculation of discharge from 2626 sexually infected patients. So, the dispute between the unitarists and dualists was finally settled. The scientists could not ignore the results got by F. Ricord, but such method of truth attainment was condemned.

The independence of syphilitic infection as a sexually transmitted disease was confirmed by studies of the protosologist F. Shaudin and the venereologist E. Hoffman. These two scientists in 1905 identified the infectious agent of syphilis. That agent was named "Treponema Pallidum" ("a pale spirochete") because of its poor ability to absorb paint. Thus, the problem of syphilis etiology was settled. In 1906 another discovery was invented by A. Wassermann jointly with A. Neisserand and C. Bruck. It was serologic reaction to diagnose syphilis – WR (Wassermann reaction).

Syphilis **-** is caused by "Treponema Pallidum". It is characterized by lesion of the skin, mucous membranes, internal organs, musculo-ske-letal system, nervous system and periodicity of disease course.

2. Etiology

The infectious agent of syphilis is a gram-negative anaerobic bacterium "pale treponema" –Treponema Pallidum. It belongs to the family Spirochaetaeceae, is spiral-shaped, 4-14 μm (micromillimeters) long, 0.2-0.35(μm) micromillimeters across, the number

of curls is 8-12. Curls are uniform, rounded, placed at the same distance from each other, they decrease in height to the end section. The smoothness, uniformity and flexibility of T. pallidum curls are an important differential diagnostic feature. The pale treponema makes smooth, diverse motions: circular around the axis, translational, pendulum-like, contractile motions (contractile/wave-like). The mobility of T. pallidum is ensured by flagella, which are located between the outer and inner membranes.

The main method of T. pallidum reproducing is the transverse division into 2 or more segments, each of which transforms into an adult. The full development cycle takes 30-33 hours.

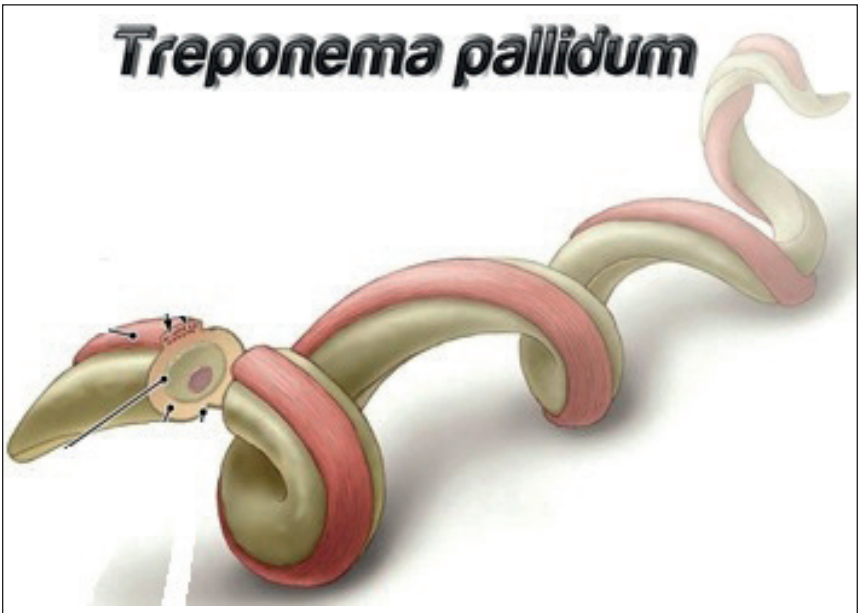
Outside the body, T. pallidum is very sensitive to external influences.

* It dies when
  – drying
  – heating to 60 ° C (within 15-20 '), to 100 ° C (in moment)
  – treatment with antiseptics (solutions of 0.05% chlorhexidine, mercuric chloride, 1-2% phenol, 70-96% alcohol)
  – pressure of acids, alkalis, salts of heavy metals, compounds of arsenic, bismuth, mercury.
* It's resistant to humid environments and low temperatures (for several days)

Except the spiral form, T. pallidum can exist in the form of low- active cysts and L-forms, grains, and polymembrane phagosomes which are the forms of survival and reproduction of T. pallidum under unfauvorable conditions, e.g. in taking sulfanilamid drugs and antibiotics (especially at subtherapeutic doses), at high temperature, radiation, latent and late forms of syphilis, a decrease in the reactivity of the organism, etc. Cysts and L-forms are formed from spiral treponema by twisting into a "glome" or into "budded balls".

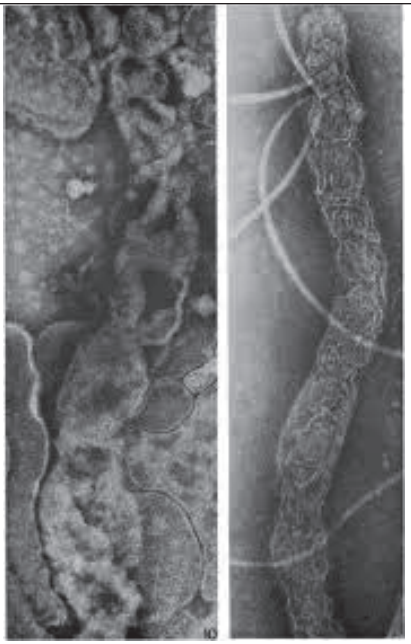
Grains - small rounded formations split off from treponema.

Polymembrane phagosomes are treponems in the cytoplasm of the phagocyte enclosed in a multilayer membrane of the phagocyte. (Pic 1)



Pic 1

Under an electron microscope, T. pallidum has a powerful outer cover. It consists of a three-layer membrane, cell wall and a mucopolysaccharide capsule-like substance. Under the cytoplasmic membrane fibrils are located (fibrils are thin threads that determine the diversity of T. pallidum motions). The cytoplasm is small-granular, it contains a nuclear vacuole, nucleolus, and mesosomes. T. pallidum agents are located predominantly extracellularly. Less commonly, infectious agents are detected in the endothelial cells of capillaries, in plasma cells, macrophages, neutrophils, and sometimes in fibroblasts and nerve fibers. (Pic 2).



Pic 2

3. Pathogenesis

The source of infection is: *a sick person.*

The ways of syphilis transmission:

a) sexual;

b) transplacental (transmission of an infection from a sick mother to the fetus through the placenta - congenital syphilis);

c) blood transfusion (transmission of infection during blood transfusion from a donor, infected with syphilis at any stage)

d) contact-household (extremely rarely);

e) professional (obstetrician-gynecologists, surgeons, dentists, pathologists, laboratory assistants, urologists, dermatovenerologists, etc.).

T. pallidum enters the human organism through damaged skin and mucous membranes (entry gates). The damage can be so slight that they stay unnoticed. Having overcome the skin-mucous barrier, T. pallidum is distributed in the body *perineurally (in the epi-, peri- and endoneurium), by the lymphogenic and hematogenous way.*

Immunity in syphilis forms while an infection exists and lasts until treponema (non-sterile (infectious) immunity disappears from the organism. After treatment the immunity stops existing. Congenital immunity is absent during syphilis disease.

Next notions are connected with the peculiarities of immunity in syphilis;

- *reinfection*– repeated infecting with syphilis of persons previously fallen ill and treated.
- *superinfection* – repeated infection with syphilis of an untreated patient, when treponemas pallidum enter again into the organism, which has already had it. As a result new syphilitic infection layers on existing syphilis and the organism responds to a new infection with eruption, corresponding to the present stage of illness.

4. Classification

The classic course of syphilis is characterized by periodicity / staging, when periods of syphilitic infection replace with characteristic clinical manifestations successively. Due to the ways of infection transmission syphilis is divided into congenital (inborn) syphilis (A50) and acquired syphilis (A51-A53)

In accordance with the International Classification of X Diseases revision (ICD-10) the following stages are distinguished:

* early congenital syphilis (A50.0 - A50.2) in children under 2 years of age is distinguished, which includes;
- early congenital syphilis with symptoms (A50.0);
- early latent congenital syphilis (A50.1)

- early congenital syphilis, unspecified (A50.2).

• late congenital syphilis (A50.3 - A50.9) in children over 2 years of age is distinguished, which includes
- late congenital syphilis with symptoms (A50.3-A50.5);
- late latent congenital syphilis (A50.6);
• late congenital syphilis, unspecified (A50.7)

• early syphilis (A51), which includes:
- primary syphilis (A51.0 - A51.2), average duration 6-8 weeks;
- secondary syphilis (A51.3 - A51.4) - the average duration of 3-4 years;
- early latent syphilis (A51.5);
- early syphilis, unspecified (A51.9);
• late syphilis (A52), which includes
- syphilis of the cardiovascular system (A52.0);
- neurosyphilis (A52.1 - A52.3);
- tertiary syphilis (A52.7)
- latent syphilis (A52.8);
- latest syphilis, unspecified (A52.9).

Except the classical course of syphilis with its periodization and characteristic clinical manifestations, there is also a possibility of atypical course of syphilis.

• *latent syphilis* - is diagnosed in individuals with positive serological reactions without active manifestations of the disease on skin and mucous membranes, without signs of specific damage of the nervous system and internal organs. Latent syphilis is divided into early syphilis - with a disease duration up to 2 years after infecting, late syphilis - with a disease duration of more than 2 years after infecting and unspecified syphilis - when determination of infection time is not possible.
• *blood transfusion, syn. decapitated syphilis (syphilis transfu-*

sionalis syn. Syphilis decapitate / d'emblee). It develops by transfusion of infected donated (or donor) blood and is characterized by the absence of hard chancre. The disease begins immediately with the clinical manifestations of secondary syphilis, as pale treponemas enter directly into the bloodstream.

- Malignant syn. galloping syphilis *(syphilis maligna)* - is diagnosed in weakened individuals, suffering from alcoholism, drug dependency, AIDS infection, tuberculosis, diabetes mellitus. It is characterized by shortened periods of syphilis and rare forms of clinical manifestations of syphilis (military papular syphilis, pustulose syphilis, etc.)

5. Incubation period

Syphilis, like any infectious process, begins with ***an incubation period (stadium incubationis),*** that covers the phase since the time of infection until hard chancre appearances where Treponema pallidum introduced into the skin or mucous membrane. The average duration of incubation period is from 2 weeks to 2 months. The incubation period can be lengthened till 3- 3,5 months or shorten till 8-10 days.

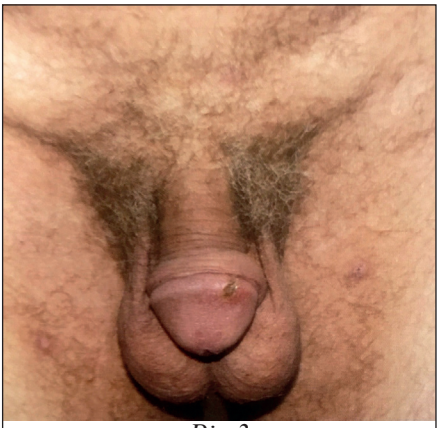
An extension of the incubation period is observed in taking antibiotics because of intercurrent diseases (**ARD** -acute respiratory disease, tonsillitis, gonococcal infection, pneumonia, furunculosis, etc.). As a result, the course of syphilitic infection can be distorted.

A shortening of the incubation period is observed:

- during reinfection
- if people infected with syphilis have concomitant confounding diseases (AIDS infection, tuberculosis, diabetes mellitus, etc.)
- with a bipolar location of hard chancres, when the introduction of the infectious agent of syphilis from several entrance gates provokes the rapid saturation of the organism by T. pallidum, accelerates the generalization of infection and the development of immune changes in the organism.

B. PRIMARY SYPHILIS (syphilis primaria)

1. Primary syphilis (syphilis primaria) (A51.0-A51.2). Begins with appearing of hard chancre. It's the first manifestation of syphilitic infection at the point of T. pallidum introduction. The average duration of the primary period is 6-8 weeks. Earlier, only the Wassermann reaction is used to diagnose syphilis. That time primary syphilis was conditionally divided into primary seronegative (syphilis primaria seronegativa) - the first 3-4 weeks of primary syphilis and primary seropositive syphilis (syphilis primaria seropositiva) - the next 3 -4 weeks of primary syphilis. But, after indroduction of treponemal tests into algorithm of serological diagnosis of syphilis the necessity for such division of primary syphilis has dropped away.



Pic 3

Clinical manifestations of primary syphilis

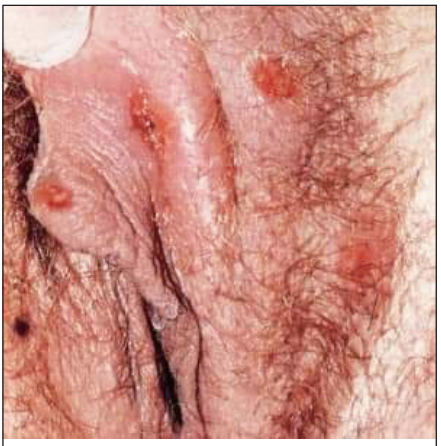
- hard chancre, syn. primary syphiloma (ulcus durum, syn. syphiloma primarium) (Pic 3)
- regional lymphadenitis syphilitic, syn. sclerenitis; concomitant bubo (lymphadenitis syphilitica, syn. Scleradenitis syphilitica, bubo-syphiliticus).
- lymphangitis syphilitical (lymphangitis syphilitica).

Hard chancre (ulcus durum) – - is more often a solitary erosion of a round shape or a saucer-shaped ulcer, the size of a little fingernail (1.0 cm), with a smooth, "varnished", with meat-red or yellowish-pink bottom. It has scanty serous discharge, clear edges, a dense infiltrate at the basement, painless, without sharp inflammatory manifestations on the periphery. In the healing process, an erosive

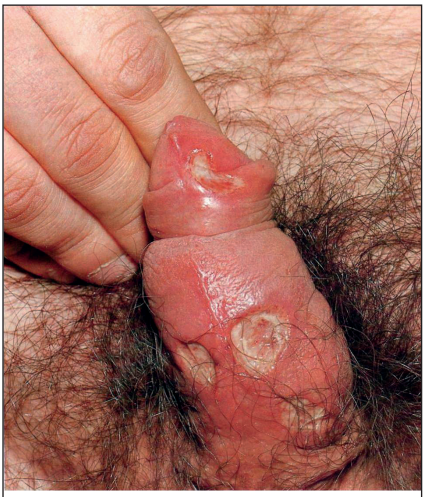
hard chancre resolves without a trace, but an ulcerative one leaves a scar. The hard chancre is usually localized on the skin and mucous membrane of the genitals, in less cases extragenital localization is noted, e.g. on the skin of the abdomen, pubis, hips, buttocks.(Pic 3)

Varieties of hard chancre:

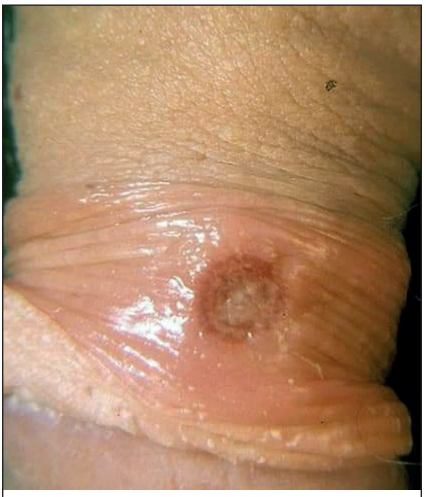
- *erosive(Pic 4), ulcerative (Pic 5)*
- *single (Pic 6), multiple (Pic 7)*



Pic 4

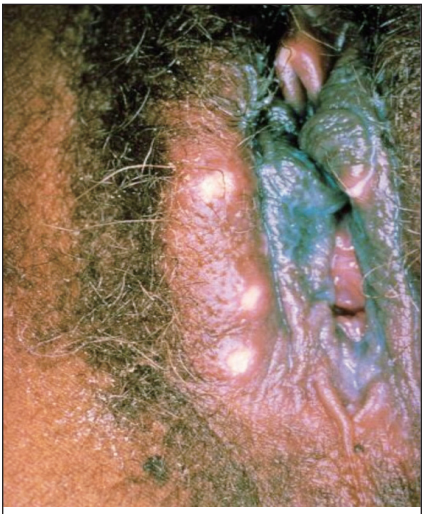


Pic 5

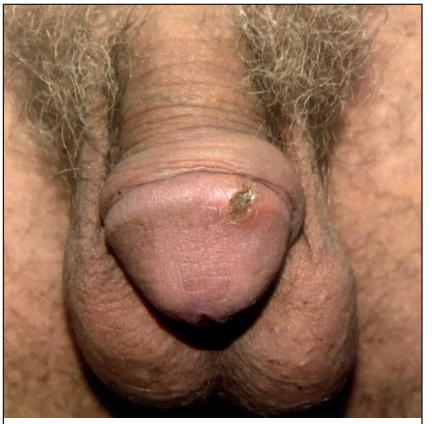


Pic 6

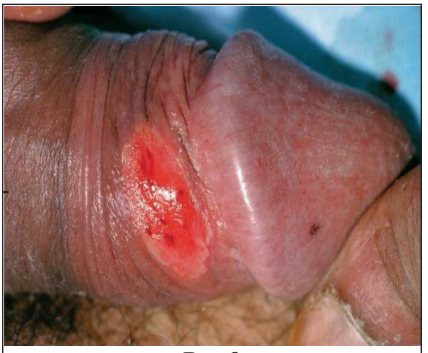
- *dwarf (1-3 mm) (Pic 8), gigantic (1.5-2 cm or more) (Pic 9)*
- *genital (Pic 10), extragenital (Pic 11,12)*
- *slot-like (in the tongue, in the corners of the mouth, in the anal fold) (Pic 13)*



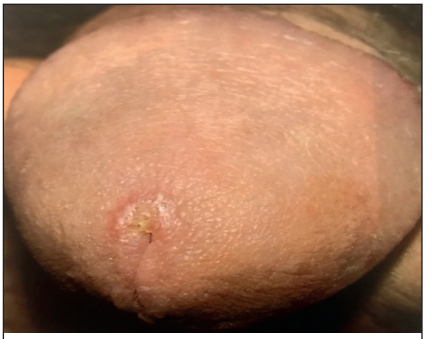
Pic 7



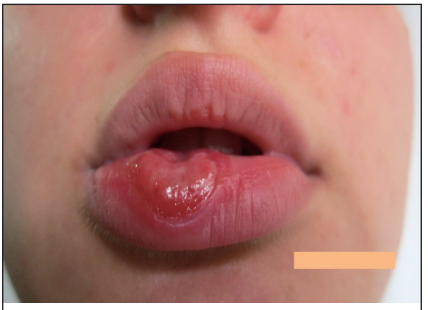
Pic 8



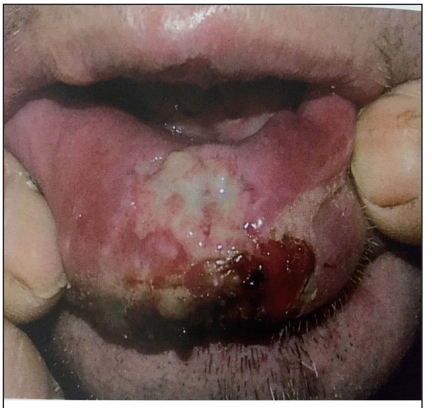
Pic 9



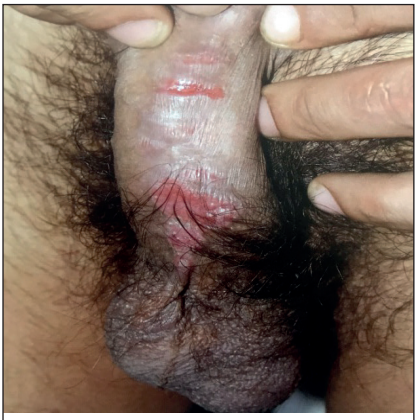
Pic 10



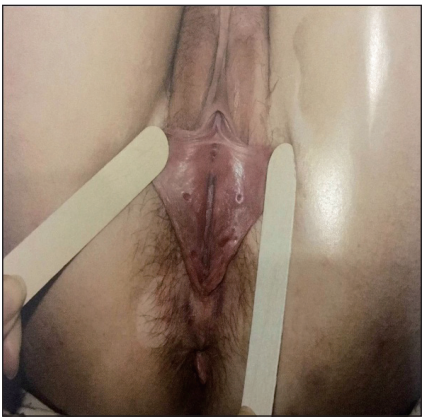
Pic 11



Pic 12



Pic 13



Pic 14

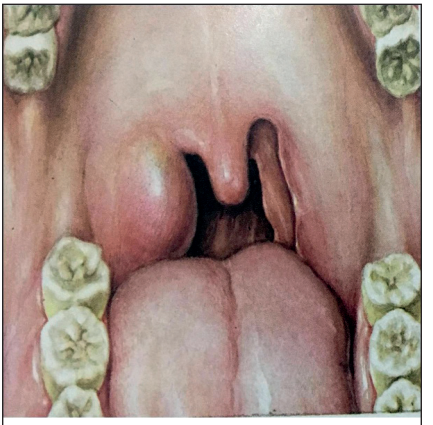
- *latent (hidden) localization of chancre on mucous membrane of uterus, urethra and anus.*
- *bipolar - the simultaneous appearance of chancres on far-away surfaces, e.g, on the skin and mucous membrane of the genital organs (genital chancre) and on the red border of the lips (extragenital chancre) surfaces, for example, on the inner surface of the thighs.(Pic 14)*

Atypical forms of hard chancre are relatively rare:

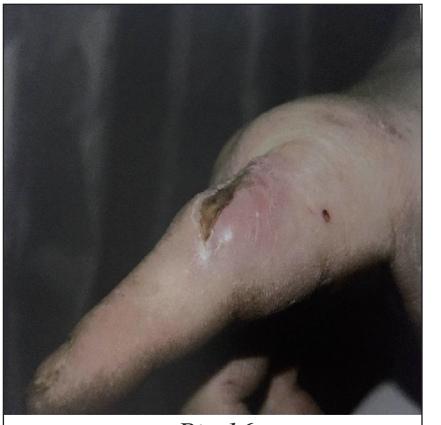
- *chancre amigdalitis (chancre-amygdalite)* - unilateral enlargement, hyperemia and densification of the tonsil, without a defect on its surface (absence of erosion or ulcer) (Pic 15)

• *chancre panaritium* ***(chancre-digiti)*** –it is usually localized on the first three fingers of the right hand and often proceeds as a banal panaritium, accompanied by soreness and profuse purulent discharge (Pic 16).

• *indurative edema* ***(oedema indurativum)*** - it's located in the labia majora, scrotum or foreskin. In this case a painless, dense swelling of these areas is observed, it does not leave pits when pressed, it has not sharp-inflammatory manifestations and passes without a defect on the surface (absence of erosion / ulcer). The skin of the affected areas is of stagnant



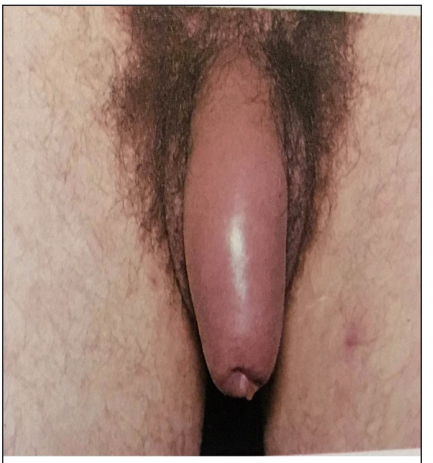
Pic 15



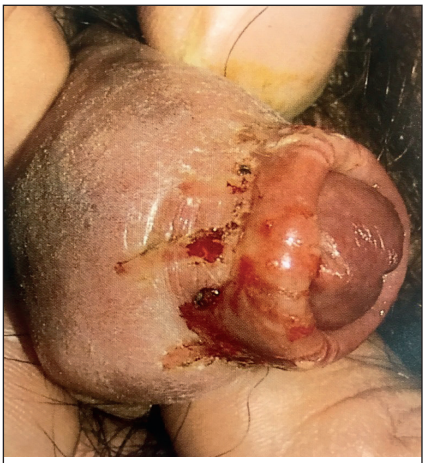
Pic 16

red color, gradually turning pale towards the periphery (Pic 17).

As a result of joining a secondary infection (bacterial, trichomonas), *complications of hard chancre* begin developing: such as balanit (balanitis), balanopostit (balanoposthitis), phimosis, paraphimosis, gangrenization, phagedenism (or ***esthiomene***). The most common complications are *balanitis (balanitis) and balanoposthitis (balanoposthitis)* - inflammation of the skin of the glans penis



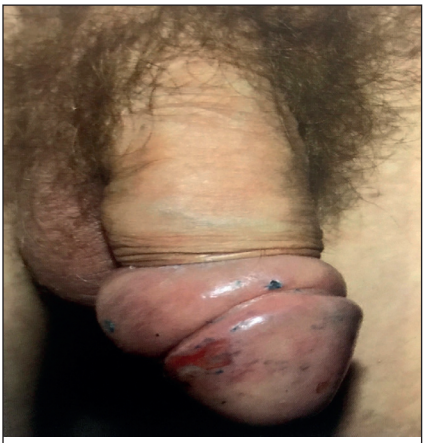
Pic 17



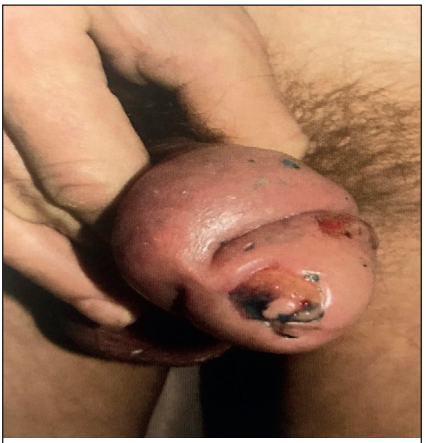
Pic 18

and inner sheet of the foreskin around the chancre. In such cases, puffiness, bright erythema, maceration of the epithelium appears around the chancre, and serous-purulent discharge intensifies.

Balanoposthitis can lead to a narrowing of the cavity of the foreskin, it does not let open the glans penis. Such condition is called *"phimosis"*(Pic 18), in this case the penis seems swollen, erythematous, painful. An attempt to forcibly liberation of the glans penis in the presence of phimosis can lead to paraphimosis (Pic 19), when the swollen and infiltrated prepuce ring strangulates the glance penis.



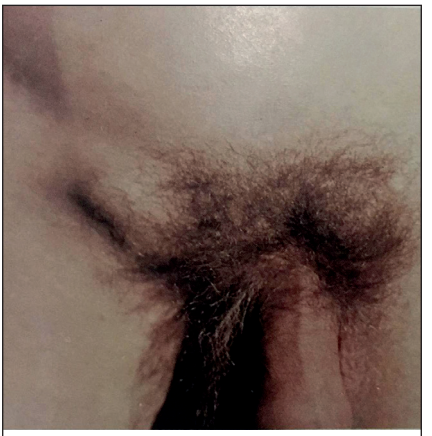
Pic 19



Pic 20

The most serious complications of hard chancre are gangrenization and phagedenism (or esthiomene), which are observed in debilitated patients and alcoholics. A black scab appears on the surface of the chancre, it's *gangrenization (gangraenisatio)* (Pic 20), that spreads beyond the boundaries of primary syphiloma - *phagedenism (phagedaenismus)*. After healing of ulcer, formed under the scab, there is a rough scar. The process is accompanied by chills, fever and other common phenomena.

Regional lymphadenitis and lymphangitis are other manifestations of primary syphilis.



Pic 21

Regional lymphadenitis gets bigger in 5-8 days after the appearance of hard chancre. Regional lymph glands increase to the size of a pea, walnut or more, they have a dense-elastic consistency, are mobile, painless, not soldered with each other and with surrounding tissues (Pic 21).

Specific lymphangitis is an inflammation of the lymphatic vessel from the hard chancre to the regional lymph glands. It is represented in the form of a dense, painless cord, sometimes in beaded form, not soldered with the surrounding tissue.

Differential diagnostics of hard chancre:

- *herpes simplex / genital*- grouped erosions with polycyclic outlines on an erythematic-edematous background, without compacting at the basement, is accompanied by burning, soreness, serological tests are negative.
- *scabies* - the absence of a dense infiltrate at the basement of the elements, the detection of paired eruptive elements characteristic for itchiness in other parts of the skin, night biopsy itching, serological tests are negative.
- *chancre form pyoderma* - serological tests are negative.
- *skin cancer* - the ulcerated cancerous tumor is located deeper, its edges are dense, irregular, often are corroded, the bottom is also irregular and bleeds easily, serological tests are negative.
- *miliary ulcerative tuberculosis* - ulcers are multiple, painful, have **irregular,** digged edges, tuberculin tests are positive, serological tests are negative.

• *soft chancre (chancroid)* is found in countries with hot climate. The incubation period is much shorter (1-5 days). Distinctive signs of ulcers in soft chancre are multiplicity, soreness, irregular shape, a tendency to peripheral growth with the appearance of new nidus of autoinoculation. Around the ulcer sharp-inflammatory nimbus is noted, at the basement - a soft infiltrate is seen; enlarged regional lymph glands are sharply painful, solder with each other and the surrounding tissues. The skin above lymph glands is hyperemic, the abscessing and opening with a significant amount of pus are frequent outcome of lymphadenitis. While bacterioscopic examination, Hemophilus ducreyi is detected, serological tests are negative.

• *Cutaneous leishmaniasis* –leishmaniomas, as a rule, are differentiated with a hard chancre of extragenital localization, because leishmaniasis is localized on the genitals very rarely. Differential / distinguishing features are following: slow development, large sizes, scalloped borders, a pasty consistency of the base, sharp inflammatory nimbus on the periphery, detection of L. tropica and negative serological reactions.

C. SECONDARY SYPHILIS (syphilis secundaria).

1. Secondary syphilis (A51.3-A51.4), along with primary syphilis, according to ICD-10 are nosological forms of *early syphilis* (A51). Secondary syphilis usually develops in 9-12 weeks after infection or 6-8 weeks later the appearance of hard chancre. Herewith, approximately in 25% of cases, a hard chancre continues to exist with manifestations of secondary syphilis. The duration of secondary syphilis (2-4 years) is the final stage of the so-called "infectious" form of syphilis - early syphilis.

Secondary syphilis is divided into;

• *secondary early syphilis (syphilis secundaria recens),*

which is diagnosed from the moment when the first "secondary sy-

philides" appears (duration - 2-3 months);

• *secondary latent syphilis (syphilis secundaria latens),* which is diagnosed in the intervals between the rashes of secondary syphilides;

• *secondary recurrent syphilis (syphilis secundaria recidiva),* which during repeated syphilis, without treatment, can be repeated for several times.

Secondary syphilis often begins with prodromal phenomena, which usually occur 7-10 days before the appearance of *secondary syphilides* and coincides with the massive hematogenous distribution of pale treponemas in a patient. Weakness, headache, pain in muscles, bones, joints, strengthening at night, fever are noted. It is noteworthy that when the clinical symptoms of secondary syphilis appear, prodromal phenomena usually disappear.

Clinical manifestations of secondary syphilis

Secondary syphilis is characterized by ***a variety of symptoms and morphological elements (syphilides),*** which are located on the skin and mucous membranes. Besides, it's characterized (in less degree) by changes in the internal parts, nervous system, musculoskeletal apparatus, etc.

Early syphilides are small, bright, numerous, symmetrical, without a tendency to merging and forming of figures. They usually are localized on the skin of the trunk and extremities. Fresh syphilides often appear in the presence of hard chancre remains and evident regional lymphadenitis. *Recurrent syphilides* are large, faded, small in numbers, asymmetric, with a tendency to merging and forming of figures. They usually are localized in places of friction and irritation (skin of the perineum, inguinal folds, mucous membranes of the mouth and genitals).

Secondary syphilis on the skin and mucous membranes manifest in the next forms

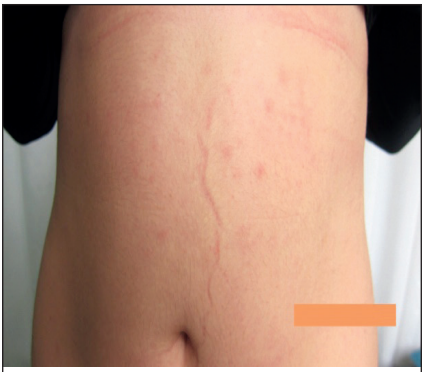
• *macules - macular syphilid (syphilidum maculatum)*

- vascular stains – *roseolous syphilid (syphilidum roseolosum)*
- pigment macules *(or spots) - pigment syphilid, syn. leukoderma (syphilidum pigmentosum, syn. Leukoderma syphiliticum)*

• papules- *papular syphilid (syphilidum papulosum)*

• pustules - *pustular syphilid (syphilidum pustulosum)*

• vesicles (rarely) - *vesicular syphilid (syphilidum vesiculosum)*

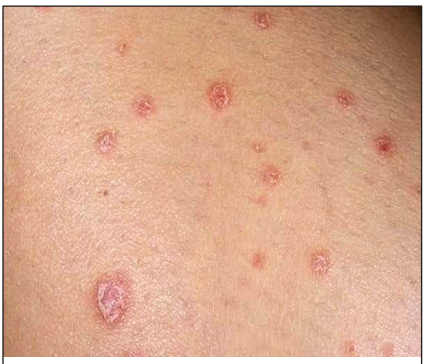


Pic 22

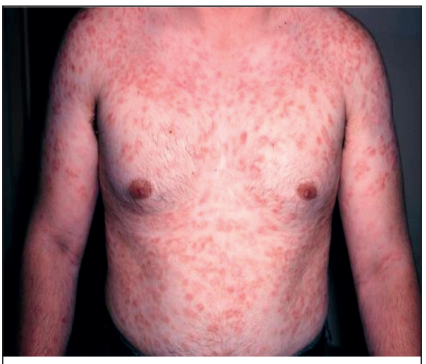
Roseolous syphilide manifests in pink spots of round shape, (their diameter can up to 1 cm), with a smooth surface, without a tendency to merging and peripheral growth, without subjective sense, in diascopy these spots disappear. Localization – mainly in the skin of the trunk, extremeties, with more bright manifestations on the lateral surfaces of the trunk. It occurs both with secondary recent and with secondary recurrent syphilis. (Pic 22).

Varieties of roseolous syphilis

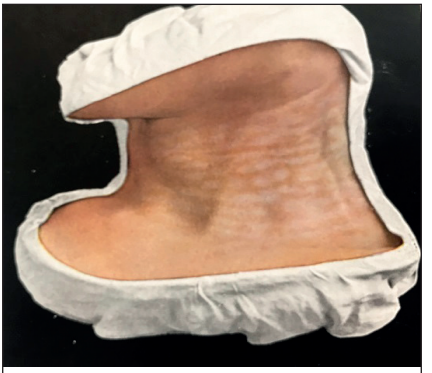
- *flaky roseola (Gibert's desease) (roseola syphilitica desquamativa)* - on the surface of roseola tabular scuts are noted, the center is hollowed.(Pic 23)
- *rising / urticar roseola (roseola syphilitica elevate / urticata)* - in this case roseola rises above the level of normal skin, resembling a blister.(Pic 24)



Pic 23



Pic 24



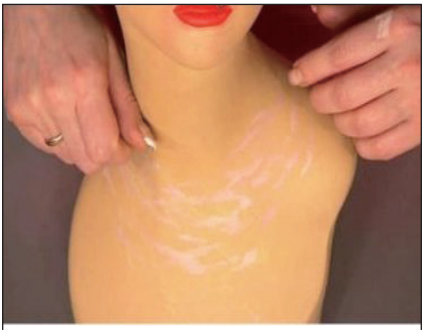
Pic 25

• *granular roseola (roseola granulata)* – roseolas are localized around the hair follicles, giving the impression of "grains".

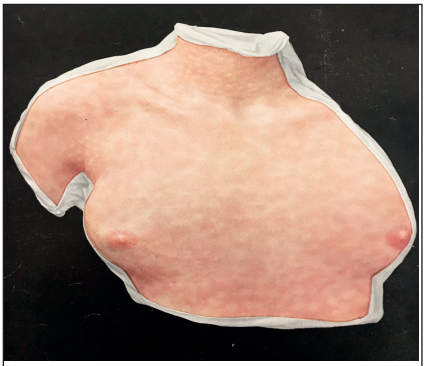
Leukoderma (pigmented syphilide) is characterized by depigmented spots on the background of slight hyperpigmentation. The spots are round, with a diameter of 0.5-1.5 cm, without a tendency to merge, they do not peel and are not accompanied by subjective sense. Localization - mainly the skin of the neck (necklace of Venus) and the upper part of body. Leukoderma is a symptom of secondary recurrent syphilis, it usually appears at 4-6 months of illness duration, exists for a long time and disappears after 6-12 months, and sometimes after 2-4 years, even with full therapy. (Pic 25)

Varieties of leukoderma:

- *macular (maculosum)(Pic 26)*
- *lacy / cellular (reticulare)(Pic 27)*
- *marble (marmoratum)*
- *necklace of Venus*



Pic 26



Pic 27

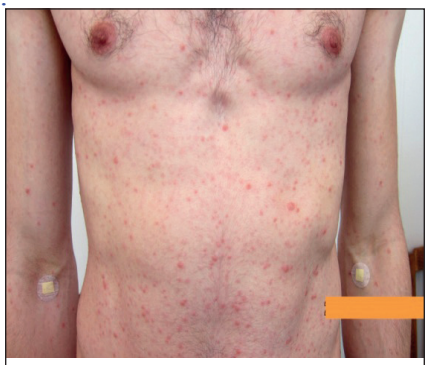
Papular syphilis is characterized by a rash of knot, which size depends on its types. They can be 0.1–2.0 cm in size, rounded in shape, with a dense-elastic consistency, not disposed to peripheral growth and merging. (pictures 25,46). First, pink papules are with a smooth, shiny surface, then get a copper-red color, begin to peel off. Peeling of papules begins from the center and ends in the center earlier than on the periphery, which causes the appearance of bordering peeling - *"Beett's collar"*. Pressure on the center of the nodule with a blunt searecher causes a sharp pain – Yadasson *symptom.* The surface of the papules located in the area of folds, on the mucous membranes is macerated, soaking erosive papules are formed. Localization - throughout all skin, on the mucous membranes of the oral cavity, genitals.

Papular syphilis is found both in secondary recent and *secondary recurrent* syphilis.

Varieties of papular syphilide:

• *miliary (miliare)* - papule size ≤ 0.2 cm in diameter; is observed with malignant syphilis;

• *lenticular (lenticulare)* - the size of the papules is 0.3-0.5 cm in diameter; (Pic 28)



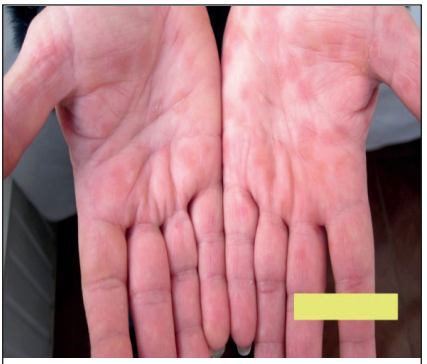
Pic 28

• *coin-like (nummiforme)* – papules > 0.5 cm in diameter, are observed in malignant syphilis;

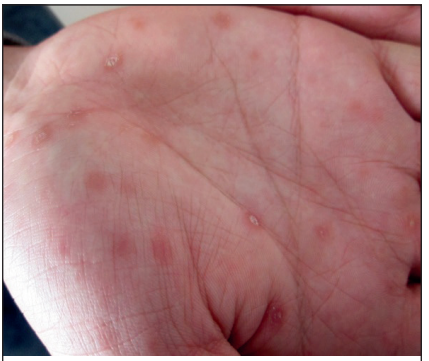
• *palmar-plantaris (palmarum et plantarum);* (Pic 29-36)

• *seborrheic (seborrhoicus)* - occurs in "seborrheic zones", more often in people with oily seborrhea;

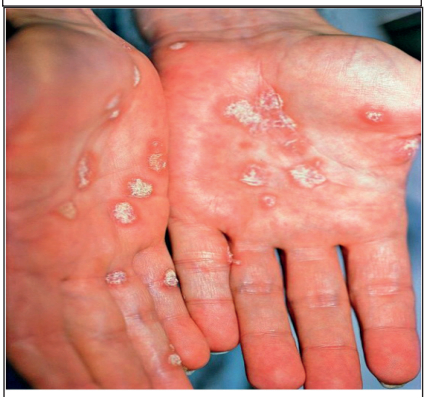
• *crown of Venus* - papules are localized in the forehead on the border with the scalp;



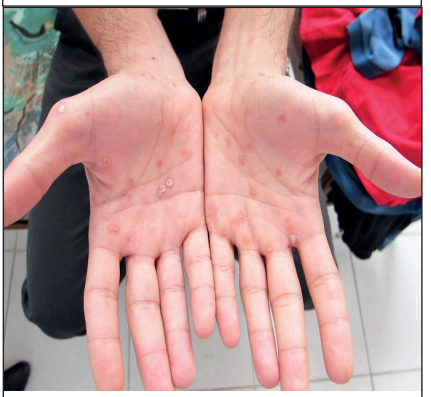
Pic 29



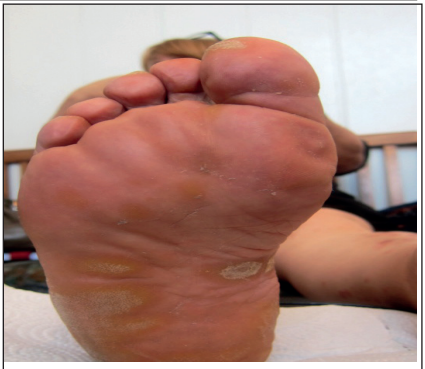
Pic 30



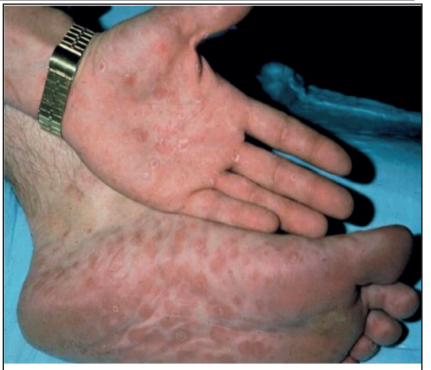
Pic 31



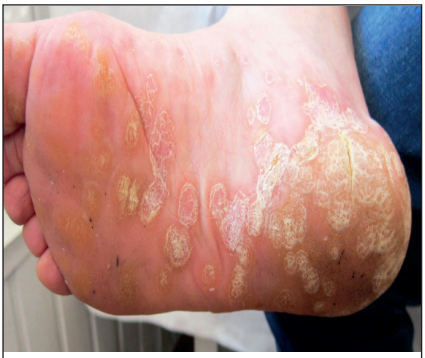
Pic 32



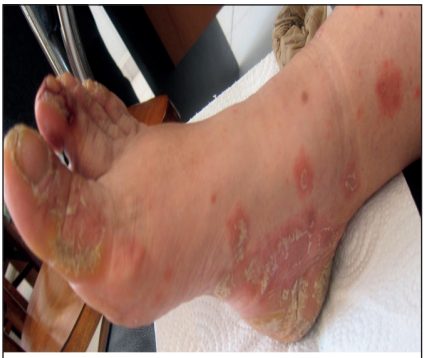
Pic 33



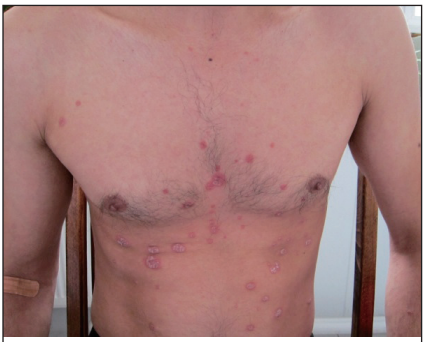
Pic 34



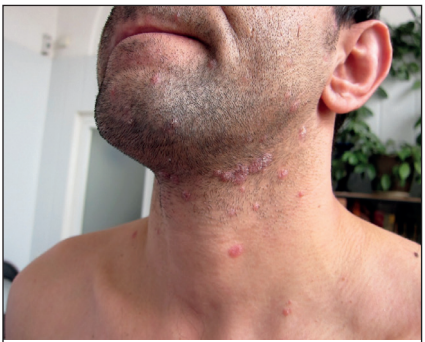
Pic 35



Pic 36



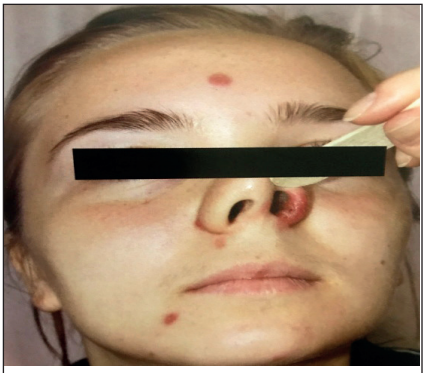
Pic 37



Pic 38

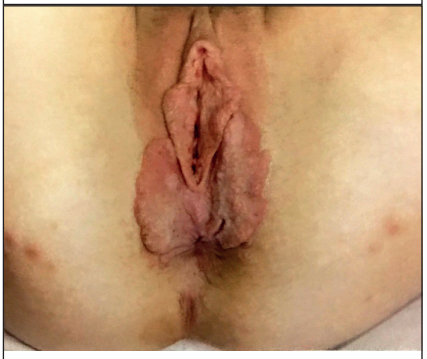
• *psoriasis form (psoriasiforme)* - on the surface of papules of silver-white tabulate the scalesare present, resembles psoriasis; (Pic 37,38)

• *weeping (madidans)* **papular syphilid** - the papules are localized on the mucous membranes and in places of friction (intergluteal, inguinal-femoral, axillary, interdigital folds, genitals, under the mammary glands in women). It leads to maceration and rejection of the corneal layer (stratum corneum) from the surface of the papules. As a result, weeping erosive papules form, in the serous discharge of which a large amount of T. pallidum is detected;(Pic 39,40)

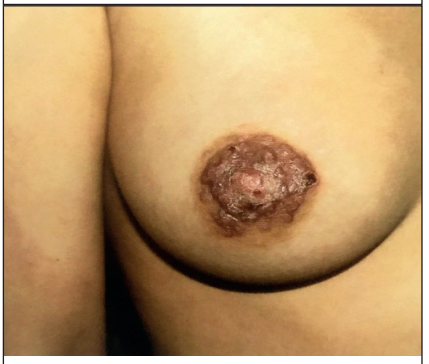


Pic 39

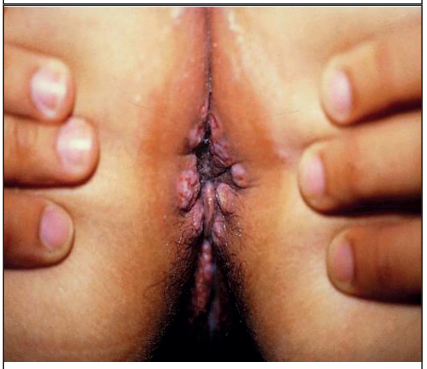
Pic 40



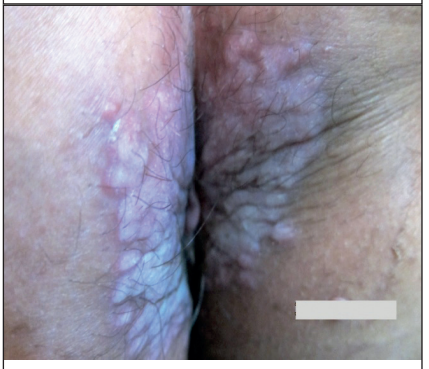
Pic 41



Pic 42



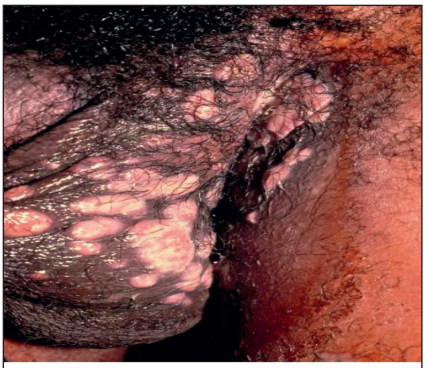
Pic 43



Pic 44

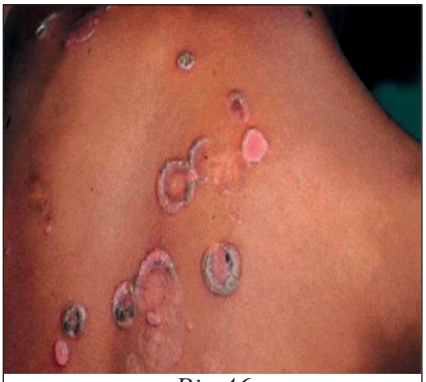
• *wide condylomas, syn. Vegetative (condylomalatum, syn. vegetans)* - arise from weeping erosive papules. On their surface under

the influence of prolonged irritation, vegetations are formed, covered with a serous adhesive patch, containing multitude of T. pallidum. (Pic 41-45)



Pic 45

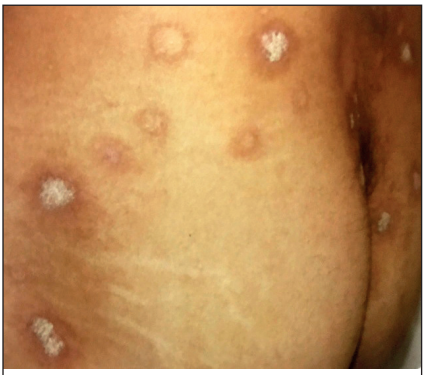
Pustular syphilide – is a rare manifestation of secondary syphilis. It's characterized by a rash of pustules and papule-pustules, usually occurs in weakened individuals and indicates a hard course of the disease. (Pic 49). Localization is observed throughout all skin covers.



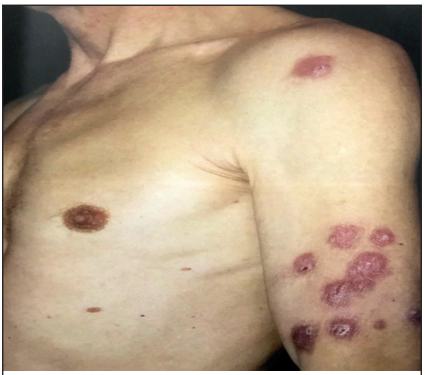
Pic 46

Varieties of pustular syphilide:

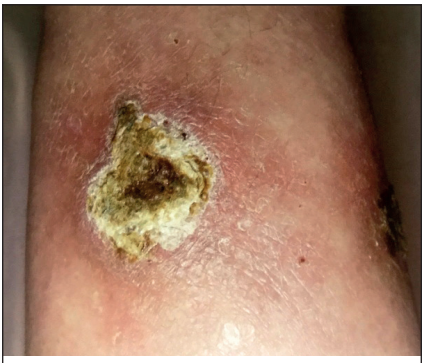
• *acneiform (acneforme)*- manifests itself by follicular papule-pustules of a conical (pineal) shape, 0.2-0.3 cm in diameter, in resolution process the crusts form. While their re-



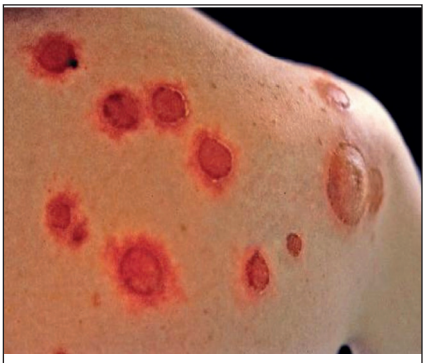
Pic 47



Pic 48



Pic 49



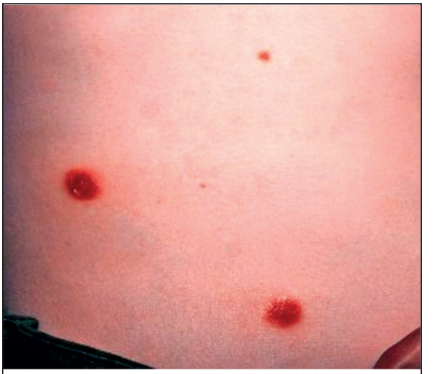
Pic 50

jection, retracted pigmented and weakly visible scars can stay;

• *smallpox (varioliforme)* - is manifested by hemispherical pustules with an umbilication in the center, it can be in size of a lentil or a pea, during the process crusts form, while the crusts rejecting pigmentation, often scars can stay; (Pic 46)

• *impetiginous (pustulosum)* - manifests itself by means of superficial, creeping pustules, papule-pustules, crusts. During the rejection of crusts the process is resolved without a trace; (Pic 47,48)

• *ectimatous (ectimatosum)* - manifests itself by means of deep pustules, during the resolution of which massive crusts are formed. Sometimes layered – rupias (Pic 49), deep ulcers, pigmented scars can form. (Pic 50,51)



Pic 51

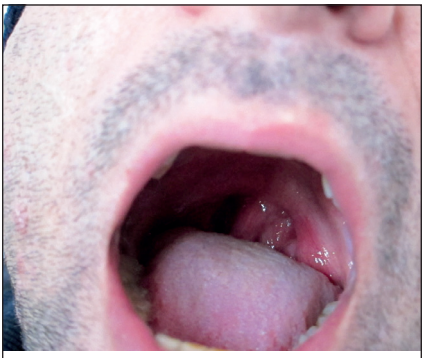
Pustular syphilide of acne, smallpox and impetiginous type occurs more often in patients with *secondary recent syphilis.* Ectimatous / rupioid pustular syphilide is observed in patients with *secondary recurrent syphi-lis.*

In secondary syphilis, the

defection of the mucous membrane of the mouth and larynx is often noted. In secondary recurrent syphilis, rashes on the mucous membranes of the mouth can be the only clinical manifestation of the disease.

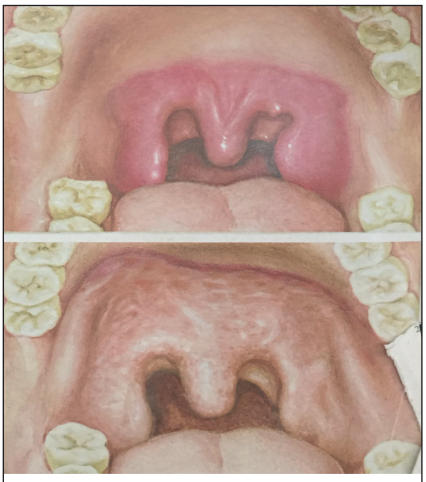
Syphilides on the oral mucous membrane are highly contagious, because they contain a large number of pale treponemas and are found in the form of *spotted (roseolous)* and *papular syphilides.* On the oral mucosa pustular syphilis is observed rarely.

Roseolous syphilide - on the mucous membrane it appears symmetrically on the arches, soft palate, tongue and tonsils. Here the merging roseolas form a continuous focus of stagnant red color, with a smooth surface, clear boundaries and slight discomfort when swallowing sometimes they don't exist *(syphilitic erythematous angina)*. (Pic 52,53)



Pic 52

Papular syphilide on the mucous membrane of the mouth can occur in any area of tongue, mucous membrane of the cheeks, gums, tonsils, soft palate. Papular syphilis manifests itself in the form of separate papules of a round shape and of dark red color, with a dense-elastic consistency. The diameter of papules is up to 1 cm or can have the form of towering *plaques* of merged papules, with a dense infiltrate at

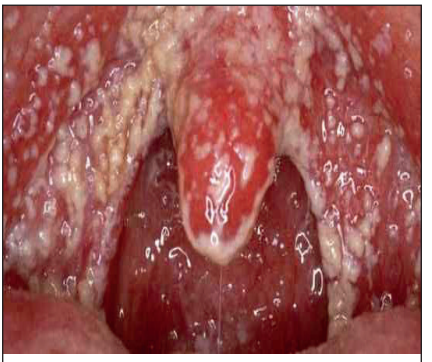


Pic 53

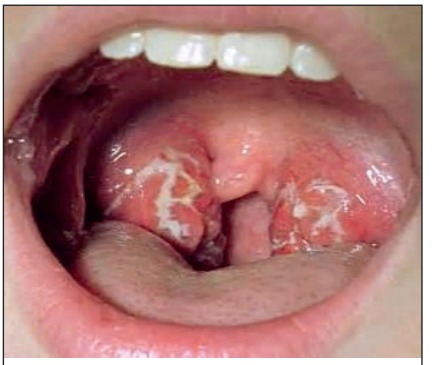
the base. The plagues are often located in the tonsils, arches and soft palate ***(syphilitic papular tonsillitis).*** (Pic 54,55) Longlasted hoarseness, turning into aphonia – *raucedo (syphilitic catarrhal laryngitis)* and hyperemia causes laryngeal mucosa..

After 2-3 days, papules/plaques get greyish-white color *("opal papules / plaques")* (Pic 56, 57) because of soaking with exudates. After 1-3 weeks, the surface of papules/plaques erodes *(erosive papules / plaques)* and T.pallidum is easily detected in the discharge. Erosive papules/plaques are extremely infective. Erosive papules in the corners of the mouth can be accompanied by soreness (syphilitic angular cheilitis).

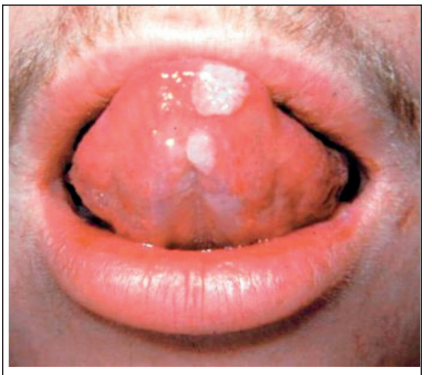
When papules are localized in the folds of the tongue, the grooves



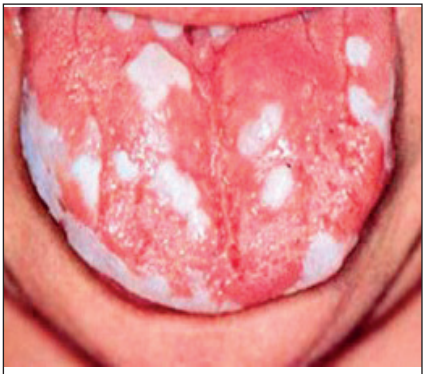
Pic 54



Pic 55



Pic 56



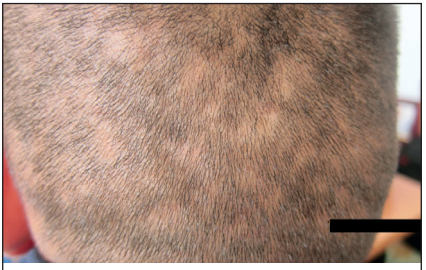
Pic 57

(sulculars) of the tongue are significantly deepened and are perceived as deep cracks. However, more often papular syphilide in the tongue is represented by papules of irregular or round shape, pinkish-cyanotic color, with a smooth polished surface. On the background of a normal or slightly coated mucous membrane of the tongue these papules give the impression that the defected areas are located below the level of the surrounding mucosa - *"glossy" papules/plaques or a symptom of a "sloping meadow" (or "hayfield").*

While defecting of the laryngeal mucosa, syphilitic *papular laryngitis* develops, it has the form of single grayish-white colored papules. These papules have not tendency to erosion / ulceration, are accompanied by hoarseness. In the framework of secondary syphilis, syphilitic laryngitis (catarrhal and papular) is more often observed in *secondary recurrent syphilis.* As for syphilitic tonsillitis (erythematic and papular) it is observed both in *secondary fresh and recurrent syphilis.*

In secondary syphilis, except rashes on the skin and mucous membranes, *syphilitic alopecia* can occur and polyadenitis can develop.

Syphilitic alopecia (alopecia syphilitica is characteristic for secondary recurrent syphilis and usually appears in 6-8 months after infection. Syphilitic baldness is not accompanied by peeling and subjective sensations.



Pic 58

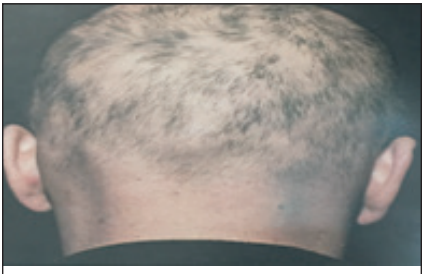
Types of syphilitic alopecia:

• microfocal (alopecia syphilitica areolaris)(Pic 58)

• diffuse (alopecia syphilitica diffusa)

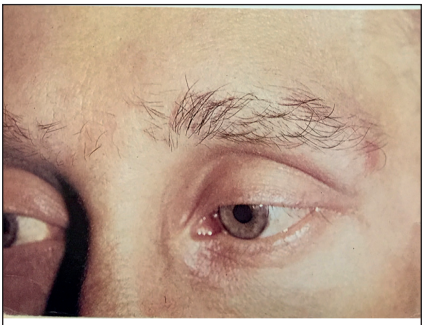
• combined (alopecia syphilitica mixta).(Pic 59)

In *microfocal alopecia,* the scalp, its temporal (crotaphic)

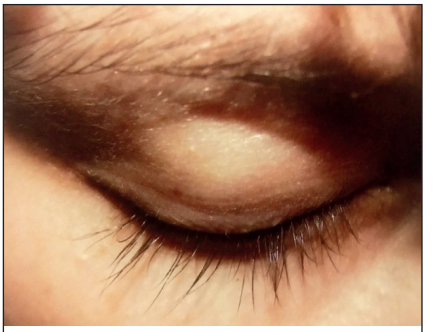


Pic 59

and occipital parts are often infected , but eyebrows, eyelashes, beard are defected less often. There are many small focies of baldness with a diameter of 1-2 cm or less, rounded in shape, usually not merging with each other. It is pathognomonic that the hair in the focies does not fall out completely, but partially. As a result their thinning occurs, and the foci looks like the "mouse-eaten" fur.

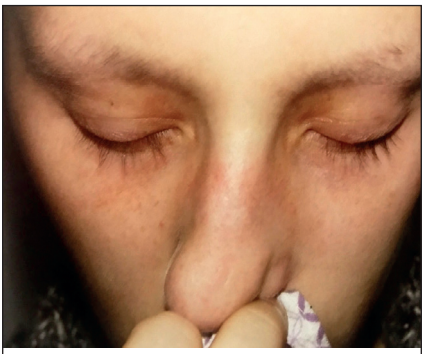


Pic 60

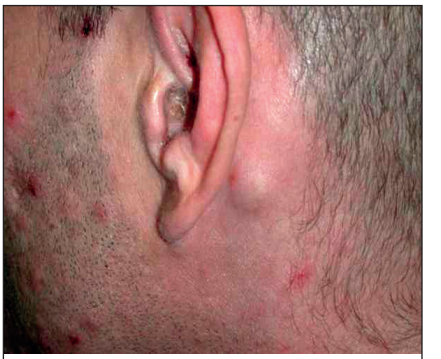


Pic 61

Hair loss in the form of small foci in the area of the eyebrows is called "omnibus" syphilis (Fournier) or *"tram"* syphilis (P.S Grigoriev). (Pic 60) When eyelashes are damaged, due to their partial loss and successive growth, eyelashes have different lengths - *step-shaped eyelashes (Pincus symptom)*. (Pic 61,62)



Pic 62



Pic 63

Diffuse alopecia is characterized by general thinning of the hair without changing the skin.

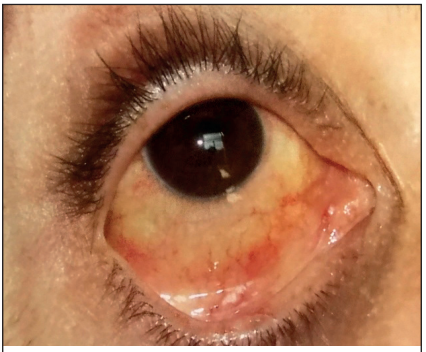
Combined alopecia is a combination of small focal and diffuse alopecia.

Polyadenitis *(polyadenitis syphilitica)* occurs in 80-90% of patients with secondary fresh syphilis, in patients with secondary recurrent syphilis it's observed much less often. Polyadenitis is manifested by an increase of lymph nodes in submandibular, cervical, axillary, inguino-femoral, cubital, etc. Enlarged lymph nodes are mobile, painless, with a dense-elastic consistency, they can be in size of hazelnut and larger, are not welded with each other and underlying tissues. (Pic 63)

Injury of internal organs, nervous system and musculoskeletal system.

Syphilis affects many internal organs and systems in its early stages. Patients with secondary syphilis, the injury of internal organs and systems (alike other manifestations of the early forms of syphilis) have not organic, but *functional character,* passes quickly. It often injures liver (hepatitis), spleen (splenitis), kidneys (nephritis, nephrosis), stomach (gastritis, gastrointestinal dyskinesia), heart (myocarditis), nervous system (neurosis, meningitis), musculoskeletal system (polyarthritis, osteoperiostitis, periostitis) are observed. Among others, more rare lesions, dry pleuritis, otitis media, retinitis are note (Pic 64,65)

Pic 64



Pic 65

Differential diagnosis of syphilides of secondary syphilis:
Manifestations on the skin

* roseolous syphilide

- *toxidermy* - has acute onset and course. Spots are of bright color, predisposed to peripheral growth and merging, their surface is smooth, rarely peeling. Subjectively - itching and burning. Serological tests are negative; *Giber's pink lichen* - the disease begins with the appearance of a single pink spot of oval form. Due to peripheral growth that spot gets a diameter of 2 cm or looks like a crumpled cigarette paper and with a scaly crown on the periphery, which looks like a "medallion" type- a maternal plaque. After 7-10 days, similar elements of smaller sizes appear, they are located along the Langer lines – daughterly elements. Subjectively - mild itching. Serological tests are negative;
- *pityriasis verticolor (chromophytosis or multi-colored) lichen* - non-inflammatory pink spots of pinkish color, slightly scaly, prone to peripheral growth and merging into large foci, often in the upper half of the body. Subjectively - mild itching. The following symptoms are characteristic- positive Besnier's symptoms (latent peeling), Balzer symptom (with 5% tincture of iodine), a pale yellowish-green glow under the Wood's lamp, serological tests are negative;

* papular syphilide
- *lichen planus* (lichen acuminatus, Wilson's lichen) - papules are flat, shiny, polygonal, of a livid color, with a navel-lik (omphaloid) impressing in the center. There can be seen Wickham net in the form of whitish-opal stripes. Subjectively severe itching. Serological tests are negative.
- *psoriasis* –papules are of a Round pinkish-red (papules) color and of rounded form, on the surface are of silver-round color, scales(on the surface) are easily exfoliated, a tendency

to merging with forming of plaques. The psoriatic triad is characteristic: a stearinis spot, terminal cover-up and pinpoint bleeding/blood (hematic) dew. Subjectively - mild itching. Serological tests are negative.

- *pointed condyloma* (or genital warts) - papules in color of normal skin or pinkish-red, on a thin stalk, with a lobed surface resembling cauliflower, serological reactions are negative.
- *lichenoid tuberculosis of the skin* (tubercoulosis cutis lichenoides) - papules of soft consistency, yellowish-red, prone to grouping, positive tuberculin tests are positive, serological tests are negative.
- *tuberculosis papulonecrotica* - a long course, localization on extension surfaces of the extremities, " stamped" scars can appear in the place of nodular rashes, tuberculin tests are positive, serological tests are negative;

* pustular syphilide

- *chickenpox* - an acute onset with a high temperature, a serious general condition of the patient, the absence of a dense-elastic infiltrate at the base of pustules, negative serological tests
- *acne vulgaris* (black-heads) – acute character of inflammation, abnormity, the presence of severe seborrhea and comedones, the age of patients, a chronic course with frequent recurrence, serological tests are negative.
- *iodide (iodic) and bromide (bromatus) acne* - large pustules, the presence of an hard-inflammatory nimbus along the periphery of the elements, solution of the process after stopping of iodine or bromine intake, serological tests are negative.
- *impetigo* (crusted tetter or superficial pioderma)- acute beginning, rapid spread, merging of rashes into large foci, serological tests are negative.
- *vulgar ectima (ecthyma vulgaris)* - the presence of a pustule with an acute-inflammatory reaction of the skin, the absence

of infiltration in the base of the pustule and around it, serological tests are negative

- *infiltrative suppurative trichophytosis* (on the scalp - kerion celsi) - the acute nature of the disease, soreness, merging of rashes into large foci, detection of mycelium in the foci of lesion, serological tests are negative;

* pigmented syphilide

- *vitiligo* - the complete absence of pigment in the affected area, large foci of depigmentation, prone to peripheral growth and merging, serological tests are negative.
- *pityriasis (versicolor) lichen (chromophytosis)* - whitish non-inflammatory spots, slightly scaly, prone to peripheral growth and fusion into large focies. More often are observed in the upper half of the body. Subjectively - mild itching. The following symptoms are characteristic- positive Besnier's symptoms (latent peeling), Balzer symptom (with 5% tincture of iodine), a pale yellowish-brownish glow under the Wood's lamp, serological tests are negative;

• syphilitic alopecia

- *alopecia areata* -focies of alopecia are usually single, larger, sharply limited, with a shiny smooth surface and a complete absence of hair. The area of shaken hair along the periphery is noted, serological tests are negative.
- *superficial trichomycosis* - in the lesions peeling is noted, hair does not fall out, but breaks off, while microscopy mycelium is detected, serological tests are negative.

Manifestations on the mucous membranes

* macular syphilide

- catarrhal sore throat - a clear violation of the general condition, fever, pain, tonsils are swollen in bright red color, serological tests are negative.

* papular syphilid
- *plane* (tabulate) leukoplakia - grayish-white plaques, sharply delineated, with a rough surface, are not exfoliating while scraping, serological tests are negative.
- *lichen planus* - papules of grayish-white color are grouped in the form of lace, net, rings, serological tests are negative.
- *candidiasis of the oral mucosa* - is characterized by a whitish cheesy coating, after removing of which a red velvety surface can be seen, by microscopy pseudomycelia is detected, serological tests are negative.

* erosion on the red border of the lips and the mucous membrane of the oral cavity in *lichen planus, lupus erythematosus, pemphigus, erythema multiforme, leukoplakia, herpes* simplex have not induration in base, are painful, serological tests are negative

D. TERTIARY SYPHILIS (Syphilis tertiaria).

1.Tertiary syphilis with manifestations on the skin and mucous membranes (A52.7), along with cardiovascular syphilis (A52.0), neurosyphilis (A52.1-52.3) and with tertiary manifestations of syphilis in other organs (A52.7), form the nosological structure *late syphilis* (A52). Tertiary syphilis in patients with untreated syphilitic infection manifests itself after 3-5 years, possibly after 10-30 years. Elderly and children's age, chronic diseases, alcoholism can improve tertiary syphilis in patients. The clinical manifestations of tertiary syphilis (tertiary syphilides) are local, accompanied by the destruction of the organs and tissues in which they are located, leave scars and are *of organic, ever-lasted, chronic character.* Manifestations of tertiary syphilis are not practically infectious, because single treponemas, located in the depth of the infiltrate, die during their disintegration. At the same time, tertiary syphilides, especially gummas, press and then destroy the organs they are located in, creating a danger for patient's life. Morphologically tertiary

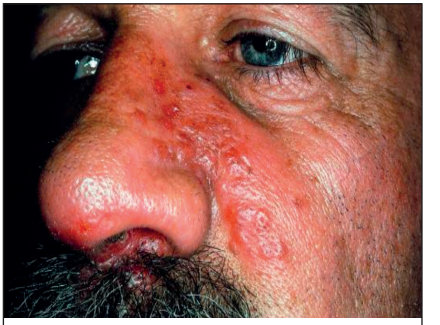
syphilides are infectious granulomas. In tertiary syphilis 25-35 % of non-treponemal serological reactions have negative results. But treponemal tests are almost always positive. Manifestations of tertiary syphilis respond to antisyphilitic therapy well. Tertiary syphilis is divided into *active (syphilis tertiaria activa) and latent (syphilis tertiaria latens)*

Clinical manifestations of tertiary syphilis

Lesions on the skin and mucous membranes in tertiary syphilis - tertiary syphilides appear in small quantities and manifest as:

- **tubercular syphilide** (syphilidum tuberculosum)
- **gummous syphilide** (syphilidum gummosum)
- **tertiary roseola** (roseola syphilitica tertiaria)

Tubercular syphilide is often located asymmetrically in the limited area of skin .Tubercules have hemispherical or flat form of brownish-red colour with bluish tinge, diametr which is 0,4-0,6 sm. Tubercules also have dense consistency, flat surface, and clear boundary. They have form, brownish-red color with a bluish tinge, diameter 0.4 - 0.6 cm, dense texture, clear borders, smooth surface.(Pic 66) . Tubercles (papillas) usually do not appear at the same time, but at certain intervals (jerkily), their number varies from a ten to a hundred or more. The tubercles exist for several months, then resolve, gradually dissolving ("dry way") or ulcerating. In dry resolution of the tubercles the *cicatricial atrophy* is formed. In case of ulceration of the tubercles, *ulcers of regular, rounded shape,* with steep, even (not digged out) edges are formed. These ulcers have serous-purulent-hemorrhagic masses at the bottom and a tightly elastic infiltrate both around and at the base.



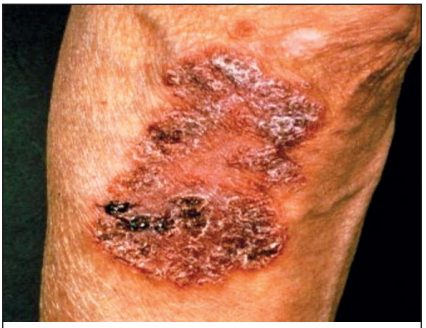
Pic 66

After ulcer healing, *sunken scars with a depigmented center and pigmented periphery remain.* On syphilitic scars, tubercles never appear again. Sensations of Tuberculous syphilis does not produce subjective feelings.

Varieties of nodular syphilide:

• *grouped nodular syphilide* - the tubercles are located in a bunch, with a layer of healthy skin between them. They appear with a time interval. That's why the tubercles are at different stages of evolution and as a result mosaic scars form.

• *serpiginous (creeping) nodular syphilide* –it's characterized by the eccentric spread of nodular syphilide in one direction with the comprehension of large areas. In these areas three zones are distinguished: the central areas - scars / cicatricial atrophy, the middle area - ulcerated tubercles, peripheral - fresh tubercles. (Pic 67)



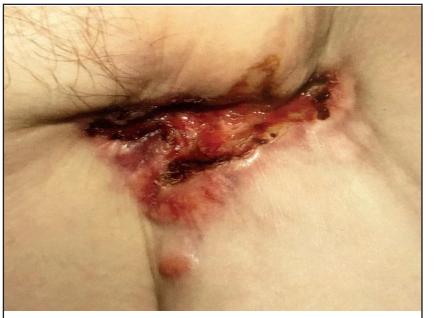
Pic 67

• *nodular syphilide by the site (or area)* - separate tubercles are not visible, a plaque with a diameter of 5-10 cm or more is formed. They are sharply protuberant (protruded) above the skin level, are of brownish-red color and dense consistency.

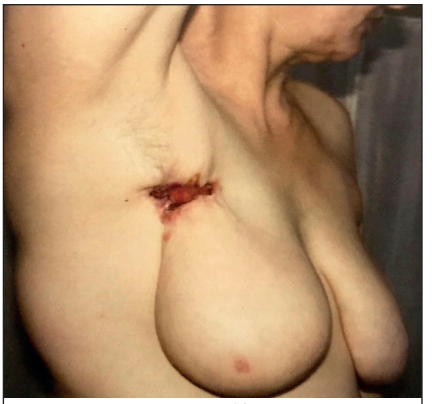
• *dwarf nodular syphilide* - grouped in small areas, dense dark red tubercles in 0.1-0.2 cm size.

Gummatous syphilide (syphiloma) on the skin is often located in the forehead, in extensor surface of forearms and lower legs. The number of gummas is counted in cells (more often one, less often several cells). *Gumma is a knot (or nod),* formed in subcutaneous fat, up

to 1 cm in size. It's reddish color, dense, painless, mobile, not joint with skin and underlying tissues. Gradually increasing to 2-3 cm or more, the knot (node) unites with all skin and underlying tissues, lose its mobility, the color acquires a brownish-bluish tint. In the center, the node softens, opens, releasing a sticky viscous liquid resembling gum-arabic (the name "gumma" is associated with it) and an *ulcer with dense sheer edges* is formed.



Pic 68



Pic 69

At the bottom of the ulcer a gummy rod of necrotic infiltrate is placed. After rejection of that rod the ulcer is filled with granulations and *an inverted stellar scar* is formed.(Pic 68,69) In less cases, gumma can resolve without the forming of an ulcer with the final formation of atrophic scar. This process usually lasts 3-4 months, sometimes it is accompanied by minor subjective sensations.

Varieties of gummosis syphilide (syphiloma):

• *solitary gumma* - is a solitary node, which is usually localized on the front surface of the lower leg.

• *fibrous (fibrotic) gumma* - periarticular nodularity, are placed more often around knee or elbow joints. While resolving, the periarticular gummas are reduced, flattened, the infiltrate is replaced by fibrous tissue. So, the woody density of the nodes is determined

by this peculiarity.

• *gummous syphilis by the site (or area).*

Tertiary roseola (Fournier's erythema) in tertiary syphilis occurs rarely.

The characteristic features are;

• limitation / poorness of rashes -macula

• large sizes

• configuration in the form of arcs, rings, garlands with a diameter of 5-15 cm

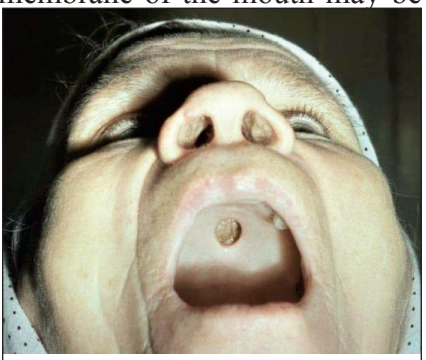
• pale pink color

• favorite localization - trunk, lower back, buttocks, hips

• symmetry

• chronic course

Mucosal lesions in tertiary syphilis are represented by gummous syphilis, diffuse gummous infiltration, tubercular (nodular) syphilis. Alike skin, syphilitic rashes on the mucous membranes are practically not contagious, but, being destructive rashes, they destroy the tissues in which they are located. It often leads to disfunction of organs. The mucous membrane of the mouth may be the only site of tertiary syphilis manifestation.



Pic 70

• **Gummatous syphilid of mucous membranes** - it's favorite localization: oral cavity (hard / soft palate, tongue), nasal cavity, oropharynx, larynx. (Pic 70). The node that appeared in these areas goes through all stages of the development of gum with the transition to the underlying tissues. It leads to hard destructive processes.

After the disintegration of gumma in the area of the hard palate, the underlying bone tissue becomes necrotic and sequeste-

red, *perforation* of the hard palate develops. As a result the communication of the oral cavity with the nasal cavity appears which leads to disturbances in food intake and speech function. **After the disintegration of gumma in the nasal cavity,** the nasal arch and tip of the nose fall in. So, the nose gets the shape of a *"saddle-shaped"* (sellar), *"lorenate form"* or *"goatish"* nose. When the soft palate and tongue are affected, cicatricial changes lead to a shortening of the soft palate, destruction of the small tongue (lingual) and deformation of the tongue. Scars in the throat area also lead to serious consequences.

• **Diffuse infiltration of the tongue** is a more hard form of the pathological process which overtakes the submucosal and muscle layer of the tongue. *The tongue is enlarged at first,* it's dense, inactive, the surface of the tongue is uneven (smooth sections are combined with transverse and extentional cracks). In the process of diffuse infiltration evolution, the *tongue becomes sclerotic,* it becomes compact and reduces in volume.

• **Nodular syphilide** occurs on the mucous membrane of the mouth less than gummous one, it is often localized on the mucous membrane of the lips, alveolar outgrowths, in soft and hard palate. Nodular syphilide can manifest on the mucous membranes as *isolated tubercles,* resolving with the forming of ulcers and focal scars, and in the form of extensive *tubercular infiltrates,* quickly ulcerating and scarring with characteristic scalloped outlines.

• **Lesions of internal organs and systems.**

In late syphilis (e.g. tertiary, cardiovascular syphilis, neurosyphilis), lesions of internal organs and systems are of organic, non-passing character and manifest both in the form of gummy processes in the tissues of different organs and in the form of specific lesions of the interstitial tissue of organs, which can be attributed to true (vera) visceral syphilis. Visceral syphilis has no specific signs and does not differ from the corresponding nosological for-

ms of non-syphilitic genesis. Among syphilitic visceropathies, the cardiovascular system (80% - from early and 90-94% - from late syphilitic visceropathies) and the liver (8.5 - 10% - from early and 4 - 6% - from late syphilitic visceropathies) is affected more often. Other internal organs (kidneys, lungs, stomach, intestines, endocrine glands) are affected extremely rarely - 1-2%.

Cardiovascular syphilis (A52.0) - specific damage of myocardium, aorta, coronary arteries; it appears as a result of the development of a toxic-infectious process at any stage of syphilis and manifests itself in the form of *myocarditis, aortitis.* Every fifth patient with syphilitic aortitis has a dangerous complication - an aortic aneurysm, the rupture of which often leads to instant death (mortality).

The liver is very sensitive to syphilitic infection. Specific liver damage can be observed even before the getting of positive serological reactions, and is manifested by yellowness of the sclera, with the subsequent development of hepatitis. In late syphilis, specific liver lesions develop in type the form of *focal gummous hepatitis, diffuse miliary gummous or infiltrative hepatitis and chronic hepatitis.*

The damage to bones and joints is a frequent manifestation of syphilitic infection. In late syphilis, periostitis, *osteitis, osteomyelitis, arthritis* (rarely) are possible. Joint lesions are rare in late syphilis, passes as polyarthritic synovitis and are accompanied by arthralgia, hyperthermia and general intoxication. The joints are swollen, the skin above them is hyperemic, active motions are limited. The knee, shoulder, elbow and ankle joints *(Clutton's joints)* are affected most commonly, the appearance of them (Clutton's joints) is associated with the activation of infection, passing latently. Clinically, Clutton's joints are manifested by pain, a spherical swelling of the joint, intra-articular effusion with a slight violation of the joint function. Two-sidedness of lesions is noted. In radiological (X-ray) examination changes in the joint are not detected.

Lesions of the nervous system – **neurosyphilis** (A52.1-A52.3) are conditionally divided into *early neurosyphilis* (up to 5 years from the time of infection) and *late neurosyphilis* (5 years after infection). The development of late neurosyphilis is connected with untimely beginning of specific therapy or with imperfect therapy, concurrent chronic infections, intoxication and traumas. Depending on the nature of the damage of the nervous tissue, neurosyphilis is divided into meningeal, meningovascular, parenchymatous, gummous. In the early stages of neurosyphilis, mainly meningial and meningovascular lesions of the nervous system (meninges and blood vessels) and syphilitic hydrocephalus are observed.

Meningeal neurosyphilis manifests itself as;

- acute generalized *syphilitic meningitis* (headache, rising of body, vomiting, photohobia, stiff neck)
- *basal spinal syphilitic meningoneuritis* (pain, atrophy usually of neck muscles, loss of sensitivity, weakening of tendon reflexes, spastic paraplegia)

Meningovascular neurosyphilis manifests as;

- *cerebrovascular neurosyphilis* (dizziness, headache, insomnia, memory loss, mood change, hemiparesis, hemiplegia, epilepsy, stroke)
- *spinal meningovascular neurosyphilis* (paresthesia), spastic weakness of lower limbs, loss of sensitivity, paraplegia, atrophy of muscles, impaired of sphincters function)

Degenerative lesions of nervous parenchyma (nerve cells, nerve fibers, glia) is considered as a result of specific inflammatory process (parenchymal neurosyphilis) and pressure of specific gummas on nervous tissue (gummy neurosyphilis). Degenerative lesion is predominantly observed in late neurosyphilis along with meningeal and meningovascular late manifestations.

Parenchymal neurosyphilis manifests itself as;

- *spinal cord* – parenchyma of back horn and roots of spinal cord (paresthesia, shooting pain, loss of sphicters function,

positive symptoms of Romberg and Argyll Robertson, hearing loss) are affected

- *progressive paralysis* – parenchyma of frontal, parietal lobes and ventricles of brain (irritability; forgetfulness; impair of concentration and headache are followed by emotional liability, memory, speech, thought disorders; behavior change until completely disintegration of personality)
- *atrophy of optic nerve* – it can be isolated symptom that causes blindness

Gummatous (diffuse) neurosyphilis manifests as cerebral or spinal meningeal neurosyphilis which are caused by brain and spinal cord compression by gummas, that proceed from pia mater. *Neurological picture* is characterized by diffuse symptoms coupled with headache and increased intracranial pressure. The symptoms of completely transverse lesion of spinal cord can develop in gummas of spinal cord.

Differential diagnosis of syphilides of tertiary syphilis;

Manifestations on skin

- tubercular (nodular) syphilide
- *tuberculous lupus erythematosus* - tubercles (lupomas) are flat, slightly protrude above the level of healthy skin, soft consistency, are of brick-red color, are resolved by forming a scar. Positive tests of sound (zond) and apple jelly are characteristic, serological tests are negative.
- *Cutaneous leishmaniasis* – is characterized by yellowish-pink tubercles, pasty or dense consistency, the presence of lymphangitis in the form of a dense band along the periphery of the foci. In microscopy Borovsky's bodies (corpuscles) are detected, serological tests are negative.
- gummous syphilid
- *scrofuloderm* — is characterized by nodes of soft consistency; when completely softened is the blant-edged, digged ulcers are formed; at the bottom of the ulcer there are sluggish granulati-

ons; the ulcers are liquid, purulent, of ocher-yellow color. The formed scars have bridge-like skin intersections, on the periphery – skin nipples (dermal papillaes) are placed. Positive tuberculin tests, serological tests are negative.

- *Indurative erythema (eritema induratum)* - nodes are painful, multiple, located symmetrically on the extensor surface of the lower legs, tuberculin tests are positive serological tests are negative.
- *skin cancer* - ulcers of irregular shape, with dense inverted edges, blant-edged and easily bleeding bottom, serological tests are negative.

Manifestations on the mucous membranes

• *miliary ulcerative tuberculosis* - painful ulcers with soft, corroded, digged edges, easily bleeding, bottom is covered with papillary growths, tuberculin test are positive, serological tests are negative.

E. CONGENITAL SYPHILIS.

A50 Congenital (in-born) syphilis (syphilis congenita) – develops as a result of intra-uterine infection of the fetus through the placenta from a mother with syphilis.

The source of infection is *a mother with syphilis.* Mothers usually transmit the infection to the fetus transplacentally and possibly during childbirth through contact with infectious lesions on the genitals.

The mother transfer transplacental infection to her child

- through the umbilical vein
- through the lymph nodes of the umbilical vessels
- with a mother's blood flow through the placenta damaged by treponem toxins (a healthy placenta is impenetrable for T. pallidum.

Penetrating the placenta, T. pallidum causes its edema, hyperplasia and necrotic changes. The mass of the placenta increases by 2 times (is doubled) and in comparison with the mass of the fetus is 1: 3 (normal 1: 6).

The disease can manifest itself in various periods of life: in prenatal, shortly after birth, after a considerable (long) time after birth.

Depending on this (cause specific) such forms of syphilis are distinguished:

• fetal syphilis

• *early congenital (inborn) syphilis (syphilis congenital praecox)* A50.0-A50.2, it manifests itself in children under the age of 2 years

• *late congenital syphilis (syphilis congenital tarda) A50.3-A50.7* is manifested in children older than 2 years.

Fetal, early and late congenital syphilis can occur both with clinical manifestations (manifest-A.50.0; A50.3-A50.5), and without them (latent - A50.1, A50.2, A.50.6, A50.7).

Syphilis of the fetus. In the first months of pregnancy, the fetus is not affected, because T. pallidum penetrates the fetus only with the development of placental blood circulation, not earlier than 5 months of pregnancy. Syphilis of the fetus usually leads to fetal death of the fetus and dead birth at 6-7 months of pregnancy (macerated fetus).

Specific clinical features of fetal syphilis:

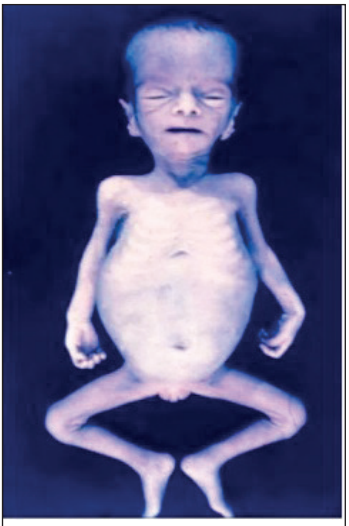
• fetus is of small size and mass with facts of cachexia.

• the skin is macerated, exfoliates by layers, the folds on skin, especially on the face folds of " aged wrinkles" type are formed due to hypotrophy of the subcutaneous tissue.

• extremities are cyanotic, cold. (Pic 71)

• voice is weak, thin, newborns cannot suckle and scream

• damage of internal organs (liver, spleen, lungs) is observed, the organs



Pic 71

increase and condense due to the development of diffuse inflamma-tory infiltration and subsequent proliferation of connective tissue.

• osteochondritis and osteoperiostitis - bone lesions are detected radiological at 5-6 months of fetal development and are the most frequent and reliable feature of fetal syphilis.

A50.0 Early congenital (inborn) syphilis (manifest) can first manifest itself both in infancy (0-12 months), it's *syphilis of infants,* and at the age of 1-2 years - *syphilis of early childhood.* Sometimes a baby is already born with features of syphilis.

The pathognomic symptoms of manifest early congenital syphilis are following:

• syphilitic pemphigus of newborns (pemphigus neonatorum syphiliticus), syn. syphilitic pemphigoid

• Hochsinger diffuse skin infiltration (infiltration diffuses Hochsinger)

• syphilitic rhinitis (rhinitis syphilitica)

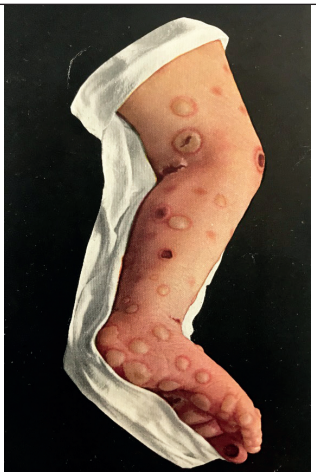
•osteochondritis of the long tubular bones of Wegener (osteochondritis syphilitica).

Syphilitic pemphigus

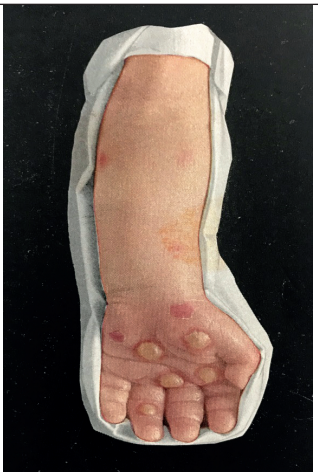
- may exist already at birth or appears in the first days of life
- is localized on the skin of palms, plantas, flexors of the extremities, rarely in other areas
- is characterized *by strained blisters* (bullas) with serous, serous-purulent and serous-hemorrhagic contents. These blisters can be of a pea size and more, are surrounded by a lilac-tinted corolla; when opening the blisters, erosion and crusts form; in the contents of the *blisters T. pallidum is found* (Pic 72,73.74).

Hochsinger Diffuse Skin Infiltration

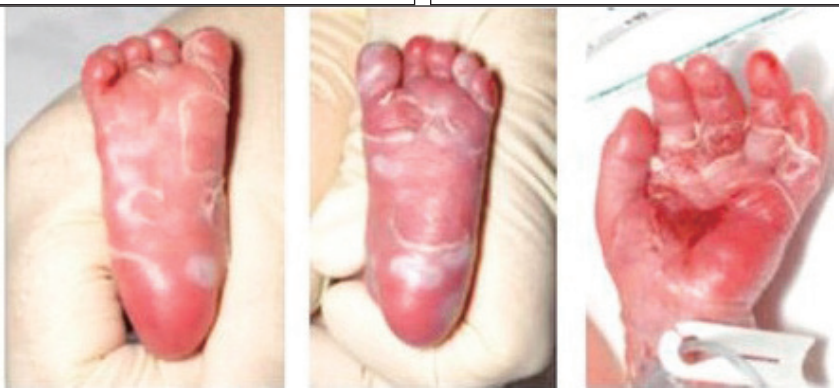
- occurs more often at 8-10 weeks of a child's life
- is localized on the skin of the palms, plantas, face, scalp, `buttocks.



Pic 72

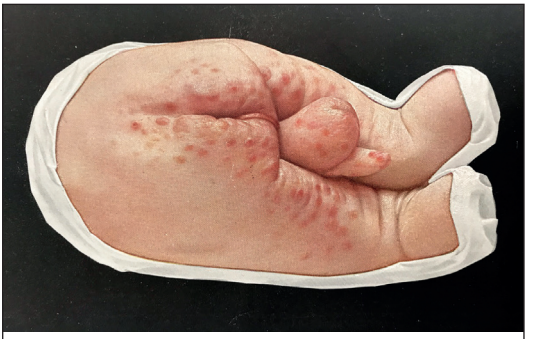


Pic 73

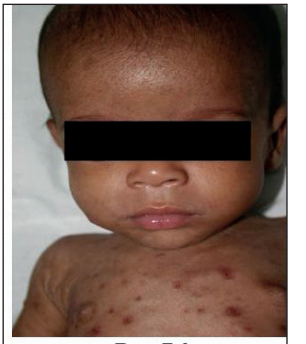


Pic 74

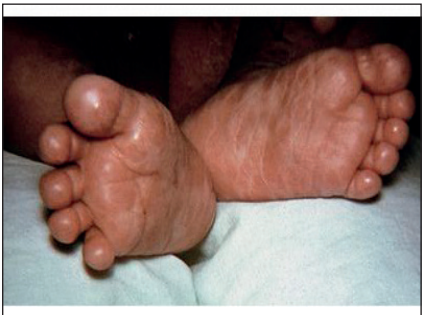
- the process begins with focal erythema, on this background infiltration develops; the skin acquires a cyanotic- florid shade, becomes strained, loses elasticity, easily crackes with the formation of superficial and deep wrinkles , which often lead to lifelong scars. E.g. the thin radiant scars of Robinson-Fournier on the chin, lips and in the corners of the mouth, as a result of the resolving of diffuse papular infiltration in these areas of the face in early congenital syphilis. (Pic 75,76,77)



Pic 75



Pic 76



Pic 77

Syphilitic rhinitis

- often occurs in fetal period and manifests itself from the first days of life, it can be often the only and earliest manifestation of syphilis in infants

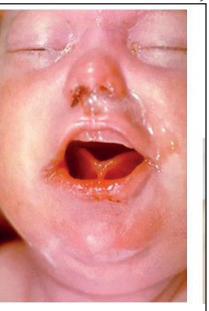
- 3 stages of syphilitic rhinitis are characteristic.

- *dry*- manifested by swelling of the nasal mucosa and respiratory difficulty

- *catarrhal*- characterized by discharge from the nose of the mucous secretion, and subsequently of purulent-bloody secretion.

- *ulcerative* - manifested by ulceration of the nasal mucosa, pletorical fetid discharge, the formation of crusts, which leads to the closure of the nasal passages by secret and causes a hissing sniffling. The baby cannot breathe through the nose, begins to breathe through the mouth and is forced to break away from the chest when breast-feeding.(Pic 78)

- in the nasal discharge *T.pallidum is found*

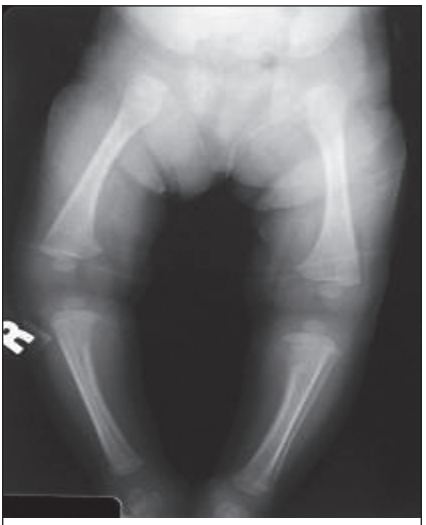


Pic 78

- transfer of the pathological process to the bone-cartilaginous part of the nasal septum leads to its destruction and to deformation of the nose *("saddlelike", "goatish", "lornet-like).*

Osteochondritis of long tubular bones - is one of the main, and often the only sign of early congenital syphilis. (Pic 79) Syphilitic osteochondritis is not an inflammatory process, but it's the result of excessive calcinosis in cartilage cells.

- it is formed from 5 months of fetal life and lasts up to 1 year after birth;
- long tubular bones are affected, most often in the upper extremeties; the pathological process is localized between the epyphysis and the diaphysis.
- radiologically 3 stages of osteochondritis are distinguished:



Pic 79

I - the presence of *a light, slightly serrated strip with a width of 2 mm* (normal - 0.5 mm) between the epyphysis and the diaphysis in the area of preliminary calcinosis.

II - the presence of *alight, expanded calcinosis zone* (up to 2-4 mm) with serrations facing the epyphysis.

III - the presence of *a dark strip of rarefaction (up to 2-4 mm wide),* between the epyphysis and the diaphysis, representing a newly formed granulation tissue under the cartilaginous layer.

In the future, as a result of necrosis of granulation tissue, the epyphisis can separate from the diaphysis, as a result of which an intraepiphysial fracture occurs. It is false paralysis-like state, *Parro pseudo-paralysis.* Motion activity in the extremities is broken, but

nerve conduction is kept, as a result of which the affected extremity is completely motionless. Child's attempts to passive motion are accompanied by a cry of the child due to pain, because sensitivity is preserved. The child is in a forced position of the extremities: the lower extremity is bent at the hip (thigh joint) and knee joints, the upper extremity hangs like a whip. When the wrist joints are diseased, the hands are bent like a "seal legs".

Osteochondritis are often accompanied by *periostitis and osteoperiostitis* of long tubular bones, sometimes of cranial (scull) bones ("Olympic forehead" – unevenly protruding frontal and parietal tubercles, "tower forehead", acrocephalic skull, dolichocephalic skull, microcephalic skull, hydrocephalic skull, skull of buttock form - protruding frontal tubers with the groove located between them).

Dactylitisis is one of the forms of specific bone changes in infants. It is a lesion of the proximal, rarely middle phalanges of the fingers, which is manifested by a cylindrical or spindle-shaped thickening of the bone.

In early congenital syphilis, except pathognomonic manifestations, *typical manifestations* are noted, that occur not only in congenital, but also in early acquired syphilis;

- papular syphilid on the skin and mucous membranes
- roseolous syphilid occur (rarely)
- syphilitic alopecia
- syphilitic hoarseness (raucedo)
- visceral injury, i.e. injury of internal organs (specific hepatitis, glomerulonephritis, pneumonia, myocarditis, endo- and pericarditis, orchitis, etc.)
- injury of the nervous system (meningitis, meningoencephalitis, hydrocephalus). An early symptom of hydrocephalus *is Systo symptom* - the motiveless of child crying during the day and night.
- eye damage (chorioretinitis, optic atrophy). Sometimes chorioretinitis is the only manifestation of congenital syphilis. In general *4 types of chorioretinitis* are distinguished. In the first type, in the

FO (fundus oculi) in the equatorial region pigmented lesions focuses are noted, vision affected little. The second type is characterized by a combination of yellowish-red and depigmented areas along the periphery of the FO – it's a symptom of *"salt and pepper."* In the third type, a change in the choroid and injury of the vessels of the eye retina are noted, vision *is often affected.* The fourth type is manifested by secondary pigmental degeneration of eye retina.

A50.3-A50.5 Late congenital (manifest) syphilis is diagnosed in children older than 2 years, usually aged 7-14 years. Late congenital syphilis is not infectious. Most characteristic features - reliable (pathognomonic), probable signs and dystrophy.

Reliable signs of late congenital syphilis - *Hutchinson triad (Hutchinsoni trias)*

• *parenchymal keratitis,* more often bilateral, is manifested by photophobia, tear-secretion, blepharospasm with diffuse / focal clouding of the cornea (aglia).

• *labyrinthine deafness,* often bilateral, manifests itself as deafness, which is preceded by dizziness, ringing and tinnitus.

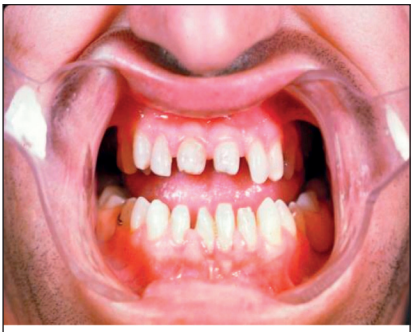
• *Hutchinson teeth* - the upper middle incisors are barrel-shaped or in the form of a screwdriver, with a wider surface at the level of the tooth neck and a narrow cutting edge that has a half-lunar hollow. The symptom is considered reliable if a difference in the width of the neck and cutting surface is no less than 2 mm. The signs of the Hutchinson triads, mentioned above, are rarely found simultaneously; more often one of them is noted. (Pic 80)

Plausible features of late congenital syphilis *(require to be proved)*

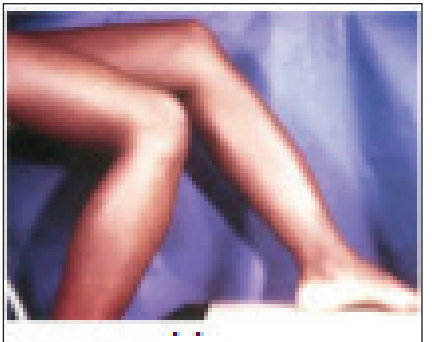
• *Sword-shaped lower legs* - symmetric changes of the shin-bones in the form of a curvature of the lower legs anteriorly on the type of sword blade. (Pic 81)

• chorioretinitis

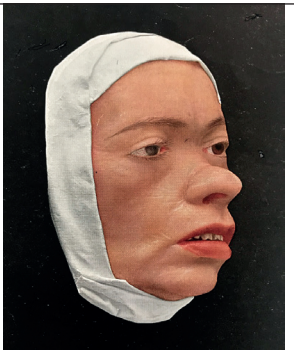
• deformations of the nose (saddle, goaty, in the form lorgnette) (Pic 82,83)



Şəkil 80



Şəkıl 81



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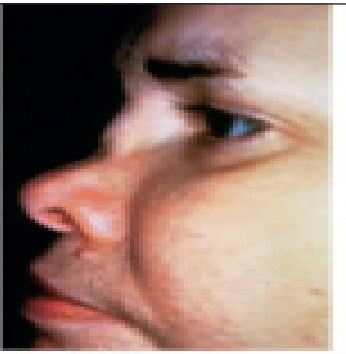


Şəkil 83

• *Robinson-Fournier radiant scars around mouth.*

• *buttock-shaped skull* (frontal and parietal tubers are scaled up and protuberant and, they are separated by a longitudinal cavern).

• *Clutton's joints* - syphilitic gonitis passes as chronic synovitis of the knee joints without affecting of cartilage and epyphysis. The joint functions are not disordered, pain and temperature increase is not observed.

• *injury to the nervous system - juvenile neurosyphilis* (hemiparesis, hemiplegia, speech disorders, dementia, cerebral palsy, Jackson's epilepsy - convulsive twitching of one extremity and half of the face). Progressive paralysis, spinal cord, encephalitis, meningitis, polyneuropathy are rarely observed.

Dystrophy in late congenital syphiliss (is found in many chronic infectious diseases)

• *symptom of Austidian) / Igumenakis* - thickening of the sternal end of the right clavicle (Pic 84- at the picture shown brachial end of left clavicle)

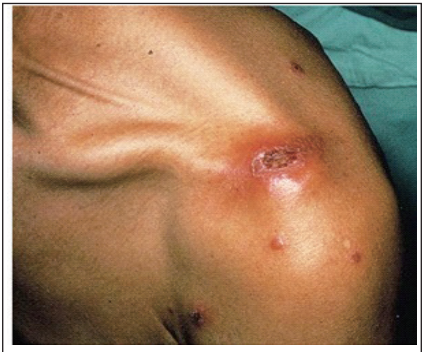
• *dystrophy of the cranial bones* ("Parrot Olympic forehead")

• *high gothic / lanced palate.*

• *axiphoidia* - absence of the xiphoid appendix of the metasternum

• *Dubois-Gissard symptom* - infantile little finger

• *Gachet diastema* - widely spaced upper incisors



Şəkil 84

• *Carabelli tubercle* – the fifth additional tubercle on the chewing surface of the first molar of the upper jaw.

• *additional dental tubercles* - usually surround by dense ring the apex of the lower molars, giving them the shape of a "mulberry".

• *bulldog lower jaw* - shortening of the upper jaw due to syphilitic rhinitis, on background of which the lower jaw looks proportionally larger.

In late congenital syphilis manifestations characteristic of late acquired syphilis are also noted:

• *nodular and gummy syphilids* on the skin and mucous membranes

• *injury of internal organs:* liver, spleen, cardiovascular system

• *lesions of the skeletal system* (periostitis, osteoperiostitis, osteomyelitis, osteosclerosis).

Differential diagnosis of syphilitic pemphigus:

• *epidemic pemphigus of newborns* - in terms of arising and appearance of the epidemic pemphigus of newborns is similar to syphilitic pemphigus. The ordinary localization in the trunk, very rarely in the palms and soles, the detection in the blisters of Staphylococcus spp. are distinctive signs of blisters in epidemic pemphigus. Negative serological tests and the absence of specific clinical and serological symptoms in the mother are also distinctive signs of blisters in epidemic pemphigus.

F. DIAGNOSTICS OF SYPHILIS.

The diagnose of syphilis is based on:
- clinical anamnestic datas
- laboratory test results
- results of hardware (technical) research methods (radiography, ultrasound scan, EEG (electroencephalography), ECG (electrocardiogram), echocardiography, CT scan, MRI (Magnetic resonance imaging).

Laboratory diagnostics of syphilis is based on direct and indirect serological diagnostics methods. **The direct diagnostics** of syphilis is used to identify the causative agent of disease – T. pallidum or its genetic material.

The research materials are following:
- tissue fluid (serum) from the surface of erosive / ulcerative and weeping syphilides
- contents of blisters
- nasal discharge in specific rhinitis
- punctate from lymph nodes
- cerebrospinal fluid - CSF (cerebrospinal fluid)
- amniotic fluid.

The direct diagnosis of syphilis is an absolute criterion for diagnostics and is carried out by the following methods:

- ***dark-field microscopy (DFM)***- microscopy of native drugs in a dark field of vision. The study is based on the Tyndall effe-ct, when inside lighting the studied objects diffract the light falling on them in all directions and are seen clearly in a mic-roscope with a dark-field condenser. Pale Treponema appears as moving spiral or a thin dotted line with a silver tint.
- ***direct immunofluorescence (DIF)*** - is carried out under an immunofluorescence microscope, where swabbings treated with specific to T. pallidum monoclonal antibodies labeled with fluorescin are viewed. A specific bright green glow of pale treponemas is observed.
- ***polymerase chain reaction (PCR)*** - identification of T. pallidum DNA (deoxyribonucleic acid) . The method is based on the principle of natural replication (self-reproduction) and amplification (reproduction) of certain sections of T. pallidum DNA under the influence of the DNA polymerase enzyme (ferment) in process of repeated temperature cycles. The synthesized amplicons are detected by *method of gel electrophoresis in the presence of a fluorescent coloring material which selectively connects with the molecules of pathogenic nucleic acid of infecting agent.*

Direct methods of the syphilis diagnostics are used to confirm the manifest forms of acquired and congenital syphilis. *In the absence of clinical manifestations of the disease, using direct diagnostic methods for syphilis is almost impossible*

Indirect serological laboratory methods are widely used for syphilis testing.

The research material:

- blood
- amniotic fluid

• cerebrospinal fluid - CSF (cerebrospinal fluid)

Serological diagnostics of syphilis is aimed in *detecting of antibodies* associated with syphilitic infection in the blood, in cerebrospinal or amniotic fluid of patients. Serological diagnostics is an extremely valuable method for the diagnosis of syphilis and confirms both *manifest and latent forms of syphilis.*

The first serological reaction for the diagnosis of syphilis was proposed by A. Wasserman, A. Neusser, C. Bruck in 1906. These scientists used the phenomenon of complement binding reaction developed (worked out) by French scientists I. Border, O. Gengon (1901). The essence of the phenomenon of I. Border, O. Gengon lies in the ability of the patient's serosity to produce antibodies that are strictly specific to the foreign substance which has entered the body - the antigen, with the subsequent forming of the antigen-antibody complex and sorbing of complement. Indication of mentioned complexes occurs by means of a hemolytic system (sheep erythrocytes and rabbit hemolytic serum), which are added to the reaction. If the test result is positive, the precipitate is visible in the test tube; in the case of a negative answer, in the test tube hemolysis is noted. This reaction was named after A. Wasserman - the Wasserman reaction (RW). In 2006, after 100 years from the day this reaction was staged, an international farewell to RW took place.

Currently, dermatovenerologists have at their disposal a whole options of serological tests with different sensitivity, specificity and economically reasonable. Serological tests used for syphilis diagnostics are divided into non-treponemal tests **(NTT)** and treponemal ones **(TT).**

Nontreponemal serological tests (NTTs) are performed with an antigen of non-treponemal origin - *cardiolipin-cholesterol-lecithin complex.* The following NTTs are used to diagnose the syphilis:

- ***MPR - microprecipitation reaction***
- ***RPR - reaction of fast plasma reagins / RapidPlasmaReagins***

• ***VDRL-Venereal disease research laboratory test***

The principle of serological NTTs is following: when a patient's plasma / blood serum containing specific antibodies is combined with a non-treponemal antigen, an antigen-antibody complex is formed. It manifests itself by aggregation according to the type of flocs, precipitates, agglutinates.

The result is evaluated macroscopically / visually (RMP / RPR) and microscopically (VDRL) 4+, 3 +, 2 + in proportion to the size of the formed aggregates. NTT is carried out in qualitative and quantitative versions (the titer of antibodies is determined).

Serological NTTs are used for:

- screening of inhabitant for syphilis
- determination of the activity of syphilitic infection (by the height of the antibody titer)
- monitoring the effectiveness of antisyphilitic therapy (by antibodytiter).

NOTE:

- serological NTTs become positive from 6-7 weeks of illness or 2-3 weeks after the appearance of hard chancre;
- serological NTTs in late forms of syphilis are usually negative, because precipitins are the first to be eliminated from the body during a prolonged course of syphilitic infection.

Treponemal serological tests (TT) are performed with a specific treponemal antigen - a pathogenic pale treponema, both **whole-cell** and in the form of **recombinant** proteins synthesized by genetic engineering method or peptides obtained by fabricated chemical synthesis.

The following serological TTs are used to diagnose syphilis

- TPI test - reaction of pale treponemas immobilization/ Treponema pallidum immobilization test, worked out by R. Nelson, M. Mayer (1949).The principle of TPI is that when the patient's blood serum containing specific antibodies – immobilizins is joined with an antigen - a suspension of live pathogenic pale treponema, the latter lose their mobility.The test is estimated according the number of motionless treponemas under dark-field microscopy. When immobilizing more than 50% of pale treponemas, the test is positive, 30-50%- test is weakly positive, 20-30% is doubtful, less than 20% is negative.
- FTA–immune fluorescence reaction / Fluorescent treponemal antibody, is worked out by R. Weller, A. Coons (1954). The FTA principle is that when a patient's blood serum containing specific antibodies is combined with an antigen (it's a suspension of killed pathogenic treponemas) and with fluorescein-labeled anti-human immunoglobulins, an antigen-antibody complex is formed. In this complex the treponems colored with fluorescein turn yellowish-greenish become visible by fluorescence microscopy. The test is evaluated by the intensity of the glow 4+, 3+, 2+.
- ***TPHA-passive hemagglutination reaction / Treponema pallidum hemagglutination assay,*** worked out by T. Rathlev (1965).

The principle of RPHA / TPHA is that when the patient's blood serum containing specific antibodies is connected to the microtiter plates with the antigen sensibilized by pale treponema erythrocytes of animals, *erythrocytes agglutination is observed.* **The test is evaluated visually:**

"4+" - red blood cells (erythrocites) evenly line the entire surface of the cavity (sharply positive)

"3+" - part of the red blood cells slides to the center of the cavity (positive)

"2+" - red blood cells form a cover-up in a small area of the cavity

"1+" and "-" - red blood cells at the bottom of the hole form a loose precipitate or localized in form of "button".

- ***ELISA - enzyme immunoassay / Enzyme-linked immunosorbent assay,*** worked out by E. Engvall, S. Avrames (1971).

The principle of ELISA is that the antigen - a pale treponema, fixed in the cavities of a hard-phase bearer (plate) when connected to the patient's blood serum containing specific antibodies and to antibodies to human immunoglobulins labeled with enzymes (peroxidase or alkaline phosphatase) *causes color reaction. ELISA* creates possibility of differentiated and total determination of IgM and IgG antibodies to T.pallidum.

In the differentiated determination of IgM and IgG antibodies to T. pallidum by ELISA, in the cavities of the solid-phase carrier the antibodies to human immunoglobulins — IgM, IgG and IgA are fixed . When combined with the patient's blood serum, bearer's antibodies recognize antibodies of a similar class of serum and form an antibody-specific immunoglobulin complex.

After the antigen a conjugate pale treponema labeled with an enzyme is introduced into the reaction, staining occurs (in the case of the presence of specific antibodies in the patient's blood serum). *The test is evaluated spectrophotometrically* with the automatic output of digital datas - positivity coefficient (CP).

- ***IB - immunoblotting*** is a variant of ELISA, it also allows the differentiated and total determination of IgM and IgG antibodies to T. pallidum.

When setting up IB as antigens, Tre15, Tr17, Tr47, Tr44, and TmpA treponem proteins are used, which have high diagnostic importance for syphilis. These proteins are got while separation of treponemal proteins during T. pallidum electrophoresis.

The IB principle is that antigens - recombinant analogs of the Tre15, Tr17, Tr47, Tr47, Tr44, TmpA treponem proteins, applied in the form of transversal stripes (blots) onto test strips are treated

with the test serum and conjugate – goat antibodies to IgM / IgG human labeled with enzymes or radioactive substances. In the presence of specific antibodies to T. pallidum in the patient's blood serum, antigen-antibody complexes are formed. They *are detected by the color reaction in the form of colored bands in the corresponding zones of the strip.* The test is evaluated by coloration, the intensity of which is proportional to the content of antibodies in the analyzed test.:

Serological TT is used for:
- screening of inhabitant for syphilis
- confirmation of positive NTT results

Note:
- FTA and ELISA become positive from the 3rd week of the disease and have been remained positive after the full therapy for a long time
- TRHA and TPI become positive from the 7-8th week of the disease and remain positive for many years after the full therapy.
- IgM appear on the 2-4th week after infecting and disappear in untreated patients approximately in 18 months, in early treated syphilis – in 3-6 months, in late treated syphilis – in 12 months.
- IgG usually appears on the 4th week after infecting, reaches, as a rule, higher titers than IgM and can be kept for a long time, even after the clinical recovery of patients.

To verify the diagnose of neurosyphilis, a study of **cerebrospinal fluid (CSF)** is carried out. While investigating CSF defines;
- **cytosis** - qualitative and quantitative composition of cellular elements in 1 mm3 of CSF
- **protein level**
- **results of serological tests** with CSF (FTA , ELISA,

TRHA, TPI, IB)

NOTE:

• *normal* CSF is transparent and colorless, it's relative density 1006-1008, pH 7.4-7.6; contains not more than 5-8 cells in 1 mm3 (lymphocytes) and not more than 0.45 g / l of protein; serological reactions to syphilis are negative.

• *pathological changes* in the CSF are evaluated by one or two indicators:

- number of cells more than 5-8 in 1mm3
- protein level more than 0.45 g / l
- the presence in 1 mm3 of 5 to 10 cells indicates functional changes, more than 10 cells indicates organic disorders of the nervous system.

G. SYPHILIS TREATMENT:

Depending on the purpose of the intended antisyphilitic therapy, the following treatment methods of syphilis are distinguished:

- ***specific treatment*** - carried out in order to cure all persons with a confirmed diagnosis of syphilis;
- ***preventive treatment*** - is carried out with the aim of preventing syphilis to persons without clinical and serological manifestations of syphilis who were in close household or sexual contact with patients with early syphilis (if no more than 2 months have passed from the moment of contact);
- ***prophylactic treatment*** - carried out with the aim of preventing congenital syphilis, it's carried out
  - to pregnant women who have received specific therapy for syphilis before or during pregnancy
  - newborns born without clinical and serological manifestations of syphilis from mother untreated or inadequately treated during pregnancy.

.• ***testing treatment (ex juvantibus)*** – is carried out to persons with suspected specific damage to the internal organs, nervous system or musculoskeletal system if confirming the diagnosis of syphilis with serological or clinical indicators is not possible.

Syphilis is treated with antibacterial drugs.

Penicillins

• durant drugs

- ***retarpen / extensillin (benzatinbenzylpenicillin)*** - 2.4 million units. I/ M, 1 time in 7 days, №1-3.
- ***bicillin-1 (dibenzylethylenediamine sol (sulphate) of benzylpenicillin)*** - 2.4 million units. I/ M, 1 time in 5 days №3-6 (contraindicated in children under 2 years old)
- ***bicillin-3 (dibenzylethylenediamine, novocaine and sodium salt(or sulphate) of benzylpenicillin in a ratio of 1: 1: 1)*** - 1.8 million units. I/ M, 2 times a week № 2-10 (contraindicated in children under 2 years old)
- ***bicillin-5 (dibenzylethylenediamine and novocaine-salt(orsulphate) of benzylpenicillin in a ratio of 4: 1)*** - 1.5 million units. I/ M, 2 times a week № 2-10 (contraindicated in children under 2 years old).

• medium durability

- ***benzylpenicillin novocaine salt sulphate*** - 600 thousand units. I/ M, 2 times a day, daily, for 7-20 days
- ***procain benzylpenicillin 600 thousand units*** - 1.2 million units I/ M, 1 time per day, daily №. 7-20.

• water soluble

- ***benzylpenicillin crystalline sodium salt*** - 1 million units

v / m, every 4 hours (6 times a day), daily, for 14-28 days

• semi-synthetic
  - ***ampicillin sodium salt(sulphate)*** 1 million units. in / m, 4 times a day (every 6 hours), daily for 10-28 days
  - ***oxacillin sodium salt sulphate*** 1 million units in / m, 4 times a day (every 6 hours), daily for 10-28 days.

Cephalosporins:
• ***ceftriaxone*** 0.5-1.0 v / m, 1 time per day, daily № 5-20

Tetracyclines:
• ***doxycycline*** 0.1 by mouth (**per os**), 2 times a day, daily for 10-30 days (contraindicated for pregnant women, children under 8 years old).

Macrolides:
• ***erythromycin*** 0.5 by mouth, 4 times a day, daily for 10-30 days

NOTE:
• **the drug of choice (first line drug) is benzylpenicillin**
• in case of penicillin intolerance, **reserve preparations are used - alternative drugs** *(ceftriaxone, doxycycline, erythromycin, ampicillin, oxacillin)*
• treatment of patients with late forms of syphilis is carried out in two courses with a break between courses of 2 weeks.
• treatment of patients with neurosyphilis is carried out according to one of the following methods:
  - a single dose of benzylpenicillin crystalline sodium salt of 10-12 million units. Dissolved in 400 ml of isotonic sodium chloride solution and injected intravenously for 1.5-2 hours 2r / day daily. Solutions are used immediately after preparation for 14-20 days.

- a single dose of benzylpenicillin crystalline sodium salt of 2-4 million units. diluted in 10 ml of isotonic sodium chloride solution and injected intravenously, slowly for 3-5 minutes into the ulnar vein (subject to the possibility of installing a catheter) 6 r / day daily for 14-20 days
- to prevent the aggravation reaction (in the form of the appearance or aggravation of neurological symptoms) in the first 3 days of penicillin therapy, it is recommended to take prednisolone in a daily dose of 90-60-30 mg (once in the morning)

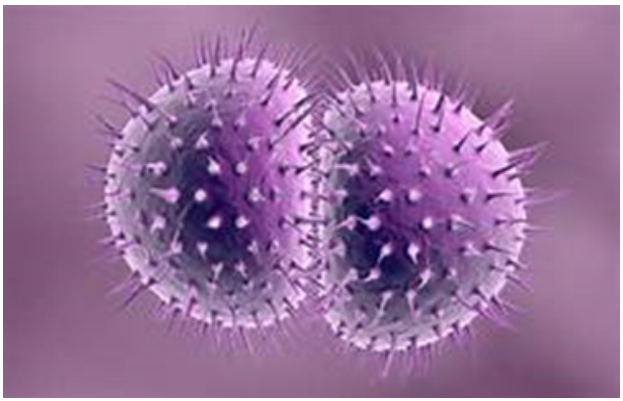
• treatment of children with syphilis is carried out in adult mode in the following doses:
- benzylpenicillin crystalline sodium salt at the rate of 100 thousand units / kg / day - for children up to 6 months, 75 thousand units / kg / day - for children from 6 months to 1 year, 50 thousand units / kg / day - for children over 1 year old
- procain benzylpenicillin and benzylpenicillinnovocaine salt at the rate of 50 thousand units / kg / day
- ceftriaxone at the rate of 50 mg / kg / day - for children up to 2 months, 80 mg / kg / day - for children from 2 months to 12 years.

• in the treatment of patients with secondary syphilis, Jarisch-Lukashevich-Herxheimer type reaction (exacerbation) is noted. The reaction occurs on the first day of antibiotic treatment, several hours after the first injection or internal administration of the drug. It is characterized by a sharp rise of temperature (up to 40 ° C), chills, increased brightness of syphilis. The reaction is due to intoxication of the body due to the death of pale treponemas.

GONOCOCCAL INFECTION (GI)

Causative organism: Neisseria gonorrhoeae. (Pic 1)

It is a Gram-negative intracellular diplococcus , which infects the mucosal surfaces of the human genital tract (urethra, endocervix, rectum), pharynx and conjunctiva. It is transmitted by direct inoculation of infected secretions from one mucous membrane to another. Up to 50% of infected women and 10% of infected men are asymptomatic. GI is the most common sexually transmitted disease in high-income countries. It occurs in 20% of men and 40% of women.



Pic 1

The word gonorrhea derives from an old Greek word meaning 'flow of seed [semen]'.

Ultrastructure

It appears as 3 layered envelope cytoplasm. Pili (Pilus) or fimbriae are present on the surfaces of virulent gonococci of colonial types 1 and 2. These pili are required for successful attachment of the organism to the host cells.

There are 3 major membrane proteins (PI, II and III) of which PI is the most abundant.

The outer membrane contains, like other gram-negative bac-

teria, lipopolysaccharide which has an endotoxic activity and is a target for bactericidal action of antibody and complement.

The existence of capsule is uncertain.

It is rapidly destroyed outside the body by dryness, heat (42C), weak antiseptics (soap and H2O) and human saliva.

L Form (Lister institute) alteration in the morphology of organism (failure of synthesis of wall) which may arise spontaneously in 20% of infected subjects or may be induced by repeated subculture in media containing penicillin. L forms are insensitive to penicillin, but are sensitive to tetracycline, erythromycin and aminoglycosides.

GI has a predilection for columnar epithelium, while transitional and stratified squamous epithelium are more resistant to the organism. So, bladder, upper urinary tract, preputial sac, vulva, vagina and uterus are less often involved.

Virulence of Neisseria gonorrhea depends on:

(A) Pili.

(B) Lipopolysaccharide (of the membrane) endotoxin activity .

(C) proteases – inhibition of IgA secretion.

Site of involvement

* In men: the urethra, littres, Cowpers glands, prostate, rectum, seminal vesicles and epididymis.
* In female: skenes and Bartholin's gland, part of urethra and urethral glands, cervix and fallopian tubes.

Mode of infection

It nearly always results from sexual contact with infected persons, either in heterosexual, homosexual or orogenital sexual relations.

Accidental non-venereal infection from towels or lavatory seats can occur but rare.

In newly born, infection may be transmitted from maternal passages during birth in infected women.

The incubation period is 2–14 days, with most symptoms in males occur between 2 and 5 days.

Classification

Currently using the following classification of GI.

1-Fresh GI (to 2 months)

A-Acute GI .

B- Subacute GI .

C- Asymptomatic GI .

2-Chronic GI (More than 2 months or it is not known what time it is.)

3- Gonococcus carriage

A54.0 Gonococcal infection (GI) of the lower parts of the genitourinary tract without abscessing of periurethral and adnexal glands.

Urethritis

Cystitis

Vulvovaginitis

Cervicitis

A 54.1 Gonococcal infection(GI) of the lower parts of the genitourinary tract with abscessing of periurethral and adnexal glands.

Gonococcal abscess of Bartholin's glands.

A 54.2 Gonococcal pelvioperitonitis and other gonococcal infection (GI) of the genitourethral organs.

Epididymitis

Orchitis

Prostatitis

Pelvic inflammatory disease in women

A 54.3 Gonococcal eye infection.

Gonococcal :

Conjuntivitis

Iridocyclitis

Gonococcal ophthalmia of the newborn

A 54.4 Gonococcal infection(GI) of the musculoskeletal system.

Gonococcal :

Arthritis
Bursitis
Osteomyelitis
Synovitis
Tenosynovitis

A54.5 Gonococcal pharyngitis

A 54.6 Gonococcal infection(GI) of the anorectal region.

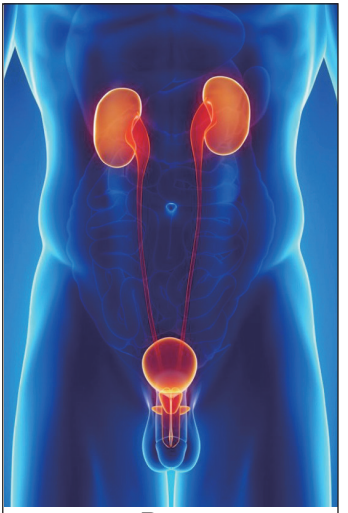
A 54.8 Other gonococcal infections(GI) :

brain abscesses
endocarditis
meningitis
myocarditis
pericarditis
peritonitis
pneumonia
sepsis
skin lesions.

Clinical features

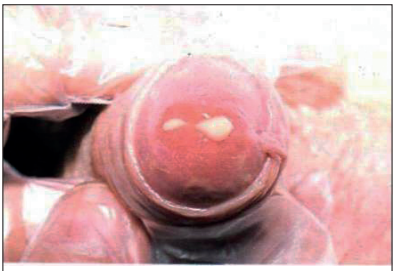
In men: GI gives rise to early prominent symptoms in the form of rapidly progressive purulent urethritis. These cause them to seek early medical advice. When treatment is inadequate or delayed, periurethral abscess, acute prostatitis and even urethral stricture are likely to develop (Pic 2).

In women: on the contrary, the initial endocervical infection may be either symptomless or there is mild vaginal discharge. In the absence of



Pic 2

therapy, dangerous complications as pelvic inflammatory disease, infertility or ectopic pregnancy are likely to occur.



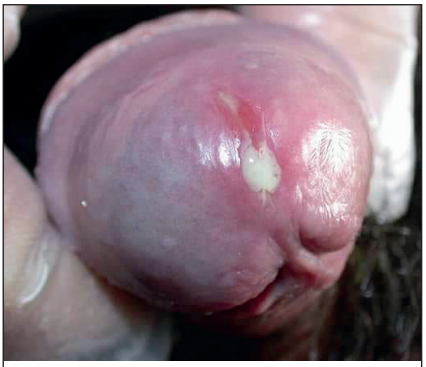
Pic 3

Clinical features in male

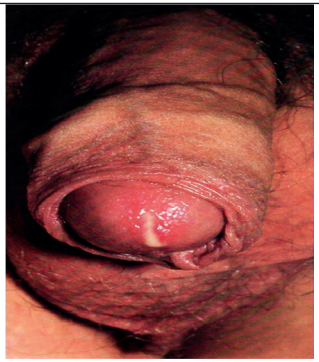
Acute anterior urethritis: profuse, thick creamy, yellowish or yellowish –green discharge with little dysuria.

On examination: red and edematous external meatus and inguinal LN (Lymph nodes) can be enlarged and tender. If the condition is neglected - acute posterior urethritis may occur within 12-14 days and the patient may feel dysuria, frequency and urgency, terminal hematuria or priapism (persistent and painful erection of the penis) with the discharge (Pic 3-6).

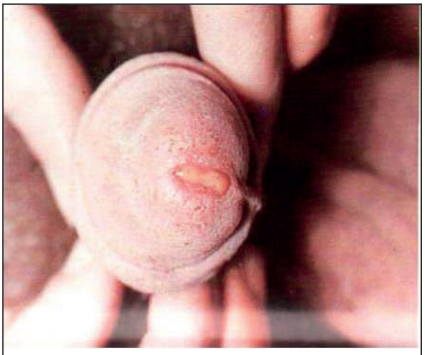
General symptoms, malaise, fever and etc., may develop. Both glasses of urine in the two glass urine test are hazy.



Pic 4



Pic 5



Pic 6

Asymptomatic infection

Occurs in 5-10% of cases (gonococcal carriers).

It is more common in women and usually discovered during examining sex contacts of gonococcal cases.

Examination is carried out after the urine has been held overnight, when a little mucopus can usually be "milked" from the meatus and shreds are present in the urine.

Local complications in the male

A) Complications of anterior urethritis

Gonococcal balanitis (shallow ulcers near frenulum): in uncircumcised patients with profuse discharge, penile lymphangitis and edema occur-bull headed clap syndrome.

Tysonitis: if ducts of the glands are obstructed - red, tender swellings on one or both sides of ducts.

Paraurethral ducts infections: on pressure, small beads of pus may be seen at the openings of ducts.

Littritis: Occlusion of the ducts - small seed-like abscesses along the line of urethra felt by massaging of urethra.

Periurethral abscess: painful local swelling either at the bulb or at the fossa navicularis and rarely fistulae occur.

Infiltration of copus spongiosum- painful and angulated erections..

Cowperitis and abscess formation: fever, malaise, severe pain in the perineum with frequency, urgency and painful defecation, acute retention of urine may occur. The condition is always unilateral. It is detected by rectal examination with the forefinger in the rectum and the thumb on the perineum. Chronic cowperitis - morning gleet in the addition to other signs and symptoms..

Urethral stricture (rare): it may follow (after a period of years) healing of subepithelial infiltrations or small periurethral abscesses. Symptoms occur due to urinary obstruction, ascending in-

fection of urinary tract and even renal failure. It occurs commonly in the bulb.

B) Complications of posterior urethritis

Prostatitis (acute or chronic): may occur as a complication of posterior urethritis. However it is very rare today. Chronic prostatitis is usually the result of associated nonspecific infection.

Prostatic abscess: the symptoms become more severe, with increased freguency, terminal dysuria, pain in the perineum, suprapubic pain and pain on defecation. Acute retention of urine may ensue. The patient is ill, with headache, malaise and fever 40c.

Rectal examination: reveals a large, very tender swelling which bulges into the rectum , such an abscess is likely to open into the posterior urethra with profuse discharge of pus per urethra and relief of symptoms. Occasionally, it opens into the rectum- gonococcal proctitis.

Seminal vesiculitis: may occur in acute posterior urethritis and is always associated with acute prostatitis. The symptoms and signs are those of the associated acute posterior urethritis and prostatitis: fever, urgency of micturition and terminal hematuria (pathognomonic of acute infection of the seminal vesicles). The semen is blood stained and there may be priapism (persistent painful erection of the penis)

During rectal examination one or both seminal vesicles may be felt as elongated, swollen, sausage-shaped masses extending upwards and outwards from the center of the upper border of the prostate.

Chronic infection is due to incomplete resolution and is usually is association with chronic prostatitis, symptoms as in chronic prostatitis + spasmodic pain during ejaculation, morning gleets, hemospermia and even sterility due to scarring of seminal vesicles (fructose in se-men).

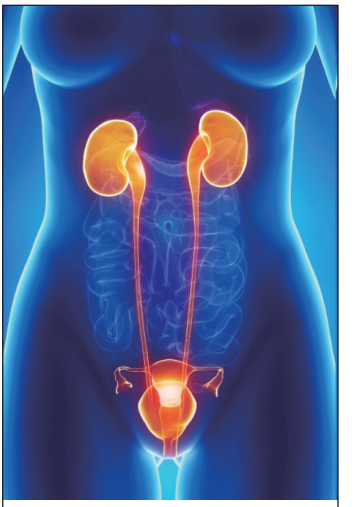
Epididymitis: can be followed by unilateral acute painful, hot

and red swelling of the scrotum. If the vas is involved lower abdominal pain simulating appendicitis and peritonitis. Infection reaches the epididymis as a result of retrograde passage of infected urine along vas (ductus) deferens or by surface continuity along the mucous membrane of the vas deferens.

The swelling is due to an inflamed epididymis and may be associated with inflammatory hydrocele. The cord may be thick ended and tender.

Clinical feature in the female

About 50% of cases are asymptomatic. Any profuse vaginal discharge if often due to associated trichomoniasis (about 50% of cases).



Pic 7

Sites of infection: the cervix (90% of cases), urethra, rectum (50% of cases). (Pic 7).

Urethritis: little dysuria or frequency and purulent secretion at urinary meatus. Cystitis is not uncommon due to short female urethra (4 cm).

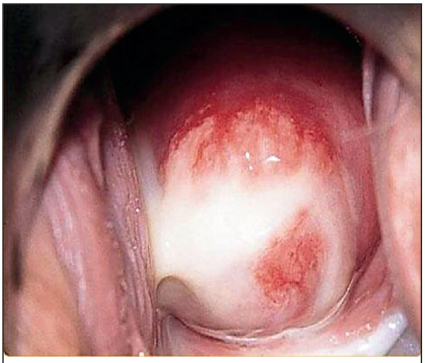
Cervicitis: low backache and may be purulent cervical secretion.(Pic 8,9)

On examination: the cervix may appear normal or there may be reddening around the external os.

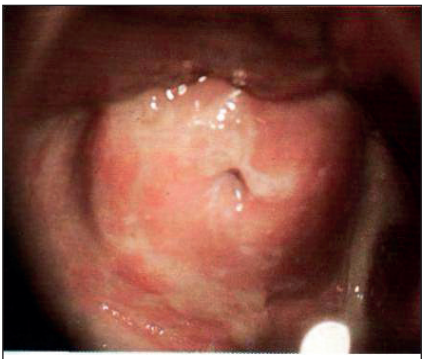
Proctitis: frequently causes no symptoms or rectal discharge and bleeding.

Diagnosis: while the patient is in lithotomy position, specimens are collected for grams stain and more important for gonococcus culture from

a) Endocevix b) urethra
c) Rectum d) pharynx (if oral sex).



Pic 8



Pic 9

Wet films from the vagina for the detection of trichomonas and candida is also important.

Local complication in the female

1. Skenitis:

The paraurethral ducts of skene (lined by columnar epithelium) open at lateral margins of the urinary meatus.

When infected, beads of pus can be expressed from the ducts, abscess formation of the gland are very rare.

2. Bartholinits :

Infection of the glands – pus on compression of the ducts. If the duct is blocked, abscess of the gland develops – painful, tender swelling in the lower third of the labia majora. There is difficulty in sitting and walking.

3. Pelvic inflammatory diseases (PID): it is the most important complication of gonorrhea in female, accounting for about 10% of untreated patient. It may lead to ectopic pregnancy or infertility.

4. Fits-Hugh- Curtis syndrome (perihepatitis): it affects 4-14% of patient with salpingitis.

The organisms reach the liver directly via the peritoneum or via the lymphatics or through hematogenous spread.

There is pain and tenderness of sudden inset in upper right quadrant of abdomen which is by deep breath and coughing. It may be

referred to the right shoulder region, in most cases, it accompanies an attack of pid or a week after.

Genital examination: cervicitis, salpingitis with urethritis.

GI in pregnancy

The prevalence of gonorrhea in pregnancy is approximately 1-10%.

Gonococcal infection(GI) could be associated with pelvic inflammatory disease(PID) in early pregnancy. Later in pregnancy, GI may be associated with premature rupture of membernes, pretermlabor, and postpartum infection. Pregnant women infected with gonorr-hea should be treated with cephalosporin, and not with quinolones or tetracylines.

Extragenital GI (Pic 10-12)

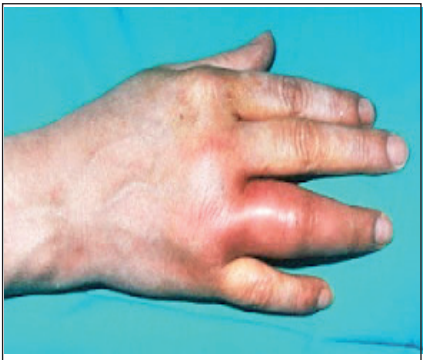
1) Anorectal gonorrhea "proctitis"

The stratified squamous epithelium of anal canal is resistant to gonococci, but the rectal columnar epithelium is not.

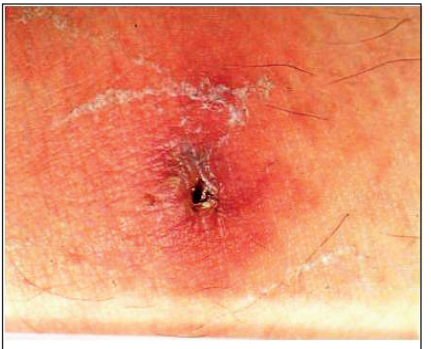
Mode of infection

In males: it always results from rectal sex with an infected partner in homosexuals or accidentally through infected thermometers or rubber gloves.

In female: it is usually due to spread of infection through the infected vaginal discharge, probably during defecation or as a result of anal coitus.

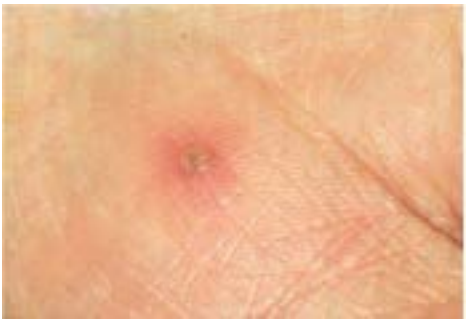


Pic 10



Pic 11

Clinical features: in 10% of cases, the condition is asymptomatic. There may be mild anal pruritus or pain, tenesmus, mucopurulent discharge and scanty rectal bleeding. On proctoscopy –red and edematous mucosa with scanty mucopurulent discharge.



Pic 12

Diagnosis: it is confirmed by identification of the gonococcus in smears from the secretion and culture on Thayer-martin selective medium.

2) Oropharyngeal gonorrhea

It always results from orogenital sexual practice. In 10% of cases, it is asymptomatic. Sore throat with mild tonsillitis or pharyngitis (on examination) may be found.

3) Gonococcal conjunctivitis

It is rare in adults occurring from direct contamination of the eye with infectious discharge by fingers or towels. There is local pain, discomfort and copious purulent yellow discharge. The lids and conjuctivae are edematous and reddened, Gram-stained smear of the exudate is diagnostic.

Gonorrhea in children

a) Gonococcal vulvo-vaginitis

Before puberty, the vulval and vaginal epithelium is immature stratified squamous epithelium, with poor glycogen content and alkaline pH in vaginal mucosa, this allows gonococcal vulvovaginitis to occur.

Mode of infection

Accidental contamination through infected thermometers or towels. The possibility of sexual abuse must always be considered.

Clinical features: Discharge on the child's underclothing, local soreness, itching and dysuria.

On examination: reddened, edematous vulva with a purulent discharge. Gram-stained smears and culture on selective media should be done.

b) Ophthalmia neonatorum

It is still an important cause of blindness in some developing countries. Infection occurs from infected women during birth. Gonococci are responsible for 20% of cases usually in 1st week.

Other organisms causing neonatal ophthalmia: Clamydia (80% of cases in 2nd or 3rd week 0, staph. Pyogenes and H. influenza.

Clinical features: It develops within 7 days of birth, always bilateral, as rapid fulminating conjunctivitis. The eyes are inflamed with profuse purulent discharge (Pic 13), edematous lids and intense conjunctivitis. Keratitis, then corneal ulceration may occur.

Pic 13

Prevention: silver nitrate 1% eye drops or better tetracycline ointment 1%.

Disseminated gonorrhea "Gonorrhea septicemia"

It occurs in 1-2% of patients within 2-3 weeks of primary infection . women are more commonly affected :

As women more frequently have asymptomatic infection and remain untreated so long .

Dissemination of bacteria has been associated with menstruation , pregnancy , pelvic surgery and intrauterine devices .

It is manifested by systemic symptoms associated with early

bacteremic cutaneous lesions and late localized septic joint effusions arthritis dermatitis syndrome''.

Precipitating factors

Most infections are due to AHU auxotype strains which are usually sensitive to penicillin .

Attacks are commoner in pregnancy .

Attaks are commoner around the time of menstruation (within 1 week of the onset of the most recent menstrual period) due to :

a-Changes in PH of cervical mucus --- bacterial growth .

b- Endocervical shedding of gonococci.

c- decrease bactericidal enzymes in cervical mucus .

C8 deficiency may have a role .

Circulating immune complexes have been found in many patients.

Clinical features

There is septicemia manifestated by triad of (3):

1- fever
2-Arthralgia
3- skin lesions

And (5)

1-Cutaneous lesions (60%): appears in crops . few in number commonly around joints of extremities . there is red maculopapular lesions. Often develop vesicopustules with hemorrhagic center, in some cases, it may be painful and ulcerated .

Most of cutaneous lesions are due to embolization of organisms to the skin with the development of microabscesses.

2-Suppurative arthritis (85% of patients): 2 forms :

Asymmetrical arthritis with tenosynovitis: of the knees and small joints of hands and feet.

One or two single large joints (e.g. knee, wrist or ankle)showing acute septic arthritis - swollen , hot painful and tender joint. The joint fluid is purulent and gonococci are usually isolated.

3-Endocarditis

4-Perihepatitis (fitz-hugh-crtis syndrome),see before.

5-Iridocyclitis
Diagnosis
Demonstrating gonococci from oral, rectal or genital sites.
Blood or synovial fluid culture --- gonococci
Direct fluorescent antibody test (+ve >50%) from skin lesions.

Diagnosis of GI

A Suggestive diagnosis is defined by the presence of:

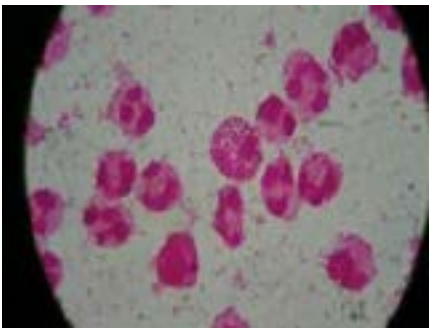
i. a mucopurulent endocervical or urethral exudate on physical examination .
ii. sexual exposure to a person infected with N. gonorrhoeae.

A Presumptive diagnosis of GI is made on the basis of one of the following three criteria:

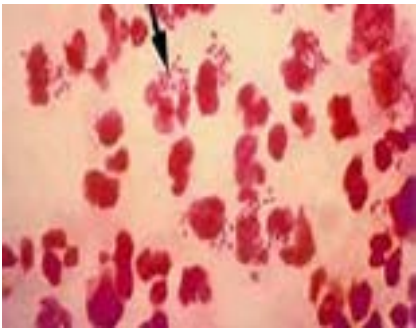
i. typical gram-negative intracellular diplococci on microscopic examination of a smear of urethral exudate from men or endocervical secretions from women*;
ii. growth of a gram-negative, oxidase-positive diplococcus, from the urethra (men) or endocervix (women), on a selective culture medium, and demonstration of typical colonial morphology, positive oxidase reaction, and typical gram-negative morphology;
iii. detection of N. gonorrhoeae by a nonculture laboratory test (Antigen detection test ,direct specimen nucleic acid probe test ,nucleic acid amplification test

1-Microscopie It is used to correct diagnosis (Pic. 14-15).
2-Bacterial
3-Enzym substrate test
The production of three enzymes - a glycosidase (beta-galactosidase) and two aminopeptidases (gamma-glutamylaminopeptidase and hydroxyprolylaminopeptidase) - has been used to differentiate between Neisseria and related species isolated on selective medium for N. gonorrhoeae

4-Fluorescrence antibody test



Pic 14



Pic 15

Fluorescent antibody test for gonorrhea as a screening procedure, especially for women in the low-risk group. The test is more economic and probably more sensitive than culture for mass screening of asymptomatic women

5- Nucleic acid amplification test

Nucleic acid amplification test (NAAT) is the recommended method of testing for gonorrhea. NAAT is a molecular test that detects the genetic material (DNA) of Neisseria gonorrhoeae . It is generally more sensitive and specific than other gonorrhea tests and can be performed on a vaginal swab on women, or urine from both men and women.

Treatment of GI

The selection of an antibiotic depends mainly upon efficacy & patterns of antibiotic resistance in the locality . single dose treatment is preferred.

General lines

Avoid sexual excitation, sexual intercourse and alcohol.

Avoid self – examination of the urethra to prevent traumatic urethitis .

Avoid local antiseptics to prevent chemical urethritis .

The sexual partner should be traced and treated

I) uncomplicated infection (genital and anal infections)

both in woman & men penicillin

it has a bactericidal action by interference with cell wall synthesis, e.g.

procaine penicillin 2-4 million units IM + probenecid 1gm orally.

Ampicillin or amoxicillin 3 gm single dose orally + probenecid 1 gm orally

Advantages: cheap, single dose, less toxicity and can be used in pregnancy.

Disadvantages: allergic reactions, not effective on associated NGU, may mask syphilis, and resistant (B – lactamase producing) are now present.

Probenecid: 1gm is given orally before injection – inhibition of penicilin renal tubular secretion and displacing penicillin from serum binding protein—higher and more prolonged level of blood penicillin.

In case allergic to penicillin or in cases of PPNG infections:

Ciprofloxacin* (ciprobay, ciprocin , ciprone) 500mg single oral dose . it should not be used in pregnant patient or those with a history of convulsions (spectinomycin is preferable).

Because ciprofloxacin is not treponemicidal , it may be given to those patient being investigated for suspected syphilis.

Spectinomycin (togamycin)2gm IM single.

Kanamycin (kantrex)2gm IM single especially in gonococcal proctitis .it is nephrotoxic

Cephaloridine (keflodin or ceporan).2gm IM

Thiamphenicol (thiophenicol)tab.2gm oraly

Rifampicin(rimactane)900mg orally.

Ceftriaxone(rocephin)250 mg IM single.

Oflaxacin(tarivid)two tab .400mg.

Norfloxacin(noroxin)800mg.

Pefloxacine(peflacin)400mg.

Co-trimoxazole(septrin): 8 tab as a single oral dose or 4 tab/ 12 hours . for 3 days

Clavulanic acid 125mg+amoxicillin (augmentin cap) 8 capsules in a single dose

Sulbactam + ampicillin (unasyn IM amp . 1.5 gm)3gm single or 6 tablets (375mg) single dose.

In case of coexisting chlamydial infection

Azithromycin (zithromax) single dose 1 gm orally

Tetracyclines *, e.g . oxytetracycline 500 mg orally 4 times/day for 7 days or doxycycline (vibramycin) 100mg twice daily for 7days.

Erythromycin stearate 500 mg twice daily for 14 days if tetracyclines are contraindicated as in pregnancy.

Pharyngeal infection

Ceftriaxone (250 mg)single IM , or

Cotrimoxazole10 tab . once dialy for 5 days

II) disseminated infection , e.g. gonococcal arthritis

benzyl penicillin , 10 million units daily IV for 3 days followed by amoxicillin 500 mg orally for 4 days

ceftriaxone 1.0 g IM or IV daily , spectinomycin 2.0 g twice daily IM or ciprofloxacin 500 mg 12 hrs for 7 days .

in gonococcal meningitis : extend the treatment for 2 weeks.

Gonococcal endocarditis : extend the treatment for 4 weeks , Hospitalization is a must.

Treatment of concurrent chlamydial infections

III) gonococcal conjunctivitis and ophthalmia neontorum

adults : admission to hospital and frequently irrigate the eye with saline solution.

Spectinomycin 2.0 gm , or ceftriaxone 250mg single IM or kanamycin 2.0 gm single IM or cotriamoxazole 10 tab. For 3 days.

Infants born to mothers with gonorrhea: single IM of ceftriaxone 50mmg\kg (125mg)or kanamycin 25mg\kg (maximum 75mg).

Infants with signs of conjunctivitis: isolated immediately and in addition tetracycline ointment 1% instilled into each eye hourly on the first day and 8 hourly for the next 10 days.

When facilities for routine screening of gonorrhea in preg-

nant women are not available , tetracycline ointment 1% should be applied for infant after gently cleaning the eyelids. Wrythromycin ointment 1% is similary effective. Silver nitrate eye drops 1% ar oxic.

IV) gonococcal salpingitis or epididymitis

procaine penicillin 4.8 million unites IM or 3.5 gm ampicillin + 1.0 gm probenecid orallyfollowed by ampicillin 500 mg orally 4 times\day for 10 days

tetracline 500 mg 4 times\day for 10 days.

Spectinomycin 4.0 gm IM followed by tetracycline 500 mg 4 times /days for 10 days in cases of PPNG.

Surveillance of gonorrhea and prognosis

Patients should abstain from alcohol and sexual intercourse for 2 weeks.

Patients should been see on :

Third day after treatmen , holding urine for 3 hours before examination, urethral secretions (should be stopped with treatment) should be examined , if still present. Culture and sensitivity tests for penicillin-resistant organism should be done.

Causes of treatment failure

Reinfection – treat with penicillin.

Infection with PPG strains – use spectinomycin 2 gm IM or ciprofloxacin 500 mg orally.

Postgonococcal urethitis 25-50% of cases . it is caused by C , trachomatis in 80% of cases—doxycycline 100 mg twice daily for 7-14 days , or tetracycline 500 mg\6 hours daily for 7-14 days

After 1 week there should be no discharge and the urine should be clear if there is urethral discharge or hazy urinepresist – NGU or post- gonococcal urethritis (many pus cells and no gonococci).

Males with gonococcal proctitis shoud be seen **at the end of first week** when rectal swabs and cultures should be (-) negative.

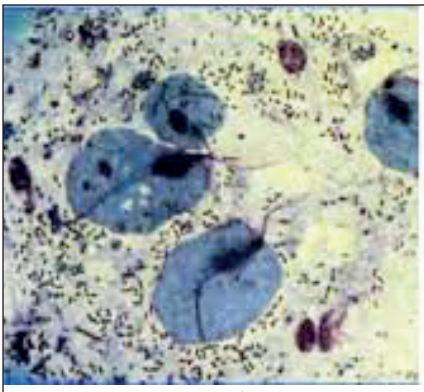
After 2 weeks later – patients examined for possible prostate-vesiculitis.

After 3 weeks – test blood samples for syphilis and HIV and patients are examined for urethral stricture.

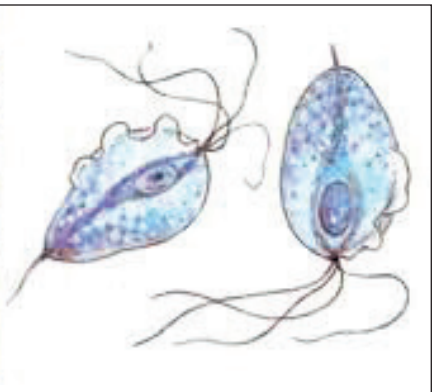
UROGENITAL TRICHMONIASİS

INTRODUCTION

Trichomoniasis is a very common sexually transmitted infection (STI) caused by a tiny protozoan parasite called Trichomonas vaginalis that invades genital epithelia (Pic 1). The World Health



Pic 1



Sxem 1

Organization (WHO) estimates that the number of infections occurring globally each year exceeds those of chlamydia and gonorrhea combined. It is important to note that the majority of infections are subclinical with no patient-reported symptoms.

This highly prevalent pathogen predominately affects women and may play a role in development of upper genital tract

complications and cervical cancer, lead to adverse outcomes of pregnancy, and increase risk of HIV acquisition or transmission.

Epidemiology of T. vaginalis

Several factors limit our understanding of the epidemiology of trichomonas. First, the prevalence in women is 5 to 10 times higher than in men . Second, a commonly held belief is that infection must result in symptomatic disease in women despite strong evidence to the contrary. Many healthcare providers have considered asymptomatic infection to be merely a nuisance rather than a threat to reproductive health. As a result, screening in asymptomatic populations has been uncommon. Despite very strong evidence regarding the negative effects of untreated infections, this dogma persists in many clinical settings, which results in a gross underutilization of screening and diagnostic tools. Thus, the majority of people tested for trichomonas are women with symptoms or attending an STI clinic that routinely provides such testing. The fact that most women diagnosed with trichomonas have symptoms, since women without symptoms are not screened, reinforces the assumption that all infections must cause symptoms.

As a result, reports of trichomonas prevalence may represent populations at elevated risk (i.e. symptomatic women or women from STI endemic regions of the world) and should be considered in the appropriate context. Finally, as will be described below, the diagnostic methods used to identify trichomonal infection vary widely in sensitivity.

Studies of the epidemiology of T. vaginalis infection have described risk factors similar to those identified for other STI. Risk factors include infection with other STI, previous infection with T. vaginalis, lower socioeconomic status, incarceration in a correctional facility, and sexual behaviors that increase risk of infections. These behaviors include higher numbers of sexual partners, inconsistent condom use, sex in exchange for money

or drugs, and intravenous drug use. Patients with any of these risk factors should be considered for evaluations of infection with trichomonas.

Importantly, unlike the classic age distribution seen with C. trachomatis, and to a less dramatic degree with N. gonorrhoeae, T. vaginalis prevalence appears to increase with age. However, all studies that have examined age have found that prevalence rates decline after age 50. Further, no evidence of long-term infection has been shown. Changes in prevalence may be related to changes in susceptibility as a result of hormonal or other changes to the vaginal micro-environment as women age. More research is clearly needed to improve our understanding of the biological factors that may affect women's risk of infection with T. vaginalis, including the impact of other microbial community members. The vaginal microbiome may both affect susceptibility and be affected by the presence of active trichomonal infection .

Given the shared mechanism of transmission, it is not surprising that T. vaginalis infection often occurs with other STI and reproductive tract infections (RTI) such as bacterial vaginosis (BV) and yeast (Candida spp.) infection. BV and yeast infections that are concurrent with trichomonal infections may hinder diagnosis of T. vaginalis. Women who are tested for STI, BV, or yeast infections should be evaluated for the presence of trichomonas, and this evaluation may require more sensitive diagnostic methods than microscopy. This is now possible using molecular assays that can simultaneously detect all three of these conditions.

Biology and Pathogenesis of T. vaginalis

Trichomonas vaginalis is a flagellated protozoan that is highly motile Trichomonads, which are approximately the size of lymphocytes (15–25 μm in length), have several long flagella that are involved in motility as well as an asymmetric undulating

membrane that is clearly visible with light microscopy. T. vaginalis is strictly anaerobic and can survive in a variety of pH conditions ranging from highly acidic (pH 3.5), which is common during bacterial vaginosis, to basic (pH 8.0). As a result of sensitivity to atmospheric oxygen, drying conditions and temperatures below 35 °C, T. vaginalis does not survive ex vivo for extended periods (greater than a few hours) and organisms lose motility quickly at room temperature . Therefore, transmission by means other than sexual contact is rare.

Upon entry into the vaginal milieu, T. vaginalis encounters the mucous layer that is the first line of defense from microbial colonization. Trichomonads produce enzymes that degrade mucin, the major component of mucous, thus allowing the organisms to come into contact with the cells of the vaginal epithelium . Trichomonas also produces adhesins that enable attachment of the pathogen to the cell surface of vaginal epithelium. These adhesins are upregulated during times of high iron concentration. This mechanism may allow trichomonads to remain adhered to cells during menses . Contact with epithelial cells results in their destruction and recruitment of inflammatory cells to the vagina, resulting in vaginal discharge. However, there are many factors that influence the level of cytotoxicity and local immune response. As a result, infection can cause a range of outcomes, from completely asymptomatic disease to heavy discharge, odor, and itching.

Clinical Features of T. vaginalis Infection

Urogenital Trichmoniasis in men

T.vaginalis infection in men is known to be an important cause of urethritis, prostatitis, and potentially male factor infertility .

Symptoms rarely occur in men but may include discharge,

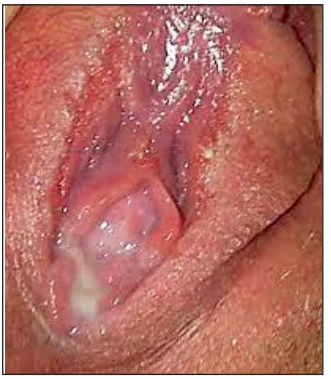
which may or may not contain significant quantities of lymphocytes or red blood cells, dysuria, pruritus, increased urinary frequency, or prostatitis. On rare occasions, men may have urethral strictures or epididymitis. Symptoms generally appear within 7–10 days following exposure, and it is possible that the infection may resolve spontaneously . Few longitudinal data are available to predict the frequency of such resolution. The vast majority of men with T. vaginalis have no signs or symptoms of infection, thus confusing the measurement of natural clearance of disease. Diagnosis and treatment of these men remains clinically important in order to reduce the spread of the organism to sexual partners.

Asymptomatic carriers of trichomoniasis are an important reservoir of infection, and diagnosis based solely on either the clinical signs or symptoms presented by the patient is unreliable . Although T.vaginalis is commonly described in the context of nongonococcal/nonchlamydial urethritis, trichomonas often occurs in men with chlamydia or gonorrhea. Therefore, when screening for chlamydia and gonorrhea is appropriate, inclusion of screening for trichomonas should also be considered. With the development of nucleic acid-based diagnostics, this testing can be performed on the urine samples being tested for chlamydia and gonorrhea.

Similar to men, women infected with T. vaginalis are also predominately without symptoms.

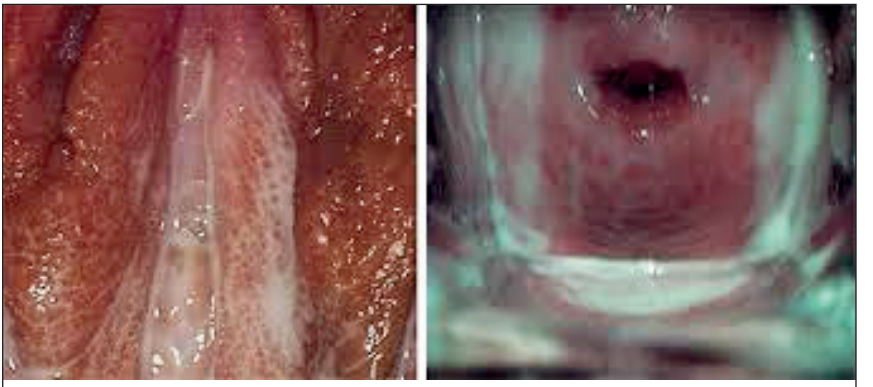
Urogenital Trichmoniasis in women

Women may experience vaginal discharge, vaginal itching, musty odor, dysuria, pelvic pain, irregular bleeding, and pain or bleeding on coitus (Pic 2). Clinical signs of infection in women include punctate bleeding of the cervix, often referred to as a strawberry cervix ,which is seen in less than 10% of cases without the aid of colposcopy, and a frothy discharge that is usually white but may be yellow or grayish in appearance. Vaginal pH greater



than 4.5 may be noted in some women with trichomoniasis, but is not a highly reliable indicator.

In women, T.vaginalis infection has been linked to pelvic inflammatory disease (PID), adverse outcomes of pregnancy and cervical cancer . The cervical cancer relationship is likely indirect since trichomonal infection is strongly associated with HPV persisten-



Pic 2

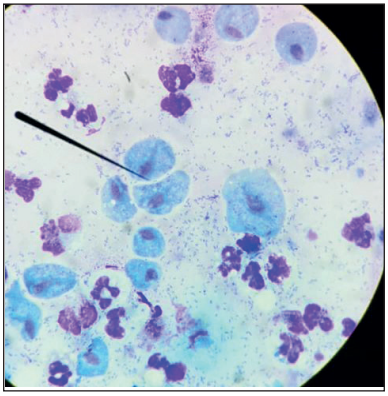
ce or recurrence . While the relationship between T. vaginalis and PID in women with HIV has been shown to be strong , in women without HIV the relationship was not significant .

Meta-analyses have confirmed the strength of the relationship between trichomonal infection and poor birth outcomes . These data emphasize the need for T. vaginalis control communities with high burden of disease and high likelihood of pregnancy complication. During pregnancy, screening should be performed during the first trimester to avoid safety concerns related to metronidazole use in the third trimester.

Diagnosis of T. vaginalis

T. vaginalis was first identified visually by microscopy of genital secretions .

The traditional diagnostic method for trichomoniasis has been wet mount with microscopic (Pic 3) visualization of motile Trichomonas vaginalis parasites on slide preparations from vaginal or urethral secretions. Ideally, specimens should be examined within 10 minutes to observe motile parasites, which are diagnostic. Wet mount is an inexpensive diagnostic test; however, sensitivity is estimated at 51-65%, and varies based on the individual performing the test and how promptly the slide is interpreted.



Pic 3

Culture has been considered the gold standard for diagnosis of trichomoniasis with a specificity approaching 100%, but it is not widely used and its sensitivity can be as low as 75–96%. Clinical specimens can be inoculated into transport systems such as Amies gel medium to maintain viability for up to 24 hours at room temperature. Culture systems such as InPouch TV , allow for direct inoculation, culture and microscopic examination. Additionally, these systems can be used to transport specimens after inoculation. Such systems are useful when immediate transportation of specimens to the laboratory is not available. The specimen should be inoculated as soon as possible (within an hour of collection) to maintain viability of the organism.

Neither conventional nor liquid-based Papanicolau (Pap) smears are suitable for routine screening or diagnosis of Trichomonas vaginalis, because sensitivity is poor; in addition, positive predictive value is low in settings where the prevalence of infection is low.

The OSOM (formerly Xenostrip) Trichomonas Rapid Test is an immunochromatographic capillary-flow enzyme immunoassay dipstick test and the only rapid antigen test commercially available in the US. It is performed on vaginal secretions with results available within 10 minutes. This point-of-care test is FDA-cleared for females and CLIA waived. Test specifications include sensitivity 82–95% and specificity 97–100%.

The Affirm VPIII Microbial Identification Test is an FDA-cleared nucleic acid probe test for the diagnosis of three causes of female vaginitis: Trichomonas vaginalis, Gardnerella vaginalis and Candida albicans. Sensitivity for Trichomonas vaginalis is 63% and specificity 99.9%. This is considered a same-day test as it produces results in 45 minutes; however, it is characterized as a CLIA moderate complexity test.

Nucleic acid amplification tests (NAATs) are the most sensitive tests available for detection of Trichomonas vaginalis. The APTIMA Trichomonas vaginalis Assay was FDA-cleared in 2011 for use with urine, endocervical and vaginal swabs, and endocervical specimens collected in the Hologic PreserveCyt solution from females only. Sensitivity is 95–100% and specificity is also 95–100%. The BD ProbeTec Trichomonas Vaginalis Qx Amplified DNA Assay launched in Europe (EU cleared) in 2012, but is not FDA-cleared in the United States at this time.

Diagnosis of Trichomonas vaginalis in men has been challenging given the low sensitivity of microscopy and lack of FDA clearance to date for any NAATs or point-of care tests for use with male specimens. Some laboratories have verified the performance characteristics of NAATs through a validation process for male urine specimens or penile-meatal swabs. Culture of urine, semen, and/or urethral swabs may be other diagnostic options for men.

Treatment of T. vaginalis

Treatment reduces symptoms and signs of T. vaginalis infection and might reduce transmission.

A. Recommended Regimen

Metronidazole 2 g orally in a single dose
OR Tinidazole 2 g orally in a single dose

B.Alternative Regimen

Metronidazole 500 mg orally twice a day for 7 days

Metronidazole gel does not reach therapeutic levels in the urethra and perivaginal glands. Because it is less efficacious than oral metronidazole, it is not recommended.

Other Management Considerations

Providers should advise persons infected with T. vaginalis to abstain from sex until they and their sex partners are treated (i.e., when therapy has been completed and any symptoms have resolved). Testing for other STDs including HIV should be performed in persons infected with T vaginalis.

Follow-up

Because of the high rate of reinfection among women treated for trichomoniasis, retesting for T. vaginalis is recommended for all sexually active women within 3 months following initial treatment regardless of whether they believe their sex partners were treated. Testing by nucleic acid amplification can be conducted as soon as 2 weeks after treatment. Data are insufficient to support retesting men.

Management of Sex Partners

Concurrent treatment of all sex partners is critical for symptomatic relief, microbiologic cure, and prevention of transmission and reinfections. Current partners should be referred for presumptive therapy to avoid reinfection. Partners should be advised to abstain from intercourse until they and their sex partners have been adequately

treated and any symptoms have resolved. EPT might have a role in partner management for trichomoniasis and can be used in states where permissible by law; however, no one partner management intervention has been shown to be superior in reducing reinfection rates. Though no definitive data exist to guide treatment for partners of persons with persistent or recurrent trichomoniasis in whom nonadherance and reinfection are unlikely, partners benefit from undergoing evaluation and receiving the same regimen as the patient.

Pregnancy

If treatment is considered, the recommended regimen in pregnant women is metronidazole 2 g orally in a single dose. Symptomatic pregnant women, regardless of pregnancy stage, should be tested and considered for treatment. Treatment of T. vaginalis infection can relieve symptoms of vaginal discharge in pregnant women and reduce sexual transmission to partners. Although perinatal transmission of trichomoniasis is uncommon, treatment also might prevent respiratory or genital infection of the newborn.

Note: Women can be treated with 2 g metronidazole in a single dose at any stage of pregnancy.

Some clinicians advise deferring breastfeeding for 12–24 hours following maternal treatment with a single 2-g dose of metronidazole. Maternal treatment with metronidazole (400 mg three times daily for 7 days) produced a lower concentration in breast milk and was considered compatible with breastfeeding over longer periods of time

Recommended Regimen for Women with HIV Infection

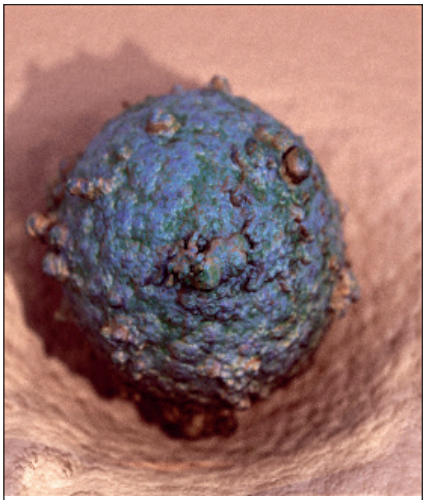
Metronidazole 500 mg orally twice daily for 7 days

In women with HIV infection who receive a diagnosis of T. vaginalis infection, retesting is recommended within 3 months following initial treatment.

CHLAMYDIAL INFECTION

İntroduction – Chlamydia is the most common sexually transmitted infections caused by the bacterium *Chlamydia trachomatis.* It causes an ocular infection called "trachoma". In females, infertility and ectopic risks increase with *Chlamydia trachomatis* infections. Lymphogranuloma venereum (LGV), caused by distinct serovars of *Chlamydia trachomatis,* is a less common disease characterized by enlarged lymph nodes or severe proctocolitis.(Pic 1)

Etiology *C. trachomatis* is responsible for a wide range of infections including trachoma, newborn conjunctivitis, and genital infections in women and men. *C. trachomatis* is an obligate intracellular organism, dependent on the host cell's adenosine triphosphate (ATP) production. *C. trachomatis* has features of both bacteria and virus. *C. trachomatis* has a cell wall like gram-negative bacteria but it cannot synthesize its own ATP or grow on artificial media, hence its similarity with a virus.



Pic 1

Risk Factors

The classic risk factors for chlamydial infection include age less than 26, low socioeconomic status, minority group member, multiple sexual partners, and new partners. In younger women, columnar cells are more likely to be on the ectocervix (ectopy), where they can be exposed to semen carrying the organism. As a women age, the columnar cells are located higher in the cervical canal.

Infectivity and Transmission

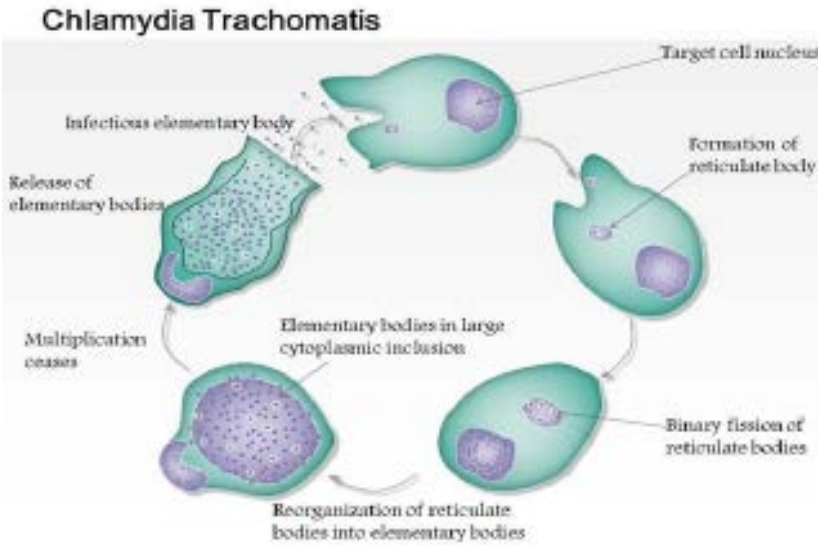
C. trachomatis is a relatively infectious agent. Vertical transmission of *C. trachomatis* is more efficient than horizontal transmission. Over 60 % of newborns who deliver through a chlamydia-infected cervix will acquire the infection.

Pathophysiology

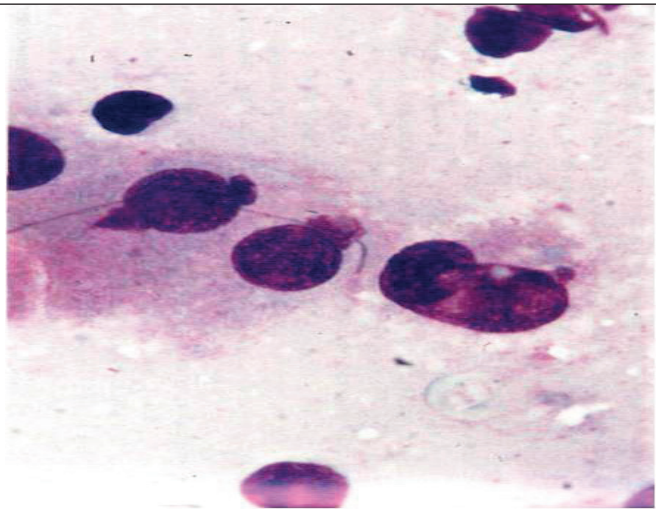
Chlamydia is unique among bacteria, having an infectious cycle and two developmental forms. These include the infectious form called the elementary body (EB) and the reticulate body (RB). The bacterium is transmitted through direct contact with infected tissue, including vaginal, anal or oral sex, and can even be passed from an infected mother to the newborn during childbirth.(Pic 2)

Histopathology

Typical intracytoplasmic inclusions and free chlamydiae are identifiable in Giemsa-stained cell scrapings from the eye. Stained conjunctival scrapings are positive in 90% of infants with neonatal conjunctivitis, and 50% of adults with inclusion conjunctivitis. Cytology techniques can be used to evaluate endocervical scrapings, but the sensitivity and specificity are low.(Pic3)


Chlamydia Trachomatis
Target cell nucleus
Infectious elementary body
Formation of reticulate body
Release of elementary bodies
Multiplication ceases
Elementary bodies in large cytoplasmic inclusion
Binary fission of reticulate bodies
Reorganization of reticulate bodies into elementary bodies

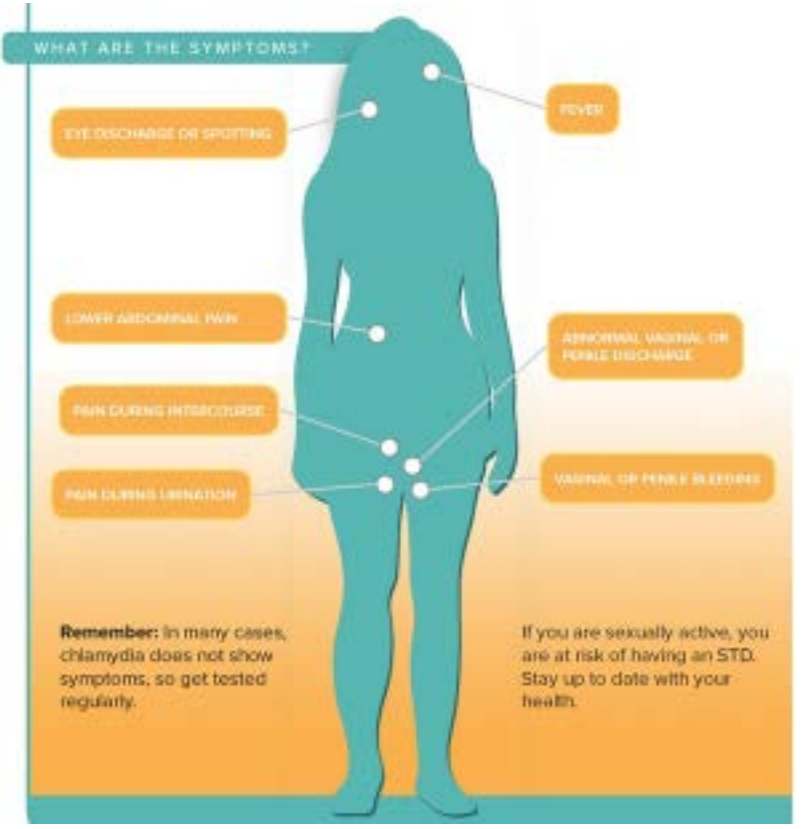
Pic 2



Pic 3

Clinical Manifestations

The range of infections with *C. trachomatis* is impressive. The predominant infections are urethritis, cervicitis, and proctitis, but chlamydial infection can spread locally to the Bartholin's glands,



Pic 4

endosalpinges, or epididymis. In pregnancy, chlamydial infection is a risk factor for low birth weight infants and preterm delivery. Postpartum, an infected woman is at increased risk for developing endometritis. Her newborn can develop conjunctivitis and pneumonia. Men who have chlamydial urethritis are at risk for developing Reiter's syndrome.

Infections in Women (Pic 4)

Cervicitis

The cervix is the most common site of infection for women. Women with chlamydial cervicitis generally are asymptomatic or report only nonspecific symptoms, such as vaginal discharge or postcoital spotting or bleeding. The incubation period for *C. trachomatis* is 6–14 days.

C. trachomatis infects only columnar cells in the cervical squamocolumnar region or in the endocervix. In women with cervical ectopy and mucopurulent cervicitis, *C. trachomatis* should be considered, but mucopurulent cervicitis should not be used as definitive evidence of chlamydial cervicitis. The presence of leukocytes in endocervical samples studied under magnification is a better predictor of chlamydial infection.

Urethritis/Urethral Syndrome

Women with chlamydial urethritis may complain of dysuria, slight discharge in urine, or urinary frequency. These symptoms are focused in the suprapubic area and start after she has finished voiding, which may help distinguish that infection from bacterial cystitis. Only selective antibiotics will treat chlamydial infections, the symptoms will not resolve with typical antibiotic therapies for

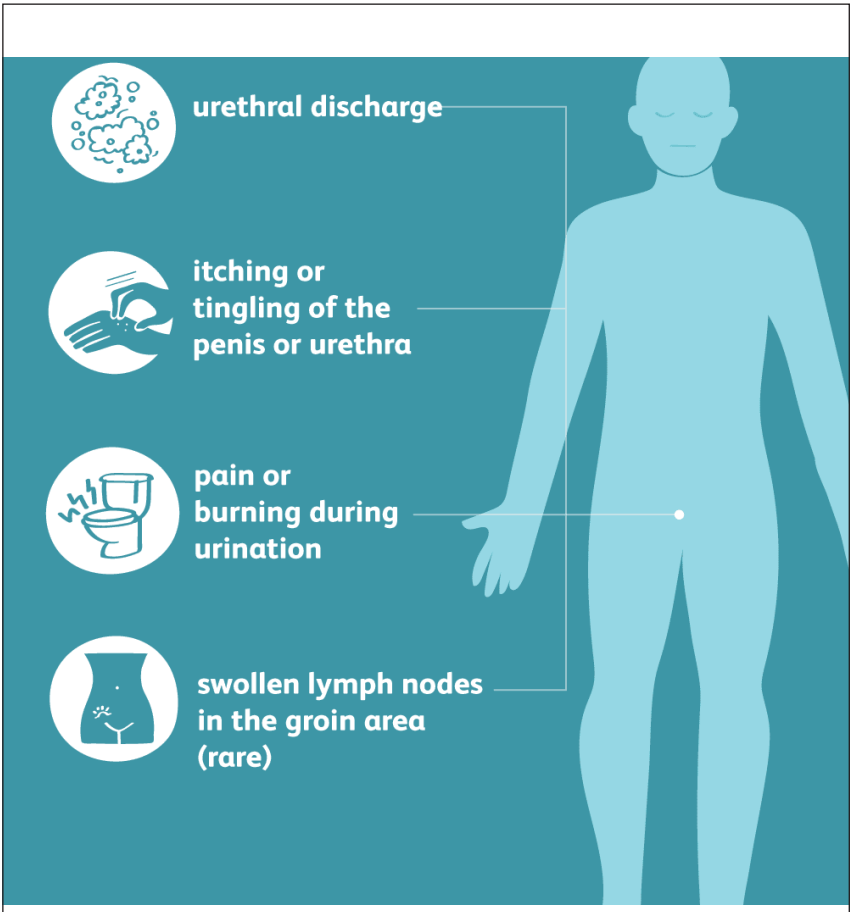
bacterial cystitis. The differential diagnosis includes infection with Mycoplasma or Ureaplasma as well as urethral trauma and atrophic urethritis. It is rare for chlamydial urethritis to exist independent of a cervical infection in a woman.

Bartholinitis

The Bartholin's gland and ducts are lined with columnar epithelium and are susceptible to infection with *C. trachomatis*. Women with Bartholin's abscesses complain of acute onset of vulvar pain and swelling, which becomes quite intense as the abscess expands. Generally treatment required for abscess is incision and marsupialization and adjuvant antibiotic treatment is not recommended.

Salpingitis

Sperm has been implicated in the transport of C. trachomatis into the upper genital tract in women. Symptoms may appear at any time during a woman's menstrual cycle, in contrast to gonococcal pelvic inflammatory disease (PID), which classically develops at the end of a woman's menses. The clinical presentation of chlamydial salpingitis is much more subtle than gonococcal salpingitis, because the fallopian tubes may not be distended with chlamydial infection even though the endosalpinges may suffer profound architectural damage as a result of chlamydial heat shock proteins. Women with significant upper tract infection may be asymptomatic or have only mild flu-like discomforts that they attribute to other causes. Because of this very unremarkable clinical symptomatology and the relative paucity of clinical findings on examination and laboratory testing, the CDC revised its requirements for the criteria of PID to lower the threshold for diagnosis.

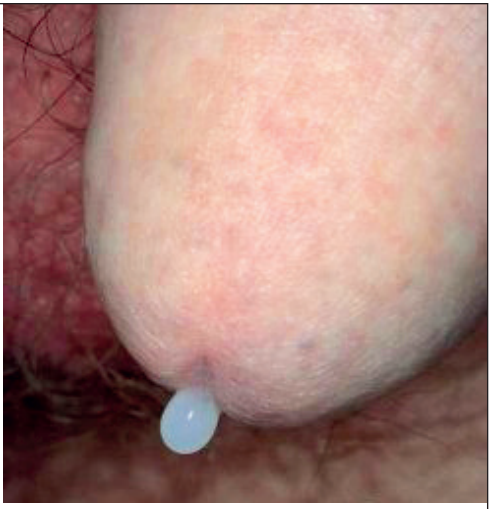


Pic 5

Infections in Men (Pic 5)

Chlamydial Urethritis

Nongonococcal urethritis is most commonly caused by *C. trachomatis.* The typical incubation period from exposure to infection



Pic 6

is 1–2 weeks. Men who are symptomatic generally present with complaints of dysuria, urinary frequency, and urethral discharge. urethritis is often asymptomatic; therefore, infected men are a major reservoir for infection of their sexual partners (Pic 6).

Prostatitis

The symptoms, associated with prostatitis, are perineal pain, back pain, and pain with urination or ejaculation. Acute prostatitis in young men can occur with *C. trachomatis.* More than one in 5 men with chronic prostatitis with inflammation seen on prostatic secretions had evidence of chlamydial infection . These results suggest that *C. trachomatis* may be one of the causative agents of chronic prostatitis.

Epididymitis

Tenderness with swelling in the testicle is a sign of epididymitis. More commonly occurs in younger men. Other infectious etiologies for epididymitis include *N. gonorrhea* and *E. coli.* Chlamydial epididymitis has a milder course than other etiologies. Chronic epididymitis is defined as testicular pain persisting for at least 3 months. A patient with chronic epididymitis can also have a scrotal mass. Male infertility may be associated with chlamydial infections because the inflammatory process may damage the epididymis and

the sperm collection tubules. Men with fertility problems have been found by serology to have more likely had a previous infection of Chlamydia, but definitive proof is not yet been established.

Infections in Men or Women

Proctitis

Chlamydial proctitis can occur in women and MSM who practice receptive anal inter- course. *C. trachomatis* was found in specimens from 5 % of rectums and 13 % of cervixes of 115 consecutive women presenting for examination. Rectal bleeding and microscopic evidence of proctitis without diarrhea was commonly found. With MSM, the infection is due to unprotected anal intercourse. With symptomatic men and women, sigmoidoscopy and appropriate testing for infectious organisms is required. Human immunodeficiency virus (HIV) antibody status should be established. If the patient is HIV-infected, uncommon pathogens need to be considered. With negative HIV tests, treatment for both gonorrhea and chlamydial infections is appropriate.

Reactive Arthritis/Reiter's Syndrome

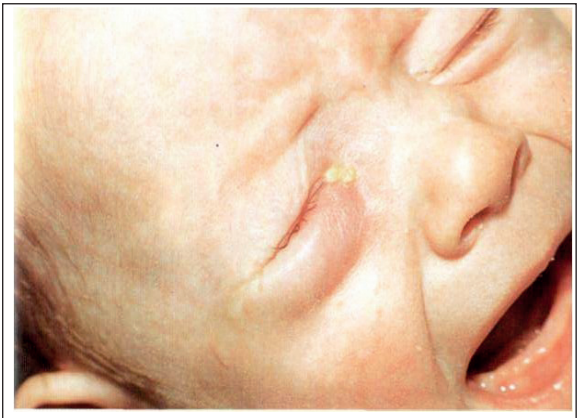
Reactive arthritis is an inflammatory synovitis in which no viable organisms can be isolated from the joint and is precipitated by an immunologic response to an infectious agent. Reiter's syndrome is composed of a triad of conjunctivitis, urethritis, and arthritis. Often individuals will not manifest all elements of the triad. Men are approximately 9 times more likely to develop Reiter's syndrome than women. Multiple joint involvement is common, usually affecting the knees or feet. Joint symptoms develop 2–4 weeks after urogenital infection, but 10 % of affected individuals have no history of urethritis. Conjunctivitis and associated iritis and uveitis

usually develop after the arthritis. A scaly skin rash (keratoderma blennorrhagica) on the palms or soles is also seen.

Many organisms have been implicated in reactive arthritis and Reiter's syndrome, including *C. trachomatis*. In genetically susceptible individuals, the immune system reacts to the infectious agent leading to the inflammatory response in the synovial surface.

Chlamydial Infection in the Newborn

Neonatal chlamydial infection usually develops from vertical transmission. Although the most common method of transmission is thought to be direct contract as the fetus delivers through an infected cervix, there have been reported instances where neonatal infection occurred with Cesarean section delivery, with and without ruptured membranes.



Pic 7

Chlamydial neonatal conjunctivitis has an incubation period of 10–14 days (Pic 7). The orbit of the eye swells and exudates are seen. C. trachomatis will be found in a high proportion of specimens. Because *C. trachomatis* can also be found in the nasopharynx, systemic treatment is required rather than a local ophthalmic solution. Diagnosis can be made by assessing *C. trachomatis* IgM antibody titers. Long-term complications of pneumonia can include abnormal pulmonary function tests and asthma.

Evaluation

Among *C. trachomatis* infections, only trachoma is diagnosable on clinical grounds. Other chlamydial infections are associated with specific clinical syndromes but require laboratory confirmation. If there is no testing available, treatment is recommended based on clinical presentation.

DIAGNOSIS

Urine testing is currently primarily used to detect bacterial STIs. Chlamydia urine tests are widely available. The "gold standard" for diagnosing bacterial STIs, such as chlamydia, used to be bacterial culture. That involved attempting to grow bacteria out of samples that were taken directly from the cervix or urethra.

These days, bacterial DNA testing is considered a better option. It works differently than bacterial culture. Instead of trying to grow bacteria, these tests just look for bacterial DNA. This can be done using a process called LCR (ligase chain reaction) or with other DNA amplification techniques.

These types of testing are sensitive to even very small amounts of bacterial DNA. Even better, they do not require a live bacterial sample. As such, they can be run on urine samples, not just urethral or cervical swabs.

Nucleic acid amplification tests (NAATs) are the most sensitive tests for detecting chlamydia infections. NAATs can be performed on endocervical, urethral, vaginal, pharyngeal, rectal, or urine samples (first-void is preferred).The accuracy of NAATs on urine samples has been found to be nearly identical to that of samples obtained directly from the cervix or urethra. On wet mount, a finding of leukorrhea (more than 10 white blood cells per high-power field on microscopic examination of vaginal fluid) has been associated

with chlamydial infections of the cervix. Oropharyngeal and rectal swabs may be obtained in persons who engage in receptive oral or anal intercourse.

Treatment/ Management

The goal of treatment is the prevention of complications associated with infection (e.g., PID, perihepatitis), to decrease the risk of transmission. Treatment for uncomplicated urogenital chlamydia infection is with azithromycin as a single-dose therapy. Doxycycline is an alternative

Chlamydial infection and gonococcal infections often coexist. In men, the driver behind co-treatment for urogenital gonococcal infection should be by detection of the organism on NAAT or gram stain. In women, the gram stain is less helpful due to the possibility of normal Neisseria species colonization within the vaginal flora. Therefore, co-treatment should be dependent on an assessment of individual patient risk and local prevalence rates.

Differential Diagnoses

In the differential diagnoses, one should consider other infections that infiltrate the genital and urinary systems of men and women. Such diseases include:

- Bacterial vaginosis
- Fitz-Hugh-Curtis syndrome
- *Mycoplasma genitalium* infection
- Periurethral abscess
- Prostatitis
- Salpingitis
- Tubo-ovarian abscess
- *Ureaplasma* infection

Treatment Planning

Uncomplicated Genital Chlamydia:

The World Health Organization (WHO) recommendations for treatment of uncomplicated genital chlamydia infections are the following:

- Azithromycin 1 g by mouth as a single dose or
- Doxycycline 100 mg by mouth twice daily for 7 days, or one of these alternatives: tetracycline 500 mg orally 4 times daily for 7 days, erythromycin 500 mg orally twice daily for 7 days, or ofloxacin 200-400 mg orally twice daily for 7 days

Anorectal Chlamydial infection:

In anorectal chlamydial infections, the WHO recommendation is oral doxycycline 100 mg twice daily for 7 days over oral azithromycin 1 g as a single dose.

Chlamydial infection in pregnancy:

WHO recommends the following for the treatment of chlamydial infection in pregnancy:

- Azithromycin recommended over erythromycin, amoxicillin, and erythromycin
- Azithromycin 1 g by mouth as a single dose or
- Amoxicillin 500 mg orally 3 times daily for 7 days or
- Erythromycin 500 mg orally twice daily for 7 days

Lymphogranuloma Venereum:

The WHO recommends the following for the treatment of lymphogranuloma venereum (LGV):

- In adults and adolescents with LGV, the guidelines suggest doxycycline 100 mg orally twice a day for 21 days over azithromycin 1 g orally weekly for 3 weeks.

- Good practice dictates the treatment of LGV, particularly for men who have sex with men and for people with HIV infection.
- When contraindications to doxycycline are present, azithromycin should be the therapeutic choice.
- When neither treatment is available, erythromycin 500 mg orally 4 times a day for 21 days is an alternative.
- Doxycycline should not be used in pregnancy.

Prognosis

Antibiotic treatment has a 95% effectiveness rate for first-time therapy. Although treatment failures with primary therapies are quite rare, relapse may occur. Reinfection is common, and is usually related to nontreatment of infected sexual partners or acquisition from a new partner. Death is rare but can be caused by progression to salpingitis and tubo-ovarian abscess with rupture and peritonitis. The most significant morbidity occurs with repetitive infection with chlamydiae, which leads to scarring of the fallopian tubes and subsequent sterility.

HUMAN PAPİLLOMAVİRUS AND GENİTAL WARTS

Introduction

Unknown until the second half of the twentieth century, human papillomavirus (HPV) is now recognized as being one of the most common sexually transmitted infections (STI) in the world, accoun-ting for more than one third of the new cases of STIs each year. Most HPV infections cause no symptoms, other types can cause genital warts, and still others cause invasive squamous cell anogenital carcinoma.

Prevalence/Incidence

Precise estimates of the incidence of HPV infection are not available for several reasons. First, HPV is not a reportable disease. Most infections are subclinical. Of the patients who develop findin-gs with HPV infection, most have only indirect indication of infe-ctions, such as abnormal cervical cytology. In patients who have more obvious manifestations of infection, such as external genital warts, no formal testing is done to document the presence of HPV. Finally, HPV also causes recurrent outbreaks of lesions. Because most first infections are asymptomatic, it may be difficult to recog-nize new cases from recurrent infections, which must be done to calculate incidence. Despite these limitations, several studies per-formed over the past 20 years have demonstrated a steady rise in the number of new cases of genital HPV.

Risk Factors

Risk factors for HPV acquisition are similar to those for other STIs, and include multiple recent sex partners and changing sex

partners in the last year. Coinfection with other STDs and early age at first intercourse increase the risk of HPV infection. Expression of the virus and clearance of viral infection are related to immunocompetence of the host. Human immunodeficiency virus (HIV) infection increases the risk of HPV infection and the risk of developing HPV-related disease.

Infectivity and Transmission

HPV is most commonly transmitted during sexual activity, which involves skin-to- skin contact; microabrasions in the area of contact permit the virus to be transmitted from one sexual partner to another. Even in the absence of visible lesions, such as a genital wart, the microabrasions expose the HPV-infected cells in the basal epithelium of the host and increase viral shedding.

HPV can also be transmitted from one woman to another.

Oral–genital contact can transmit infection.

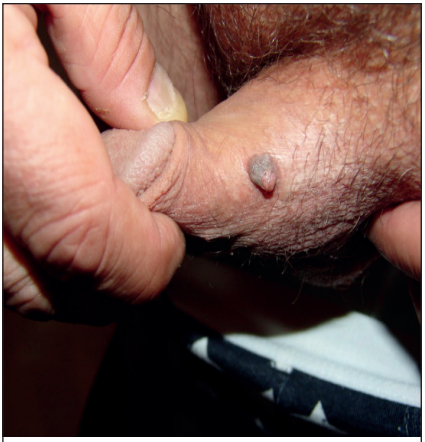
Perianal infection is quite common.

Transmission of the virus to the anogenital area has been reported in tanning beds and saunas. Other nondirect transmission may be possible via sex toys, exam tables, door knobs, and contamination of exam lights adjusted by examining hands.

Vertical transmission from mother to her newborn is possible, though rare, during delivery through an HPV-infected birth canal. The most serious complication that occurs for the newborn is respiratory/laryngeal papillomatosis. Genital warts and facial lesions in the infant can also result from exposure during delivery. However, it is not yet clear that cesarean delivery prevents HPV transmission to the baby and should only be performed if genital warts obstruct the birth canal.

Etiology

More than 120 different types of human papillomaviruses have been identified(Pic 1). All known HPV share a similar structure and genomic organization of small, non-enveloped virions with a doub-



Pic 1

le-stranded, circular DNA of 7800–7900 base pairs encased in an icosahedral protein capsid. In general, genital HPV types have been classified into two groups based on the oncogenic potential–low- and intermediate/high-risk groups The low-risk types (mainly 6 and 11) are responsible for almost half of the external genital warts. The high-risk HPV types are primarily involved in the development of squamous cell cancerous lesions of the uterine cervix, anus, vulva, and penis, but also contribute to external genital warts. Four HPV types (6, 11, 16, and 18) account for 90 % of genital HPV infection.

Clinical Course

The usual reservoirs of genital HPV infection are the moist mucosa and adjacent squamous epithelia of the male and female genitalia, the cervix, and the anus. Microabrasions that develop during sexual activity enable the infected partner to shed virus and the uninfected partner to become more susceptible to infection. Repeated trauma in the area increases infectivity as wound healing stimulates cell division, increasing episomal viral replication. The virus enters the basal epithelial cells in areas such as the inner labia minora in woman and the prepuce and frenulum in men. Anal epithelium is also traumatized easily during sex, permitting HPV infection. The virus also preferentially infects the rapidly dividing cells within the transitional zone of the cervix. After introduction of the virus into the host basal epithelial cells, the virus sheds its protein capsule and coexists within the host cell as a circular episome.

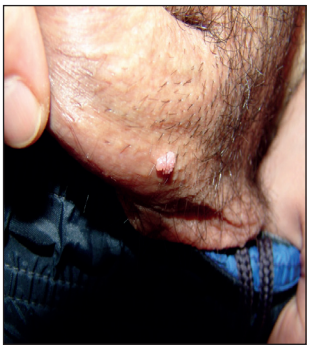
The virus then enters into a latent incubation period of 1–8 months, during which time there are no visible manifestations of the infection. The active growth phase starts when the first lesion develops. It is not known what induces the transition from latent to infective stage, but many host, viral, and environmental factors are involved. During the active infection phase, the HPV replicates independent of host cell division and induces the host cells to proliferate, creating a myriad of lesions from flat to papillary warts. Viral counts are highest in the superficial layers of the epithelium, increasing infectivity. During this phase, patients generally seek therapy.

Approximately 3 months later, the host immune system mounts a response. The innate immune system is recruited and interferons slow HPV replication and trigger the cell-mediated immune response. An immunocompetent cell-mediated immune system and cytokine production are needed for HPV clearance, but there are still challenges to viral clearance in immunocompetent hosts. HPV has some protection from the host response because the virus is intracellularly located. In addition, the epithelial cells in the perineum do not present antigens well to the host, so the HPV may not be recognized by the immune system. HPV blocks the host response by depleting local intraepithelial lymphocytes, Langerhan's cells, and CD4+ cells and down regulating cytokine production. However, lysis of the infected cells exposes the HPV to the host and triggers more intense defense.

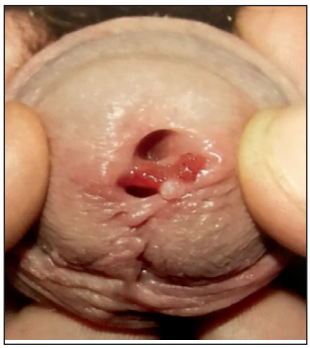
About 80–90 % of people will clear the infection so that the virus can no longer be detected. Only 10–20 % of individuals will have persistent infection that can express itself either as a latent infection, which may be periodically reactivated, or as a persistent (and more difficult-to-treat) infection. Recurrences are more likely when host immune system is compromised by chemotherapy, corticosteroid therapy, or HIV infection.

Clinical Manifestations Genital warts can be found on the external genitalia, the vagina, cervix, anus, mouth, and larynx(-pic2-3). Most patients with genital warts are asymptomatic. Pa-

tients with external genital warts may complain of a bump or mass they palpate or see on inspection. Infected or large lesions may be tender or associated with spotting, odor, or tenderness. Larger internal warts may produce dyspareunia or postcoital spotting. Urethral lesions may impair flow of urine or ejaculate. Condyloma acuminata are the classical external genital warts. They are raised, acuminate, exophytic lesions, which on keratinized skin are white, gray, or flesh-colored warty lesions. On mucosal surfaces, low-risk HPV tends to have finger- like projections and blend in color with surrounding tissue.



Pic 2



Pic 3

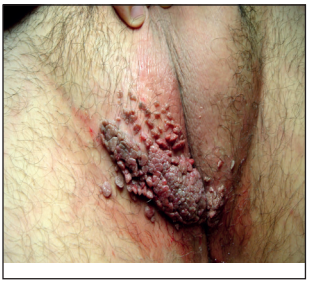
Another presentation of HPV in the genital area are papillomas. Papillomas are raised, possibly pigmented lesions, which are slow-growing and sometimes pedunculated. They are often mistaken for skin tags or moles and are most commonly found on keratinized skin.

The high-risk HPV usually causes flat genital warts. They may be hyperpigmented, white or red, depending on the impact HPV has on local melanocytes.

In women, external warts may present anywhere on the vulva, perineum, and perianal area. External genital warts in men may involve the squamous epidermis of the penis, foreskin, scrotum, perineum, and perianal area. Internal warts affect the mucous membranes of the urethra, anus, vagina, and oral cavity (pic 4-5). Squa-

mous cells on the cervix can also be involved as can the transitional epithelium of the urethra. Oral HPV lesions are not common, but can be found in women with external genital warts.

Pic 4



Pic 5

The differential diagnosis for genital warts in women includes vestibular papillomatosis or micropapillomatosis labialis. These are congenital papillations that fill the vestibule with symmetric, smooth-contoured projections. One single projection arises from a base. In contrast, condyloma acuminata have multiple projections from one base and vary in size and distribution. The projections with vestibular papillomatosis may turn white after the application of acetic acid, but that observation does not confirm HPV infection, because there are many other causes of acetowhitening, including acute candidal infection, contact dermatosis, etc. In men, pearly penile papules that are found circumferentially around the tip of the penis may be misdiagnosed as HPV- related external genital warts. These normal papules are symmetrical and are located just under the corona and either side of the adjacent frenulum.

Other lesions that are in the differential diagnosis for the lesions caused by HPV include sebaceous cysts, molluscum contagiosum (especially in HIV-infected patients), and rudimentary hair shafts on the penis. For flat lesions, the differential diagnosis includes vulvar epithelial neoplasia, vaginal intraepithelial neoplasia, and cervical intraepithelial neoplasia depending on location. Condyloma lata, other dermopathies, and invasive carcinoma must also be considered.

Diagnosis

Genital warts are commonly diagnosed by clinical examination. They may appear as typical peaked, cauliflower-like lesions; smooth papules; papules with a rough, horny layer; or as flat lesions. Testing for HPV is not useful in either the clinical diagnosis or the management of external genital warts. HPV testing for high risk types is only clinically useful for women being screened for cervical cancer.

Biopsy of a suspicious lesion should be performed and sent for pathological analysis. Lesions are considered suspicious when they are surrounded by thickened skin, pigmentation, or unexplained ulcerations; raised, bleeding, red, or pigmented; indurated, fixed, or large (>2 cm); unresponsive to targeted therapy; and whenever a suspicion for malignancy exists. Warts in hosts who are immunocompromised (HIV-infected) and/or who are at risk for HPV-related malignancy (chronic warts, heaving smoking) should also be biopsied. Biopsy is also indicated if the diagnosis is uncertain. Examination of other areas susceptible to infection is also necessary.

Treatment of Genital Warts

Because warts can be disfiguring and prone to superinfection, treatment is generally recommended. However, it must be recognized that about 20–30 % of patients with genital warts will spontaneously clear the warts. In another 60 % of individuals, localized destruction of the wart will recruit host defenses and clear the HPV infection.

The goal of treatment is clearance of visible warts. Some studies show that treatment may reduce infectivity, but there is no evidence that treatment of warts reduces the risk for cancer or eliminates the virus. Therapies can be used alone or in combination. Factors that may influence selection of treatment include wart size, wart number, anatomic site of wart, wart morphology, patient preference, as well as cost of treatment, convenience, adverse effects, and provider experience.

It should be noted that warts on moist skin surfaces or intertriginous folds will usually respond to all treatments better than warts found on dry, keratinized skin. Selection of a treatment modality should recognize that warts found on the keratinized skin of the circumcised penis or labia majora will probably require more treatment sessions than those found under the foreskin of the penis or on the inner folds of the labia minora. Most genital warts will respond within 3 months of treatment regardless of treatment modality chosen.

Imiquimod 5 % Cream

Imiquimod is a topical cell-mediated immune response modifier that is recommended for treatment of external genital warts. The patient is instructed to apply a thin layer of cream to visible genital warts. Imiquimod acts as a local immune modulator. It induces local interferon and cytokine release, which triggers both the innate and cell-mediated immune response systems. Complete clearance of warts occurs in 72–84 % of women with use of imiquimod but complete clearance rates in men are only half those seen in women. However, many patients who do not completely clear all their lesions will have a substantial reduction in the numbers and size of remaining lesions. In clinical trials, 81 % of subjects had at least a 50 % reduction in wart area. HPV recurrence rates after treatment with Imiquimod appear to be lower (5–19 %) than with other self-administered treatments. Imiquimod is FDA pregnancy category C.

Podofilox 0.5 % Solution or Gel

Podofilox contains purified extract of podophyllin and is recommended for the treatment of external genital warts not involving mucosal epithelium. The solution should be applied to the lesion with a cotton swab; the gel should be applied with a finger. The total wart area treated at any application should not exceed 10 cm2 and the total volume of podofilox applied should be limited to 0.5 mL per day. The mechanism of action of podofilox is to disrupt

cell division. It arrests the formation of the mitotic spindle in metaphase and prevents cell duplication. It may also induce damage in local blood vessels and induce immune response by releasing interleukins. The safety of podophyllin during pregnancy has not been established.

Sinecatechin Ointment 15 %

Sinecatechin ointment is a green-tea extract that was recently approved for the treatment of external anogenital warts. The mechanism of action is not well understood but probably related to green tea's antioxidative properties as well as potential anti- viral and antitumor effects. It is not recommended for HIV-infected patients, immunocompromised patients including those with HIV, or those with clinical genital herpes as the safety and efficacy has not been established.

Trichloroacetic Acid (TCA) 80–90 % or Bichloracetic Acid (BCA) 80–90 %

These acids coagulate the proteins within the wart and act as chemical cautery. They can be used for the treatment of warts on keratinized and mucosal epithelia. TCA or BCA is recommended for the treatment of external genital warts, vaginal warts, and anal warts. TCA and BCA are not absorbed into systemic circulation and are safe to use during pregnancy.

Podophyllin Resin 10–25 % Sodium This chemical is compounded in a tincture of benzoin that is cytotoxic and antimitotic and induces tissue necrosis. Podophyllin is recommended for the treatment of external genital warts and urethral meatus warts. Podophyllin should not be applied to the cervix, vagina, oral cavity, or anal canal. The safety of podophyllin during pregnancy has not been established.

Cryotherapy Cryotherapy freezes the water within the mitochondria of the cell and causes thermally induced cytolysis. Cryotherapy is safe to use during pregnancy. Liquid nitrogen is recommen-

ded for the treatment of external genital warts, vaginal warts, urethral meatal warts, anal warts, and oral warts. Overall, clearance rates with cryotherapy are up to 90 %, recurrence rates approach 40%.

Surgical Therapies This therapy is reserved for large or medium lesions and those that are unresponsive to medical therapies. Various techniques that can be used in different settings include scissor excision, shave excision, curettage, LEEP, electrocautery, and laser. Carbon dioxide laser therapy may be useful for extensive vulvar warts and anal warts, especially if other therapies have failed. It is also the preferred treatment for immunocompromised, nonpregnant patients with large lesions. All the lesions may be destroyed in one treatment, although healing may be uncomfortable.

Alternative Therapies Alternative regimens include intralesional interferon, photodynamic therapy, and topical cidofovir. But they may cause more side effects or have limited efficacy data.

Combination Therapies The CDC treatment guidelines note that because each of the available treatments has shortcomings, some clinics employ combination therapy (i.e., the simultaneous use of two or more modalities on the same wart at the same time). As data is limited on the efficacy and risk of this practice, clinicians may want to use different treatment modalities sequentially.

Patient Education and Counseling Patients often may ask how long the infection has been there and when and where was the infection acquired. It is difficult for the clinician to answer these questions accurately. The HPV infection may be subclinical (without visible lesions) for many months or years. A period of decreased immunity (as seen in pregnancy) or increased stress may trigger the growth of warts. It is important for the patient to understand three other points:

- Genital HPV infection is common among sexually active adults.
- Genital HPV infection is usually sexually transmitted, but the sex partner probably is not aware that infection is present.
- HPV testing is not warranted for the patient or the partner.

GENITAL HERPES

Introduction

Herpes simplex virus (HSV) has a long and confusing history. More than 2,500 years ago, Hippocrates first used the word "herpes," derived from the Greek word "to creep," to describe how the lesions of this contagious ulcerative disease seemed to creep or crawl along the skin. Galen first noted that recurrences develop at the same anatomic site. However, over time, the word herpes was used to describe many skin conditions from lupus to zoster. The definition of herpes (particularly oral lesions) became more rigorous in the seventeenth century. In the 1830s, recurrent genital herpes was described and 60 years later was identified as a "vocational disease"—a sexually transmitted infection (STI). The virus itself was not identified until the 1950s. In 1971, it was proposed that two different types of HSV caused infection. HSV-1 commonly causes labial or pharyngeal infection, and transmission is primary by nongenital contact. HSV-2 typically affects the genital area and is transmitted by intimate sexual contact. However, both viruses are capable of causing either genital or oral-pharyngeal infections that appear identical on examination. In the United States, HSV infection is one of the most common STIs and is the leading cause of genital ulcers.

Prevalence and Incidence

The full extent of the HSV epidemic in the United States is not known because (1) HSV infection is not a reportable disease in most states, (2) most people carrying the virus are not aware that

they are infected, and (3) it is not possible in many cases for people to distinguish between an initial outbreak (incidence) and a recurrence (prevalence).

Serology studies suggest that 50 million people in the United States have genital HSV infection. In Europe, HSV-2 is found in 8–15 % of the general population. In Africa, the prevalence rates are 40–50 % in 20-year-olds. Between the two most recent iterations of National Health and Nutritional Examination Surveys (NHANES)—NHANES in 1988–1994 and NHANES in 1999–2004—the seroprevalence of HSV-2 among civilian, noninstitutionalized people aged 14–49 in the United States decreased by 19 % from 21 to 17 %. By contrast, 57.7 % of the same group was seropositive for HSV-1 in 1999–2004, which represents a 6.9 % decline. Seroprevalence for HSV-2 increases with age, being virtually nonexistent in children under age 12, and stabilizing after age 30; this pattern is consistent with the virus being an STI. By contrast, HSV-1 seroprevalence in children under 5 is 20 % and rises in a linear fashion until age 20. This pattern is not characteristic of an STI. More than 85 % of the world's adult population is seropositive for HSV-1.

The NHANES surveys found that women (23.1 %) are more likely to be seropositive than men (11.2 %). Seropositivity is highest among blacks (40.3 %), followed by whites (13.7 %) and Hispanics (11.9 %). Lifetime numbers of sex partners influenced seropositivity, varying from 2.6 % of patients with no sex partners to 39.9 %, for people with at least 50 partners. Patient history is very unreliable for obtaining information about this infection.

Of the 50 million Americans who are HSV seropositive, only 9 % is aware of having had a previous infection. Even when seropositive individuals are asked specific questions, only 25–33 % admits having had symptoms consistent with genital herpes. Approximately 75 % of source partners discover their own infection only when their newly infected partner is diagnosed.

It is estimated that there are 1.6 million new cases of genital

HSV infections in the United States each year, and 10 million recurrences annually. Worldwide, 20 million new people are infected each year.

Herpes infections are troubling enough by themselves, but they also represent a risk factor for acquiring and spreading other STIs. Herpes is one of the most common infections found in HIV-infected adults; 90 % of HIV patients are also infected with HSV. Several studies have established a causative relationship between HSV genital ulcerations and HIV acquisition, transmission, and progression. High titers of HIV are found in genital herpes ulcerations. In addition, HIV infection reactivation is accompanied by an increase in plasma HIV viral load. A meta-analysis of studies that documented HSV-2 infection before HIV acquisition found that the HSV more than doubled the risk; the relative risk was 2.1 (95 %, C1: 1.4–3.2). About 52 % of HIV infection is attributable to HSV-2 coinfection. The population attributable risk percentage varied with HSV-2 prevalence and ranged from 19 to 47 %.

Risk Factors

HSV-2 infects all economic classes, race, ages, and ethnic groups. However, there are identifiable risk factors for HSV-2 infection, which reflect biological and behavioral influences. Major risk factors for seropositivity include female gender, ethnicity (African-American or Hispanic), history of STIs, increasing number of sex partners, sexual contact with commercial sex workers, cocaine use, and low socioeconomic status or level of education. In addition, older age and young age at sexual debut are important factors. Each additional sex act per week increases the risk of acquiring genital herpes. In a study of discordant monogamous couples, risk factors for HSV acquisition were female gender and the absence of HSV-1 antibodies. Other risk factors that have been shown to be independent predictors of HSV-2 infection in women include cigarette smoking, douching, history of having intercourse with an

uncircumcised male partner, the presence of vaginal group B streptococcus, and abnormal vaginal flora.

Infectivity and Transmission

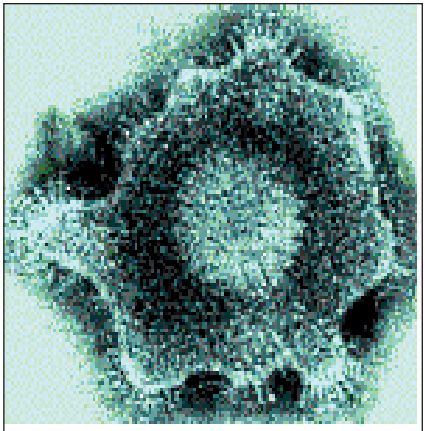
Herpes is highly contagious. In a study of newly acquired HSV infections the median number of sex acts before transmission was 40. Seventy-five percent of sexual partners of HSV-2-infected people contract the disease. In a study of seronegative sexually active individuals, the annual rates of infection were 1.6 % for HSV-1 and 5.1 % for HSV-2; the primary route of transmission of HSV-2 infection is genital-to-genital skin contact with an infected partner who is shedding virus symptomatically or asymptomatically. HSV-2 is responsible for about 80 % of genital herpes infections, even though there are as many initial cases with HSV-1 infection, which is usually acquired through oral–genital contact, HSV-2 is more likely to cause recurrent episodes. HSV-1 genital infections are higher in men who have sex with men (MSM).

Asymptomatic shedding is responsible for most of the transmission of HSV. HSV DNA has been detected by polymerase chain reaction (PCR) from genital samples of HSV-2-infected women on 28 % of days. In discordant couples, 69 % of transmission occurred when the infected partner was asymptomatic. Transmission of HSV between discordant sexual partners occurs at a rate of about 10 % per year. Asymptomatic shedding is more common with HSV-2 than with HSV-1 infection.

Although transmission of HSV infections generally results from intimate skin- to-skin contact with an infected individual, it can also result from exposure to infected saliva, semen, vaginal secretions, or fluid from active herpetic lesions.

Drying and room temperature quickly inactivate the virus. The-refore, HSV transmission is not believed to occur often through exposure to fomites.

Etiology



Pic 1

HSV belongs to the Herpesviridae family, which also includes the cytomegalovirus, Epstein–Barr virus, and varicella-zoster virus. HSV-1 and HSV-2 are two of the eight human herpes viruses; neither is found in other animal species. (Pic 1)

HSV is an enveloped, double-stranded DNA virus. HSV-1 and HSV-2 are distinguished by antigenic differences in their envelope proteins. However, the genomes of the two viruses are 50 % homologous. There are multiple specific strains of HSV-1 and HSV-2.

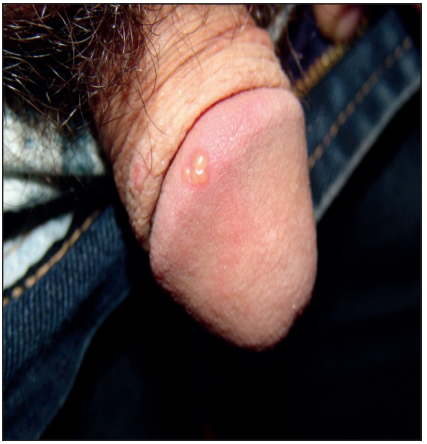
After contact with abraded skin or mucosal surfaces, the virus replicates and initiates infection in the epidermal cells of the target area. Following this initial infection, the virus travels in a retrograde fashion within axons of sensory nerves to the dorsal nerve root ganglion where it continues to replicate to establish lifelong latency. HSV-2 usually migrates to the sacral nerve roots (S2, S3, and S4). Recurrent outbreaks localized to the dermatomes innervated by the infected nerve are quite common, especially with HSV-2. In patients with an initial primary episode of genital herpes, the risk of having at least one recurrence during the first year is nearly 90 %. Although some HSV-2-infected patients may not experience symptomatic recurrences, virtually all will have repeated episodes of asymptomatic viral shedding from their genital secretions. This shedding places their sexual contacts at risk for acquiring the infection.

Clinical Manifestations

There are three types of HSV genital infections: primary infection, non-primary initial infection, and recurrent infection. A primary infection is the first HSV infection that occurs in a patient without prior exposure to HSV, as demonstrated by the fact that the patient has no antibodies to HSV. An initial, non-primary infection is defined as a first HSV infection with one HSV type in a patient who is already infected with another type of HSV (e.g., a new HSV-2 infection in a patient with prior HSV-1 infection). Because HSV-1 is so prevalent, most initial genital infections (usually with HSV-2) are initial, non-primary infections. Recurrent infections are outbreaks owing to reactivation of a previously acquired HSV infection (not a reinfection).

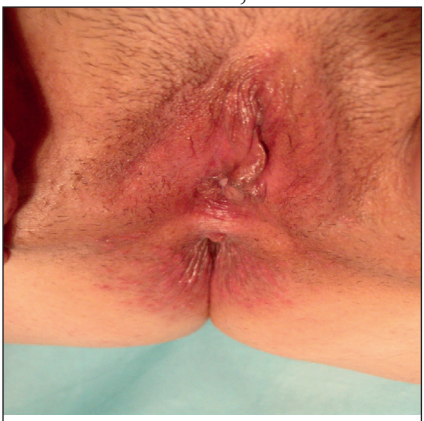
The incubation period after genital exposure to HSV-1 or HSV-2 is approximately 4 days (range 2–12 days). Almost half of first-episode genital herpes is caused by HSV-1. The local and systemic symptoms with primary genital infections are generally the same intensity and duration for both HSV-1 and HSV-2 .

The classical clinical presentation of genital herpes starts with widespread multiple painful macules and papules(pic-2), which then mature into clusters of clear, fluid- filled vesicles and pustules. The vesicles rupture and form ulcers. Skin ulcers crust, whereas lesions on mucous membranes heal without crusting. Scarring does not usually occur after re-epithelization. Secondary bacterial infections may produce ulcers that extend into the dermis or that cause cellulitis. In women, the ulcers occur

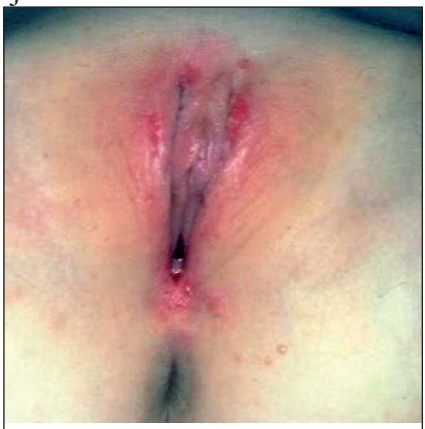


Pic 2

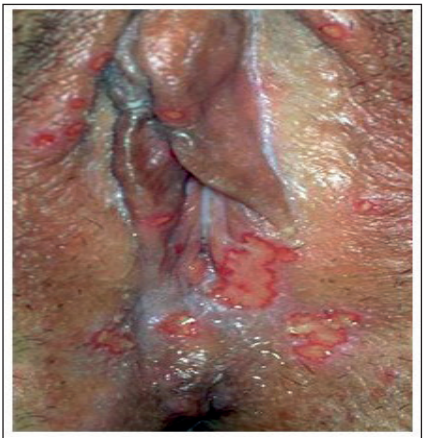
at the introitus, labia, perineum, or perianal area (pic 3-4). Patients complain of dysuria, vulvar pain, dyspareunia, and increased vaginal discharge and bleeding (pic 5-6). Patients may volitionally retain urine because the pain with urination is so severe. On average, initial primary infections last 12 days, but viral shedding continues for 20–21 days. The infection may be spread by autoinoculation to other areas of the genitalia as well as to the buttocks and thighs and to distant sites, such as the conjunctiva. Urethral involvement



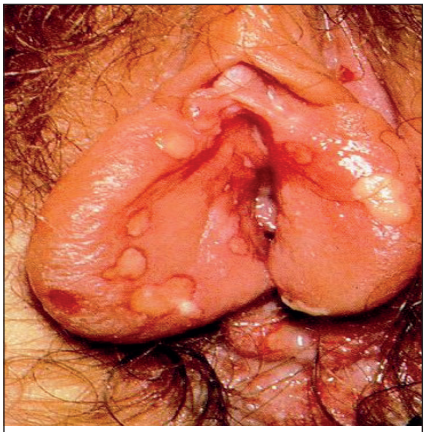
Pic 3



Pic 4



Pic 5



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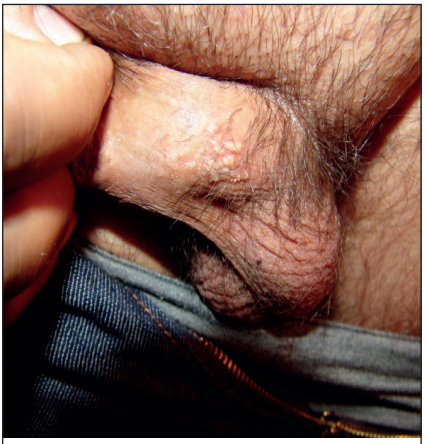

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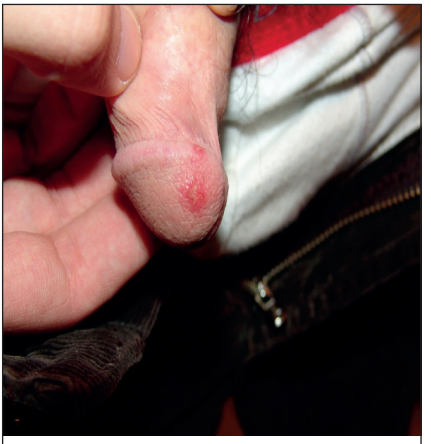

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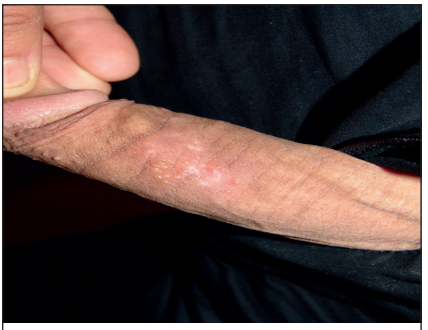

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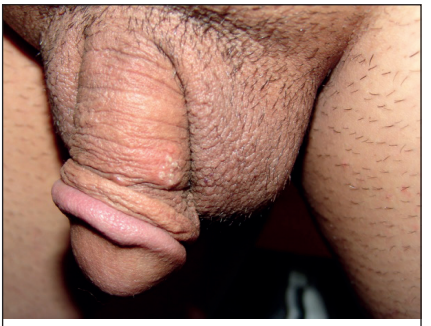


Pic 10

is common; 82 % of patients with initial infection have urethritis with positive urethral cultures. Cervical infection, which is found in 80 % of women, causes increased vaginal discharge and postcoital spotting and bleeding. Men usually develop lesions on the penile shaft or glands(pic 7-10). The patient usually develops tender inguinal adenopathy. Perianal infections are also common in MSM. Pharyngitis may develop with oral exposure.

Initial primary infection is associated with a higher rate of systemic involvement and greater severity of local disease than is seen with initial non-primary genital herpes infection. With primary in-

fections, 66 % of women and 40 % of men develop constitutional symptoms such as fever, malaise, nausea, headache, myalgia, hepatitis, meningitis, and autonomic nervous system dysfunction as a result of viremia. Approximately 30 % of women and 10 % of men have headache, stiff neck, and photophobia with or without fever ; 4 % of individuals will develop viral meningitis. The meningitis is transient and requires no treatment; it resolves without any sequelae. Infection in the sacral plexus may affect sensation in the pelvis as well as detrusor function; 10–15 % of women with initial disease will develop urinary retention that requires catheterization. This nerve dysfunction may last 6–7 weeks. HIV-infected individuals are at higher risk of developing the more serious clinical manifestations, including dissemination, encephalitis, and meningoencephalitis.

Most initial genital herpes infections are not "classical" in their presentation. The majority of initial infections are asymptomatic or atypical; patients note nonspecific symptoms of discharge, dysuria, pain, erythema, back pain, pruritus, soreness, fissure, and folliculitis and think they have a rash, allergy, yeast infection, cystitis, zipper trauma, jock itch, or bike seat irritation. Clinicians often fail to diagnose HSV infection and attribute the signs and symptoms to other diagnoses, particularly when there are only small blisters or ulcers, vaginal lesions, urethritis or cervicitis without external lesions, excoriation, fissures, or nonspecific erythema. About 1 in 7 men who present with sores, blisters, ulcers, crusting, or small cuts/slits had HSV and about 1 in 9 women with redness, irritation, or rash have HSV. The relative mildness of the symptoms and subtlety of the physical findings may occur because most initial infections with HSV-2 occur in people who carry antibodies to HSV-1. There are generally fewer lesions with these non-primary initial infections. Systemic symptoms develop in only 16 % of people with initial non-primary infections. The duration of infection in this situation is shorter (9 days) and viral shedding lasts only 1 week. Thus,

genital herpes infection should be considered routinely in any patient with genital lesions. This would include patients with genital erythema, rash, skin fissuring, pain, burning, or genital itch.

Recurrent infections are more common and occur more frequently with HSV-2 than with HSV-1 infection. Within 1 year of diagnosis of initial primary HSV-2 genital infections, 90 % of people will have at least one recurrence, whereas only 55 % of HSV-1-infected people have repeat outbreaks. In one study, nearly 40 % of the HSV-2-infected subjects had six or more recurrences. Median time to recurrence with HSV-2 was 49 days, whereas median time to recurrence of HSV-1 was 310 days. Most recurrences are asymptomatic. About half of patients who recognize recurrences report prodromal symptoms, such as localized tingling, pruritus, or pain 30 min to 48 h before eruption. Some patients experience more painful and prolonged prodromes including shooting pain in the buttocks, hips, or legs for up to 5 days. Recurrent herpes outbreaks are usually less severe than primary outbreaks. The numbers of lesions are generally fewer. The lesions may appear the same as in primary outbreaks but heal in half the time or they may present as fissures or vulvar erythema rather than typical ulcers. About 10–15 % patients with recurrent genital herpes will have coexisting cervical disease. Systemic manifestations do not occur with recurrences in immunocompetent patients. Over time, recurrence rates decrease.

Frequently, women who have HSV-related ulcers become superinfected with Candida. Prompt attention to treating that infection can decrease the patient's discomfort.

Factors other than HSV type that have been associated with frequency of recurrent outbreaks include fatigue, menstruation, intercourse, and trauma. The most common cause of recurrence of HSV in HIV-infected patients is the degree of immunosuppression. Although it is commonly believed that acute episodes of stress are associated with onset of recurrent herpes, studies have concluded

that only persistent stress lasting longer than 1 week and depression are psychological stressors that are associated with onset of recurrent outbreaks.

Testing Techniques

Until recently, viral isolation in cell culture and determination of the type of HSV with fluorescent staining has been the mainstay of herpes testing in patients presenting with characteristic genital lesions. The cytopathic cell changes induced by the herpes virus in tissue culture usually occurs within 3 days of inoculation but the cell culture is not considered negative for herpes until a final negative reading on day 15. The rate of recovery of the virus depends on the stage of the clinical disease being tested. There is a 90 % chance of obtaining a positive culture when the specimen is obtained from the base of a freshly unroofed vesicle or pustule, but that sensitivity decreases to 70 % when the specimen is obtained from an existing herpes ulcer and drops to only 27 % when a crusted lesion is used as a specimen source. The probability of recovery of the virus from a patient with recurrent herpes, which has a much shorter duration of viral shedding and a lower viral load, is only 30 %.

The Tzanck preparation is a histological examination of lesions that identifies the presence of a DNA virus with multinucleated giant cells typical of HSV. Although the test is rapid, it is not specific for HSV. Similar changes can be found in sites infected with the varicella virus. Similarly, cytological detection of HSV infection (e.g., from pap smear) is not only insensitive, it is nonspecific and has a low positive predictive rate. It should not be used for diagnosis.

PCR assay for HSV DNA has been shown to be more sensitive than viral culture and has a specificity that exceeds 99.9 %. The PCR test is the standard of care test for the diagnosis of herpes central nervous system infection. The PCR is highly accurate and faster than tissue culture. Its use in clinical practice is currently expanding due to its higher sensitivity than traditional tissue cell culture

Commercially available blood tests that can identify prior exposure by testing for HSV-specific glycoproteins G2 (HSV-2) and G1 (HSV-1) immunoglobulin (IgG) G antibodies. These two Food and Drug Administration (FDA)-approved tests for laboratory use are HerpeSelectTM-1 enzyme-linked immunosorbent assay (ELISA) IgG, and Herpe Select 1 and 2 Immunoblot IgG (for HSV-1 and HSV-2) . They have a sensitivity of detecting HSV-2 of 98 % and a specificity of 97–100 % because of their ability to detect glycoprotein G-2 for HSV-2 and glycoproteins G-1 and C-1 for HSV-1. Two point of care tests are also available: Biokit HSV-2 and SureVac HSV-2.

The older tests should never be ordered to determine a specific type of herpes. Seroconversion of an initial primary herpes attack will usually occur 12 weeks after the outbreak. Therefore, HSV-2 serological testing cannot detect a primary infection; it can be used only to rule out recurrent infections. The CDC list of appropriate use of serologic testing .

Screening in the general population should generally not be offered. More detail of situations in which testing might be appropriate is provided here.

1. Diagnosis of HSV-2
    1. (a) Patients who present with a 3-month or greater history of recurrent genital lesions suggestive of recurrent genital herpes but have no lesions on exam or have recent negative viral culture for herpes. A negative HSV-1 and HSV-2 serological test would rule out genital herpes as the cause of the lesions, whereas a positive HSV-2 serology would support the diagnosis of recurrent genital herpes. Interpretation of a positive HSV-1 test would be more difficult. However, it must be recognized that the recurrent symptoms may be owing to an unrelated lesion.

2. (b) Patients who have first presentation of genital symptoms when culture or antigen detection is negative or not available. Note: testing would have to be delayed by 12 weeks to allow for antibody formulation.

2. HIV-infected patients. Because of the high coinfection rate with HSV, all HIV- infected patients should be offered type-specific HSV serological testing.
3. Partner consideration. The evaluation of patient who is in a partnership or is considering partnership with a person with documented genital herpes and is concerned about the possible transmission. If the asymptomatic person is HSV-2-seropositive, then the couple can be reassured that further transmission between them cannot take place. If the asymptomatic person is seronegative, then the couple should be counseled regarding preventive measures (condom use) to reduce the chance of transmission.
4. Screening can be selectively offered to those patients as part of a comprehensive evaluation of individuals with a STI and those who are at risk for STIs.
5. Pregnancy applications. The CDC recommends against universal screening in pregnancy. However, screening should be offered to asymptomatic pregnant women whose partners have genital herpes, as well as prenatal patients who are HIV-infected. Discordant couples with an infected man should be counseled regarding the risk of acquiring and transmitting herpes and advised about preventive measures (e.g., abstinence during the third trimester) to avoid an initial primary infection. If the woman is seropositive, she should be counseled regarding the signs and symptoms of genital herpes near term and counseling on plans for route of delivery.

6. Other authors have suggested a broader utilization of serological testing in clinically apparent initial infections, although these applications have not been endorsed or found to be cost effective. These authors have suggested that an HSV-2 titer could be used to counsel women on the likelihood of recurrence (HSV-2 is more likely to occur than HSV-1 infection). Others have recommended routine serological testing for both HSV-1 and HSV-2 antibodies to establish if the clinical outbreak is a primary, non-primary, or a recurrent lesion. The rationale is that if the patient has an HSV infection and if the serology is HSV-1- and HSV-2-negative, then the patient has an initial primary outbreak with exposure during the 14 days before the onset of symptoms. On the other hand, if the serology is HSV-1-positive but HSV-2-negative, then this is an initial non-primary outbreak; in such settings, one could probably come to that conclusion because 80 % of genital herpes is HSV-2. However, the patient would require a repeat testing for HSV-2 in 3 months to confirm this diagnostic impression. If the serology is HSV-2-positive, then the patient has an initial non-primary clinical out- break of recurrent genital herpes with exposure sometime more 14 days prior.

Diagnosis

The clinical diagnosis of genital herpes can be difficult. This is because the infection presents with “nonclassical” or atypical characteristics or with no symptoms at all. Although the most common cause of genital ulceration is an HSV infection, other etiologies should be considered, including chancroid, traumatic ulceration, primary syphilis, Behçet’s syndrome, recurrent aphthous ulcers, fixed drug reaction, Crohn’s disease, contact dermatitis, Reiter’s syndrome, psoriasis, erythema multiforme, and lichen planus. The clinical diagnosis of genital herpes should always have laboratory

confirmation, if possible.

For the last 20 years, the gold standard for diagnosis has been a positive viral culture. However PCR testing is more sensitive than viral culture. Viral culture results can be available in 48–72 h and have a false- negative rate of 5–30 %. Patients who present with new onset of genital herpes should also be tested for HIV infection. Testing for other STDs depends on the clinical presentation. Cultures are more likely to detect the virus if they are obtained from the freshly exposed base of a newly ruptured vesicle than if they come from an ulcerated or crusted lesion. Primary infections are more likely to produce positive result than are recurrent infections. Because of the transient nature of viral shedding, a negative culture does not exclude genital herpes. In the patient who has recurrent infections in which isolation of the virus has been difficult, one option is to have the patient return for viral cultures 1 or 2 days into the next outbreak. Another option is to order serological testing for type-specific HSV antibodies to rule out recurrent infections as described earlier.

Treatment

The CDC recommended therapies for initial infections and episodic and suppressive therapies for recurrent infection are displayed in Table 1.

Treatment Recommendation for Initial Herpes Genitalis

All patients with initial clinical episodes of symptomatic genital herpes should be treated with an antiviral agent for 7–10 days or until the lesions clear. Local measures, such as saline irrigation, sitz baths, topical anesthesia, use of electric blow dryer on cool setting, and warm compresses are helpful to prevent secondary infection of the lesions and to offer comfort. Careful attention must be paid to limit the spread of infection by autoinoculation. Because the effe-

ctiveness of antiviral therapy is dependent on initiation of therapy as early in the clinical stage of disease as possible, treatment with antivirals should be started based on presumptive clinical diagnosis alone, before culture results are available.

The CDC lists three different drugs in four different treatment options for initial clinical episodes of genital herpes (see Table 1). Acyclovir (ZoviraxTM) was the first drug approved for the treatment of genital herpes. Acyclovir is a purine nucleoside analog that is a competitive inhibitor of viral DNA polymerase. Acyclovir completely inactivates the viral DNA polymerase and terminates viral DNA chain elongation. If given early in the initial stage of HSV infection, acyclovir will reduce the duration of symptoms by an average of 2 days, the time to heal the ulcers by 4 days, and viral shedding by 7 days compared to placebo. In contrast to valacyclovir and famciclovir, acyclovir has poor oral bioavailability and a relatively short intracellular half-life, which means that acyclovir requires a three times a day oral dosing schedule. For severe herpes infection requiring hospitalization, an intravenous formulation of acyclovir is available. The advantage of oral acyclovir therapy over other oral agents is lower cost, small tablets, and the availability of a liquid formulation. The disadvantages of oral acyclovir are the three times a day dosing frequency.

Valacyclovir (ValtrexTM) is a prodrug of acyclovir that is converted to acyclovir in the liver. The oral bioavailability of valacyclovir is much better than acyclovir and approaches the level of intravenous acyclovir. The advantage of valacyclovir is a twice daily dosing schedule. The disadvantage of valacyclovir is higher cost and unavailability of nonoral formulations.

Famciclovir (FamvirTM) is the oral form of penciclovir, a nucleoside analog with properties similar to acyclovir with an improved oral bioavailability Famciclovir is more expensive than acyclovir.

All oral antiviral agents have been shown to be equally effective. Acyclovir, valacyclovir, and famciclovir have excellent sa-

fety profiles with few adverse side effects. It is estimated that more than 80 million people have taken either acyclovir or valacyclovir without significant complications. HSV infections that are resistant to any of the recommended antiviral therapies are rare and generally restricted to immunocompromised patients. If resistance to acyclovir/valacyclovir/ famciclovir develops, foscarnet 40 mg/kg body weight intravenously every 8 h is frequently effective. Compounded topical cidofovir gel 1 % applied to lesions once daily for 5 days also might be effective. Acyclovir has been used daily by patients for more than 10 years without any significant adverse effects.

After initiation of therapy, a follow-up visit with the patient should be scheduled in 7–10 days. Test results are usually available by that time, which will provide the caregiver the opportunity to provide more extensive counseling. If examination reveals new lesions or a failure of lesions to reach the crusting phase, then an additional course of antiviral agents should be prescribed.

The use of topical 5 % acyclovir ointment is no longer an FDA-approved as treatment during the initial outbreak because the oral medication is more effective and the use of ointment increases the risk of autoinoculation. Other treatments that should be discouraged owing to documented lack of treatment efficacy include l-lysine, goldenseal, and garlic. Lithium has been noted to decrease frequency of recurrent herpes but has not been proven effective in the treatment of the initial infection. According to the CDC complicated HSV such as aseptic meningitis, disseminated infections, hepatitis, or pneumonitis should be treated initially with acyclovir 5–10 mg/kg IV every 8 h for 2–7 days or until clinical improvement is observed, followed by oral acyclovir to complete at least 10 days of total

Agent	Regimen
First clinical episode	
Acyclovir	400 mg orally 3 times a day for 7–10 daysa
Famciclovir	200 mg orally 5 times a day for 7–10 daysa
Valacyclovir	250 mg orally 3 times a day for 7–10 daysa
Severe disease	1 g orally twice a day for 7–10 days
Acyclovir	5–10 mg/kg body weight intravenously every 8 h for 2–7 days or until clinical resolution is attained, followed by oral antiviral therapy to complete at least 10 days of therapy
Episodic therapy for recurrent genital herpes	
Acyclovir	400 mg orally 3 times a day for 5 days 800 mg orally twice a day for 5 days
Famciclovir	800 mg orally three a day for 2 days 125 mg orally twice a day for 5 days
Valacyclovir	1000 mg orally twice daily for 1 day 500 mg once, followed by 250 mg twice daily for 2 days 500 mg orally twice a day for 3 days 1 g orally once a day for 5 days
Daily suppressive therapy for recurrent genital herpes	
Acyclovir	400 mg orally twice a day
Famciclovir	250 mg orally twice a day
Valacyclovir	500 mg orally once a day 1 g orally once a day

Table 1 Treatment of genital herpes—CDC STI treatment guidelines 2010

Treatment of Recurrent Genital Herpes

If started at the first prodromal symptoms or sign of a recurrence, antiviral treatment of episodic outbreaks will not only reduce the severity and duration of lesions, but may also completely abort the clinical attack, stopping the lesions from progressing beyond the papule stage. The episodic dosing schedules recommended by the CDC for acyclovir (Zovirax) vary by dose and duration of treatment. The episodic recommended dose for valacyclovir and famciclovir are also specified in the CDC recommendation.

The antiviral dosage schedule for suppressive therapy may be different for patients with more frequent (>10) outbreaks annually. All three antivirals appear to be equally effective in preventing outbreaks of genital herpes and reduce asymptomatic viral shedding by 80–90 %.

In serodiscordant couples, suppressive daily antiviral therapy should be strongly considered to reduce further transmission of the infection during the first year when the incidence of asymptomatic viral shedding is highest. However, it should be noted that many couples who are discordant for genital herpes by patient history are found to be concordant by serological testing. Year-long suppressive therapy or longer should be offered to patients with frequent recurrent outbreaks, initial primary infections or patients with stressful or painful recurrences.

Immunocompromised patients are more likely to have prolonged or severe episodes of herpetic outbreak. Higher dose therapy is recommended for episodic therapy for HIV-infected persons, e.g., acyclovir 400 mg orally 3 times daily for 5–10 days; famciclovir 500 mg orally twice daily for 5–10 days; or valacyclovir 1.0 g orally twice a day for 5–10 days. For daily suppressive therapies, acyclovir 400– 800 mg is recommended orally twice to 3 times a day or 500-mg doses of famciclovir or valacyclovir orally twice a day.

Pregnancy-Related Issues

About 22 % of pregnant women are infected with HSV-2 and 2 % will acquire HSV during pregnancy. Initial HSV infection is particularly severe if it develops during pregnancy; pregnancy does not appear to increase the rate of recurrence of maternal outbreaks.

The most serious consequences of maternal infection are adverse fetal impacts and newborn infection. An initial maternal genital herpes outbreak in the first trimester of pregnancy has been associated with fetal chorioretinitis, microcephaly, and skin lesions but not spontaneous abortion or fetal death. Neonatal HSV infection occurs in about 1,500 cases each year. Neonatal HSV infection has three clinical presentations: disseminated disease involving multiple organs, such as the liver, lungs, and the central nervous system (25 % of cases); disease localized to the skin, eyes, and mouth (40 % of cases); and localized central nervous system disease (35 % of cases). Up to 30 % of infected neonates will die and up to 40 % of survivors will have neurological damage, despite antiviral therapy.

Infection can be transmitted from the mother to her fetus/newborn in three ways: transplacentally (5–8 %), intrapartum exposure (85 %), or postpartum exposure (8–10 %). The likelihood and severity of neonatal infection is influenced by the mother's antibody status. If a woman develops initial primary infection during pregnancy, there is a 5 % chance of transplacental transmission to the baby.

Most neonatal infections result from fetal exposure during delivery. The remaining confirmed cases of neonatal herpes may have been acquired postnatally, either from the mother, a relative, or hospital worker as a result of oral contact or contact with an infected finger (whitlow).

Neonatal herpes infections develop in 30–50 % of exposed infants whose mothers have an initial primary infection near time of delivery. The risk of neonatal herpes from an asymptomatic mother with a history of recurrent HSV at term or who acquire HSV in the first-half of pregnancy is much lower (<1 %). Only infants delive-

red to women who are actively shedding from recurrent infections at the time of delivery will acquire infection. It has been estimated by PCR techniques that 6–10 % of HSV-2- seropositive women shed virus in labor. However, because of the ubiquitous nature of this infection, more neonatal infections result from recurrent infections than from initial maternal infections. Infrequently, the infant may be infected by a caregiver with oral herpetic lesion or herpes whitlow, which involves the distal fingers.

The role of testing for HSV infection in pregnancy is under debate. The cost effectiveness of routine HSV screening in pregnancy is controversial.

It has been suggested that type-specific HSV-2 serology testing be performed on women who have no personal history of HSV but whose partners are known to be infected. Women who tested negative could be advised to avoid sexual contact, at least during the third trimester and encouraged to use condoms (or abstinence) throughout the rest of pregnancy. The effectiveness of antiviral therapy for the partner to decrease the risk of HSV transmission to pregnant women has not been studied.

Women who develop primary HSV infection during pregnancy should be treated with acyclovir. Acyclovir, valacyclovir, and famciclovir are classified as pregnancy category B drugs by the FDA. More than 1200 pregnancy outcomes have been followed in infants exposed in utero at all stages of fetal development to acyclovir. No significant differences in rates of birth defects or adverse pregnancy outcomes have been reported. Experience with valacyclovir and famciclovir is too limited in the CDC estimation to provide information about the safety of its use in pregnancy.

For women who are known to have recurrent outbreaks of genital lesions, suppressive therapy with antiviral agents starting at 36 weeks gestational age has also been shown to reduce the rate of symptomatic outbreaks and asymptomatic shedding and the need for cesarean section. Therefore the American College of Obstetricians and Gynecologists advise beginning acyclovir 400 mg three-ti-

me a day or valacyclovir 500 mg twice a day from 36 weeks until delivery. The use of scalp monitors in labor should be discouraged in women who are known to shed HSV, but the American College of Obstetricians and Gynecologists says the use is not contraindicated if needed to assess fetal condition adequately in women with a history of HSV but without symptoms or lesions.

Cesarean delivery is recommended for women who have active genital lesions or prodromal symptoms at the time of rupture of membranes or labor. Operative delivery has been shown to reduce the risk of transmission significantly in initial infection. Vaginal delivery is recommended for women who do not have lesions or symptoms at the time of delivery. C-section is not needed if the patient has lesions in extragenital areas, such as the buttocks or legs. The lesions can be covered and the patients can be allowed to deliver vaginally.

The pediatrician should always be informed of the maternal/patient history of herpes and the status of the mother at the time of delivery. Acyclovir may be recommended if the mother acquired the infection during pregnancy (especially third trimester) pending the results of the maternal and/or newborn culture.

Breastfeeding is not contraindicated except in mothers who have active HSV infections on the nipple or other sites on their breasts. Mothers should use caution when handling newborns and may take antiviral therapies when breastfeeding to diminish shedding.

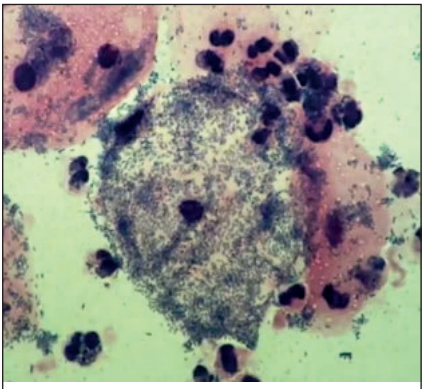
Partner Notification and Reporting Requirements

HSV is not a reportable disease in most states. Patients should be advised to talk with their sex partners about their diagnosis. If the partner is infected with the same HSV type, no precautions need to be taken. Patients should understand most infected partners are not aware that they carry the virus. All new sex partners should be informed of the potential for infection and that safer sex practices may reduce, but do not eliminate, the possibility of transmission.

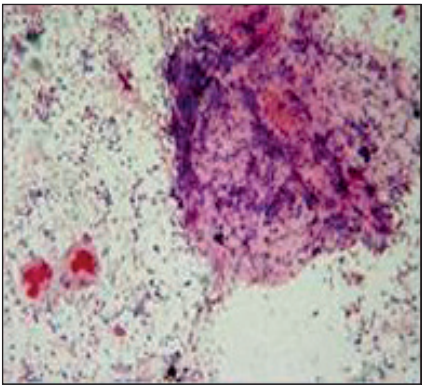
BACTERIAL VAGINOSIS

DEFINITION

Bacterial vaginosis (BV) is the most prevalent cause of vaginal symptoms among women of childbearing reproductive age. Many primary care providers perceive BV as a trivial and ill-defined syndrome of uncertain etiology. These perceptions may explain why clinicians still commonly prescribe ineffective treatments for BV. When it is symptomatic, BV produces slightly increased quantities of malodorous vaginal discharge. Although past conventional practice allowed the diagnosis of BV only after excluding other causes of vaginal discharge, such as trichomoniasis, vulvovaginal candidiasis, or cervicitis, these conditions can undoubtedly coexist with BV. Physical examination and analysis of vaginal fluid among women with BV reveal the following: a thin homogeneous, white, uniformly adherent vaginal discharge; elevation of the pH of vaginal fluid above 4.5; development of a fishy odor after mixing vaginal fluid with 10% (wt/vol) KOH; and "clue cells" on microscopic examination of vaginal fluid. Whereas Gram stain of normal vaginal fluid shows a predominance of lactobacilli, the Gram stain of vaginal fluid from a woman with BV shows a decrease or absence of lactobacilli and a predominance of Gram-variable coccobacilli consistent with Gardnerella vaginalis or anaerobic Gram-negative rods species (pic 1-2). Culture of vaginal fluid reveals mixed flora. Biochemical analysis of vaginal fluid from women with BV usually shows characteristic changes that are likely due to bacterial metabolism.



Pic 1



Pic 2

HISTORY

Nearly a century ago, Doderlein described a nonmotile bacillus, which he considered to be the normal flora of the vagina of pregnant women. The Doderlein bacillus later became known as Lactobacillus. In 1899, Menge and Kronig reported isolation of both facultative and strictly anaerobic microorganisms, as well as the Doderlein bacillus, from the vagina of most women. These early studies established that normal vaginal flora includes a mixture of microorganisms, with Lactobacillus spp. as the predominant species.

"Leukorrhea," or white discharge from the vagina, became the focus of much research in the first quarter of the century. Some thought that vaginal discharge resulted from infection of the uterus and treated the condition by curettage of the endometrium. In 1913, Curtis demonstrated that the endometria of women with leukorrhea lacked a white discharge, thus suggesting a vaginal, not endometrial, origin.

He confirmed that the vaginal flora of clinically normal, married women consisted of Doderlein's bacilli and that the greater the deviation of vaginal flora from the normal state, the greater the likelihood of vaginal discharge. Curtis linked vaginal discharge

with high concentrations of blackpigmented anaerobes, curved anaerobic motile rods, and anaerobic cocci, and with Gram-variable diphtheroidal rods, which probably represented Gardnerella. Curtis' 1913 paper established three central themes: (1) the discharge arose from the vagina and not from the uterus, (2) women having white discharge did not have large numbers of Doderlein bacilli, and (3) the presence of anaerobic bacteria in the vagina, especially anaerobic rods, correlated with vaginal discharge. Research on vaginal flora continued in the early 1920s when Schroder reported three different types of vaginal flora, which corresponded to the "rheinheitgrad" (grade of cleanliness) of the vagina.

He considered the flora of the first group, dominated by acid-producing rods (Doderlein's bacillus), the least pathogenic. A second group had a mixed flora with Doderlein's bacillus in the minority. The third group, designated as the most pathogenic type of flora, had mixed vaginal flora without lactobacilli. Despite observations by Curtis and Schroder linking vaginal discharge with a shift in the community of vaginal flora (from predominance of lactobacilli to predominance of anaerobes), other workers attempted to attribute the symptoms of nonspecific vaginitis to a single microorganism. In 1950, Weaver again reported a link between lack of lactobacilli, presence of anaerobes spp., and nonspecific vaginitis.

However, the lack of association of other aerobic and facultative bacteria with abnormal vaginal discharge led him to conclude that no particular organisms caused this syndrome. The recognition of the association of G. vaginalis with nonspecific vaginitis by Gardner and Dukes in 1955 .provided the first clear evidence that G. vaginalis caused nonspecific vaginitis. However, because these investigators failed (erroneously) to find an association between other anaerobic bacteria and BV, workers over the next 25 years tended to ignore the potential role of microorganisms other than G. vaginalis. Confusion surrounding the etiology of this

syndrome has prompted the use of various names to describe BV. Prior to 1955, leukorrhea or nonspecific vaginitis was the term most frequently used. Gardner and Dukes first applied the name Haemophilus vaginalis vaginitis to this syndrome in 1955, and today some clinicians still use the term Gardnerella vaginitis or vaginosis; others have used the term anaerobic vaginosis.

The term bacterial vaginosis is now relatively widely accepted, as BV is associated with vaginal overgrowth not only by anaerobic bacteria, but also by certain facultative bacteria, genital mycoplasmas, and a broad range of other microrganisms. Since vaginal inflammation, as defined by neutrophil predominance in vaginal fluid, is not always seen as a feature of this infection, the term "vaginosis" replaced the more familiar term "vaginitis."

EPIDEMIOLOGY AND RISK FACTORS

Most women found to have BV (84%) reported no symptoms.

Women who have not had vaginal, oral, or anal sex can still be affected by BV (18.8%), as can pregnant women (25%), and women who have ever been pregnant (31.7%).

Prevalence of BV increases based on lifetime number of sexual partners. Non white women have higher rates (African-American 51%, Mexican Americans 32%) than white women (23%).

Factors that increase the risk of BV are multiple partners, exposure to semen, prior trichomoniasis, intrauterine device usage, smoking, indigent population and frequent use of scented soap.

PATHOGENESIS

BV results from the replacement of the normal vaginal flora (Lactobacillus) with a mixed flora consisting of G. vaginalis, anaerobes, and M. hominis. Thus, most studies of the pathogenesis of BV have focused on how the microbial ecosystem of the vagina becomes altered. The epidemiologic data described above are consistent with the notion that introduction of a particular set of

organisms via sexual intercourse may initiate the change in vaginal flora characteristic of BV.

Lactobacillus spp. may help normal women to resist vaginal and cervical infection. Vaginal lactobacilli inhibit G. vaginalis, Mobiluncus, and anaerobic Gram-negative rods in vitro.

Some strains of Lactobacillus produce H2O2, and studies have demonstrated that H2O2 -producing strains of lactobacilli more frequently colonize the vagina of normal women, compared to women with BV.

The H2O2 produced by the vaginal lactobacilli may inhibit the growth of anaerobic rods, Gardnerella , Mobiluncus, and Mycoplasma

The redox potential (Eh) of the vaginal epithelial surface is lower in women with BV than in normal women.

After the women with BV were treated with metronidazole, the redox potential of the vaginal epithelium returned to the normal range, a result suggesting that the low vaginal Eh was not a persistent underlying host factor.

It is thought that amines produced by the microbial flora, perhaps via the action of microbial decarboxylases, account for the characteristic abnormal fishy odor that is produced when vaginal fluid is mixed with 10% KOH. This so-called “whiff test” is thought to be due to volatilization of aromatic amines including putrescine, cadaverine, and trimethylamine at alkaline pH. Mobiluncus is known to produce trimethylamine, but the other microbial sources of the amines are still unknown. Trimethylamine can be detected at relatively high concentrations in the vaginal fluid of VB, with a median concentration of 5 mM. The presence of trimethylamine in the vaginal fluid is thought to be largely responsible for symptoms of malodor experienced by women with BV.

The vaginal fluid of women with BV has increased levels of endotoxin, sialidase, and glycosidases, which degrade mucin and decrease its viscosity.

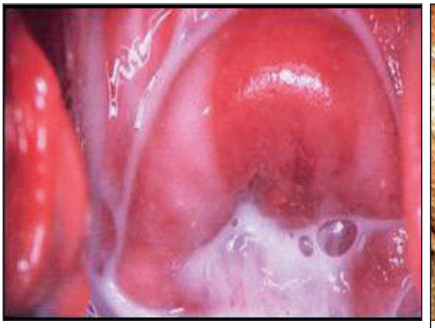
An increased host response to BV has been documented in the form of increased levels of several cytokines and chemokines in the cervical mucus of both pregnant and nonpregnant women with BV . In addition, secretory leukocyte protease inhibitor is decreased in the vaginal fluid of women with BV.

The effects of BV on the vaginal epithelium and on epithelial cell turnover have not yet been well studied. Nonetheless, the increased vaginal concentrations of anaerobic pathogens in BV may increase the risk of ascending upper genital tract infections, including cervicitis and endometritis.

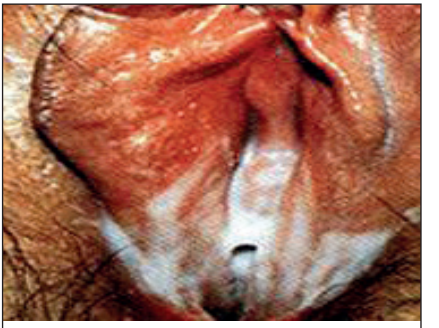
CLINICAL MANIFESTATIONS

In a cross-sectional study of clinic patients, BV by Gram stain criteria was significantly associated with symptoms of vaginal malodor (49% of patients with BV vs. 20% without BV) and vaginal discharge (50% of patients with BV vs. 37% without BV), and with signs of a nonviscous homogeneous, white, uniformly adherent vaginal discharge (69% women with BV vs. 3% without BV)(pic3-5).

The malodor is attributed to the abnormal presence of amines, particularly trimethylamine. The discharge adheres uniformly to the vaginal walls, often visibly on the labia and fourchette before insertion of a vaginal speculum. Although a third of women with BV describe their vaginal discharge as yellow, most

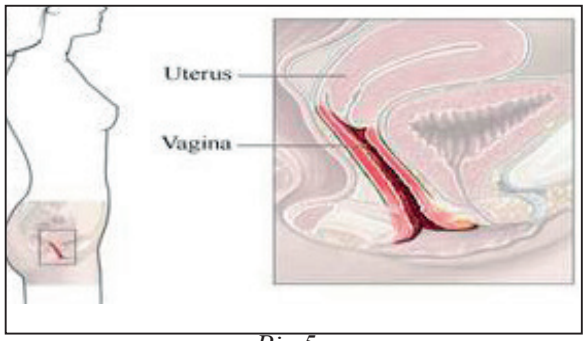


Pic 3



Pic 4

studies have found no significant increase in the mean number of polymorphonuclear leukocytes in vaginal discharge in this syndrome.



Pic 5

Nearly all women with BV have a vaginal pH of 4.5 when measured with pH paper having an appropriate pH range, although this finding is by no means specific for BV.

A fishy odor was noted when vaginal fluid was mixed with 10% KOH (the "whiff test") in 43% of those with BV versus 1% of those without BV. Microscopic evaluation of vaginal fluid at high power (400) revealed clue cells representing 20% of vaginal epithelial cells in 81% of those with BV versus 6% of those without BV.

Clue cells are epithelial cells heavily coated with bacteria sufficient to obscure the cell borders.

DIAGNOSIS

There are two main categories of diagnostic tests for BV: clinical criteria and laboratory-based testing.

Gram-stained microscopy is the reference method for diagnosing BV.

A. Nugent score – This is used as a gold standard for studies and relies upon estimating the relative proportions of bacterial morphotypes on a Gramstained vaginal smear to give a score between 0 and 10.

A score of <4 is normal, 4-6 is intermediate,and >6 is BV. However, it does not take bacterial morphotypes other than those associated with BV into account. The clinical implica-

tions of 'intermediate flora' are unclear but they are associated with complications.

B. Hay–Ison criteria – These are also based on the findings on a Gram-stained smear but are easier and quicker to use in clinical practice and do include non-BV-associated bacteria.

Grade 0: Not related to BV, epithelial cells only, no lactobacilli, indicates recent antibiotics

Grade 1: (Normal): Lactobacillus morphotypes predominate

Grade 2: (Intermediate): Mixed flora with some lactobacilli present, but Gardnerella or Mobiluncus morphotypes also present

Grade 3 (BV): Predominantly Gardnerella and/or Mobiluncus morphotypes, clue cells. Few or absent Lactobacilli.

Grade 4: Not related to BV, Gram-positive cocci only, no lactobacilli

Clinical criteria for diagnosis of BV (Amsel)

The presence of three of the four criteria is required; as three are clinical criteria it is possible to make a diagnosis of BV without microscopy or the use of a microbiology laboratory. Compared to Gram-stained microscopy, the presence of three of the four clinical criteria has a sensitivity of 60–72% for the diagnosis of BV.

1. Homogeneous grey-white discharge
2. pH of vaginal fluid > 4.5 (measured using narrow gauge pH paper)
3. Fishy odour (if not recognisable, use few drops of 10% KOH)
4. Clue cells present on wet mount microscopy (>20% of all epithelial cells)

Other methods of diagnosing BV

Commercial tests for BV are also available. OSOM BV Blue (Sekisui Diagnostics, Framingham, MA, USA) is a point-of-care

test which measures sialidase levels and has sensitivity of 91.7% compared to microscopy.

The BD MAXTM Vaginal Panel (Becton, Dickinson and company, Franklin Lakes, NJ, USA) is a microbiome-based, nucleic acid amplification assay that detects BV. The manufacturer insert quotes a sensitivity of 90.7% for the diagnosis of BV.

The Guidelines Group recommends that the current best test to diagnose BV in women is microscopy using the Hay–Ison Criteria

TREATMENT

Gardner first described triple sulfa cream as a treatment for "H. vaginalis vaginitis" in 1955. Subsequently, sulfa creams have been shown to have low efficacy and are inappropriate for treatment of BV. Over the past 25 years, numerous studies of various therapies for BV have repeatedly shown that only those antimicrobial compounds with broad activity against most anaerobic bacteria are highly effective for the treatment of this syndrome.

Treatment is recommended for women with symptoms. The established benefits of therapy in nonpregnant women are to relieve vaginal symptoms and signs of infection. Other potential benefits to treatment include reduction in the risk for acquiring *C. trachomatis, N. gonorrhoeae, T. vaginalis,* HIV, and herpes simplex type 2.

Recommended Regimens

- **Metronidazole** 500 mg orally twice a day for 7 days
  OR
- **Metronidazole** gel 0.75%, one full applicator (5 g) intravaginally, once a day for 5 days OR
- **Clindamycin** cream 2%, one full applicator (5 g) intravaginally at bedtime for 7 days

Alcohol consumption should be avoided during treatment with nitroimidazoles. To reduce the possibility of a disulfiram-like reac-

tion, abstinence from alcohol use should continue for 24 hours after completion of metronidazole. Clindamycin cream is oil-based and might weaken latex condoms and diaphragms for 5 days after use (refer to clindamycin product labeling for additional information).

Women should be advised to refrain from sexual activity or use condoms consistently and correctly during the treatment regimen. Douching might increase the risk for relapse, and no data support the use of douching for treatment or relief of symptoms.

Alternative Regimens

- **Tinidazole** 2 g orally once daily for 2 days
  OR
- **Tinidazole** 1 g orally once daily for 5 days
  OR
- **Clindamycin** 300 mg orally twice daily for 7 days
  OR
- **Clindamycin** ovules 100 mg intravaginally once at bedtime for 3 days*

*Clindamycin ovules use an oleaginous base that might weaken latex or rubber products (e.g., condoms and vaginal contraceptive diaphragms). Use of such products within 72 hours following treatment with clindamycin ovules is not recommended.

Alcohol consumption should be avoided during treatment with nitroimidazoles. To reduce the possibility of a disulfiram-like reaction, abstinence from alcohol use should continue for 72 hours after completion of tinidazole.

Alternative regimens include several tinidazole regimens or clindamycin (oral or intravaginal). An additional regimen includes metronidazole (750-mg extended release tablets orally once daily for 7 days); however, data on the performance of this alternative regimen are limited.

Certain studies have evaluated the clinical and microbiologic efficacy of using intravaginal lactobacillus formulations to treat BV

and restore normal flora. Overall, no studies support the addition of any available lactobacillus formulations or probiotic as an adjunctive or replacement therapy in women with BV. Further research efforts to determine the role of these regimens in BV treatment and prevention are ongoing.

Other Management Considerations

All women with BV should be tested for HIV and other STDs.

Follow-Up

Follow-up visits are unnecessary if symptoms resolve. Because persistent or recurrent BV is common, women should be advised to return for evaluation if symptoms recur. Detection of certain BV-associated organisms has been associated with antimicrobial resistance and might be predictive of risk for subsequent treatment failure. Limited data are available regarding optimal management strategies for women with persistent or recurrent BV. Using a different recommended treatment regimen can be considered in women who have a recurrence; however, retreatment with the same recommended regimen is an acceptable approach for treating persistent or recurrent BV after the first occurrence. For women with multiple recurrences after completion of a recommended regimen, 0.75% metronidazole gel twice weekly for 4–6 months has been shown to reduce recurrences, although this benefit might not persist when suppressive therapy is discontinued. Limited data suggest that an oral nitroimidazole (metronidazole or tinidazole 500 mg twice daily for 7 days) followed by intravaginal boric acid 600 mg daily for 21 days and then suppressive 0.75% metronidazole gel twice weekly for 4–6 months for those women in remission might be an option for women with recurrent BV. Monthly oral metronidazole 2g administered with fluconazole 150 mg has also been evaluated as suppressive therapy; this regimen reduced the incidence of BV and promoted colonization with normal vaginal flora.

Management of Sex Partners

Data from clinical trials indicate that a woman's response to therapy and the likelihood of relapse or recurrence are not affected by treatment of her sex partner(s). Therefore, routine treatment of sex partners is not recommended.

Special Considerations

Allergy, Intolerance, or Adverse Reactions

Intravaginal clindamycin cream is preferred in case of allergy or intolerance to metronidazole or tinidazole. Intravaginal metronidazole gel can be considered for women who are not allergic to metronidazole but do not tolerate oral metronidazole. It is advised to avoid consuming alcohol during treatment with nitroimidazoles. To reduce the possibility of a disulfiram-like reaction, abstinence from alcohol use should continue for 24 hours after completion of metronidazole or 72 hours after completion of tinidazole.

Management during pregnancy and breast feeding

A recent retrospective, case–control study found an association between the use of a number of antibiotics prescribed in the first trimester of pregnancy and spontaneous abortion. Statistically significant associations were found with metronidazole. Clindamycin was not tested in this study. Sexually transmitted genital infections themselves can cause pregnancy loss so failure to treat them effectively may also result in spontaneous abortion. The associations found might result from women being prescribed the antibiotics for genital infections with the increased risk of pregnancy loss being due to the infections rather than the antibiotics, i.e. confounding by indication. Meta-analyses have concluded that there is no evidence of teratogenicity from the use of metronidazole in women during the first trimester of pregnancy. Metronidazole can be used in all stages of pregnancy and during breast feeding. Symptomatic women with BV should be treated at diagnosis, although some clinici-

ans have preferred to defer treatment until the second trimester. The British National Formulary advises against high-dose regimens in pregnancy. Metronidazole enters breast milk and may affect its taste. The manufacturers recommend avoiding high doses if breastfeeding or if using a single dose of metronidazole, breastfeeding should be discontinued for 12–24 h to reduce infant exposure. Tinidazole is pregnancy category C (animal studies have demonstrated an adverse event, and no adequate, well-controlled studies in pregnant women have been conducted), and its safety in pregnant women has not been well evaluated. The manufacturer states that the use of tinidazole in the first trimester is contraindicated. There appears to be less risk with oral preparations after the first trimester. The Guidelines Group recommends that the current best treatment for BV in pregnant women is metronidazole.

HIV Infection

BV appears to recur with higher frequency in women who have HIV infection. Women with HIV who have BV should receive the same treatment regimen as those who do not have HIV infection.

PELVIC INFLAMMATORY DISEASE

The role of BV in spontaneous PID not associated with abortion or instrumentation of the uterus is less clear, even though anaerobes have long been linked with salpingitis.

Many of the bacteria recovered from the endometrium and fallopian tubes of patients with PID are those present in the vagina in high numbers among women with BV. However, the proportion of women with BV who develop overt symptoms and signs of PID without instrumentation may be relatively low compared to the proportion of those infected with N. gonorrhoeae and C. trachomatis . Further, the interactions between C. trachoma-

tis,N. gonorrhoeae, and facultative bacteria in producing PID is not known, and the relationship between BV or intermediate flora and acquisition of

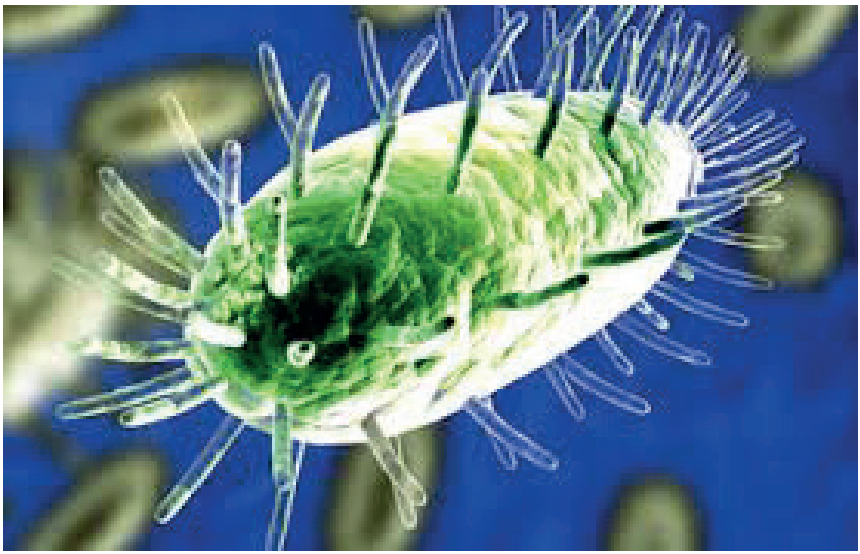
C. trachomatis and N. gonorrhoeae is probably complex and may depend in part on the microbiologic composition of BV itself.

The studies suggest that women with BV may have clinically inapparent or "silent" endometritis. However, whether BV-associated endometritis leads to salpingitis and infertility is the focus of ongoing studies.

GENİTAL MYCOPLASMAS

Introduction

Mycoplasmas are the smallest bacterial cells that are capable of living and replication outside of the host cell(pic 1). They are classified into the Class Mollicutes, family Mycoplasmataceae



Pic 1

with more than 130 species identified. Genital mycoplasmas comprise those that primarily colonize genitourinary tract. They belong to two genera: genus Mycoplasma and genus Ureaplasma. Mycoplasma genitalium, Mycoplasma hominis, and Ureaplasma spp. are considered pathogenic for humans. Additionally, Ureaplasma urealyticum organisms are recognized to present two distinct species, designated as U. parvum and U. urealyticum.

Biology

Mycoplasmas and ureaplasmas are the smallest free-living bacterias. Due to their small size, they can pass through the bacteriological filters . Their genomes belong to the smallest ones among the bacteria

Permanent lack of cell wall differentiates them from bacterial L forms, for which the lack of the cell wall is a temporary reflection of environmental conditions .

Genital mycoplasmas are facultative anaerobes.

Pathogenesis

The genital mycoplasmas are parasites or commensals residing in genital tract of humans. Limited biosynthetic capabilities of mycoplasmas, and the needs to obtain the nutrients from the host (because they cannot synthesize) explain their parasitic nature.

Several virulence factors play a key role in the pathogenesis of infection caused by genital mycoplasmas: (i) expression of specific adhesion proteins; (ii) antigenic variation; (iii) production of enzymes; (iv) facultative intracellular localization; and (v) capacity to induce host immune response.

The ability of mycoplasmas to survive within host cells is a significant feature, and it might help explain the chronic nature

of many mycoplasma infections and the persistence of asymptomatic carriers. Chronic disease course facilitated by intracellular location of genital mycoplasmas might have implications in long-term sequalae such as a male's or a couple's fertility.

Epidemiology

Genital mycoplasmas can be transmitted by direct contact between hosts, most commonly through genital-genital or oral-genital contact.

Following puberty, Ureaplasma spp. and M. hominis can be isolated from the lower genital tract in many healthy sexually active adults, but there is evidence that these organisms play etiologic roles in some genital tract diseases .

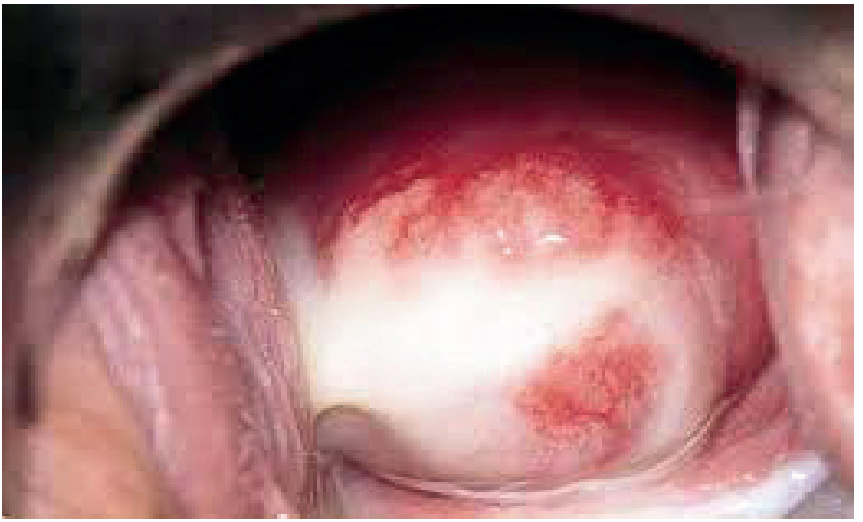
Genital mycoplasmas can be also transmitted vertically from mother to off spring, either at birth or in utero.

Ureaplasma spp. and M. hominis can be transmitted from infected females to the fetus or neonate by at least three different routes: (i) ascending from lower genital tract to cause intrauterine infection and invade amniotic sac, (ii) hematogenous route through placental infection through involvement of the umbilical vessels, and (iii) through passage of an infected maternal birth canal. After puberty, colonization with genital mycoplasmas occurs primarily as a result of sexual contact.

Clinical Presentation

Genital mycoplasmas can cause disease of lower and upper urogenital tract both in men and women, and rarely extragenital clinical manifestation. One of the main issue concerning genital mycoplasmas is clinically asymptomatic silent colonization by these bacteria, which are potentially pathogenic and may play a role in long-term consequences of urogenital tract infection both sexes.

Urogenital Infections in Women (Pic2)



Pic 2

Bacterial Vaginosis

Detection of M. hominis is very strongly associated with bacterial vaginosis. Women with this syndrome not only have M. hominis in the vagina more often but also in much larger numbers than women who do not have bacterial vaginosis. Although mycoplasmas are resistant to metronidazole, this antibiotic is often effective in treating the disease and eliminating M. hominis, suggesting that M.hominis prospers in the milieu created by the other bacteria (i.e. Gardnerella vaginalis), and when this and other bacteria are eradicated, M. hominis is also eliminated .

Cervicitis

M. genitalium has an independent role in causing cervicitis, suggesting that among the women with cervicitis and detected M. genitalium, 70% of cervicitis can be attributed to this pathogen.

Moreover, it seems that M.genitalium is the only genital mycoplasma regarded as causing cervicitis.

Pelvic Inflammatory Disease (PID)

PID is the clinical syndrome caused by spread of the microorganisms from the lower to the upper genital tract.

There is no evidence that ureaplasmas cause PID and there is a little evidence to suggest that M. hominis does.

PID may result in longterm reproductive sequelae, including infertility, ectopic pregnancy, and chronic pelvic pain.

M. genitalium is often asymptomatic, increasing the likelihood for "silent" PID and its sequelae.

Infections in Pregnancy

The genital mycoplasmas have been implicated in several adverse outcomes of pregnancy with spontaneous preterm labor and preterm birth as the most common ones. Ureaplasmas induce cytokines and inflammation, making a casual association with poor pregnancy outcomes unquestionable. Ureaplasmas were isolated more frequently from spontaneously aborted fetuses, stillbirths, or preterm infants than from induced abortions or normal full-term infants. However, the vaginal presence of M. hominis together with other abnormal vaginal flora, such as bacterial vaginosis or coinfection with ureaplasmas, seems to enhance the risk of adverse pregnancy outcome.

Urogenital Infections in Men

Nongonococcal Urethritis (NGU)

M. genitalium was initially grown in culture medium from men with acute NGU . Since the introduction of nucleic acid amplification tests (NAATs), M. genitalium, which is difficult to grow, has been increasingly identified in the genital tract of patients with

urethritis. Further numerous studies in which diagnosis of urethritis was made by microscopy, M. genitalium has been strongly and almost uniformly associated with acute NGU.

Epididymitis and Prostatitis

Acute epididymitis is often associated with urethritis, and M.genitalium and U. urealyticum are considered as pathogens of urethritis.

Laboratory Diagnosis

Specimen Collection

The most common specimens from urogenital tract are swabs (urethral, vaginal, and cervical). Mycoplasmas are extremely sensitive to adverse environmental conditions, particularly dryness and heat, and they cannot survive outside the host for a long period.

Molecular Methods

NAATs are particularly important for diagnosis of microorganism that cannot be proven using traditional methods – culture and serology. PCR systems have been developed for all the clinically important genital mycoplasma. Conventional PCR methods can take two to three days, which make a real-time PCR assays are now the preferred PCR method for detection of genital mycoplasmas. Advantages of real-time PCR over the traditional PCR techniques include not only rapid turnaround time, but also less handling of PCR product, and improved diagnostic sensitivity. Moreover, possibility of real-time PCR to provide quantitative data to determine the bacterial load may be important for interpretation of results for organisms that are known to colonize asymptomatic people.

Serology

Serological test methods for Ureaplasma spp., M. hominis, and M.genitalium include enzyme immunoassay, microimmunofluorescence, and metabolism inhibition, but no serologic tests for genital mycoplasmas have been standardized and made commercially available for diagnostic use, so they cannot be recommended for routine diagnostic purposes.

Treatment

Recommended regimens (uncomplicated infections):

- Doxycycline 100mg bd for seven days followed by azithromycin 1g orally as a single dose then 500mg orally once daily for 2 days[A] where organism is known to be macrolide-sensitive or where resistance status is unknown
- Moxifloxacin 400mg orally once daily for 10 days if organism known to be macrolide-resistant or where treatment with azithromycin has failed[B]

[A] Given that most individuals will have had doxycycline as first-line treatment for uncomplicated infection, a repeat course is unnecessary once the *M. genitalium* positive result is known. Azithromycin should be given immediately after doxycycline, and ideally within 2 weeks of completing doxycycline. If this is not possible, the course of doxycycline should be repeated prior to giving azithromycin.

[B] Treatment failure is defined as persistent symptoms following treatment, or a positive test of cure taken five weeks post-treatment.

Treatment of complicated urogenital infection (PID, epididymo-orchitis)

1. There are few studies examining the efficacy of extended azithromycin regimens in the treatment of PID and epididymo-orchitis caused by *M. genitalium*. Data from a recent PID RCT showed

high rates of macrolide resistance mutations in specimens positive for M. genitalium. Given the need for prompt and effective treatment in complex STI syndromes, patients with confirmed M. genitalium infection, or who have a partner who has tested positive for M. genitalium should be given moxifloxacin as a 14-day regimen.

2. Recommended regimens (complicated infection):

- Moxifloxacin 400mg orally once daily for 14 days

Partner notification (PN)

Only current partner(s) (including non-regular partners where there is likely to be further sexual contact) should be tested and treated if positive. This is to reduce the risk of re-infection to the index patient. Partners should be given the same antibiotic as the index patient unless there is available resistance information to suggest otherwise.

Rectal infection

This should be managed in the same way as urogenital infection. For severe proctitis, a longer course of moxifloxacin (14 days) may be considered.

Pregnancy and breastfeeding

1. Pregnancy

Data on *M. genitalium* and its association with adverse pregnancy outcomes are limited, however it has been associated with a small increased risk of preterm delivery and spontaneous abortion. Azithromycin use during pregnancy is unlikely to increase the risk of birth defects or adverse pregnancy outcomes. A three-day course of azithromycin can be used for uncomplicated *M. genitalium* infection detected in pregnancy. The use of moxifloxacin in pregnancy is contra-indicated. In women with likely macrolide resistance, or with upper genital tract infection in pregnancy, options are limited.

Although doxycycline is considered safe for use in the first trimester by the FDA, the BNF advises against its use in all trimesters. There are no data regarding the use of pristinamycin in pregnancy. An informed discussion should be had with the pregnant woman around the risks associated with the use of these medicines in pregnancy and the risks of adverse outcomes associated with *M. genitalium* infection, and where possible treatment should be delayed until after pregnancy.

2 Breastfeeding

Very low levels of azithromycin are detected in breast milk, and systemic exposure in infants does not exceed that observed when azithromycin is administered for treatment, therefore risk is considered to be low. Infants should be monitored for possible side effects due to effects on the gastrointestinal flora including diarrhoea and candidiasis.

Doxycycline is excreted into breast milk and is contraindicated in nursing mothers due to the risk of tooth discolouration and effects on bone growth. Use of moxifloxacin is contraindicated during breastfeeding. Pristinamycin is contraindicated during breastfeeding due to its side effect profile.

HIV

Treatment of *M. genitalium* in HIV-positive individuals is the same as that for HIV-negative individuals.

Prevention and Control

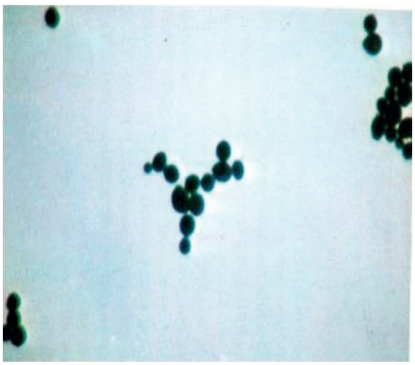
Since genital mycoplasmas are primarily transmitted by sexual contact, standard precaution measures for safe sexual intercourse (i.e. condom use) will prevent the colonization of infection. To prevent adverse pregnancy outcomes, it is reasonable to screen, detect, and treat genital mycoplasmas in pregnancy, or even better, bacterial vaginosis, in which M. hominis is linked, as are ureaplasmas to a lesser extent, using antibiotics active against a

range of microorganisms. M.genitalium infection should always be treated. Special attention should be given to the treatment of PID, especially those conditions persisting after standard regimen of therapy, due to current CDC recommendation for PID treatment does not include drugs for M. genitalium infection . Since a high proportion of M. genitalium infections is asymptomatic, to prevent long-term consequences, screening in high-risk population should be considered (i.e. those with other sexually transmitted disease detected) .

UROGENITAL CANDIDIASIS (CANDIDIASIS)

Etiology

Candida albicans (C. albicans), a dimorphous fungus (yeast and filamentous forms), exists as a commensal in oral mucosa (50% of normal humans) and vagina (25% of normal women). (**Pic 1)**



Pic 1

The commensal becomes pathogenic in the presence of following predisposing factors:

- *Moisture:* areas of occlusion (intertriginous areas) and prolonged immersion in water (nail folds).
- *Obesity:* friction and maceration in the folds encourages growth of candida.
- *Diabetes* and other endocrinopathies.
- Use of broad-spectrum antibiotics and metronidazole.
- *Pregnancy and oral contraceptive pills:* due to change of vaginal flora.
- *Immunocompromised states:* may lead to systemic candidiasis or to chronic mucocutaneous candidiasis. Oral candidiasis

is the most common fungal infection seen in HIV-positive patients, occurring in 50% of HIV-positive patients and in 90% of AIDS patients.

Clinical Features

Candidal infection may present as:

- Acute mucocutaneous candidiasis.
- Chronic mucocutaneous candidiasis.
- Systemic candidiasis.

Acute mucocutaneous candidiasis

The sites of predilection of acute mucocutaneous candidiasis are shown in

Flexural candidiasis (candidal intertrigo)

- ***Predisposing factors:*** Obesity, moisture, wearing of occlusive clothing, and diabetes.
- ***Morphology:*** Begins in depth of fold (at sites of friction) as a moist glazed area of erythema and maceration. The edges show frayed scaling and satellite subcorneal pustules
- ***Sites of predilection:*** Any skin fold (especially in obese individuals) can be affected. Inframammary area (in women), axillae and groins, natal cleft, and in between fingers and toes

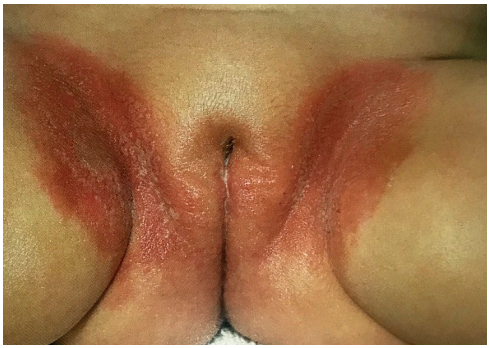
Candidal paronychia

- ***Predisposing factors:*** Wet work (cooks, bakers not to forget housewives), diabetes and presence of genital candidiasis (because of direct inoculation).
- ***Morphology:*** Cuticles are lost and proximal nail fold be-

comes red and rolled. On pressing, small bead of pus can be expressed from under the proximal nail fold. Over period of time, the adjoining nail plate becomes yellow-brown and ridged.

Genital candidiasis

- ***Predisposing factors:*** Diabetes, pregnancy, use of oral contraceptives and broad-spectrum antibiotics. May be sexually transmitted. **(Pic 2)**
- ***Morphology:*** Cuticles are lost and proximal nail fold becomes red and rolled. On pressing, small bead of pus can be expressed from under the proximal nail fold. Over period of time, the adjoining nail plate becomes yellow-brown and ridged.



Pic 2

Genital candidiasis

- ***Predisposing factors:*** Diabetes, pregnancy, use of oral contraceptives and broad-spectrum antibiotics. May be sexually transmitted.
- ***Manifestations:*** Depends on the gender of patient.

- ***Candidal vulvovaginitis:*** presents as intense itching in the vulva and presence of white curdy vaginal discharge. When severe, the vulva becomes edematous and erythematous.
- ***Candidal balanoposthitis:***
- Presents as fragile papulopustules on glans or coronal sul-

cus. Rupture to form well-defined, erythematous erosions, which may show a collarette of white scales .

- Sometimes presents with transient erythema and burning immediately after intercourse (due to hypersensitivity to candida) with a partner with candidal vulvovaginitis.

Oral candidiasis

Always a disease of diseased (except in neonates). Several different patterns recognized:

- ***Acute pseudomembranous candidiasis (thrush):***

* Most common form of oral candidiasis.
  Seen in infants. Also older patients on broad-
* spectrum antibiotic and steroid therapy.
* Presents as white adherent plaques, which are difficult to remove. On removal, an erythematous base is revealed.
* Seen on buccal mucosa, tongue, palate, and gingiva.

- ***Acute atrophic candidiasis:***

Seen on dorsal aspect of tongue as patchy depapillated areas.

- ***Angular stomatitis:***
- Usually in denture wearers.
- Manifests as white plaques at the angle of the mouth.

- ***Chronic atrophic candidiasis:***
- In denture wearers.
- Sharply defined areas of erythema and edema on the palate (area in contact with dentures).

• ***Candidal leucoplakia:*** Rough white-grey plaque on buccal mucosa or tongue with erythematous halo. Cannot be removed. Has premalignant potential.

Chronic mucocutaneous candidiasis

Heterogeneous group of clinical syndromes.

Predisposing factors

• ***Genetic susceptibility:*** Both autosomal recessive and dominant variants recognized.

• ***Associated with endocrinopathies:*** Associated with hypoparathyroidism, Addison's disease and thymomas.

• Manifestations

Persistent candidal infection in oral mucosa (all forms), skin and nails.

Systemic candidiasis

• Seen against a background of severe illness, leucopenia, and immunosuppression (AIDS/ iatrogenic).

• Cutaneous and visceral infections.

Investigations

• KOH mount shows budding yeasts and pseudohyphae.

• Culture from suspected lesion. A positive culture, however should be interpreted cautiously in the absence of a positive KOH mount.

• Rule out diabetes in patients with recurrent infection. Rule out immunocompromised states in recurrent/extensive/atypical disease.

Treatment

General measures

• Predisposing factors should be sought and eliminated. Diabetes mellitus should be ruled out and patients taking long-term

broad-spectrum antibiotics (including metronidazole) should stop taking them.

- Intertriginous areas should be kept dry by adequate wiping after a bath. In paronychia, prolonged immersion in water is best avoided. Use of gloves may help.

Specific treatment

Topical agents

Imidazoles (broad spectrum), amphotericin, and nystatin are effective.

- ***Candidal intertrigo:*** Topical azoles (clotrimazole, miconazole, and ketoconazole) are effective.
- ***Candidal paronychia:*** Topical azole lotions and a topical antibiotic. If acute paronychia is superimposed, then a course of oral antibiotic therapy may facilitate response.
- ***Oral candidiasis:*** Lotions and oral suspensions of azoles. Or nystatin.
- ***Genital candidiasis:*** Imidazole pessaries for vaginal infection. Topical azoles for balanoposthitis.
- Systemic therapy

•Systemic therapy is recommended in the following situations:

- ***Candidal vulvovaginitis:*** Single dose fluconazole (150 mg) or itraconazole (400 mg). Weekly doses of fluconazole (150 mg) for recurrent problem.
- ***Recurrent oral candidiasis:*** In immunocompromised patients (e.g., HIV infection), fluconazole, 150 mg weekly dose.
- ***Chronic mucocutaneous candidiasis:*** Requires prolonged therapy.

GRANULOMA INGUİNALE (DONOVANOSİS)

Introduction

Granuloma inguinale, also known as Donovanosis, is a chronic, ulcerative, progressively destructive bacterial infection of the genital and anal skin and subcutaneous tissue caused by the bacterium *Klebsiella granulomatis* (formerly known as Calymmatobacterium granulomatis).

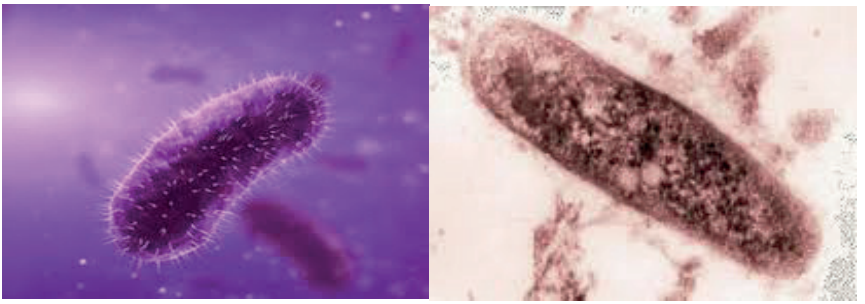
The differential includes other causes of genital ulceration (syphilis, LGV, herpes, chancroid), other granulomatous conditions, and carcinomas. When a biopsy from a large necrotic lesion that appears neoplastic shows only inflammatory changes, consider granuloma inguinale and order special stains to reveal K. granulomatis.

Infectivity/Transmissibility

The infection can be spread as an STI, but can also be spread by close, personal, nonsexual contact. It is not highly contagious; usually repeated or chronic exposure is needed to contract the infection. It is also found in sexually abstinent children and very old adults without sexual contact, which suggests that nonsexual transmission is possible. Indirect contact through vaginal contamination by fecal organisms may be an important contributor, as autoinoculation may be.

Etiology

The bacteria that causes donovanosis is known as *Klebsiella granulomatis comb. Nov.* The causative agent of donovanosis was originally named *Calymmatobacterium granulomatis* by Aragao and Vianna in Brazil. After the original naming, it was found to have similarities to other Klebsiella species in respect to testing, structural aspects, and histologic appearance. It is intracellular and encapsulated. It has been demonstrated to function as a facultative aerobe .(Pic 1)



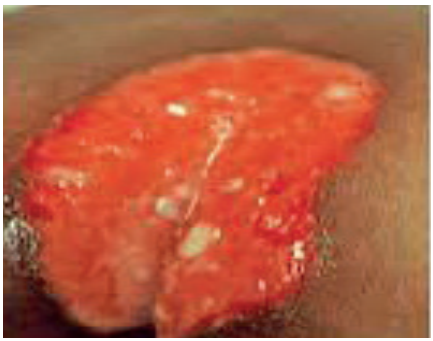
Pic 1

Epidemiology

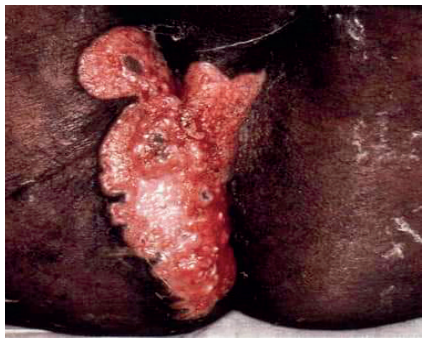
It has generally been accepted as a sexually transmitted infection based on a literature review done at the time. There are also high rates of infection among age groups with increased sexual activity. Donovanosis has been diagnosed in women with lesions primarily located on the cervix, and men who have sex with men have a higher incidence of anal lesions. Also, there have been some cases of fecal transmission and children infected in nonsexual ways. There are case reports of children infected by sitting on adult's laps and neonates infected during vaginal delivery. Some other risk factors are poor hygiene and low socioeconomic status.

Clinical Presentation

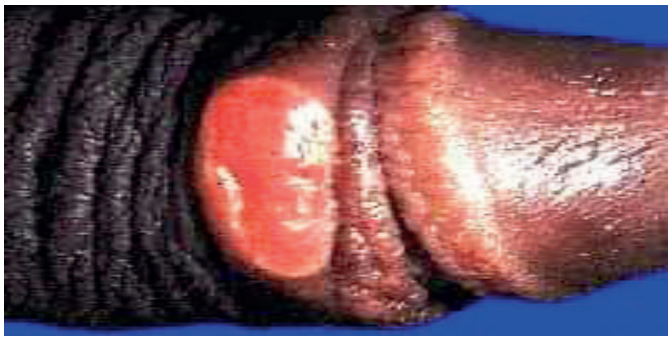
Granuloma inguinale is an acute or chronic infection characterized by ulcerating, necrosing, superinfected lesions of the skin, and subcutaneous tissues in the anogenital area. The incubation period varies from 1 to 2 weeks. In women, the usual sites of infection are the inner aspect of labia and fourchette (Pic 2,3). In men, the lesions are generally found on the penis (Pic 4). The lesion is



Pic 2



Pic 3



Pic 4

friable and bleeds easily on contact. The skin over each nodule ulcerates. The characteristic lesion is an area of coalesced beefy-red ulcers with fresh granular tissue. As the adjacent areas of ulceration grow together, the normal vulvar/penile architecture is destroyed.

Four different types of granuloma inguinale have been described:

- Ulcerogranulomatosis (the most common type) marked by beefy-red, non-tender ulcers that bleed easily if touched and may become quite extensive if not treated.
- Hypertrophic or verrucous ulcer, which presents as a growth with an irregular edge.
- Necrotic type with a foul-smelling, deep ulcer causing tissue destruction.
- Dry, sclerotic, or cicatricial lesion.

Massive swelling of the labia is common. Inguinal swelling may occur. The pseudo buboes, formed because of subcutaneous granulation, break down and are replaced by ulcers. As the infection progresses, scarring and lymphatic obstruction produce marked enlargement of the vulvar area. Long-standing infection can cause irreversible genital deformities such as skin depigmentation; stenosis of the urethral, vaginal, and anal orifices; and massive edema. Loss of sexual function often follows because of destruction of genital tissue, scarring, and deformities.

Extragenital lesions have been reported up to 6 % of cases. Involvement on the face, neck, mouth, larynx, pharynx, and chest have all been reported. Metastatic lesions involving bones, joints, and liver have been reported.

Diagnosis

In endemic areas, the infection is usually diagnosed by its clinical presentation. Identification of Donovan bodies using special stains in either smears or crushed specimens, taken from the depth of the ulcer and the fresh edge, confirms the clinical diagnosis. Biopsies should be taken with punch biopsy or small curettes. Donovan bodies are seen on Giemsa stain or Wright stain as clusters

of dark-staining bacteria that appear as small, straight, or curved dumbbell-shaped “safety pin” (bipolar) appearance in the cytoplasm of macrophages. Biopsy may be necessary to rule out carcinoma.

Standard laboratory approaches are not fruitful. K. granulomatosis is difficult to culture; it has been cultured successfully only in chick embryonic yoke sac. In vitro antibiotic sensitivity testing is unavailable. Serological tests are nonspecific.

Treatment / Management

The CDC recommends that treatment should last until all lesions are healed. First-line treatment is azithromycin 1g followed by 500 mg daily. Relapses can occur 6 to 18 months after seemingly successful treatment. Erythromycin is the medication of choice in pregnancy. There is no change in the recommendations for HIV positive patients. The 2016 European Guidelines for donovanosis treatment recommends azithromycin as a first-line treatment that can be given as 1g initially then 500 mg daily or 1g weekly. Children should be given azithromycin 20 mg/kg for a disease treatment course or prophylaxis for 3 days if exposed during birth. Azithromycin was shown to be effective against donovanosis and has the added benefit of short, intermittent dosing, which may facilitate treating endemic populations.

Differential Diagnosis

The differential diagnosis for genital ulcers is broad and includes primary syphilis, secondary syphilis (condylomata lata), chancroid, lymphogranuloma venereum, genital herpes, neoplasm, amoebiasis, and several others. Lesions that have a more destructive appearance should be evaluated for carcinoma in addition to other

causes. Additionally, women with cervical lesions should also undergo testing for carcinoma and tuberculosis. If the diagnosis of donovanosis is confirmed, the patient should undergo HIV testing due to being at increased risk of transmission with donovanosis lesions.

Prognosis

The prognosis for uncomplicated donovanosis is positive with appropriate treatment. There is the possibility of relapse, which can occur even after symptoms appear to have resolved. If left untreated, there can be significant scarring and tissue destruction. Malignant transformation is also possible.

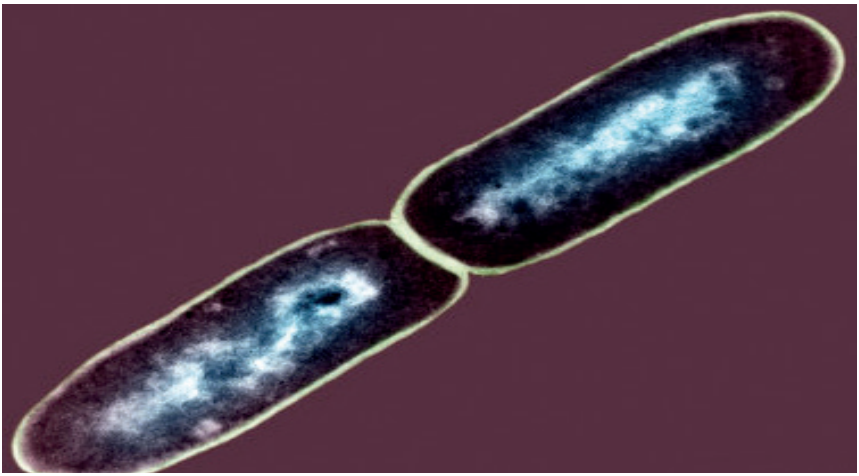
Complications

Possible complications include neoplastic change, pseudo-elephantiasis, hematogenous spread, polyarthritis, osteomyelitis, vaginal bleeding, and stenosis of the urethra, vaginal, or anus. Symptoms include fever, malaise, anemia, night sweats, weight loss, and sepsis. Also, many patients receiving care after having endured the disease process for a significant amount of time may have suffered emotionally. The lesions can be embarrassing and distressing to the patient. Always consider mental health disorders such as anxiety or depression and include suicide screening in these patients.

CHANCROİD

Introduction

Chancroid is commonly referred to as "soft chancre." It is a highly contagious STI caused by *Haemophilus ducreyi* (Pic 1). H. ducreyi was first identified as the causative organism for chancroid in 1889 when August Ducrey inoculated the forearms of infe-



Pic 1

cted patients with pus from their genital lesions . Causation was made even clearer later when Bezancon and others inoculated the forearms of healthy volunteers with culture-purified organisms *(H. ducreyi)* and produced characteristic soft chancres from which the organisms were reisolated .

The infection causes genital ulceration, regional lymphatitis,

and bubo formation. It is a major cause of genital ulcer disease in many resource-poor countries in Africa, Asia, and Latin America. The genital ulceration caused by chancroid causes significant distress and increases the transmission and acquisition of HIV infection. If a genital ulcer is present, the relative risk of acquiring HIV ranges from 3 to 18, with a per act increase in transmission of 10- to 100-fold. About 10 % of the US patients with chancroids are coinfected with HIV or *Treponema pallidum;* this rate is higher than the rate found in infected individuals in other countries.

Risk Factors

Commercial sex workers are felt to have been reservoirs of infection in the out- breaks that have occurred in the last decade. This is because chancroid is most commonly diagnosed in men who have recent exposure. Uncircumcised men are more susceptible to infection

Infectivity and Transmissibility

Chancroid is a relatively contagious infection. 70 % of women who are sex partners of chancroid-infected men are infected. The probability of sexual transmission with a single exposure has been estimated to be 0.35. An estimated delivery dose of approximately 30 colony-forming units of *H. ducreyi* organisms has been reported to form a papule formation rate of 95 % and a pustule formation rate of 69 % in a human experimental challenge model.

Etiology

Chancroid is caused by a small, nonmobile facultative anaerobic, Gram-negative rod bacterium, *H. ducreyi.* The organism is only remotely related to Haemophilus influenza and has been reclassified in the *Actinobacillus* cluster of the Pasteurellae. *H. ducreyi* infects only humans. It is believed that the organism gains entry

into the skin and mucosal surfaces only through microabrasions and other trauma; it is not able to penetrate normal skin.

Epidemiology

Chancroid is extremely rare in the developed countries. Challenges in understanding its true global incidence are based on difficulties in isolating the causative agent and the limited diagnostic and surveillance modalities are available to the clinician.

As chancroid is a genital ulcerative disease, its lesions are more readily apparent. Therefore, it's more commonly reported among men. Uncircumcised males tend to have a greater incidence than those individuals who are uncircumcised. The likelihood of transmitting the disease to an infected individual during a single sexual encounter has been noted to be 0.35.

Chancroid also has been found to be a significant cofactor in the heterosexual acquisition and transmission of HIV disease. Genital ulcers may increase the risk of HIV infection as much as 50- to 300-fold per each unprotected encounter of vaginal intercourse. This phenomenon occurs by increasing the infectiousness and host susceptibility for HIV infection. Interruption of the mucosa in genital ulcer disease provides a portal of entry for HIV. This, combined with an increase and activation of HIV susceptible cells, allows for enhanced viral replication and the acquisition of HIV disease.

HIV disease, in turn, may alter the appearance and clinical course of chancroid. This may include an increase in the incubation period, multiple ulcerating lesions, delays in healing, and poor response to standard courses of antibiotics, or treatment failures.

Histopathology

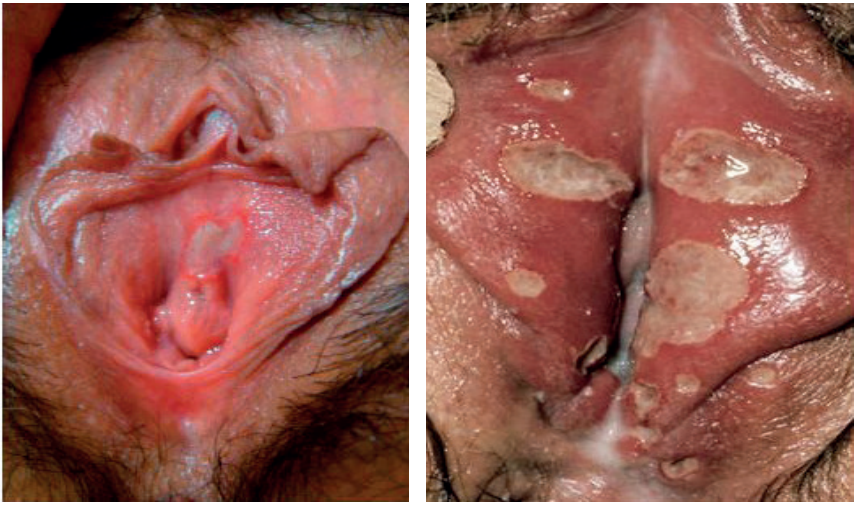
H. ducreyi is a small, fastidious gram-negative rod which requires an enriched growth medium cultivated in a high humidity, CO2-enriched environment. On Gram stain, long strands of orga-

nisms are seen in a pattern often referred to as a “school of fish” or “railroad track” in appearance. One may use this pattern when interpreting clinical specimens, but its presence is inconsistent, and therefore, its absence should not be viewed as eliminating *H. ducreyi* as the causative agent.

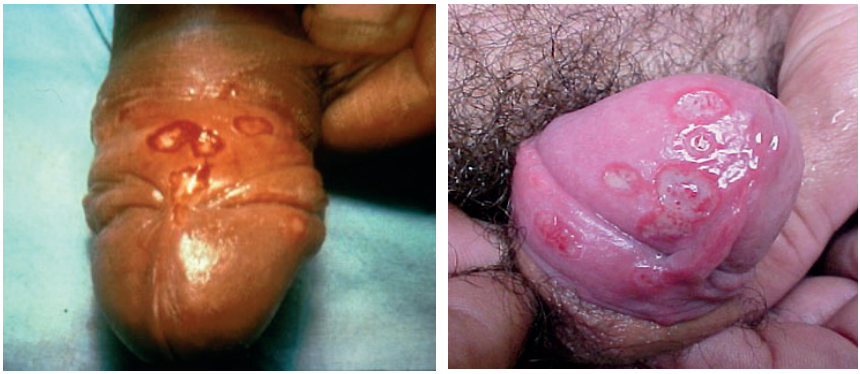
Clinical Manifestations

The lesions of chancroid are generally limited to the genital areas. In women, they are found on the labia, clitoris, vestibule, and fourchette (Pic 2). In men, the lesions are most commonly cited in the inner surface of the prepuce and frenulum (Pic 3).

The incubation period of chancroid is 3–11 days, with the most common frequency being 4–7 days. A small papule develops at the site of entry. The papule is haloed by erythema. In 2–3 days, the lesion becomes pustular or vesiculopustular, and ulcerates. The base of the ulcer is soft, shallow, and necrotic-appearing; the edges are irregular, ragged, and undermined and are surrounded by



Pic 2



Pic 3

deep red-colored halos. The ulcers are covered by a grey-colored, foul-smelling exudate. There is no induration around the lesion. The lesion is exquisitely painful and tender. In men, the most common initial presentation is a single ulcer. In women, multiple ulcers form and often become interconnected in serpentine streaks measuring up to 2 cm. Many times, they are bilateral (the so-called kissing lesions) created by autoinoculation. Mixed infections with syphilis and herpes simplex can complicate the diagnosis of chancroid.

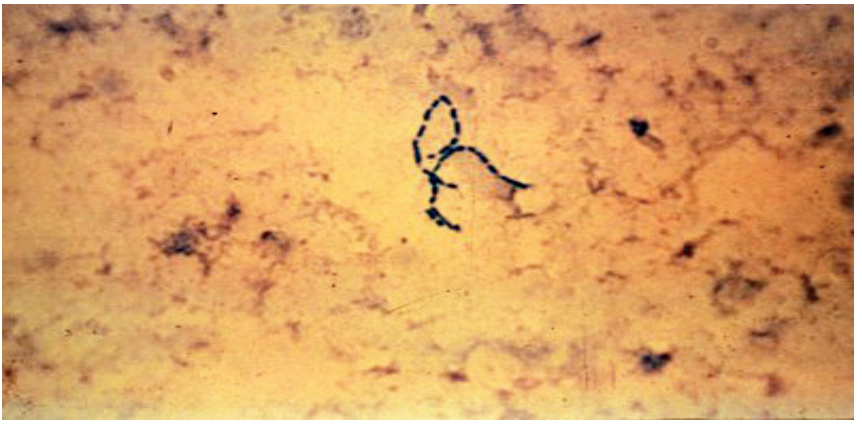
In 7–10 days, a bubo develops in about half the cases. The bubo is unilateral (same side as lesion) and unilocular in up to two-thirds of the time. It is an acute, painful, tender inflammatory inguinal adenopathy. Untreated buboes may rupture and form large weeping ulcers in the inguinal area. Phimosis may develop in men. Extragenital infections are possible but rare.

Symptoms in men relate to the lesions themselves; the pain of the adenopathy lesion will prompt men to seek professional care. In women, the symptoms generally are more nonspecific; infected women complain of dysuria, dyspareunia, vaginal discharge, or rectal bleeding depending on the location of infection.

Relapses after antibiotic therapy occur in up to 5 % of patients.

Diagnostic Testing

The classical presentation of a painful ulcer and tender suppurative inguinal adenopathy is almost pathognomonic for chancroid. However, this complex occurs in only about one-third of cases. Therefore, the diagnosis of chancroid generally relies on other tests. The exudates from the lesion or from aspiration of the lesion may reveal the Gram-negative rods extracellularly located in chains with clustering. The Gram stain patterns of H. ducreyi have been described as "schools of fish," "railroad tracks," and "fingerprints (Pic 4)." However, the sensitivity of the Gram stain is only 50 %, and should not be used to rule out chancroid. Definitive laboratory diagnosis depends on culture and isolation of H. ducreyi; but those



Pic 4

tests are rarely available in standard labs. Even in the best of situations, the sensitivity of cultures is only about 80 %. Because H. ducreyi is so fastidious, it must be plated directly onto the culture media or plated on Stuart's, Amies', and thioglycolate heminbased transport media and transported at 4 °C.

PCR (Polymerase Chain Reaction) and multiplex PCR tests have been described for H. ducreyi, but none has received Food

and Drug Administration approval. The PCR tests lose sensitivity if they are used to test genital ulcer specimens. But these tests are still superior to culture tests. Multiplex PCR is particularly useful in the face of coinfection, because it can detect the presence of H. ducreyi as well as herpes simplex virus, and T. pallidum.

Studies have shown that the accuracy of clinical diagnosis of H. ducreyi infection is related to the prevalence of chancroid in the population, as well as the experience of the clinician. Overall, the accuracy ranges from 33 to 80 %. Complicating this situation is also the fact that coinfection of HIV and H. ducreyi is common. HIV can modify the appearance of chancroid.

Despite these limitations, the diagnosis is often made on clinical grounds, and testing is used to rule out other infections that cause genital ulceration, such as syphilis or herpes. The CDC (Centers for Disease Control) recommends that the probable diagnosis of chancroid be made if:

- The individual has one or more painful genital ulcers.
- There is no evidence of syphilis by dark-field examination of the lesions, or by serology performed at least 7 days after the onset of the ulcers.
- Either the clinical presentation of the genital ulcers and regional adenopathy are typical for chancroid or test results for herpes simplex virus are negative.

Patients diagnosed with chancroid should be tested for HIV, not only because of the high concordance but also because HIV-infected patients do not respond to therapy as well.

Treatment / Management

Untreated genital lesions associated with chancroid in individuals not seeking care will spontaneously resolve within 1 to 3

months. Untreated individuals run the risk of progressing to painful regional lymphadenitis and, in approximately 25% of cases, the development of suppurative buboes.

Antibiotic treatment should be initiated for any individuals with either a confirmed or presumed diagnosis of chancroid. Consideration should be given to frequent co-infections, most often with either syphilis or herpes, and the potential need to initiate empiric treatment if there is any question regarding compliance in follow-up with diagnostic testing. In addition, the role played by chancroid as a co-factor in the transmission of HIV should trigger testing or treatment of known HIV positivity.

The Centers for Disease Control and Prevention recommends the following antibiotic options:

- Azithromycin 1 gm, orally as a single dose or
- Ceftriaxone 250 mg, intramuscularly (IM) as a single dose or
- Erythromycin 500 mg, orally 3 times per day for 7 days or
- Ciprofloxacin 500 mg, orally twice a day for 3 days

Objective improvement in symptoms and findings should occur within one to 2 weeks of the initiation of antibiotics, although the response of the associated regional lymphadenitis may occur more slowly. Fluctuant lymphadenitis may require needle aspiration or incision and drainage to assist in their resolution.

Lack of improvement with appropriate antibiotics may be the result of incorrect initial diagnosis, coinfection with another STI or HIV, drug resistance, or non-compliance with multi-dose regimens.

Sexual partners should be treated if exposed within the preceding 10 days of symptom development. Reinfection is possible due to contact with the source individual without the use of barrier protection, although it has been experimentally demonstrated that

initial treatment with single dose azithromycin may offer prophylactic protection for as long as 7 weeks after treatment.

Differential Diagnosis

The differential diagnosis includes herpes simplex infection, the most common cause followed by syphilis, and then distant chancroid. Clinical differentiation is difficult and inaccurate and may be made additionally challenging by co-infection with HIV or superimposed bacterial infection. Consideration also should be given to granuloma inguinale in the appropriate endemic setting as well as lymphogranuloma venereum if inguinal lymphadenitis is noted.

Prognosis

Prognosis is an expected full recovery with antibiotic treatment, although lesions will spontaneously resolve without treatment as previously noted. Lack of treatment puts the patient at risk of developing suppurative lymphadenitis. Non-response to treatment should trigger a further investigation as to the causative organism or the patient's compliance with the treatment regimen.

Complications

Complications associated with chancroid include the development of fistulous tracts secondary to suppurative lymphadenitis and the destruction of the deep tissues of the genitalia by either secondary or superinfection by anaerobes such as Bacteroides or Fusobacterium.

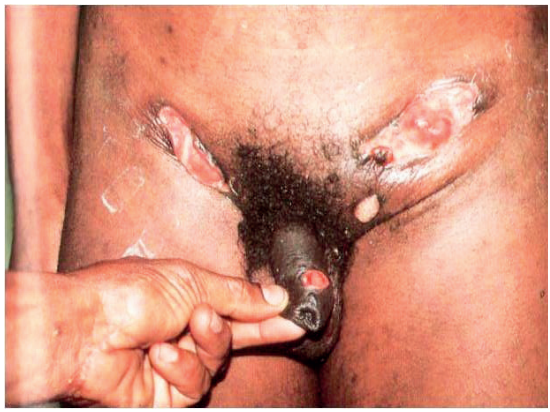
Pearls and Other Issues

- **Chancroid** represents an increasingly small number of the total cases of genital ulcer disease.
- **Chancroid** is a difficult clinical diagnosis, and syndromic management should be the mainstay of treatment.
- Regional lymphadenopathy develops in approximately 50% of infections.
- Single dose antibiotic treatment is the preferred management approach.
- Genital ulcer disease has been found to be a significant co-factor in the transmission of HIV disease.

LYMPHOGRANULOMA VENEREUM

Introduction

LGV was not identified as a separate pathological entity until 1913. Before that time, it was confused with chancroid, syphilis, or herpes. It has also been called tropical, strumous, climatic bubo, lymphogranuloma inguinale, poradenitis inguinalis, and Durand–Nicolas–Favre disease. LGV is a chronic STI caused by *Chlamydia trachomatis*. LGV has three stages of clinical manifestations–a small, short-lived, relatively asymptomatic primary lesion; a secondary stage characterized by inguinal adenopathy or acute hemorrhagic proctitis and systemic symptoms; and a third stage marked by ulceration, fistula formation, rectal strictures, and genital elephantiasis. Because of the ulcerative nature of LGV, patients are at increased risk of transmitting or acquiring HIV and other STIs **(Pic 1)**.



Pic 3

Epidemiology

Although LGV is found worldwide, it most commonly occurs in tropical areas. LGV is endemic in East and West Africa, India, part of Southeast Asia, Central American, South American, and the Caribbean. For example, a surveyed clinic in Ethiopia reported several thousand cases each year. By contrast, LGV is relatively rare in the United States and occurs sporadically. Peak years of infection are in the 30s. Although LGV infections are 5 times more likely to occur in men than in women, the long-term complications are more common in women because the infection is more asymptomatic in women and, therefore, more frequently goes undetected until a more advanced stage.

Risk Factors

As an STI, the risk of the infection is increased by a history of multiple sexual partners and young age. Most cases were found among MSM practicing anal-receptive sex. Travel to endemic countries is another risk factor in those engaging in high-risk sexual practices.

Infectivity and Transmission

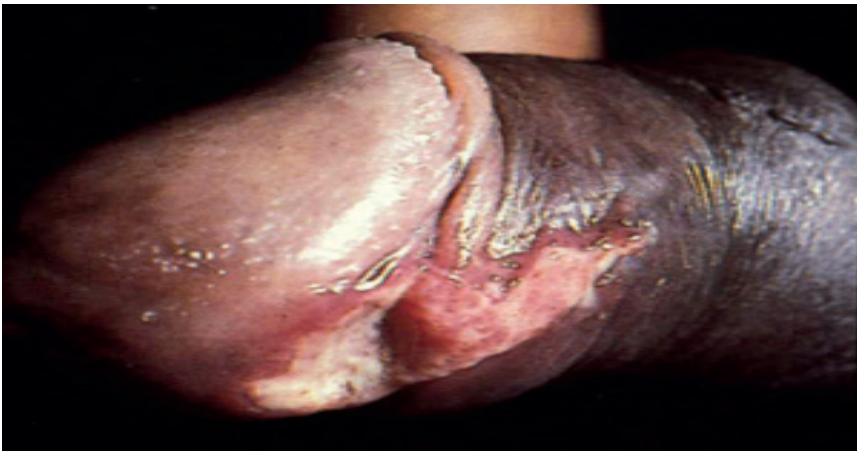
LGV is spread by sexual contact. It is not known if LGV can be transmitted as a fomite on shared sex toys or by fisting, which would be important to know when counseling MSM. The infectivity is not known, but is generally thought to be less than gonorrhea.

Etiology

LGV is an STI caused by *C. trachomatis,* serotypes L1, L2, and L3. *C. trachomatis* cannot penetrate intact skin or mucous membranes. It enters the body through micro- abrasions in the skin.These strains are more invasive in tissue culture than the strains that cause chlamydial cervicitis and urethritis. It is believed that most of the extensive tissue damage seen with LGV is caused by a cell-mediated "hypersensitivity" to chlamydia antigen.

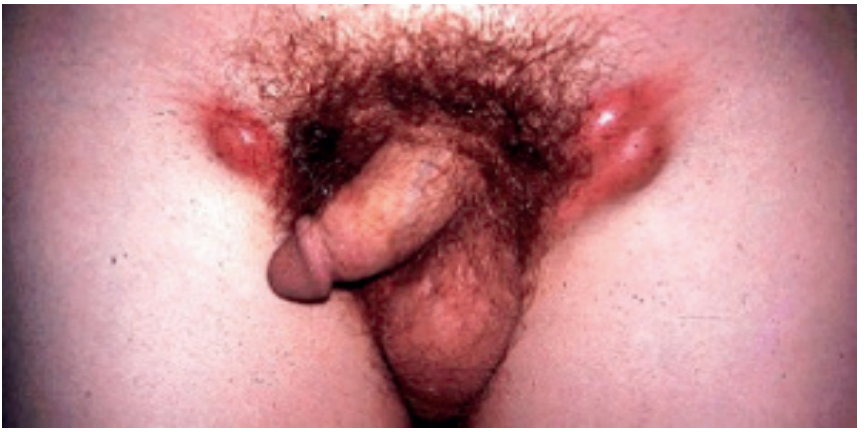
Clinical Manifestation

The incubation period for LGV is 3–30 days. The disease has both systemic manifestations and a wide spectrum of anogenital lesions, lymphadenopathy with destruction, and distortion of the genital areas. Subclinical infections are also possible, especially in women. The clinical manifestations progress through three stages. ***The primary lesion*** is generally self-limited and painless except in primary rectal LGV, which may present with proctitis and diarrhea, discharge, and ulcerations. Such lesion, which develops at the site of inoculation, is typically small (2–10 mm in diameter). It can take one of four forms: a small, nonpainful papule; a shallow ulcer or erosion; a small herpetiform lesion; or nonspecific urethritis. The initial lesion usually bursts quickly and forms an ulcer that oozes pus, but heals rapidly thereafter. In women, the lesion typically forms in the posterior vaginal wall, the fourchette, cervix, or vulva. In men, this occurs in the coronal sulcus, but may develop on the frenulum, prepuce, penis, urethral glans, or scrotum. It may be associated with a cordlike lymphangitis of the dorsal penis and form large painful lymphangial nodule called a "bubonulus". If the bubonulus ruptures, both draining sinuses of the urethra and deforming scars on the penis can develop. In women, LGV cervicitis can spread into the parametrium or salpinges. Alternatively, the lesion



Pic 2

may remain undetected in the urethra, vaginal vault, or rectum as it ulcerates (Pic 2).



Pic 3

Most people first seek care during the second stage of the infection because the first stage goes unnoticed by them. The secondary stage of LGV represents the spread of the infection into lymphatic tissue (Pic 3). ***The secondary stage*** develops days to months (ave-

rage 10–30 days) after the primary lesion. The first symptoms of the second stage may be systemic—such as fever, malaise, headache, anorexia, myalgia, and arthralgia. In the inguinal syndrome, these symptoms are followed rapidly by the development of adenopathy. The inguinal syndrome is the most frequent clinical manifestation of LGV. The superficial inguinal nodes are most often involved, but femoral nodes may also be affected. Adenopathy is unilateral in two-thirds of cases in women. Initially firm, discrete, multiple, slightly tender nodes develop. As the inflammation of the lymph nodes becomes more intense in the following few weeks, the nodes enlarge, necrose, and form fluctuant abscesses or buboes. These become adherent to the subcutaneous tissue and the overlying skin. If both the inguinal and femoral nodes are involved, Poupart's ligament creates a groove between the nodes and the patient develops the classic "groove sign"; this occurs in 10–20 % of cases. If untreated, the bubo ruptures in one-third of cases. Rupture relieves the pain and fever, but multiple sinus tracts form in the base of the ulcer and drain thick pus for months. Even after rupture, buboes recur in 20 % of untreated patients. Buboes that do not rupture undergo slow involution and form chronic inguinal masses.

Another second stage manifestation of LGV is the anogenitorectal syndrome, in which perianal or perirectal lymphatic tissue (usually of the distal left side of the large intestine) becomes inflamed, resulting in hemorrhagic proctocolitis, perirectal abscesses, ischiorectal or rectovaginal fistulas, or anal fistulas. Ultimately, anal or rectal strictures result. The clinical and histological presentations of LGV proctocolitis may mimic the initial manifestations of inflammatory bowel disease. The rectal strictures of LGV must be distinguished from carcinoma, tuberculosis, actinomycosis, and schistosomiasis.

A minority of patients infected with LGV will progress to ***the third stage*** of the infection, which involves the external genita-

lia and the rectal area. Because healing from LGV infection is by fibrosis, the normal structure of the lymph nodes is altered, which causes obstruction of the lymphatics of the scrotum, penis, or vulva. The chronic infection of the lymphatics, and the resulting edema and sclerosing fibrosis of the subcutaneous tissue cause induration and enlargement. This presents clinically as elephantiasis. In men, elephantiasis occurs within the penoscrotal area.

It is believed that much of the tissue damage in LGV is caused by a cell-mediated hypersensitivity to chlamydia antigens. The term (esthiomene), which is derived from the Greek word for "eating away," is used to describe the findings of LGV of the lymphatic system of the vulva, penis, and scrotum. Ulceration of the lesion starts superficially, but later becomes destructive. In women, the areas of the labia major, genitocrural folds, and lateral areas of the perineum are most frequently involved.

Other clinical presentations include papillary growths in the urethral meatus of women, smooth pedunculated perianal lesions ("lymphorrhoids"), and follicular conjunctivitis. Rarely, the infecting organism enters the blood stream and involves unusual sites, such as the gallbladder, liver, or pericardium. Primary infections of the oral cavity or pharynx have also been reported.

Diagnosis

Diagnosis is based primarily on clinical findings; routine laboratory confirmation may not be possible. However, given the wide variety of clinical manifestations, clinical diagnosis may be difficult. This difficulty is compounded by the relative rarity of this infection, which means that many clinicians may not recognize the clinical findings.

Serological tests such as microimmunofluorescent or complement fixation tests are most commonly used to support the clinical

diagnosis. Titers of complement fixation tests more than 1:64, or a fourfold increase in titer, are considered diagnostic as are titers more than 1:128 on the microimmunofluorescent test.

The most accurate tests used to diagnose LGV today are those using polymerase chain reaction (PCR) and other amplification techniques, although non-culture nucleic acid testing is not specific for LGV. In research settings and specialized laboratories, the genotype can be determined by performing restriction endonuclease pattern analysis of the amplified outer membrane protein A gene. Cultures of aspirates from the buboes or lesions are often performed, but are positive in only 30–50 % of suspected lesions.

Evaluation of gastrointestinal syndromes that may have been sexually transmitted requires either anoscopy or sigmoidoscopy and testing for *C. trachomatis,* syphilis, herpes, *N. gonorrhoeae,* and common enteric pathogens that can be sexually transmitted. In order to evaluate rectal strictures, mucosal biopsy may be needed to rule out carcinoma or other chronic infections.

Treatment

Treatment should be started empirically pending return of laboratory test results. If the laboratory test results all return negative, therapy can be discontinued, if appropriate. The goal is to cure the infection and prevent ongoing tissue damage. Antibiotics are needed for 3 weeks. In addition, buboes may require aspiration through intact, uninfected tissue or incision and drainage to prevent inguinal/femoral ulcerations. Patients should be followed clinically until all signs and symptoms have resolved.

Recommended regimen	Alternative regimen
Doxycyclinea 100 mg orally twice a day for 21 days	Erythromycin base 500mg orally 4 times a day for 21 days

Pregnancy-Related Issues

Transplacental congenital infection can occur, but most neonatal infection occurs because of exposure during passage through an infected birth canal. For infected pregnant and lactating women, the Centers for Disease Control and Prevention (CDC) recommends only the use of erythromycins. Doxycycline is contraindicated in pregnancy.

Information on HIV infection / AIDS: etiology, pathogenesis, epidemiology and diagnosis. Measures to combat HIV infection

Introduction

* **HIV** - Human Immunodeficiency Virus (HIV)

* **HIV** infection is an infectious disease that develops as a result of infection with the Human Immunodeficiency Virus and is characterized by increasing damage to the immune system

* **AIDS - Acquired Immune Deficiency Syndrome** - a disease caused by deep damage to the human immune system in the final stages of HIV infection and characterized by severe, untreatable secondary diseases (opportunistic infections, malignant tumors, etc.)

History of HIV / AIDS discovery and research

Published in the Bulletin of the US Centers for Disease Control (CDC) on June 5, 1981 "Pneumocystis pneumonia. Los Angeles "in the article by D. Francis et al. for the first time reported the symptoms of the disease;

In early 1982, a CDC report called the disease "Acquired Immunodeficiency Syndrome (AIDS)" by M. Gottlieb and others.

In 1983, L. Montagnier, F. Barre-Sinoussi and others. (France) first reported a virus from an AIDS patient;

1986 - The viruses are named "Human Immunodeficiency Virus (HIV)", the viruses are called HIV-1 and HIV-2, respectively, and the disease is called HIV infection.

History of HIV / AIDS

* 1987 - The first antiretroviral (ARV) drug was introduced to treat AIDS;

* 1988 - December 1 is declared World AIDS Day by the United Nations;

1995 - Highly active antiretroviral therapy (YAART) was introduced;

* 1996 - United Nations Joint Program on AIDS - UNAIDS was established;

* 2001 - UN General Assembly adopts a resolution to combat AIDS;

* 2006 - The UN General Assembly adopts the Universal Aid Program for the Prevention, Treatment, Care and Support of HIV / AIDS.

* 2011 - The UN General Assembly adopts a political declaration on HIV / AIDS.

* 2016- The UN General Assembly adopts a new political declaration on HIV / AIDS.

The causative agent of HIV infection is the Human Immunodeficiency Virus

- As a lymphotropic virus, it belongs to the genus Lentivirus (lat. Lenti-slow) of the family Retroviridae (lat. Retro-back);
- Has a unique genome structure and transcriptase enzyme;
- Virus RNA is converted to DNA by the action of the transcriptase enzyme;
- The DNA copy of the virus enters the cell genome (integrates).

HIV target cells

Stem cells: CD4 + T-lymphocytes (helpers / inducers)

Additional cells: Macrophages

Monocytes

Dendritic cells

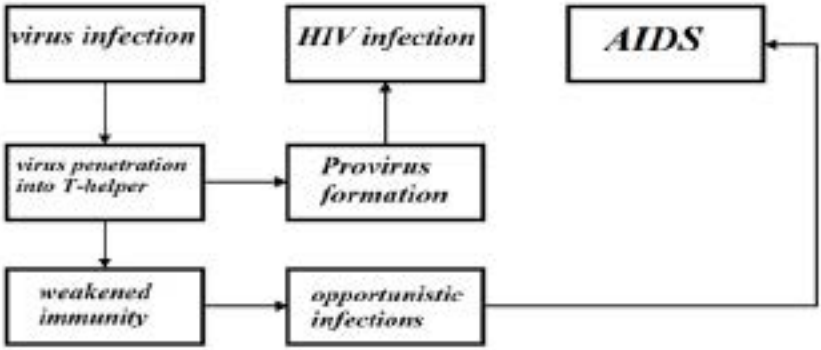
B-lymphocytes

Natural killers

Breast cells

Cells of the central nervous system (microglia cells, astrocytes, capillary endothelial cells

Stages of pathogenesis of HIV infection



HIV - epidemiological features of infection

Source of infection:

A person infected with HIV at any stage of the disease

HIV-containing biological fluids:

→ blood

→ sperm

→ cervical secretion

→ breast milk → spinal cord fluid

Ways of HIV infection

Sexual transmission:

Homo- and heterosexual contact with an HIV-infected person, especially as a result of casual unprotected sexual contact.

Parenteral:

As a result of transfusion of HIV-containing blood and its drugs;

During organ transplantation of an HIV-infected donor;

Using HIV-contaminated medical supplies and solutions, including injecting drugs;

As a result of the use of hygienic, cosmetological, hairdressing and other household appliances contaminated with HIV.

Perinatal:

As a result of pregnancy, childbirth and breastfeeding

Probability of HIV transmission (WHO):

Way of infection Probability of infection,%

Blood transfusion- 92.5

From mother to child -15 - 30

Use of common needles and syringes for drug injection 0.8

Anal sex: passive partner 0.5

The needle sinks into the skin 0.3

Contact with mucous membranes 0.1

Vaginal sexual contact: women 0.15 - 1.01

Anal sex: active partner 0.065

Vaginal sexual contact: men 0.01 - 0.15

Oral sexual contact: passive partner 0.01

Oral sexual contact: active partner 0.005

Sensitivity to the environment:

HIV is sensitive to all known disinfectants;

All types of ionizing radiation and ultraviolet radiation are

destructive to HIV;

HIV is destroyed in 30 minutes at a temperature of 56 ° C;

When the plasma is dried at 25 ° C, the virus is killed after 7 days, at 30 ° C - after 3 days, at 55 ° C - after 5 hours;

The liquid contains HIV activity for 15 minutes at a temperature of 23 - 27 ° C, at a temperature of 36 ° C - 11 days;

The activity of the virus in frozen blood and percussion is maintained for many years;

The activity of the virus in frozen sperm is maintained for several months.

Clinic of HIV infection, clinical stages:

HIV infection belongs to the group of slow-moving viral infections

It is characterized by numerous clinical manifestations, no clear pathognomonic symptoms

Regardless of the specialty, it is important for every doctor to know the clinical signs of different stages of HIV infection.

After the initial diagnosis of HIV infection is confirmed by laboratory methods, the stage of the disease is determined in accordance with the clinical classification.

What to do to determine the stage of HIV infection:

Detailed collection of anamnesis

Careful and detailed examination of the patient

Carrying out special laboratory tests: determination of CD4 lymphocyte count and viral load

Detection of secondary diseases:

Conduct laboratory tests to detect opportunistic infections

Views of specialists in the field: phthisiologist, narcologist, dermatovenerologist, oncologist, ophthalmologist, dentist, gynecologist and others

There are currently several clinically accepted classifications of HIV infection in the world:

Classification of stages of HIV infection, according to the CDC

(Centers for Disease Control, USA) - first proposed in 1986, revised in 1993. The classification is based on clinical signs and immunological examinations.

Classification of clinical stages of HIV infection, according to the WHO (World Health Organization) - submitted in 1993 and revised in 2006. Based on clinical signs only, it consists of 4 stages.

The WHO classification is applied in the Republic of Azerbaijan(WHO 2012):

Acute HIV infection

- Asymptomatic course
- Acute phase of HIV infection (acute retrovirus syndrome)

Clinical stage I

- Asymptomatic course
- Generalized lymphadenopathy in Persia

Clinical stage II

Seborrheic dermatitis

Angular cheilitis

Recurrent aphthous stomatitis (2 or more times in the last 6 months)

Belt herpes (rash within 1 dermatome)

Recurrent respiratory infections (sinusitis of 2 or more, otitis media, bronchitis, pharyngitis or tracheitis within 6 months)

Onychomycosis

Itchy rash of papules

Clinical stage III

Pulmonary tuberculosis

Hairy leukoplakia of the oral cavity

Unexplained chronic diarrhea lasting more than 1 month

Fever of unknown etiology (lasting more than 1 month)

Recurrent candidiasis stomatitis (2 or more times in the last 6 months)

Severe bacterial infections (eg, pneumonia, pleural empyema,

piomyositis, bone and joint infections, meningitis, bacteremia).

Acute ulcerative necrotic stomatitis, gingivitis, periodontitis

Clinical stage IV

Extrapulmonary tuberculosis

Unexplained weight loss (more than 10% in 6 months)

HIV-related cachexia syndrome

Pneumocystis pneumonia

Recurrent severe bacterial pneumonia (2 or more per year)

Candidiasis of the esophagus, trachea, bronchi and lungs

Cytomegalovirus retinitis (± colitis)

Infections caused by the herpes simplex virus: with damage to internal organs or chronic ulcers of the skin and mucous membranes (more than 1 month);

Progressive multifocal leukoencephalopathy

Toxoplasmosis

Cryptococcal meningitis

Cryptosporidiosis

HIV-encephalopathy

Lymphoma

Kaposi's sarcoma and tumors associated with HIV infection

Disseminated infection caused by atypical mycobacteria (M. avium-intracellulare mycobacterial complex)

Cardiomyopathy associated with HIV infection

HIV-related nephropathy

Stages of development of HIV infection and stages of clinical classification

HIV infection goes through the following stages in its development:

Infection

Acute retrovirus syndrome

Latent phase (asymptomatic period)

AIDS-related symptom complex

Secondary Disease Period (AIDS)

Death

According to the WHO classification:

The acute phase of HIV infection includes asymptomatic course and acute retrovirus syndrome

Clinical stages I, II and III include the AIDS symptom complex.

AIDS belongs to the fourth clinical stage.

Acute HIV infection

Asymptomatic course

Acute phase of HIV infection (acute retrovirus syndrome)

Acute phase of HIV infection (acute retrovirus syndrome)

The clinical condition observed in the early stages of HIV infection is called acute retrovirus syndrome. It is observed in 40-90% of people infected with HIV. Common symptoms in the clinic of acute retrovirus syndrome: fever, rash, lymphadenopathy, pharyngitis, arthralgia, myalgia, headache, weight loss, diarrhea, rarely serous meningitis. Acute retrovirus syndrome can be suspected in high-risk individuals with mononucleosis-like symptoms, serous meningitis, and viral infections.

Periodic frames of signs.

In most cases, symptoms appear 2-4 weeks after infection. Symptoms develop rapidly. It usually lasts 10-20 days, on average 14 days. Severe and long-term prognosis predicts the rapid development of HIV infection in the future.

Latent phase of HIV infection

The latent period between HIV infection and the onset of the disease is about 10 years. About 10% of adults develop the disease during the first 2 years.

In 5-10% of adults, the number of CD4 cells remains unchanged, and the symptoms of the disease are not observed even after 10 years. High viral load means rapid disease progression.

Clinical stage I

It is a post-acute phase of HIV infection, the course of which can be different:

- Asymptomatic course
- Persistent generalized lymphadenopathy (PGL) - is defined as persistence of lymph nodes enlarged in 2 or more areas (except the groin area) for more than 3 months.

Stages II and III (AIDS-related complex)

These include individual symptoms and infectious diseases: fatigue, night sweats, loss of appetite, weight loss, subfebrile fever, chronic diarrhea, candidiasis of the oral cavity, simple and herpes zoster, lymphadenopathy, anemia, thrombosis.

Initially, it is characterized by a relatively light, then heavy and prolonged course.

Stage III - Candidiasis

Candida is an infection caused by a genus of yeast. In most cases, candidiasis is caused by C. albicans. Candidiasis of the skin and mucous membranes is considered a manifestation of immunodeficiency. In most cases, candidiasis of the esophagus and oral cavity precedes other opportunistic infections. Oral candidiasis is caused by alcoholism, glucocorticoids, etc. during normal immunological status. can be.

Hairy leukoplakia of the mouth

Hairy leukoplakia was first described in 1984 by D. Greenspan, a homosexual living with AIDS. This is a benign proliferation of epithelial cells of the oral mucosa that is not prone to malignant degeneration. Epstein - Barr virusSelectively infects B lymphocytes and epithe-lial cells, associated with the active spread of Barr virus. Affected cells undergo active proliferation, not lysis. They look like white le-sions on the tongue, and many of the spots give a dark appearance. The virus is caused by a weakened immune system, which is why it is so common in HIV. There is no cure for leukoplakia lesions of the mouth, based on a common HIV treatment plan.

Clinical stage IV (AIDS stage)

Weakening of the immune system at this stage allows the development of secondary infections and tumors. Life-threatening opportunistic infections (tuberculosis, pneumocystis pneumonia, toxoplasmosis), neoplastic processes (Kaposi's sarcoma, lymphomas, invasive childhood cancer) and damage to the nervous system (HIV-encephalopathy, polyneuropathy).

Secondary diseases that occur in immunodeficient individuals are called opportunistic diseases (English word "opportunity"). Diagnosis of AIDS in people living with HIV is based on the diagnosis of secondary diseases. They are considered AIDS-indicator diseases.

Secondary HIV-related infections and diseases

Bacterial infection	Fungal infection	Virus infection	Infections caused by protozoa	Other diseases
Tuberculosis Respiratory tract infections Intestinal infection Atypical infections caused by mycobacteria Bartonelosis	Candidiasis Esophagitis Cryptococcosis Histoplasmosis Pneumocystis pneumonia Coccidomycosis	Herpes simplex Herpes zoster Virus infections Citomegalovirus Herpes simplex infections type 8	Toxoplasmosis Cryptosporidosis Microsporidosis Isosporiasis Leishmaniasis	Sarcoma kaposhi Non-Hodgkin lymphomas Uterine cancer Vascular myelopathy

Clinical stage IV - Kaposi's sarcoma, which can cause skin cancer. Forms dark skin lesions along blood vessels and lymph nodes and may be red, brown, or purple. This condition often occurs in the later stages of HIV when the T4 cell count is low and the immune system is weak.

The result

HIV infection is slow, many have a latent asymptomatic course

At any stage of the infection, even in the absence of symptoms, the infected person is able to transmit the virus to others.

Despite the availability of etiotropic treatment, HIV infection is still an incurable disease

Diagnosis of HIV infection

The diagnosis of HIV infection is made through a comprehensive assessment of epidemiological data, the results of clinical observations and laboratory tests.

Laboratory diagnosis of HIV infection is carried out in 3 main areas:

Etiological diagnosis - confirmation of the fact of infection with the detection of specific markers of HIV in the body (HIV antigens, antibodies against them and the genetic material of the virus);

Nosological diagnosis - determination of signs of immunodeficiency, primarily a decrease in the amount of CD4 cells;

Additional diagnostics - complications specific to HIV infection, e.g. detection of secondary infections and tumors.

Etiological (specific) diagnosis of HIV infection

Specific diagnostic methods of HIV infection:

Serological methods - determination of HIV antigens and antibodies against them in the blood;

Molecular-genetic methods - determination of the HIV genome in blood and other biological fluids and tissues.

Stages of diagnosis of HIV infection

1. Preliminary screening examination of serum:

Immunoenzyme assay - IFA (Enzyme-linked immunosorbent assay - ELISA). Conducted by a test system;

2. Reference (confirmation) examination of serum:

IFA. Conducted by 2-3 test systems (3-4 generation test systems are used - p24Ag + HIVAb);

3. Expert examination of serum:

Immunoblotting method (IB)

Polymerase chain reaction (PCR)

Necessary measures to combat the HIV / AIDS epidemic

Ensuring the safety of donor blood, medical, etc. application of universal security measures in enterprises;

Expanding the coverage of pregnant women with HIV testing;

Carrying out ARV-prophylaxis of HIV transmission from mother to child;

Expanding the involvement of risk groups (IDU, SI, KSK, prisoners, migrants, patients with STDs, etc.) in HIV testing;

Ensuring that all people living with and in need of HIV are diagnosed, prevented, treated, cared for and supported by HIV / AIDS;

Application of harm reduction programs (replacement of syringes and needles, distribution of condoms, introduction of replacement opioid therapy, etc.);

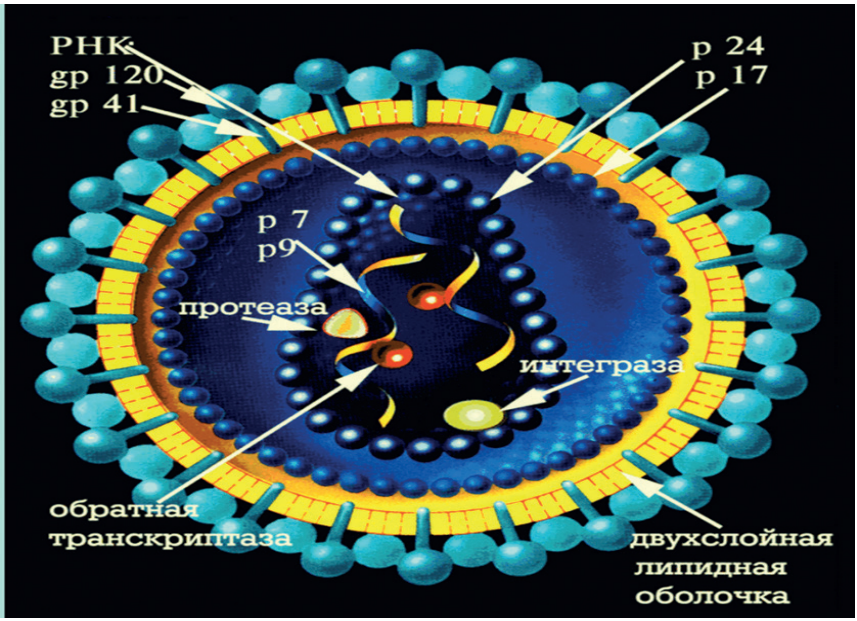
Improving the epidemiological surveillance system for HIV infection;

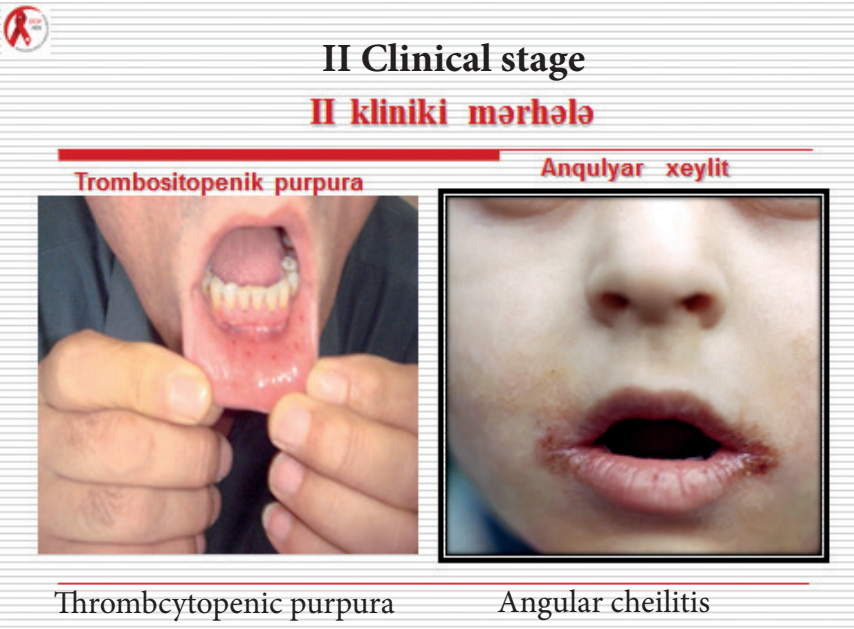
Expanding health education among the general population and at-risk groups.

Treatment. People living with HIV are treated in two ways:

1. Etiotropic treatment - antiretroviral therapy (ART)

2. Prevention and treatment of opportunistic infections

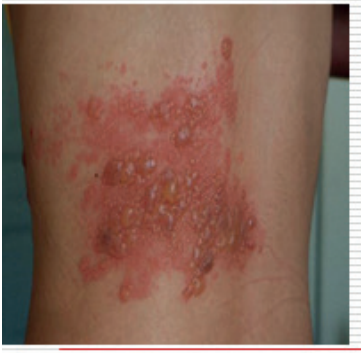


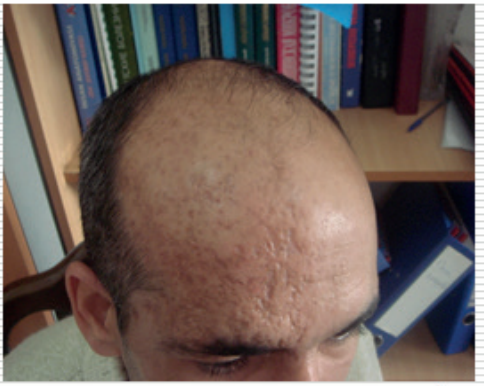


Thrombcytopenic purpura Angular cheilitis

II Clinical stage - Herpes Zoster

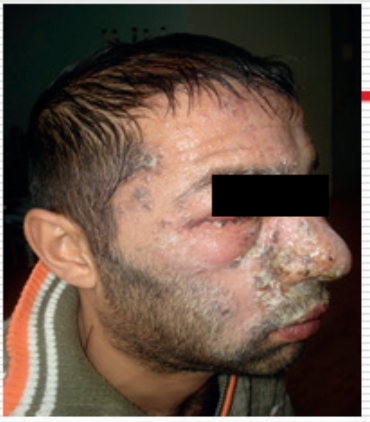
II kliniki mərhələ - Kəmərləyici herpes

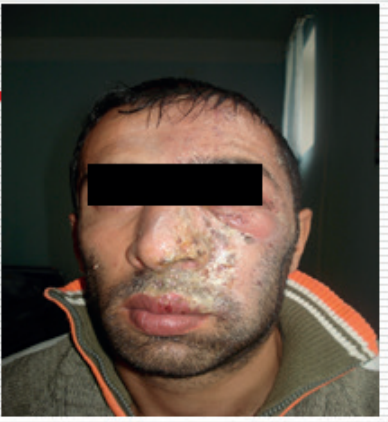




II Clinical stage - Herpes Zoster

II kliniki mərhələ - Kəmərləyici herpes





II Clinical Stage - onychomycosis

II kliniki mərhələ - Onixomikoz

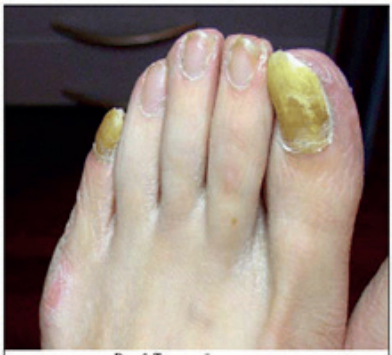
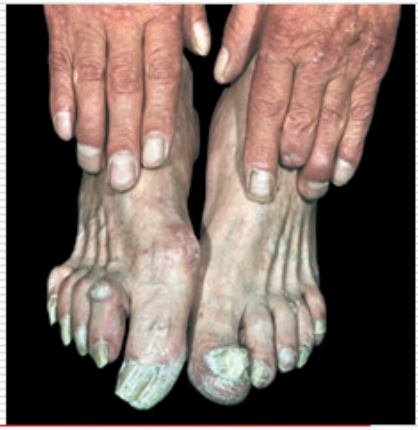


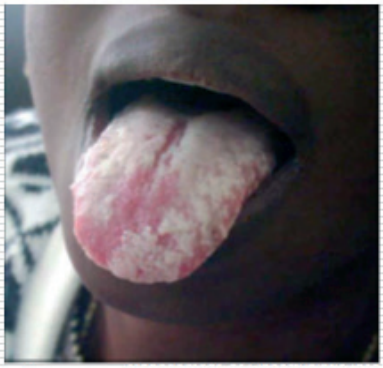
Рис. 6. Тотальный онихомикоз



III Clinical stage - Candidiasis

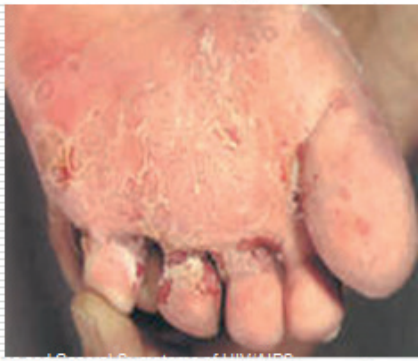
III kliniki mərhələ -Kandidoz

Ağız boşluğunun kandidozu



Candidiasis of oral cavity

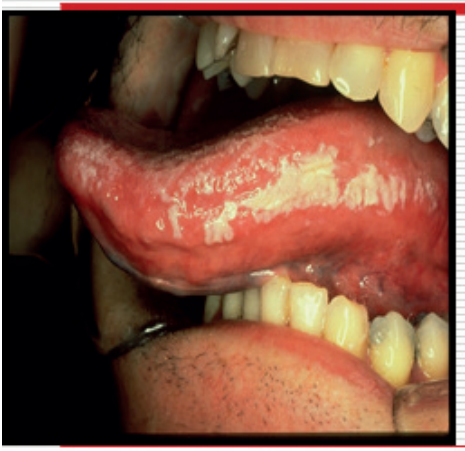
Dərinin kandidozu : qaşınan dermatit

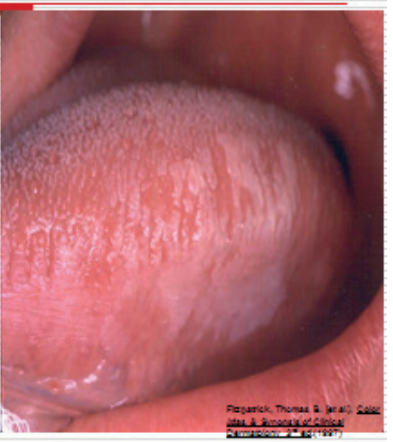


Candidiasis of the skin

III Stage oral hairy leukoplakia

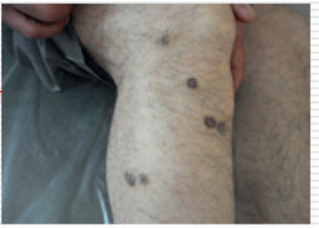
III mərhələ - Ağız boşluğunun tüklü leykoplakiyası

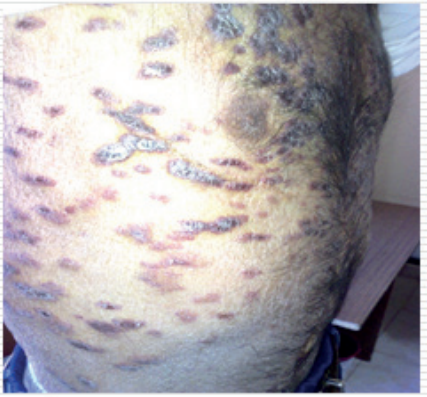


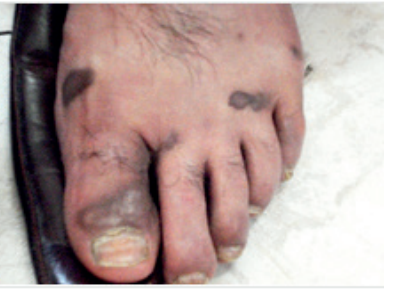


IV Kaposi Sarcoma

IV mərhələ - Kaposi sarkoması

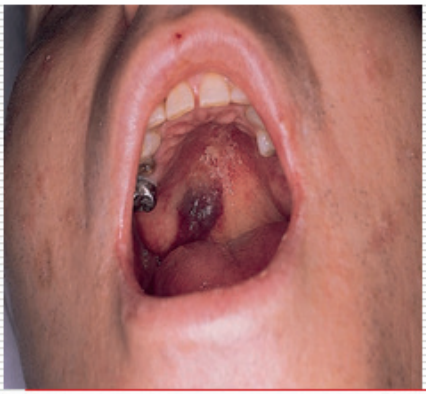


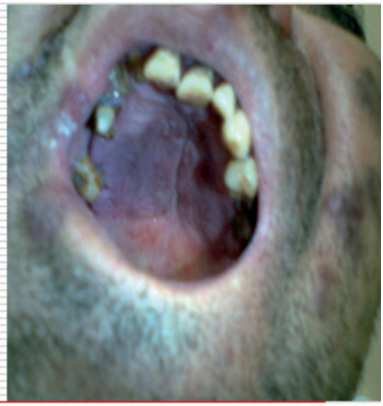




IV Stage - Kaposi Sarcoma

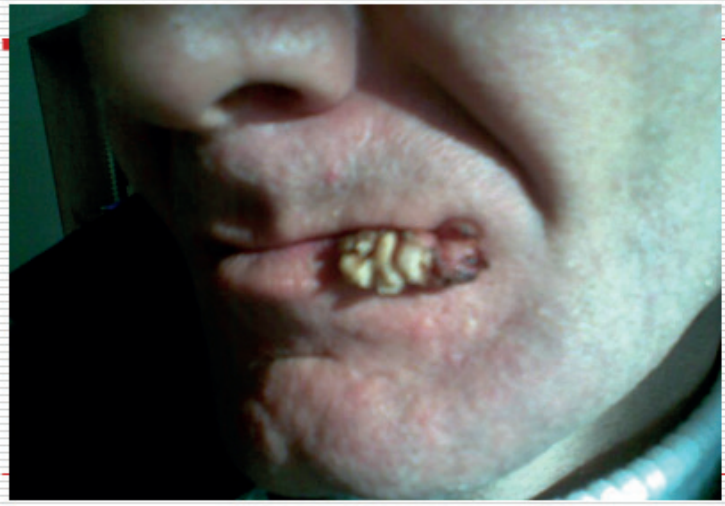
IV mərhələ - Kaposi sarkoması





IV Stage - Sarcoma of lip

IV mərhələ – Dodağın karsinoması



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