Sexually transmitted diseases

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ABBREVIATIONS

BV:	Bacterial Vaginosis
CDC:	Centre of Disease Control and Prevention
STD:	Sexually transmitted disease
PID:	Pelvic inflammatory disease
VDRL:	Veneral Disease Research Laboratory
TP-PA:	Treponema Pallidum particle agglutination
RPR:	Rapid plasma reagin
FTA-ABS:	Fluorescent treponemal antibody-absorption
EPT:	Expedited partner therapy
NAAT:	Nucelar Acid Amplification Test
HPV:	Human papilloma virus
PCR:	Polymerase chain reaction
US:	United States
IM:	Intramuscular
LGV:	Lymphogranuloma venerum
CIN:	Cervical intraepithelial neoplasia
CIS:	Carcinoma in situ
CT:	Computed tomography
MRI:	Magnetic resonance imaging
DNA:	Deoxyibonucleic acid
NSAID:	Nonsteroidal anti-inflammatory drug
CNS:	Central nervous system
HIV:	Human immunodeficiency virus
HSV:	Herpes simplex virus
IgG:	Immunoglobulin G

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Abstract

Sexually transmitted diseases (STDs)

Julian Voit

Sexually transmitted diseases are caused by various microorganisms and the transmission can be through vaginal, anal, or oral sex. The most common pathogens are bacterial vaginosis, chlamydia, gonorrhea, human papillomavirus, LGV, syphilis, trichomoniasis, and Herpes simplex virus types 1 and 2. If a person gets infected, there is a possibility to be asymptomatic or symptomatic. The main complaints in symptomatic patients are vaginal discharge, ulcerative skin lesions, and pelvic or abdominal pain. It is very important to recognize and treat such an infection early since many complications arise from that. Possible transmission from an infected mother to her baby during pregnancy and birth, Infertility due to fallopian tube scarring, or the growth of a neoplasm associated with HPV can cause long-lasting damage and health problems. Due to the risk of repeated transmission between sexual partners, it is recommended to also treat the partner in a diagnosed infection. The best way to avoid such infections is to prevent them, by using barrier protection, vaccination programs, but also educating school children before they become sexually active. If infected, various antimicrobial treatment options are available. Good bacterial coverage with tetracyclines, macrolides, fluoroquinolones, and cephalosporins helps eradicate the infection. Treatment options exist for viral and parasitic diseases and help to shorten the disease course in viral infection or eliminate the parasite from the body. This paper will focus on the diagnosis and treatment of the most common sexually transmitted diseases.

Keywords: STD, women, CDC, diagnostic criteria, treatment regimen

Sažetak

Spolno prenosive bolesti (SPB)

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Spolno prenosive bolesti mogu biti uzrokovane raznim mikroorganizmima, a prijenos može biti vaginalnim, analnim ili oralnim seksom. Najčešći uzročnici su bakterijska vaginoza, klamidija, gonoreja, humani papiloma virus, LGV, sifilis, trihomonijaza, te virus Herpes simplex tip 1 i 2. Zaražena osoba može biti asimptomatska ili simptomatska. Najčešći simptomi kod simptomatskih bolesnika su iscjedak iz rodnice, ulcerozne lezije kože, te bolovi u zdjelici ili trbuhu. Iznimno je važno rano prepoznati i liječiti takve infekcije, zbog mogućih dugoročnih zdravstvenih komplikacija kao što su mogućnost prijenosa infekcije sa zaražene majke na dijete tijekom trudnoće i rođenja, neplodnost zbog ožiljakastih promjena u jajovodima ili rast novotvorine povezane s HPV-om. Kod dijagnosticirane infekcije, zbog rizika od ponovljenog prijenosa između spolnih partnera, preporučuje se i liječenje partnera. Najbolji nacin izbjegavanja takvih infekcija je prevencija sto ukljucuje odgovorno spolno ponasanje uz pomoc barijernih kontracepcijskih sredstava ili redovitu upotrebu prezervativa prilikom spolnog odnosa, programa cijepljenja, te edukacijom školske djece prije nego što postanu seksualno aktivni. Postoje razne mogućnosti za liječenje SPB-a. Dobra pokrivenost bakterijskih uzročnika tetraciklinima, makrolidima, fluorokinolonima i cefalosporinima pomaže u iskorjenjivanju infekcije. Ujedno postoje i mogućnosti liječenja virusnih i parazitskih bolesti koje pomažu u skraćivanju tijeka bolesti kod virusne infekcije ili uklanjanju parazita iz tijela. Rad će bit usmjeren na dijagnozu i liječenje najčešćih spolno prenosivih bolesti.

Ključne riječi: STD, žene, CDC, dijagnostički kriteriji, režim liječenja

Introduction

Sexually transmitted diseases are infections that get transmitted from one person to another via sexual contact. This contact can be through vaginal, anal, or oral sex. Worldwide more than 340 million cases of new sexually transmitted diseases caused by bacteria or parasites get diagnosed each year (1). This makes it so important to have prevention and good diagnostic procedures for quick recognition and early treatment since many complications are associated with an infection. STDs usually have a characteristic clinical picture with vaginal discharge, erythematous or ulcerative skin lesions, and pelvic or abdominal pain. However, in some women, an infection can be asymptomatic and does not produce any complaints. This often leads to long-time exposure to the offending microorganism which causes damage to the lower reproductive organs and long-term complications (2). Severe complications can be seen in untreated gonococcal and chlamydial infections causing PID in 40 percent of patients (1). This infection may cause fallopian tube inflammation with scarring, leading to ectopic pregnancy or infertility. Additional symptoms from the development of adhesion formation between pelvic structures can cause the acute infection to produce chronic problems. In infections caused by Treponema pallidum, chlamydia, or gonorrhea, a possible transmission to the newborn can lead to pneumonia or congenital syphilis (3). Human papillomavirus infection has the potential to cause cervical cancer which is one of the most common cancers in women. Additionally, not only does the patient suffer from the symptoms caused by the infection, but also the social pressure and discrimination by the society that can come with an STD can be quite debilitating. This can lead to patients refusing to seek treatment and symptoms progress and the person can spread the disease further (4). With large numbers of new infections each year, there is an enormous financial burden on states for diagnosis and treatment of these infections, as well as the inability of the patient to work at his job. This makes it once more clear that good prevention plans have to be established. Especially the health education and vaccination programs for younger people, who are not yet sexually active, have to be prioritized to help them practice safe sex and prevent the spread of new STDs. Many different pathogens can cause infection but this paper will focus on the etiology, diagnosis, treatment, and complications of the most common ones.

Gardnerella Vaginalis

Bacterial vaginosis is a clinical syndrome that describes an abnormal vaginal flora due to overgrowing of anaerobic bacteria. This overgrow of these bacteria causes a reduction or even absence of the normal vaginal bacteria, which are hydrogen peroxide producing Lactobacilli. The reasons for this change are still unknown whether it comes from the disappearance of the lactobacilli or whether the disappearance results in the occurrence of BV (5).

Bacterial vaginosis by itself is not a disease that has to be reported to the Centers for Disease Control and Prevention and hence not a sexually transmitted disease. Nevertheless, there is an increased probability of developing BV by having multiple sex partners, oral sex, vaginal douching, cigarette smoking, and black race (6). Protective measures are mainly the use of condoms as well as avoiding the use of vaginal douches. It has been proposed that the rates of STD infection of women are increased in the setting of recurrent BV (7).The most common cause of vaginal discharge in reproductive women is BV. The main symptoms include a malodorous, nonirritating vaginal discharge, which is characteristic but not always present (5). On closer examination, there is usually no further erythema on the vagina and also no abnormalities on the cervix.

Diagnosis

The clinical diagnostic criteria first proposed by Amsel in 1983 include: 1. microscopic evaluation of vaginal-secretion saline preparation, 2.release of volatile amines produced by anaerobic metabolism, and 3. determination of the vaginal pH (8). The saline preparation also called “wet prep”, is a swab-collected sample of the vaginal discharge mixed with drops of normal saline to be viewed on a microscope slide. In the case of BV, the cells that are visible and pathognomonic under the microscope are Clue cells which have been originally described by Gardner and Dukes (9). These epithelial cells contain many attached bacteria that under the microscope create an uneven cellular border. For the test to be rated positive at least 20 percent of epithelial cells visible on the slide should be Clue cells and this test for BV has a positive predictive value of 95 percent (5).

The second test that is used in the diagnosis is the so-called “whiff test”. In this test, a 10-percent potassium hydroxide (KOH) solution is added to a sample of fresh vaginal secretions which leads to the release of volatile amines that have a fishy odor. This odor sometimes is even noticeable without the KOH. The detection of Clue cells and a positive whiff test is pathognomonic for Bacterial Vaginosis even in asymptomatic patients. The third part of the diagnostic algorithm is checking the vaginal pH. In BV infection, the vaginal pH is lower than 4.5, which stems from a decreased acid production by normal vaginal bacteria (5).

Treatment

Treatment options are available for nonpregnant women and show cure rates from 80 to 90 percent at week one. The recommended regimen is metronidazole 500mg orally twice daily for 7 days, metronidazole gel 0.75% one full applicator 5g intravaginally once daily for 5 days, or a clindamycin cream 2% 5g intravaginally at bedtime for 7 days (6). However, the recurrence rate is quite high with 50 percent of women having symptoms again due to vaginal flora changes. The treatment of male partners is not recommended and does not benefit the women with recurring BV. Additional treatment options are vaginally introduced lactobacilli, acidifying vaginal gels, and the use of probiotics but they have not proven to be consistently effective (11).

Complications

Several gynecologic complications have been described as being associated with BV. These include endometritis, vaginitis, postabortal endometritis, pelvic inflammatory disease unassociated with Neisseria gonorrhea or Chlamydia trachomatis, and acute pelvic infections that might occur after pelvic surgery (5). Pregnant women face an increased risk of preterm delivery (10).

Fungal Infection - Candidiasis

Vaginal discharge in women is most often associated with BV, trichomoniasis, or candidiasis. The symptoms in BV are more of a foul-smelling discharge compared to a discharge that is associated with burning, itching, and irritation in infectious vaginitis. These symptoms are quite nonspecific and between 7 and 70 percent of women complaining of vaginal discharge, will not have a definite diagnosis (12). In case the infective origin has not been detected, reassurance and an STD screening may help because treatment for infection should not be given.

Diagnosis

A full clinical evaluation with history before the vaginal infection has to be obtained as well as a thorough gynecologic examination of the vagina, cervix, and vulva. Several tests are performed to aid in finding the right diagnosis. First, an inspection of a saline preparation is performed. Following that, a KOH-prep is used to cause osmotic swelling and lysis of the cells which helps better visualizing fungal buds and hyphae. The last test is a vaginal pH measurement taken with a pH paper strip from the roof of the vagina. The strip soaks up vaginal fluid and after removing it will change color to reflect the pH. Then the color change is compared to the reference chart on the test strip dispenser (13).

The most common fungal infection is caused by candida albicans, which is a normal fungus that can be found in asymptomatic people in the vagina, rectum, and mouth. However other candida species like C tropicalis and C glabrata can cause infection in a small percentage of women. Risk factors for developing this infection are warmer climate, immunosuppression, obesity, diabetes mellitus, pregnancy, and a recent broad-spectrum antibiotic therapy (13). With people practicing more oral sex, it was reported that there is a connection between candidiasis and orogenital sex (14). The symptoms of this infection are plenty and include pain, pruritus, vulvar erythema, and edema with excoriations. A whitish curdy or cottage-cheese like discharge is seen during the infection. Due to candida albicans dimorphic properties, it is possible to see yeast buds and hyphae when doing a saline prep mixed with 10-percent KOH. Vaginal culture is not recommended but in some cases, it can be done after unsuccessful empiric treatment (13).

Treatment

According to the CDC, vulvovaginal candidiasis can be categorized into “uncomplicated” and “complicated”. Uncomplicated infections are infrequent or sporadic, mild to moderate in gravity, caused by candida albicans, and affect nonimmunocompromised women (13). The treatment options for vulvovaginal candidiasis are plenty. The recommended regimens in the over the counter section are clotrimazole 1% cream 5 g intravaginally daily for 7-14 days, or clotrimazole 2% cream 5 g intravaginally daily for 3 days, or miconazole 2% cream 5 g intravaginally daily for 7 days, or miconazole 4 % cream 5 g intravaginally daily for 3 days. For over the counter suppositories options are miconazole 100 mg vaginal suppository once daily for 7 days, or miconazole 200 mg vaginal suppository once daily for 3 days or miconazole1,200 mg vaginal suppository as a single application. Medication with a needed prescription against Candidiasis are butoconazole 2 % cream 5 g intravaginally as a single application, or terconazole 0.4% cream 5 g intravaginally daily for 7 days, or terconazole 0.8% cream intravaginally daily for 3 days, or terconazole 80 mg vaginal suppository once daily for 3 days. The only oral recommended drug is fluconazole 150 mg orally as a single dose. It is possible that in 10 to 20 percent the infection can be categorized as complicated (15). This would be in the case in immunocompromised patients, infections with non-albicans species, or recurrent disease. The definition for recurrent candida infection is 4 or more candida infections in one year. The therapy plan for these women has to be adapted and a prolonged course is needed to treat the patient. In the case of recurrent C albicans infection, local intravaginal therapy for 7 to 14 days or oral fluconazole in 100mg, 150mg, or 200mg doses are taken once daily every third day for a total of 3 doses. It is possible to perform a suppressive maintenance therapy with oral fluconazole 100 to 200 mg weekly for 6 months. Due to its poorer response to azole therapy, non-albicans infections should be treated with 600mg boric acid gelatin capsules intravaginally daily for 2 weeks (13).

Complications

Complications with azole therapy are associated with prolonged use due to its ability to elevate liver enzymes with oral use. This might pose a problem with patients' subjet to additional chronic medications and their interactions. Possible drugs that can cause interactions with azoles are warfarin, calcium-channel-blockers, protease

inhibitors, cyclosporine A, phenytoin, rifampin, and trimetrexate. To avoid this a local intravaginal application should be used in these cases (13).

Trichomoniasis

Trichomoniasis, a protozoan infection is the most prevalent non-viral STD in the world (16). This infection is mainly diagnosed in women because of its asymptomatic nature in men. 70 percent of men who are partners of infected women will show trichomonads in the urinary bladder. This STD compared to other STDs also seems to increase with the age of the patient. It is commonly seen with a co-infection especially N gonorrhea and is an indication for high-risk sexual behavior. The parasite has a predilection for squamous epithelium that causes lesions which can create susceptibility to other sexually transmitted diseases. During birth, vertical transmission to the baby is possible and it can persist up to one year (17).

Diagnosis

The incubation period for T vaginalis ranges from 3 days to 4 weeks and sites of infection are the vagina, urethra, endocervix, and bladder. In around 70% of infected people, no symptoms are experienced. However, if symptoms are seen, they can span from mild to severe inflammation. Typical symptoms if they are expressed are a foul-smelling, thin, and yellowish-green vaginal discharge. Dysuria, dyspareunia, vulvar pruritus, vaginal spotting, and pain can be experienced additionally (18). These clinical findings sometimes can be the same as in patients with PID. The vaginal spotting caused by subepithelial hemorrhages also called “strawberry spots” is visible on the vagina and cervix. Microscopically, Trichomonads are oval, anaerobic protozoa, slightly larger than white blood cells, and are flagellated on their anterior pole. They can be visualized on a saline preparation, which is highly specific but only 60 to 70 percent sensitive. The motility of the parasites decreases in cold temperature so that examination of the saline preparation under the microscope has to be done within 20 min after obtaining the sample. In Trichomoniasis, the vaginal pH is elevated which gives additional information about the cause of the symptoms (17).

Even though the most sensitive, culture is not readily feasible due to its impracticality and need of Diamond media which only a few laboratories have. Nucleic amplification tests for the trichomonal DNA are specific and sensitive but not all laboratories are equipped. A test for office use exists in the form of the OSOM Trichomonas Rapid Test which is an immunochromatographic assay with 83.3 percent sensitivity and 98.8 percent specificity. Results are on hand in 10 min. Compared to a wet mount with a sensitivity of 71.4% and specificity of 100%, the OSOM performed significantly better (17, 19). Additionally, trichomonas can be visualized on a pap smear. The sensitivity is around 60 percent with a specificity of 97% (20). However, a saline preparation and microscopic evaluation are necessary to confirm the diagnosis after and before treatment. Sexual contacts of positive patients have to be evaluated or referred for evaluation. STD testing is done for all women diagnosed positive (17).

Treatment

The treatment options for trichomoniasis according to the CDC are either oral metronidazole 2g once or tinidazole 2g once. Possible side effects of these drugs are disulfiram-like reactions with alcohol and thus the patient should refrain from drinking alcohol for 24 hours after metronidazole and 72 hours following tinidazole (21). Following the completion of the therapy, the patient will be re-evaluated after 3 months. In 30 percent of women, a recurrence is noticed. This can be diminished, by treating sex partners, abstain from sex during treatment, and the use of condoms. In some patients, some strains are resistant to metronidazole but are susceptible to tinidazole. In these cases, cultures are performed in patients with recurrent disease or patients with no response to the first treatment. Tinidazole 500mg orally three times daily for 7 days or 4 times daily for 14 days is effective for resistant trichomoniasis (17, 22).

Mycoplasma hominis and Ureaplasma urealyticum

The characteristics of mycoplasmas and ureaplasmas are that as the smallest free-living organisms they lack a cell wall. This poses particular challenges when diagnosing an infection due to their inability to be visible with gram stain (23). Normally they adhere to mucosal epithelial cells of the urogenital tract but there is a

possibility that dissemination to other sites of the body can occur and cause extragenital infections. This is especially important with immunocompromised patients. M. hominis and Ureaplasma are naturally present in the genital flora in sexually active men and women. However women are more susceptive to colonization and by adulthood, up to 80 percent have Ureaplasma spp, and around 50 percent Mycoplasma hominis in their vaginal secretions (24, 25). Both organisms have been associated with several genital infections and complications. Unfortunately, this is difficult to confirm because they are part of the normal flora and whether they are causative agents or only co-isolates. Usually an infection with M. hominis does not cause inflammatory vulvovaginitis, but there is a possibility that an increased bacterial overload of Mycoplasma or ureaplasma in association with bacterial vaginosis can lead to the development of urethritis or vulvovaginitis. This suggests that a symbiotic role between BV and Mycoplasma exists. Although efforts have been put into proofing this, several studies have not been able to answer this question (26, 27).

Diagnosis

Diagnosis of these organisms is based on clinical suspicion given the symptoms and when the initial microbiology testing with gram stain is negative or after unsuccessful antibiotic therapy. In these cases, more thorough testing is recommended. It is not uncommon that due to the difficulties in diagnosing, many infections will remain undiagnosed for a long time and cause problems to the patient. Microbiologic testing can be performed with culture on specific media or NAATs. The choice solely depends on the availability of the laboratories (23).

Treatment

There are no specific treatment guidelines for Mycoplasma hominis or Ureaplasmy urealyticum and a treatment plan has to be developed according to the resistances of each organism and the resistances of the country. However, it is recommended to give doxycycline 100 mg orally twice daily for both M. hominis and Ureaplasma. The duration is usually 7 days for uncomplicated lower genital tract infection and 14 days for more advanced infections and PID. In pregnancy or with young children, clindamycin is recommended for M. hominis and azithromycin for ureaplasma.

Treatment is also given to the sexual partners to reduce the risk of sexual transmission (23).

Chlamydia trachomatis

Chlamydia trachomatis is one of the most prevalent STDs in the United States. Women under the age of 25 seem to make up the highest percentage of all affected. Almost two-thirds of new chlamydia infections occur with ages ranging from 15-24 years and it is estimated that around 5 percent of sexually active young women in that age group have chlamydia. Furthermore, the correlation between ethnicities was shown due to its 5.6 times increase in non-Hispanic black women compared to non-Hispanic whites (28). Chlamydia has commonly an asymptomatic presentation and therefore women with risk factors that were previously mentioned for gonorrhea are eligible for screening. Due to its obligate intracellular nature, this organism infects columnar cells and leads to an endocervical glandular infection producing a mucopurulent discharge. On clinical examination, the endocervix is edematous and hyperemic. Further symptoms can be dysuria resulting from urethritis (29).

Diagnosis

Methods for diagnosing the infection are microscopically inspecting the secretions in a saline preparation and identifying more than 20 leukocytes per high power field. Additionally NAAT and enzyme-linked immunosorbent assay can be used in endocervical swabs. Due to its common co-infection, both gonococcal and chlamydial tests are frequently used together. As previously mentioned with the gonorrhea tests, it is also possible to get samples from the vagina, cervix, and first-void urine. In suspected or confirmed chlamydial infection a test for other STDs is mandatory (29).

Treatment

The recommended oral regimen from the CDC is azithromycin 1 g once as a single dose or doxycycline 100 mg twice daily for 7 days. Alternative treatment options are erythromycin base 500 mg four times daily for 7 days or erythromycin ethyl succinate 800 mg four times daily for 7 days or levofloxacin 500 mg once daily for 7 days or ofloxacin 300 mg twice daily for 7 days. After the treatment, it is not necessary to

retest if the symptoms are resolved (30). As in gonococcal infection, it is recommended to obtain from sex until the patient and the partner are asymptomatic to prevent further infection. As previously mentioned, the EPT in heterosexual partners is sanctioned for certain patients by the CDC (31).

Complications

Due to its common asymptomatic presentation, a chlamydia infection often goes unnoticed. However, some serious complications and long-term effects can be seen in such cases. As previously mentioned for the gonococcal infection, C trachomatis can spread into the upper reproductive system and cause pelvic inflammatory disease. This can either be symptomatic or subclinical with no symptoms. In about 10 to 15 percent symptomatic PID presentation can be seen in untreated women with chlamydia infection. It is important to mention, that both acute and subclinical presentations can cause damage to the upper reproductive organs. Complications from the damage can be chronic pelvic pain, tubal factor infertility, the formation of abscesses, and potentially fatal ectopic pregnancy. Another possible complication would be the development of perihepatitis also called “Fitz-Hugh-Curtis Syndrome”. This syndrome is an inflammation of the liver capsule and the surrounding peritoneum. The main symptom would be right upper quadrant pain. Pregnancy-related complications are preterm delivery, ophthalmia neonatorum, and pneumonia in the newborn. Possible reactive arthritis can occur after a symptomatic or asymptomatic chlamydial infection, which can present as part of a syndrome called Reiter´s syndrome, with urethritis and conjunctivitis (28).

Human Papillomavirus

HPV is the cause of a great proportion of vulvar, vaginal, and anal neoplasia by infecting human squamous or metaplastic epithelial cells. The virus itself is a double-stranded DNA virus and every one of the 150 viral types contains a specific protein capsid. 40 of those can infect the lower genital tract (32). In the United States the most prevalent sexually transmitted disease is genital HPV and because of that most sexually active adults get infected at some point (33). The distribution among females from age 18 to 59 was 42.5% in the years 2013-2014 (34). From a clinical point of

view, HPV can be categorized into low risk and high risk. In low-risk types, HPV is seldom oncogenic and mostly causes genital warts, laryngeal papillomatosis, and a small percentage of subclinical infections. The main strains causing this are HPV types 6 and 11. On the other hand, the high-risk types 16, 18, 31, 33, 35, 45, and 58 are accountable for around 95 percent of cervical cancers in the world (35). The most oncogenic with a percentage of 45 to cause CIN 3 lesions and a 55 percent of causing cervical cancer is type 16. Even though HPV type 16 can be found in more than 20 percent of cervical HPV infections as well as being the most common type found in low-grade lesions without neoplasia, infection with it does not cause neoplasia in many of the infected women. Evidence suggests additional influence by host, viral and environmental factors that can tip the scale towards the development of lower genital tract neoplasia (36).

Risk factors for acquiring a genital HPV infection are sex at an early age as well as the number of lifetime sex partners and recent ones (37). The transmission happens via sexual contact of mucous membranes, genital skin, or body fluids with the person experiencing a subclinical infection or genital warts. Due to the great difference in transmission modes, it is advised that all women should undergo cervical cancer screening if they are sexually active. Possible infection of non-genital HPV types by nonsexual contact or by fomite transfer has been described which would explain the presence of genital warts in pediatric and adolescent patients (38, 39). Vertical transmission and resulting congenital HPV infection is a rare occurrence.

Different outcomes can happen in an HPV infection and most of them are subclinical, but a small number of infections can cause genital warts. Furthermore, HPV infections can be only temporary but some are persistent which is needed for the development of high-risk HPV related cancers. The definition of latent infection is that of infected cells that do not produce symptoms and remains dormant. The viral levels are undetectable due to the lack of replication which makes it difficult to determine if the virus is eradicated or if it is in a latent state. Productive infections on the other hand are having a high replication life cycle. Given that their malignant potential is fairly low, the only change visible is the desquamation of infected squamous epithelium (40). The worst kind of infection is the neoplastic infection in which the HPV genome integrates into the host cell genome. This leads to the transcription of HPV oncogenes E6 and E7 that cause the increased degradation of tumor

suppressor genes p53 and pRb. Without this important safety mechanism, the cell is vulnerable to malignant transformation and DNA mutations can accumulate (32). Depending on the phase of progression, different stages are histologically differentiated. Low-grade lesions are defined as HPV changes and CIN 1 and the high-grade changes encompass CIN 2, CIN 3, and CIS.

If an infection is present, low-risk types have a higher rate to clear by themselves than their high-risk counterparts (41), but it is seen that high-risk types very commonly infect women who start becoming sexually active (42). There is a possibility that different types of HPV can infect a person simultaneously (43). As previously mentioned, the persistent infection with a high-risk type is necessary to cause neoplasia which luckily does only happen in a minority of patients. However, in around 65 percent of women in infection with types 16/ 18 lasting more than 6 months, a squamous intraepithelial lesion will develop (44). Therefore the risk of malignant transformation increases the longer the person is exposed to the infection (45).

Diagnosis

The classical diagnosis is based on cervical clinical inspection and the performance of a Pap smear followed by cytologic and histologic analysis. As these are very subjective and inaccurate due to human error, an HPV DNA test utilizing NAAT or PCR should be carried out. The possibility to test for certain strains is available, with the main focus on testing for types 16 and 18 for risk assessment and tailored treatment. Due to the possibility of latent infections, a negative HPV test does not eliminate the risk of infection. An HPV test is unnecessary in the case of clinical visible genital warts or invasive cancer on histology and cytology (36).

Treatment

Treatment options are available to eradicate latent or subclinical infections and the main treatment is aimed to treat genital warts, high-grade neoplasia, and invasive cancers. Given that most HPV infections are self-limited, treatment is commonly not needed. The most important action avoiding a future HPV infection is successful prevention. Condoms are good in decreasing the surface where a possible infection can spread, but due to their limited area of coverage, the transmission is still possible (46). The best option is to get vaccinated against HPV. There are three vaccines

available and the best one is Gardasil 9 which protects against types 6, 11, 16, 18, 31, 33, 45, 52, and 58. To get the best immune response 3 vaccinations over 6 months have to be administered. The second dose is given 1 to 2 months after the first and the last dose after 6 months. The CDC recommends that vaccines should be given to girls aged 11 to 12 (as early as age 9) and for everyone to the age of 26 who was previously unvaccinated (47). The immunologic response is very good and coverage should last 5 to 8 years and the test showed no need for booster dosing is necessary. The positive implementation of the vaccine in countries showed a drastic decline in genital warts and Pap smear findings (48).

Neisseria gonorrhea

Due to its common asymptomatic presentation, it is recommended that women at risk should go for screening. Associated risk factors of N gonorrhea are age less than 24 years, new or multiple sex partners, current or prior STDs, a partner with other concurrent partners, a partner with an STD, having a commercial sex worker profession, and sex without barrier protection. However, it is not recommended to screen women at low risk (49).

Most women with N gonorrhea are asymptomatic, but symptomatic women can present with vaginitis or cervicitis. A typical odorless, nonirritating, and white-yellow vaginal discharge is seen in patients with cervicitis and appears one to 14 days after the infection. Additionally, intermenstrual bleeding, postcoital bleeding, or bleeding after inserting a cotton swab into the cervical canal, can be noticed. Besides causing infection in the vagina and cervix, N. gonorrhea can infect the urethra, the Bartholin, and Skene glands and ascend into the endometrium and fallopian tubes to cause an infection in the upper reproductive system. This can cause discomfort during urination (49, 50). Under the microscope, the organism is a gram-negative coccobacillus that invades columnar and transitional epithelium causing it to become intracellular. Therefore the vaginal squamous epithelium is not infected (49).

Diagnosis

The preferred diagnostic test is the nuclear acid amplification test which is available at most laboratories and has replaced bacterial culture in the last years. The sample

is gathered from the vagina, endocervix, or the first-void urine especially in hysterectomy patients without a cervix. The sensitivity and specificity of a vaginal swab and cervical swab are the same but are preferred over the urine sample. In case of pharyngeal or anal infection, non-culture tests are not FDA approved and should not be used in these scenarios (51). All gonorrhea-positive patients must be tested for STDs and all sexual partners 60 days before diagnosis are evaluated and tested. During the treatment, the patient and the sexual partner should refrain from having sex until the infection has been cleared (49).

Treatment

The CDC supplies guidelines for treatment in case of affected partners. The so-called expedited partner therapy enables the sexual partner to get a prescription for the necessary medication without prior clinical assessment. This does not replace traditional patient referral if it is possible but helps in decreasing the spread of the infection. EPT is sanctioned for N gonorrhea and C trachomatis but not for other STDs like syphilis and Trichomoniasis. Furthermore, not all states are legalizing this form of prescribing medicine in the United States (31, 49).

As treatment options, the CDC suggests a single dose of ceftriaxone 500 mg IM for persons weighing less than150 kg. For patients weighing more than 150 kg, 1g of IM ceftriaxone is recommended in the case of uncomplicated cervical or urethral gonorrhea infection. The alternative regimen is cefixime 800 mg orally once, or Gentamicin 240 mg IM as a single dose plus azithromycin 2g orally once as a single dose. In case of an uncomplicated pharyngeal infection, the recommended treatment option is chosen. For a cephalosporin allergy, a single oral dose of gemifloxacin 240 mg plus azithromycin 2 g is recommended. In the case of azithromycin allergy, ceftriaxone alone is enough. If the alternative regimen is used, however, azithromycin is to be swapped with doxycycline 100 mg orally twice daily for 7 days (52).

Complications

Complications associated with an untreated gonococcal infection can have a serious and permanent impact on the patient. The spread into the uterus and fallopian tubes can cause pelvic inflammatory disease which can be mild or severe with fever and abdominal pain. The formations of abscesses, damage to the fallopian tubes, and possible infertility or ectopic pregnancy are the most dangerous complications.

Possible dissemination of the gonococcal infection can lead to arthritis, tenosynovitis, and/or dermatitis. This infection can be an acute threat to life (50).

Treponema pallidum

Treponema pallidum is a spirochete that causes the sexually transmitted disease syphilis. The risk of infection is increased in women with lower socioeconomic status, adolescents, people who start having sex at an early age, and high numbers of sexual partners. There is approximately a 30 percent chance of getting the infection after exposure (53). In 2018 the total amount of syphilis cases in the US was the highest since 1991. The number of syphilis in all stages increased by 13.3 percent in the years 2017-2018 to a total of 115,045 (54). When contracting syphilis, the infection has four different stages that can be differentiated from each other. In primary syphilis, the patient would present with a chancre. These chancres are usually round, firm, and painless. They appear at the site where the bacterium entered the body. The time to develop these lesions can be from 10 days to 12 weeks with a mean incubation period of 3 weeks. This lesion spontaneously heals in 3 to 6 weeks which leads to people forgetting about their symptoms and the progression of the disease, if no treatment was initiated (53, 55).

After 6 weeks to 6 months after the chancre appeared, secondary syphilis begins with the start of bacteremia. In this stage, a skin rash or lesions on mucous membranes develops. This rash also actively sheds spirochetes like the chancre in primary syphilis did (53). This rash may cause the formation of rough, red, or reddish-brown lesions that appear on the soles and palms of the patient. Additionally, large grey or white lesions may develop in warm and humid areas like the groin, axilla, or mouth. These plaques are called condyloma lata and are highly infectious. Due to its systemic nature, additional symptoms can be fever, swollen lymph nodes, patchy hair loss, sore throat, weight loss, headache, and fatigue (55). Malaise and even kidneys, liver, joints, and the CNS can be involved. The term early latent syphilis is referred to the period during the first year without treatment after the first symptoms appeared. Late latent syphilis however is defined as the time greater than 1 year after the initial infection. Tertiary syphilis can appear up to 20 years after latency and presents with

possible cardiovascular, CNS, and musculoskeletal involvement. Cardiovascular and neurosyphilis are however less prevalent in women with men being affected twice as often (56).

Diagnosis

Because of its poor capability to retain gram stain, the best way to visualize the spirochetes is by darkfield microscopy or direct fluorescent antibody testing of the collected sample from the lesion. In recent years nontreponemal serologic tests have been developed to support population screening, which are: 1. Venereal Disease Research Laboratory (VDRL) or 2. Rapid plasma reagin (RPR) tests. Treponema-specific tests however are: 1. fluorescent Treponema antibody-absorption (FTA-ABS) or 2. Treponema pallidum particle agglutination (TP-PA) tests. If a woman tests positive who has not been previously been treated for syphilis or a 4 fold increase in the titer in a woman who was treated previously, a conformation test with a treponemal-specific test should be performed. Basically, for a woman with a positive serological test or high clinical suspicion, FTA-ABS or TP-PA tests should be performed for diagnosis confirmation. To assess the quantitative measurement for antibody titers and response to treatment, RPR and VDRL are used (56).

After treatment, surveillance with sequential nontreponemal tests, like RPR or VDRL is used to follow up the patient. Clinical and serologic evaluation after a period of 6 and 12 months is the standard. The measured serologic response should be compared to the titer from the start of the treatment to evaluate the treatment success. To be treated successfully, the titer has to decrease by 4 by 6 months after treatment for primary or secondary syphilis. Failure for the titer to drop fourfold in 6-12 months after the treatment for primary or secondary syphilis indicates treatment failure or reinfection (57). In latent syphilis or patients with initially high titers, the same requirements have to be reached in 12 to 24 months. Commonly, these tests become non-reactive after the drop in titers, but in some people, a continuing low titer level remains. These patients are called serofast. In these women with remaining reactive treponemal-specific tests, there is a high probability of them having a positive test for the rest of their life (56).

Treatment

In connection with treating the patient, it is important to find out about the stage of syphilis the person is in. For the primary, secondary, and early latent phases it is recommended to use 2.4 million units of benzathine penicillin G as an intramuscular injection once. Alternatively, an oral regimen for penicillin-allergic or nonpregnant women would be doxycycline 100mg orally twice per day. For the late latent, tertiary, and cardiovascular syphilis the recommended regimen is benzathine penicillin G 2.4 million units intramuscular injected weekly for 3 doses for a total of 7.2 million units. For the alternative regimen, doxycycline 100mg orally twice daily for 4 weeks is advised (57). This alternative regiment is only advisable if the patient is compliant and can be surveilled after the treatment. If this is not possible the patient should be desensitized and treatment with IM benzathine penicillin G is initiated (56). During the first 24 hours after treatment starts, a reaction called Jarisch-Herxheimer can be seen. It appears as an acute self-limited febrile response and is associated with myalgia and headaches. It is important to instruct the patients about this possible reaction and how they can manage it. This happens mostly in early syphilis stages due to a higher bacterial burden (57). During the follow-up period, the patient is seen at 6-month intervals and blood is taken for serology. As mentioned before, a fourfold decrease of titer values is anticipated at 6 months. In the case that this did not happen, the patient either failed treatment or got reinfected. The recommended regiment for retreatment would be 2.4 million units of benzathine penicillin G IM once weekly for 3 weeks (56).

Herpes simplex virus

Ulcers are defined as the total loss of the epidermis and invasion of the dermis. This is compared to erosion which is only the superficial and partial loss of the epidermis without penetration into the dermis. The differentiation between those two is done on basis of a clinical examination and a biopsy is generally not taken. If a biopsy is taken the main focus is directed to visualize the border of the lesion. If the lesion is suspected to be a malignant lesion a biopsy is mandatory.

The most common genital ulcers in the group of sexually active young women in the United States are derived from a herpes simplex infection or syphilis, but there is a chance that some present with chancroid, lymphogranuloma venerum, or granuloma inguinale. Due to the increased risk and association of these sexually transmitted diseases with HIV, it is highly advisable to offer HIV and STD testing to these women as well as to their sexual partners (58).

The Herpes virus is causing a chronic viral infection by entering sensory nerve endings and then gets carried to the dorsal root ganglion via retrograde axonal transport where the virus lies dormant until a spontaneous reactivation. These reactivations can come through different triggers and cause the virus to be transported to the surface of the skin. There the virus is shed and depending on the person may cause the formation of lesions or not. There have been studies that suggested the virus to be associated with immune mechanisms that control latency and reactivation (59).

Two different types of herpes simplex virus exist. HSV-1 is the most common type for oral lesions and HSV-2 is more typically found in the genital area. However, it is not uncommon that the two types can be found vice versa due to the increase of oral sex practice. The estimation by the CDC is that annually 776,000 people in the United States catch a new genital herpes infection. In the age group 14 to 49, 11.9 percent have HSV-2 infections. This number in reality is higher due to the increasing number of genital HSV-1 infections (60). This discrepancy between those two types results from the common mild or unrecognized nature of HSV-2. The infected patients shed the virus via sexual contact while being asymptomatic are completely unsuspecting of their disease. Around 65 percent of patients are women who suffer from an active infection (58).

If the patient will experience symptoms after the first contact will depend on whether there are antibodies present from a previous infection or not. With no antibodies present the percentage of developing symptoms can be as high as 70 percent and 90 percent of symptomatic patients will develop symptoms again within one year. The average incubation period is one week (58).

As the virus infects the epidermal cells, the cell walls lyse and blisters form on an erythematous base. These blisters eventually rupture leaving a painful ulcer that

heals by forming a crust but can get secondarily infected. There are three characteristic stages of a herpes simplex infection: 1. a vesicle with or without pustule formation that lasts around one week; 2. ulceration; and 3. crusting. The virus can be shed in the first two stages of the infectious episode (58). Additional symptoms are burning and severe pain that comes with the initial vesicular lesion, but also during the ulceration stage, urinary frequency and pain from direct contact with urine can cause discomfort. With vulvar and urethral involvement, it is possible to experience micturition problems. These lesions can be found on the vagina, cervix, bladder, anus, and rectum depending on the contact area. Additional to the local symptoms, unspecific symptoms such as low-grade fever, malaise, headache, lymphadenopathy, cervicitis, and myalgia are common in affected women (61).The severity of the lesion depends on the viral load that the person is exposed to, but a sound immune system will inhibit the viral growth and healing will start in 1 to 2 days. However, early therapy with an antiviral drug can decrease the viral load and shorten the course of the disease. In immune-deficient patients, a higher susceptibility is seen in acquiring the virus but will show a decreased response, and healing is delayed (62).With formerly uninfected patients the vesicular phase as well as the time to heal are longer and take around 7 to 10 days for the pain to disappear and 2 to 3 weeks to fully heal. Compared to previously HSV-2 exposed patients this is one week longer to heal and the previously exposed experience significantly less pain and tenderness.

It is not uncommon to experience a recurrence of HSV-2 infection and two-thirds of women having a prodrome before the episode. The described symptoms are mainly paraesthesia or tingling in the area before vesicle formation. These symptoms however can be noticed even though there is no actual outbreak and vesicle formation (62).

Diagnosis

To test for an active HSV infection, the preferred methods are HSV DNA NAAT like a polymerase chain reaction or viral culture. The main advantage of PCR compared to culture is that it is more sensitive and yields quicker results. Due to the intermittent viral shedding, even a negative culture or PCR is not indicative of an absent HSV infection. The use of serologic testing is detecting antibodies against surface glycoproteins. These antibodies are very specific and sensitivity ranges from 80 to 98 percent (60). Only the IgG antibodies must be ordered because measuring the IgM

response can lead to false findings due to its not type-specific nature and the possibility of being positive during a recent outbreak. If the patient shows obvious clinical symptoms and findings, it is recommended to start treatment and additional STD screening right away. The tests for the additional screening should include infections from syphilis, gonorrhea, trichomoniasis, and HIV, chlamydia, and hepatitis B (62).

Treatment

The main treatment for Herpes simplex virus infection is the use of an antiviral drug combined with an analgesic. The analgesic can be from the NSAID family or a light narcotic-like acetaminophen with codeine. Topical anesthetic ointments may provide additional relief. The regimen for the first clinical episode is acyclovir 400mg three times daily for 7-10 days, or acyclovir 200mg five times daily for 7-10 days, or famciclovir 250mg three times daily for 7-10 days, or valacyclovir 1g twice daily for 7-10 days. In case the recovery is incomplete after 10 days the treatment can be extended (63). For the episodic therapy in recurrent episodes it is recommended to use Acyclovir 400mg three times daily for 5 days, or acyclovir 800mg twice daily for 5 days or acyclovir 400 mg orally three times a day for 5 days, or acyclovir 800 mg orally three times a day for 2 days, or valacyclovir 500 mg orally twice a day for 3 days. In patients with frequent recurrent episodes a suppressive therapy is introduced with acyclovir 400mg twice daily, or famciclovir 250mg twice daily, or valacyclovir 0.5 or 1g once daily. Additional to the treatment it is very important to instruct the patient about sexual transmission and how to reduce it, as well as its obstetric consequences (63). The baby can get infected in the vaginal canal with HSV during natural delivery and in an active infection, options have to be discussed with the obstetrician (64). Furthermore, it is advised that infected patients are not having sexual contact with uninfected partners during an acute episode or prodromal symptoms. The use of condoms reduces the risk of transmission (65). Even though the treatment may increase the speed of healing, it cannot eliminate the latent virus or prevent future recurrent infections. The perfect time of starting therapy in an episode is within one day of lesion outbreak or during the prodrome phase. In women with recurrent episodes, suppressive therapy can be applied which reduces the transmission of recurrence by 50 percent (66).

Chancroid

This infection is caused by Haemophilus ducreyi, a gram-negative bacillus. The average incubation period lasts between 3 and 10 days and gains entry into the host through mucous membranes or the skin. In the US this infection is more common in the black and Hispanic population but is counted as one of the more uncommon STDs in general (67).

The symptoms are an initial erythematous papule that turns pustular and then ulcerates in 48 hours. Under the microscope, the edges can be visualized and an irregular, erythematous nonindurated margin can be seen. These ulcers are painful and the ulcer base is described as red and granular. The typical location of these lesions in women is the vestibule, clitoris, labia, and fourchette. Additional symptoms in 50 percent of patients are unilateral or bilateral lymphadenopathy. These lymph nodes may form fistulas and drain to the skin where new ulcers form.

Diagnosis

The diagnosis is based on culture with a special media but this has a specificity of less than 80 percent (67). It is possible to make a probable diagnosis if certain criteria are met: 1. Presence of one or more painful genital ulcers; 2. Lymphadenopathy; 3. No evidence of syphilis infection was confirmed by darkfield microscopy or by serologic test; and 4. a negative herpes simplex virus PCR or culture.

Treatment

For the treatment, the CDC recommends 1 g azithromycin orally as a single dose, or ceftriaxone 250 mg IM in a single dose, or ciprofloxacin 500 mg orally twice a day for 3 days, or erythromycin base 500 mg orally three times a day for 7 days. A re-examination after 3-7 days is recommended since within that timespan the resolution of the infection should be seen. However, treatment response is not as good in patients with an HIV infection and a longer treatment course should be applied (68).

Granuloma Inguinale

Granuloma inguinale, also called Donovanoisis is an infection caused by the intracellular gram-negative bacterium Calymmatobacterium (Klebsiella) granulomatis. It is characterized by its mild contagious nature and repeated exposure to cause the infection. The incubation period is fairly long and ranges from weeks to months. Symptoms are painless inflammatory nodules that progress to ulcers that can bleed easily due to their great vascular supply. In the case of secondary infection, the ulcers can become painful. Lymphadenopathy is not always visible but if they are, more ulcers can appear along the draining nodes. The primary mode of healing is by forming a scar where the ulcer was (67).

Diagnosis

Diagnosis of K. granulomatis is difficult due to culture problems of the organism. The best way is to visualize dark-staining Donovan bodies on tissue crush preparation or biopsy.

Treatment

The recommended treatment regimens by the CDC are 1 g azithromycin orally once per week or 500 mg daily for at least 3 weeks until all lesions have completely disappeared. Alternative regimens are doxycycline 100 mg orally twice a day for at least 3 weeks, or ciprofloxacin 750 mg orally twice a day for at least 3 weeks, or erythromycin base 500 mg orally four times a day for at least 3 weeks, or trimethoprim-sulfamethoxazole one double-strength (160mg/800mg) tablet orally twice a day for at least 3 weeks. All the alternative regimen treatments have to be taken until all lesions have completely healed additionally to the 3 weeks of required treatment. Possible recurrences have been described up to 18 months after successful therapy (69).

Lymphogranuloma venerum

The cause of this sexually transmitted disease is caused by 3 specific strains of Chlamydia trachomatis called L1, L2, and L3. The classical risk groups are people with a lower socioeconomic status as well as people who have multiple sexual partners. The time until disease presentation can last from 3 days to 2 weeks and its progress can be split into 3 distinct phases: 1. Formation of small vesicles or papules; 2. Inguinal or femoral lymphadenopathy; 3. Anogenitorectal syndrome (70). Typical sites of inoculation are the posterior wall of the vagina, the cervix, and the fourchette but other sites can be affected as well. The resolution of these papules happens quickly and with no scar formation.

In the second phase, femoral and inguinal lymphadenopathy can be seen. The very characteristic “groove sign” is a cluster of multiple enlarged lymph nodes on both sides of the inguinal ligament with the central gap in between. This can be observed in up to 20 percent of affected women. The rupture of these lymph nodes can lead to a sinus formation with pus draining to the skin. Additionally, systemic infections commonly develop with fever as well as malaise, and even pneumonitis, arthritis, and hepatitis have been described.

The third stage of the infection is composed of a mucoid discharge from the ulcers and rectal pruritus. In a possible secondary infection, the formation of pus can be seen. Due to lymphatic obstruction after lymphangitis, elephantiasis of the external genitalia followed by fibrosis of the rectum can cause long term complications. Possible stenosis of the vagina and urethra has been described in LGV infection. Additional symptoms are rectal bleeding, crampy abdominal pain with abdominal distention, and fever. The life-threatening diagnosis of peritonitis after a bowel perforation is also possible (70).

Diagnosis

The diagnosis can be made through clinical suspicion, epidemiologic history, and elimination of other etiologies. Usage of NAATs for C. trachomatis on rectal swabs is the preferred method of testing. Additionally, serologic testing with titers of >1:64 supports the diagnosis of LGV infection.

Treatment

Treatment options according to the CDC are doxycycline 100 mg orally twice a day for 21 days or erythromycin base 500 mg orally four times a day for 21 days. The follow-up of the patients is recommended until signs and symptoms have been completely cleared. Further testing for other sexually transmitted diseases like gonorrhea, HIV, and syphilis is advised (71).

External genital warts

The cause of genital warts in patients is the human papillomavirus. This virus has many different strains, but serotypes 6 and 11 make up for 86 percent of all HPV infections (72). The appearance of warts can be multiple, with some looking like flat papules and others like the classic verrucous, exophytic condyloma accuminata. The location of these warts will depend on the place where contact to an infected site happened but it will develop in the mouth, lower reproductive tract, urethra, or anus. In general genital warts are asymptomatic, but in some cases, pruritus or pain can be experienced depending on the location.

Diagnosis

To diagnose these lesions, a clinical inspection is usually sufficient (73). In case of suspected neoplasia, a biopsy can be performed. To make the diagnosis of HPV infection, knowing the serotype is not necessary (74).

Treatment

When infected, condyloma accuminata usually resolve spontaneously, but many women prefer surgical removal. The surgical options are sharp or electrosurgical excision, laser ablation, or cryotherapy. Cavitational ultrasonic surgical aspiration can be used in large lesions that want to be removed. It is however unclear if the effect of treatment helps in the case of future transmission.The use of topical agents instead of surgery is also possible through different preparations. The 3.75 or 5 percent imiquimod cream can be applied by the patient and is an immunomodulatory topical agent. It causes macrophages to release cytokines, of which interferon-γ is the most crucial. It stimulates the body's cell-mediated immune response to act against HPV

(74). Another option is a 15-percent sinecatechin ointment extracted from green tea leaves. Podofilox 0.5 percent solution or gel can also be applied by the patient and is effective. A possible treatment with proteolytic agents like trichloroacetic acid and bichloroacetic acid can be done by the treating physician. Additionally, intralesional injections of interferon are an effective treatment for HPV, but due to its high cost and associated pain, it is just an alternative (73).

Among these therapy options, there is no proven superiority of one specific one. However, the patients and provider preference are the main deciding factor. It is important to note, that no treatment causes 100-percent clearance, with an average of 30 to 80 percent. Therefore recurrences are common following the treatment of an active HPV infection (74).

Molluscum contagiosum

This disease is caused by a DNA poxvirus called molluscum contagiosum. The means of transmission are due to human-to-human contact or by infected fomites. The average incubation period ranges from 2 to 7 weeks and the clinical presentation is a characteristic popular white, pink or flesh-colored lesion with central umbilication. It often has a pearly appearance. These lesions can be single or multiple and can be found anywhere but are commonly seen on the vagina, vulva, thighs, and buttocks. Symptoms include pruritus, inflammation, erythema, and pain (73, 75). This virus is contagious until the lesion disappears. Due to its characteristic appearance, the main diagnostic procedure is visual inspection however a swab can be performed of the lesion and sent for laboratory workup with Giemsa, Gram, and Wright stains.

The finding of large intracytoplasmic molluscum bodies is diagnostic. Even though most lesions regress by themselves in 6 to 12 months, some patients prefer surgical removal.

Treatment options are cryotherapy, electrosurgical needle coagulation, or sharp needle tip curettage of a lesion's umbilicated center. The application of the same topical agents used for genital warts also proved effective in the treatment of molluscum contagiosum (73).

Pelvic inflammatory disease

Pelvic inflammatory disease is caused by an infection of the upper reproductive system. The main structures involved are the fallopian tubes. Due to its difficulty to diagnose a lot of women are not treated for it or are treated even though they don't have it. However, it is crucial to start treatment early due to the severe complications associated with this disease. The infectious agent can most of the time not be identified since cultures of the endocervix, endometrium, and cul-de-sac yield different results. However, treatment is mainly directed at the most common pathogens. N. gonorrhea and C. trachomatis are the typical causes and T. vaginalis sometimes causing the infection as well. The infection starts due to ascending of pathogens into the upper reproductive tract from the lower tract. This can happen especially during menstruation when the endocervical barrier is removed (76).

PID can be differentiated into 3 different categories: silent PID, active PID, and chronic PID. Silent PID is believed to happen after multiple or continuous low-grade infections in an asymptomatic patient. It is not defined as a clinical diagnosis, but more an explanation that was provided to a woman with tubal-infertility without upper tract infection. In serologic testing, it was found that many of these patients have antibodies against C. trachomatis or N. gonorrhea (76). The internal structure of the fallopian tubes shows flattened mucosal folds, extensive deciliation of the epithelium, and secretory epithelial cell degeneration (77). Additionally, sonographic findings like hydrosalpinx or fine adhesions between the liver capsule and the anterior abdominal wall can be seen.

Diagnosis

Diagnostic criteria for acute pelvic inflammatory disease according to the CDC are uterine tenderness, adnexal tenderness, or cervical motion tenderness. Additional specificity for this disease can be given if: 1. Oral temperature is higher than 38.3 degrees, 2. mucopurulent cervical discharge or cervical friability is present, 3. Abundant WBCs on saline microscopy of cervical secretions, 4. Elevated erythrocyte sedimentation rate or C-reactive protein, and 5. presence of cervical N. gonorrhea or C. trachomatis (78). In the acute setting of PID, the symptoms tend to show up during or after menstruation and symptoms are lower abdominal or pelvic pain, yellow discharge, heavy menstrual bleeding, chills, fever, dysmenorrhea, or dyspareunia.

Unfortunately, none of these symptoms are specific for the diagnosis of this disease and high clinical suspicion is needed. Patients with PID may develop abdominal peritonitis. In that case, usually, only the lower abdomen is involved however, an extension to the liver capsule will cause right upper quadrant pain. This condition is called Fitz-Hugh-Curtis syndrome. Typical symptoms of this perihepatitis include sharp pleuritic pain that accompanies the pelvic pain. On auscultation, a friction rub can be heard over the right anterior costal margin (79).

In women with lower abdominal pain or pelvic pain, testing is aimed at identifying PID. A possible pregnancy is excluded by checking the beta-human chorionic gonadotropin in serum or urine. Liver enzymes are checked in those suspected to have additional Fitz-Hugh-Curtis syndrome and saline preparations of the cervical secretions are performed. Routine STD testing should be done as well to exclude additional infections. One of the most useful tools for diagnosing PID is Sonography. Sonography can visualize the fallopian ducts which have the following characteristics in acute PID: 1. Distended, Ovoid-shaped tube filled with anechoic or echogenic fluid, 2. Thickening of the fallopian tube wall, 3. incomplete internal septa, 4. a “cogwheel” appearance when the inflamed fallopian tubes are visualized in cross-section (80). The ultrasound can also be used to visualize a possible tubo-ovarian abscess or exclude any other cause of the abdominal pain. In the case that sonography does not find any pathology, imaging with CT or MRI are suitable alternatives (79).

The diagnosis of a chronic pelvic inflammatory disease can be given in cases of acute PID with following pelvic pain. Additionally, a hydrosalpinx can be used as a criterion for the diagnosis of chronic PID. In reality, it is a diagnosis based on histologic findings from a pathologist, making the clinical use of this diagnosis limited (81).

Treatment

Treatment options for PID are multiple. However, it is very important to recognize the symptoms and start treatment early to guarantee the successful recovery of the patient. The main goal is to get rid of the infection, relieve the patient’s symptoms and prevent any complications. The prevention of complications is not always possible since tubal damage or occlusion can lead to ectopic pregnancy, chronic pelvic pain, infertility, or abscess formation. The CDC recommends IM or oral treatment in mild to

moderately severe PID with ceftriaxone 250 mg IM in a single dose plus doxycycline 100 mg orally twice a day for 14 days with or without metronidazole 500 mg orally twice a day for 14 days. Another option is cefoxitin 2 g IM in a single dose and probenecid 1 g orally administered concurrently in a single dose plus doxycycline 100 mg orally twice a day for 14 days with or without metronidazole 500 mg orally twice a day for 14 days. In case there is no improvement within 72 hours, the patient should be reassessed to confirm the diagnosis and intravenous therapy should be initiated. The intravenous therapy options are for severe disease or patients with a tubo-ovarian abscess. The recommended intravenous regimen from the CDC is cefotetan 2 g IV every 12 hours plus doxycycline 100 mg orally or IV every 12 hours or cefoxitin 2 g IV every 6 hours plus doxycycline 100 mg orally or IV every 12 hours or clindamycine 900 mg IV every 8 hours plus gentamicin loading dose IV or IM 2 mg/kg, followed by a maintenance dose 1.5 mg/kg every 8 hours. Due to the pain of IV doxycycline, it is advised to administer it orally whenever possible. The alternative parenteral regimen is Ampicillin/Sulbactam 3 g IV every 6 hours plus Doxycycline 100 mg orally or IV every 12 hours. In the case of an abscess, it is crucial that additionally to the antibiotic treatment the abscess gets drained surgically and necrotic tissue removed (78).

After 3 months it is advised to retest all women who got a diagnosis of chlamydial or gonococcal PID. If this is not possible then retesting at the next possible time within 12 months after treatment is recommended (78).

Prevention

In the year 2008 around 499 million curable sexually transmitted infections were registered worldwide. In addition to that, more than 500 million people were approximated to have a viral STD. These infections carry many psychosocial as well as sexual burdens. For example infertility, pregnancy complications, cancers, or disease-related social pressure make these infections worse than just the initial symptoms they cause. Given the number of infected people, this puts an enormous strain on treatment costs on the health care system. Not only does the immediate treatment cost, but also the treatment of complications that could occur years later (82). This is why it is so important to find new ways to successfully prevent the spread of those diseases. Public health policies tackling this problem are aimed at the prevention and control of STDs. They try to educate young children before they become sexually active, find asymptomatic carriers, and treating their partners (83). A form of STD education can be done via social media. With this technology and its heavy use among the young population, it can be incorporated more into their schedule in school as well as extracurricular life. Studies have shown this is possible but more research has to be done to better and more efficient approach each gender specifically (84).

The best way to reduce or prevent any sexually transmitted diseases on a personal level is to follow the Prevention guidelines issued by the CDC. The option to prevent any STD one hundred percent is not to have sex and abstain from it. However, being the best option, in theory, it is not the most realistic one. The next best way in preventing infections is by getting vaccinations against HPV and hepatitis B virus. This is a safe and effective way to prevent HPV as well as further transmission and everyone under the age of 26 years should follow this recommendation. Unfortunately, there are not adequate vaccinations for every viral STD, and more research has to be done in that field. Another way to decrease the risk for STDs is by reducing the number of sex partners and staying in a mutual monogamy relationship. This however only works if regular STD tests are performed and both parties can be certain that they are STD-free. The final prevention method is the use of condoms. Nest to being effective in reducing the risk of transmitting an STD they additionally prevent unwanted pregnancies (85).

Conclusion

Given that STDs have a certain social stigma throughout the world and that a lot of people feel insecure or too embarrassed to seek medical attention, makes it even more important that this problem gets tackled. Better sexual education and health promotion are essential to increase awareness in the population that is endangered at increasingly younger ages due to earlier sexual activity.

The increase of STDs in the last years proves that reliable identification of symptoms in sick patients is crucial to prevent further spread. Therefore a regular STD test once a year can be beneficial to identify symptomatic or asymptomatic women and eliminate possible short or long-term complications. All this can be avoided by regular testing and the great ability of treatment options to deal with all the mentioned infections to protect the patients' health as well as the health of their sexual partners. Furthermore, the increased use of barrier protection like condoms is the best choice against all sexually transmitted diseases and would help decrease the incidence of new STDs all over the world.

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Biography

Julian Voit was raised in a non-medical professional home. During his teenage years, he got introduced to the basic medical field when he joined the lifeguard team in his hometown. After high school, his interest in medicine grew but unfortunately due to insufficient high school grades, he was unable to study medicine in Germany. After starting brewery and beverage technology studies at the Technical University in Munich he decided to quit and follow his dreams by going abroad and applying for the medical program at the Zagreb medical university.