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Sexually transmitted infections

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Summary

In no other medical field former rare infections of the 1980th and 1990th occur again as this is seen in the field of venerology which is as well based on the mobility of the population. Increasing rates of infections in Europe, and increasing bacteriological resistances face health professionals with new challenges. The WHO estimates more than 340 million cases of illnesses worldwide every year. Diseases caused by sexually transmitted infections (STI) in a strict sense are syphilis, gonorrhea, lymphogranuloma venereum, granuloma inguinale, and chancroid. In a wider sense, all illnesses are included which can mainly be transmitted through sexual contact. The term "sexual contact" has to be seen widely, from close physical contact to all variants of sexual behavior. This CME article is an overview of the most common occurring sexually transmitted infections in clinical practice. Both, basic knowledge as well as recent developments are discussed below.

Introduction

Since the beginning of history, in every era, there are records and descriptions of sexually transmitted infections (STI). Around 1917, in response to the dramatic increase in the number of people with STIs, against the backdrop of an economic crisis, the field of genito-urinary medicine was established in Great Britain; even today, it includes all facets of sexual health. Over time, people and their sexual behavior have changed, and so have the pathogens underlying sexually transmitted infections. *Gonococci*, for instance, are resistant to nearly every known class of antibiotics. A similar development is now being seen with chlamydia. This makes evident the urgent need for a new "springtime" for sexual prevention work, as occurred during the 1980s in response to HIV. About 250 000 deaths occur annually worldwide due to HPV-associated cervical carcinoma. One thing is clear: sexually transmitted infections are not a matter of "youthful folly." People of all ages, every sexual orientation, and all socio-economic levels are affected. All healthcare professionals are thus advised to be aware of our changing society when taking medical histories and weighing diagnoses, in order to ensure prompt detection and optimal treatment.

Neisseria gonorrhoeae (Table 1)

In 1879 Albert Neisser described the Gram-negative bacterium *Neisseria gonorrhoeae*, which is usually arranged in pairs. Historical accounts and descriptions of the disease date back to the third book of Moses in the Bible. *Neisseria gonorrhoeae*

Gonococci have the ability to develop resistances through plasmid-mediated resistance, on the one hand, and chromosomal changes on the other. Furthermore, they can pass on these changes to each other.

have a marked affinity for cylindrical epithelium, while stratified squamous epithelium and transitional epithelium remain virtually uninfected. *Gonococci* have the ability to develop resistances through plasmid-mediated resistance, on the one hand, and chromosomal changes on the other. Furthermore, they can pass on these changes to each other. Antibiotic resistances to penicillin, macrolides, tetracyclines, and fluoroquinolones are well established. Recent data have now shown resistances to cefixime and ceftriaxone. Given its variable superficial antigens, people do not develop immunity to gonococcal infection. Reinfections are possible and common.

Clinical appearance of gonorrhea

Gonococcal infections can affect genital, rectal, pharyngeal, or extragenital (gonococcal blepharoconjunctivitis) regions.

Gonococcal infections can affect genital, rectal, pharyngeal, or extragenital (gonococcal blepharoconjunctivitis) regions. Men with genital gonorrhea typically develop a highly purulent discharge 2–6 days after infection. In women, gonorrhea is often asymptomatic and may go undetected. Gonorrheal urethritis (GU) accounts for about 20% of infectious types of urethritis. By definition, urethritis is present if there are more than five leukocytes in five visual fields (400x magnification) in a specimen and more than ten leukocytes in five visual fields in a first-catch urine sample. Typical clinical symptoms include a purulent discharge (referred to in men as the "drip") or pain, which some patients describe as a sensation of "passing broken glass." Milder symptoms can also occur. Gonorrhea is indistinguishable from chlamydia or non-gonococcal non-chlamydial urethritis (NGNCU) based on clinical appearance alone (i.e., a rather thin and watery discharge).

Double infections with gonorrhea and chlamydia occur in up to 20 % of patients.

Double infections with gonorrhea and chlamydia occur in up to 20 % of patients. In ascending infections, the posterior part of the urethra may become infected (posterior gonorrheal urethritis). Patients may also develop prostatitis, vesiculitis, funiculitis, epididymitis, Cowperitis, cavernitis, or even gonococcal sepsis, perihepatitis gonorrhoica, endocarditis, meningitis, or gonarthritis.

In about 50 % of women, gonorrhea remains asymptomatic.

In about 50 % of women, gonorrhea remains asymptomatic. The primary infection usually affects the cervix. The clinical appearance consists of increased vaginal discharge. Isolated urethral infections can occur; thus pathogens should be isolated from the cervix and the urethral opening. As in men, ascending infections per continuitatem in the urogenital tract provide a reservoir for further infections. Up to 20 % of women infected with *N. gonorrhoeae* also develop acute salpingitis or PID (pelvic inflammatory disease). Accompanying infection of the Bartholin glands is also common. This is often clinically apparent as labial swelling. In very rare instances, there may be gonococcal hepatitis (Fitz-Hugh-Curtis syndrome) with accompanying inflammation of the peritoneum. Due to the high infectiousness of the pathogens, the use of a condom during heterosexual intercourse can reduce the rate of infection by around 60%.

Isolated urethral infections can occur, and thus pathogens should be isolated from the cervix and the urethral opening.

Pharyngeal gonorrhea has very few clinical symptoms. Yet it is one of the largest pathogen reservoirs; unprotected fellatio results in infection about 25 % of the time. Anorectal gonococcal infection often also occurs with few or no symptoms. Possible symptoms include bloody or mucus-coated stool, discharge, urgency, and tenesmus. Patients may also have pain upon defecation. Pruritus and eczema may occur as secondary phenomena in the sense of irritative-toxic anal eczema.

Diagnosis

The gold standard is diagnosis by bacterial culture. This is suitable for material from the cervix, urethra, rectum, and throat; the sensitivity for specimens from the genital region is high.

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(NAAT), which, in addition to high specificity, also have the advantage of identifying potential chlamydia infection, gonorrhea culture identification tests have become a less popular method in recent years. Yet, given the current problem of resistances, bacterial cultures should continue to be used [1, 2]. If there is clinical suspicion of gonorrhea, urethral, pharyngeal, and anal specimens should be obtained for pathogen identification. In patients with gonorrhea, screening for other STIs (chlamydia, syphilis, HIV infection) is mandatory. The patient's informed written consent must be obtained before performing an HIV test.

If there is clinical suspicion of gonorrhea, urethral, pharyngeal, and anal specimens should be obtained for pathogen identification.

Complications

In women, the most common complications are prolonged symptoms due to the untargeted use of antibiotics, gonococcal arthritis, and ascending infections. In rare instances, gonococcal sepsis due to hematogenous spread may occur.

Therapy

The previously recommended treatment with one-time oral administration of a second-generation cephalosporin has been replaced in all guidelines by dual therapy (in Germany: 1 g ceftriaxone by i.v./intramuscular administration along with one dose of 1.5 g oral azithromycin). In 2013 the Centers for Disease Control (CDC) published data on combination therapy with 240 mg of intramuscularly administered gentamycin along with oral azithromycin, 2 g, as well as one with oral gemifloxacin, 320 mg, and oral azithromycin, 2 g. Both treatment regimens were equally effective and are an alternative in patients with extensive resistance. A clinical check, and a control culture, should be performed after 7 days; NAAT should not be done until after 3 weeks, because false positives can result if it is performed too soon. Partner treatment is indicated [1–4]. In Austria, and in the German federal state of Saxony, gonorrhea is a notifiable disease. The guidelines by the German STI society (Deutsche STI-Gesellschaft [DSTIG]) on the diagnosis and treatment of gonorrhea will be published shortly (see Table 1).

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Chlamydia trachomatis (Table 2)

Chlamydia trachomatis is a Gram-negative bacterium which can only proliferate within infected cells, because their metabolism depends on the host cells. The primary host cells of the genus *Chlamydia trachomatis* (*CT*) are mucosal epithelia. The World Health Organization (WHO) estimates that there are 92 million infections worldwide.

Clinical appearance and diagnosis

Serological tests can identify various chlamydia trachomatis serovars. The serovars L1–L3 are the causative pathogens in lymphogranuloma venereum (lymphogranuloma inguinale, Durand-Nicolas-Favre disease), which is referred to as the fourth classic sexually transmitted infection. The *Chlamydia trachomatis* serovars A, B, and C are the causative pathogens in trachoma (Egyptian ophthalmia), a form of chronic conjunctivitis, which can lead to blindness if left untreated. The *Chlamydia trachomatis* serovars D through K are primarily transmitted by sexual contact; they are the pathogens responsible for non-gonorrheal urethritis, salpingitis, proctitis, and epididymitis. Other serovars cause non-sexually transmitted chlamydial infections.

The serovars L1–L3 are the causative pathogens in lymphogranuloma venereum.
The *Chlamydia trachomatis* serovars A, B, and C are the causative pathogens in trachoma.

Table 1 Source: DSTIG, Guideline on STI therapy; www.dstig.de.

Disease	In...	Standard therapy	Alternatives	Diagnosis
Gonorrhea *Neisseria gonorrhoeae*	**Adults** Urogenital, rectal, pharyngeal *Prepare culture before starting therapy*	Ceftriaxone* 1.0 g, i.v./intramuscular administration. One dose with 1.5 g oral azithromycin	*Only if susceptibility detected (culture) e.g..:* *urogenital/rectal:* 400 mg oral cefixime with 1.5 g oral azithromycin, each one time *pharyngeal:* 2.0 g oral azithromycin, one dose	NAAT (material: specimen [urethral, cervical, vulvovaginal, anal, conjunctival, pharyngeal], in men also first-catch urine) *Pharyngeal pos. confirm NAAT results with 2nd test (NAAT with another target or culture)* Culture (selective media, 5–10 % CO_2, 35–37°C, 70–80 % rel. humidity) plus possible biochemical/molecular identification; resistance analysis (material: specimen as for NAAT [see above]) *Microscopy:* (material: specimen with culture as for NAAT [see above]) *Necessary therapy controls (clinical appearance/culture after 3–7 days, NAAT after 3 weeks)* *Before therapy, perform gonococcal detection and culture*
	Children	*In newborns and children weighing < 50 kg:* ceftriaxone* 50 mg/kg of body weight (max. 125 mg) i.v./intramuscular administration. One dose *In children weighing ≥ 50 kg:* ceftriaxone* 0.5–1.0 g i.v./intramuscular administration		
Gonococcal conjunctivitis	**Adults**	**Medical emergency!** Always start calculated treatment immediately. Treatment options are as above; additional lavage with 0.9% saline solution		
	Children (Prophylaxis)	1 % silver nitrate ($AgNO_3$)		
Disseminated gonococcal infection (DIG) (sepsis)	**Adults**	Ceftriaxone* 1 g i.v. every 24 hours, ≥ 7 days		*Clinical presentation:* (signs of sepsis, pustules about the joints) and blood culture with antibiogram

**Important note:* Cross-sensitivity of β-lactams. *For intramuscular administration, 1.0 g ceftriaxone powder is dissolved in 4 ml 1% lidocaine hydrochloride. Injection in one or two portions (right/left); deep intragluteal injection. Never give lidocaine intravenously.*

The *Chlamydia trachomatis* serovars D through K are primarily transmitted by sexual contact. Men who are infected initially have urethritis (inclusion body urethritis, Waelsch urethritis); women may have an inflammation of the cervix.

The *Chlamydia trachomatis* serovars D through K are primarily transmitted by sexual contact. Men who are infected initially have urethritis (inclusion body urethritis, Waelsch urethritis); women may have an inflammation of the cervix. After an incubation period lasting from four days to one month, a glassy, sometimes purulent urethral discharge develops. Occasionally, patients have pain, although women tend to be asymptomatic. In both men and women, proctitis may occur after contact. Ascending infections are a complication: in men – often facilitated by urinary flow problems – especially prostatitis; in women salpingitis, which may lead to sterility. A serious complication is *pelvic inflammatory disease* (PID).

Table 2 Source DSTIG, Guideline on STI therapy; www.dstig.de.

Disease	In...	Standard therapy	Alternatives	Diagnosis
Chlamydial infections *Chlamydia trachomatis*	**Serovars D—K** Urethritis, cervicitis, pharyngitis, proctitis	Doxycycline 100 mg 2 × daily, given orally for 7–10 days (not for use in pregnant women)	Azithromycin** 1.5 g, given orally. One dose. Moxifloxacin 400 mg 1× daily, given orally for 7 days	NAAT (material: specimen [cervical, urethral, vulvovaginal, anal, conjunctival, pharyngeal], first-catch urine) Control with PCR tests at the earliest after 6 weeks
	Pregnancy	Amoxicillin 500 mg 3 x daily, given orally for 7 days	Azithromycin** 1.5 g, given as a single oral dose (off label) Erythromycin 500 mg, 4 × given orally for 7 days	
	Children	*Children weighing < 45 kg:* Erythromycin 10 mg/kg of body weight 4 × daily, given orally for 14 days *Children aged 8 years and older. Or weighing ≥ 45 kg:* Azithromycin 1 g, given as a single oral dose		
	Serovars L1, L2, L3 Lymphogranuloma venereum or (hemorrhagic) colitis/ proctocolitis	Doxycycline 100 mg 2 × daily, given orally ≥ 21 days (not for use in pregnant women)	Azithromycin 1.5 g, given orally. Days 1, 8, 15 *Therapy controls are essential*	NAAT plus genotype identification (material: specimen, tissue, puncture)

***In co-infection with M. genitalium or oral azithromycin for more than 5 days (day 1: 500 mg; days 2–5: 250 mg)*

The *Chlamydia trachomatis* serovars L1–3 cause lymphogranuloma venereum (LGV). The disease consists of four stages.

The *Chlamydia trachomatis* serovars L1–3 cause lymphogranuloma venereum (LGV). The disease consists of four stages. In the first stage, following an incubation period of four to ten days, an initial papule appears which later develops into a papulovesicular lesion and ultimately ulcerates. Lymphadenopathy occurs shortly after initial contact with the pathogen; especially in the inguinal region, the nodes may swell to the size of an egg. Depending on where the initial infection occurs, the intra-abdominal lymph nodes may be involved. In the second stage of disease, which begins two to four weeks after the primary lesion appears, lymphadenopathy is the main feature. The lymph nodes can be easily moved toward the subcutis, but not toward the surface, and are highly sensitive to pressure. As swelling progresses, the nodes appear to be about to break through the skin. There is also abscess formation, with subsequent perforation and drainage of pus; the lesions heal with scarring. The third stage is characterized by genital elephantiasis. The condition persists for years with enlargement of the labia, which have a rubbery consistency, along with formation of bulging areas and furrows, and papillomatous lesions. Men may have elephantiasis of the scrotum or penis. If the Gerota

nodes are involved, stasis may occur above the level of the anus with a thickened, infiltrated, and rectal stenosis with ulcerations.

The disease is endemic in tropical and subtropical countries. In Europe, it mainly affects men who have sex with men (MSM), in particular those infected with HIV. A precise and thorough sexual history inquiry in regard to sexual behavior (receptive anal intercourse, anilingus, cunnilingus, use of sex toys) is essential for diagnosing this disease, which has been increasingly diagnosed in MSM in the past decade.

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Screening, precautions, and prevention

Chlamydial infection (CT-D–K) is a main contributor to chronic inflammation of the lesser pelvis, possibly leading to sterility or ectopic pregnancy. Routine screening examinations are recommended for all women under 25 years of age, although only about 7 % follow this recommendation. Chlamydial infection is transmitted by mucosal contact with infectious material. The best means of protection against infection through sexual contact is to use a condom, although it only minimizes the risk (by around 60%), rather than eliminating it. Diagnosis is by NAAT. If the result is positive, more precise differentiation of the serovars should be performed.

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Therapy

Chlamydial infections are treated for 7 days with oral doxycycline, 2 × 100 mg daily. Lymphogranuloma venereum is also treated with doxycycline, 2 × 100 mg, for at least 3 weeks. Alternatively, 1.5 g of oral azithromycin may be given on days 1, 8, and 15. In the literature, there are reports of azithromycin resistances. If symptoms persist, despite azithromycin therapy, a new specimen should be obtained and tested by NAAT 6 weeks after treatment. AWMF guidelines on the diagnosis and treatment of chlamydia are currently underway.

Herpes simplex (Table 3)

The Herpes simplex virus (HSV) is a double-stranded DNA virus. There are two types: type 1 is known as herpes labialis (in 80 % of patients it affects the lips, and in 20 % it affects the genital region), and type 2 is called herpes genitalis (it affects the genital region in up to 80 % of patients, and in up to 20 % it affects the face). HSV belongs to the *Herpesviridae* family. After the initial infection, it characteristically persists in the sensory ganglia of the host, sometimes without causing any symptoms.

Clinical presentation and diagnosis

Symptoms of herpes simplex (HSV1 and HSV2) usually begin with tingling or itching, before painful, fluid-filled blisters develop. Other possible symptoms include erosions or ulcers, after the blisters have opened, as well as edema and a clear discharge. These may be located on the face (HSV1) or in genital or anal (HSV2) regions. Initial clinical manifestations also include regional lymphadenopathy or fever, or the patient may be completely asymptomatic. It generally takes two to three weeks before initial clinical signs (e.g., blisters and redness) have completely resolved. There are also increasing reports of patients acquiring HSV1 and HSV2 sequentially at the same site. Recent data have shown asymptomatic colonization with herpes simplex in up to 50 %.

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Table 3 Source DSTIG, Guideline on STI therapy; www.dstig.de.

Disease	In...	Standard therapy	Diagnosis
Genital herbes *Herpes simplex*	**Adults** *Primary infection* (urethritis, vulvovaginitis, proctitis, gingivostomatitis, balanoposthitis)	▸ Acyclovir 400 mg 3 × daily, given orally for 7–10 days or 200 mg 5 × daily for 7–10 days ▸ Famciclovir 250 mg 3 × daily, given orally for 7–10 days ▸ Valacyclovir 1.0 g 2 × daily, given orally for 7–10 days	▸ Clinical presentation ▸ NAAT (material: specimen, tissue)· ▸ Antigen test (fast, but less sensitive) (material: specimen)
	Adults *Reactivation, interventional*	▸ Acyclovir 800 mg 2 × daily, given orally for 5 days or 400 mg 3 × daily, given orally for 5 days or 800 mg 3 × daily, given orally for 2 days ▸ Famciclovir 125 mg 2 × daily, given orally for 5 days or 1.0 g 2 × daily, given orally (only day1) ▸ Valacyclovir 500 mg 2 × daily, given orally for 3 days or 1.0 g 1 × daily, given orally for 5 days ▸ Possibly local therapy with acyclovir or foscarnet sodium *Begin interventional treatment immediately at first signs of reactivation*	
		▸ Acyclovir 400 mg 2 × daily, given orally ▸ Famciclovir 250 mg 2 × daily, given orally ▸ Valacyclovir 500 mg 1 × daily, given orally or 1.0 g 1 × daily, given orally *Long-term suppressive therapy for several months. Tailor dosage to individual patient.*	
	Immunosuppression (e.g., HIV)	Possibly 2–3 × higher dosages and longer treatment durations; possible i.v. administration	

Screening and prevention

Nine out of ten people are infected with HSV1, and about 20 % with HSV2, which causes genital herpes.

Infection may occur through sexual contact or during birth, if the newborn is infected with the herpes virus in the birth canal. Both HSV1 and HSV2 are transmittable by oral sex. To prevent the spread of acute herpes infection, unprotected oral sex should be avoided. Nine out of ten people are infected with HSV1, and about 20 % with HSV2, which causes genital herpes. Many people can remain asymptomatic for years. Recent studies suggest that co-infection with herpes simplex, during unprotected sex, may facilitate the transmission of HIV.

Therapy

Treatment of herpes labialis is usually local, e.g., with 1 % penciclovir cream, 5 % acyclovir cream, or 2 % foscarnet cream. Systemic treatment for severe

infection may consist of 400–800 mg acyclovir 3 times daily for 2–7 days. Intravenous drug administration is rarely necessary. Therapy is generally systemic with acyclovir, valacyclovir, or famciclovir; the dosage varies depending on whether it is a first-time infection, recurrent episode, or whether the patient has an immune deficiency [5, 6]. In patients with frequent recurrences, long-term antiviral suppression therapy (6 months) may be considered. Partner treatment is advisable.

Human papillomavirus (HPV) (Table 4)

Human papillomaviruses (HPV) are double-stranded DNA viruses with a genome with about 8 000 base pairs. HPV infects epithelial cells in the skin and mucous membranes. More than 150 HPV types have been completely classified to date, and new HPV types are continually being identified.

Clinical presentation and diagnosis

HPV1–4 are the classic cutaneous HPV types. These types cause benign warts. HPV types belonging to the beta genus are ubiquitous on human skin; these can cause cutaneous squamous cell carcinoma in patients with an inherited disorder called epidermodysplasia verruciformis.

HPV1–4 are the classic cutaneous HPV types. These types cause benign warts (verrucae vulgares). HPV types belonging to the beta genus (e.g., HPV 5, 8, 9, 12, 14, 15, 17, 19, 20, 21, and 47) are ubiquitous on human skin; these can cause cutaneous squamous cell carcinoma in patients with an inherited disorder called epidermodysplasia verruciformis. The rare focal epithelial hyperplasia (Heck disease), which infects the oral cavity, is caused by HPV 13 and HPV 32.

Alpha HPV types may be divided based on their oncogenic potential into low-risk types (e.g., HPV 6 and HPV 11) and high-risk types (e.g., HPV 16 and HPV 18).

The most clinically relevant are the approximately 40 HPV types belonging to the alpha genus; these are primarily found in anogenital regions. Alpha HPV types may be divided based on their oncogenic potential into low-risk types (e.g., PV 6 and HPV 11) and high-risk types (e.g., HPV 16 and HPV 18). Infections with alpha HPV types are very common among sexually active people. It has been estimated that about 80 % of people will acquire HPV during their lifetime. People between the ages of 20 and 30 years old have the highest contamination rate. In more than 90 % of healthy (immunocompetent) people, HPV infection can be eliminated within a short time (12 months). Immune deficiency generally leads to persistent HPV infections with a resulting increased risk of developing anogenital dysplasia and tumors.

More than 99 % of all cervical carcinomas, and more than 90 % of all anal carcinomas are HPV-positive, and HPV is detected in up to 70 % of all carcinomas of the penis, vulva, and vagina.

High-risk HPV types are responsible for the development of anogenital carcinoma. More than 99 % of all cervical carcinomas, and more than 90 % of all anal carcinomas are HPV-positive, and HPV is detected in up to 70 % of all carcinomas of the penis, vulva, and vagina. Up to 30 % of carcinomas on the head or neck region (especially tonsillar carcinoma) are caused by HPV. HPV-induced premalignant anogenital lesions are referred to histologically as intraepithelial neoplasias. They may be divided into three grades, depending on the dissemination/spread of the dysplastic cells in the epithelium. In the cervical region, these precursor lesions are known as cervical intraepithelial neoplasia (CIN); in the anal region, on the penis or vulva, they are known as anal (AIN), penile (PIN), or vulvar (VIN) intraepithelial neoplasia [7].

Anal carcinomas are considered dangerous tumors, although, compared to other gastroenterological tumors, they are relatively rare and make up only about 1 % of these tumors [8]. In HIV-negative MSM, the relative risk for the development of anal carcinoma is 35 per 100 000; among HIV-positive MSM, the risk of anal cancer is at least twice as high (70–100 per 100 000). Because modern antiretroviral therapy (ART) can significantly extend the lifespan of people with HIV,

Table 4 Source DSTIG, Guideline on STI therapy; www.dstig.de.

Disease	In...	Standard therapy	Alternatives	Diagnosis
HPV infection *Human papillomavirus*	**External genital warts in adults**	▸ Podophyllotoxin 0.5 % solution or gel, 0.15 % cream; 2 × daily for 3 days, then 4 day pause (4 cycles) ▸ miquimod 5 % cream 3 × per week up to 16 weeks. ▸ Sinecatechin or green tea catechins, 10 % ointment 3 × daily up to 16 weeks. ▸ Cryotherapy ▸ Trichloroacetic acid 80–85 % ▸ Excision, curettage, electrosurgery/laser therapy	*Vaccine prevention:* ▸ HPV vaccination recommended in girls and boys aged 12 years and older (prior onset of sexual activity). Immunization is covered by insurance for girls aged 12–17 years old *During pregnancy:* ▸ Trichloroacetic acid, cryotherapy or laser therapy, surgical removal	▸ Clinical (condylomata), colposcopy, acetic acid test (1–5 %), rule out condylomata lata based on syphilis serology, histopathology ▸ NAAT, hybrid capture (material: specimen, tissue)
	Anal intraepithelial neoplasias (AIN)	*Ablative therapy:* ▸ Electrocautery removal, possibly additional surgical excision of circumscribed areas. *Alternatively:* laser ablation (e.g., Co_2 laser) ▸ Infrared coagulation is first-line therapy in U.S., but approved for use in Germany	*Topical therapy:* ▸ If there is perianal involvement, imiquimod, possibly administer as suppository in intra-anal involvement (off-label), 3 × weekly for up to 16 weeks. ▸ In intra-anal involvement 85 % trichloroacetic acid (e.g., weeks 0, 4, 8, 12) ▸ 5-FU (administer 1 g 2 × for 16weeks), higher rate of side effects than with imiquimod!	▸ Digital rectal examination ▸ Anal cytology (analogous to cervical cytology, in all high-risk patients for AIN) as basic screening *In ASCUS-ASC-H, LSIL, HSIL high-resolution anoscopy:* 1. Application of 5 % acetic acid or Lugol solution (with cotton swab) ca. 2 min. 2. Insert the anoscope, adjust the colposcope (distance ca. 30 cm). Focus 3. Examine the patient, beginning in the distal rectum (to the greatest widening). Withdraw the anoscope to visualize the dentate line (transformation zone), the anal canal, and perianal region 4. Possible photo documentation of findings ▸ Always biopsy all suspicious areas (histopathology)
	Anal *margin* carcinoma	▸ Excision for operable lesions (generally < 2 cm)	▸ Radio-chemotherapy for very large, inoperable tumors	
	Anal *canal* carcinoma	▸ *Combined radiation treatment and chemotherapy:* radiation with 50 Gy (1.8 Gy daily) 5-FU (1 000 mg/m², days 1–5 and days 29–33) and mitomycin C (10 mg/m², days 1, 29)	▸ Primary excision for very small, operable tumors < 2 cm diameter)	

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the number of patients with anal carcinoma has also risen sharply. In the future, due to the longer life expectancy of people with HIV, anal cancer may presumably become one of the central problems facing modern HIV medicine. It is therefore enormously important to educate HIV-infected men, in particular, about the risks, precursor lesions, and preliminary clinical signs, as well as about prevention and treatment options.

Screening, precautions, and prevention

In the majority of European countries, the HPV vaccination is covered by statutory health insurance for girls aged 12–17 years, although immunization is advisable in women up to age 26. Since January 2013, HPV vaccination of boys and men has also been recommended by the vaccination committee for the state of Saxony (Sächsische Impfkommission, SIKO). In Australia, boys have already been included for a year in the HPV vaccination program. Young men, and especially men who have sex with men (MSM), should be informed about the vaccine [9]. Similar to preventive cytological examinations, which were introduced in 1971 for cervical carcinoma (PAP test), analogous screening methods are now being used for people at risk for developing anal carcinomas. People with HIV, especially HIV-infected men who have sex with men, are particularly likely to develop anal carcinoma and precursor lesions. Condoms offer the best form of protection against HPV infection through sexual contact, although they do not give full protection.

Similar to preventive cytological examinations, which were introduced in 1971 for cervical carcinoma (PAP test), analogous screening methods are now being used for people at risk for developing anal carcinomas.

Therapy

Topical therapy of warts is surgery or laser vaporization. After surgical treatment of anogenital warts, adjuvant therapy is with 5 % imiquimod cream for eight weeks, given that the mechanical irritation can lead to reactivation of inactive viruses in the skin surrounding the warts. Several studies have shown lower recurrence rates after combined use of destructive surgical techniques and adjuvant, conservative methods.

After surgical treatment of anogenital warts, adjuvant therapy is with 5 % imiquimod cream for eight weeks.

Syphilis (Table 5)

The bacterium responsible for syphilis is *Treponema pallidum*. Other names used for syphilis in the past include lues, hard chancre, or the French disease. In recent years, syphilis has experienced a Renaissance like virtually no other STI.

Clinical appearance and diagnosis

The disease course may be divided into three stages: early-stage syphilis is the first year after infection. All phases of disease occurring after this are known as late-stage syphilis. In the Anglo-American literature, the early stage of syphilis is defined as two years.

Early-stage syphilis is the first year after infection. All phases of disease occurring after this are known as late-stage syphilis.

In the first stage of disease (primary syphilis), about 9 to 90 days (3 weeks on average) after the infection, a painless ulceration with a firm border (ulcus durum or "hard chancre") develops on the part of the body that came into contact with the pathogen (usually vaginal, genital, anal, oral, or pharyngeal). The ulcerations may go unnoticed, as they are often very small or located on less visible parts of the body; usually they heal after 6 weeks, even without treatment. There is painless swelling of the lymph nodes at the infection site after 3 weeks, and the swelling

Table 5 Source: DSTIG, Guideline on STI therapy; www.dstig.de.

Disease	In...	Standard therapy	Alternatives	Diagnosis
Syphilis *Treponema pallidum*	**Adults** Early-stage syphilis (<1 year)	Benzathine penicillin G 2.4 mil. 1 × intramuscular dose.	▸ Ceftriaxone* 1.0 g daily, i.v. administration for 10 days (Only in patients with penicillin allergy; doxycycline should not be given to pregnant women) ▸ Doxycycline 100 mg 2 × daily, given orally for 14 days	▸ Serology (material: serum)- *Screening:* TPHA, TPPA or immunoassay *Confirmation:* FTA-ABS, EIA, Western blot *Activity:* VDRL, RPR, cardiolipin CBR, IgM antibody test, IgM Western blot ▸ NAAT (for epithelial lesions and if there is suspected early-stage infection; Material: smear, tissue from the epithelial lesion) ▸ Dark field microscopy (for epithelial lesions and suspected early-stage infection; Material: ulcer discharge from a primary sore or from lesions) *Follow-up after 3, 6, 9, and 12 months*
	Adults Late-stage syphilis (> 1 year or unknown time of inoculation	Benzathine penicillin G 2.4 mil. 3 × intramuscular doses (i.e., on days 1, 8, and 15)	▸ Ceftriaxone* 1.0 g daily, i.v. administration for 14 days (Only in patients with penicillin allergy; doxycycline should not be given to pregnant women) ▸ Doxycycline 100 mg 2 × daily, given orally for 28 days	
	Children	As in adults, with modified benzathine penicillin G dosage: 50 000 IU/kg/intramuscular administration (maximum adult dosage: 2.4 mil. per dosage)		
	HIV co-infection	Stage-appropriate treatment as for non-infected persons. Increased risk of neurosyphilis		*CSF evaluation is advisable in patients with neurological symptoms or if the inoculation time is unknown*
Congenital syphilis	**Newborns**	Penicillin G 200 000–250 000 IU/kg of body weight/daily, i.v. administration, as follows: 1st week of life = 2 single doses; 2nd–4th weeks of life = 3 single doses; from 5th week of life onward 4 single doses		*s. o.*
Neurosyphilis *Also ocular syphilis or otosyphilis*	**Adults**	Penicillin G 3–4 mil. i.v. 6 × daily ≥ 14 days or penicillin G 10 mil i.v. 3 × daily ≥ 14 days	Possibly ceftriaxone* 2.0 g daily, i.v. administration for 14–21 days (initially 4 g)	*CSF evaluation to check treatment success.* *Parameters:* CSF-VDRL; ITpA, pleocytosis and protein concentrations
	Children	Penicillin G 0.025 mil/kg of body weight, i.v. administration, 6 × daily ≥ 14 days		
	In patients who are allergic to penicillin, desensitization is preferred, or accompanying administration of corticosteroids 1.5 g/kg of body weight. Caution: type I allergies.			

Important note: Herxheimer reaction: prednisone, 0.5–1 mg/kg of body weight, for prevention
* Important note: Cross-reactivity of β-lactams

The ulcerations may go unnoticed, as they are often very small or located on less visible parts of the body; usually they heal after 6 weeks, even without treatment.

persists. In the second disease stage (secondary syphilis), there is hematogenous spread of treponemes 6 weeks to 6 months after the infection. Patients may have generalized symptoms such as loss of appetite, sometimes fever or muscle, bone, or joint pain, as well as elevation of transaminase levels on serology; typically, there is initially a maculopapular, non-pruritic rash ("roseola rash"), which heals without scarring. Later, polymorphous rashes can occur. Sometimes the mucous membranes are involved (mucous plaques), and sometimes the palms of the hands and the soles of the feet may be involved (palmoplantar syphilis). Condylomata lata may occur in intertriginous areas. The skin changes which are seen in stage 2 syphilis contain treponemes. Transmission of the pathogen is thus possible, if uncommon. Stage 2 syphilis may persist, with oscillating symptoms, for up to two years. About two-thirds of all syphilis patients do not seek medical care until the 2nd stage of disease. 75 % of untreated patients are asymptomatic after stage 2; in about 25 % of patients, tertiary syphilis occurs (stage 3) after a period of latency (12 months to 10 years).

Stage 2 syphilis may persist, with oscillating symptoms, for up to two years. About two-thirds of all syphilis patients do not seek medical care until the 2nd stage of disease.

During stage 3, gummas (singular: gumma) can develop. These granulomas may also ulcerate. They can affect any organ. In people with syphilis, they are often found in the cutis and subcutis, as well as in the bones. Fatal complications can occur during this stage due to vascular involvement, for instance, the aorta (syphilitic aortitis or aortic aneurysm).

Along with asymptomatic disease, meningitis, cranial nerve abnormalities, and psychiatric symptoms may occur.

In late-stage syphilis, central nervous system (neurosyphilis) symptoms can occur. Along with asymptomatic disease, meningitis, cranial nerve abnormalities, and psychiatric symptoms may occur. Tabes dorsalis and progressive paralysis are also associated with neurosyphilis and are disease-defining features. Immune deficient patients, especially those with HIV, have a greater risk of developing neurosyphilis.

The standard method is a screening test, e.g. the *Treponema pallidum* particle agglutination test (TPPA) or the *Treponema pallidum* hemagglutination test (TPHA). If the results are suggestive of syphilis, the diagnosis should be confirmed by another test (e.g., FTA-ABS or immunoblot). Tests such as the Venereal Disease Research Laboratory (VDRL) or measuring rapid plasma regain (RPR) titer may be used for monitoring disease activity.

Direct pathogen detection and/or serological tests are performed for the diagnosis and monitoring of syphilis. The standard method is a screening test, e.g. the *Treponema pallidum* particle agglutination test (TPPA) or the *Treponema pallidum* hemagglutination test (TPHA). If the results are suggestive of syphilis, the diagnosis should be confirmed by another test (e.g., FTA-ABS or immunoblot). Tests such as the Venereal Disease Research Laboratory (VDRL) or measuring rapid plasma regain (RPR) titer may be used for monitoring disease activity. Positive test results must be reported (Robert Koch Institute). In patients with suspected neurosyphilis, cerebrospinal fluid evaluation is warranted. Patients with HIV who are uncertain when they were infected (late syphilis) should also undergo cerebrospinal fluid evaluation.

Screening, precautions, and prevention

The transmission of the sensitive pathogens is generally by means of direct contact with infected anogenital or oral mucosa (rarely through skin contact), i.e., through sexual contact, or from a mother to her unborn baby. Transmission cannot occur through contact with personal belongings. Prompt diagnosis and strict treatment with regular monitoring of treatment success (clinical and serological) can reduce the spread of disease, as can information about and examination of all sex partners in the three months prior to infection.

Therapy

Penicillin is the first-line treatment for syphilis. In regard to medication, a distinction is made between "early-stage" syphilis (all clinical forms up to one year

Careful clinical and serological follow-up should be performed for every patient with syphilis every three months for one year (in immunodeficient/HIV-infected patients, follow-up is for two years).

after infection) and "late-stage" syphilis (up to one year after infection for all clinical forms, or if the inoculation time is unknown). Resistances to macrolides – especially azithromycin – have been reported [10]. Table 5 contains treatment recommendations. Careful clinical and serological follow-up should be performed for every patient with syphilis every three months for one year (in immunodeficient/HIV-infected patients, follow-up is for two years).

Summary

The field of venereology is more relevant than ever. Given the rising number of syphilis infections, resistant forms of gonorrhea, as well as chlamydial urethritis and HPV-associated diseases, there is a clear need for a thorough understanding of venereology. Along with knowledge of medical facts, doctors should be aware of changing sexual behaviors. E-dating platforms, smartphone apps for quick and anonymous sex, as well as events which explicitly offer *unsafe sex*, represent only a fragment of the changes that sexuality – especially the opportunity for fast, anonymous encounters – has changed in recent decades. *"The range of sexual practices is not completely covered by the imagination of the doctor."* Integrating this knowledge into the work of the physician will become even more relevant in the future. This has been shown by the experience that recurrent symptoms can often be explained by a detailed sexual history, and often the "main diagnostic clue" can be found in a comprehensive patient history.

Current guidelines are available at:
www.dstig.de
www.Iusti.org
www.awmf.org

References

1 Bignell C, Fitzgerald M. UK national guideline for the management of gonorrhoea in adults. Int J STD AIDS 2011; 22: 541–7.
2 van Dyck E, Leven M, Pattyn S et al. Detection of *Chlamydia trachomatis* and *Neisseria gonorrhoeae* by enzyme immunoassay, culture, and three nucleic acid amplification tests. J Clin Microbiol 2001; 39: 1751–6.
3 Cook RL, Hutchison SL, Ostergaard L et al. Systematic review: noninvasive testing for Chlamydia trachomatis and *Neisseria gonorrhoeae*. Ann Intern Med. 2005; 142: 914–25.
4 Update to CDC's Sexually transmitted diseases treatment guidelines: oral cephalosporins no longer a recommended treatment for gonococcal infections. Morb Mortal Wkly Rep 2010; 61: 590–4.
5 Williams JR, Jordan JC, Davis EA, Garnett GP. Suppressive valacyclovir therapy: impact on the population spread of HSV-2 infection. Sex Transm Dis 2007; 34: 123–31.
6 Gupta R, Warren T, Wald A. Genital herpes. Lancet 2007; 370: 2127–37.
7 Kreuter A, Brockmeyer NH, Hochdorfer B et al. Clinical spectrum and virologic characteristics of anal intraepithelial neoplasia in HIV infection. J Am Acad Dermatol 2005; 52: 603–8.
8 Yanofsky VR, Patel RV, Goldenberg G. Genital warts: a comprehensive review. J Clin Aesthet Dermatol 2012; 5: 25–36.
9 Nielson CM, Harris RB, Dunne EF et al. Risk factors for anogenital human papillomavirus infection in men. J Infect Dis 2007; 196: 1137–45.
10 French P, Gomberg M, Janier M et al; IUST. IUSTI: 2008 European Guidelines on the Management of Syphilis. Int J STD AIDS 2009; 20(5): 300–9.

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Fragen zur Zertifizierung durch die DDA

1. Wie viele Erkrankungsfälle an Gonorrhoe gibt es jährlich weltweit?

a) 10 Millionen
b) 15 Millionen
c) 30 Millionen
d) 60 Millionen
e) 90 Millionen

2. Die aktuelle Therapie der Gonorrhoe lautet:

a) 400 mg Cefixim p.o.
b) 1,5 g Azithromycin p.o
c) 2 g Ceftriaxon i.v./i.m und 1,5 g Azithromycin p.o
d) 1 g Ceftriaxon i.v./i.m und 1,5 g Azithromycin p.o
e) 2 g Azithromycin p.o

3. Der Goldstandard für die Diagnostik der Gonorrhoe ist:

a) Methylen-Blaufärbung aus Sekret
b) Gram-Färbung aus Sekret
c) Nachweis mittels Polymerase-Kettenreaktion
d) Gonokokken-Kultur
e) Nativpräparat

4. Das Lymphogranuloma venereum...

a) ist eine seltene Erkrankung, die nur in den Tropen vorkommt.
b) betrifft immer mehr Männer, die Sex mit Männern haben (MSM).
c) wird durch *Chlamydia trachomatis* Serovare D–K hervorgerufen.
d) wird durch 100 mg Doxycyclin 2 x täglich für 7 Tage therapiert.
e) ist die fünfte klassische Geschlechtskrankheit.

5. Eine Chlamydien-Urethritis wird laut den DSTIG-Leitlinien wie folgt behandelt:

a) Doxycyclin 200 mg einmal täglich für 7 Tage
b) Ceftriaxon 2 g i.v. Singleshot
c) Doxycyclin 100 mg 2 x täglich für 7 Tage
d) Ceftriaxon 1 g i.m.
e) Biocef 400 mg p.o. Singleshot

6. Welche Aussage trifft **nicht zu?**

a) Eine Herpes-Infektion erhöht das Risiko für eine HIV-Infektion.
b) 90 % (80 %) der Bevölkerung hatte mit dem HSV1 Kontakt.
c) 90 % der Bevölkerung hatte mit dem HSV2 Kontakt.
d) 20 % der Bevölkerung hatte mit dem HSV2 Kontakt.
e) Es gibt ein klinisch stummes Virus-Shedding.

7. Folgende HPV-Typen zählen zu den häufigsten onkogenen HPV-Viren:

a) HPV 1–4
b) HPV 5, 8, 9, 12
c) HPV 6 und 11
d) HPV 16 und 18
e) HPV 110

8. Männer, die Sex mit Männer praktizieren (MSM), haben ein...

a) geringeres Risiko an HPV-assoziierten analen Malignomen zu erkranken.
b) ein gleiches Risiko verglichen mit Heterosexuellen.
c) ein gering erhöhtes Risiko.
d) ein deutlich erhöhtes Risiko.
e) ein gleiches Risiko, wenn einen HIV-Therapie eingenommen wird.

9. Unter Frühsyphilis versteht man...

a) das Auftreten von Krankheitssymptomen bis zum Abheilen des Primärulkus.
b) das Auftreten eines luetischen Exanthems.
c) die Zeitspanne vom Zeitpunkt der Infektion für die Dauer von einem Jahr.
d) alle Krankheitssymptome die 6 Wochen bis 6 Monate nach Infektion auftreten.
e) das Auftreten von klinischen Veränderungen an nur einer Lokalisation.

10. Die Therapie der Frühsyphilis besteht in:

a) dreimalig 2,4 Mega Benzathinpenicillin i.m.
b) einmalig 2,4 Mega Benzathinpenicillin i.m.
c) Azithromycin 1,5 g Singlelshot
d) Doxycyclin 200 mg für 21 Tage
e) Amoxicillin/Clavulansäure 3 x 500 mg für 14 Tage

Liebe Leserinnen und Leser,
der Einsendeschluss an die DDA für diese Ausgabe ist der 18. Juli 2014.
Die richtige Lösung zum Thema „Kutane Lymphome“ in Heft 1 (Januar 2014) ist: (1e, 2c, 3c, 4a, 5b, 6e, 7c, 8b, 9c, 10c).

Bitte verwenden Sie für Ihre Einsendung das aktuelle Formblatt auf der folgenden Seite oder aber geben Sie Ihre Lösung online unter http://jddg.akademie-dda.de ein.

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