Bei Plaque-Psoriasis und Psoriasis-Arthritis*

* TREMFYA® ist indiziert: 1) für erwachsene Patienten mit mittelschwerer bis schwerer **Plaque-Psoriasis**, die für eine systemische Therapie in Frage kommen; 2) allein oder in Kombination mit MTX für die Behandlung der aktiven **Psoriasis-Arthritis** bei erwachsenen Patienten, wenn das Ansprechen auf eine vorherige nicht-biologische krankheitsmodifizierende antirheumatische (DMARD-)Therapie unzureichend gewesen ist oder nicht vertragen wurde.[1]

\# PASI 90: 84% (Wo 48; n=534) Non Responder Imputation (NRI)[2]; PASI 100: 52,7% (Wo 252; n=391) Treatment Failure Rules (TFR)[3]; Signifikante Überlegenheit vs. Placebo in Bezug auf ACR20 (64% vs. 33%, p<0.0001; NRI) nach 24 Wochen in der 8-Wochen-Dosierung (n=248) in bionaiven Patienten mit aktiver PsA.[4]

1. Aktuelle Fachinformation TREMFYA®.
2. Reich K et al. Lancet. 2019;394(10201):831-839.
3. Griffiths CEM et al. Poster Presentation Coastal Dermatology Symposium 2020, October 15-16th.
4. Mease P et al. The Lancet 2020; https://doi.org/10.1016/S0140-6736(20)30263-4 (Supplementary)

▼ Dieses Arzneimittel unterliegt einer zusätzlichen Überwachung. Daher ist es wichtig, jeden Verdacht auf Nebenwirkungen in Verbindung mit diesem Arzneimittel zu melden.

TREMFYA® 100 mg Injektionslösung in einer Fertigspritze/ in einem Fertigpen. Wirkstoff: Guselkumab. **Zusammensetz.:** Fertigspritze/Fertigpen enth. 100 mg Guselkumab. Sonst. Bestandt.: Histidin, Histidinmonohydrochlorid-Monohydrat, Polysorbat 80, Sucrose, Wasser f. Injektionszw.. **Anw.geb.:** Für d. Bhdlg. erw. Pat. m. mittelschwerer bis schwerer Plaque-Psoriasis indiziert, d. für e. syst. Therapie in Frage kommen. Als Monotherapie od. in Komb. m. Methotrexat für d. Bhdlg. erw. Pat. m. Psoriasis-Arthritis indiziert, d. auf e. vorherige nicht-biolog. kranheitsmodifiz. antirheumat. (DMARD)-Therapie unzureich. angesprochen od. diese nicht vertragen haben. **Gegenanz.:** Schwerwieg. Überempfindl. gg. Guselkumab od. e. d. sonst. Bestandt., klin. relev. aktive Infektionen (einschl. aktive Tuberkulose), Schwangersch., Stillzeit. **Bes. Warnhinw. u. Vorsichtsmaßn.:** Um d. Rückverfolgbark. b. biolog. Arzneim. zu verbessern, sollten Name u. Ch.-Bez. d. verabreich. Prod. deutl. protokoll. werden. Vors. b. Infektionen, Tuberkulose, Impfungen (vor Anw. v. Lebendimpfst. muss d. Bhdlg. m. Tremfya nach d. letzt. Gabe f. mind. 12 Wo. ausgesetzt werden). B. Erhöh. v. Leberenzymwerten (ALT/AST) u. Verdacht auf arzneimittelinduz. Leberschädig. sollte d. Bhdlg. vorüberg. unterbr. werden. B. schwerwieg. Überempfindl.reakt. sollte d. Anw. v. Tremfya unverzügl. abgebrochen u. e. geeign. Bhdlg. eingel. werden. Frauen im gebärfäh. Alter sollen währ. u. f. mind. 12 Wo. nach d. Bhdlg. e. zuverläss. Verhütgs.meth. anw.. Arzneim. f. Kdr. unzugängl. aufbewahren. **Nebenwirk.:** *Sehr häufig* (≥ 1/10), *Häufig* (≥ 1/100 bis < 1/10), *Gelegentlich* (≥ 1/1.000 bis < 1/100). *Sehr häufig:* Atemwegsinfekt.. *Häufig:* Kopfschm., Diarrhoe, Arthralgie, Reakt. a. d. Injektionsst., Transamin. erhöht. *Gelegentlich:* Herpes-simpl-Infekt., Tinea-Infekt., Gastroenteritis, Überempfindl.reakt., Anaphylaxie, Urtikaria, Hautausschlag, Neutrophilenzahl erniedr.. Verschreibungspflichtig. **Pharmazeut. Unternehmer:** JANSSEN-CILAG International NV, Turnhoutseweg 30, B-2340 Beerse, Belgien. **Örtl. Vertreter für Deutschland:** Janssen-Cilag GmbH, Johnson & Johnson Platz 1, D-41470 Neuss. **Stand d. Inform.:** 12/2020.

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Bacterial sexually transmitted infections

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An increase in all STIs is observed worldwide. In addition to an increased sexual risk behaviour, antibiotic resistance is on the rise.

Many infections are asymptomatic and constitute a reservoir for further Transmission.

Each diagnosis of a STI should be followed by an investigation for all other STI pathogens. In addition, a partner notification should be performed to interrupt the infection chain.

Summary

Worldwide, the incidence of bacterial sexually transmitted infections (STIs) has shown a significant increase in recent years. In Germany, this circumstance is reflected by a rise in the number of reported syphilis cases. There has also been an uptick in the incidence of non-notifiable STIs such as gonorrhea and infections caused by *Chlamydia trachomatis* and *Mycoplasma genitalium*. A key factor in the spread of these infections is their varied clinical presentation, which includes urogenital, pharyngeal and rectal involvement as well as a large number of asymptomatic cases. New real-time multiplex PCR methods allow for rapid and targeted detection of STI pathogens. The most common bacterial STI is urogenital chlamydial infection caused by serovars D–K, which affects young adults in particular. Lymphogranuloma venereum (LGV) caused by L serovars often presents as chlamydial proctitis. In recent years, *Neisseria (N.) gonorrhoeae* has shown a significant development of resistance, with high-level monoresistance and multiresistance to antibiotics commonly used for treatment. It is therefore imperative that sensitivity testing of *N. gonorrhoeae* be performed in addition to nucleic acid amplification tests (NAATs). Increased drug resistance has also been observed for *Mycoplasma genitalium*, a fact that complicates treatment.

Introduction

Venereal diseases are infections primarily transmitted through sexual contact. Today, the term *sexually transmitted infections* (STIs) has replaced the term *sexually transmitted diseases* (STDs) to emphasize the fact that many of these infections are asymptomatic. The prevalence of STIs depends on socio-economic conditions, cultural and moral beliefs, as well as diagnostic and therapeutic options. Given that HIV has become treatable and pharmaceutical pre-exposure prophylaxis (PrEP) for HIV has become available, STIs are again on the rise worldwide. While PrEP with regular dosing of tenofovir/emtricitabine prevents HIV transmission when condoms are not used, it does not protect against other STIs. Apart from increased sexual risk behavior, antibiotic resistance is also more and more common. On principle, any diagnosis of STI must prompt health professionals to test for all other STI pathogens as well. In addition, sexual partners must be informed (partner notification) to ensure that the chain of infection is interrupted.

Sexually transmitted infections can be caused by a multitude of microorganisms. The present CME article reviews the most common bacterial pathogens.

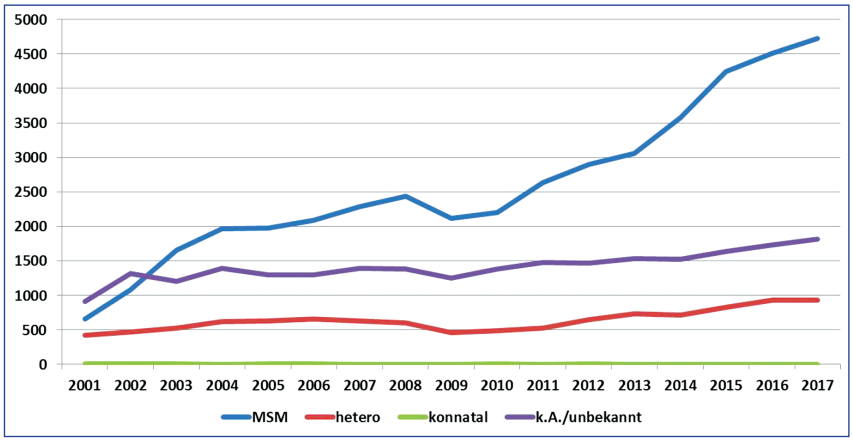

Figure 1 Reported syphilis cases by year of diagnosis and probable route of transmission, 2001–2017 (date 03/2018). *Abbr.:* MSM, men having sex with men; hetero, heterosexual transmission; congenital, mother-child transmission; n.a., not reported (source: RKI).

Treponema pallidum

Pathogen

Syphilis is a sexually transmitted infectious disease caused by *Treponema (T.) pallidum* subspecies pallidum (*T. pallidum*).

Epidemiology

In the past five years, there has been a significant increase in the incidence of syphilis in Germany. This affects preponderantly MSM in large cities in particular.

According to an estimate by the World Health Organization (WHO) in 2012, there are about six million new syphilis infections per year worldwide [1]. In 2015, the European Center for Disease Prevention and Control (ECDC) received 28,000 notifications of infection [2], corresponding to a 49 % increase since 2010. In Germany, syphilis is a notifiable disease pursuant to the German Protection against Infection Act. Laboratories are required to send anonymized notifications to the Robert Koch Institute. In 2017, the incidence of syphilis in Germany was 9.1/100,000, an increase of 83 % compared to 2010. High incidences were observed in metropolitan areas in particular, such as Berlin, Cologne, Munich, Frankfurt and Dusseldorf. In men, the incidence was 17/100,000, and thus 17 times higher than among women. The median age was 40 years. Eighty-two percent of infections were diagnosed in men who have sex with men (MSM) [3, 4] (Figure 1).

Clinical presentation of syphilis

Without treatment, syphilis takes a varied clinical course that spans several decades and includes four stages (primary, secondary and tertiary syphilis as well as quaternary syphilis, also referred to as metasyphilis).

Without treatment, syphilis is characterized by a decades-long clinical course that may include four different stages, resulting either in death or in spontaneous resolution after the secondary stage (75 %) (Table 1)

Primary syphilis

Infection with *Treponema pallidum* is usually caused by sexual contact (genital, anal, oral). After an incubation period of approximately three weeks, a painless ulcer (primary lesion, chancre) develops at the site of infection (Figure 2). As the

Table 1 Stages and clinical manifestations of syphilis (overview).

Primary syphilis	Regional infection (primary lesion) with regional lymphadenopathy
Secondary syphilis	Hematogenous spread: syphilids, generalized lymphadenopathy, general symptoms
Latent seropositive syphilis	Seropositivity with signs of active infection (IgM positive, high cardiolipin antibody titers), no clinical symptoms
Tertiary syphilis	Hyperergy → spontaneous resolution, or → tuberoserpiginous syphilids, gummas → Neurosyphilis (s. below) → cardiovascular syphilis (e.g., aneurysms)
Metasyphilis	Hyperergy/anergy →Tabes dorsalis, general paresis
Neurosyphilis (stages II–IV)	Asymptomatic/symptomatic meningovascular syphilis, otosyphilis (deafness), ocular syphilis (optic nerve neuritis, iritis), basilar meningitis, acute transverse dorsal myelitis, cerebral gummas, general paresis, tabes dorsalis
Congenital syphilis	Early congenital syphilis Late congenital syphilis (from 3rd year of life), stigmata

primary lesion can also occur in extragenital sites, frequently affecting the oral mucosa, a wide range of differential diagnoses has to be considered (Table 2). Lymphogenic spread leads to nontender regional lymphadenitis. Spontaneous remission occurs within 2–3 weeks; this is followed by a latency period of 4–6 weeks during which patients appear to be clinically healthy.

Given that the interaction between pathogen and host plays an important role in syphilis, cellular immunodeficiency is associated with special clinical features that are observed in all disease stages (Table 3). Immunocompromised patients may experience a shorter incubation period and develop multiple primary lesions.

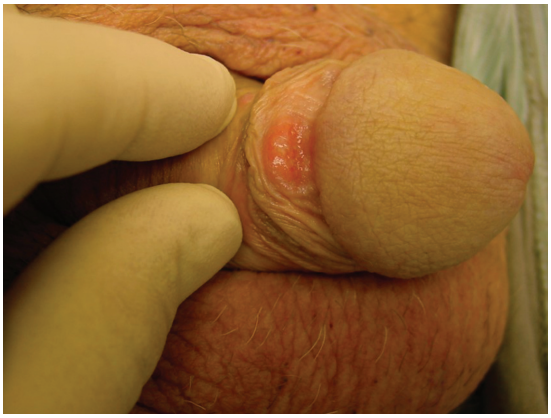

Figure 2 Primary lesion (chancre) (photo: H. Schöfer, FFM).

Table 2 Clinical differential diagnosis of syphilis.

Primary lesion (chancre)	*Anogenital region:* Genital herpes, traumatic injury, chancroid (soft chancre), lymphogranuloma venereum, ulcers in secondary or tertiary syphilis, erosive balanitis, cutaneous tuberculosis, malignant tumors (e.g., squamous cell carcinoma) *Oral/perioral region:* furuncle of the lip, lip carcinoma, giant aphthae, ulcerating herpes, CMV ulcer, vegetating pyoderma
Secondary syphilis	*Rashes:* drug eruption, viral rash (e.g., measles), disseminated lymphoma, Kaposi's sarcoma, vasculitis, pityriasis lichenoides chronica, generalized lichen planus *Anogenital/intertriginous region (condylomata lata):* condylomata acuminata, Bowen's disease, bowenoid papulosis, squamous cell carcinoma *Oral mucosa:* tonsillitis, diphtheria, aphthae, Plaut-Vincent angina, perlèche (angular stomatitis) *Scalp:* alopecia areata/diffuse hair loss, impetigo
Tertiary syphilis	*Tuberoserpiginous syphilids:* Lupus vulgaris, cutaneous sarcoidosis, tinea corporis (ringworm), necrolytic migratory erythema, cutaneous histoplasmosis, mycosis fungoides *Gummas:* Furuncles, carbuncles, abscesses, septic spread, panniculitis, actinomycosis, erythema induratum of Bazin, tuberculosis colliquativa cutis, lupus panniculitis

Table 3 Special characteristics of syphilis in HIV-infected patients.

General	HIV-infected patients have a higher risk of contracting syphilis and vice versa (same route of infection, same risk behavior) Syphilis in HIV-positive patients usually shows a "normal" clinical course. In rare cases, however, clinical findings and disease course may be different.
Primary syphilis	Primary lesions can persist over a longer period of time (until the onset of secondary syphilis); they can be painful or occur as multiple lesions. Genital ulcers increase the risk of HIV transmission.
Secondary syphilis	May occur while the primary lesion is still present. The rash may be pruritic and be associated with ulcer and crust formation as well as general symptoms (malignant syphilis). Early progression to tertiary syphilis (formation of granulomas, corymbiform syphilids and others) possible.
Neurosyphilis	Significantly increased risk of early neurosyphilis (already during secondary syphilis), also presenting as ocular syphilis or otosyphilis.
Serological diagnosis	Atypical serological features of syphilis may occur, including complete seronegativity in secondary syphilis. Decrease in activity markers is usually prolonged in immunodeficiency [5, 6]

Secondary syphilis

Secondary syphilis is characterized by bacteremia. Between week 7 and week 12, patients previously thought to be perfectly healthy suddenly fall ill. The clinical presentation is highly varied:

- General symptoms (fatigue, malaise, generalized lymphadenopathy, headaches, myalgia or arthralgia)
- Involvement of various organs: hepatitis, arthritis, iridocyclitis, meningitis
- Varied cutaneous and mucosal manifestations (syphilis is the "great imitator"), e.g., roseola syphilitica (Figure 3), leucoderma colli syphiliticum ("necklace of Venus")
- Syphilids: maculopapular, nonpruritic rash, typically affecting the palms and soles (Figure 4, 5),

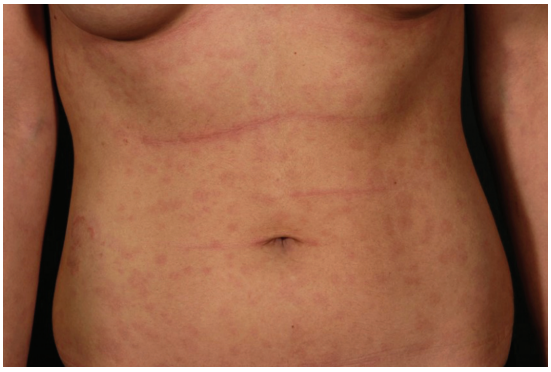

Figure 3 Secondary syphilis. Roseola syphilitica (photo: H. Schöfer, FFM).

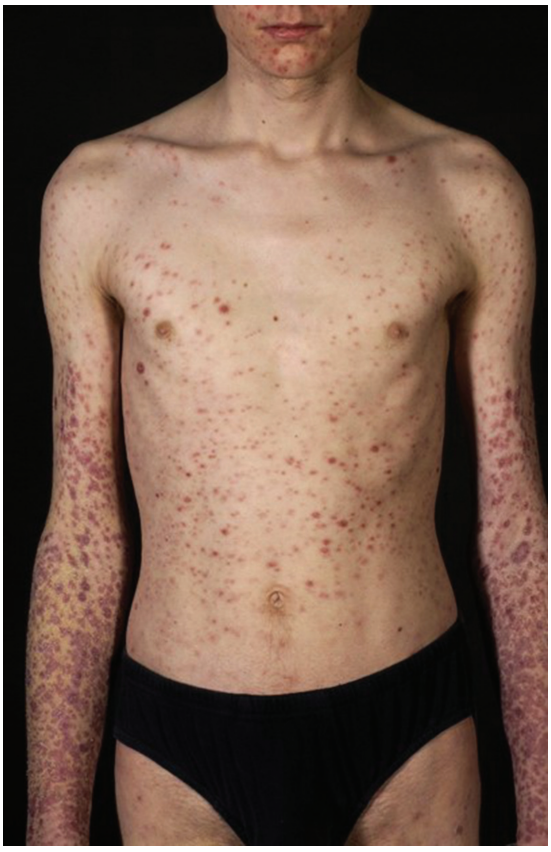

Figure 4 Secondary syphilis. Maculopapular syphilid (photo: H. Schöfer, FFM).

- Diffuse hair loss (syphilitic alopecia),
- Syphilitic angina (specific angina) and mucous patches,
- Condylomata lata (Figure 6).

Malignant syphilis primarily occurs in men as well as in individuals with immunodeficiency, HIV or a history of syphilis. Apart from general symptoms, affected patients may show ulcerating lesions with typical crusts that look like oyster shells (referred to as rupial lesions) (Figure 7, 8).

All signs and symptoms may disappear spontaneously after 4–12 months. Subsequently, the disease enters an asymptomatic stage (latent syphilis) or resolves spontaneously (over the course of months or years). Clinical manifestations may differ in HIV patients [5, 6].

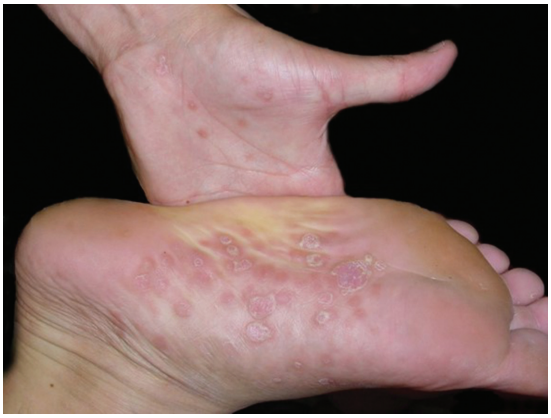

Figure 5 Secondary syphilis. Palmoplantar syphilid (photo: H. Schöfer, FFM).

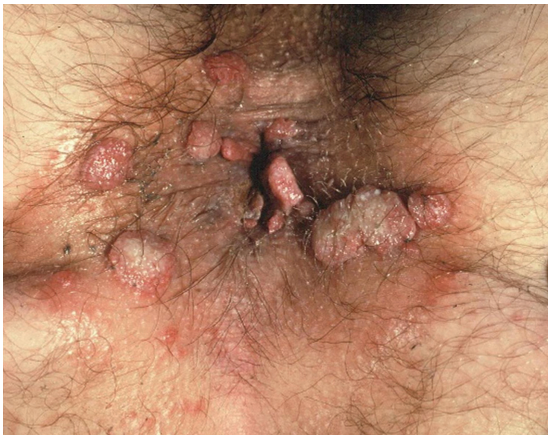

Figure 6 Condylomata lata (photo: H. Schöfer, FFM).

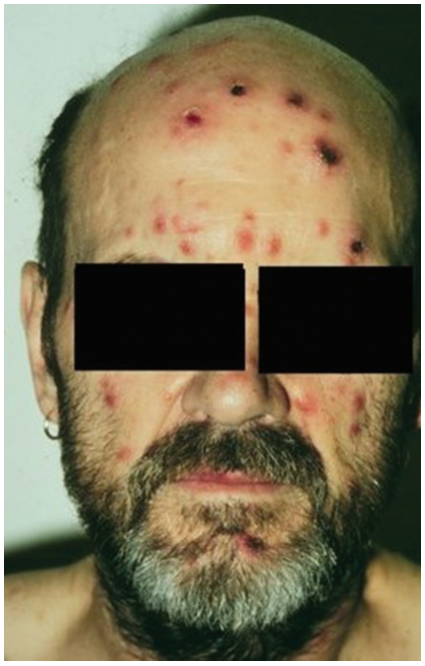

Figure 7 Secondary syphilis. Malignant syphilis (photo: H. Schöfer, FFM).

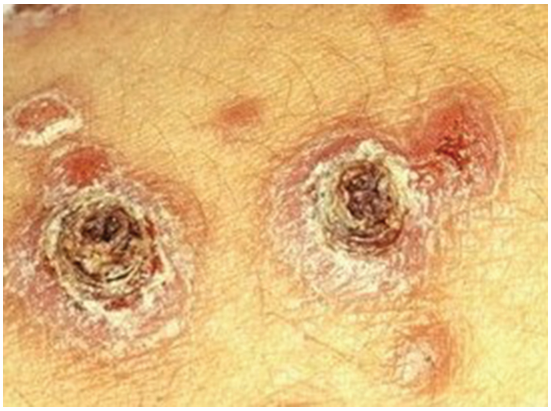

Figure 8 Secondary syphilis. Rupial lesions (photo: H. Schöfer, FFM).

Tertiary syphilis

Late-stage cutaneous, cardiovascular and neurological manifestations of syphilis have become uncommon since the introduction of penicillin. About 75 % of all untreated cases show spontaneous resolution after the secondary stage. The remaining 25 % (after a latency period of 3–10 years) develop tertiary syphilis, characterized by a hyperergic, granulomatous response to treponemes present in the affected tissues. Clinical findings include tuberous syphilids and/or gummas; these lesions are considered to be non-infectious. Today, clinical manifestations of tertiary syphilis are reported only very rarely. Fatal outcomes may occur in patients with cardiovascular involvement (e.g. syphilitic aortitis, syphilitic aortic aneurysm) or with gummas arising in parenchymatous organs and in the brain (e.g., stroke caused by cerebral gummas). Patients with HIV may show premature signs of tertiary syphilis, frequently at the same time as the manifestations of secondary syphilis occur [5, 6].

Quaternary syphilis (metasyphilis)

Approximately 15 % of untreated syphilis patients develop late neurological manifestations, even after decades. *Tabes dorsalis* with lancinating pain, loss of reflexes, ataxia and impaired pupillary reflex (Argyll-Robertson pupil) as well as *general paresis* with memory loss, speech impairment and personality changes are subsumed under the term metasyphilis. The latter is distinct from tertiary syphilis in that it is characterized by a hyperergic response in the presence of numerous pathogens, which results in inflammatory destruction and degeneration of neurological structures. In individuals with undiagnosed congenita syphilis, the onset of metasyphilis may be in early adulthood.

Neurosyphilis

In secondary syphilis and metasyphilis, treponemes can cross the blood-brain barrier and cause neurosyphilis with neurological and psychiatric manifestations. This risk is increased in immunodeficiency or HIV infection.

Treponemas may cross the blood-brain barrier and trigger neurological signs and symptoms not only in metasyphilis but also in the bacteremic stage of secondary syphilis. This risk is increased in patients with immunodeficiency or HIV. Apart from meningitis symptoms, manifestations may include cognitive dysfunction, impaired vision or hearing as well as motor or sensory loss.

Congenital syphilis

As regards the transmission of syphilis to the unborn child, the disease stage of the mother during pregnancy plays an important role. Treponemes can be transferred

to the fetus once the placenta has matured (from the 17th week of gestation). Significant treponemal bacteremia during that time will result in spontaneous miscarriage. If the infection occurred in the more distant past and if there are therefore only few pathogens in the mother's blood, the child will develop early congenital syphilis, which is clinically very similar to secondary syphilis.

Blood-stained nasal discharge (syphilitic rhinitis) is pathognomonic for congenital syphilis. Another important diagnostic sign is epiphyseal dislocation, typically of the proximal end of the ulna (resulting in Parrot's pseudoparalysis).

In mild cases of untreated late congenital syphilis, typical clinical manifestations occur in late childhood:

- Parrot's furrows (radial furrows that extend from the lips to the adjacent skin)
- Hutchinson's triad: interstitial keratitis, 8th nerve deafness, and dental anomalies (Hutchinson incisors),
- Saddle nose, saber shins.

Screening for syphilis is therefore a mandatory component of prenatal care in the first trimester of pregnancy. As a result, congenital syphilis has become extremely rare in Europe.

Latent syphilis

The natural course of syphilis is characterized by several asymptomatic phases (latent infection). Even in the absence of clinical signs, increased specific IgG antibody levels, high cardiolipin antibody titers and a positive IgM titer indicate the necessity for treatment. In untreated syphilis cases, a distinction is made between the incubation period and two periods of latent infection.

The natural course of syphilis is characterized by several asymptomatic phases (latent infection). Even in the absence of clinical signs, increased specific IgG antibody levels, high cardiolipin antibody titers and a positive IgM titer indicate the necessity for treatment.

- *Incubation period:* from the day of infection until the primary lesion appears. Mean duration is three weeks (9–90 days). In this early stage of the disease until about three weeks post infection, serological tests are still negative.
- *Early latent syphilis:* from the time the primary lesion has healed until the onset of secondary syphilis (3–8 weeks). During this phase, the diagnosis can only be made serologically.
- *Late latent syphilis:* from the end of secondary syphilis until the onset of tertiary or metasyphilis. The diagnosis can only be made serologically. Duration: 3–5 years for tertiary syphilis and up to 30 years for quaternary syphilis. Late latent syphilis can persist for the rest of the patient's life or heal spontaneously (in about three-quarters of all patients).

Diagnosis

Laboratory diagnosis of syphilis is primarily based on a number of serological tests (Figure 9). A positive screening test (TPPA or EIA/CMIA) is followed by a confirmation test (FTA-ABS test or EIA/CMIA or TPPA) and, if necessary, by testing for markers of disease activity (lipoid antibodies and IgM antibodies) to determine whether there is an indication for treatment.

Laboratory diagnosis of syphilis is based on a number of serological tests. A positive screening test is followed by a confirmation test and, if necessary, by testing for markers of disease activity. Treatment response can be monitored by measuring lipoid antibodies (VDRL or RPR test).

Given that antibodies are detectable only about three weeks post infection, the very early stage of the disease cannot be reliably diagnosed serologically. If there is clinical suspicion but a negative screening test, repeat testing is required. In case of epithelial lesions, dark-field microscopy (DFM) or nucleic acid amplification tests (NAATs) may be used for direct pathogen detection. Although NAATs are more sensitive than DFM, its sensitivity using swab specimens is still only about 80 % [7]. A negative NAAT result does therefore not rule out an infection. Immunohistochemical markers are available to detect treponemes in tissue biopsies.

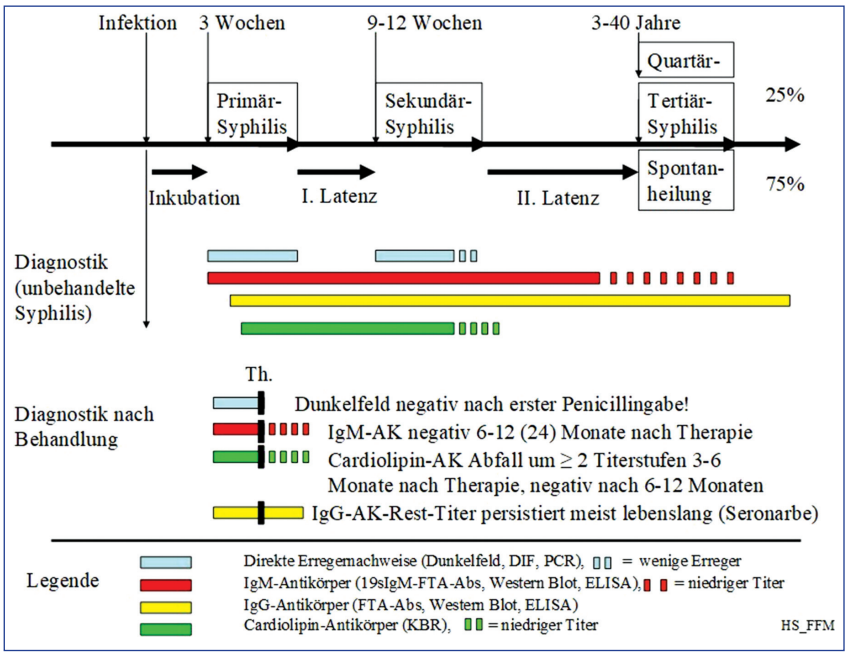

Figure 9 Serological diagnosis of syphilis. *Abbr.:* TPHA/TPPA, *Treponema pallidum* hemagglutination test/particle agglutination test; EIA, enzyme immunoassay; CLIA, chemiluminescence immunoassay; FTA-ABS test, fluorescence treponema antibody absorption test. Rapid diagnostic test may also be used as screening tests if they have a sensitivity and specificity comparable to conventional screening tests. TPHA/TPPA or EIAs can be used as confirmation tests if they have not previously been used as screening test (AWMF 2014).

Serological findings may be different in HIV patients. For example, there have been reports of seronegative secondary syphilis [8, 9]. In such cases, direct pathogen detection should be sought (DFM, histology, NAATs).

Treatment response can be monitored by measuring lipoid antibodies (VDRL or RPR test). These tests are usually performed every three months for one year; in HIV patients, for two years. A drop in the VDRL titer by more than two dilutions (factor 4) after 3–6 months indicates that antibiotic treatment has been effective [10]. Persistent lipoid antibody titers can be observed in roughly 12 % of patients. They do not necessarily mean that treatment has failed but can have other causes such as anti-cardiolipin activity due to other infections or autoimmune diseases [11]. An increase in VDRL titers indicates reinfection or relapse, e.g., in patients with neurological involvement caused by *Treponema pallidum* infection (early neurosyphilis) and inadequate treatment. Given that the various testing systems available are not entirely comparable, monitoring should always be conducted using the same laboratory and the same testing method in order to ensure conclusive results.

While resistance of *T. pallidum* to penicillins, cephalosporins and doxycycline have not yet been reported, there is widespread resistance to macrolide antibiotics [12]. High-level macrolide resistance is based on mutations in 23S rRNA, which can be detected with PCR-based tests [13].

Since its introduction in the treatment of syphilis back in 1943, penicillin has remained the treatment of choice for all stages of the disease. There have as yet been no reports of resistance. Treatment is administered parenterally, with dosing being based on disease stage.

Treatment

Since its introduction in the treatment of syphilis back in 1943, penicillin has remained the treatment of choice for all stages of the disease. There have as yet been no reports of resistance.

As *T. pallidum* replicates very slowly (every 30 to 33 hours only), longer treatment durations are required (> 10 days, usually 14 days). In this context, a distinction is made between early syphilis (all clinical manifestations within the first year post infection) and late syphilis (all clinical manifestations after the first year post infection, or in cases in which the disease duration is unknown). According to WHO criteria, serum penicillin levels of > 0.018 µg/mL (0.03 IU/mL) are effective in killing treponemes. Penicillin G is the drug of choice as it easily passes the blood-brain barrier.

Given that only 30 % of the oral penicillin dose is absorbed and given that many patients are unreliable in terms of treatment adherence, it is generally recommended that syphilis be treated parenterally.

Only about 25 % of the mother's serum concentration will cross the placenta and reach the fetus. During pregnancy macrolides should be used in exceptional cases only (see table 6), tetracyclins are contraindicated.

Treatment of syphilis in HIV patients is the same as for other patients.

Treatment of syphilis in HIV patients is the same as for other patients. Early neurological involvement must be ruled out. Regular clinical and serological follow-up is necessary, particularly in patients whose behavior is associated with an increased likelihood of reinfection.

The treatment recommendations for the various stages and clinical forms of syphilis according to current AWMF guidelines are summarized in Tables 4–6 [14, 15].

Neisseria gonorrhoeae

Pathogen

Neisseria (N.) gonorrhoeae (Figure 10) is a bacterium marked by considerable genetic variability. Capable of incorporating and exchanging DNA as well as transferring altered DNA sequences, the pathogen is known to readily develop mutations. This fact is crucial not only for the development of antibiotic resistance. It also plays an important role in the diagnostic workup using NAATs, given that the sensitivity of a given molecular test may be decreased by genetically altered target regions [16].

Table 4 Treatment of early-stage syphilis (according to AWMF S2K guidelines for "Diagnosis and Treatment of Syphilis", 2014) [14].

Clinical stage	Antibiotic	Dosage	Treatment duration
Primary syphilis	1. Benzathine penicillin	2.4 million I.U. by gluteal intramuscular injection L/R (1.2 million I.U. each side)	Single dose
	2. In case of penicillin allergy:		
	2a. Doxycycline	100 mg PO b.i.d.	14 days
	2b. Erythromycin	0.5 g PO q.i.d.	14 days
	3. Alternatives:	2 g IV daily, short infusion	10 days
	3a: Ceftriaxone	(30 min)	
Secondary syphilis	Same as primary syphilis (if neurosyphilis has been ruled out)		
Latent syphilis: Incubation, early latent and beginning of late latent syphilis (Figure 9)	Same as primary syphilis (if neurosyphilis has been ruled out)		

Table 5 Treatment of late syphilis and neurosyphilis [14].

Clinical stage	Antibiotic	Dosage	Treatment duration
Latent syphilis of unknown duration or late latent syphilis	Same as late syphilis: see below tertiary syphilis		
Tertiary syphilis	1. Benzathine penicillin	2.4 million I.U. by gluteal intramuscular injection L/R 1.2 million I.U. each side	Day 1, 8, 13
	2. In case of penicillin allergy: 2a. Doxycycline 2b. Erythromycin	 100 mg PO b.i.d. 0.5 g PO q.i.d.	 28 days 28 days
	3. Alternatives: 3a: Ceftriaxone	2 g IV daily, short infusion (30 min) or IM	14 days
Neurosyphilis (stage II–IV)	1a. Penicillin G, crystalloid solution	3–4 million IU IV six times a day, or (equally effective) 10 million IU IV t.i.d. or (equally effective) 5 million IU IV five times a day	at least 14 days
	1b. Ceftriaxone	2 g IV daily (initially 4 g)	14 days
	2. In case of penicillin allergy: Ceftriaxone or penicillin desensitization (Chisholm 1997) 3rd choice: Doxycycline	200 mg b.i.d.	28 days

Table 6 Treatment of syphilis in special situations [14].

Clinical stage	Antibiotic	Dosage	Treatment duration
Syphilis in HIV-infected individuals	1. Benzathine penicillin; same as in HIV-negative patients If neurosyphilis cannot be ruled out: same as neurosyphilis (see above)	2.4 million I.U. by gluteal intramuscular injection L/R 1.2 million I.U. each side	Early syphilis: single dose Late syphilis: days 1, 8, 13
Syphilis during pregnancy	Based on clinical stage 1. Benzathine penicillin 2. In patients with penicillin allergy: desensitization 3. Alternatives (only in exceptional cases): Erythromycin ethylsuccinate, E. stearate or E. glucoheptonate or Cephalosporins	2.4 million I.U. by gluteal intramuscular injection L/R 1.2 million I.U. each side	Early syphilis: single dose Late syphilis: days 1, 8, 13
Congenital syphilis	Penicillin G, crystalloid solution	Total daily dose: 200,000–250,000 IU/kg IV Newborns: 2 SDs From 2nd week of life: 3 SDs From 5th week of life: 4 SDs	14 days (possibly longer in case of HIV infection)

Abbr.: SD, single dose per day
Note: In cases of HIV infection and pregnancy: rigorous monitoring of therapeutic effect is essential because of increased incidence of treatment failure.

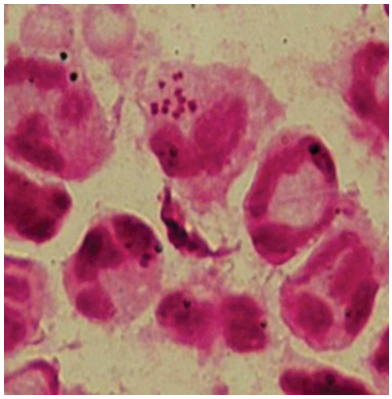

Figure 10 Gram stain: gram-negative intracellular diplococci (*Neisseria gonorrhoeae*) (photo: S. Buder).

Epidemiology

According to WHO estimates, gonorrhea is the fourth most common sexually transmitted infection. Apart from the federal state of Saxony, gonococcal infections are not notifiable in Germany.

According to WHO estimates from 2012, gonorrhea is currently the fourth most common sexually transmitted infection worldwide (70.3 million cases per year) after trichomoniasis, chlamydia infections and genital warts [17]. In 2015, the ECDC received almost 70,000 notifications [2]. Gonococcal infections are not notifiable in Germany, except for the federal state of Saxony. In 2017, the incidence of reported gonococcal infections in Saxony was 21.2/100,000, corresponding to a twofold increase compared to 2007 [18]. However, these figures do not reflect the situation for Germany as a whole.

Clinical presentation

Humans are the only natural reservoir of *N. gonorrhoeae*. The incubation period is 1–14 days. The clinical picture is predominantly characterized by mucosal manifestations at the site of infection that may lead to local complications as well as ascending infections or disseminated gonococcal infections. In addition a large number of asymptomatic cases occurs (approximately 50%).

Humans are the only natural reservoir of *N. gonorrhoeae*. Transmission only occurs through mucosal contact, e.g., during sexual intercourse or childbirth. The incubation period is 1–14 days.

The clinical picture is predominantly characterized by mucosal manifestations at the site of infection that may lead to local complications as well as ascending infection or disseminated gonococcal infection. In addition to the broad clinical spectrum, about 50 % of all infections remain asymptomatic and thus constitute a significant reservoir for transmission. Despite the potential absence of clinical signs and symptoms, the pathogens remain virulent and can be transmitted to partners who may then develop symptomatic gonorrhea [19].

In men, "classic" gonococcal urethritis presents with purulent urethral discharge in combination with dysuria, about 2–6 days after exposure. Around one-quarter of patients have only mild discharge in the morning but show no other symptoms during the rest of the day [20]. In women, the cervix and the cervical canal are the most common site of infection, associated with clinical symptoms such as vaginal discharge and dysuria.

Salpingitis, epididymitis or pelvic inflammatory disease (PID) may occur when an ascension of the infection takes place. PID could be caused by *N. gonorrhoeae* but also by *Chlamydia trachomatis* or other bacterial species (often as mixed infection). These ascending infections are clinically important because of their late sequelae, including infertility or chronic pelvic pain due to adhesions.

Disseminated gonococcal infection (DGI) occurs in about 0.5–3 % of patients. It has usually been reported in women, often after events such as menst-

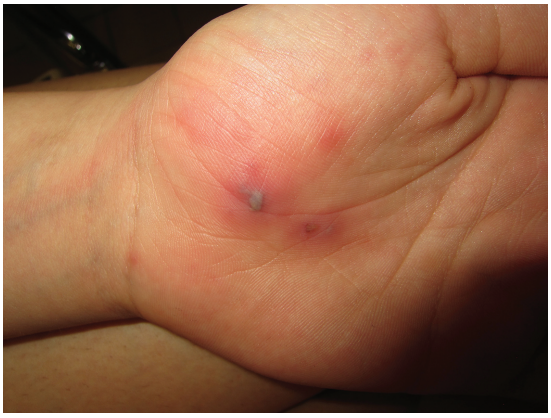

Figure 11 Vasculitic pustules on the palms in a patient with DGI (photo: P.K. Kohl).

ruation, insertion of an intrauterine device (IUD), or childbirth. Classic DGI is clinically characterized by a triad consisting of undulating fever, acute painful polyarthritis and acral vasculitic skin lesions. It may, however, also present with an oligosymptomatic or monosymptomatic clinical picture (e.g., gonococcal monoarthritis). Pathogenetically, the acute polyarthritis is caused by immune complexes (sexually acquired reactive arthritis, SARA), whereas cases of monoarthritis are often caused by direct gonococcal infection. Cutaneous manifestations include hemorrhage, papules, pustules or necrosis in acral areas [21] (Figure 11).

Possible gonorrhea-related complications in pregnant women encompass premature rupture of membrane, premature birth or septic abortion. Without treatment, the newborn is at risk of developing ophthalmia neonatorum or oropharyngeal infection.

Neonatal gonococcal conjunctivitis is contracted in utero or during the passage through an infected birth canal. About five days postpartum, the newborn develops a purulent conjunctivitis that, if left untreated, may rapidly affect the cornea and lead to blindness. Approximately 35 % of children with ophthalmia exhibit concurrent oropharyngeal involvement. Given that this complication of gonorrhea has become very rare in industrial countries, postnatal silver nitrate prophylaxis is no longer routinely offered in Germany.

In adults, gonococcal ophthalmia is a highly acute disease that usually occurs unilaterally in patients with known anogenital gonorrhea. For this reason, patients must be informed about the risk of autoinoculation.

As roughly 90 % of all cases of gonococcal pharyngitis remain asymptomatic [19, 22], a pharyngeal swab is useful in detecting a possible reservoir for transmission. The pharynx is especially important as a site of genetic exchange between *N. gonorrhoeae* with nonpathogenic, commensal *Neisseria* strains or other bacterial species. Likely, this is how most cases of antibiotic resistance are acquired.

In MSM, the rectum is frequently the primary site of infection (proctitis). Asymptomatic rectal gonorrhea is a reservoir for infection [20].

Current situation of antibiotic resistance

The worldwide development of antimicrobial resistance in *Neisseria gonorrhoeae* is a serious problem for the treatment and control of gonorrhoea. Treatment opportunities are dramatically limited because many of the previously recommended therapeutic agents are no longer effective.

Antibiotic resistance of *N. gonorrhoeae* is a global problem for the treatment and control of gonorrhea. Resistance has been developed for all antibiotic agents that have been used for treatment [22]. In recent years the threat of a potentially untreatable highly resistant pathogen (multidrug-resistant *N. gonorrhoeae* [MDR-NG] and extensively drug-resistant *N. gonorrhoeae* [XDR-NG]) has been discussed worldwide.

Parenterally administered ceftriaxone currently remains the last effective antibiotic for routine use. However, there have been reports from around the world of resistance development and treatment failure [23].

In order to evaluate these trends for Germany, the Gonococcal Resistance Network (GORENET), the *N. gonorrhoeae* resistance surveillance initiative of the Robert Koch Institute (Berlin) and the Reference Laboratory for Gonococci, has been collecting isolates and data from susceptibility tests since 2014 (Figure 12).

In terms of resistance to ceftriaxone (currently the first-line agent), the situation remains stable in Germany (0.5 % resistant strains). The rates of resistance to ciprofloxacin in Germany were 53–71 % in 2014 and 2017; for penicillin, 15–29 %. Resistance to azithromycin has shown a remarkable development. Since 2014 an increase to 12 % resistant strains with a high rate of intermediate susceptible isolates could be observed. This trend reversed slightly in 2016/17. In December 2015, the first case of urogenital gonorrhea caused by high-level azithromycin-resistant *N. gonorrhoeae* (minimal inhibitory concentration [MIC] > 256 mg/L) was reported in Germany [22]. In the same year, Great Britain reported an outbreak due to a strain with high-level azithromycin resistance [24].

Apart from high-level resistance, multi-resistance has been observed with increasing frequency. In 2015, the first multi-resistant strain resistant to ceftriaxone, cefixime, azithromycin, doxycycline, penicillin and ciprofloxacin was isolated in Germany. Treatment was eventually possible by dual therapy with an increased ceftriaxone dose. In early 2018, strains with combined high-level resistance to azithromycin (MIC > 256 mg/L) and resistance to ceftriaxone (MIC 0.5 mg/L) were isolated in Great Britain and Australia, which led to failure of ceftriaxone in the treatment of an pharyngeal gonorrhea. As these infections had been acquired in Southeast Asia, physicians should actively inquire about travel-associated diseases, as these may be associated with significant drug resistance [25, 26]. Increased awareness of local and global trends in drug resistance is extremely important.

Given the current trends in antibiotic resistance, new therapeutic approaches are required. Apart from testing new classes of antibiotics in the treatment of gonorrhea [27, 28], the feasibility of a new vaccine against *N. gonorrhoeae* has also been investigated, using an existing vaccine against *Neisseria meningitidis* [29, 30].

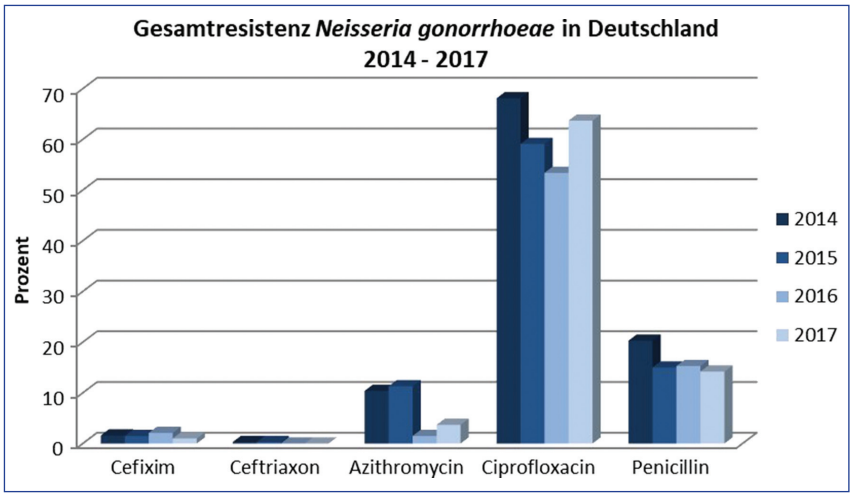

Figure 12 Distribution of resistance of *Neisseria gonorrhoeae* in Germany, GORENET 2014–2017 (source: Reference Laboratory for Gonococci).

Diagnosis

The diagnosis of gonorrhea is made by culture-based pathogen detection and/or nucleic acid amplification tests (NAATs). While NAATs are highly sensitive they do not provide information about antimicrobial susceptibility. Therefore a culture-based susceptibility testing must be performed.

The diagnosis of gonorrhea is made by culture-based pathogen detection and nucleic acid amplification tests (NAATs).

While NAATs are much more sensitive than bacterial cultures [31], they do not allow for antibiotic susceptibility testing. While obtaining material for NAAT testing, it is therefore imperative to additionally collect material for culture-based susceptibility testing.

In men, the swab is taken from the urethra following a period of four hours without urination. Female patients undergo endocervical swabbing. Urine is not suitable for bacterial cultures in either gender. For bacterial cultures to be diagnostically useful, the time between swabbing and arrival of the specimen in the laboratory (in a suitable transport medium) should ideally be no longer than 4 hours [32–35].

For NAAT-based detection in men, urethral swabs and first-void urine (the first 10 mL!) are equally suitable. In women, NAAT-based detection of gonococci from swabs (vaginal or endocervical) is more sensitive than from first-void urine [36]. Following appropriate instructions, sampling for diagnostic tests may also be performed by patients themselves [37].

Modern real-time multiplex NAAT technology allows for a diagnosis to be established in less than two hours. Many NAAT platforms offer simultaneous detection of *N.gonorrhoeae, C. trachomatis* and *M. genitalium* from the same sample.

The most recent developments using real-time multiplex NAAT technology allow for a diagnosis to be established in less than two hours. Many NAAT platforms also offer simultaneous detection of *Chlamydia (C.) trachomatis* and *Mycoplasma (M.) genitalium* from the same sample [36].

The choice of samples to be taken depends on the patient's sexual history and clinical symptoms [35]. Detection rates can be markedly increased by taking additional pharyngeal and anal swabs. Positive NAAT results in rectal and pharyngeal specimens should be confirmed to rule out false-positive results due to interaction with commensal *Neisseria* spp.. *Dual target assays* are useful in this regard, as the results thus obtained are based on amplification of two different target regions [35, 38]. Hence, only one sample is required for lab testing.

Additional pharyngeal and anal swabs can help increase detection rates.

Detection of disseminated gonococcal infection (DGI) is difficult. Gonococci can be cultured from the blood of DGI patients in only 20–30 % of cases, due to episodic bacteremia, and in less than 50 % of cases from joint aspirates or skin biopsies [34]. More frequently, gonococci can be isolated from primary infection sites (usually in the genital region), even though about one-half of these patients are asymptomatic. Nucleic acid amplification tests also improve detectability from cutaneous (pustule) swabs, joint aspirates, as well as pharyngeal and anogenital swabs.

A test of cure is recommended after 4 weeks following treatment. Follow-up tests should include all sites where infection may occur (urethra, rectum, pharynx).

It is recommended that the therapeutic response be monitored every time treatment has been administered. Follow-up NAAT testing should be performed no sooner than four weeks after treatment, given that NAATs cannot distinguish between living and dead microorganisms [39]. Follow-up exams should include all sites where infection may occur (urethra, rectum, pharynx).

Treatment

Calculated treatment of uncomplicated gonorrhea currently uses a dual therapeutic approach that consists of ceftriaxone 1-2 g IV or IM single-dose in combination with Azithromycin 1.5g PO single-dose.

Table 7 provides a comprehensive overview of the treatment of gonorrhea, depending on the site of infection and the patient population involved [34]. Given the rapid changes in terms of antibiotic resistance, gonorrhea should always be treated in accordance with current guidelines (in Germany, see AWMF S2K guidelines for "Diagnosis and Treatment of Gonorrhea", 2019) [34].

Table 7 Treatment of gonorrhea (according to AWMF S2K guidelines for "Diagnosis and Treatment of Gonorrhea", 2019) [34].

Site of infection and availability of pathogen identification	Patient compliance in terms of treatment monitoring	Treatment
Uncomplicated gonorrhea (urethra, cervix, rectum, pharynx) Pathogen identification not yet available	Unknown/not definitively ensured	Ceftriaxone 1–2 g IV or IM plus Azithromycin 1.5 g PO (as single dose in both cases) If IM dosing is contraindicated and IV dosing is not possible: Cefixime 800 mg PO (or 400 mg PO twice) plus Azithromycin 1.5 g PO (as single dose in both cases) (Cefixime is insufficiently effective in case of pharyngeal infection! In such cases, treatment with ceftriaxone is required.)
Uncomplicated gonorrhea (urethra, cervix, rectum, pharynx) Pathogen identification not yet available	Certain	Ceftriaxone 1–2 g IV IM (single dose as monotherapy) Additional diagnostic workup required (*C. trachomatis, M. genitalium*) Clinical follow-up and discussion of findings and 4 weeks after treatment, monitoring of treatment response using NAATs; samples must be taken from all affected sites (urethra, rectum, pharynx)
Uncomplicated gonorrhea (urethra, cervix, rectum, pharynx) N. *gonorrhoeae* has been identified, co-infection (*Chlamydia trachomatis, Mycoplasma genitalium*) has been ruled out	Certain	Ceftriaxone 1–2 g IV or IM (single dose monotherapy) Follow-up 4 weeks after treatment for monitoring of treatment success using NAATs; samples must be taken from all affected sites (urethra, rectum, pharynx)
Uncomplicated gonorrhea (urethra, cervix, rectum, pharynx) *N. gonorrhoeae* has been identified, and results of susceptibility testing are available Co-infection (*Chlamydia trachomatis, Mycoplasma genitalium*) has been ruled out	Certain	Treatment according to susceptibility testing, third generation cephalosporins may be spared to prevent further development of resistance. Ciprofloxacin 500 mg PO as single dose or Ofloxacin 400 mg PO as single dose or Doxycycline 100 mg PO b.i.d. for 7 days or Ceftriaxone 1–2 g IV or IM as single dose or Cefixime 800 mg PO or 400 mg PO twice (as single dose) (The latter agent is insufficiently effective for pharyngeal infections! Cefixime is not recommended for treatment of pharyngeal gonorrhea.) Follow-up 4 weeks after treatment for monitoring of treatment response; samples must be taken from all affected sites (urethra, rectum, pharynx)
Gonorrhea during pregnancy	Unknown/uncertain	All recommendations also apply to the treatment of pregnant women.

Continued

Table 7 Continued

Site of infection and availability of pathogen identification	Patient compliance in terms of treatment monitoring	Treatment
Disseminated gonococcal infection		Ceftriaxone 2 g IV every 24 hours plus Azithromycin 1.5 g PO (as single dose) until susceptibility test results are available. Treatment according susceptibility testing at the appropriate dose over a minimum of 7 days (or longer if necessary). Other manifestations, e.g., meningitis, endocarditis, arthritis: Ceftriaxone 2 g IV every 12 hours plus Azithromycin 1.5 g PO (as single dose) Treatment for at least 10–14 days (or longer if necessary). Endocarditis requires treatment for at least four weeks.

Calculated treatment of uncomplicated gonorrhea currently uses a dual therapeutic approach that consists of ceftriaxone 1–2 g IV or IM in combination with azithromycin 1.5 g PO.

In compliant patients (pregnant women, as patients attending special clinics or their general practitioner), single-dose treatment with ceftriaxone 1–2 g IV or IM (as monotherapy) may be given in order to avoid overtreatment and a further increase in resistance to azithromycin. This also applies to patients with an infection solely caused by *N. gonorrhoeae*. Follow-up is mandatory in order to monitor the therapeutic response and, if necessary, to subsequently treat a possible co-infection with *C. trachomatis* or *M. genitalium*.

Patients are recommended to be sexually abstinent until one week after treatment [34].

Chlamydia trachomatis

Pathogen

There are two biovars of *Chlamydia trachomatis*. While serovars D–K of the trachoma biovar are associated with urogenital infections, the lymphogranuloma venereum biovar (serovars L1–L3) causes LGV (invasive infection).

The species *Chlamydia trachomatis* occurs only in humans. There are two biovars: the trachoma biovar (serovars A–K) and the lymphogranuloma venereum (LGV) biovar (serovars L1–L3).

Within the trachoma biovar, serovars D–K are responsible for urogenital chlamydial infections. *Chlamydia trachomatis* occurs in three developmental forms:

- infectious elementary bodies (extracellular),
- replicating reticulate bodies (intracellular),
- aberrant reticulate bodies (intracellular).

Elementary bodies are metabolically inactive. After entering the host cell, they transform (inside inclusion bodies) into reticulate bodies, which divide by binary fission. Once a critical number has been reached, the reticulate bodies transform back into elementary bodies; the latter are released by lysis or exocytosis and can then infect other target cells [40]. Apart from reticulate bodies, another

intracellular developmental form has been described. These are morphologically aberrant, non-replicating persistent forms that occur under adverse conditions and may persist over long periods of time (Figure 13).

While serovars A–K remain in the mucosa, L serovars are invasive organisms characterized by systemic spread even in early disease stages. They give rise to an inflammatory response that primarily affects the lymphatic system.

Epidemiology

Urogenital chlamydial infection caused by serovars D–K is among the most common STIs worldwide. Many infections are asymptomatic but can be detected by screening.

Urogenital chlamydial infection caused by serovars D–K is among the most common STIs worldwide. According to the WHO, urogenital infections with *C. trachomatis* (131 million worldwide) were second only to *Trichomonas vaginalis* infections in 2012 [1, 2]. In Germany, chlamydial infections are not notifiable. Since 2008, women under 25 have been entitled to undergo screening for chlamydia at the expense of the statutory health insurance funds. Screening for chlamydia in pregnant women is mandatory.

Since 2008, the Robert Koch Institute (Berlin) has collected data on chlamydia tests and positive test results as part of a laboratory surveillance system. The highest percentage of positive tests was found in women aged 15–24. In men, the highest percentage of positive chlamydia tests (20.5 %) was observed in individuals aged 20–24 [41].

Lymphogranuloma venereum (LGV) is endemic in Asia, Africa, South America and the southeastern United States. In Europe, LGV infection is found almost exclusively in MSM, clinically presenting as proctocolitis with a common association with HIV.

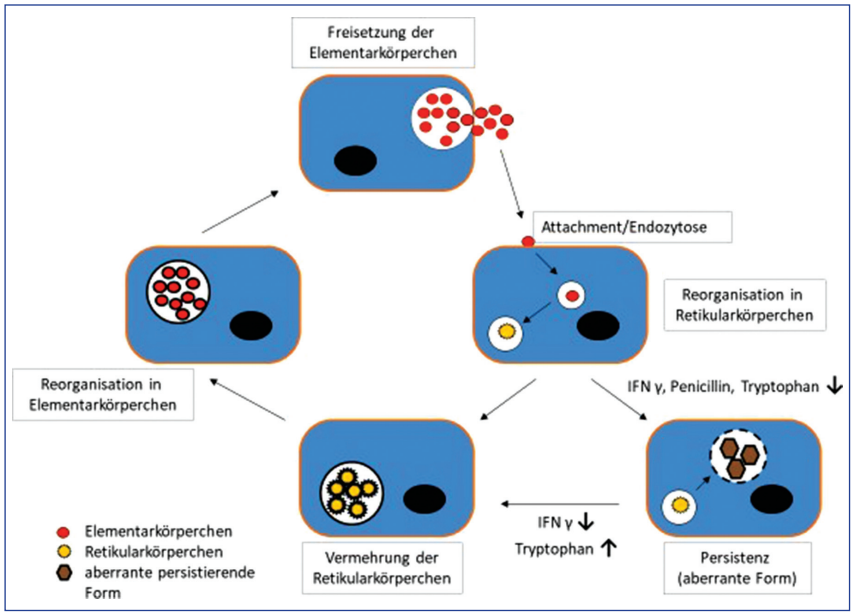

Figure 13 *Chlamydia trachomatis* replication cycle. Infectious, metabolically inactive elementary bodies (EB) infect mucosal epithelial cells. After entering the cell, EB are transformed (inside inclusion bodies) into metabolically active reticulate bodies (RB). RB replicate by binary fission and redifferentiate into EB; the latter are released from the inclusion bodies and can subsequently infect neighboring cells. Under certain conditions (low tryptophan levels, IFNγ, antibiotics), morphologically aberrant, non-replicating persistent reticulate bodies may be formed. Once conditions improve, they transform back into replicating RB or EB.

In Europe, LGV infection is found almost exclusively in MSM, clinically presenting as proctocolitis; there is a common association with HIV.

LGV is not a reportable disease in Germany. In a prevalence study, serovars L1–3 were found in 1.7 % of HIV-positive MSM and 0.6 % of HIV-negative or untested MSM. The vast majority of these men were asymptomatic [42].

Clinical presentation

Chlamydial infections (serovars A–K) are infectious diseases of the conjunctivae, the respiratory tract or the urogenital tract. The clinical picture is predominantly characterized by signs and symptoms at the site of infection, followed by manifestations associated with ascending infection and its sequelae.

Chlamydial infections (serovars A–K) are infectious diseases of the conjunctivae, the respiratory tract or the urogenital tract. The clinical picture is predominantly characterized by signs and symptoms at the portal of entry, followed by manifestations associated with ascending infection and its sequelae. Given that urogenital chlamydial infections remain asymptomatic in about 50 % of men and 80 % of women [42], they are frequently undiagnosed. Asymptomatic carriers are a significant reservoir for infection.

Chlamydia trachomatis causes about 30 % of all cases of urethritis in men [20]. Following an incubation period of 1–3 weeks, patients experience urethral discharge and dysuria. Ascending infection associated with painful epididymitis (chlamydial epididymitis) is possible [43]; however, the role of chlamydial infections in impaired fertility remains unclear and is the subject of controversial debate [44, 45].

The most common site of chlamydial infection in women is the cervix. Infection of the female urethra may occur as secondary or sole manifestation. Clinical features include discharge, abdominal pain and intermenstrual bleeding (endometritis). Further ascension of the pathogen may result in obstruction of the fallopian tubes and eventually lead to infertility. Clinically, chlamydial salpingitis is characterized by subacute abdominal pain. Further progression of the infection can result in inflammation of the entire pelvis (pelvic inflammatory disease, PID).

Chlamydial proctitis in women frequently indicates that the genital infection has spread to the rectum. In MSM, up to 15 % of all cases of proctitis [42] are caused by *C. trachomatis*. Clinical manifestations are varied and range from completely asymptomatic cases to patients with anorectal pain and mucopurulent discharge.

If there is evidence of chlamydial proctitis, which may clinically resemble chronic inflammatory bowel disease, LGV infection must be considered and should be analyzed by testing for serovars L1–3.

If there is evidence of chlamydial proctitis, which may clinically resemble chronic inflammatory bowel disease, LGV infection must be considered and should be analyzed by testing for serovars L1–3.

As pharyngeal infections are usually asymptomatic, they frequently go undetected. Spontaneous resolution without complications is possible.

There is an increase in premature births in women infected with chlamydia. Women with chlamydial cervicitis may transmit the pathogen to the newborn during delivery. Possible complications include conjunctivitis or afebrile pneumonia.

Chlamydia trachomatis conjunctivitis is usually caused by autoinoculation from the genital region. The term ‘swimming pool conjunctivitis’, formerly used synonymously, is incorrect.

Similar to *N. gonorrhoeae* infection, patients may develop reactive (sterile) arthritis, predominantly affecting large joints, 4–10 weeks after chlamydia infection (sexually acquired reactive arthritis, SARA). Patients with HLA-B27 and HLA-DR4 are more commonly affected. The clinical course is usually favorable.

Diagnosis and resistance situation

NAAT testing is the method of choice for detecting *Chlamydia trachomatis*.

NAAT testing is the method of choice for detecting *Chlamydia trachomatis*. One advantage of amplification methods is that it allows for pathogen detection from urethral, cervical, vulvovaginal, conjunctival, pharyngeal and anal swabs, and – in

men – also from first-void urine. Modern real-time NAATs yield results within a few hours. In addition, many assays offer simultaneous testing for *N. gonorrhoeae* using the same specimen.

Detection of chlamydia infection in the anogenital area using commercial NAATs does not allow for differentiation between serovars D–K (chlamydial proctitis) and serovars L1–3 (LGV). Additional genotype differentiation is therefore advisable.

Detection of chlamydia infection in the anogenital region using commercial NAATs does not allow for differentiation between serovars D–K (chlamydial proctitis) and serovars L1–3 (LGV). The latter make up a significant percentage of infections in MSM and require longer antibiotic treatment durations. Genotype identification in a separate assay is offered by only a small number of laboratories; this particular service is currently not covered by statutory health insurance funds and must be paid by patients themselves. LGV can be distinguished from non-LGV infection by analyzing the *pmpH* gene. This does not require an additional test if the appropriate *pmpH* region is used as the second target sequence in a dual-target NAAT assay [46, 47].

Given that NAATs cannot differentiate between living and dead microorganisms, it is recommended that a test of cure should performed not before eight weeks after treatment. To date, there has been no evidence of "classic" resistance mechanisms in chlamydia as cause for treatment failure; however, persistent aberrant reticulate bodies may lead to reactivation of infection.

Given that NAATs cannot differentiate between living and dead microorganisms, early follow-up tests aimed at assessing the therapeutic response are not recommended. Such tests should be performed no sooner than eight weeks after treatment.

To date, there has been no evidence of "classic" resistance mechanisms in chlamydia as cause for treatment failure. Lack of therapeutic success can be attributed to lack of compliance, insufficient duration or dosage of antibiotic treatment, or reinfection from an untreated sexual partner. Persistent aberrant reticulate bodies may possibly also play a role. They have been shown to be induced by cell wall-active antibiotics in vitro and in animal models. Given their limited metabolism and replicative inactivity, they express no target structures that would make them readily amenable to antibiotic treatment [48] (Figure 13).

Treatment

First-line treatment of urogenital chlamydial infections is doxycycline 100 mg PO twice daily for 7–14 days, or a single dose of azithromycin 1.5 g PO. In LGV, doxycycline 100 mg PO is given twice daily for at least 21 days.

Table 8 provides an overview of the therapeutic options for chlamydial infections (according to the German AWMF S2K guidelines for "Infections caused by *Chlamydia trachomatis*", 2016) [49]. First-line treatment of urogenital chlamydial infections is doxycycline 100 mg PO twice daily for 7–14 days, or a single dose of azithromycin 1.5 g PO. In LGV, doxycycline 100 mg PO is given twice daily for at least 21 days.

Mycoplasma genitalium

Pathogen

Ureaplasma urealyticum, Ureaplasma parvum and *Mycoplasma hominis* are part of the urogenital microbiome in sexually active individuals and rarely cause symptoms.

The term 'mycoplasma' applies to the entire group of pathogens. These microorganisms lack a cell wall. For humans, the genera *Mycoplasma* and *Ureaplasma* are of clinical importance. *Ureaplasma* spp. can be distinguished from *Mycoplasma* spp. by their ability to hydrolyze urea (ureolysis).

Colonization of the genital tract with *Ureaplasma (U.) urealyticum*, *U. parvum* and *Mycoplasma hominis* can be considered part of the urogenital microbiome in sexually active individuals. Only in rare cases will *U. urealyticum* or *M. hominis* cause urethritis.

Mycoplasma genitalium, plays a significant role in acute or persistent/recurrent urethritis (non-gonococcal, non-chlamydial urethritis, NGNCU).

Mycoplasma genitalium, on the other hand, plays a significant role in acute or persistent/recurrent urethritis (non-gonococcal, non-chlamydial urethritis, NGNCU), especially in men. Women typically develop cervicitis, which may be

Table 8 Treatment of *Chlamydia trachomatis* infections (according to AWMF S2K guidelines for "Infections caused by *Chlamydia trachomatis*", 2016) [49].

Infection	Treatment
Urethritis, cervicitis, pharyngitis, proctitis (serovars D–K)	Doxycycline 100 mg PO b.i.d. for 7–14 days or Azithromycin 1.5 g PO (single dose)
Urogenital chlamydia infection during pregnancy	Azithromycin 1.5 g PO (single dose) (off-label use) or Erythromycin 500 mg PO q.i.d. for 7 days
Neonatal conjunctivitis or pneumonia	Erythromycin syrup 40 mg/kg/day PO (split into 4 daily doses) for 14 days or Azithromycin 10 mg/kg PO
LGV (serovars L1–3)	Doxycycline 100 mg PO b.i.d. for at least 21 days or Azithromycin 1.5 g PO on days 1, 8, 15
Trachoma	Doxycycline 100 mg PO b.i.d. for 7 days or Azithromycin 500 mg PO for 3 days

followed by ascending infection and PID eventually full-blown PID. However, a large number of *M. genitalium* infections are asymptomatic.

Epidemiology

Besides *C. trachomatis*, *Mycoplasma genitalium* is thought to be the second most common causative agent of non-gonococcal urethritis.

Besides *C. trachomatis*, *Mycoplasma genitalium* is thought to be the second most common causative agent of non-gonococcal urethritis and has been found in approximately 25 % of NGNCU cases [50] and 10 % of PID cases [51, 52]. Given that testing for *Mycoplasma* is rarely done in routine clinical practice and infection is not notifiable, there is only scarce epidemiological data from a small number of studies. In Great Britain, for example, the prevalence has been shown to be highest in men aged 25–34 (2.1 %) and in women aged 16–19 (2.4 %). Nearly all men and more than 50 % of women show no symptoms [53, 54].

Clinical presentation

Clinically, *M. genitalium* infection primarily presents with urethritis and cervicitis. Ascending infection may lead to complications. There is also a large number of asymptomatic infections.

Acute or chronic urogenital infection with *M. genitalium*, and in rare cases also the initial infection with *U. urealyticum* and *M. hominis*, presents with moderate discharge and dysuria.

Women experience mucopurulent cervicitis, which may be followed by ascending infection and PID eventually full-blown PID. Proctitis and reactive arthritis (SARA) have also been reported.

The incubation period is unclear but is thought to be between 2 and 4 weeks.

Resistance situation

Due to its plastic genome, the pathogen is able to develop single- or multidrug resistance [55]. Currently, there is concern about the development of macrolide

Mycoplasma genitalium is capable of developing resistance to doxycycline, macrolides and fluoroquinolones as well as multidrug resistance, a fact that severely limits therapeutic options.

resistance, particularly to Azithromycin. Tetracycline resistance is also common (doxycycline, minocycline).

Resistance to fluoroquinolones has been reported and may preclude moxifloxacin as an alternative therapeutic agent. Pathogens resistant to moxifloxacin usually also show macrolide and doxycycline resistance.

As regards the situation in Germany, there is only scarce published data derived from a small test series. In that study, mutations associated with macrolide resistance were found in ten out of 19 isolates, suggesting widespread macrolide resistance of *M. genitalium* in Germany [56].

Diagnosis

Mycoplasma genitalium infections are diagnosed using NAATs.

Mycoplasma genitalium infections are diagnosed using NAATs. In clinical studies, the sensitivity and specificity of commercial NAATs was found to be 82–98 % and 98–100 %, respectively [55, 57]. Suitable test material includes swabs (vaginal, cervical, urethral, anorectal) and first-void urine. Some multiplex tests allow for simultaneous detection of multiple pathogens (*N. gonorrhoeae, C. trachomatis, M. genitalium*) from the same sample. While there are also NAAT-based detection methods for other *Mycoplasma* and *Ureaplasma* spp., not all of them can reliably differentiate between *U. urealyticum* (causative agent of urethritis) and commensal *Ureaplasma* spp. [58–60].

Molecular testing for macrolide resistance has recently become available but is currently offered by only a small number of specialized laboratories worldwide.

Given the resistance situation for *M. genitalium* with increased resistance to doxycycline, macrolides, fluoroquinolones and also multidrug resistance, resistance testing is required. Macrolide resistance is caused by mutations in 23S rRNA [56, 61, 62]. Recently, a commercial NAAT assay for *Mycoplasma* has become available that can simultaneously detect macrolide resistance mutations in 23S rRNA [63]. However, there are currently only a small number of specialized laboratories worldwide that offer this type of molecular resistance testing.

In Germany, this test is currently not covered by statutory health insurance funds.

In light of the increasing antibiotic resistance and the possibility of persistent or recurrent NGNCU, it is generally recommended that the response to treatment be monitored in all patients. This should be done using NAATs and no sooner than three weeks after initiation of treatment [55].

Treatment

Treatment recommendations for *M. genitalium* infections are inconsistent. Current recommendations include azithromycin 500 mg PO on day 1, followed by 250 mg on days 2–5, or doxycycline 100 mg PO twice daily for 7 days.

Treatment recommendations for *M. genitalium* infections are inconsistent and currently the subject of intense debate among experts. The former treatment recommendation of azithromycin 1 g (as single-dose) has been replaced by the new recommendation of azithromycin 500 mg PO on day 1, followed by 250 mg on days 2–5. While this is considered to be possibly more effective, there is some controversy about whether this dosing regimen may facilitate the development of resistance. Although doxycycline (100 mg PO twice daily for 7 days) is likewise recommended as first-line treatment by some guidelines, treatment failure is more common with this regimen [64–66]

In case of persistent infection or treatment failure with azithromycin, moxifloxacin (400 mg PO for 7–10 days) should be administered.

In case of persistent infection or treatment failure with azithromycin, moxifloxacin (400 mg PO for 7–10 days) is recommended. Overall, chronic *M. genitalium* infections may pose a considerable therapeutic challenge.

For multiresistant pathogens, the only remaining treatment option is pristinamycin (1 g four times a day for 10 days), a streptogramin antibiotic (Table 9). Besides being expensive, this agent has to be ordered through an international pharmacy in Germany [64, 65].

Table 9 Treatment of *Mycoplasma genitalium* infections [64].

Infection	Treatment
Mycoplasma genitalium	Azithromycin 500 mg PO day 1 and 250 mg PO on days 2–5 or Doxycycline 100 mg PO b.i.d. for 7 days
Mycoplasma genitalium in case of resistance to azithromycin	Moxifloxacin 400 mg PO for 7–10 days
Mycoplasma genitalium in case of treatment failure with moxifloxacin	Pristinamycin 1 g PO q.i.d. for 10 days
NGNCU	Doxycycline 100 mg PO b.i.d. for 7–10 days or Azithromycin 500 mg PO on day 1, followed by 250 mg PO on days 2–5

Abbr.: NGNCU, non-gonococcal, non-chlamydial urethritis

Partner notification

Following the diagnosis of an STI, the sexual partner(s) should be notified in order to be able to interrupt the chain of infection. In patients with symptomatic gonococcal, *C. trachomatis* or *M. genitalium* infection, all potential sexual partners over the preceding eight weeks need to be examined and, if necessary, treated. In asymptomatic patients, this applies to all partners over the last six months. In symptomatic patients with primary syphilis, all potential sexual partners over the past three months must be examined and treated if necessary; in secondary syphilis, this period is extended to six months; in early latent syphilis, to two years [67]. As partner notification primarily starts with the index patient, great care and empathy are required to ensure that sexual partners actually undergo diagnostic testing and subsequent treatment. If appropriate, notification can be undertaken in an anonymized manner by patients themselves, given that physicians are bound by medical confidentiality. The sexual partners of individuals with chlamydial, gonococcal or mycoplasma infections can be treated without prior diagnostic tests if they experience clinical symptoms. This is also possible if the history suggests an exposure risk or if testing is not feasible or declined.

Summary

Worldwide, sexually transmitted infections are playing an increasingly important role. Apart from the overall increase in incidence, the development of antibiotic resistance that has been generating great concern. Furthermore, many affected patients are asymptomatic and thus constitute a hidden reservoir for further transmission. Following the diagnosis of an STI, patients should be tested for other STI pathogens as well (*Treponema pallidum, Neisseria gonorrhoeae, Chlamydia trachomatis, Mycoplasma genitalium, HIV, HBV, HCV, HPV and HSV*). In addition, partner notification is essential to interrupt the chain of infection.

The increase in syphilis infections is epidemiologically well documented by the number of reported cases. The condition is characterized by different stages,

multiform clinical manifestations and a prolonged disease course. In addition, there are periods of latent infection. Immunodeficiency or HIV infection increases the risk of neurosyphilis. Laboratory diagnosis of syphilis is based on a number of serological tests. Parenteral administration of penicillin is still the treatment of choice for all disease stages.

Antibiotic resistance of *N. gonorrhoeae* poses a worldwide problem in terms of treatment and control of gonorrhea. NAAT-based detection of *N. gonorrhoeae* should therefore always be supplemented by suseptibility testing using bacterial cultures. Today, modern real-time multiplex PCR methods allow for simultaneous detection of Neisseria gonorrhoeae, *Chlamydia trachomatis* and *Mycoplasma genitalium* from the same sample. Detection rates can be increased by additional pharyngeal and anal swabs. Calculated treatment of uncomplicated gonorrhea currently includes a dual therapeutic approach. The response to treatment should always be monitored using NAATs.

While serovars D–K of *Chlamydia trachomatis* are the causative agents of urogenital infections, serovars L1–3 are the pathogens responsible for causing LGV (invasive infection). In Europe, LGV infection is seen almost exclusively in MSM, clinically presenting as proctocolitis with a common association with HIV. NAAT testing is the method of choice for detecting *C. trachomatis*. While there is no evidence of "classic" antibiotic resistance in chlamydia, persistent aberrant reticulate bodies may lead to reactivation of infection. First-line treatment of urogenital chlamydial infection is doxycycline for 7–14 days; in LGV, a longer treatment cycle is indicated (21 days).

Mycoplasma genitalium plays an important role in acute or persistent urethritis. The pathogen is capable of developing single- and multidrug resistance, thus severely limiting therapeutic options. Infections with *Mycoplasma genitalium* are detected using NAATs. Molecular testing for macrolide resistance has recently become available but is currently offered by only a few specialized laboratories worldwide.

Conflict of interest

S. Buder: None. H. Schöfer: Consultant/expert for Galderma, GSK-Stiefel and Medigene; lectures for Novartis, Taurus, Allmirall and Ferrer (Barcelona). T. Meyer: Consultant (Roche), lecture fees (Cepheid, AbbVie, Hain, Ifi). V. Bremer: None. P.K. Kohl: None. A. Skaletz-Rorowski: None. N. H. Brockmeyer: None.

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Fragen zur Zertifizierung durch die DDA

1. Welche Infektionen sind nach dem Infektionsschutzgesetz (IfSG) meldepflichtig und vom Labor an das Robert Koch-Institut zu melden?
a) Infektionen mit *Treponema pallidum*
b) Infektionen mit High-Level-resistenten *Neisseria gonorrhoeae*
c) alle Infektionen mit *Chlamydia trachomatis*
d) nur Infektionen mit *Chlamydia-trachomatis*-Serovaren L1–L3 (LGV)
e) Infektionen mit *Mycoplasma genitalium*

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2. Welcher Test ist als Suchtest Test für *Treponema-pallidum*-Infektionen am besten geeignet?
a) TPPA
b) Dunkelfeld-Mikroskopie
c) PCR
d) IgG-Westernblot
e) VDRL

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3. Bei einem 30-jährigen Mann mit mehreren Sexualpartnerinnen in den letzten sechs Monaten wurde eine Gonorrhoe diagnostiziert. Welche Erkrankung gehört nicht in das Spektrum der möglichen und daher abzuklärenden Begleiterkrankungen?
a) Chlamydien-Urethritis
b) HIV-Infektion
c) Syphilis
d) Hepatitis B
e) Infektion mit Mykobakterien

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4. Welche Aussage zur Diagnostik einer unkomplizierten Gonorrhoe ist falsch?
a) Mittels moderner Real-Time-Multiplextechnologie ist eine schnelle Diagnostik in wenigen Stunden möglich, wobei ein gleichzeitiger Nachweis von *Chlamydia trachomatis* aus derselben Probe erfolgen kann.
b) Für die kulturelle Diagnostik benötigt *Neisseria gonorrhoeae* als anspruchsvoller Erreger spezielle Wachstumsbedingungen beim Transport und im Labor.
c) Die Diagnose einer Gonorrhoe kann bei urethralem Ausfluss als klinische Blickdiagnose gestellt werden.
d) Der molekulare Erregernachweis (NAAT) ist der Kultur in Sensitivität und Spezifität überlegen.
e) Bei einem Erregernachweis mit NAAT sollte zusätzlich immer eine Kultur zur Empfindlichkeitstestung angestrebt werden.

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5. Welche Aussage zur Gonorrhoe trifft nicht zu?
a) Die Gonorrhoe ist die vierthäufigste sexuell übertragbare Erkrankung nach Trichomoniasis, *Chlamydia-trachomatis-Infektionen* und Infektionen mit HPV.
b) Asymptomatische Infektionsverläufe werden durch gering virulente Erreger hervorgerufen und sind daher nicht infektiös.
c) Aufgrund zunehmender Resistenzen bei *Neisseria gonorrhoeae* ist eine kulturelle Diagnostik und Empfindlichkeitstestung bei jeder Gonorrhoe sinnvoll.
d) Eine Therapieerfolgskontrolle sollte nach jeder abgeschlossenen Therapie einer Gonorrhoe erfolgen.
e) Derzeit ist Ceftriaxon i.v. in dualer Therapie mit Azithromycin p.o., jeweils als Einmalgabe, die Therapie der Wahl bei der kalkulierten Therapie einer Gonorrhoe.

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6. Die Nachweisverfahren für *Neisseria gonorrhoeae* beinhalten die kulturelle Anzucht der Erreger und NAAT-Analysen. Warum sollte das diagnostische Vorgehen bei Verdacht auf eine Gonokokken-Urethritis insbesondere die Kultur aus Abstrichmaterial beinhalten?
a) Weil die Kultur die höchste Sensitivität aller diagnostischer Verfahren besitzt.
b) Weil Gonokokken anspruchslose Bakterien sind, die auf einfachen Nährböden schnell angezüchtet werden können.
c) Weil auf den üblicherweise verwendeten Nährmedien Gonokokken leicht von apathogenen Neisserien unterschieden werden können.
d) Weil nur über die Untersuchung der angezüchteten Erreger eine Aussage zur Antibiotikaempfindlichkeit möglich ist.
e) Weil die Meldepflicht von Gonokokken-Infektionen den kulturellen Nachweis der Erreger erfordert.

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7. Welche der folgenden Erkrankungen kann als Komplikation/Folgeerkrankung bei urogenitaler *Chlamydia-trachomatis*-Infektion auftreten?
a) Pyelonephritis
b) Hepatitis
c) Endokarditis
d) reaktive Arthritis
e) Optikusneuritis

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8. Für die Diagnostik von *N. gonorrhoeae, C. trachomatis* und *M. genitalium* kann als Untersuchungsmaterial Urin eingesetzt werden. Hierbei müssen jedoch bestimmte Einschränkungen beachtet werden. Welche Aussage ist falsch?
a) Urin eignet sich nicht für die Kulturdiagnostik und Empfindlichkeitstestung von *N. gonorrhoeae.*
b) Mittelstrahlurin ist nicht geeignet.
c) Eine Menge von 10 ml sollte nicht überschritten werden, da es sonst zu Verdünnungseffekten kommen kann und die Sensitivität der NAAT-Testung beeinträchtigt wird.
d) Für Frauen ist die Diagnostik mittels Urin nicht ausreichend sensitiv

und eine Abstrichdiagnostik zu favorisieren.

e) Bei Erststrahlurin handelt es sich um den ersten Morgenurin.

9. Welcher Übertragungsweg ist neben Sexualkontakten für die Akquirierung einer *Chlamydia-trachomatis*-Infektion von Bedeutung?

a) perinatale Transmission
b) aerogene Übertragung
c) Küssen
d) Nadelstichverletzung
e) Kontakt mit kontaminierten Oberflächen (Toilette)

10. Welche Aussage zu Mycoplasma genitalium ist falsch?

a) *Mycoplasma genitalium* ist der zweithäufigste Erreger einer nichtgonorrhoischen Urethritis.
b) Infektionen mit *Mycoplasma genitalium* können zu aufsteigenden Infektionen bis zum Vollbild einer *pelvic inflammatory disease* (PID) führen.
c) *Mycoplasma genitalium* lässt sich durch eine Einmalgabe von Makroliden zuverlässig therapieren.
d) Asymptomatische Infektionen kommen sehr häufig vor.
e) Infektionen mit *Mycoplasma genitalium* werden durch NAAT nachgewiesen.

Liebe Leserinnen und Leser,
der Einsendeschluss an die DDA für diese Ausgabe ist der 30. April 2019. Die richtige Lösung zum Thema „Rickettsiosen: Der Hautbefund führt oft zur Diagnose – Eine Übersicht“ in Heft 12 (Dezember 2018) ist: (1c, 2b, 3c, 4a, 5d, 6e, 7c, 8c, 9e, 10d).

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.