Gram-Negative Bacterial Infections

Infectious diseases transmitted by gram-negative pathogens are - in some cases - zoonotic diseases with great pathogenic potential, which is why they are investigated as biological weapons in some countries. The remaining listed bacteria are no less dangerous so that every clinical practitioner benefits from having a good overview of clinical presentations, diagnostics, and treatment of these diseases.

Bartonella

Characteristics of Bartonella

The genus bartonella comprises four species that are well recognized as pathogens in human beings. Bartonella are emerging pathogens, and in recent years many other bartonella species have also been associated with human diseases. Bartonella are fastidious, zoonotic pathogens transmitted by animal bites, scratches and arthropods and can show iatrogenic transmission by needle sticks injuries or blood transfusion. The facultative intracellular bacteria are very demanding concerning cultivation and grow slowly in aerobic environments. *Endothelial cells* or *erythrocytes* serve as host cells. Blood-culture-negative endocarditis is commonly undiagnosed presentation of infection with several bartonella species.
Bartonella are short pleomorphic coccoid gram-negative rod-shaped bacteria. Some species have pili, with which they can actively move. For cultivation, hemin is needed. Due to the slow growth, the most common identification methods are practically not applicable.

### Infection with Bartonella Henselae

An infection with *Bartonella henselae* especially occurs in children and teenagers in fall and winter. The reservoirs for the pathogen are pet cats; in 10 – 70% of cats, the bacteria can be detected (especially in warm areas, 0% in Norway however). *Bartonella henselae* is transmitted either directly via skin lesions caused by the cats or via the cat flea.

At the site of the lesion, a small, crusted papule forms, which does not itch and can be present for several months. Also, one-sided lymphadenitis can be observed, mostly in the area of the armpits or at the neck, which sometimes develops to necrolysis. After two to three weeks, this lymph node swelling regresses.

Due to the reticular abscess formation, that can be identified histologically, the cat-scratch disease is also referred to as benign lymphoreticulosis. If it is combined with non-purulent conjunctivitis, this is called Parinaud’s oculoglandular syndrome. In immunosuppressed patients, manifestations may include encephalitis, endocarditis, osteomyelitis, or sepsis.

Due to the angiogenetic potential of the pathogen via a protease-sensitive factor, *Bartonella henselae* can also trigger bacillary angiomatosis and peliosis hepatis. These are vasculoproliferative disorders. They cause lobular capillary proliferations that are lined with endothelium and can bleed severely.

In peliosis hepatis, these capillary proliferations can be found in the liver; in bacillary angiomatosis, on the skin. They are reddish-brown papules, which can ulcerate and also lead to bone lesions. These diseases are very frequently observed in HIV-positive patients. A CT image of peliosis hepatis looks like this:

![CT image of peliosis hepatis](Image: "Follow up of a patient with peliosis hepatis over 7 years with full remission." by Braegel. License: CC BY-SA 4.0)

In differential diagnosis, toxoplasmosis and the Kawasaki syndrome have to be considered. Also other causes of lymphadenitis, like tuberculosis, CMV, and infectious
mononucleosis, should be ruled out.

**Detection of Bartonella Henselae**

With an **immunofluorescence test**, specific **IgG antibodies** can be detected. In problematic cases, a direct detection using **PCR** on the basis of biopsy material is another option. Cultivation lasts up to 120 days and is, therefore, not a practical procedure.

Histology of the lymph nodes shows a **granulomatous inflammation** with a central necrosis. It is surrounded by **epitheloid and giant cells**. An increase in inflammation parameters can be detected in the blood. Furthermore, patients might also develop **hemolysis** and **thrombocytopenia**.

**Treatment of Cat Scratch Disease**

In the majority of the cases, the disease heals up without any therapy. In case of complications, **azithromycin** can be used.

**Infections with Bartonella Quintana**

Infections with **Bartonella quintana** occurred mainly during the world wars in Eastern Europe: This is the origin of the term ‘trench fever’. The transmitters of **Wolhynia fever**, as it is also called, are clothes and head lice, whose feces remain infectious for many years.

After an incubation time of 10 – 30 days, sudden symptoms like headaches, aseptic meningitis, and fever set in. As the fever has a recurrence time of five days, the disease is also referred to as **five-day fever**. Afterwards, bone pain may persist for months, mostly in the area of the shin and the spine. Headaches also stay for some time.

Nowadays, this infection mostly concerns homeless people and patients with AIDS. In immunosuppressed individuals, Bartonella quintana can be the trigger of the above mentioned forms of bacillary angiomatosis, peliosis hepatitis, and especially of endocarditis.

The detection is analog to Bartonella henselae, e.g. via PCR on the basis of heart valve biopsy material.

**Treating Infections with Bartonella Quintata**

Treatment consists of antibiotics that reach intracellular concentrations. Those are **doxycycline**, **erythromycin**, and **azithromycin**. In AIDS patients, long-term antibiosis can be advisable.

**Infections with Bartonella Bacilliformis**

**Sand flies** serve as vectors for this type of bartonellas. After transmission, the bacteria mainly live in erythrocytes. Secondarily, they can also be present in the spleen and other organs. The hemolytic form of this type of bartonellosis is the **Oroya fever**.

Lymph node swelling and **hepatosplenomegaly** occurs – accompanied by very high fever and severe hemolysis. This is followed by a phase of severe immunosuppression, which used to have lethal consequences in the past as without antibiotic treatment, it led to secondary infections.

Without antibiotic treatment, a **verruca peruana** (Peru wart) forms after two to four months. Mostly, it heals up spontaneously after several months.
**Note:** After an infection with bartonella, affected individuals no longer qualify for blood donations.

The following table provides you with an overview of the most important species of the genus bartonella:

<table>
<thead>
<tr>
<th>Species:</th>
<th>B. henselae</th>
<th>B. quintana</th>
<th>B. bacilliformis</th>
<th>B. elizabethae</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reservoir:</td>
<td>Cat</td>
<td>Human</td>
<td>Human</td>
<td>Rat</td>
</tr>
<tr>
<td>Occurrence:</td>
<td>Worldwide</td>
<td>Worldwide</td>
<td>South America</td>
<td>Unknown</td>
</tr>
<tr>
<td>Vector:</td>
<td>Cat flea, ticks</td>
<td>Head and clothes lice</td>
<td>Sand flies</td>
<td>Unknown</td>
</tr>
<tr>
<td>Clinical Pictures:</td>
<td>Cat scratch disease, bacterial angiomatosis, peliosis hepatis, endocarditis, encephalitis, sepsis</td>
<td>Trench fever, bacterial angiomatosis, endocarditis, chronic lymphadenopathy</td>
<td>Carrion disease, sepsis</td>
<td>Endocarditis</td>
</tr>
</tbody>
</table>

**Brucella**

The most important brucelloses for humans are Malta fever, mostly caused by *B. melitensis*, and Bang disease, which is caused by *B. abortus*.

**Characteristics of Brucella**

These bacteria are **gram-negative rod-shaped bacteria, which vary in length from coccoid to short**. They are immobile and obligatorily host-bound. Only under favorable conditions can these pathogens maintain their infectious capacity outside of the host for several months.

These aerobic bacteria use livestock like cattle, sheep, and swine as reservoirs.

Therefore, it is especially people in contact with livestock, like veterinarians, farmers, shepherds, milkers, or zookeepers, who are at risk of contracting an infection. In countries in which brucellosis is endemic, there is also an increased risk for other people if they consume insufficiently heated milk of raw milk products.

The following are important representatives of the genus brucella:

<table>
<thead>
<tr>
<th>Species:</th>
<th>Pathogen Reservoir:</th>
<th>Disease:</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Brucella melitensis</em></td>
<td>Goats, sheep, camels</td>
<td>Malta fever, also undulating fever</td>
</tr>
<tr>
<td><em>Brucella abortus</em></td>
<td>Cattle</td>
<td>Bang disease</td>
</tr>
<tr>
<td><em>Brucella suis</em></td>
<td>Swine</td>
<td>Swine brucellosis</td>
</tr>
</tbody>
</table>
Infections with Brucella Abortus and Militensis

While Germany is officially considered free of brucellosis due to thorough supervision of livestock, brucellosis does occur in Europe, especially in Mediterranean countries. The transmission occurs via direct contact with animals or their excretions (the pathogen lives primarily in the animals’ urinary tract).

Depending on the portal of entry (e.g. the respiratory or the digestive tract), local inflammations with unspecific symptoms can be observed. Due to hematogenic spreading, basically every organ can be affected. Typical non-caseating granulomas form.

The bacteria mainly proliferate in the cells of the reticuloendothelial system and in reproductive organs. In up to 90 % of the infections, the disease has a subclinical process. After an incubation time of 5 – 60 days, symptoms like fatigue, joint pain, hepatosplenomegaly, and high fever accompanied by shivering and night sweats can be observed.

Since the fever is regularly interrupted by fever-free intervals, it is also referred to as undulating fever with respect to its wave-like course. Other clinical presentations include endocarditis with an inflammation of the aortic valve, chronic processes with neurological symptoms, and spondylodiscitis. Skeletal system is commonly affected in children. Arthritis, spondylitis, and osteomyelitis are commonly reported in such cases. During pregnancy, the infection often leads to miscarriage.

This is a typical non-caseating granuloma:

Detection of Brucella

For cultivation, blood cultures, abscess material, bone marrow, and other tissues can be used. Every suspicion has to be communicated to the laboratory since there is the danger of contagion and cultivation must only occur in an S3-laboratory.

A further method is the detection of antibodies in the serum. For this, slow agglutinations and the Rose-Bengal test can be used. It is an Ag-agglutination test.
with bengal-dyed test antigen from \textit{B. abortus}.

As differential diagnoses, \textit{tuberculosis} and \textit{yersiniosis} should be considered.

\textbf{Treatment of Brucellosis}

In any case, a combination therapy is recommendable. The gold standard is \textit{doxycycline} for six weeks and \textit{streptomycin} for two to three weeks.

Usually, the disease and resulting death have to be reported to the competent authorities.

\section*{Coxiella}

\textbf{Characteristics of Coxiella Burnetii}

The only species of this genus is \textit{Coxiella burnetii}. There is a close relation to \textit{rickettsia}, \textit{legionella}, and \textit{francisella}.

This strictly intracellular bacterium is gram-negative and rod-shaped, however, it cannot be imaged with Gram stain, but with \textit{Gimenez stain}.

Due to its ability to sporulate, \textit{C. burnetii} can remain infectious in dust, hay, and wool for a time span of up to ten months and more. The pathogen can be present in two antigen-forms: \textit{phase I}, which is very infectious, and \textit{phase II} with lesser virulence.

Recently, \textit{C. burnetii} has been classified as a potential bioterrorism agent by CDC and it caused a large outbreak in the Netherlands.

\textbf{Infection with Coxiella Burnetii}

\textbf{Q fever} (i.e., Query fever) is a zoonosis spread worldwide– exceptions are New Zealand and Antarctica. The pathogen reservoirs are artiodactyls like sheep and cattle, but also cats, dogs, and wild animals. The transmission mostly occurs \textit{via inhalation of contaminated dusts}. Only in exceptional cases, human-to-human transmission occurs.

At-risk populations are primarily individuals with occupational exposure, like butchers, fur processors, and veterinarians. Even a minor dose of ten bacteria can lead to contagion.

After an incubation time of two to four weeks, symptoms like high fever, shivering, muscles aches, and severe headaches occur in 50 \% of the cases. Primary infection can be asymptomatic in a large number of patients Also \textit{interstitial pneumonia} and \textit{hepatitis} are potential complications. X-ray images of Q fever pneumonia (lower image) compared to the normal state (upper image) look like this:
In roughly one percent of the diseased, chronic infection with Q fever endocarditis occurs. Especially patients with cardiac valvular defects, cardiac valve prostheses, or immunosuppressed are predisposed. After an infection, there is long-lasting immunity; however, during pregnancy or with a weakened immune system, the bacteria can be reactivated as they can survive in macrophages.

Observational studies have shown association of C. burnetii infection with long term syndromes like atherosclerosis, chronic fatigue syndrome and lymphoma.

**Treatment of Q Fever**

For the treatment of Q fever, antibiotics that act intracellular, like tetracyclines and macrolide antibiotics, are used. In chronic cases, long-term
antibiotic treatment for up to four years can be necessary. Hydroxychloroquine along with doxycycline is indicated in endocarditis. A whole cell inactivated vaccine is available and has been used in occupational workers in Australia, and during the epidemic in Netherlands.

**Detection of Coxiella Burnetii**

When patients present with fever of uncertain genesis and atypical pneumonia, Q fever should be considered as a possibility.

In the acute stage of the inflammation, tests mostly reveal antibodies against the phase-II-antigens. The detection of phase-I-antibodies suggests a chronic course. However, cross-reactions with *Chlamydia pneumoniae* and Bartonella spp. have to be considered.

Using immunofluorescence and electron microscopy, pathogens can also be directly detected in biopsy material. Laboratory tests must be performed in S3 laboratories. Detection of *C. burnetii* DNA by PCR is also used to diagnose infection. The direct and indirect pathogen detection has to be reported to authorities.

**Hemophilus**

The species Hemophilus consists of gram-negative, facultative anaerobic and capnophilic immobile rod-shaped bacteria. They have a characteristic need for growth factors hemin and NAD or NADP. These factors are released from erythrocytes through heat, which is why hemophilus is typically cultivated in boiled blood agar. *Haemophilus influenzae* is a commensal of the human nasopharynx which can cause various diseases of the upper respiratory tract such as pneumonia, otitis media and bronchitis.

**Infections with Hemophilus Influenza**

Non-encapsulated stocks of these bacteria cause infections of the respiratory tract; encapsulated stocks cause systemic infections like sepsis, purulent meningitis, and epiglottitis. This polysaccharide capsule inhibits phagocytosis. Since during the growth process, the substance of the capsule is released into the surroundings, it can be used for diagnostics.

The most dangerous capsule type is B as it can cause sepsis and meningitis. Also, some stocks of *HiB* have IgAse, which cleaves IgA-antibodies and thus inhibits the local immune system, e.g., in the respiratory tract. The portion of penicillinase-producing stocks also grows. As Hib conjugate vaccines are widely used, most infections are now caused by Hia strain.

Infections with non-encapsulated stocks usually have endogenous origins since roughly 80% of the population are asymptomatic carriers. *H. influenzae* can primarily be found in the pharyngeal epithelium.

**Capsulated stocks**, on the other hand, are transmitted by droplets. The symptoms of such an infection include inflammation of paranasal sinus, bronchitis, and meningitis. Even with appropriate antibiotics, the mortality of hemophilus meningitis is more than five percent. If the disease does heal up, neurological defects like hearing damage or mental disorders remain in most cases.

Further complications are sudden-onset epiglottitis with risk of suffocation, pleuritis, and sepsis. The only effective prophylaxis is vaccination against the most dangerous capsule type B beginning in the second month of life.
Infections with Haemophilus Ducreyi

Especially in tropical African, South Asian, and South American regions, this pathogen is widely spread. After contamination through sexual intercourse, rotund ulcers develop in the area of the labia, the glans, and the penis shaft, which are called *ulcus molle* or chancroid.

These ulcers are extremely painful. Also, there is a swelling in the inguinal lymph nodes, called *bubo*.

As differential diagnosis, *syphilis* has to be considered.

STIs with H. Ducreyi are on decline, and it is now emerging as a pathogen responsible for chronic limb ulceration that is similar to yaws.

**Therapy of infections with haemophilus**

Typically, ulcus molle can be easily treated with a single intramuscular injection of *ceftriaxone*. However, the treatment of an infection with hemophilus influenzae should include administration of *amoxicillin* and *clavulanic acid* or *moxifloxacin*.

**Detection of Hemophilus**

Possible materials for cultivation are *sputum*, blood, and *cerebrospinal fluid*. The optimal cultivation is in boiled blood. Hemophilus can grow in the hemolytic zone of *Staphylococcus aureus* (satellite phenomenon) since S. aureus produces NAD. The colonies are smooth, slightly translucent, and have a characteristically salty smell – some say it smells like sperm.

**Further Pathogenic Species of Hemophilus**

*Hemophilus aegyptus*, which is primarily spread in North Africa, is the pathogen of *purulent conjunctivitis*. Another human-pathogenic bacterium is *Hemophilus parainfluenza*, which can be in rare cases the pathogen of *endocarditis*. 
Leptospira

Characteristics of Leptospira

Leptospira (Greek: ‘leptos’ for thin and ‘spira’ for curl) are very thin and long bacteria that are helicoidally wound in the middle.

Their ends are thick so that in a scanning electron microscope image, they resemble a cane. By rotating around its own axis, leptospira can move actively.

They are obligatorily aerobic, do not form spores, and are katalase-positive.

Infections with Leptospira Interrogans

Leptospirosis is a potentially fatal zoonosis endemic in many tropical regions and causes large epidemics after heavy rainfall and flooding.

Interrogans is the most important pathogen of leptospirosis. Natural hosts are mainly rats and mice, but also swine and cattle. They are transmitted through contact with urine, blood, or tissue of infected animals.

The serovar L. interrogans icterohaemorrhagiae is the cause of the most common leptospirosis called Weil disease. Other serovars with similar clinical presentation are L. interrogans australis (sugar cane fever) and L. interrogans Pomona (swineherder’s disease).

About 90% of the infections have a mild process with flu-like symptoms. Severe processes are accompanied by liver and kidney failure. Higher mortality is seen in patients older than 60 years of age.

Detection of Leptospira

The generation time of leptospira is roughly ten hours. As comparison, the generation time of E. coli is twenty minutes. Thus, cultivation takes relatively long. In bouillons, leptospira typically grow in a flat disc one to three centimeters below the surface of the culture medium.

In contrast to most other bacteria, microscopy of leptospira is only possible via dark-field or phase contrast microscopy. However, most important is serology with the detection of IgM and IgG antibodies.

Treatment of Leptospirosis

The medication of choice is penicillin. However, there is-as with other spirochaete bacteria-the risk of a Jarisch-Herxheimer reaction. In the second stage of the disease, the immune reaction dominates, which is why only symptomatic treatment should be performed at this point. Leptospires are susceptible to β-lactams, macrolides, tetracyclines, fluoroquinolones, and streptomycin.

Rickettsia

Characteristics of Rickettsia
Rickettsias are obligatory cell parasites, whereby they escape the immune system of the host. In order to reach the host cells, the rOmpB protein of the rickettsia binds to the KU70 protein of the eukaryotic cell.

Proliferation also takes place in the cytoplasm of the host cell. The release occurs through exocytosis or lysis.

These bacteria are pleomorphic, non-sporogenic, and of special interest for researchers since the genome of rickettsia is very similar to that of mitochondria. Thus, they corroborate the endosymbiotic theory.

**Infections with Rickettsia**

Generally, human-pathogenic rickettsias are divided into three groups. They are either pathogens of the tick bite fever, the spotted fever, or of the Tsutsugamushi fever.

These are the pathogens of the tick bite fever:

<table>
<thead>
<tr>
<th>Pathogen:</th>
<th>Disease:</th>
<th>Occurrence:</th>
</tr>
</thead>
<tbody>
<tr>
<td>R. rickettsia</td>
<td>Rocky Mountain fever</td>
<td>Western Hemisphere</td>
</tr>
<tr>
<td>R. africae</td>
<td>African tick bite fever</td>
<td>Africa</td>
</tr>
<tr>
<td>R. sibirica</td>
<td>Siberian tick bite fever</td>
<td>Siberia</td>
</tr>
<tr>
<td>R. conorii</td>
<td>Boutonneuse fever</td>
<td>Mediterranean countries</td>
</tr>
<tr>
<td>R. japonica</td>
<td>Japanese spotted fever</td>
<td>Japan</td>
</tr>
</tbody>
</table>

The pathogen of spotted fever is *R. prowazekii* and *orienta tsutsugamushi* is the actuator of *Tsutsugamushi fever*. Vectors are ticks, fleas, mites, and lice.

**Rocky Mountain Fever**

After a few days, fever, headaches, nausea, and diarrhea occur. Approximately one week after the first symptoms, a typical skin rash consisting of elevated, violet, non-itching maculae appears. These maculae actually are petechiae.

Complications can affect the lung and the kidneys.

**Spotted Fever**

The incubation time of spotted fever amounts to roughly 10 - 14 days. The first symptoms are shivering, fever, and clouded awareness. Later, petechial bleedings occur, which give the disease its name.

**Tsutsugamushi Disease**
This disease is spread in Southwest Asia and presents with a severely manifested exanthema. If the disease takes a severe course, it can lead to encephalitis, as do other rickettsioses.

**Detection of Rickettsia**

Since rickettsias are intracellular parasites, cultivation is only possible on living cells and chicken embryo cultures. Antibody detection is also possible serologically since the serum of a patient containing rickettsia antibodies cross reacts with Proteus-OX19. This is called Weil-Felix reaction.

Spotted fever belongs to the reportable diseases.

**Treatment of Rickettsioses**

Roughly five percent of all rickettsioses end lethally. Immediate treatment with intracellularly efficient antibiotics like doxycycline is crucial, even if only a clinical suspicion exists.

**Ehrlichia**

Ehrlichia belong to the rickettsiales and have similar characteristics. They also are intracellular parasites and are transmitted to humans via ticks. In the host, they persist in monocytes and granulocytes. The infection mostly takes a bland course; in rare cases, symptoms resembling the Rocky Mountain spotted fever can occur.

**Chlamydia**

**Characteristics of Chlamydia**

Chlamydia are very small gram-negative bacteria, which live obligatorily intracellular. Vegetative forms are called reticulate bodies, the infectious ones are called elementary bodies.
Elementary bodies are relatively resistant against environmental influences and can survive outside the host organism for some time. The reticulate bodies destroy the host cell after proliferation via lysis and are thereby released.

Current findings state that there is a third form: the **aberrant bodies**. They are considered an outlasting form for unfavorable conditions since their metabolism is extremely reduced. Presumably, they are the actuators of **reactive arthritis**.

### Detection of Chlamydia

Due to their parasitic metabolism, a culture of chlamydia is only possible on living cells. Suitable are **Hela cells** (human cells from the **Cervix-Ca** of a patient) but also **McCoy cells**.

Serologically, chlamydia can be detected via **immunofluorescence** with marked antibodies due to the **lipopolysaccharides** on their cell wall. It looks like this:
Clinically, the detection of chlamydia-antibodies using **ELISA** is very common.

Much more specific than the above mentioned tests are molecular biological methods like **PCR**. The WHO reports a specificity of 99.2 – 99.8 % for **Chlamydia trachomatis**.

The differentiation between chlamydia and chlamydophila species can be achieved with **Lugol’s solution**. This iodine potassium-iodide solution detects the glycogen that is only produced by chlamydia.

**Infections with Chlamydophila**

**C. Pneumoniae**

This species is almost exclusively present in humans. Transmission is typically **aerogenic**. In immunocompetent individuals, the infection is symptom-free or triggers **pharyngitis**. After four to six weeks, **post-infectious arthritis** and **tendinopathies** can occur.

In immunosuppressed persons, Chlamydophila pneumonia is a frequent pathogen for lung inflammations. On x-ray images of the lung, a small-spotted, untypical infiltration can be seen. Treatment includes administration of **clarithromycin** or doxycycline. The level of endemic infection is considered to reach up to 70 %.

Since C. pneumonia can outlast in the body for a long time in the form of reticulate bodies, these bacteria are associated with arthritis and arteriosclerosis. Studies prove that the **antibody-titers** in patients with coronary diseases are higher than in the rest of the population.

**C. Psittaci**

The clinical picture caused by this bacterium is referred to as **ornithosis** or parrot disease. As the name suggests, birds like parrots, pigeons, or seagulls are the reservoir of C. psittaci. Transmission occurs through the inhalation of the infectious dust of feces.

The primary proliferation of chlamydophila takes place in the **ciliated epithelium** of the
respiratory tract. Subsequently, secondary proliferation and bacteremia occur in the reticulo-endothelial system, for instance, the spleen and the liver. Therefore, possible findings include hepato- and splenomegaly. In the lung, the infection leads to atypical pneumonia with interstitial edema and necrosis of the alveolar walls.

Usually, the diagnosis is made in exposed people based on the clinical picture. Endangered occupational groups are, for example, people who work in poultry farming.

Cultivation of Chlamydia psittaci must only be done in laboratories of protection level 3. It is a reportable disease. As with C. pneumoniae, treatment consists of tetracyclines.

### Infections with Chlamydia Trachomatis

There are several serotypes of Chlamydia trachomatis, which are divided into three groups according to the diseases they cause:

<table>
<thead>
<tr>
<th>Serotype:</th>
<th>Disease:</th>
<th>Transmission:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serovar A - C</td>
<td>Trachoma: severe conjunctivitis, often leads to blindness</td>
<td>Poor hygiene</td>
</tr>
<tr>
<td>Serovar D - K</td>
<td>Genital chlamydiosis, conjunctivitis, paratrachoma (swimming pool conjunctivitis), pneumonia in newborns, late sequel: reactive arthritis</td>
<td>Sexual intercourse; perinatally; contaminated water (e.g., in whirlpools)</td>
</tr>
<tr>
<td>Serovar L1 - L3</td>
<td>Lymphogranuloma venerum</td>
<td>Sexual intercourse</td>
</tr>
</tbody>
</table>

### Trachoma

Trachoma caused by the serotypes A - C is primarily spread in tropical countries. Transmission occurs through shared contact with towels, the direct contact of mucosae, and via flies.

After an incubation time of about five days, bilateral conjunctivitis develops. After some time, a yellow-whitish lymph follicle forms in the conjunctiva of the upper eyelid. The swelling of the upper eyelid leads to ptosis trachomatosa. Due to scarring, an entropium forms that causes friction on the cornea at every blinking of the eye, which in turn leads to infection and scarring of the cornea. If this condition is left untreated, it often results in blindness.

The WHO has summarized four measures for elimination of trachoma with the acronym 'SAFE'. It stands for: Surgery, Antibiotics, Facial cleanliness, and Environmental improvement.

### Urogenital Infections with Chlamydia

Genital chlamydia is the most common bacterial sexually transmitted infection in developed countries with majority of infections affecting young adults.

The Robert Koch Institute (Germany) assumes a level of endemic infection of approximately 4.5 % of the population. In women, the infection ascends from the urethra to the fallopian tubes. Such a salpingitis can make the fallopian tubes agglutinate due to scarring, which can lead to sterility or extrauterine gravidities.

Proliferation in the small pelvis is called pelvic inflammatory disease, which is accompanied by chronic pain. In the Fitz-Hugh-Curtis syndrome, the chlamydiae cause a perihepatitis, which is accompanied with liver capsule pain and increased levels of
transaminases.

Typical infections in men are **prostatitis** and **epididymitis**-which can also lead to sterility.

The **paratrachoma** (inclusion body conjunctivitis) is also caused by the serotypes D – K; this conjunctivitis includes purulence production. Transmission often occurs in insufficiently chlorinated swimming pool water.

**Lymphogranuloma Venerum**

![Image: "Follow up of a patient with peliosis hepatis over 7 years with full remission." by Braegel. License: CC BY 2.0](image)

This disease can frequently be found in tropical areas and is characterized by small, painless ulcers at the portal of entry, which regress after roughly two weeks. After that, **lymphadenitis** develops.

This painful lymph node swelling often develops in the groin and lasts for several weeks. Without treatment, obstructions of the lymph drainage pathways can occur over the years, leading to the formation of lymphedema.

Treatment consists of macrolides and tetracyclines and must include both sexual partners.

**Reactive Arthritis**

Reactive arthritis is an immune-mediated inflammation reaction after a primary chlamydia infection of the mucosa. The combination of **urethritis**, **conjunctivitis**, **aseptic arthritis**, and **skin lesions** was formerly known as Reiter’s syndrome.

Nowadays, however, this name should no longer be used because its eponym was Hans Reiter, president of the Reich health department of Nazi Germany and unconditional supporter of the dogma of racial hygiene. The current term is **urethra-oculo-synovial syndrome**.

**Popular Exam Questions on Infectious Diseases with Gram-Negative Pathogens**

Solutions can be found below the references.

1. **In the morning, a three-year-old child is brought to the kindergarten in full health. After the midday nap, the parents receive a phone call that the child**
suddenly exhibits severe salivation and muffled speech. Since after a few minutes, he could hardly breathe, it had to be brought to the hospital immediately. An infection with which pathogen is most likely?

A. Streptococcus pyogenes  
B. Haemophilus influenza B  
C. Corynebacterium diphtheriae  
D. Chlamyphila pneumoniae  
E. Bordetella pertussis

2. Three weeks ago, a 25-year-old man came back from a four-week vacation on a cattle ranch. He now complains about high fever, which is always interrupted by fever-free intervals. He feels very fatigued, and in abdominal sonography, his primary care physician notices a swelling of liver and spleen. Due to increasing deterioration of his overall condition, he is brought to the hospital, where endocarditis is diagnosed. Which pathogen is most likely to cause this condition?

A. Bartonella henselae  
B. Brucella abortus  
C. Brucella melitensis  
D. Burkholderia mallei  
E. Francisella tularensis

3. A 21-year-old man presents in his primary care physician’s practice with dysuric symptoms during urination. He also reports that this is sometimes accompanied by blood and mucous effusion from the urethra. During clinical examination, the physician notices lymphadenitis in both groins. They show blue-reddish discoloration. Which of the following statements concerning the diagnosis and therapy is not true?

A. The most likely pathogen is Chlamydia trachomatis serovar D – K.  
B. The lymph node swelling is a lymphogranuloma venerum.  
C. Treatment should be administration of doxycycline.  
D. In the context of post-exposition prophylaxis, treatment of the sexual partner is also necessary.  
E. In this patient, another typical symptom could be a unilateral epididymitis.

References

Chlamydien-Infektion in Deutschland via rki.de

Correct answers: 1B, 2B, 3A

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