Campylobacter, Helicobacter, Spirillum

■ *Campylobacter*, *Helicobacter*, and *Spirillum* belong to the group of spiral, motile, Gram-negative, microaerophilic bacteria. *C. jejuni* causes a form of enteritis. The sources of infection are diseased animals. The pathogens are transmitted to humans in food. The diseases are sometimes also communicable among humans. The pathogens are identified for diagnostic purposes in stool cultures using special selective mediums. *Helicobacter pylori* contribute to the pathogenesis of type B gastritis and peptic ulcers. *Spirillum minus* causes rat bite fever, known as sodoku in Japan where it is frequent. ■

The genera *Campylobacter*, *Helicobacter*, and *Spirillum* belong to the group of aerobic, microaerophilic, motile, Gram-negative rod bacteria with a helical/vibrioid form (p. 220). Human pathogens are found in all three genera.

Campylobacter

Classification. For several years now, *Campylobacter* bacteria have been classified together with *Arcobacter* (medically insignificant) in the new family *Campylobacteriaceae* (fam. nov.). The genus *Campylobacter* comprises numerous species, among which *C. jejuni* (more rarely *C. coli*, *C. lari*) as well as *C. fetus* have been observed as causative pathogens in human infections.

Morphology and culture. *Campylobacter* are slender, spirally shaped rods 0.2–0.5 μm thick and 0.5–5 μm long. Individual cells may have one spiral winding or several. A single flagellum is attached to either one or both poles.

Campylobacter can, under microaerophilic conditions, and in an atmosphere containing 5% O_2 and 10% CO_2, be cultured on blood agar plates. The optimum proliferation temperature for *C. fetus* is 25 °C and for *C. jejuni* 42 °C.

Pathogenesis and clinical pictures. The details of the pathogenic mechanisms of these pathogens are largely unknown. *C. jejuni* produces an enterotoxin similar to the STa produced by *E. coli* as well as a number of cytotoxins. *C. jejuni* causes a form of enterocolitis with watery, sometimes bloody diarrhea and fever. The incubation period is two to five days. The manifest illness lasts less than one week.

C. fetus has been identified in isolated cases as a pathogen in endocarditis, meningitis, peritonitis, arthritis, cholecystitis, salpingitis, and sepsis in immunocompromised patients.

Diagnosis. To isolate *C. jejuni* in stool cultures, mediums are used containing selective supplements (e.g., various anti-infective agents). The cultures are incubated for 48 hours at 42 °C in a microaerophilic atmosphere. Identification is based on growth requirements as well as detection of catalase and oxidase.

C. fetus is readily isolated in most cases, since it is usually the only organism found in the material (e.g., blood, cerebrospinal fluid, joint punctate, pus, etc.).

Therapy. Severe *Campylobacter* infections are treated with macrolides or 4-quinolones. Resistance is known to occur.

Epidemiology and prevention. *Campylobacter jejuni* is among the most frequent enteritis pathogens worldwide. The bacteria are transmitted from animals to humans via food and drinking water. Direct smear infection transmission among humans is possible, especially in kindergarten or family groups. There are no specific preventive measures.

Helicobacter pylori

Morphology and culture. *H. pylori* are spirally shaped, Gram-negative rods with lophotrichous flagellation. Cultures from stomach biopsies are grown on enriched mediums and selective mediums under microaerobic conditions (90% N_2, 5% CO_2, and 5% O_2) for three to four days. Identification is based on detection of oxidase, catalase, and urease.

Pathogenesis and clinical pictures. *H. pylori* occurs only in humans and is transmitted by the fecal-oral pathway. The pathogen colonizes and infects the stomach mucosa. The pathogenicity factors include pronounced motility for efficient target cell searching, adhesion to the surface epithelial cells of the stomach, urease that releases ammonia from urea to facilitate survival of the cells in a highly acidic environment and a vacuolizing cytotoxin (VacA) that destroys epithelial cells.

Once the pathogen has infected the stomach tissues an acute gastritis results, the course of which may or may not involve overt symptoms. Potential sequelae include:

1. Mild chronic gastritis type B that may persist for years or even decades and is often asymptomatic.
2. Duodenal ulceration, sometimes gastric ulceration as well.
3. Chronic atrophic gastritis from which a gastric adenocarcinoma sometimes develops.
4. Rarely B cell lymphomas of the gastric mucosa (MALTomas).

Diagnosis. Histopathological, cultural and, molecular identification of the bacteria in stomach lining biopsies. A noninvasive breath test involving ingestion of ^{13}C-labeled urea and measurement of $^{13}CO_2$ in the expelled air. Antigen detection in stool. Antibodies can be identified with an ELISA or Western blotting.

Therapy. In patients with ulcers and/or gastritis symptoms, a triple combination therapy with omeprazole (proton pump blocker), metronidazole, and clarithromycin lasting seven days is successful in 90% of cases.

Epidemiology. Based on seroepidemiological studies we know that *H. pylori* occur worldwide. Generalized contamination of the population begins in childhood and may reach 100% in adults in areas with poor hygiene. The contamination level is about 50% among older adults in industrialized countries. Transmission is by the fecal-oral route.

Spirillum minus

This species is a motile bacterium only 0.2 μm thick and 3–5 μm long with two to three spiral windings. It cannot be grown on culture mediums. *S. minus* causes spirillary rat bite fever, also known as sodoku. This disease occurs worldwide, with a high level of incidence in Japan. The organism is transmitted to humans by the bites of rats, mice, squirrels, and domestic animals that eat rodents. Following an incubation period of seven to 21 days a febrile condition develops with lymphangitis and lymphadenitis. Ulcerous lesions develop at the portal of entry. Diagnosis can be done by using dark field or phase contrast microscopy to detect the spirilla in blood or ulcerous material. Penicillin G is used to treat the infection.

Pseudomonas, Stenotrophomonas, Burkholderia

■ Pseudomonads are Gram-negative, aerobic, rod-shaped bacteria with widespread occurrence in nature, especially in damp biotopes. The most important species from a medical point of view is *Pseudomonas aeruginosa*. Free O_2 is required as a terminal electron acceptor to grow the organism in cultures. The pathogenesis of *Pseudomonas* infections is complex. The organism can use its attachment pili to adhere to host cells. The relevant virulence factors are: exotoxin A, exoenzyme S, cytotoxin, various metal proteases, and two types of phospholipase C. Of course, the lipopolysaccharide of the outer membrane also plays an important role in the pathogenesis. *Pseudomonas* infections occur only in patients with weakened immune defense systems,

notably pneumonias in cystic fibrosis, colonization of burn wounds, endocarditis in drug addicts, postoperative wound infection, urinary tract infection, sepsis. *P. aeruginosa* frequently contributes to nosocomial infections. Diagnosis requires identification of the pathogen in cultures. Multiple resistance to anti-infective agents presents a therapeutic problem.

Numerous other *Pseudomonas* species and the species of the genera *Burkholderia* and *Stenotrophomonas* are occasionally found in pathogenic roles in immunosuppressed patients. *B. mallei* causes malleus (glanders) and *B. pseudomallei* causes melioidosis.

Pseudomonas aeruginosa

Occurrence, significance. All pseudomonads are widespread in nature. They are regularly found in soils, surface water, including the ocean, on plants and, in small numbers, in human and animal intestines. They can proliferate in a moist milieu containing only traces of nutrient substances. The most important species in this group from a medical point of view is *P. aeruginosa*, which causes infections in person with immune defects.

Morphology and culture. *P. aeruginosa* are plump, 2–4 μm long rods with one to several polar flagella. Some strains can produce a viscous extracellular slime layer. These mucoid strains are frequently isolated in material from cystic fibrosis patients. *P. aeruginosa* possesses an outer membrane as part of its cell wall. The architecture of this membrane is responsible for the natural resistance of this bacterium to many antibiotics.

P. aeruginosa can only be grown in culture mediums containing free O_2 as a terminal electron acceptor. In nutrient broth, the organism therefore grows at the surface to form a so-called pellicle. Colonies on nutrient agar often have a metallic sheen (*P. aeruginosa*; Latin: aes = metal ore). Given suitable conditions, *P. aeruginosa* can produce two pigments, i.e., both yellow-green fluorescein and blue-green pyocyanin.

Pathogenesis and clinical pictures. The pathomechanisms involved are highly complex. *P. aeruginosa* usually enters body tissues through injuries. It attaches to tissue cells using specific attachment fimbriae. The most important virulence factor is exotoxin A (ADP ribosyl transferase), which blocks translation in protein synthesis by inactivating the elongation factor eEF2. The exoenzyme S (also an ADP ribosyl transferase) inactivates cytoskeletal proteins and GTP-binding proteins in eukaryotic cells. The so-called cytotoxin damages cells by creating transmembrane pores. Various different metalloproteases hydrolyze elastin, collagen, or laminin. Two type C phospholipases show membrane activity. Despite these pathogenic determinants, infections

are rare in immunocompetent individuals. Defective nonspecific and specific immune defenses are preconditions for clinically manifest infections. Patients suffering from a neutropenia are at high risk. The main infections are pneumonias in cystic fibrosis or in patients on respiratory equipment, infections of burn wounds, postoperative wound infections, chronic pyelonephritis, endocarditis in drug addicts, sepsis, and malignant otitis externa. *P. aeruginosa* frequently causes nosocomial infections (see p. 343).

Diagnosis. Laboratory diagnosis includes isolation of the pathogen from relevant materials and its identification based on a specific pattern of metabolic properties.

Therapy. The antibiotics that can be used to treat *P. aeruginosa* infections are aminoglycosides, acylureidopenicillins, carboxylpenicillins, group 3b cephalosporins (see p. 190), and carbapenems. Combination of an aminoglycoside with a betalactam is indicated in severe infections. Susceptibility tests are necessary due to frequent resistance.

Epidemiology and prevention. Except in cystic fibrosis, *P. aeruginosa* is mainly a hospital problem. Since this ubiquitous organism can proliferate under the sparest of conditions in a moist milieu, a number of sources of infection are possible: sinks, toilets, cosmetics, vaporizers, inhalers, respirators, anesthesiology equipment, dialysis equipment, etc. Infected patients and staff carrying the organism are also potential primary sources of infection. Neutropenic patients are particularly susceptible. Preventive measures i.e., above all disinfection and clinical hygiene, concentrate on avoiding exposure.

Other Pseudomonas species, Stenotrophomonas and Burkholderia

Opportunistic pseudomonads. Other *Pseudomonas* species besides *P. aeruginosa* are capable of causing infections in immunosuppressed patients. These nosocomial infections are, however, infrequent. It would therefore not be particularly useful here to list all of the species that occasionally come to the attention of physicians. Classic opportunists also include *Stenotrophomonas maltophilia* (formerly *Xanthomonas maltophilia*) and *Burkholderia cepacia* (formerly *Pseudomonas cepacia*). These species all occur in hospitals and frequently show resistance to anti-infective agents. Antibiotic therapy must therefore always be based on a resistance test.

Burkholderia mallei. This species is the causative organism in malleus or glanders, a disease of solipeds. The bacteria invade the human organism through microtraumata, e.g., in the skin or mucosa, and form local ulcers. Starting from these primary infection foci they can move to other organs,

either lymphogenously or hematogenously, and cause secondary abscesses there. Malleus no longer occurs in Europe.

Burkholderia pseudomallei. This species is the causative organism in melioidosis, a disease of animals and humans resembling malleus. The natural reservoirs of *B. pseudomallei* are soil and surface water. The pathogen invades the body through injuries of the skin or mucosa and causes multiple subcutaneous and subserous abscesses and granulomas. Starting from primary foci, the infection can disseminate and cause abscesses in a number of different organs. This disease is observed mainly in Asia.

Legionella (Legionnaire's Disease)

Legionella is the only genus in the family *Legionellaceae*. The species *Legionella pneumophila* is responsible for most legionelloses in humans. Legionellae are difficult to stain. They are Gram-negative, aerobic rod bacteria. Special mediums must be used to grow them in cultures. Infections with *Legionella* occur when droplets containing the pathogens are inhaled. Two clinically distinct forms are on record: legionnaire's disease leading to a multifocal pneumonia and nonpneumonic legionellosis or Pontiac fever. The persons most likely to contract legionnaire's disease are those with a primary cardiopulmonary disease and generally weakened immune defenses. Laboratory diagnostic methods include microscopy with direct immunofluorescence, culturing on special mediums and antibody assays. The antibiotics of choice are the macrolides. The natural habitat of legionellae is damp biotopes. The sources of infection listed in the literature include hot and cold water supply systems, cooling towers, moisturizing units in air conditioners, and whirlpool baths. Legionelloses can occur both sporadically and in epidemics.

Classification. *Legionella* bacteria were discovered in 1976, occasioned by an epidemic among those attending a conference of American Legionnaires (former professional soldiers). They are now classified in the family *Legionellaceae*, which to date comprises only the genus *Legionella*. This genus contains numerous species not listed here. Most human infections are caused by *L. pneumophila*, which species is subdivided into 12 serogroups. Human infections are caused mainly by serogroup 1.

Morphology and culture. *L. pneumophila* is a rod bacterium 0.3–1 μm wide and 2–20 μm long. Its cell wall structure is of the Gram-negative type, but gram staining hardly "takes" with these bacteria at all. They can be rendered visible by means of direct immunofluorescence.

Legionella grow only on special mediums in an atmosphere containing 5% CO_2.

Pathogenesis and clinical picture. The pathomechanisms employed by legionellae are not yet fully clarified. These organisms are facultative intracellular bacteria that can survive in professional phagocytes and in alveolar macrophages. They are capable of preventing the phagosome from fusing with lysosomes. They also produce a toxin that blocks the oxidative burst.

Two clinical forms of legionellosis have been described:

- **Legionnaire's disease.** Infection results from inhalation of droplets containing the pathogens. The incubation period is two to 10 days. The clinical picture is characterized by a multifocal, sometimes necrotizing pneumonia. Occurrence is more likely in patients with cardiopulmonary primary diseases or other immunocompromising conditions. Lethality >20%.

- **Pontiac fever.** Named after an epidemic in Michigan. Incubation period one to two days. Nonpneumonic, febrile infection. Self-limiting. Rare.

Diagnosis. Specific antibodies marked with fluorescein are used to detect the pathogens in material from the lower respiratory tract. For cultures, special culture mediums must be used containing selective supplements to exclude contaminants. The mediums must be incubated for three to five days. *Legionella* antigen can be identified in urine with an EIA. A gene probe can also be used for direct detection of the nucleic acid (rDNA) specific to the genus *Legionella* in the material. Antibodies can be assessed using the indirect immunofluorescence technique.

Therapy. Macrolide antibiotics are now the agent of choice, having demonstrated clinical efficacy. Alternatively, 4-quinolones can be used.

Epidemiology and prevention. Legionellosis can occur in epidemic form or in sporadic infections. It is estimated that one third of all pneumonias requiring hospitalization are legionelloses. Soil and damp biotopes are the natural habitat of *Legionella*. Sources of infection include hot and cold water supply systems, cooling towers, air moisturizing units in air conditioners, and whirlpool baths. Human-to-human transmission has not been confirmed. *Legionella* bacteria tolerate water temperatures as high as 50 °C and are not killed until the water is briefly heated to 70 °C.

Brucella, Bordetella, Francisella

The genera *Brucella*, *Bordetella*, and *Francisella* are small, coccoid, Gram-negative rods. They can be cultured under strict aerobic conditions on enriched nutrient mediums.

Brucella abortus, *B. melitensis*, and *B. suis* cause **brucellosis**, a classic zoonosis that affects cattle, goats, and pigs. The pathogens can be transmitted to humans directly from diseased animals or indirectly in food. They cause characteristic granulomas in the organs of the RES. The primary clinical symptom is the undulant fever. Diagnosis is by means of pathogen identification or antibody assay using a standardized agglutination reaction.

Bordetella pertussis is the causative organism of **whooping cough**, which affects only humans. The pathogens are transmitted by aerosol droplets. The organism is not characterized by specific invasive properties, although it is able to cause epithelial and subepithelial necroses in the mucosa of the lower respiratory tract. The catarrhal phase, paroxysmal phase, and convalescent phase characterize the clinical picture of whooping cough (pertussis), which is usually diagnosed clinically. During the catarrhal and early paroxysmal phases, the pathogens can be cultured from nasopharyngeal secretions. The most important prophylactic measure is the vaccination in the first year of life.

Francisella tularensis causes **tularemia**. This disease, rare in Europe, affects wild rodents and can be transmitted to humans by direct contact, by arthropod vectors, and by dust particles.

Brucella (Brucellosis, Bang's Disease)

Occurrence and classification. The genus *Brucella* includes three medically relevant species—*B. abortus*, *B. melitensis*, and *B. suis*—besides a number of others. These three species are the causative organisms of classic zoonoses in livestock and wild animals, specifically in cattle (*B. abortus*), goats (*B. melitensis*), and pigs (*B. suis*). These bacteria can also be transmitted from diseased animals to humans, causing a uniform clinical picture, so-called undulant fever or Bang's disease.

Morphology and culture. Brucellae are slight, coccoid, Gram-negative rods with no flagella.

They only reproduce aerobically. In the initial isolation the atmosphere must contain 5–10% CO_2. Enriched mediums such as blood agar are required to grow them in cultures.

Pathogenesis and clinical picture. Human brucellosis infections result from direct contact with diseased animals or indirectly by way of contaminated foods, in particular unpasteurized milk and dairy products. The bacteria invade the body either through the mucosa of the upper intestinal and respiratory tracts or through lesions in the skin, then enter the subserosa or subcutis. From there they are transported by microphages or macrophages, in which they can survive, to the lymph nodes, where a lymphadenitis develops. The pathogens then disseminate from the affected lymph nodes, at first lymphogenously and then hematogenously, finally reaching the liver, spleen, bone marrow, and other RES tissues, in the cells of which they can survive and even multiply. The granulomas typical of intracellular bacteria develop. From these inflammatory foci, the brucellae can enter the bloodstream intermittently, each time causing one of the typical febrile episodes, which usually occur in the evening and are accompanied by chills. The incubation period is one to four weeks. *B. melitensis* infections are characterized by more severe clinical symptoms than the other brucelloses.

Diagnosis. This is best achieved by isolating the pathogen from blood or biopsies in cultures, which must be incubated for up to four weeks. The laboratory must therefore be informed of the tentative diagnosis. Brucellae are identified based on various metabolic properties and the presence of surface antigens, which are detected using a polyvalent *Brucella*-antiserum in a slide agglutination reaction. Special laboratories are also equipped to differentiate the three *Brucella* species.

Antibody detection is done using the agglutination reaction according to Gruber-Widal in a standardized method. In doubtful cases, the complement-binding reaction and direct Coombs test can be applied to obtain a serological diagnosis.

Therapy. Doxycycline is administered in the acute phase, often in combination with gentamicin. A therapeutic alternative is cotrimoxazole. The antibiotic regimen must be continued for three to four weeks.

Epidemiology and prevention. Brucellosis is a zoonosis that affects animals all over the world. Infections with *B. melitensis* occur most frequently in Mediterranean countries, in Latin America, and in Asia. The *melitensis* brucelloses seen in Europe are either caused by milk products imported from these countries or occur in travelers. *B. abortus* infections used to be frequent in central Europe, but the disease has now practically disappeared there thanks to the elimination of *Brucella*-infested cattle herds. Although control of brucellosis infections focuses on prevention of exposure to the pathogen, it is not necessary to isolate infected persons since the infection is not communicable between humans. There is no vaccine.

Bordetella (Whooping Cough, Pertussis)

The genus *Bordetella*, among others, includes the species *B. pertussis*, *B. parapertussis*, and *B. bronchiseptica*. Of the three, the pathogen responsible for whooping cough, *B. pertussis*, is of greatest concern for humans. The other two species are occasionally observed as human pathogens in lower respiratory tract infections.

Morphology and culture. *B. pertussis* bacteria are small, coccoid, nonmotile, Gram-negative rods that can be grown aerobically on special culture mediums at 37 °C for three to four days.

Pathogenesis. Pertussis bacteria are transmitted by aerosol droplets. They are able to attach themselves to the cells of the ciliated epithelium in the bronchi. They rarely invade the epithelium. The infection results in (sub-) epithelial inflammations and necroses.

Pathogenicity Factors of *Bordetella pertussis*

- **Adhesion factors.** The two most important factors are filamentous hemagglutin (FHA) and pertussis toxin (Ptx). The latter can function both as an exotoxin and as an adhesin. The pathogenic cells attach themselves to the epithelial cilia.
- **Exotoxins.** Pertussis toxin: AB toxin (see p. 16); the A component is an ADP-ribosyl transferase; mechanism of action via G_s proteins (as with cholera toxin A1); increased amount of cAMP in target cells, with a variety of effects depending on the type of cell affected by the toxin.

  Invasive adenylate cyclase: AB toxin; A enters cells, acts in addition to pertussis toxin to increase levels of cAMP.
- **Endotoxins.** Tracheal cytotoxin: murein fragment; kills ciliated epithelial cells. Lipopolysaccharide: stimulates cytokine production; activates complement by the alternative pathway.

Clinical picture. The onset of whooping cough (pertussis) develops after an incubation period of about 10–14 days with an uncharacteristic catarrhal phase lasting 1–2 weeks, followed by the two to three week-long paroxysmal phase with typical convulsive coughing spells. Then comes the convalescent phase, which can last for several weeks. Frequent complications, especially in infants, include secondary pneumonias caused by pneumococci or *Haemophilus*, which are able to penetrate readily through the damaged mucosa, and otitis media. Encephalopathy develops as a delayed complication in a small number of cases (0.4%), whereby the pathomechanism has not yet been clarified. The lethality level for pertussis during the first year of life is approximately 1–2%. The infection confers a stable immunity. Adults

who were vaccinated as children have little or no residual immunity and often present atypical pertussis.

Diagnosis. The pathogen can only be isolated and identified during the catarrhal and early paroxysmal phases. Specimen material is taken from the nasopharynx through the nose using a special swabbing technique. A special medium is then carefully inoculated or the specimen is transported to the laboratory using a suitable transport medium. *B. pertussis* can also be identified in nasopharyngeal secretion using the direct immunofluorescence technique. Cultures must be aerobically incubated for three to four days. Antibodies cannot be detected by EIA until two weeks after onset at the earliest. Only a seroconversion is conclusive.

Therapy. Antibiotic treatment can only be expected to be effective during the catarrhal and early paroxysmal phases before the virulence factors are bound to the corresponding cell receptors. Macrolides are the agents of choice.

Epidemiology and prevention. Pertussis occurs worldwide. Humans are the only hosts. Sources of infection are infected persons during the catarrhal phase, who cough out the pathogens in droplets. There are no healthy carriers.

The most important preventive measure is the active vaccination (see vaccination schedule, p. 33). Although a whole-cell vaccine is available, various acellular vaccines are now preferred.

Francisella tularensis (Tularemia)

F. tularensis bacteria are coccoid, nonmotile, Gram-negative, aerobic rods. They cause a disease similar to plague in numerous animal species, above all in rodents. Humans are infected by contact with diseased animals or ectoparasites or dust. The pathogens invade the host either through microtraumata in the skin or through the mucosa. An ulcerous lesion develops at the portal of entry that also affects the local lymph nodes (ulceroglandular, glandular, or oculoglandular form). Via lymphogenous and hematogenous dissemination the pathogens then spread to parenchymatous organs, in particular RES organs such as the spleen and liver. Small granulomas develop, which develop central caseation or purulent abscesses. In pneumonic tularemia, as few as 50 CFU cause disease. The incubation period is three to four days. Diagnostic procedures aim to isolate and identify the pathogen in cultures and under the microscope. Agglutinating antibodies can be detected beginning with the second week. A seroconversion is the confirming factor. Antibiosis is carried out with streptomycin or gentamicin.

Gram-Negative Anaerobes

The obligate anaerobic, Gram-negative, pleomorphic rods are components of the normal mucosal flora of the respiratory, intestinal, and genital tracts. Among the many genera, *Bacteroides*, *Prevotella*, *Porphyromonas*, and *Fusobacterium*, each of which comprises numerous species, are of medical significance. They cause endogenous necrotic infections with subacute to chronic courses in the CNS, head, lungs, abdomen, and female genitals. A typical characteristic of such infections is that a mixed flora including anaerobes as well as aerobes is almost always found to be causative. Laboratory diagnostic procedures seek to identify the pathogens. Special transport vessels are required to transport specimens to the laboratory. Identification is based on morphological and physiological characteristics. A special technique is GC organic acid assay. Potentially effective antibiotics include certain penicillins and cephalosporins, clindamycin, and metronidazole.

Occurrence. These bacteria include a large and heterogeneous group of Gram-negative, nonsporing, obligate anaerobe rods, many of which are components of the normal human mucosal flora.

Their numbers are particularly large in the intestinal tract, where they are found 1000× as frequently as *Enterobacteriaceae*. They also occur regularly in the oral cavity, upper respiratory tract, and female genitals.

Classification. The taxonomy and nomenclature has changed considerably in recent years. The families *Bacteroidaceae, Prevotellaceae* (nov. fam.), *Porphyromonadaceae* (nov. fam.), and *Fusobacteriaceae* (nov. fam.) include significant human pathogens (Table 4.**11**).

Morphology and culture. The Gram-negative anaerobes show a pronounced pleomorphy; they are straight or curved, in most cases nonmotile, Gram-negative rods. Fusobacteria often take on gram staining irregularly and frequently feature pointed poles (Fig. 4.**22**).

Culture growth is only achieved under stringent anaerobic conditions. Some species are so sensitive to oxygen that the entire culturing procedure must be carried out in an anaerobic chamber (controlled atmosphere glove box). Anaerobes proliferate more slowly than aerobes, so the cultures must be incubated for two days or more.

Pathogenesis and clinical pictures. Infections with Gram-negative anaerobes participation are almost exclusively endogenous infections. The organisms show low levels of pathogenicity. They therefore are not found to feature any spectacular pathogenicity factors like clostridial toxins. Some have a capsule to protect them from phagocytosis. Some produce various enzymes that

Mixed Anaerobic Flora

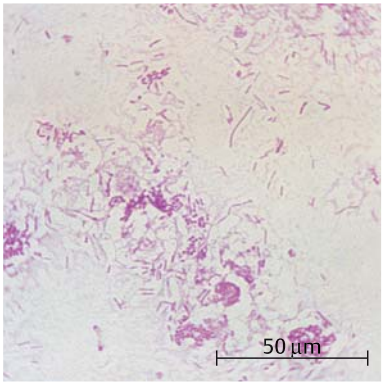

Fig. 4.**22** Gram staining of a pleural punctate preparation: Gram-negative, fusiform, pleomorphic, and coccoid rods. Clinical diagnosis: pleural empyema.

destroy tissues (hyaluronidase, collagenase, neuraminidase). Gram-negative anaerobes are almost never the sole pathogens in an infection focus, but are rather found there together with other anaerobes and aerobes.

The clinical course of infections is subacute to chronic. Necrotic abscesses are seen frequently. The compartments infected are the CNS, the oral cavity, the upper and lower respiratory tract, the abdominal cavity, and the urogenital tract (Table 4.**11**). These pathogens can infect wounds following bite injuries or surgery in areas colonized by them (intestine, oral cavity, genital tract).

Diagnosis requires isolation and identity of the bacteria involved. Since these anaerobes are components of normal flora, correct sampling techniques are very important. The material must be transported in special anaerobe containers. Cultures should always be grown under both anaerobic and aerobic conditions. Selective culture mediums are available. Identification is based on morphological and physiological characteristics. Gas chromatography can be used for organic acid assays (butyric acid, acetic acid, propionic acid, etc.). These acids are produced as final products of certain bacterial metabolic steps.

Therapy. Penicillin, usually in combination with a betalactamase inhibitor, clindamycin, cefoxitin, imipenem, and nitroimidazoles are potentially effective antibiotics. Resistance testing is only necessary in certain cases.

Table 4.11 Overview of Medically Significant Genera and Species of Gram-Negative Anaerobes

Taxonomy	Remarks and clinical pictures
Bacteroides *B. fragilis* *B. distasonis* *B. thetaiotaomicron* *B. merdae* *B. caccae* *B. vulgatus* and others	Bacteria of the normal intestinal flora; in large intestine $> 10^{11}$/g of stool. These species are also classified under the designation *Bacteroides fragilis* group. Mainly peritonitis, intraabdominal abscesses, hepatic abscesses.
Prevotella *P. bivia* *P. disiens* *P. buccae* *P. oralis* *P. buccalis* and others	Normal flora of the urogenital tract and/or oropharynx. Also known as the *Prevotella oralis* group (formerly *Bacteroides oralis* group). Chronic otitis media and sinusitis, dental abscesses, ulcerating gingivostomatitis, infections of the female genital tract, cerebral abscesses.
Prevotella *P. melaninogenica* *P. intermedia* and others	Normal oral flora; blackish-brown hematin pigment. Also known as the *Prevotella melaninogenica* group. Aspiration pneumonia, pulmonary abscesses, pleural empyema, cerebral abscesses.
Porphyromonas *P. asaccharolytica* *P. endodontalis* *P. gingivalis,* and others	Normal oral flora. Dental abscesses, gingivostomatitis, periodontitis; also contribute to infections of the lower respiratory tract (see above); cerebral abscesses.
Fusobacterium *F. nucleatum* *F. necropherum* *F. periodonticum* *F. sulci* (nov. sp.) *F. ulcerans* (nov. sp.), and others	Rods with pointed ends. Spindle forms. Normal oral and intestinal flora. Infections in the orofacial area, lower respiratory tract, and abdomen; Plaut-Vincent angina

Epidemiology and prevention. Most infections arise from the patient's own flora. Exogenous infections can be contracted from animal bites. Following intestinal surgery, suitable anti-infective agents (see above) are administered for one to two days to prevent infections.

Treponema (Syphilis, Yaws, Pinta)

Treponema pallidum, subsp. *pallidum* is the causative pathogen of syphilis. Treponemes feature 10–20 primary spiral windings and can be viewed using dark field microscopy. They cannot be grown on artificial nutrient culture mediums. Syphilis affects only humans. The pathogens are transmitted by direct contact, in most cases during sexual intercourse. They invade the subcutaneous and subserous connective tissues through microtraumata in skin or mucosa. The disease progresses in stages designated as primary, secondary, and tertiary syphilis or stages I, II, and III. **Stage I** is characterized by the painless primary affect and local lymphadenitis. Dissemination leads to **stage II**, characterized by polylymphadenopathy as well as generalized exanthem and enanthem. **Stage III** is subdivided into neurosyphilis, cardiovascular syphilis, and gummatous syphilis. In stages I and II the lesion pathogens can be viewed under a dark field microscope. Antibody assays include the VDRL flocculation reaction, TP-PA particle agglutination, and the indirect immunofluorescence test FTA-ABS. The therapeutic of choice is penicillin G. This disease is known in all parts of the world. Preventive measures concentrate on protection from exposure. Other *Treponema*-caused diseases that do not occur in Europe include nonvenereal syphilis, caused by *T. pallidum*, subsp. *endemicum*, yaws, caused by *T. pallidum*, subsp. *pertenue*, and pinta, caused by *Treponema carateum*.

The genus *Treponema* belongs to the family of *Spirochaetaceae* and includes several significant human pathogen species and subspecies. *T. pallidum*, subsp. *pallidum* is the syphilis pathogen. *T. pallidum*, subsp. *endemicum* is the pathogen that causes a syphilislike disease that is transmitted by direct, but not sexual contact. *T. pallidum*, subsp. *pertenue* is the pathogen that causes yaws, and *T. carateum* causes pinta, two nonvenereal infections that occur in the tropics and subtropics.

Treponema pallidum, subsp. pallidum (Syphilis)

Morphology and culture. These organisms are slender bacteria, 0.2 µm wide and 5–15 µm long; they feature 10–20 primary windings and move by rotating around their lengthwise axis. Their small width makes it difficult to render them visible by staining. They can be observed in vivo using dark field microscopy. In-vitro culturing has not yet been achieved.

Pathogenesis and clinical picture. Syphilis affects only humans. The disease is normally transmitted by sexual intercourse. Infection comes about

because of direct contact with lesions containing the pathogens, which then invade the host through microtraumata in the skin or mucosa. The incubation period is two to four weeks. Left untreated, the disease manifests in several stages:

- **Stage I (primary syphilis).** Hard, indolent (painless) lesion, later infiltration and ulcerous disintegration, called hard chancre. Accompanied by regional lymphadenitis, also painless. Treponemes can be detected in the ulcer.

- **Stage II (secondary syphilis).** Generalization of the disease occurs four to eight weeks after primary syphilis. Frequent clinical symptoms include micropolylymphadenopathy and macular or papulosquamous exanthem, broad condylomas, and enanthem. Numerous organisms can be detected in seeping surface efflorescences.

- **Latent syphilis.** Stage of the disease in which no clinical symptoms are manifested, but the pathogens are present in the body and serum antibody tests are positive. Divided into early latency (less than four years) and late latency (more than four years).

- **Stage III (tertiary or late syphilis).** Late gummatous syphilis: manifestations in skin, mucosa, and various organs. Tissue disintegration is frequent. Lesions are hardly infectious or not at all. Cardiovascular syphilis: endarteritis obliterans, syphilitic aortitis. Neurosyphilis: two major clinical categories are observed: meningovascular syphilis, i.e., endarteritis obliterans of small blood vessels of the meninges, brain, and spinal cord; parenchymatous syphilis, i.e., destruction of nerve cells in the cerebral cortex (paresis) and spinal cord (tabes dorsalis). A great deal of overlap occurs.

- **Syphilis connata.** Transmission of the pathogen from mother to fetus after the fourth month of pregnancy. Leads to miscarriage or birth of severely diseased infant with numerous treponemes in its organs.

Diagnosis. Laboratory diagnosis includes both isolation and identification of the pathogen and antibody assays.

Pathogen identification. Only detectable in fluid pressed out of primary chancre, in the secretions of seeping stage II efflorescences or in lymph node biopsies. Methods: dark field microscopy, direct immunofluorescence (Fig. 4.**23**).

Antibody assays. Two antibody groups can be identified:

- **Antilipoidal antibodies (reaginic antibodies).** Probably produced in response to the phospholipids from the mitochondria of disintegrating somatic cells. The antigen used is **cardiolipin**, a lipid extract from the heart muscle of cattle. This serological test is performed according to the standards

Treponema pallidum

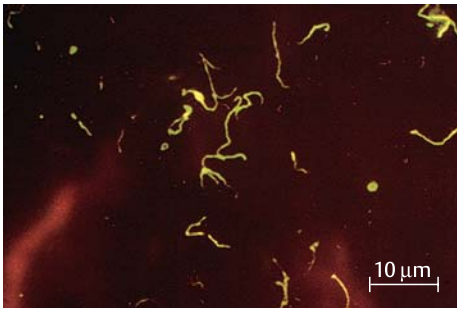

Fig. 4.**23** Serous transudate from moist mucocutaneous primary chancre. Direct immunofluorescence.

of the Venereal Disease Research Laboratory (USA) and is known as the VDRL flocculation reaction.

- **Antitreponema antibodies.** Probably directed at *T. pallidum*.
- ***Treponema pallidum* particle agglutination (TP-PA).** This test format has widely replaced the *Treponema pallidum* hemagglutination assay (TPHA). The antigens (ultrasonically-treated suspension of *Treponema pallidum*, Nichols strain, cultured in rabbit testicles) are coupled to particles or erythrocytes.
- **Immunofluorescence test (FTA-ABS).** In this **f**luorescence **t**reponemal **a**ntibody **abs**orption test the antigen consists of killed Nichols strain treponemes mounted on slides and coated with patient serum. Bound antibodies are detected by means of fluorescein-marked antihuman IgG antibodies. Selective antitreponeme IgM antibodies can be assayed (= 19S-FTA-ABS) using antihuman IgM antibodies (µ capture test).
- ***Treponema pallidum* immobilization test (TPI test).** Living treponemes (Nichols strain) are immobilized by antibodies in the patient serum. This test is no longer used in routine diagnostics. It is considered the gold standard for evaluation of antitreponeme antibody tests.

The antibody tests are used as follows:
- **Screening:** TP-PA or TPHA (qualitative).
- **Primary diagnostics:** TP-PA or TPHA, VDRL, FTA-ABS (all qualitative).
- **Special diagnostics:** VDRL (quantitative); 19S-FTA-ABS.

Therapeutic success can be determined by the quantitative VDRL test. A rapid drop in reagins indicates an efficacious therapy. The 19S-FTA-ABS can be used to find answers to specialized questions. Example: does a positive result in primary diagnostic testing indicate a serological scar or a fresh infection?

Therapy. Penicillin G is the antibiotic agent of choice. Dosage and duration of therapy depend on the stage of the disease and the galenic formulation of the penicillin used.

Epidemiology and prevention. Syphilis is known all over the world. Annual prevalence levels in Europe and the US are 10–30 cases per 100 000 inhabitants. The primary preventive measure is to avoid any contact with syphilitic efflorescences. When diagnosing a case, the physician must try to determine the first-degree contact person, who must then be examined immediately and provided with penicillin therapy as required. National laws governing venereal disease management in individual countries regulate the measures taken to diagnose, prevent, and heal this disease. There is no vaccine.

Treponema pallidum, subsp. endemicum (Nonvenereal Syphilis)

This subspecies is responsible for nonvenereal syphilis, which occurs endemically in certain circumscribed areas in the Balkans, the eastern Mediterranean, Asia, and Africa. The disease manifests with maculous to papulous, often hypertrophic lesions of the skin and mucosa. These lesions resemble the venereal efflorescences. The pathogens are transmitted by direct contact or indirectly on everyday objects such as clothes, tableware, etc. The incubation period is three weeks to three months. Penicillin is the therapy of choice. Serological syphilis tests are positive.

Treponema pallidum, subsp. pertenue (Yaws)

This species causes yaws (German "Frambösie," French "pian"), a chronic disease endemic in moist, warm climates characterized by epidermal proliferation and ulceration. Transmission is by direct contact. The incubation period is three to four weeks. Treponemes must be found in the early lesions to confirm diagnosis. Serological syphilis reactions are positive. Penicillin G is the antibiotic of choice.

Treponema carateum (Pinta)

This species causes pinta, an endemic treponematosis that occurs in parts of Central and South America, characterized by marked dermal depigmentations. The pathogens are transmitted by direct contact. The incubation period is one to three weeks. The disease often has a chronic course and can persist

for years. Diagnosis is confirmed by identification of treponemes from the skin lesions. Penicillin G is used in therapy.

Borrelia (Relapsing Fever, Lyme Disease)

■ *Borrelia recurrentis* is the pathogen of an epidemic relapsing fever transmitted by body lice that no longer occurs in the population of developed countries. *B. duttonii*, *B. hermsii*, and other borreliae are the causative pathogens of the endemic, tickborne relapsing fever, so called for the periodic relapses of fever characterizing the infection. The relapses are caused by borreliae that have changed the structure of the variable major protein in their outer membranes so that the antibodies produced by the host in the previous episode are no longer effective against them. Laboratory diagnostic confirmation requires identification of the borreliae in the blood. Penicillin G is the antibiotic of choice.

B. burgdorferi is the causative pathogen in Lyme disease, a tickborne infection. Left untreated, the disease has three stages. The primary clinical symptom of stage I is the erythema chronicum migrans. Stage II in the European variety is clinically defined by chronic lymphocytic meningitis Bannwarth. Meningitis is frequent in children. The primary symptoms of stage III are acrodermatitis chronica atrophicans Herxheimer and Lyme arthritis. Laboratory diagnostics comprises detection of specific antibodies by means of immunofluorescent or EIA methods. Betalactam antibiotics are used to treat the infection. Lyme disease is the most frequent tickborne disease in central Europe. ■

Borrelia that Cause Relapsing Fevers

Taxonomy and significance. The genus *Borrelia* belongs to the family *Spirochaetaceae*. The body louseborne epidemic form of relapsing fever is caused by the species *B. recurrentis*. The endemic form, transmitted by various tick species, can be caused by any of a number of species (at least 15), the most important being *B. duttonii* and *B. hermsii*.

Morphology and culture. Borreliae are highly motile spirochetes with three to eight windings, 0.3–0.6 μm wide, and 8–18 μm in length. They propel themselves forward by rotating about their lengthwise axis. They can be rendered visible with Giemsa stain (Fig. 4.**24**). It is possible to observe live borreliae using dark field or phase contrast microscopy.

Borrelia duttonii

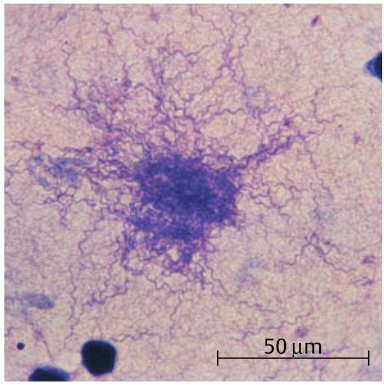

Fig. 4.**24** Preparation from the blood of an experimentally infected mouse. Giemsa staining.

Borreliae can be cultured using special nutrient mediums, although it must be added that negative results are not reliable.

Pathogenesis and clinical picture. *B. recurrentis* is pathogenic only in humans. The pathogens are transmitted by body lice. *B. duttonii*, *B. hermsii*, and other species are transmitted by ticks.

Following an incubation period of five to eight days, the disease manifests with fever that lasts three to seven days, then suddenly falls. A number of feverfree intervals, each longer than the last, are interrupted by relapses that are less and less severe. The borreliae can be detected in the patient's blood during the febrile episodes. The disease got its name from these recurring febrile attacks. The relapses are caused by borreliae that have changed their antigen structure in such a way that the antibodies produced in response to the last proliferative episode cannot attack them effectively. Borreliae possess a highly variable gene coding for the adhesion protein VMP (variable major protein) in the outer membrane of the cell wall.

Diagnosis. Borreliae can be detected in patients' blood when the fever rises. They cannot be reliably cultured. One method is to inject patient blood i.p. into mice. After two to three days, the mouse develops a bacteremia that can be verified by finding the pathogens in its blood under a microscope.

Therapy. The antibiotic of choice is penicillin G. Alternatives include other betalactam antibiotics and doxycycline.

Epidemiology and prevention. *B. recurrentis* causes the **epidemic form of relapsing fever**, which still occurred worldwide at the beginning of the 20th century but has disappeared for the most part today. The pathogens

are transmitted by the body louse. Prevention involves eradication of the lice with insecticides.

B. duttonii, *B. hermsii*, and other borreliae cause **endemic relapsing fever**, which is still observed today in Africa, the Near and Middle East, and Central America. This is a tickborne disease. Here again, the main preventive measure is elimination of the insect vectors (ticks) with insecticides, especially in residential areas.

Borrelia burgdorferi (Lyme Disease)

Classification. The etiology of an increase in the incidence of acute cases of arthritis among youths in the Lyme area of Connecticut in 1977 was at first unclear. The illness was termed Lyme arthritis. It was not until 1981 that hitherto unknown borreliae were found to be responsible for the disease. They were classified as *B. burgdorferi* in 1984 after their discoverer. Analysis of the genome of various isolates has recently resulted in a proposal to subclassify *B. burgdorferi* sensu lato in three species: *B. burgdorferi* sensu stricto, *B. garinii*, *B. afzelii*.

Morphology and culture. These are thin, flexible, helically wound, highly motile spirochetes. They can be rendered visible with Giemsa staining or by means of dark field or phase contrast microscopy methods.

These borreliae can be grown in special culture mediums at 35 °C for five to 10 days, although culturing these organisms is difficult and often unsuccessful.

Pathogenesis and clinical picture. The pathogens are transmitted by the bite of various tick species (see p. 607). The incubation period varies from three to 30 days. Left untreated, the disease goes through three stages (Table 4.**12**), though individual courses often deviate from the classic

Lyme Disease

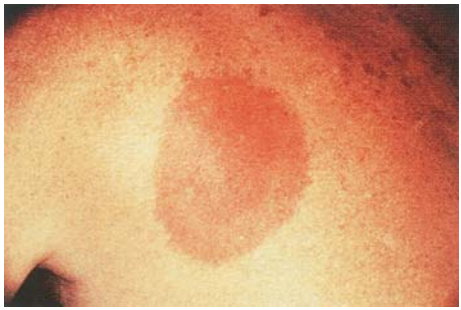

Fig. 4.**25** Erythema chronicum migrans.

Table 4.**12** Clinical Manifestations of Lyme Disease

Organ/organ system	Stage I	Stage II	Stage III
Skin	**Erythema migrans**	Diffuse erythema Lymphadenosis benigna cutis (Lymphocytoma)	**Acrodermatitis chronica atrophicans**
Lymphatic system	Local lymphadenopathy	Regional lymphadenopathy	
Nervous system		**Lymphocytic meningoradiculitis Bannwarth**, facialis paresis, aseptic meningitis	Chronic encephalomyelitis (rare delayed complication)
Joints		Brief attacks of arthritis	**Arthritis**
Heart		Carditis, atrioventricular block	

The clinical pictures in bold type represent the primary disease manifestations of the three stages.

pattern. The presenting symptom in stage I is the erythema chronicum migrans (Fig. 4.**25**).

Diagnosis. Direct detection and identification of the pathogen by means of microscopy and culturing techniques is possible, but laden with uncertainties. In a recent development, the polymerase chain reaction (PCR) is used for direct detection of pathogen-specific DNA. However, the method of choice is still the antibody test (EIA or indirect immunofluorescence, Western blotting if the result is positive).

Therapy. Stages I and II: amoxicillin, cefuroxime, doxycycline, or a macrolide. Stage III: ceftriaxone.

Epidemiology and prevention. Lyme disease occurs throughout the northern hemisphere. There are some endemic foci where the infection is more frequent. The disease is transmitted by various species of ticks, in Europe mostly by *Ixodes ricinus* (sheep tick). In endemic areas of Germany, approximately 3–7% of the larvae and 10–34% of nymphs and adult ticks are infected with *B. burgdorferi* sensu lato. The annual incidence of acute Lyme disease (stage I) in central Europe is 20–50 cases per 100 000 inhabitants. Wild ani-

mals from rodents on up to deer are the natural reservoir of the Lyme disease *Borrelia*, although these species seldom come down with the disease. The ticks obtain their blood meals from these animals.

Leptospira (Leptospirosis, Weil Disease)

■ The pathogenic species *Leptospira interrogans* is subclassified in over 100 serovars reflecting different surface antigens. The serovars are divided into 19 serogroups (*icterohemorrhagiae*, *canicola*, *pomona*, etc.). These organisms are in the form of spiral rods and can be grown in in-vitro cultures. Leptospirosis is a zoonosis that occurs worldwide. The sole sources of infection are diseased rodents and domestic animals (pigs), which excrete the pathogen in their urine. Upon contact, leptospirae penetrate skin or mucosa, are disseminated hematogenously and cause a generalized vasculitis in various organs. The incubation period is seven to 12 days. The disease at first presents as a sepsis, followed after three to seven days by the so-called immune stage. In the milder form, anicteric leptospirosis, the most frequent manifestation in stage two is an aseptic meningitis. The icteric form of leptospirosis (Weil disease) can cause dysfunction of liver and kidneys, cardiovascular disruptions, and hemorrhages. The method of choice in laboratory diagnostics is antibody identification in a lysis-agglutination reaction. The therapeutic agent of choice is penicillin G. ■

Classification. Leptospirae belong to the family *Leptospiraceae*. The genus *Leptospira* comprises two species. *L. biflexa* includes all apathogenic leptospirae and *L. interrogans* represents the pathogenic species. Based on its specific surface antigen variety, *L. interrogans* is subclassified in over 100 serovars in 19 serogroups. Some of the most important serogroups are: *icterohemorrhagiae*, *canicola*, *pomona*, *australis*, *grippotyphosa*, *hyos*, and *sejroe*.

Morphology and culture. Leptospirae are fine spirochetes, 10–20 μm long, and 0.1–0.2 μm thick (Fig. 4.**26**). They possess no flagella, but rather derive their motility from rotating motions of the cell corpus. Visualization of leptospirae is best done using dark field or phase contrast microscopy. Leptospirae can be grown in special culture mediums under aerobic conditions at temperatures between 27–30 °C

Pathogenesis and clinical picture. Leptospirae invade the human organism through microinjuries in the skin or the intact conjunctival mucosa. There are no signs of inflammation in evidence at the portal of entry. The organisms spread to all parts of the body, including the central nervous system, hematogenously. Leptospirosis is actually a generalized vasculitis. The pathogens

Leptospira interrogans

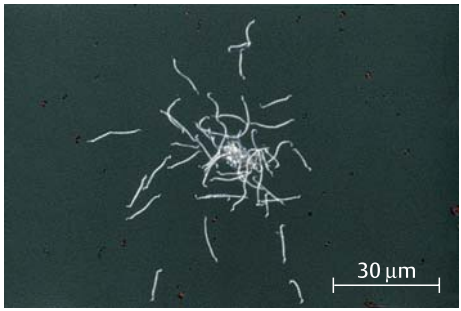

Fig. 4.**26** Serogroup *icterohemorrhagiae*. Culture preparation. Dark field microscopy.

damage mainly the endothelial cells of the capillaries, leading to greater permeability and hemorrhage and interrupting the O_2 supply to the tissues. Jaundice is caused by a nonnecrotic hepatocellular dysfunction. Disturbances of renal function result from hypoxic tubular damage. A clinical distinction is drawn between **anicteric leptospirosis**, which has a milder course, and the severe clinical picture of **icteric leptospirosis (Weil disease)**. In principle, any of the serovars could potentially cause either of these two clinical courses. In practice, however, the serogroup *icterohemorrhagiae* is isolated more frequently in Weil disease.

Both types of leptospirosis are characterized by fever with chills, headache, and myalgias that set in after an incubation period of seven to 12 days. This initial **septic** stage of the disease lasts three to seven days and is then followed by the second, so-called **immune stage**, which lasts from four to 30 days. The most important clinical manifestation of stage two anicteric leptospirosis is a mild, aseptic meningitis. The second stage of Weil disease is characterized by hepatic and renal dysfunctions, extensive hemorrhaging, cardiovascular symptoms, and clouding of the state of consciousness. The immunity conferred by survival of the infection is reliable, but only protects against the one specific serovar.

Diagnosis. Detection and identification of leptospirae are accomplished by growing the organisms in **cultures**. Blood, cerebrospinal fluid, urine, or organ biopsies, which must not be contaminated with other bacteria, are incubated in special mediums at 27–30 °C for three to four weeks. A microscope check (dark field) is carried out every week to see if any leptospirae are proliferating. The *Leptospirae* are typed serologically in a lysis-agglutination reaction with specific test sera.

The method of choice for a laboratory diagnosis is an **antibody assay**. The antibodies produced after the first week of the infection are detected

in patient serum using a quantitative lysis-agglutination test. Viable culture strains of the regionally endemic serovars provide the test antigens. The reaction is read off under the microscope.

Therapy. The agent of choice is penicillin G.

Epidemiology and prevention. Leptospiroses are typical zoonotic infections. They are reported from every continent in both humans and animals. The most important sources of infection are rodents and domestic animals, mainly pigs. The animals excrete the pathogen with urine. Leptospirae show little resistance to drying out so that infections only occur because of contact with a moist milieu contaminated with urine. The persons most at risk are farmers, butchers, sewage treatment workers, and zoo staff.

Prevention of these infections involves mainly avoiding contact with material containing the pathogens, control of *Muridae* rodents and successful treatment of domestic livestock. It is not necessary to isolate infected persons or their contacts. There is no commercially available vaccine.

Rickettsia, Coxiella, Orientia, and Ehrlichia (Typhus, Spotted Fever, Q Fever, Ehrlichioses)

The genera of the *Rickettsiaceae* and *Coxelliaceae* contain short, coccoid, small rods that can only reproduce in host cells. With the exception of *Coxiella* (aerogenic transmission), they are transmitted to humans via the vectors lice, ticks, fleas, or mites. *R. prowazekii* and *R. typhi* cause typhus, a disease characterized by high fever and a spotty exanthem. Several rickettsiae species cause spotted fever, a milder typhuslike disease. *Orientia tsutsugamushi* is transmitted by mite larvae to cause tsutsugamushi fever. This disease occurs only in Asia. *Coxiella burnetii* is responsible for Q fever, an infection characterized by a pneumonia with an atypical clinical course.

Several species of *Ehrlichiaceae* cause ehrlichiosis in animals and humans. The method of choice for laboratory diagnosis of the various rickettsioses and ehrlichioses is antibody assay by any of several methods, in most cases indirect immunofluorescence. Tetracyclines represent the antibiotic of choice for all of these infections. Typhus and spotted fever no longer occur in Europe. Q fever infections are reported from all over the world. Sources of infection include diseased sheep, goats, and cattle. The prognosis for the rare chronic form of Q fever (syn. Q fever endocarditis) is poor. Ehrlichiosis infects mainly animals, but in rare cases humans as well.

Classification. The bacteria of this group belong to the families *Rickettsiaceae* (*Rickettsia* and *Orientia*), *Coxelliaceae* (*Coxiella*), and *Ehrlichiaceae* (*Ehrlichia*, *Anaplasma*, *Neorickettsia*). Some of these organisms can cause mild, self-limiting infections in humans, others severe disease. Arthropods are the transmitting vectors in many cases.

Morphology and culture. These obligate cell parasites are coccoid, short rods measuring 0.3–0.5 μm that take gram staining weakly, but Giemsa staining well. They reproduce by intracellular, transverse fission only. They can be cultured in hen embryo yolk sacs, in suitable experimental animals (mouse, rat, guinea pig) or in cell cultures.

Pathogenesis and clinical pictures. With the exception of *C. burnetii*, the organisms are transmitted by arthropods. In most cases, the arthropods excrete them with their feces and ticks transmit them with their saliva while sucking blood. The organisms invade the host organism through skin injuries. *C. burnetii* is transmitted exclusively by inhalation of dust containing the pathogens. Once inside the body, rickettsiae reproduce mainly in the vascular endothelial cells. These cells then die, releasing increasing numbers of organisms into the bloodstream. Numerous inflammatory lesions are caused locally around the destroyed endothelia. Ehrlichiae reproduce in the monocytes or granulocytes of membrane-enclosed cytoplasmic vacuoles. The characteristic morulae clusters comprise several such vacuoles stuck together.

Table 4.**13** summarizes a number of characteristics of the rickettsioses.

Diagnosis. Direct detection and identification of these organisms in cell cultures, embryonated hen eggs, or experimental animals is unreliable and is also not to be recommended due to the risk of laboratory infections. Special laboratories use the polymerase chain reaction to identify pathogen-specific DNA sequences. However, the method of choice is currently still the antibody assay, whereby the immunofluorescence test is considered the gold standard among the various methods. The Weil-Felix agglutination test (p. 295) is no longer used today due to low sensitivity and specificity.

Therapy. Tetracyclines lower the fever within one to two days and are the antibiotics of choice.

Epidemiology and prevention. The **epidemic form of typhus**, and earlier scourge of eastern Europe and Russia in particular, has now disappeared from Europe and occurs only occasionally in other parts of the world. **Murine typhus**, on the other hand, is still a widespread disease in the tropics and subtropics. **Spotted fevers** (e.g., Rocky Mountain spotted fever) occur with increased frequency in certain geographic regions, especially in the spring. **Tsutsugamushi fever** occurs only in Japan and Southeast Asia. The blood-sucking larvae of various mite species transmit its pathogen. **Q fever** epi-

Table 4.**13** Pathogens and Clinical Pictures of the Rickettsioses and of Q Fever

Pathogen	Vector/host	Disease	Clinical picture
Typhus group			
Rickettsia prowazekii	Body louse/humans	Epidemic typhus (ET)	Incubation 10–14 days; high fever; 4–7 days after onset maculous exanthem; lethality as high as 20% if untreated
		Brill-Zinsser disease	Endogenous secondary infection by rickettsiae persisting in the RES; results from reduction of immune protection; milder symptoms than ET
R. typhi	Rat flea/rat	Murine typhus	Symptoms as in ET, but milder
Spotted fever group			
R. rickettsii	Hard tick/ rodents, tick	Rocky Mountain spotted fever (RMSF)	Incubation: 6–7 days; continuing fever 2–3 weeks; maculopapulous exanthem on extremities
R. conori	Hard tick/ rodents	Fièvre boutonneuse (Mediterranean fever)	Symptoms as in RMSF, necrotic lesions sometimes develop at bite locus
R. sibirica	Hard tick/ rodents	North Asian tick fever	Symptoms as in RMSF, necrotic lesions sometimes develop at bite locus
R. akari	Mite/rodents	Rickettsial pox	Fever; exanthem resembles that of chicken pox
Tsutsugamushi fever			
Orientia tsutsugamushi	Mite larvae/ rodents	Japanese spotted fever	Symptoms similar to ET plus local lesion at bite locus and lymphadenitis
Q fever (Query fever)			
Coxiella burnetii	Dust/sheep, cattle, goats, rodents	Q fever	Incubation 2–3 weeks; interstitial pneumonia (clinical picture often atypical); chronic Q fever (endocarditis) with onset years after primary infection, poor prognosis

Table 4.**14** Pathogens and Clinical Picture of the Ehrlichioses

Pathogen	Vector/host	Disease	Clinical picture
Ehrlichia chaffeensis	Ticks/deer, dog	Human monocytotrophic ehrlichiosis (HME); monocytes are main target of pathogen	All ehrlichioses present as mild to occasionally severe mononucleosis-like multisystem disease with headache, fever, myalgias leukopenia, thrombocytopenia, anaemia, and raised transaminases. 20–30% show various symptoms in the gastrointestinal tract and/or respiratory tract and/or CNS. Incubation time between 5–10 days. Antibiotics of choice are the tetracyclines. Cultivation from blood using cell cultures exhibits low sensitivity. Molecular techniques (PCR) better for pathogen detection. Use indirect immunofluorescence for antibody titers.
Ehrlichia ewingii and *Anaplasma phagocytophilum*	Ticks/dogs, horse, other animals	Human granulocytotrophic ehrlichiosis (HGE); granulocytes are main target of pathogen	
Neorickettsia sennetsu	Host unknown; perhaps fish. Transmission from eating raw fish	Sennetsu fever; occurs in Southeast Asia (Japan)	

demics are occasionally seen worldwide. The sources of infection are diseased livestock that eliminate the coxiellae in urine, milk, or through the birth canal. Humans and animals are infected by inhaling dust containing the pathogens. Specific preventive measures are difficult to realize effectively since animals showing no symptoms may be excreters. Active vaccination of persons exposed to these infections in their work provides a certain degree of immunization protection.

Until 1987, **ehrlichioses** were thought to occur only in animals. Tickborne *Ehrlichia* infections in humans have now been confirmed.

Bartonella and Afipia

Bartonella

Classification. The genus ***Bartonella*** includes, among others, the species *B. bacilliformis*, *B. quintana*, *B. henselae*, and *B. clarridgeia*.

Morphology and culture. *Bartonella* bacteria are small (0.6–1 μm), Gram-negative, frequently pleomorphic rods. Bartonellae can be grown on culture mediums enriched with blood or serum.

Table 4.**15** Pathogens and Clinical Pictures of Bartonelloses

Pathogen	Transmission/ host	Disease	Clinical picture
Bartonella bacilliformis	Sand fly/ humans	Oroya fever (Carrion's disease)	Incubation: 15–40 days; high fever; lymphadenitis; splenohepatomegaly; hemolytic anemia due to lysis of erythrocytes invaded by *B. bacilliformis*
		Verruga peruana phase of Oroya fever	Multiple, wartlike skin lesions on extremities, face, mucosa; onset either months after abating of Oroya fever or without an acute preceding infection
B. quintana	Lice/humans	Five-day fever (Wolhynian fever, trench fever)	Periodic relapses of fever (3–8) every 5 days, sepsis; bacillary angiomatosis (see below); also endocarditis
B. henselae	Cats to humans/cats	Cat scratch disease	Lymphadenopathy; fever; cutaneous lesion (not always present)
		Sepsis, bacillary angiomatosis	In patients with immune deficiencies (HIV); vascular proliferation in skin and mucosa (similar to verruga peruana)
		Bacterial peliosis hepatis/splenica	Cystic, blood-filled lesions in liver and spleen
B. clarridgeia		Cat scratch disease	See above

Diagnosis. Special staining techniques are used to render bartonellae visible under the microscope in tissue specimens. Growth in cultures more than seven days. Amplification of specific DNA in tissue samples or blood, followed by sequencing. Antibody assay with IF or EIA.

Therapy. Tetracyclines, macrolides.

Epidemiology and prevention. Oroya fever (also known as Carrion disease) is observed only in humans and is restricted to mountain valleys with elevations above 800 m in the western and central Cordilleras in South America because an essential vector, the sand fly, lives only there. Cat scratch disease, on the other hand, is known all over the world. It is transmitted directly from cats to humans or indirectly by cat fleas. The cats involved are usually not sick. Table 4.**14** lists the pathogens and clinical pictures for the various bartonelloses.

Afipia felis

The bacterial species *Afipia* (Armed Forces Institute of Pathology) *felis* was discovered several years ago. At first, it appeared that most cases of cat scratch disease were caused by this pathogen. Then it turned out that the culprit in those cases was usually either *B. henselae* or *B. clarridgeia* and that *Afipia felis* was responsible for only a small number. *Afipia felis* and *B. henselae* cat scratch infections present with the same clinical symptoms. Most cases of *A. felis* infections clear up spontaneously without antibiotic therapy. Should use of an antibiotic be clinically indicated, a tetracycline (or in severe cases a carbapenem or aminoglycoside) would be appropriate.

Chlamydia

■ Chlamydiae are obligate cell parasites. They go through two stages in their reproductive cycle: the elementary bodies (EB) are optimized to survive outside of host cells. In the form of the initial bodies (IB), the chlamydiae reproduce inside the host cells. The three human pathogen species of chlamydiae are *C. psittaci*, *C. trachomatis*, and *C. pneumoniae*. Tetracyclines and macrolides are suitable for treatment of all chlamydial infections.

C. psittaci is the cause of **psittacosis** or **ornithosis**. This zoonosis is a systemic disease of birds. The pathogens enter human lungs when dust containing chlamydiae is inhaled. After an incubation period of one to three weeks, pneumonia develops that often shows an atypical clinical course.

C. trachomatis is found only in humans. This species causes the following diseases: 1. **Trachoma**, a chronic follicular keratoconjunctivitis. The pathogens are transmitted by smear infection. 2. **Inclusion conjunctivitis** in newborn children and **swimming-pool conjunctivitis**. 3. **Nonspecific urogenital infections** in both men and women (urethritis, cervicitis, salpingitis, etc.). 4. **Lymphogranuloma venereum**, a venereal disease observed mainly in countries with warm climates.

C. pneumoniae is responsible for infections of the upper respiratory tract as well as for a mild form of **pneumonia**. There is current discussion in the literature concerning a possible role of *C. pneumoniae* in the pathogenesis of atherosclerotic cardiovascular disease.

Overview and General Characteristics of Chlamydiae

Definition and classification. The bacteria in the taxonomic family *Chlamydiaceae* are small (0.3–1 μm) obligate cell parasites with a Gram-negative cell wall. The reproductive cycle of the chlamydiae comprises two developmental stages: The elementary bodies are optimally adapted to survival outside of host cells. The initial bodies, also known as reticulate bodies, are the form in which the chlamydiae reproduce inside the host cells by means of transverse fission. Three human pathogen species of chlamydiae are known: *C. psittaci*, *C. trachomatis* (with the biovars *trachoma* and *lymphogranuloma venereum*), and *C. pneumoniae*.

Morphology and developmental cycle. Two morphologically and functionally distinct forms are known:

- **Elementary bodies.** The round to oval, optically dense elementary bodies have a diameter of approximately 300 nm. They represent the infectious form of the pathogen and are specialized for the demands of existence outside the host cells. Once the elementary bodies have attached themselves to specific host cell receptors, they invade the cells by means of endocytosis (Fig. 4.**27**). Inside the cell, they are enclosed in an endocytotic membrane vesicle or inclusion, in which they transform themselves into the other form—initial bodies—within a matter of hours.

- **Initial bodies**. Chlamydiae in this spherical to oval form are also known as reticular bodies. They have a diameter of approximately 1000 nm. The initial bodies reproduce by means of transverse fission and are not infectious while in this stage. At the end of the cycle, the initial bodies are transformed back into elementary bodies. The cell breaks open and releases the elementary bodies to continue the cycle by attaching themselves to new host cells.

Reproduction Cycle of Chlamydiae

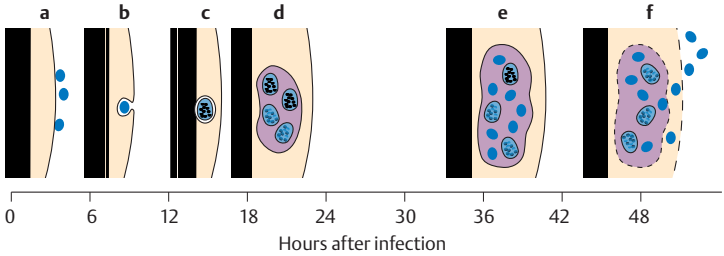

Fig. 4.**27** Two chlamydial stages: elementary body and initial body.
a Attachment of elementary body to cell membrane.
b Endocytosis.
c Transformation of elementary body into initial body inside the endosome.
d Reproduction of initial bodies by transverse fission.
e Transformation of some initial bodies back into elementary bodies.
f Lysis of inclusion vesicle and cell, release of initial and elementary bodies.

Culture. Chlamydiae exploit energy metabolism processes in their host cells that they themselves are lacking (ATP synthesis). For this reason, they can only be grown in special cell cultures, in the yolk sacs of embryonated hen eggs, or in experimental animals.

Chlamydia psittaci (Ornithosis, Psittacosis)

Pathogenesis and clinical picture. The natural hosts of *C. psittaci* are birds. This species causes infections of the respiratory organs, the intestinal tract, the genital tract, and the conjunctiva of parrots and other birds. Humans are infected by inhalation of dust (from bird excrements) containing the pathogens, more rarely by inhalation of infectious aerosols.

After an incubation period of one to three weeks, ornithosis presents with fever, headache, and a pneumonia that often takes an atypical clinical course. The infection may, however, also show no more than the symptoms of a common cold, or even remain clinically silent. Infected persons are not usually sources of infection.

Diagnosis. The pathogen can be grown from sputum in special cell cultures. Direct detection in the culture is difficult and only possible in specially equipped laboratories. The complement binding reaction can be used to identify antibodies to a generic antigen common to all chlamydiae, so that

this test would also have a positive result in the presence of other chlamydial infections. The antibody test of choice is indirect microimmunofluorescence.

Therapy. Tetracyclines (doxycycline) and macrolides.

Epidemiology and prevention. Ornithosis affects birds worldwide. It is also observed in poultry. Diagnosis of an ornithosis in a human patient necessitates a search for and elimination of the source, especially if the birds in question are household pets.

Chlamydia trachomatis (Trachoma, Lymphogranuloma venereum)

C. trachomatis is a pathogen that infects only humans. Table 4.**16** lists the relevant diseases, biovars, and serovars.

Trachoma is a follicular keratoconjunctivitis. The disease occurs in all climatic zones, although it is more frequent in warmer, less-developed countries. It is estimated that 400 million people carry this chronic infection and that it has caused blindness in six million. The pathogen is transmitted by direct contact and indirectly via objects in daily use. Left untreated, the initially acute inflammation can develop a chronic course lasting months or years and leading to formation of a corneal scar, which can then cause blindness. The **laboratory diagnostics** procedure involves detection of *C. trachomatis* in conjunctival smears using direct immunofluorescence microscopy. The fluorochrome-marked monoclonal antibodies are directed against the MOMP (major outer membrane protein) of *C. trachomatis*. The pathogen can also

Table 4.**16** Human Infections Caused by *Chlamydia trachomatis*

Disease/syndrome	Biovar	Most frequent serovars *
Trachoma	*trachoma*	A, B, Ba, C
Inclusion conjunctivitis	*trachoma*	D, Da, E, F, G, H, I, Ia, J, K
Urethritis, cervicitis, salpingitis (pharyngitis, otitis media)	*trachoma*	B, C, D, E, F, G, H, I, K, L_3
Lymphogranuloma venereum (syn. lymphogranuloma inguinale, lymphopathia venerea, Favre-Durand-Nicolas disease)	*lymphogranuloma venereum*	L_1, L_2, L_2a, L_3

* Determined with microimmunofluorescence.

be grown in cell cultures. The therapeutic method of choice is systemic and local application of tetracyclines over a period of several weeks.

Inclusion conjunctivitis. This is an acute, purulent papillary conjunctivitis that may affect neonates, children, and adults (swimming-pool conjunctivitis). Newborn children are infected during birth by pathogens colonizing the birth canal. Left untreated, a pannus may form as in trachoma, followed by corneal scarring. Laboratory diagnosis and therapy as in trachoma.

Genital infections. *C. trachomatis* is responsible for 30–60% of cases of nongonococcal urethritis (NGU) in men. Possible complications include prostatitis and epididymitis. The pathogens are communicated by venereal transmission. The source of infection is the female sexual partner, who often shows no clinical symptoms.

In women, *C. trachomatis* can cause urethritis, proctitis, or infections of the genital organs. It has even been known to cause pelvioperitonitis and perihepatitis. Massive perinatal infection of a neonate may lead to an interstitial chlamydial pneumonia.

The relevant diagnostic tools include:

1. Detection under the microscope in smear material using direct immunofluorescence (see under trachoma).
2. Direct identification by means of amplification of a specific DNA sequence in smear material and urine.
3. Growing in special cell cultures.

Lymphogranuloma venereum. This venereal disease (syn. lymphogranuloma inguinale, lymphopathia venerea (Favre-Durand-Nicolas disease) not to be confused with granuloma inguinale, see p. 305) is frequently observed in the inhabitants of warm climatic zones. A herpetiform primary lesion develops at the site of invasion in the genital area, which then becomes an ulcus with accompanying lymphadenitis. Laboratory diagnosis is based on isolating the proliferating pathogen in cell cultures from purulent material obtained from the ulcus or from matted lymph nodes. The antibodies can be identified using the complement binding reaction or the microimmunofluorescence test. Tetracyclines and macrolides are the potentially useful antibiotic types.

Chlamydia pneumoniae

This new chlamydial species (formerly TWAR chlamydiae) causes infections of the respiratory organs in humans that usually run a mild course: influenza-like infections, sinusitis, pharyngitis, bronchitis, pneumonias (atypical). Clinically silent infections are frequent. *C. pneumoniae* is pathogenic in humans only. The pathogen is transmitted by aerosol droplets. These infections are

probably among the most frequent human chlamydial infections. Serological studies have demonstrated antibodies to *C. pneumoniae* in 60% of adults. Specific laboratory diagnosis is difficult. Special laboratories can grow and identify the pathogen in cultures and detect it under the microscope using marked antibodies to the LPS (although this test is positive for all chlamydial infections). *C. pneumoniae*-specific antibodies can be identified with the microimmunofluorescence method. In a primary infection, a measurable titer does not develop for some weeks and is also quite low. The antibiotics of choice are tetracyclines or macrolides. There is a growing body of evidence supporting a causal contribution by *C. pneumoniae* to atherosclerotic plaque in the coronary arteries, and thus to the pathogenesis of coronary heart disease.

Mycoplasma

Mycoplasmas are bacteria that do not possess rigid cell walls for lack of a murein layer. These bacteria take on many different forms. They can only be rendered visible in their native state with phase contrast or dark field microscopy. Mycoplasmas can be grown on culture mediums with high osmotic pressure levels. *M. pneumoniae* frequently causes pneumonias that run atypical courses, especially in youths. Ten to twenty percent of pneumonias contracted outside of hospitals are caused by this pathogen. *M. hominis* and *Ureaplasma urealyticum* contribute to nonspecific infections of the urogenital tract. Infections caused by *Mycoplasmataceae* can be diagnosed by culture growth or antibody assays. The antibiotics of choice are tetracyclines and macrolides (macrolides not for *M. hominis*). Mycoplasmas show high levels of natural resistance to all betalactam antibiotics.

Classification. Prokaryotes lacking cell walls are widespread among plants and animals as components of normal flora and as pathogens. Human pathogen species are found in the family *Mycoplasmataceae*, genera *Mycoplasma* and *Ureaplasma*. Infections of the respiratory organs are caused by the species *M. pneumoniae*. Infections of the urogenital tract are caused by the facultatively pathogenic species *M. hominis* and *Ureaplasma urealyticum*. Other species are part of the apathogenic normal flora.

Morphology and culture. The designation mycoplasma is a reference to the many different forms assumed by these pathogens. The most frequent basic shape is a coccoid cell with a diameter of 0.3–0.8 μm. Long, fungilike filaments also occur. Mycoplasmas are best observed in their native state using phase contrast or dark field microscopy. Staining causes them to disintegrate. In

contrast to all other bacteria, mycoplasmas possess no rigid cell wall. Flagellae, fimbriae, pili, and capsules are lacking as well. Due to their inherent plasticity, mycoplasmas usually slip through filters that hold back other bacteria. Since their cell wall contains no murein, mycoplasmas are completely insensitive to antibiotics that inhibit murein synthesis (e.g., betalactams).

Mycoplasmas can be cultured on special isotonic nutrient mediums. After two to eight days, small colonies develop resembling sunny-side-up eggs and growing partially into the agar.

Pathogenesis and clinical pictures.

Infections of the respiratory organs. The pathogen involved is *M. pneumoniae*. The organism is transmitted by aerosol droplets. The cells attach themselves to the epithelia of the trachea, bronchi, and bronchioles. The mechanisms that finally result in destruction of the epithelial cells are yet unknown. The infection develops into pneumonia with an inflammatory exudate in the lumens of the bronchi and bronchioles. The incubation period is 10–20 days. The infection manifests with fever, headache, and a persistent cough. The clinical pictures of the infection course is frequently atypical, i.e., the pneumonia cannot be confirmed by percussion and auscultation. A differential diagnosis must also consider viral pneumonias, ornithosis, and Q fever. Sequelae can set in during or shortly after the acute infection, including pericarditis, myocarditis, pancreatitis, arthritis, erythema nodosum, hemolytic anemias, polyneuritis, and others.

Infections of the urogenital tract. These infections are caused by *M. hominis* and *Ureaplasma urealyticum*. These facultatively pathogenic species also occur in healthy persons as part of the mucosal flora, so that their etiological role when isolated is often a matter of controversy. *U. urealyticum* is considered responsible for 10–20% of cases of nongonococcal urethritis and prostatitis in men.

Diagnosis. These pathogens can be grown on special culture mediums. Commercially amplification tests are available for direct identification of *M. pneumoniae*. The CFT was formerly used to detect antibodies to *M. pneumoniae*; today this is done with IgM-specific EIAs. Antibody tests are of no diagnostic value in infections caused by *M. hominis* and *U. urealyticum*.

Therapy. The antibiotics of choice are tetracyclines and macrolides. *M. hominis* shows a natural resistance to macrolides, *U. urealyticum* to lincomycins. Concurrent partner treatment is recommended in urogenital infections.

Epidemiology and prevention. *M. pneumoniae* is found worldwide. Humans are the only source of infection. The pathogens are transmitted by droplet infection during close contact. Infections are frequently contracted in families, schools, homes for children, work camps, and military camps.

Incidence is particularly high between the ages of five and 15 years. About 10–20% of all pneumonias contracted outside hospitals are caused by this pathogen. *M. hominis* and *U. urealyticum* are transmitted either between sexual partners or from mother to neonate during birth. No specific prophylactic measures are available to protect against any of the mycoplasma infections.

Nosocomial Infections

Nosocomial infections occur in hospitalized patients as complications of their primary disease. Such infections are reported in an average of approximately 3.5% (Germany) to 5% (USA) of all hospitalized patients, in tertiary care hospitals in about 10% and in the intensive care units of those in about 15–20% of cases. The most frequent types of infection are urinary tract infections (42%), pneumonia (21%), surgical wound infections (16%), and sepsis (8%). The pathogen types most frequently involved are opportunistic, Gram-negative rods, staphylococci and enterococci, followed by fungi. The bacteria are often resistant to many different antibiotics. The hands of medical staff play a major role in transmission of the infections. Control of nosocomial infections requires a number of operational measures (disinfection, asepsis, rationalized antibiotic therapies, isolation), organizational measures (hygiene committee, recognition of infections, procedural guidelines, training programs), and structural measures.

Definition

The term **nosocomial infection** designates infections contracted by hospitalized patients 48 hours or more from the beginning of hospitalization. These are secondary infections that occur as complications of the primary diseases to be treated in the hospital.

Pathogens, Infections, Frequency

The significance of the different human pathogens in nosocomial infections varies widely:

Subcellular entities. Isolated cases of Creutzfeldt-Jakob disease due to unsterilized instruments have been described in the literature. Such accidents now no longer occur.

Table 4.17 Relative Frequency of Causative Pathogens in Nosocomial Infections (arranged according to the pathogen frequency levels in the column "Total")[1]

Bacteria	UTI[2]	RTI[2]	PWI[2]	SEP[2]	Other[2]	Total
E. coli	40.5	9.9	23.3	13.2	15.6	22.40
Enterococci	19.8	29.5	27.2	0.0	11.7	14.75
Staphylococcus aureus	3.2	25.4	45.5	15.8	13.0	11.11
Coagulase-negative staphylococci	4.5	9.9	14.8	34.2	10.4	8.01
Pseudomonas aeruginosa	5.4	46.5	26.0	0.0	1.3	7.65
Klebsiella sp.	4.1	20.8	15.0	10.5	3.9	6.01
Fungi	5.9	19.1	0.0	2.6	11.7	6.01
Streptococcus sp.	1.8	16.8	8.2	0.0	9.1	4.74
Proteus mirabilis	5.0	4.0	2.4	0.0	2.6	3.10
Enterobacter sp.	1.4	4.0	4.7	2.6	1.3	2.00
Serratia sp.	0.9	1.7	3.8	7.9	0.0	2.00
Other *Enterobacteriaceae*	1.9	6.3	9.7	2.6	3.9	2.00
Acinetobacter sp.	2.7	5.7	1.2	0.0	0.0	1.82
Anaerobes	0.5	0.0	4.8	0.0	0.0	1.46
Other Gram-positive bacteria	0.0	0.0	7.3	2.6	2.6	1.28
Morganella sp.	1.4	4.0	0.0	0.0	1.3	1.09
Providencia sp.	0.9	0.0	5.0	0.0	2.6	1.09
Pseudomonadaceae (exception: *P. aeruginosa*)	0.0	3.4	1.2	2.6	2.6	1.09
Other (under 1%)	0.5	0.0	5.0	2.6	1.3	3.48

[1] Data (modified) acc. to "*Nosokomiale Infektionen in Deutschland – Erfassung und Prevention (NIDEP–Studie).*" Vol. 56, Publication Series of the German Federal Health Office. Nomos Verlagsgesellschaft, Baden-Baden, 1995.

[2] UTI = urinary tract infections, RTI = lower respiratory tract infections, PWI = postoperative wound infections, SEP = primary sepsis, Other = all other infections.

There are no reliable figures available on viral nosocomial infections. A rough estimate puts viral nosocomial infections at less than 1% of the total. An example of a viral nosocomial infection is infectious hepatitis transmitted by blood or blood products.

■ **Bacteria** are the main pathogens involved in nosocomial infections. Most of the causative organisms are facultatively pathogenic (opportunistic) bacteria, which are frequently resistant to many different antibiotics. These bacteria have found niches in which they persist as so-called hospital flora. The resistance patters seen in these bacteria reflect the often wide variations between anti-infective regimens as practiced in different hospitals.

■ **Fungi.** Fungal nosocomial infections have been on the increase in recent years. It can be said in general that they affect immunocompromised patients and that neutropenic patients are particular susceptible.

Table 4.**17** lists the pathogens that cause the most significant nosocomial infections as determined in a prevalence study done in Germany (East and West) in 1995 (NIDEP Study).

Table 4.**18** shows the prevalence levels at which nosocomial infections occurred in 72 selected hospitals on a given date in the above study. The prevalence and pathogen data shown here approximate what other studies have found. Prevalence and incidence levels can vary considerably from hospital to

Table 4.**18** Frequency (prevalence) of the Most Important Nosocomial Infection Types (%)[1]

Infection	Internal medicine	Surgery	Gynecology	Intensive care	All patients
Urinary tract infections	1.57	1.45	0.91	2.35	1.46
Lower respiratory tract infections	0.63	0.30	0.09	9.00	0.72
Postoperative wound infections	0.03	1.34	0.05	1.37	0.55
Primary sepsis	0.31	0.15	0.14	2.15	0.29
Other infections	0.52	0.74	0.27	1.96	0.62
Patients with at least one infection	2.97	3.80	1.45	15.30	3.46

[1] Figures from "*Nosokomiale Infektionen in Deutschland – Erfassung und Prevention (NIDEP–Studie).*" Vol. 56, Publication Series of the German Federal Health Office. Nomos Verlagsgesellschaft, Baden-Baden, 1995.

hospital. The prevalence of nosocomial infections increases with the size of the hospital. Within a particular hospital, the infection rate is always highest in the intensive care units.

Sources of Infection, Transmission Pathways

Nosocomial infections originate either from the patient's own flora (endogenous infections) or from external sources (exogenous infections). **Endogenous infections** are the more frequent type. In such cases, the patient may have brought the pathogens into the hospital. It is, however, frequently the case that a patient's skin and mucosa are colonized within one to two days by bacteria of the hospital flora, which often shows multiple resistance to antibiotics and replaces the patient's individual flora, and that most endogenous infections are then actually caused by the specific hospital flora. The source of infection for **exogenous infections** is most likely to lie with the medical staff. In most cases, the pathogens are transmitted from patient to patient during medical and nursing activities. Less frequently, the staff is either also infected or colonized by the hospital flora. Another important cause of nosocomial infections is technical medical measures that facilitate passage of the pathogens into the body. All invasive diagnostic measures present infection risks. The patient's surroundings, i.e., the air, floor, or walls of the hospital room, are relatively unimportant as sources of infection.

Control

The measures taken to control and prevent nosocomial infections correspond in the wider sense to the general methods of **infection control**. The many different individual measures will not be listed here. The infection control program varies depending on the situation in each particular hospital and can be summarized in three general groups:

Operational measures. This category includes all measures pertaining to treatment and care of patients and cleaning measures. This includes asepsis, disinfection, sterilization, and cleaning. Further precautionary operational measures include isolation of patients that would be sources of infection and the economical and specific administration of antibiotic therapies.

Organizational measures. The organization of hospital infection control must be adapted to the structure of each particular hospital. Realization of the necessary measures, which of course always involve working time and expense, is best realized by establishing an infection control committee charged with the following tasks: determination and analysis of the situation,

definition of measures required to improve infection control by issuing binding guidelines, cooperation in the planning and acquisition of operational and structural facilities, cooperation on functional procedures in the various sections of the hospital, contributions to staff training in matters of hospital infection control. In order to carry out these tasks efficiently, the committee should have access to a working group of specialists. In larger hospitals, a hospital epidemiologist, and staff as required, are retained for these functions.

Structural measures.

These measures refer above all to new structures, which must be built in accordance with hygienic criteria. It is therefore the obligation of the planning architect to consult experts when planning the hygienically relevant parts of a construction measure. Hygienic aspects must of course also be considered in reconstruction and restoration of older building substance.