Recommendations for empiric parenteral initial antibiotic therapy of bacterial diseases in adults: Update 2010

Abstract

Under the auspices of the “Paul-Ehrlich Gesellschaft”, an expert panel of German infectious disease specialists and microbiologists compiled updated evidence-based treatment recommendations for parenteral antibiotic therapy in adult patients.

Subject-specific expert teams reviewed the available evidence from published data. Evidence levels and grades of recommendations were assigned using a standardized protocol.

The following indication areas were covered: respiratory, ENT, oral/maxillary, intra-abdominal, urinary tract, skin/soft tissue, bone/joint and eye infections, sepsis, endocarditis, meningitis, infections in the elderly and perioperative prophylaxis.

In addition, the recommendations cover relevant issues regarding the use of parenteral antibiotics: characteristics of drug classes, susceptibility testing, spread of resistance, pharmacokinetics, pharmacodynamics, drug monitoring, interactions, safety and pharmacoeconomics.

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Table 1: Definition of evidence levels

Evidence level	Definition
Ia	Evidence based on meta-analyses of randomized, controlled studies
Ib	Evidence based on at least one randomized, controlled study
IIa	Evidence based on at least one well-designed, controlled study without randomization
IIb	Evidence based on at least one well-designed, quasi-experimental study
III	Evidence based on well-designed, non-experimental, descriptive studies (e.g. comparative studies, correlation studies, case-control studies)
IV	Evidence based on reports/opinions of expert groups, consensus conferences, and/or clinical experience of recognized authorities

1 Introduction and antibiotics

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This document is an update of the recommendations published in 2004 [544]. The introduction of new agents and the results of recent studies necessitated a full revision. As in earlier updates, the current pathogen resistance situation and the results of new clinical studies and the information on the individual agents are summarized in tables.
The working groups updated the individual chapters, approved the contents within the group, and presented the results for plenum discussions at two consensus conferences. Proposals made at the two conferences were discussed and implemented as appropriate. Consensus was defined as agreement of 80% of the eligible conference participants.
The consensus panel ranked the items according to level of evidence and strength of recommendation (Table 1 and Table 2).

Table 2: Definition of grades of recommendation

Grade of recommendation	Description
A	High level of recommendation Considered as generally accepted
B	Intermediate level of recommendation
C	Low level of recommendation

Generally, a high level of evidence resulted in a high-grade recommendation. However, in some cases results from a therapeutic study with a high evidence level resulted in a low-grade recommendation and vice versa.
This process resulted in these recommendations for the empiric initial parenteral treatment for bacterial infections in adults. In cases in which several treatment options are named their microbiological activity spectrum may not be equivalent. Treatment alternatives allow the epidemiology of the pathogen to be taken into account, to avoid intolerance to antibiotics, and to escalate or de-escalate a treatment according to the situation. The treating physician can therefore better adapt his treatment decisions to the risk profiles of individual patients.

Evaluation of the licensed indications for individual antibiotics

As a result of less tight licensing requirements, many older antibiotics are approved for a much broader spectrum of diseases than substances licensed in the last 10 years by the German Federal Institute for Pharmaceuticals and Medicinal Products or the European Medicines Agency. Due to more stringent regulations in the latter period and the particular problems in Germany regarding studies in difficult disease areas (e.g. ventilator-associated pneumonia), drugs are being used to treat infections for which they are not explicitly licensed (off-label use).
In this context, we may point out the specific issues in Germany regarding clinical studies in legally incompetent patients that have been leading to discontinuation of trials in intensive care patients.
With respect to the legal aspects of off-label prescription of pharmaceuticals, the German Federal Social Court ruled on March 19, 2002 that the statutory health insurances are obliged to pay for pharmaceuticals prescribed for diseases for which they are not licensed if

- the disease is severe,
- there is no alternative treatment,
- and the available data substantiate the expectation of successful therapy.

The issues and open questions regarding off-label use routine practice are covered in a short statement in the Federal Health Newsletter.
Each physician should make his treatment decision together with each individual patient. External evidence of Grades I to III is always based on studies and therefore on standardized patient groups. The physician will base his treatment decision on the best available evidence. However he should check whether the data on which he is basing his decision really apply to the patient for whom he is making the treatment decision (i.e. correlates with the internal evidence).

Due to resistance issues in intensive care units and in oncology, is it imperative to use different antibiotic groups to minimize selection pressure, therefore off-label use of microbiological active drugs is justified (e.g. for nosocomial pneumonia).

Characteristics of antibiotics

Penicillins

The penicillin group of antibiotics is subdivided according to the chemical structure of the agents into benzylpenicillins, aminopenicillins, acylaminopenicillins and isoxazolyl penicillins. Accordingly, penicillins show widely divergent behaviour towards pathogens and beta-lactamases. Penicillins are considered bactericidal with time-dependent killing kinetics. Post-antibiotic effects are limited to a short period of time. Refer to chapter 3 for information on the optimum mode of application.
Penicillins show large variations in terms of their pharmacokinetic characteristics. The distribution is predominantly extracellular, with a distribution volume of 0.2 to 0.4 mL/kg of body weight. Penetration of penicillins in cerebrospinal fluid (CSF) is satisfactory in case of inflamed meninges and adequate dosage. The plasma half-life in patients with normal renal function is in the range of 1 to 2 hours. The majority of the administered dose is eliminated mostly unchanged via the kidneys. The fraction bound to plasma proteins is highly variable reaching values >90% for isoxazolyl penicillins.
The antibacterial spectrum of penicillins varies from narrow to extensive according to subgroup and is the key determinant for decisions on clinical use.

Benzylpenicillin (Penicillin G)

The antimicrobial spectrum of penicillin G covers most strains of streptococci, pneumococci, meningococci, spirochetes, and some anaerobic pathogens such as clostridia and *Actinomyces* species. Penicillin G is rarely effective against staphylococci due to beta-lactamases or altered binding proteins. The licensing of penicillin G allows its use for almost any systemic and local infection independent of the localization if the infection is caused by a penicillin-susceptible pathogen.
As the antimicrobial spectrum is very narrow, severe infections should not be treated with single-drug regimens before identification of the pathogen. For erysipelas and single-species infections with streptococci and pneumococci, penicillin G is still the drug of choice due to its effective tissue penetration, highly favorable tolerability, and low resistance rates in Germany (refer to chapter 2 for data on the resistance situation in Germany). Much higher rates of resistance should be expected in patients from other countries (e.g. Spain, France and Hungary).
Benzylpenicillin is also available for intramuscular depot injection as a slowly dissolving salt (benzylpenicillin benzathine). The plasma concentrations achieved with these formulations are low with delayed appearance in the blood stream. Indications for depot penicillins are prevention of recurrence in rheumatic fever and erysipelas as well as the treatment of primary syphilis.

Isoxazolyl penicillins: flucloxacillin, oxacillin

This subgroup has a narrow antimicrobial spectrum covering gram-positive organisms, with good activity against staphylococci, including penicillinase-producing strains. These penicillin derivatives are ineffective against methicillin-resistant staphylococci. They are less active than benzylpenicillins against gram-positive pathogens other than staphylococci. Therefore they should be used exclusively in the targeted therapy of infections caused by methicillin-susceptible staphylococci.
Compared to other penicillins, isoxazolyl penicillins are bound to plasma proteins to an extent of >90% and less able to penetrate infected tissues effectively.

Aminopenicillins: ampicillin, amoxicillin/clavulanic acid, ampicillin/sulbactam

The antibacterial spectrum of the aminopenicillins covers gram-positive as well as some gram-negative pathogens. They show good efficacy against streptococci, including pneumococci. Aminopenicillins are more active than penicillin G against *Enterococcus faecalis* and *Listeria* spp.
However, aminopenicillins have very limited activity against staphylococci and gram-negative pathogens, particularly enterobacteriaceae, *Moraxella catarrhalis* and *Bacteroides fragilis* due to increasing resistance mediated by beta-lactamases. Up to 80% of these strains are not susceptible. However, combination of aminopenicillins with beta-lactamase inhibitors (BLI) extends the antibacterial spectrum to a range of beta-lactamase-producing gram-positive and gram-negative pathogens as well as anaerobes and enables an empiric therapy.
Ampicillin is licensed for the treatment of acute and chronic bacterial infections caused by pathogens proven to be susceptible, independent of localization and severity of illness. This includes endocarditis, meningitis, and sepsis. The drug is also licensed for upper and lower respiratory tract infections, urogenital tract infections, intraabdominal infections, skin and soft tissue infections, as well as perioperative antibacterial prophylaxis.
Fixed combinations of amoxicillin/clavulanic acid and ampicillin/sulbactam are commercially available. Sulbactam is also available as a monosubstance for free combination with other beta-lactams.
The most common adverse effects of aminopenicillins are pseudoallergic skin reactions, a measle-like skin eruption that usually appears 5 to 10 days after the initiation of treatment. The exanthema most often affects patients with simultaneous viral infections (e.g. EBV mononucleosis).

Ureidopenicillins: mezlocillin, piperacillin, piperacillin/tazobactam, combinations with sulbactam

The antibacterial spectrum of ureidopenicillins covers gram-positive and gram-negative pathogens, including *Pseudomonas aeruginosa* for piperacillin. Because of the increasing rate of beta-lactamase-producing staphylococci, enterobacteriaceae and important anaerobes, the efficacy of ureidopenicillins used on their own is often limited.

However, the antibacterial spectrum is extended to beta-lactamase-producing pathogens by combination with beta-lactamase inhibitors (BLI). Ureidopenicillin-BLI combinations are considered appropriate for empiric initial antibiotic therapy of severe nosocomial infections.

Fixed combinations of piperacillin with tazobactam or free combinations of mezlocillin or piperacillin with sulbactam are available. Tazobactam is the most effective BLI in vitro. Well-documented studies, practical advantages and pharmacokinetic aspects favor the use of the fixed piperacilin/tazobactam combination for evidence-based antibiotic therapy. Moreover, in patients with renal failure, piperacillin and tazobactam are absorbed, distributed and eliminated with very similar kinetics while piperacillin and sulbactam show more divergent pharmacokinetics.

Ureidopenicillins are licensed for a broad spectrum of indications including systemic and local infections by susceptible pathogens (gram-positive, gram-negative, aerobic, anaerobic and mixed infections), ENT (ear, nose and throat) infections (piperacillin only), severe systemic infections including sepsis, bacterial endocarditis, meningitis, respiratory tract infections, intra-abdominal infections, renal and urinary tract infections, gynaecological infections, skin and soft tissue infections (including burns), bone and joint infections (including osteomyelitis) and perioperative antibacterial prophylaxis.

Cephalosporins

According to the recommendations of the Paul Ehrlich Society (PEG), cephalosporins are categorized into 5 groups in Germany. The previous group 5 contained only cefoxitin which is no longer available in Germany. The free position was therefore filled by ceftobiprol, a new cephalosporin active against MRSA (see group 5 below).

The pharmacodynamic properties of cephalosporins are similar to those of penicillins. In terms of pharmacokinetics, the individual agents exhibit considerable variations. Most cephalosporins are renally eliminated as unchanged substance. The average plasma half-life in patients with normal renal function is approximately 2 hours. Ceftriaxon has an average half-life of about 8 hours and is eliminated mostly via biliary excretion. Like the structurally related penicillins, cephalosporines are distributed extracellularly with a relative distribution volume of 0.2 to 0.4 l/kg of body weight.

Generally, cephalosporins are very well tolerated. Allergic reactions are less frequently observed than with penicillins. Cross-allergies to penicillins are limited (<10%). Refer to chapter 2 for resistance data.

Group 1 cephalosporins: cefazoline

Cefazoline is predominantly effective against staphylococci and streptococci. Like all cephalosporins except for ceftobiprole (see group 5 cephalosporins), cefazolin is inactive against methicillin-resistant staphylococci. The percentage of susceptible enterobacteriaceae (*Escherichia coli*, *Klebsiella* spp., etc.) has declined in recent years. Cefazoline is primarily appropriate for the treatment of infections caused by methicillin-susceptible staphylococci, and for perioperative prophylaxis.

Group 2 cephalosporins: cefuroxim, cefotiam

Compared to cefazoline, these cephalosporins have an extended spectrum in the gram-negative range which also includes *Haemophilus influenzae*. In addition, they are effective against methicillin-susceptible staphylococci (cefotiam > cefuroxime). High resistance rates must be expected with AmpC-producing enterobacteriaceae, such as *Enterobacter* spp. and *Citrobacter* spp. as well as *Morganella morganii* and *Proteus vulgaris*. These antibiotics are licensed for use against a wide range infections caused by susceptible pathogens, e.g. skin and soft tissue infections, bone and joint infections, respiratory tract infections, as well as kidney and urinary tract infections.

Group 3 cephalosporins

3a: cefotaxime, ceftriaxone
3b: ceftazidime

Group 3 cephalosporins show a wide spectrum of activity with a pronounced antibacterial effect against gram-negative bacteria. However, their spectrum of antibacterial activity is being restricted by the spread of enterobacteriaceae producing extended-spectrum beta-lactamases (ESBL) which render group 3 cephalosporins ineffective. Compared with group 1 and 2 cephalosporins, the efficacy of cefotaxim and ceftriaxon is weaker against staphylococci, while ceftazidim is inadequate for this genus of pathogens.

Group 3 cephalosporins are inappropriate for use in suspected or proven staphylococcal infections. In contrast to cefotaxime and ceftriaxone, ceftazidime is clinically ineffective against streptococci and pneumococci. Cefotaxime and ceftriaxone (group 3a) are ineffective against *Pseudomonas* while ceftazidim (Group 3b) shows good activity against this particular pathogen. The licensed indications include infections of all organ systems caused by susceptible pathogens.

Group 4 cephalosporins: cefepime, cefpirome (Austria)

The activity of group 4 cephalosporins against staphylococci is comparable to group 3a; their efficacy against *Pseudomonas* is comparable to ceftazidim. Cefepime and cefpirome are effective against pathogens overexpressing AmpC beta-lactamases (predominantly *Enterobacter* spp., *Citrobacter* spp.), which differentiates them from group 3 cephalosporins. However, ESBL-producing pathogens are still resistant.

Group 5 cephalosporins: ceftobiprole

The activity of ceftobiprole against gram-negative pathogens is comparable to group 4 cephalosporins. However, it is also active against methicillin-resistant staphylococci and *Enterococcus faecalis*. The licensed indications are currently limited to severe skin and soft tissue infections. Adherence to the recommended infusion duration of 2 hours is warranted.
Addendum: ceftobiprole had been introduced in Canada and Switzerland. Currently (November 2013), the drug is no longer available worldwide.

Carbapenems

Carbapenems are well-tolerated beta-lactam antibiotics divided into 2 groups based on their spectrum of activity. They have a very broad overall efficacy spectrum in the gram-positive and gram-negative domains, including anaerobic and ESBL-producing pathogens. In the recent years nosocomial infections due to carbapenemase-producing strains have been increasingly reported. Carbapenems have no or very limited activity against these isolates.
Stenotrophomonas maltophilia is primarily resistant to carbapenems. Carbapenems are also inactive against methicillin-resistant staphylococci and *Enterococcus faecium*.
Doripenem, imipenem/cilastatin and meropenem belong to group 1. Ertapenem is categorized in group 2 as it has no efficacy against enterococci, *Pseudomonas* spp. and *Acinetobacter* spp.
Further differentiations can be made in terms of pharmacokinetics. Carbapenems are distributed extracellularly with a relative distribution volume of 0.1 L/kg (ertapenem) and 0.2 L/kg of body weight (doripemen, imipenem, and meropenem), respectively. The protein-bound fraction is >90% for ertapenem, 25% for imipemen/cilastatin, 8% for doripemen and 2% for meropenem. All carbapemens are partially metabolized and eliminated mostly via the kidneys. The half-life of group 1 carbapenems in patients with normal renal function is approximately 1 hour. Ertapenem has a longer half-life of approximately 4 hours and may be given once daily. The dosages of doripenem, imipenem/cilastatin and meropenem are equivalent. For doripenem a longer infusion time is recommended and licensed, especially for less susceptible pathogens and severe infections.
As for penicillins, a dose-dependent epileptogenic adverse drug reaction (ADR) is known for all carbapenems (imipenem > ertapenem > meropenem > doripenem). As this ADR is reported most frequently with imipenem, this drug is not appropriate for the treatment of CNS infections. Meropenem is the only carbapenem licensed for the treatment of meningitis.

Monobactams: aztreonam

The pharmacokinetics and pharmacodynamics of aztreonam are similar to those of the penicillins. It is active exclusively against gram-negative pathogens including *P. aeruginosa*. *Acinetobacter* spp., *S. maltophilia* and ESBL-producing enterobacteriaceae are resistant. However, strains which produce metallo-beta-lactamases (MBL) are susceptible to aztreonam.
Because of the structural differences, cross-allergies with beta-lactam antibiotics are unlikely. The clinical relevance of aztreonam is limited. It can be used in combination with antibiotics effective against gram-positive bacteria.

Fluoroquinolones

As recommended by the PEG, fluoroquinolones are categorized into 4 groups. Since only groups 2 through 4 include parenterally available drugs, only these three groups will be considered here.
Fluoroquinolones show concentration-dependent bactericidal activity with a generally broad spectrum of activity. The differences between the groups are discussed in the following section.
The growing resistance rates in *Escherichia c*oli and other enterobacteriaceae clearly limit the use of fluoroquinolones for empiric initial monotherapy, particularly in nosocomial infections. Cross-resistance among all fluoroquinolones is the rule. The fluoroquinolones penetrate well into many tissues and show intracellular and extracellular distribution, with relatively high distribution volumes of 2–4 L/kg of body weight. Usually less than 40% of the drug is bound to plasma proteins.
Levofloxacin is eliminated almost exclusively via the kidneys while ciprofloxacin shows some biliary and transintestinal elimination as well. Moxifloxacin is metabolized extensively via conjugation. The half-life is 3–4 hours for ciprofloxacin, 7–8 hours for levofloxacin, and more than 10 hours for moxifloxacin, which explains the different dosing intervals.
Adverse drug reactions are reported in 4–10% of treated patients, most frequently as gastrointestinal disturbances, CNS disorders (sleeplessness and dizziness), or skin reactions.

Group 2 fluoroquinolones: ciprofloxacin, (ofloxacin)

Ciprofloxacin has excellent activity against gram-negative enterobacteria and *H. influenzae*, and good activity against *P. aeruginosa*. It is only weakly active against staphylococci and clinically inadequate against pneumococci and enterococci. Moreover, ciprofloxacin is less active against *Chlamydia*, *Legionella* and *Mycoplasma* spp. than group 3 and 4 fluoroquinolones.
Licensed indications include uncomplicated and complicated renal and urinary tract infections, ENT infections, respiratory tract infections (excluding pneumococcal infections), abdominal infections, genital organ infections, bones and joint infections, skin and soft tissue infections, bacterial sepsis, and infections in neutropenic patients. The use of ofloxacin is no longer recommended (see below).

Group 3 fluoroquinones: levofloxacin

Levofloxacin is the L enantiomer and therefore the active entity of the racemic substance ofloxacin: its antibacterial activity is twice as high. Compared with ciprofloxacin, it shows improved efficacy against gram-positive pathogens such as staphylococci, streptococci and pneumococci as well as against *Legionella*, *Chlamydia* and *Mycoplasma* spp. Against gram-negative pathogens it is similarly active as ciprofloxacin, although it is somewhat less effective against *P. aeruginosa*.
Levofloxacin is licensed for the treatment of community-acquired pneumonia, complicated urinary tract infections, and skin and soft tissue infections.

Group 4 fluoroquinolones: moxifloxacin

Due to its structural differences versus group 2 and 3 fluoroquinolones, moxifloxacin is considerably more active against gram-positive pathogens, i.e. staphylococci and streptococci, including *S. pneumoniae*. Its efficacy against *Legionella*, *Chlamydia* and *Mycoplasma* spp. is further improved. Moxifloxacin is the only fluoroquinolone with useful activity against gram-positive and gram-negative anaerobes. However, is not adequately effective against *P. aeruginosa*.
Moxifloxacin is licensed for the treatment of community-acquired pneumonia and complicated skin and soft tissue infections.

Macrolides and azalides: erythromycin, clarithromycin, azithromycin

Macrolides have good antibacterial activity against *Mycoplasma*, *Legionella* and *Chlamydia* spp. as well as streptococci, including *S. pneumoniae* and *Bordetella pertussis*. Macrolide resistance rates of pneumococci have reached values beyond 20% in Germany but are recently declining. Data on resistance rates are given in chapter 2.
Erythromycin has inadequate activity against *H. influenzae*. The microbiological activity of clarithromycin, its active metabolites and azithromycin is somewhat higher but the clinical efficacy of these drugs against infections with this pathogen is still considered insufficient.
Macrolides are basically bacteriostatic agents but develop bactericidal effects at higher concentrations. Their pharmacodynamics are time-dependent. In addition to the antibacterial activity, an immunomodulatory effect of macrolides is being discussed.
The macrolides show dose-proportional pharmacokinetics. The half-life is below 2.5 hours for erythromycin, between 2 and 5 hours for clarithromycin, and above 14 hours for azithromycin. The volumes of distribution also show significant differences: approximately 0.7 L/kg for erythromycin, 4 L/kg for clarithromycin and 25 L/kg of body weight for azithromycin.
The macrolides are extensively metabolized in the liver. They are eliminated primarily via biliary excretion.
The most frequent side effects of macrolides are gastrointestinal disorders and elevated liver enzyme levels. Extensive drug interactions are a problem with erythromycin and clarithromycin.
Licensed indications are respiratory tract infections (including those with *Chlamydophila pneumoniae* or *Legionella)*, whooping cough, diphtheria, scarlet fever and erysipelas.

Glycopeptides: vancomycin, teicoplanin

Vancomycin and teicoplanin are exclusively active against gram-positive pathogens. Their spectrum of activity covers staphylococci including methicillin-resistant strains, streptococci, enterococci inclucing *E. faecium*, *Corynebacterium* spp., and *Clostridium difficile*. Resistance of *Staphylococcus aureus* against glycopeptides has been described only in individual cases to date. Teicoplanin resistance has been observed in coagulase-negative staphylococci. Elevated minimal inhibitory concentrations (MICs) of vancomycin in MRSA are considered to be asscociated with treatment failure and higher mortality rates (see chapter 2).
The glycopeptides should be used only if other agents cannot be used due to resistance or allergies, as they are clinically less effective against non-resistant pathogens and have tolerability issues (see below).
The antibacterial activity of glycopeptides is time-dependent, with a slow onset of the therapeutic effect. The volume of distribution is 0.4–0.9 L/kg for vancomycin and 1 L/kg for teicoplanin. Glycopeptide pharmacokinetics show extensive intraindividual and interindividual variability. The plasma half-life is usually 4–6 hours for vancomycin and 70–100 hours for teicoplanin.
In plasma, 55% of vancomycin is bound to proteins, compared to 90% of teicoplanin. Glycopeptides are eliminated predominantly unchanged via the kidneys. Glycopeptides are potentially nephrotoxic and ototoxic, depending on the drug used. Plasma level monitoring of

vancomycin is therefore essential. Alternative antibiotics should be used in patients with renal dysfunction.
Intravenous infusion of vancomycin requires appropriate dilution and infusion times to avoid a "red man syndrome". The licensed indications cover bacterial sepsis, endocarditis, and infections of bones and joints, respiratory tract, skin and soft tissue, kidneys and urinary tract.

Aminoglycosides: amikacin, gentamicin, tobramycin

Aminoglycosides are effective against gram-negative bacteria, primarily enterobacteriaceae. Against *P. aeruginosa*, tobramycin and amikacin are more active than gentamicin. Aminoglycosides are less effective against gram-positive pathogens. They are used in combination with beta-lactam antibiotics to enhance efficacy in *Enterococcus* infections.
Aminoglycosides exert a broad, rapid concentration-dependent bactericidal effect. Target serum and/or tissue concentrations should exceed 5 times the minimum inhibitory concentration (MIC) of the pathogen. The postantibiotic effect of aminoglycosides may last for several hours, depending on the serum concentration, the agents used in combination and the patient's immune function. The efficacy of aminoglycosides is pH-dependent: they are inactive in acidic and anaerobic environments.
Aminoglycosides are distributed extracellularly and eliminated as unchanged drugs via the kidneys. The mean relative volume of distribution is approximately 0.25 L/kg of body weight (range 0.1 to 0.8 L/kg). The plasma half life is in the range of 2 hours in patients with normal renal function and considerably longer in patients with renal impairment. Therefore, the creatinin clearance must be considered when treating high-risk patients and therapeutic drug monitoring is mandatory. Particularly in combination treatment with beta-lactam antibiotics, the entire daily dose should be administered once daily rather than three times daily to reach the highest possible peak concentration. There is evidence for a lower toxicity rate and better clinical results with the once daily dosage. Within a 24-hour dosing interval, the target minimum concentration of <1 mg/L and (extrapolated) peak concentration between 15 and 20 mg/L for gentamicin and tobramycin and about 60 mg/L for amikacin should be achieved in patients with normal kidney function. There is insufficient data on the once-daily dosage in the treatment of endocarditis and these cases should be treated conventionally.
Aminoglycosides have pronounced ototoxic and nephrotoxic potential and should be used only if strictly required. If used appropriately (once daily dosing, short duration of treatment with plasma level monitoring), these antibiotics have an acceptable tolerance level (see chapter 4). The licensed indications include severe (nosocomial) infections caused by gram-negative bacilli, febrile neutropenia, and *Pseudomonas* infections in cystic fibrosis. Aminoglycosides should never be used as single agents. Rather, they are usually combined with beta-lactam antibiotics. They may be used in combination with aminopenicillins for enterococcal endocarditis and *Listeria* infections. Duration of therapy with aminoglycosides is usually limited to 3–5 days.

Oxazolidinones: linezolid

Linezolid is active only against gram-positive pathogens. It has a good efficacy against gram-positive cocci, primarily staphylococci including methicillin-resistant strains and enterococci including vancomycin-resistant strains (VRE). It is bactericidal against streptococci and bacteriostatic against staphylococci and enterococci.
The relative volume of distribution is about 0.6 L/kg of body weight. Approximately 30% of the drug is bound to plasma proteins. The half-life in plasma is 5 to 7 hours with primarily renal elimination.
Linezolid is licensed for community-acquired and nosocomial pneumonia as well as complicated skin and soft tissue infections.
Due to the potential side effect of thrombocytopenia, regular monitoring of the blood count during therapy is necessary. Treatment duration should not exceed 28 days.

Lincosamides: clindamycin

Clindamycin has a predominantly bacteriostatic, time-dependent effect on staphylococci, streptococci, *Bacteroides* spp., *Corynebacterium* spp. and *Mycoplasma pneumoniae*. Due to its mechanism of action, clindamycin inhibits the production of toxins by staphylococci and streptococci and is therefore an important combination partner in the treatment of infections with toxins as a major pathogenic factor.
The relative distribution volume is in the range of 0.6 l/kg of body weight and the half-life is 2 to 3 hours. More than 80% of clindamycin is converted to active metabolites. Licensed indications include infections of bones and joints including septic arthritis, maxillodental infections, ENT infections, respiratory tract infections, pelvic and intra-abdominal infections, skin and soft tissue infections as well as scarlet fever, sepsis and endocarditis caused by clindamycin-susceptible pathogens.

Tetracyclines: doxycycline

The antibacterial spectrum of doxycycline covers gram-positive and gram-negative pathogens as well as *Chlamydia* and *Mycoplasma* spp. Doxycycline has primarily bacteriostatic activity and acts both extra- and intracellularly. The relative distribution volume is 0.8 L/kg of body weight with a half-life of 10 to 22 hours. Doxycycline is metabolized to a small extent and eliminated primarily via biliary and renal routes. Doxycycline has a broad spectrum of indications including the treatment of infections caused by susceptible pathogens primarily in the ENT region, respiratory tract, urogenital tract, abdom-

inal region and biliary tract as well as borreliosis. Intravenous doxycycline is currently the drug of choice for rickettsiosis, plague, brucellosis, and query fever among others.

Glycylcyclines: tigecycline

Tigecycline has a broad spectrum of activity that extends to multiresistant gram-positive pathogens such as MRSA and VRE and multiresistant gram-negative bacteria such as ESBL-producing enterobacteriaceae and multiresistant *Acinetobacter baumannii*. It includes anaerobes and *Chlamydia*, *Mycoplasma* and *Legionella* spp. as well. Tigecycline is inactive against *P. aeruginosa*, *Proteus* spp., and *M. morganii*. The mode of action is primarily bacteriostatic. However, bactericidal activity has been observed e.g. for *S. pneumoniae* and *H. influenzae* [574], [584]. The volume of distribution is the range of 7 to 9 L/kg of body weight. The average terminal half-life is 42 hours. 59% of the substance is eliminated via bile and faeces and 33% via urine. Tigecycline is licensed for the treatment of complicated skin and soft tissue infections as well as complicated intra-abdominal infections.

Ansamycins: rifampicin

In vitro, rifampicin is active against mycobacteria, staphylococci including methicillin-resistant strains, streptococci and *E. faecalis*, among others. It acts strongly bactericidal or bacteriostatic against proliferating cells, depending on the drug concentration and the activity of the pathogen. Rifampicin should not be used as monotherapy due to a high risk of rapid resistance development. In plasma 70–90% of rifampicin is bound to protein. The agent has a high tissue penetration and accumulates intracellularly. Rifampicin has a relative distribution volume of >1 L/kg of body weight. The half-life depends on the duration of treatment. In long-term therapy, the half-life is as low as 2–3 hours due to autoinduction of metabolism. Rifampicin is eliminated via bile and urine.
The most frequent side effects are liver dysfunction and gastrointestinal disturbances. Changes of blood cell count may be observed. As a strong inducer of cytochrome P450 enzymes rifampicin has a high potential for pharmacokinetic interactions with other drugs.

Nitroimidazoles: metronidazole

Metronidazole is active against anaerobic gram-positive and gram-negative bacteria, except for propionibacteria and actinomycetes. Metronidazole exerts a concentration-dependent bactericidal effect. The relative distribution volume is in the range of 0.5 L/kg of body weight with a half-life of 6 to 8 hours. In plasma 10–20% of metronidazole is bound to protein. The agent is metabolized in the liver and eliminated primarily via urine.
Metronidazole is licensed for the treatment of proven or suspected infections caused by anaerobes in various localizations (including brain abscesses) and for perioperative prophylaxis. Metronidazole is usually used in combination with other antibiotics for mixed aerobic and anaerobic infections and in monotherapy for *Clostridium difficile*-associated disease.
Adverse drug reactions include peripheral and central neuropathies.

Fosfomycin

Fosfomycin has a broad spectrum of activity that covers gram-positive and gram-negative pathogens, with bactericidal activity against MRSA, ESBL-producing enterobacteriaceae and *P. aeruginosa*.
Fosfomycin is not bound to plasma proteins and is eliminated as unchanged drug via the kidneys. Its plasma half-life is 2 hours. Fosfomycin penetrates highly effectively into various tissues.
It is licensed for a wide spectrum of infections, including severe diseases such as sepsis, meningitis, brain abscess, endocarditis, bone and joint infections, respiratory tract infections, skin and soft tissue infections, kidney and urinary tract infections and ENT infections. Fosfomycin is not recommended for monotherapy of severe infections but can be used in combinations with many other antibiotics.
The most frequent side effects are associated with the high sodium content and increased potassium excretion.

Cotrimoxazole

Cotrimoxazole is a combination drug containing sulfamethoxazole and trimethoprim. It shows broad-spectrum activity against gram-positive and gram-negative pathogens as well as protozoa and *Pneumocystis jirovecii*. Both agents are distributed intracellularly and extracellularly. The substances are metabolized in the liver. The average half-life of the active drugs is 6.4 hours for sulfamethoxazole and 7.8 hours for trimethoprim. Excretion occurs primarily via urine and to a lower extent via bile.
Like many older antibiotics, cotrimoxazole is licensed for a broad spectrum of indications. Rational indications include *Pneumocystis* pneumonia, *S. maltophilia* infections and nocardiosis. Reversible bone marrow suppression and allergic reactions (sometimes including Stevens-Johnson or Lyell syndrome) may occur, particularly in long-term usage.

Cyclic lipopeptides: daptomycin

Daptomycin is active exclusively against gram-positive bacteria including multi-resistant pathogens such as MRSA and VRE. It is bactericidal in both growth and stationary phases of the pathogen life cycle. The half-life is in the range of 8–9 hours, 92% of the drug is bound to proteins. Daptomycin has a low distribution volume of 0.1 l/kg of body weight. The agent is eliminated primarily via urine, 5% of the parent drug is excreted with faeces.
Daptomycin is licensed for the treatment of bacteremia,

endocarditis, and skin and soft tissue infections [298], [308], [470].

Polymyxins: colistin

Colistin shows bactericidal activity against gram-negative pathogens, including multi-resistant strains of *P. aeruginosa* and *A. baumannii* as well as ESBL- or carbapenemase-producing enterobacteriaceae. *Proteus* spp., *M. morganii*, *Serratia marcescens*, *Burkholderia-cepacia* complex, *Neisseria* spp. and *M. catarrhalis* are resistant against colistin. Recent data on the pharmacokinetics and pharmacodynamics are limitied. Nephrotoxicity and neurotoxicity, side effects that were frequently reported in the past, have more rarely been observed in newer case series and studies. Intravenous colistin is recommended exclusively for infections caused by multiresistant gram-negative pathogens [367].

2 Microbiology

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The effective and economical use of antibiotics is based on rational and reliable microbiological diagnostics. An essential prerequisite for the adequate treatment choice for empiric therapy is a sound knowledge of the usual spectrum of pathogens and the current local, regional, national and international resistance situation. This knowledge is also required for hospital hygiene and infection prevention management. A close cooperation of treating physician, microbiologist and hygiene specialists is required. Cooperation starts with the optimal choice, correct collection and adequate transportation of the specimen material, as mistakes made at this stage cannot be amended later. Pure cultures of the pathogen are a mandatory prerequisite for susceptibility testing and require the best possible specimen material ("tissue samples are superior to smears"). The collaboration continues with the joint evaluation of the detected microorganisms and their susceptibility, the clinical diagnosis, an agreement on rational antibiotic therapy and hospital hygiene measures if appropriate.
The close coordination between the clinical wards and the microbiology/hospital hygiene departments should enable joint compilation and implementation of local guidelines on antibiotic use, surveillance of resistance and nosocomial infections and anti-epidemic hygiene measures. The clinical microbiologist and/or the infection control specialist should be locally available for regular participation in patient visits and ad-hoc case discussions. This allows well-targeted diagnoses and ensures rational antibiotic use.

Susceptibility testing

The susceptibility of a pathogen to an antibiotic is established through the determination of in vitro activity. The reference method is the determination of the minimum inhibitory concentration (MIC in mg/L) according to ISO 20776-1 [130]. The minimum requirement is the use of methods complying to ISO 20776-2 in the laboratory routine. Agar diffusion tests are used as well.
The numerical value of the MIC and the inhibition zone diameter (in mm) provide information on the susceptibility of a pathogen in vitro. Clinical interpretation of the results is achieved with the help of threshold concentrations (cut-off values) in the categories susceptible, intermediate (if defined) or resistant. European harmonized cut-off values as developed by the European Committee of Antimicrobial Susceptibility Testing (EUCAST) (http://www.eucast.org/%20clinical_breakpoints/) are available for most antibiotics. In Germany, the Medical Standards Committee of the German Institute for Standards (DIN) is responsible for the provision of the cut-off values. To date the recommendations of the US Clinical Laboratory Standards Institute (CLSI) are used in parallel to European standards. The cut-off values of EUCAST and DIN are almost always identical. However, they often diverge from the CLSI values, potentially resulting in pronounced differences of resistance rates. Therefore resistant rates derived from different standards cannot be directly compared.
When interpreting a microbiological result, a species-specific consideration of the antibiogram is essential. In cases of doubt and in cases with critical therapeutic relevance of resistance results, additional methods including nucleic acid detection (PCR) or antigen detection can be used to confirm the evaluation of special susceptibility in selected pathogens.
In addition, even an optimal microbiological diagnosis cannot exclude discrepancies between antibiogram and treatment outcome. The most frequent causes are mistakes in the pre-analytical phase resulting in the examination of a bacterial isolate which is not the actual pathogen. Quality problems may also result from prolonged transportation times of the sample material, which can easily lead to the inactivation of sensitive pathogens, overgrowth of irrelevant pathogens and drying out of sample material.
Potential reasons for clinical failure with a sensitive pathogen or clinical success with a resistant pathogen are summarized in Table 3. In conclusion, any susceptibility testing has its methodological limitations. While correlation to the clinical situation is imperfect it still can help to predict clinical efficacy!

Resistance situation

The resistance situation of important bacterial species in Germany and in Central Europe is investigated at regular intervals by the PEG Working Group for Susceptibility Testing and Resistance in selected laboratories in Germany, Austria and Switzerland using uniform and

Table 3: Reasons for discrepancies between antibiograms and clinical treatment outcomes

Testing of non-relevant pathogens
Mistakes in administration of the drugs (e.g. inactivation of the antibiotic due to incompatibility, interactions with coadministered drugs)
Insufficient concentration of the antibiotic at the site of infection due to inadequate dosage
Impaired distribution
Accumulation of the antibiotic in the infected area
Discrepancy between the effect of the antibiotic in vivo and in vitro (e.g. causes by pH or pO_2)
Possible antagonism of antibiotic combination
Lack of compliance
Immune deficiency
Development of resistance during treatment
Change of pathogen
Susceptibility in individual cases despite group resistance (laboratory problem)
Spontaneous healing

standardized methods (PEG Resistenzstudie, http://www.p-e-g.de/resistenz). Moreover, data are available from the PEG Working Group on Blood Culture Studies [41], the German Network for Antimicrobial Resistance Surveillance (GENARS, http://www.genars.de/), which is now being continued within the framework of the ARS (see below), and the SARI Project (sari.ipse-freiburg.de). The European Antimicrobial Resistance Surveillance Network (EARS-net) supplies country-specific resistance data for isolates from patients with systemic infections (EARS-net, http://www.rivm.nl/earss). Further data sources regarding the monitoring of important pathogens include the national and international resistance surveillance studies carried out by the pharmaceutical industry (G-TEST [268], MYSTIC [528], TEST [382], ZAAPS [244] etc.) as well as the national reference centres (NRZ, http://www.rki.de/DE/Content/Infekt/NRZ/nrz_uebersicht_ gesamt_node.html).

Recently, the Robert Koch Institute created the Antibiotics Resistance Surveillance System (ARS, https://ars.rki.de/) operating within the framework of the German Antibiotics Resistance Strategy (DART). It provides data on the resistance situation in both hospital and community-based care. A summary of data on the use of antibiotics and the spread of resistances in human and veterinarian medicine is available in the GERMAP 2008 and 2010 report (http://www.p-e-g.org/econtext/germap) initiated by the Federal Ministry of Consumer Protection and Food Safety, the PEG and the Infection Diseases Department in Freiburg, and which will be regularly updated in the future.

Within the framework of the PEG Resistance Study of 2007, 5,908 bacteria strains from different sample sources (wounds 26%, respiratory tract 20%, urinary tract 18%, blood 12%) were investigated in 26 laboratories. About 56% of the samples were from patients treated in general wards, 24% from intensive care patients and 18% from outpatients. The results indicate that the resistance rates of many pathogens have increased considerably in the last decade. The PEG Blood Culture Study conducted in 2006/2007 included 7,652 isolates from 14 laboratories. The following section discusses important resistance trends in the time between 1998 and 2007 as identified from the PEG Resistance Study and some results from the 2006/2007 Blood Culture Study.

Beta-lactam antibiotics

According to the results of the resistance study for *Escherichia coli*, ampicillin resistance has increased from 41% in 1998 (n=783) to 55% in 2007 (n=648) while cefuroxim resistance increased from 6% to 15%. The percentage of strains with extended spectrum beta-lactamases (ESBL) which inactivate group 3, 4 and 5 cephalosporins (as identified by the new cephalosporin classification, see chapter 1) has increased from 1% to 10% for *E. coli* and from 4% in 1998 (n=275) to 10% in 2007 (n=273) for *Klebsiella pneumoniae*. In the 2006/2007 blood culture study, the percentage of isolates with resistance to cefotaxim was 8% for *E. coli* (n=1523) and 15% for *K. pneumoniae* (n=315). Between 1998 (n=859) and 2007 (n=761), the resistance of *Pseudomonas aeruginosa* to ceftazidim and piperacillin (± beta-lactamase inhibitor) increased from 5–6% to 12–14%.

The percentage of methicillin (i.e. oxacillin) resistant strains of *Staphylococcus aureus* (MRSA) increased from 12% in 1998 (n=873) to 20% in 2007 (n=782). In 1990 (n=1310), the MRSA rate had been as low as 2%. The frequency of methicillin (i.e. oxacillin) resistant strains of Staphylococcus epidermidis slightly increased from 68% to 74% between 1998 (n=555) and 2007 (n=423). In the 2006/2007 study, 24% and 81% of blood culture isolates of *S. aureus* (n=1108) and *S. epidermidis* (n=194), respectively, were resistant to oxacillin.

Penicillin-resistant pneumococci are very rare in Germany. The rate of isolates with reduced susceptibility to penicillin was 10% in the 2007 resistance study (n=406) and 5% in the 2006/2007 blood culture study (n=79). Carbapenem-resistant enterobacteriaceae as well are still rarely encountered in Germany. The percentage of *P. aeruginosa* strains with reduced susceptibility to meropenem and imipenem was 10% to 14% of isolates from 411 patients in general wards as opposed to 20%

to 23% of isolates from 196 patients treated in intensive care units. 26% of *P. aeruginosa* isolates (n=224) in the 2006/2007 blood culture study showed reduced susceptibility to meropenem.

Fluoroquinolones

The percentage of ciprofloxacin-resistant strains increased from 8% in 1998 to 26% in 2007 for *E. coli* and from 14% to 18% for *P. aeruginosa*. In the 2007 resistance study, resistance to levofloxacin was 26% for *E. coli* and 20% for *P. aeruginosa*. Reflecting the multiresistance of MRSA isolates, the percentage of *S. aureus* strains resistant to fluoroquinolones increased from 17% to 28%. In the 2006/2007 blood culture study, 32% of the 1,523 *E. coli* isolates and 27% of the 224 *P. aeruginosa* isolates were resistant to ciprofloxacin and 31% of the 1,108 *S. aureus* isolates were resistant to moxifloxacin.

Macrolides

The rate of macrolide-resistant strains in pneumococci was 14% in the 2007 resistance study (n=406) and 25% in the 2006/2007 blood culture study (n=79). The data on invasive pneumococci from the National Reference Centre for Streptococci shows a decrease of the resistance rates from 16% to 13% for adults and 21% to 14% for children in 2008 (1,907 adults, 280 children) versus 2007 (1,676 adults, 284 children).

Glycopeptides

Glycopeptide resistance rates of staphylococci remained favourably low according to results from both the 2007 resistance study and the 2006/2007 blood culture study. While vancomycin-resistant MRSA strains (VRSA; MIC>8 mg/l) exhibiting vanA resistance mechanisms are extremely rare worldwide, the so-called VISA (vancomycin-intermediate *S. aureus*) with a MIC of 4–8 mg/L (according to CLSI criteria) have already been observed in many countries. Changes in the cell wall are believed to be responsible for the reduced susceptibility in these strains. Heterogeneous VISA (hVISA) are potential VISA precursor strains which appear to be vancomycin-susceptible in MIC testing but contain subpopulations of organisms with increased MIC values (≥4 mg/l) [21], [31], [111]. In addition, a slow but steady increase in the average vancomycin MIC for MRSA and MSSA below the suspectibility break points has been reported (referred to as MIC creep or MIC shift in the literature) [447], [496], [564]. These changes are of particular importance as the antibacterial activity of vancomycin against MRSA is already reduced in strains with an MIC apporaching 2 mg/l and vancomycin treatment of bacteremic infections caused by these pathogens has been associated with high failure rates [340], [450]. Consequently, the EUCAST reduced the susceptibility cut-off values for vancomycin and teicoplanin (resistant: >2 mg/l) in 2009.

For *Entercoccus faecium*, the percentage of vancomycin-resistant strains detected in the resistance study increased from 5% in 1998 (n=110) to 11% in 2007 (n=250), whereas vancomycin-resistant isolates of *Enterococcus faecalis* were not found in 2007 (n=488). In the 2006/2007 blood culture study, vancomycin-resistance was observed in 4% and <1% of *E. faecium* and *E. faecalis* isolates, respectively.

Trimethoprim/sulfamethoxazol

For *E. coli*, an increase in the resistance rates from 27% in 1998 to 34% in 2007 was detected.

Daptomycin, linezolid, tigecycline

Resistance rates of staphylococci (including MRSA), enterococci (including VRE) and streptococci against daptomycin and linezolid are still very low worldwide. As in any antibiotic treatment, development of resistance during therapy remains a possibility, however [174], [221], [225], [506]. Recent reports described a plasmid-encoded mechanism of resistance against oxazolidinones in staphylococci, which may promote the spread of resistance [311].

Currently, tigecycline-resistant gram-positive pathogens remain rare as well. Practically all isolates of *E. coli* (including ESBL-producing strains) are susceptible to tigecycline, while 5% to 10% of *Enterobacter cloacae* and *K. pneumoniae* isolates are found to be resistant [268]. Development of resistance during treatment is possible in *Acinetobacter baumannii* and *K. pneumoniae* [20], [249], [426].

Imipenem-resistant strains of *A. baumannii* tend to be less susceptible to tigecyclin than imipenem-susceptible strains of this pathogen [268]. Evidence-based summaries of the resistance situation for important bacterial pathogens (Grade A evidence) are given in Table 4.

The results of the "PEG Resistenzstudie" (Resistance Study) are mainly provided by laboratories in tertiary care hospitals. Therefore, they cannot necessarily be extrapolated to other areas of medical care. The increase in resistance rates is largely due to the surge in multiresistant pathogens, which may cause pronounced difficulties in antibiotic treatment. In many cases, resistance rates and pathogen patterns in nosocomial infections correlate with the antibiotic usage pattern in the reporting hospital. Any empiric antibiotic therapy must take pathogen epidemiology and local resistance situation into account. Particularly on intensive care units, the regular acquisition of resistance data is a necessary prerequisite for successful treatment. However, the absolute usage figures are probably less important in clinical practice than the failure to comply with general rules of hygiene and infection control measures.

Table 4: Evidence-based information on resistance for important bacterial pathogens (grade A evidence)

Bacteria	Relevance as pathogen and resistance characteristics
Acinetobacter baumannii Group	Growing importance as pathogen of nosocomial infections. Multiple resistances are common. Many different plasmid-encoded and chromosomal beta lactamases (including ESBL), altered permeability and aminoglycoside-modifying enzymes. Carbapenem-resistant strains increasing. Resistance to colistin is rare. Monotherapy associated with risk of rapid development of resistance. Susceptible to intrinsic activity of beta-lactamase inhibitor sulbactam, but no clinical data available.
Burkholderia cepacia complex	Common pathogen in patients with cystic fibrosis, usually with multiple resistances Altered permeability or increased efflux (particularly of fluoroquinolones), various plasmid-encoded beta-lactamases, rarely overexpression of chromosomal beta-lactamases. Commonly susceptible to trimethoprim/sulfamethoxazol when resistant to beta-lactams or fluoroquinolones.
Campylobacter jejuni	Increasing resistance to macrolides and fluoroquinolones.
Citrobacter freundii *Enterobacter spp.* *Morganella morganii* *Proteus vulgaris* *Providencia spp.* *Serratia spp.*	Common pathogens in nosocomial infections. Avoid monotherapy with Group 3 cephalosporins or acylaminopenicillins as mutants with derepressed chromosomal beta lactamases of type AmpC may appear on treatment, leading to resistance. Occurrence of ESBL is observed. For details see *Escherichia coli* and *Klebsiella* spp. Cefepim is active in vitro against hyperproducers of AmpC but not against ESBL-producing pathogens. AmpC beta-lactamases are not inhibited by beta-lactamase inhibitors. Proteus vulgaris may express beta lactamases which cause resistance to cefotaxim but not to ceftazidim and cefepim.
Clostridium difficile	Epidemic isolates of PCR-ribotype 027 show resistance to erythromycin and fluoroquinolones but are susceptible to metronidazol, vancomycin, clindamycin, daptomycin and tigecycline.
Corynebacterium jeikeium and similars	Hospital isolates are frequently multiresistant. High intrinsic resistance against many antibiotics. Cephalosporins are always ineffective.
Entercoccus faecalis *Entercoccus faecium*	*Enterococcus faecalis* is a common pathogen. Only 2% of strains are resistant to ampicillin but 30%–40% show high-level resistance to gentamicin, some with cross-resistance to streptomycin. Penicillinase-producing strains are reported rarely. *Enterococcus faecium* is increasingly common, sometimes more prevalent than *E. faecalis* in intensive care units. Resistance rates: 80%–90% of strains are ampicillin-resistant; 30%–40% have a high level of resistance to gentamicin, in part with cross-resistance to streptomycin. Effective antibiotics are daptomycin, glycopeptides (except for VRE), linezolid and tigecycline. In endocarditis or life-threatening *E. faecalis*-infections, synergistic combinations of an aminopenicillin with gentamicin (or streptomycin), even though routine tests show a low level of resistance (reversal of the Eagle effect). In these situations testing for high-level resistance to gentamicin (or streptomycin) is necessary as this combination is no longer synergistically effective at high levels of resistance. As an exception, the aminoglycoside should not be given as a once-daily dosage but rather is apportioned with the beta-lactam antibiotic. Resistance to vancomycin (mostly vanA, vanB) and teicoplanin (vanA) due to acquisition of additional plasmid-encoded genes which change the target for glycopeptides. The most reliable detection of resistance to vancomycin by screening tests. The vanA genotype is predominant in Europe. Enterococci may show in vitro susceptibility to group 1 to 4 cephalosporines or clindamycin. These antibiotics are clinically ineffective, however. Imipenem is effective against ampicillin-susceptible entercocci only. Practically all *E. faecium* strains are resistant. Fluoroquinolones are ineffective.
Escherichia coli	Frequent nosocomial pathogen. Often resistant to older standard antibiotics (e.g. aminopenicillins, trimethoprim/sulfamethoxazol). Increasing resistance to fluoroquinolones (26%–30%) and increasing of ESBL-producing strains. Caveat: fluoroquinolone-resistant strains are often multiresistant. ESBL-producing strains usually have a parallel resistance to fluoroquinolones and often also a resistance to ampicillin +/- beta-lactamase inhibitor and sometimes also to piperacillin +/- beta-lactamase inhibitor. Clinically poor efficacy of cephalosporins in infections caused by ESBL producers, even if resistance test shows susceptibility. Occurrence of carbapenem-hydrolyzing beta-lactmases still very rare but increasing worldwide. Resistance to tigecyclin and fosfomycin very rare.

(Continued)

Table 4: Evidence-based information on resistance for important bacterial pathogens (grade A evidence)

Bacteria	Relevance as pathogen and resistance characteristics
Klebsiella spp.	May be susceptible to beta-lactamase unstable aminopenicillins and acylaminopenicillins in resistance tests. These antibiotics are clinically ineffective, however. In some cases, they are effective in combination with beta-lactamase inhibitors. Resistances to these combinations occur in about 20% of strains. Increasing occurrence of fluoroquinolone-resistant and ESBL-producing strains. May cause hospital epidemics. For details see *Escherichia coli*. Occurrence of carbapenemases still rare but increasing worldwide. Resistance to tigecycline in about 10% of isolates of *Klebsiella pneumoniae*.
Listeria monocytogenes	Primary resistance to all cephalosporins.
Neisseria meningitidis	No resistance to cefotaxim/ceftriaxone reported to date. Decolonization of carriers with ciprofloxacin, rifampicin or ceftriaxon.
Proteus mirabilis	Usually susceptible to many antibiotics. Occurrence of ESBL rare. For details see *Escherichia coli*.
Pseudomonas aeruginosa	Combination therapy recommended for severe infections (sepsis, pneumonia) until anti-biogram available, except for uncomplicated infections or targeted treatment. Piperacillin/beta-lactamase inhibitor combination usually has no advantage over piperacillin alone. Make sure to use adequate piperacillin dosages.
Salmonella spp.	Endemic occurrence in certain countries, mostly developing countries, often associated with multiresistance (contracted during travel abroad). Group 1 and 2 cephalosporins as well as animoglycosides and tetracyclines are clinically ineffective, even if susceptibility is observed in resistance tests.
Staphylococcus aureus, methicillin (oxacillin) susceptible (MSSA)	Approximately 80% of the MSSA strains produce penicillinases. They are resistant to all penicillase-susceptible penicillins even if the susceptibility test indicates susceptibility. Therapy recommended with isoxazolylpenicillins (penicllinase-stable), group 1 and 2 cephalosporins, and beta lactam/beta-lactamase inhibitor combinations. Benzylpenicillins are the drugs of choice for penicillin-susceptible isolates if beta-lactamase-producing mixed or accompanying organisms are excluded. In case of allergy to beta-lactam antibiotics preferably use clindamycin, alternatively linezolid or daptomycin (minority recommended vancomycin) (with adherence to licensed indications). Use of quinolones not recommended. In severe infections, combinations of penicillinase-resistant penicillins with rifampicin, fosfomycin or fusidic acid may be appropriate (no monotherapy with these drugs due to rapid development of resistance; available study data are limited).
Staphylococcus aureus methicillin (oxacillin) resistant (MRSA)	The prevalence of MRSA varies greatly from clinic to clinic. Carries an additional beta-lactam binding protein due to acquisition of additional chromosomal genes (mecA) within a mobile genetic element (SCCmec cassette). For reliable detection use mecA PCR only. Detection of SCCmec cassettes may suffice in screening for nasal MRSA colonization. MRSA is regarded resistant to all beta-lactams, even if some appear to be effective in susceptibility testing in vitro (exception: ceftobiprol and ceftarolin, but clinical studies still limited). Healthcare-associated MRSA (haMRSA, nosocomial MRSA) are mostly resistant to fluoro-quinolones (>90%), erythromycin and clindamycin (70%–80%). <5% strains are resistant to trimethoprim/sulfamethoxazol, doxycycline, fosfomycin or rifampicin. Isolates with resistance to daptomycin, linezolid or tigecycline are very rare. The prevalence of community-associated (caMRSA) is still low (1–2%) in Germany. Most caMRSA isolates in Germany belong to the clonal lines t044 (ST-80, mostly resistant to tetracyclines and fusidic acid), and t008/t024 (also known as St-8 or USA300), with resistance to macrolides and partially to fluoroquinolones. Antibiotics for treatment of MRSA infections include glycopeptides and – depending on licensed indications – linezolid, daptomycin and tigecycline; as well as other drugs (e.g. clindamycin) depending on susceptibility. In severe infections, combinations of vancomycin with rifampicin, fosfomycin or fusidic acid might be considered (see MSSA for comment). MRSA with resistance to vancomycin (MIC>2 mg/L according to EUCAST) are extremely rare in Germany. Sporadic occurrences of strains with vancomycin MICs of 4–8 mg/L (designated as VISA or GISA according to CLSI nomenclature) are reported in Japan, USA and France. So-called hetero-VISA occur in Germany (exact frequency is unknown). Reliable evidence of vancomycin-resistant MRSA with vancomycin MIC>8 mg/l is reported only in the USA, India and Iran.

(Continued)

Table 4: Evidence-based information on resistance for important bacterial pathogens (grade A evidence)

Bacteria	Relevance as pathogen and resistance characteristics
Staphylococcus epidermidis and other coagulase-negative staphylococci	Approximately 70% and 90% of nosocomial *Staphylococcus epidermidis* and *Staphylococcus haemolyticus* strains, respectively, are methicillin-resistant. Resistance to glycopeptide antibiotics particularly in *S. epidermidis* and *S. haemolyticus* (teicoplanin > vancomycin) is possible, but still rare (but more common than in *S. aureus*); often development of heterogeneously resistant subpopulations. See MRSA for other resistance characteristics.
Stenotrophomonas maltophilia	Mostly resistant to many beta-lactams (including carbapenems due to various beta lactamases, some of them inducible). Isolates from patients with cystic fibrosis usually multiresistant. Some multiresistant strains retain susceptibility to fluoroquinolones (levofloxacin, moxifloxacin), trimethoprim/sulfamethoxazol, doxycycline and tigecycline.
Streptococcus pneumoniae	Susceptible to penicillins: Penicillin resistance is rare in A, CH, and D (in D max. 2%). Rate of intermediately susceptible strains 3%–8%(–15%). Penicillin-resistant strains also show reduced susceptibility to cephalosporins. Commonly parallel resistance to macrolides, sulfamethoxazol/trimethoprim and tetracyclines. Penicillin resistance is due to modified penicillin-binding proteins. Combination with beta-lactamase inhibitors is not useful.
Groups A, B, C, F, G streptococci Oral streptococci	Usually susceptible to benzylpenicillin and other beta-lactams (*Streptococcus pyogenes* 100%). Penicillin resistance rate is 5%–10% in oral streptococci (e.g. *Streptococcus anginosus* [*S. milleri*] group) isolated as pathogens in neutropenic patients with sepsis. Resistance to macrolides is more frequent depending on use. Penicillin tolerance should be considered with *Streptococcus sanguinis*, *Streptococcus gordonii*, and potentially *Streptococcus mitis* (endocarditis). The combination of benzylpenicillin plus gentamicin is synergistic and bactericidal, even if low-level resistance to gentamicin is observed in susceptibility testing. For other resistance characteristics, see *Streptococcus pneumoniae*.

Mechanisms of antibiotic resistance

Resistance mechanisms of bacteria can be categorized in 3 groups:

- deactivating enzymes
- modification of target structures
- modification of access to target structures (increased efflux, decreased influx).

The genetic determinants of resistance may be an intrinsic component of the bacterial chromosome but are more often found on chromosomal and/or extrachrom osomal mobile genetic elements (e.g. resistance plasmids, transposons, insertion sequences, genomic islands), which are responsible for a rapid horizontal spread of resistance among bacteria.

Collateral damage inflicted by antibiotics

Adverse ecological effects such as the selection of antibiotic resistance in the physiologically colonizing flora, the occurrence of *Clostridium difficile*-associated diarrhoea, and the colonization and infection with multiresistant pathogens, e.g. ESBL-producing enterobacteriaceae, MRSA or vancomycin-resistant enterococci (VRE), are summarized as collateral damage of antibiotic use. The risks of collateral damage associated with various antibiotics can be identified in epidemiological studies.

Patients with gram-negative infections treated with fluoroquinolones are at increased risk of being infected by fluoroquinolone-resistant pathogens [399]. This correlation was shown e.g. in a study of patients with urinary tract infections: those who had been treated with ciprofloxacin in the year before the onset of urinary tract infection were significantly more likely to be infected with ciprofloxacin-resistant *E. coli* [26]. In another study, there was a significant correlation between the detection of fluoroquinolone-resistant *E. coli* in community-acquired urinary tract infections and the level of fluoroquinolone use in the population [198]. Moreover, there is evidence that the use of fluoroquinolones increases the risk of acquiring MRSA and ESBL-producing pathogens [399]. This correlation may explain why the majority of MRSA and ESBL-producing pathogens are resistant to fluoroquinolones.

In numerous case-control studies, the use of group 3 cephalosporins has been identified as a risk factor for ESBL-producing pathogens. These drugs were also identified as a risk factor for infections with MRSA and VRE. These drugs probably also increase the risk of pathogens producing carbapenemases as these enzymes inactivate cephalosporins as well [399].

Carbapenems have a central role in the treatment of life-threatening infections. As a result of the increase in ESBL-producing pathogens which are resistant to cephalosporins and usually also to fluoroquinolones, the importance of carbapenems has increased significantly.

Because new antibiotics with new efficacy mechanisms against gram-negative bacteria will not be reliably available in the coming years, an increase in carbapenem resistance would have a dramatic impact on therapy. It has already been shown that the use of imipenem and meropenem is associated with a higher risk of colonization with MRSA, ciprofloxacin-resistant *P. aeruginosa* and

VRE than therapy with cephalosporins, fluoroquinolones or piperacillin/tazobactam [509]. Carbapenems are also a risk factor for infections with *S. maltophilia*.

Medical measures against increasing resistance

The development of bacterial resistance during treatment is due to genetic variability and the selection of rare resistant variants through the use of antibiotics. Containment of resistance is primarily based on the reduction of selective pressure and the prevention of transmission of (multi)resistant pathogens. Resistance development and the spread of resistant bacteria can be influenced by the following measures:

- rational, patient-specific, targeted use of antibiotics
- adequate dosage and duration of treatment
- combination therapy (using the same dosages as in monotherapy) in cases with higher risk of resistant variants appearing on monotherapy, e.g. empiric treatment of severe infections such as pneumonia or sepsis in which the involvement of *P. aeruginosa* is suspected
- parallel use of different classes of antibiotics for the same indication
- adjustment of therapy after microbiological results become available
- restrictive prophylactic and topical use of antibiotics
- strict adherence to hand disinfection rules and further infection control measures
- continued compilation of statistics on pathogens and resistance (local, regional and supraregional) as a basis for infection control measures in hospitals and guidelines for antibiotic therapy (§ 23 section 1 infection protection act)
- enhanced involvement of infectious disease specialists in hospitals
- continued education in antibiotic therapy and increased interdisciplinary cooperation of all professional groups involved in infectious disease therapy
- vaccination

3 Pharmacokinetics and pharmacodynamics

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Pharmacology

Besides the antimicrobial properties of a substance (pharmacodynamics), its pharmacokinetics, i.e. the behaviour of a drug inside the human body, has a decisive role in determining its clinical utility. Ultimately it is a question of whether or not the concentration at the site of action is adequate to inhibit the growth of the pathogen. Adverse drug effects and interactions should be minimized.

Correlating pharmacokinetic parameters or simplistically plasma and tissue concentrations with antimicrobial characteristics in vitro or in vivo for the purpose of predicting efficacy, is the realm of PK/PD (pharmacokinetics/pharmacodynamics).

Pharmacokinetics

Pharmacokinetic properties of drugs are determined by their physicochemical characteristics. The acidity or basicity of a substance and its lipophilic or hydrophilic properties will determine how it behaves under physiological conditions inside the human organism. Beta-lactam antibiotics and aminoglycosides, for example, do not pass easily through membranes and therefore are found mostly in extracellular compartments. A summary of pharmacokinetic parameters of the individual groups of antibiotics is given in Table 5.

The distribution volume is an important pharmacokinetic parameter describing the distribution of the drug throughout the body. Lipophilic substances easily passing through membranes are taken up passively and intracellularly. Therefore, they show a large distribution volume: it may be as high as multiple body volumes for fluoroquinolones and macrolides. Drugs with large distribution volumes will have low plasma and interstitial levels but high intracellular concentrations. In contrast, water-soluble substances do not readily penetrate the cell membranes and therefore are found mainly in the plasma and interstitium, i.e. the concentration in these compartments is a most relevant measure.

An important determinant of drug distribution is the protein binding in serum. Antibiotics bind primarily to albumin, depending on their physicochemical properties. The concentration-dependent binding is reversible. A dynamic balance exists between free and bound drug. Generally speaking, only the free drug is responsible for efficacy. As shown for some antibiotics, high protein binding has no negative effects on the efficacy as long as there is a high enough unbound concentration at the site of action. Clinical studies which appear to substantiate a negative influence by the protein binding, were often conducted with inadequate total dosages [295], [363], [455].

Tissue concentrations are similarly important in predicting efficacy. A tissue concentration, as determined from biopsy material or surgical resected tissue, describes the average concentration in a tissue homogenate. These tissue concentrations fail to describe complex processes and heterogenous distribution inside the tissue. Measurements of tissue concentrations may be relevant, for example, in the comparison of two drugs or drug groups. The development of microdialysis could represent a big step forward in this field. The measurement of antibiotic concentrations are important in localizations such as cerebrospinal fluid, epithelial lining fluid, alveolar cells, pleural fluid, peritoneal fluid, and pancreatic or prostate secretion. Poor circulation, peculiarly structured cell membranes and the existence of specific tissue receptors

Table 5: Phamacokinetic characteristics of parenteral antibotics

Antibiotic	Plasma concentration (C_{max}, AUC)	Half-life ($t_{1/2}$)	Plasma clearance	Volume of distribution	F_U	Metabolization rate	C_I/C_E	TS/TR/GFR
Beta-lactams	Medium to high	Short to medium	Slow to fast	Low	Medium to high	Low	$C_I<<C_E$	TS>>>TR
Fluoroquinolones	Low	Medium to long	Medium to fast	Medium to high	Low to medium	Low to medium	$C_I>>C_E$	
Aminoglycosides	Low	Short	Medium	Low	High	Low	$C_I<<C_E$	GFR
Tetracyclines	Low	Medium	Medium	Medium to high	Medium	Low to medium	$C_I>C_E$	TR>TS
Glycyclcyclines (tigecycline)	Low	Long	Fast	Medium to high	Medium	Medium	$C_I>C_E$	--
Glycopeptides	Medium	Medium to long	Slow to medium	Medium	High	Low		GFR
Macrolides	Low	Short to long	Medium to fast	Low to high	Low to medium	Low to high	$C_I>>C_E$	TR
Oxazolidinones (linezolid)	Medium	Medium	Medium	Medium	Medium	Medium to high		TR>TS
Fosfomycin	Medium	Short	Fast	Low	High	Low	$C_I<<C_E$	GFR
Cyclic lipopeptides (daptomycin)	High	Medium	Slow	Low	Medium to high	Low	$C_I<<C_E$	GFR
Classification								
Low	<10 AU	<3 h	<50 mL/min	<0,3 L/kg	<10% per dose			
Medium	10–100 AU	3–10 h	50–150 mL/min	0,3–1,5 L/kg	10%–50% per dose			
High	>100 AU	>10 h	>150 mL/min	>1,5 L/kg	>50% per dose			

C_{max}=maximum plasma concentration, F_U=percentage of dose excreted unchanged in the urine, AU=area units (AUC; 3 classes with arbitrary area units to simplify the comparison of drug classes), C_I/C_E=ratio of drug concentrations in the intracellular (C_I) and extracellular space (C_E), TS/TR/GFR=proportion of tubular secretion, tubular reabsorption and glomerular filtration rate, AUC=area under the serum concentration-time curve.

may impede homogeneous distribution of antibiotics and therefore influence treatment success. Table 6 shows the access of antibiotics to various compartments.

Table 6: Compartments with easy and difficult accessibility for antibiotics

Easy accessibility	Difficult accessibility
Connective tissue	Abscesses
Intra-abdominal organs e.g. liver	Ocular vitreous body
Lungs (ELF [epithelial lining fluid], bronchial mucosa)	Heart valves
Muscles	Bones/bone marrow
Kidneys	Pancreas
Peritoneum	Prostata
Others	CNS (CSF)

Interaction of pharmacokinetics and pharmacodynamics

As data on the concentration profiles at the site of infection are limited, analysis of pharmacokinetics is currently based on plasma concentrations for many drugs. Different indices are recommended for drug groups according to their mechanism of action.

The differences in the pharmacodynamic profiles of antibiotic groups are explained by their divergent bactericidal activity – e.g. concentration-dependent bactericidal activity of fluoroquinolones and aminoglycosides versus time-dependent (i.e. not concentration-dependent) bactericidal activity of beta-lactam antibiotics and macrolides (see Table 7). It was shown for aminoglycosides and fluoroquinolones that the ratio of maximum concentration (C_{max}) and minimal inhibitor concentration (MIC) of the pathogen correlates with treatment success. In contrast, for beta-lactam antibiotics, the time (i.e. percentage of the dose interval) with plasma concentration above the MIC of the pathogen (t>MIC) is the relevant parameter. For fluoroquinolones, the ratio of AUC (area under the concentration-time curve) and MIC is also deemed important in predicting the outcome (area under the 24-hour concentration-time curve over the MIC: AUC24/MIC). Data available for oxazolidinones so far indicate that concentration and time are both relevant for the antimicrobial effect. This model was validated in humans for some groups of antibiotics.

Table 7: PK/PD parameters of antibiotics

Antibiotic class	C_{max}/MIC	AUC/MIC	t>MIC
Beta-lactams	–	–	X
Macrolides	–	–	X
Azithromycin	–	X	–
Tetracyclines	–	X	–
Glycylcyclines	–	X	–
Glycopeptides	–	X	X
Fluoroquinolones	X	X	–
Aminoglycosides	X	–	–
Oxazolidinones	–	X	X
Fosfomycin	–	–	X
Lincosamides	–	–	X
Cyclic lipopeptides	X	X	–

–: Poor correlation between parameters and clinical effect
X: Good correlation between parameters and clinical effect

Considering the PK/PD indices, when choosing a dose regimen, is vitally important particularly in immunosuppressed patients and for infections in poorly accessible localizations (abscesses, osteomyelitis, meningitis, necrotizing infections; see Table 6). In addition, pathophysiological and therapeutic factors in the critically ill (capillary leakage due to endothelial damage, hypoalbuminemia, extracorporeal circulation, intravenous administration of high fluid volumes, vasopressor use) may result in enhanced distribution volumes and, due to increased renal perfusion in the absence of adequate organ function, increase the clearance of hydrophilic antibiotics and thus decrease their plasma concentrations.

Data on PK/PD correlations provide guidance when adjusting the dosage to individual needs with the help of therapeutic drug monitoring (TDM), particularly in high-risk populations (e.g. critically ill patients, elderly patients, and those with organ dysfunction). Clearance and distribution volumes determine the half-life of a drug. Both parameters are used to determine the time with plasma concentrations above MIC and the total exposure (AUC). They thus have an important role in the calculation of dose intervals.

Functional impairment of drug-excreting organs (mainly kidneys and liver) results in a reduced clearance of antibiotics and prolongation of the half-life, which may result in an increased rate of side effects. Reduced kidney and liver function is less important for antibiotics with wide therapeutic range (broad concentration range between effective and toxic levels, e.g. for penicillins, cephalosporins, carbapemens, macrolides, lincosamides, fluoroquinolones and linezolid) than for antibiotics with narrow therapeutic margins (e.g. aminoglycosides and vancomycin). Therefore, besides microbiological efficacy, the degree of renal and extrarenal excretion plus any nephrotoxic and/or hepatotoxic potential of the antibiotic itself or its metabolites play an important role in the choice of suitable antibiotics.

These antibiotics (potentially nephrotoxic: aminoglycosides and vancomycin; potentially hepatotoxic: amoxicillin/clavulanic acid, flucloxacillin, fluoroquinolones, and intravenous tetracyclines) should be used only in vital indications if the function of the relevant organs is impaired. Potential risks by accumulation of toxic metabolites should be considered in patients with pronounced renal or hepatic impairment. As a rule, antibiotics with high extrarenal elimination should be chosen in patients with impaired kidney function and antibiotics primarily excreted via the kidneys should be used for patients with liver dysfunction.

Antibiotics primarily excreted via the kidneys are eliminated by glomerular filtration and tubular secretion (e.g. penicillins) and may be reabsorbed in different amounts. In patients with renal dysfunction, the dosage should be adapted to the degree of impairment, according to the creatinin clearance. Parameters of relevance for dose adjustments include

- percentage of drug eliminated via the kidneys in individuals with normal kidney function,
- drug toxicity
- degree of renal impairment.

Generally, recommendations of the manufacturer should be followed when choosing the dosage for patients with organ dysfunction. In the absence of such recommendations, the adaptation of the dosage regimen for renal dysfunction should be carried out by calculating the individual excretion factor (Q) according to Dettli [129], [252].

Helpful links to websites on dosage adaptation for renal impairment include: http://www.zct-berlin.de/niereninsuff/; http://www.dosing.de/; http://doseadapt.unibas.ch/. Unlike creatinine clearance in renal insufficiency, clinical scores (Child Pugh score, MELD score) in liver insufficiency are inadequate predictors for drug metabolization and elimination.

Liver diseases have a varying and unpredictable influence on cytochrome P450 isoenzyme activities. Available tests provide only a rough estimate of the function of individual isoenzymes. The reduction in hepatic clearance and the associated need of dose adjustments may be relevant for antibiotics which are almost completely metabolized by liver enzymes, primarily those with high lipophilia and low polarity which are poorly excreted via the kidneys (antibiotics with high extrarenal clearance include clindamycin, chloramphenicol and minocyclin).

High-grade hepatic dysfunction with reduced metabolic capacity should also be considered when choosing the dosage of tetracyclins, clavulanic acid, flucloxacillin, macrolides and streptogramins. For antibiotics with high presystemic elimination rates (first-pass effect), the bioavailability and therefore the plasma concentration may increase significantly in patients with impaired hepatic function (e.g. ciprofloxacin). In patients with renal and liver dysfunction, the loading dose (initial dose), which is dependent on the distribution volume should be the same as for patients with normal kidney and liver function. If the initial dose of the antibiotic is reduced, the effective concentration may be reached after a delay of several days. This may jeopardize treatment success of antibiotic therapy, which primarily depends on the initial choice and adequate drug exposure.

A particular challenge in pharmacotherapy is the dosing of antibiotics in obese patients. The pharmacokinetics of many antibiotics are unpredictable in these patients due to alterations in drug distribution. There is no clear relationship between the lipophilic properties of the drug and its distribution in obese patients. Alterations in distribution volumes and clearance as well as problems in estimating kidney function based on creatinine clearance are among the factors commonly leading to underexposure in obese patients who receive standard dosages of antibiotics. Subtherapeutic concentrations may lead to therapeutic failure and development of resistance. As higher distribution volumes and higher clearance should generally be expected for these patients, weight-based dose adjustments are required. Which weight parameter (TBW – total body weight, IBW – ideal body weight, LBW – lean body weight or ABW – adjusted body weight) should be used as the basis of dosage calculation depends on the drug itself and on the mode and duration of administration [160], [211], [373], [394].

In difficult-to-treat patients, therapeutic drug monitoring (TDM) is advisable but rapid testing is available for only few antibiotics (e.g. for aminoglycosides and glycopeptides). Dosage recommendation should be followed particularly for pediatric patients with cystic fibrosis, sepsis, burns or high body weight. The pharmacokinetic characteristics of the individual drugs are summarized in Table 5.

Therapeutic drug monitoring

Many antibiotics are characterized by substantial interindividual and intraindividual variability of pharmacokinetic parameters, particularly regarding elimination and distribution volume. This is particularly true for intensive care patients with multiple organ failure and major alterations in fluid volumes (e.g. due to capillary leakage and infusion therapy). Plasma concentrations achieved with standard dosages may therefore show major variations resulting in underexposure and therapeutic failure or elevated plasma levels with the risk of toxic effects.

Therapeutic drug monitoring (TDM) is used to determine the optimum dose regimen for individual patients by measuring drug plasma levels and applying pharmacokinetic principles.

Prerequisites and/or indications for TDM primarily include the following:

- Concentration-effect correlations are known for therapeutic and toxic effects.
- The drug has a narrow therapeutic range. Exceeding this range by a relatively small margin results in a risk of toxic effects.
- The pharmacokinetics of the drug is subject to substantial intraindividual and/or interindividual variability.
- Pharmacokinetic targets (C_{max}, C_{min}, AUC) are known.
- Analytical methods providing adequate sensitivity can be used with reasonable expenditure.

For many antibiotics, e.g. penicillins and cephalosporins, the risk of toxic effects is small as they have a relatively broad therapeutic range. Treatment with these antibiotics rarely requires plasma level based adjustments. In contrast, aminoglycosides and glycopeptides are examples of antibiotics where TDM is strongly recommended for safe use. Table 8 shows recommendations of target areas for maximum and minimum levels of commonly used aminoglycosides and glycopeptides with respect to patient group.

When using aminoglycosides, single-dose application of the entire daily dosage is associated with increased clinical efficacy, less toxicity and economic advantages [17], [45], [87], [92], [110], [128], [153], [223], [228], [344], [386]. Based on PK/PD parameters, peak levels clearly above the MIC of the pathogen (C_{max}/MHK>10) are targeted for aminoglycosides [404], [436]. The mean MIC of gentamicine for pathogens with reduced susceptibility (e.g. *Pseudomonas aeruginosa*) is 2.0 mg/L. Therefore, the target peak levels are at least 20 mg/L [423]. There is insufficient data for once daily use in endocarditis and neutropenic patients.

For the glycopeptides vancomycin and teicoplanin, the pharmacodynamic parameters require continuous drug levels above the MIC of the pathogen. As a rule, trough levels are determined in TDM [315]. When treating life-threatening infections (meningitis or pneumonia) and in-

Table 8: Recommended targets for minimum and maximum levels in TDM of aminoglycoside and glycopeptide antibiotics (modified from Burton et al. [93])

Antibiotic	Trough level (mg/L)	Comments	Peak level (mg/L)	Comments
Amikacin	<1	Correlates with toxicity; in life-threatening infections up to 2 mg/l	55–65*	For evaluation of efficacy (once daily dosing)
Gentamicin	<1		15–25*	
Tobramycin	<1		15–25*	
Vancomycin	10–15	15–20 mg/l in life-threatening infections and for pathogens with reduced susceptibility**		
Teicoplanin	10–20	20–25 mg/l for endocarditis, bone and prosthetic joint infections		

* Dependent on the degree of clinical severity of the infection and the MIC of the pathogen
** Increased nephrotoxicity above 15 mg/l must be taken into account [227]
Trough level = serum level at the end of the dosing interval
Peak level = serum level immediately after the end of the infusion from a separate venous access

fections by pathogens with reduced susceptibility, a vancomycin trough level of 15–20 mg/L should be achieved [259], [309], [403]. However, there is an increased risk of nephrotoxicity at vancomycin trough levels of 15 mg/L and above [227].
When treating infections of bone or prosthetic joint infections and endocarditis, teicoplanin trough levels of 20–25 mg/L are recommended [492].

Continuous infusion of beta-lactam antibiotics

Beta-lactam antibiotics are effectively active if the MIC of the pathogen is exceeded as continuously as possible during the growth phase of the cell wall. Initially, the bactericidal efficacy increases with ascending concentrations up to this value; however exceeding this level will not improve treatment results. This pharmacokinetic-pharmacodynamic relationship is described as time-dependent rather than concentration-dependent bactericidal. For beta-lactam antibiotics, the concentration of the unbound antibiotic should exceed the MIC of the pathogen at the site of infection for at least 40–60% of the dosing interval [375]: 40% appears adequate for carbapenems, the higher value applies for cephalosporines, with penicillins requiring around 50%.
There is not a large variation in the pharmacokinetic data for beta-lactam antibiotics. After parenteral administration, beta-lactam antibiotics disperse rapidly in the extracellular region. In dynamic equilibrium, similar concentrations are reached after intermittent administration and after bolus administration followed by continuous infusion [40], [57], [58], [292], [346], [347].
Manufacturers typically recommend the administration of beta-lactam antibiotics (1) 2 to 4 (6) times daily, depending on pharmacokinetic parameters. Thus, adequate levels of free active drug that exceed the MIC of susceptible pathogens are reached in licensed indications which are supported by clinical studies. However, when using intermittent administration concentrations often fail to exceed the MIC of the pathogen as long as possible in the infected region as has been shown in PK/PD simulations and in experimental and clinical investigations. This is particularly true for patients with large extracellular distribution volumes and increased clearance rates. This primarily applies to patients with capillary leakage e.g. due to sepsis, patients with cystic fibrosis, drainage, bleeding, large burns, ascites, severe pancreatitis, BMI >30 kg/m^2, cardiac insufficiency, edema, hemofiltration (depending on net fluid balance), dialysis and pregnancy. In contrast, desiccated patients, dialysis patients after a dialysis session, and patients with volume restrictions have smaller distribution volumes than normal patients. Individualized antibiotic therapy is recommended for high-risk and elderly patients [91], [186], [270], [284], [291], [313], [376], [377], [434], [435], [437], [454], [473].
These newer considerations are already followed for doripenem. Doripemen can be administered by short infusion or prolonged infusion over 4 hours [162]. Recommendations for continuous administration of beta-lactam antibiotics are based on theoretical considerations supported by experimental investigations or simulations. Evidence from clinical investigations supports advantages for continuous administration with prolonged maintenance of serum levels above MIC even at low daily dosages [12], [13], [86], [88], [89], [90], [98], [120], [178], [282], [283], [288], [348], [349], [424], [438], [512], [515], [516] with comparable clinical and microbiological efficacy and safety [190], [200], [376]. However, a significant superiority of continuous administration was shown in only few cases to date [312] and reduction of mortality has not been shown yet.
The stability of beta-lactam antibiotics after reconstitution is limited. This implies inactivation by degradation and decomposition products which may potentially trigger allergies. This aspect is neglected in numerous investigations on the stability of drugs. Solutions of beta-lactam antibiotics are considered to be stable within a given interval if less than 10% of the drug is degraded. The rate of degradation depends on solvent, light exposure, drug concentration, type of administration device, manufacturing and temperature. In out-patient antibiotic therapy (APAT) with portable pumps carried close to the body stability may be significantly reduced due to increased ambient temperature.
The use of the recommended solvent is a point of high practical importance to achieve optimum solubility and stability. Practically all penicillins (dry substances) must

be dissolved in water for injection in order to accelerate solubility and avoid particle formation. Further dilution in the usual infusion solvents is generally feasible. For many beta-lactam antibiotics, there is a list of incompatibilities with other drugs if administered via the same infusion system. To follow the manufacturer specifications on compatibility is imperative.

The most frequent side effects of penicillins include allergic and pseudoallergic reactions. These reactions are caused by the instable beta-lactam structure or specific side chains. Immediate and delayed-type reactions may occur. Immediate-type allergies to penicillin following prior sensitization (e.g. by food containing penicillins or contact with moulds) usually evolve within minutes as urticaria-type exanthema and/or angioedema, potentially with life-threatening respiratory or cardiovascular complications. About 10% of delayed-type reactions are polymorphic, e.g. maculopapular exanthema. Serum-sickness-like symptoms are observed in 2% to 4% of cases. Allergic reactions are generally more frequent after parenteral than after oral administration.

Penicillins have variable stability in solution, depending on molecular side chains and the pH of the solvent. Degradation products of penicillins act as haptens and may form covalent bonds with host proteins. The hapten-protein complex may induce an allergic immune reaction.

Degradation products of penicillins have a significant allergenic potential. The most common degradation product is penicilloic acid, a product generated by beta-lactam ring opening. The penicilloyl-protein complex is designated the major determinant (major epitope). It is the cause of most penicillin allergies. The penicilloate, penilloate, penicillenate, penicilloinic acid, penicillanyl, penamaldate, penaldate and D-penicillamine determinants are minor determinants (minor epitopes). These minor determinants appear to be more important for critical clinical events (shock), even though anaphylactic reactions due to penicilloylic acid sensitization were also described.

Improper storage and preparation may induce the formation of larger amounts of degradation products which greatly increase the risk of allergic reactions to penicillin solutions. Thus the incidence of proven (0.9%) or probable (1.7%) adverse drug reactions was significantly lower with short infusions of freshly prepared penicillin solutions compared to continuous administration or infusion of stored solutions (8.3%, 6.7%, respectively) [369], [370], [371]. However, these differences could not be confirmed in further clinical studies.

The type and extent of degradation observed with a beta-lactam antibiotic depends on the substance. As a rule, acylaminopenicillins, isoxazolylpenicillins, cephalosporins and aztreonam are more stable than benzylpenicillins due to their molecular structure. Ring opening induced by nucleophilic or electrophilic (less frequent) attacks is however also possible in cephalosporins as observed for example with ceftazidim and other cephalosporins [474]. The chemical stability of carbapenems varies greatly, only doripenem may be administered by prolonged 4-hour infusions (as described in the label) [162].

Summary

- Due to pharmacokinetic/pharmacodynamic considerations, the continuous infusion of beta-lactam antibiotics is superior to intermittent administration in achieving the goal of exceeding the MIC of the pathogen as continuously as possible.
- Few clinical data are available on any significant superiority of this treatment regimen.
- Continuous and intermittent infusions of a beta-lactam antibiotic has comparable side-effect profiles.
- Continuous administration is recommended for patients whose pharmacokinetic parameters (distribution volume, clearance) deviate significantly from normal populations (e.g. patients with cystic fibrosis or patients with severe septic infections caused by pathogens with reduced susceptibility).
- Continuous administration of the antibiotic should be preceded by a single bolus administration.
- Economic advantages may be associated with continuous administration, as in non-severely ill patients, steady-state serum concentrations are achieved with lower daily dosages compared to intermittent infusion.
- Due of limited stability at room temperature, some beta-lactam antibiotics are not suitable for continuous administration. In these cases, only prolonged infusion (3 hours) is possible.
- Strict adherence to the manufacturer's recommendations on the type of solvent and concentrations of the antibiotic solution is mandatory. Deviations may cause considerably reduced stability.
- It is essential to use a dedicated intravenous line or lumen specifically for the continuous administration of a beta-lactam antibiotic as numerous incompatibility reactions with other drugs can occur.
- Continuous or prolonged infusions are not licensed except for doripemen. Use of these regimens in practice therefore must be considered "off-label use".

Drug interactions

Interactions with other drugs are an important cause of adverse reactions. Particularly the inhibition of hepatic monooxygenases (cytochrome P450 isoenzymes), for example by some macrolides and fluoroquinolones as well as azole antifungals, may cause an increased risk of side effects.

In addition, some drugs, for example rifampicin, barbiturate and carbamazepine, induce enhanced expression of cytochrom P450 isoenzymes, resulting in lower plasma levels with reduced efficacy of the affected drug.

Further important drug-drug interactions of antibiotics are listed in Table 9.

Table 9: Interactions of antibiotics with other drugs: mechanisms and effects

Antibiotic	Comedication	Effects
Penicillins	Acidic pharmaceuticals, e.g. probenecide, salicylate, indometacine, sulfinpyrazone, phenylbutazone	Reduction in tubular penicillin secretion, increased risk of seizures at high dosages
Cephalosporins	Nephrotoxic drugs, e.g. aminoglycosides	Enhanced nephrotoxicity, particularly in patients with impaired kidney function
Fluoroquinolones	NSAIDS	Increased risk of seizures
Ciprofloxacin	Mineral-based antacids, H2 receptor antagonists	Decreased absorption of quinolones with loss of efficacy
Levofloxacin	Warfarin	Enhanced warfarin effect. Some fluoroquinolones block hepatic elimination of R-warfarin
Moxifloxacin	Drugs associated with prolongation of the QT interval (terfenadine)	Increased risk of ventricular arrythmia, particularly torsade de pointes
Macrolides	Theophylline	Risk of theophyllin intoxication due to reduced theophyllin metabolism
	Ergot alkaloids	Risk of ergotism due to competitive blocking of hepatic degradation
	Carbamazepine	Risk of symptoms associated with carbamazepine overdosing (e.g. nausea, vomiting) due to reduced metabolization of carbamazepine
	Ciclosporin A	Increased nephrotoxicity due to reduced metabolism of cyclosporine
	Statins, particularly simvastatin, lovastatin and atorvastatin	Rhabdomyolysis
	Warfarin	Increased risk of bleeding due to reduced metabolization of warfarin
	Drugs associated with prolongation of the QT interval (terfenadine)	Increased risk of ventricular arrhythias, particularly torsade de pointes
	Protease inhibitors and non-nucleosidic reverse trancriptase inhibitors	Increased side effects
Tetracyclines (doxycycline)	Barbiturate, phenytoin, carbamazepine	Accelerated degradation of tetracyclines due to enzyme induction
	Drugs with high protein binding, e.g. sulfonylurea, cumarin analogues (e.g. phenprocoumon)	Increased effect of strongly protein-bound drugs. Doxycyclin, which is 95% bound to plasma proteins, displaces these drugs from proteins.
	Carbamazepine	Risk of symptoms associated with carbamazepine overdosing (e.g. nausea, vomiting) due to reduced metabolization of carbamazepine
	Cyclosporine	Increased nephrotoxicity due to reduced metabolism of cyclosporine
	Phenprocoumon, Warfarin	Increased risk of bleeding due to reduced metabolism of anticoagulants
Glycylcyclines (tigecycline)	Oral anticoagulants (warfarin)	Occasionally increased INR values
Linezolid	MAO inhibitors (moclobemide)	Increased blood pressure, serotonin syndrome
Daptomycin	Drugs associated with myopathy (statins)	Increased CPK values, rhabdomyolysis
Lincosamides	Non-depolarizing muscle relaxants	Increased neuromuscular blockade with respiratory depression
Glycopeptides	Nephrotoxic and ototoxic drugs, e.g. aminoglycosides, amphotericin B, cyclosporins, cisplatin, loop diuretics	Increased risk of nephrotoxicity and/or ototoxicity
Aminoglycosides	Non-depolarizing muscle relaxants	Favouring/triggering/potentiating neuromuscular blockade
	Nephrotoxic or otoxic drugs, e.g. vancomycin, colistin, amphotericin B, cyclosporine, cisplatin, loop diuretics	Increased risk of kidney and/or hearing damage
Rifampicin	Substrates of the cytochrom P450 system and P glycoprotein	Increased clearance of the drug due to enzyme induction resulting in reduced efficacy

4 Safety and tolerability

Ralf Stahlmann, Hartmut Lode

Adverse drug reactions must be expected in about 10% of patients treated with most parenterally administered antibiotics. In some drugs, the side-effect rates are even higher. Therefore the differences in the tolerability of the available medications are of major importance. However, any comparison of results generated in different clinical trials is inadequate to evaluate differences in the tolerability of antibiotics. Despite broad standardization of clinical trials, data generated in single head-to-head trials, preferably double-blind studies, are the only reliable basis for direct comparisons of different drugs. This applies for side effects as well as for clinical efficacy. The number of patients treated in clinical studies in insufficient to derive reliable conclusions on infrequent side effects. Therefore, evaluations of pooled data from multiple clinical studies or even the experience gained from postmarketing surveillance must be considered. However, the limitations associated with this type of data should be taken into account.

In general the adverse drug reactions of most antiinfectives prescribed for parenteral therapy predominantly affect three organ systems:

- gastrointestinal tract (e.g. nausea, vomiting, diarrhea),
- skin (e.g. rashes/eruptions, urticaria, phototoxicity),
- CNS (e.g. headaches, dizziness, sleep disturbances).

There are significant differences in the severity and the frequency of a given side effect. Toxic, allergic and biological effects may be differentiated according to the pathogenesis of the adverse effects. In some cases it remains unclear if, for example, a disturbance of the gastrointestinal tract is due to direct effects on the affected organs or whether the changes are caused by the impact on the bacterial flora.

As a rule, any administration of an antimicrobial drug has an effect on the bacterial flora. The type and extent of the changes are determined primarily by the pharmacokinetic characteristics of the antibiotic. Therefore the biological side effects of a drug must be considered in the risk/benefit assessment of each antibacterial treatment.

Beta-lactam antibiotics

Parenterally administered beta-lactam antibiotics are generally well tolerated. The side effects are usually mild and temporary. Treatment discontinuation is rarely required. In about 1–2% of patients, hypersensitivity may occur as a morbilliform or scarlatiniform erythema. This may be associated with edema of face, tongue or glottis (e.g. Quincke's edema) in rare cases (0.5–1%). Pneumonitis and/or interstitial pneumonia and interstitial nephritis are extremely rare. In isolated cases (<0.1%) severe acute allergic reactions (anaphylaxis with life-threatening shock) (independent of the administered dose) occur, usually within 30 minutes after administration. This type of reaction is more frequently reported for penicillins than for other beta-lactam antibiotics. Patients should be monitored for allergic reactions during the first 30 minutes after the administration of any beta-lactam antibiotic.

Cross-allergies of penicillins and cephalosporins are quite rare. Aztreonam may be used in patients who developed skin eruptions or other types of acute hypersensitivity reactions to penicillins or other beta-lactams, as cross-allergies are very rare based on the available experience. In some patients, allergies to aztreonam have been observed, These are more likey caused by the structure of the side chain than the beta-lactam ring itself. As the aztreonam side chain is identical with the corresponding structure in ceftazidim, aztreonam should not be used after an allergic reaction to ceftazidim and vice versa [18], [568].

Reduction on blood counts (thrombocytopenia and/or eosinophilia, rarely (<2%) as leukopenia) are mediated by allergic or toxic mechanisms. The effects are general reversible within a few days of treatment discontinuation.

Gastrointestinal intolerability manifested as loss of appetite, nausea, vomiting, adominal pain, meteorism or soft stools are often observed in patients receiving beta-lactam antibiotics. Diarrhea (more than 3 bowel movements with loose stool per day) occurs in 2–10% of patients.

In patients receiving intravenous ceftobiprol, the rate of gastrointestinal disturbances such as nausea and vomiting was dependent on duration of the infusion. Patients often reported dysgeusia during the clinical trials [381].

Reversible moderate changes in liver function parameters (e.g. transaminases, alkaline phosphatase) occur in up to 10% of patients. In some cases, transient cholestatic hepatitis was observed. The risk increases with increasing age and duration of therapy. Amoxicillin/clavulanic acid should only be used with liver function monitoring in elderly patients (>65 years).

During treatment with ceftriaxone, alterations of gallbladder ultrasound images have been observed in rare cases. These changes disappear after discontinuation or completion of therapy (transient biliary pseudolithiasis).

In patients with certain risk factors (severely impaired kidney function or epilepsy, breached blood-brain barrier, e.g. meningitis), seizures may occur after administration of beta-lactam antibiotics in very high doses. As observed in animal experiments, the seizure risk is lower with newer carbapenems versus imipenem/cilastatin. Therefore meropenem rather than imipenem/cilastatin is licensed for the treatment of meningitis [585].

If meropenem or other carbapemens are used in combination with valproic acid, the plasma concentrations of the antiepileptic are significantly reduced and may result in an increased risk of seizures. Valproic acid is predominantly metabolized by glucuronidation. However, the parent drug may subsequently be released from the metabolite by hydrolysis. Carbapenems apparently block this hydrolysis of the glucuronide resulting in a reduction of the plasma levels of free valproic acid. Therefore, the valproic

acid serum level must be monitored and the dosage adjusted correspondingly if a carbapenem is used concomitantly [345].
Long-term and repeated use of beta-lactam antibiotics (particularly those with broad antibacterial spectrum) may lead to superinfection or colonization with resistant pathogens or yeasts (e.g. oral thrush, vulvovaginitis).

Fluoroquinolones

During treatment with fluoroquinolones (e.g. ciprofloxacin, levofloxacin, moxifloxacin) adverse effects occur in about 4–10% of patients [494], [531].
Adverse effects most often affect the gastrointestinal tract or the CNS (e.g. sleep disturbances, dizziness). Regarding skin reactions, the phototoxic potential of fluoroquinolones has attracted particular notice. Basically, direct exposure to sunlight (or UV light from other sources) should be avoided in all treatments with fluoroquinolones.
Cardiotoxic effects were observed in animal experiments after administration of fluoroquinolones withdrawn from the market including sparfloxacin. Minor changes of QTc time may occur in humans as well. These resulted in the recommendation that fluoroquinolones should not be combined with other arrhythmogenic drugs. Patients with hypokalemia and hypomagnesemia have a higher risk of torsades de pointes [232]. In very rare cases, hepatic reactions from hepatitis to liver failure have been observed in conjunction with fluoroquinolones.
Fluoroquinolones are contraindicated for children, adolescents and pregnant women. The clinical relevance of typical fluoroquinolone effects on immature cartilage remains controversial, however. Ciprofloxacin is increasingly being used for example e.g. in teenage cystic fibrosis patients. No increase in the rates of clinically relevant joint disturbances was reported. Inflammation or ruptures of the achilles tendon may occur as rare adverse effects of all fluoroquinolones [472]. Among the fluoroquinolones available for parenteral therapy, ciprofloxacin inhibits the cytochrome P450 isoenzyme 1A2. Therefore, the metabolism of theophylline, caffeine and other pharmacological agents; e.g. clozapin, may be inhibited to a clinically relevant extent [83].

Macrolides, azalides

Besides the classical macrolide erythromycin, clarithromycin and azithromycin are currently available for parenteral therapy. Due to its divergent structure, azithromycin is also categorized as an azalide. Macrolides/azalides often cause local intolerability reactions at the infusion site.
Besides local intolerability, the most frequent side effects of these antibiotics – including their parenteral use – are gastrointestinal disorders. The gastrointestinal reactions are caused primarily by direct stimulation of smooth muscles as the macrolides/azalides act as motilin agonists. The newer derivates of the erythromycins (clarithromycin, azithromycin) are better tolerated gastrointestinally than the classical macrolide [183].
Macrolides may cause allergic reactions. These are clearly less frequent than with penicillin or other beta-lactam antibiotics.
Cases of reversible hearing loss have been reported in association with high doses of erythromycin (intravenous administration). Cardiotoxic effects may also occur after administration of macrolides due to QTc prolongation with a potential for serious arrhythmia (torsades de pointes). This risk appears to be relatively small with azithromycin [481].
Interactions between erythromycin/clarithromycin and numerous other pharmaceuticals metabolized by the cytochrome P450 monooxygenases (e.g. CYP3A) have long been known. The phase I metabolism of carbamazepine, glucocorticoids, terfenadine, theophylline, cyclosporins and many other drugs is inhibited by macrolides. Particularly drugs associated with QTc prolongation (e.g. terfenadine, pimozide) may cause torsades de pointes when administered in combination with these macrolides. Based on available experience to date, inhibition of metabolizing enzymes is not associated with the azalide azithromycin. Cases of interaction with digitalis glycosides have been described for all macrolides/azalides, these are apparently caused by other mechanisms [475].

Glycopeptides

Hypersensitivity reactions such as fever, urticaria and exanthema may be associated with the use of glycopeptides (vancomycin, teicoplanin) [350].
Rapid infusion of vancomycin may trigger the release of mediators, causing red skin discoloration (red man syndrome), pain and cramps in the chest and back muscles. These reactions generally disappear within 20 minutes to a few hours after the end of infusion. As these symptoms rarely occur after slow infusions, it is imperative that vancomycin is adequately diluted and infused over a sufficiently long period of time. Similar reactions almost never occur with teicoplanin [350].
Gastrointestinal disorders (e.g. nausea, vomiting) may sometimes occur during treatment with glycopeptides. Acute renal failure has been observed in some cases after the administration of vancomycin in high doses. The risk of nephrotoxic reactions increases with higher doses and if vancomycin is combined with other potentially nephrotoxic drugs [227], [310], [446]. Temporary or permanent hearing impairments have occasionally been reported [173].
Alterations of blood counts are rarely observed with glycopeptides (transient neutropenia, thrombocytopenia or eosinophilia). Glycopeptides may cause pain at the injection site (thrombophlebitis).

Aminoglycosides

Aminoglycosides have a narrow therapeutic range. All drugs of this group are potentially nephrotoxic and ototoxic. In addition they may disrupt neuromuscular signal transmission and are therefore contraindicated in patients with myasthenia gravis [192], [207].
Aminoglycosides accumulate in cochlear hair cells and in the renal cortex. Therefore the risk of toxic damage increases significantly if treatment is continued for more than 8 days or if the patient has been preexposed to an aminoglycoside within 6 weeks before the start of treatment [140].
Ototoxicity and nephrotoxicity tend to be less likely if the entire daily dose is given in a single short infusion versus three divided doses. A once-daily dosing also appears to be beneficial with respect to the antibacterial effect, this dosing concept has become increasingly accepted in recent years [192], [445].
Vestibular (dizziness, nystagmus) and cochleal damage occur particularly in patients with renal impairment or in those treated with high dosages. Initially hearing loss primarily affects high frequencies [207].
Allergic reactions to aminoglycosides are rare [192].

Oxazolidinones (linezolid)

Linezolid is the first oxazolidinone used in human medicine. During clinical trials it was as well-tolerated as the comparator drugs. Gastrointestinal disturbances, e.g. vomiting, and mild CNS reactions were the most common side effects. Hematologic events (thrombocytopenia, neutropenia, anemia) were observed in patients receiving prolonged linezolid treatment (>2 weeks). Therefore, the blood counts should be monitored weekly during treatment with linezolid.
Peripheral neuropathy and/or optical neuropathy, very rarely associated with progression to blindness, were reported in patients treated with linezolid. These affected patients who were treated for longer than the maximum recommended duration of 28 days. Cases of lactate acidosis also occurred in long-term treatment [42], [361], [488].
Linezolid is an inhibitor of monoaminoxidase. Relevant interactions with concomitantly used adrenergic or serotonergic drugs may therefore occur. This may be relevant in simultaneous treatment with selective serotonin reuptake inhibitors and other drugs such as tricyclic antidepressants, serotonin-5-HT1 receptor agonists (triptanes), directly or indirectly acting sympathicomimetics (including adrenergic bronchodilators, pseudoephedrine or phenylpropanolamine), vasopressors (e.g. epinephrine, norepinephrine), dopaminergic drugs (e.g. dopamine, dobutamine) and pethidine or buspirone. Linezolid should not be used in conjunction with these drugs [334], [513].

Lincosamides (clindamycin)

The most frequent side effect of clindamycin is diarrhea due to the deterioration of physiological gut flora (5–20%). Severe pseudomembranous enterocolitis may occur in patients treated with clindamycin [391]. Serum bilirubin and liver enzyme levels may sometimes be elevated on clindamycin. Hypersensitivity reactions are comparatively rare. Hematological disturbances including e.g. thromboyctopenia and leukopenia are mostly observed in patients receiving longer clindamycin treatment courses [481].

Metronidazole

The most frequent side effects of metronidazole are gastrointestinal disorders, i.e. bitter-tasting regurgitation, metallic taste alteration and nausea. Diarrhea is rare [452]. Potential neurological disturbances include headache, dizziness, ataxia, and paraesthesia. Reversible peripheral neuropathy may occur with high dosages and long-term treatment. Cases of aseptic meningitis in association with metronidazol have been described [254]. Allergic reactions and haematological disturbances are possible [261]. A disulfiram effect occurring on metronidazole with simultaneous alcohol consumption has been reported – available data on this effect are contradictory however [543].

Tetracyclines (doxycycline) and glycylcyclines (tigecycline)

Doxycycline

From the tetracycline group, only doxycycline can be administered intravenously. Gastrointestinal disturbances are the most frequent side effects of doxycycline. Nausea, vomiting or diarrhea (occasionally pseudomembranous enterocolitis) may occur. Tetracyclines are potentially phototoxic. CNS reactions may appear as headache, nausea and photophobia. Severe anaphylactic reactions are very rare. Rapid injection may cause dizziness, flushing, reddening of the face and collapse. Intravenous administration is associated with local irritation and may cause local inflammation (thrombophlebitis). In this case, treatment should be change to oral administration if possible [453].

Tigecycline

In clinical pivotal studies, tigecycline caused gastrointestinal side effects (e.g. nausea) more frequently than the comparator drugs [175]. In the phase III studies, tigecycline was associated with vomiting in 19%, imipenem in 14% and vancomycin/aztreonam in 3.6% of the patients. Increases in transaminase levels were observed more commonly in patients receiving vancomycin/aztreonam, skin reactions were significantly more frequent than in

the tigecycline group (19% vs. 10.6%). In all groups, the rates of treatment discontinuations due to adverse events were similar. Gastrointestinal side effects are dose-dependent and occurred more commonly in female patients [398].
Concomitant therapy with tigecycline and warfarin resulted in increased plasma concentrations of R and S warfarin (AUC values) by 68% and 29%, respectively. Although no direct effect on coagulation was observed, monitoring of the INR during concomitant therapy is advised.

Daptomycin

Daptomycin was as well tolerated as the comparator drugs in clinical trials [169]. The most frequent side effects were constipation (6.2%), nausea (5.8%), injection site reactions (5.8%), and headache (5.4%). Daptomycin may cause adverse effects on skeletal muscle [289], [385]. In an early phase I study, many cases of reversible CPK (creatine phosphokinase) values were observed at a dosage of 3 mg/kg of body weight every 12 hours. These effects occur less frequently with once daily administration. In addition, increased transaminase levels associated with effects on the skeletal muscles may occur. Regular observation for clinical signs of myopathy and CPK monitoring (once weekly) are generally recommended for daptomycin use [22].
As daptomycin is primarily excreted renally, increased plasma levels of daptomycin are expected when administered concomitantly with drugs that decrease renal filtration (NSAIDs, COX-2 inhibitors). Treatment with drugs that may cause myopathy should be discontinued during treatment with daptomycin as, in some cases, a significant increase in CPK was observed and, in isolated cases, rhabdomyolysis occurred [395]. If a simultaneous administration cannot be avoided, the CPK values should be monitored more frequently than once per week and the patient should be carefully observed.

Colistin

Among the polymyxins, polymyxin E (colistin) in particular experienced a renaissance in the last few years [301]. Adverse effects of colistin include gastrointestinal disorders, CNS symptoms (dizziness, paraesthesia) and skin reactions [109]. The nephrotoxicity of polymyxins is dose-dependent. Colistin appears to be less nephrotoxic than polymyxin B. However, this advantage is at least partially abrogated by the required higher dosages. Therefore similar rates of nephrotoxic reactions are expected in clinical use. Only insufficient data on the nephrotoxicity of both antibiotics are available yet. In clinical studies, nephrotoxic reactions were observed in 7–45% of patients. Note, however, that different definitions of nephrotoxicity were used and that some of the data came from patients with severe underlying diseases, making the interpretation of these results rather difficult [255]. Using the RIFLE criteria in a group of relatively young male patients mostly without underlying diseases, almost every second patient had mild, reversible nephrotoxicity. Treatment was discontinued in 21% of patients due to renal dysfunction [218]. Significant nephrotoxic reactions were reported for the majority of patients who already had renal impairment before treatment was started [335]. For patients with existing kidney dysfunction, the dosage must be reduced to the level recommended by the manufacturer.

Fosfomycin

The most frequent adverse effects of fosfomycin include gastrointestinal symptoms (nausea, sickness, vomiting, diarrhea) and skin eruptions (exanthema). Fatigue, headache and taste disturbances were observed as additional side effects. Hematological changes such as eosinophilia or aplastic anemia are observed rarely or very rarely. Anaphylactic shock and liver dysfunctions occurred very rarely. However, phlebitis at the administration site is a frequent adverse event [144], [163], [165], [251].
Administration of 1 g of fosfomycin (equivalent to 1.32 g of fosfomycin sodium) carries 14.5 mmol Na+. Therefore, serum electrolytes should be monitored when using recommended dosages. This is particularly important in patients with, for example, congestive heart disease, edema, or secondary hyperaldosteronism. The amounts of sodium administered with fosfomycin may increase the elimination of potassium and cause a net loss of potassium. Therefore, replacement of potassium may be necessary to avoid hypokalemia.

Rifampicin

Gastrointestinal intolerance is often observed during treatment with rifampicin. Symptoms include loss of appetite, gastric pain, nausea, vomiting, meteorism and diarrhea. Cases of pancreatitis are occasionally reported [95].
Hypersensitivity reactions are frequently seen with rifampicin [321]. The most frequent manifestations are fever, multiform exsudative erythema, pruritus and urticaria. Occasionally, severe reactions such as dyspnea, pulmonary edema, other edemas and shock have been observed. A lupus-like syndrome with fever, asthenia, muscle and joint pain, and antinuclear antibodies has been reported very rarely.
Hepatic side effects of rifampicin are frequent to very frequent, primarily manifesting as elevated transaminases, alkaline phosphatase, gamma glutamyltranspeptidase and less frequently serum bilirubin. These values often normalize on treatment [203].
Visual disorders, loss of vision and neuromyelitis optica may occur as severe side effects. A reddish brown discoloration of tear fluid is a harmless effect caused by the color of the active drug.
In rare cases the use of rifampicin results in eosinophilia, leukopenia, granulocytopenia, thrombocytopenia,

thrombocytopenic purpura, hypoprothrombinemia or haemolytic anaemia.
Rifampicin is a potent inducer of cytochrome enzymes, phase II enzymes and transporter proteins. It causes, for example, a significant induction of the CYP3A4, 1A2, 2C9, 2C8 and 2C18/19 isoenzymes in the intestinal epithelium and the liver, thereby accelerating the metabolism of other drugs. It inhibits N-acetyltransferases. Rifampicin also blocks transport proteins for organic anions (OATP2).
In view of the complex and diverse effects on the pharmcokinetically relevant metabolization and transport systems, hospital physicians should expect pharmacokinetic interactions with other drugs in any concomitant use of rifampicin [491].

5 Respiratory infections

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Respiratory tract infections are the most common infectious diseases in adults treated in hospitals and practices. The successful treatment of bacterial infections is favoured by early diagnosis followed by adequate antimicrobial treatment which requires calculated treatment at least in the initial phase.
Viruses are the predominant pathogens of upper respiratory tract infections whereas bacteria are more prevalent in infections of the lower respiratory tract.
Pneumococci are the most frequent bacterial pathogens of community-acquired respiratory tract infections. *Haemophilus influenzae*, *Moraxella catarrhalis*, *Mycoplasma pneumoniae*, *Legionella* spp. and enterobacteriaceae are important organisms as well. *Staphylococcus aureus* and *Chlamydophila pneumoniae* may occasionally be isolated.
The CAPNETZ analysis provided current epidemiological data for Germany.
The spectrum of pathogens causing nosocomial pneumonia is significantly broader and includes, besides the pathogens observed in community-acquired infections, potentially multiresistant nosocomial pathogens such as methicillin-resistant *S. aureus* (MRSA), extended spectrum beta-lactamase (ESBL) producing enterobacteriaceae, *Pseudomonas aeruginosa*, *Acinetobacter* spp. and *Stenotrophomonas maltophilia*.
The resistance situation in pneumococci is still favourable in Germany, with <10% of the isolates showing reduced susceptibility to penicillin and a maximum of 2% being resistant. A trend towards reduced resistance rates has been observed for macrolides (see chapter 2).
In Germany, *H. influenzae* and *M. catarrhalis* as well are still susceptible to the recommended antibiotics.
The resistance situation of pathogens involved in nosocomial pneumonias has not yet been investigated in a large epidemiological study in Germany. Large variability of resistance across hospitals and even across departments means that current information on the local epidemiology and susceptibility is particularly important for the local implementation of treatment recommen-dations and guidelines.
The PEG Resistance Study, which includes about 20% respiratory tract isolates, has shown an increasing prevalence of ESBL-producing enterobacteriaceae in Germany. The percentage of ESBL producers increased particularly in *Escherichia coli* (from 1% to 10%) and in *Klebsiella pneumoniae* (from 4% to 10%).
Data aquired by the Krankenhaus-Infektions-Surveillance-System (KISS) (Hospital Infections Surveillance System) during 2007 and 2008 show that the proportion of MRSA in ventilator-associated pneumonia is almost 37% in the participating intensive care units.
Previous antibiotics treatment within the last 3 months predisposes patients to infections caused by pathogens with resistance particularly to the antibiotic class used. This association has been shown for beta-lactam, macrolide and fluoroquinolone antibiotics.
In the following chapter on community-acquired lower respiratory tract infections, reference will be made exclusively to the S3 guidelines on the epidemiology, diagnostics, antimicrobial treatment and management of adult patients with community-acquired respiratory tract infections [230]. These guidelines were produced by the Paul-Ehrlich Society for Chemotherapy (PEG), the German Pneumology Society (DGP), the German Infectiology Society and the CAPNETZ foundation.

Acute exacerbations of COPD (AECOPD)

Definition of AECOPD

AECOPD is defined as acute deterioration of respiratory symptoms in known chronic obstructive pulmonary disease (COPD) which requires additional treatment beyond the chronic platform therapy.

Aetiology of AECOPD

Almost half of all AECOPD episodes are caused by infectious agents, primarily respiratory viruses including respiratory syncytial virus (RSV), rhinoviruses, coronaviruses, adenoviruses, human metapneumovirus (HMP), and influenza viruses.
The most frequent bacterial pathogens are *H. influenzae*, *S. pneumoniae*, *M. catarrhalis*, enterobacteriaceae, and *P. aeruginosa*.

Clinical symptoms of AECOPD

The cardinal symptoms of AECOPD include:

- increasing dyspnea
- more frequent coughing
- increase in amount and/or viscosity of sputum
- chest tightness
- unspecific signs such as
  - early tiring
  - sleep disruption

Table 10: Treatment recommendations for patients with AECOPD with a general indication for antibiotic therapy

Antibiotic	Oral dosage (per day)	IV dosage (per day)	Duration of therapy
For moderate to severe AECOPD (hospitalized patients in general or intensive-care units) with Stockley Type II without known colonization with *P. aeruginosa*, without bronchiectasis, not on ventilation and/or without individual evidence of *P. aeruginosa**			
Drug of choice			
Amoxicillin + clavulanic acid	>70 kg: 3x875/125 mg		
	<70 kg: 2x875/125 mg	3x2.2 g	7 days
Sultamicillin	2x750 mg		7 days
Ampicillin + sulbactam		3x3.0 g	7 days
Ceftriaxon		1x2.0 g	7 days
Cefotaxim		3x2.0 g	7 days
*Alternatives**			
Levofloxacin	1x500 mg	1x500 mg	5 days
Moxifloxacin	1x400 mg	1x400 mg	5 days
For AECOPD with Stockley Type II and known colonization with *P. aeruginosa* and/or with bronchiectasis and/or with individual evidence of *P. aeruginosa* and for patients on mechanical ventilation*			
Piperacillin/tazobactam		3x4.5 g	8 days
Cefepim		3x2.0 g	8 days
Ceftazidim**		3x2.0 g	8 days
Imipenem		3x1.0 g	8 days
Meropenem		3x1.0 g	8 days
Or			
Levofloxacin	2x500 mg	2x500 gm	8 days
Ciprofloxacin**	2x750 mg	3x400 gm	8 days

* The primary decision criterion for choosing one of the listed drugs is previous antibiotic treatment within the last 3 months for patients with recurrent exacerbations: switching class versus the one used in the latest episode is recommended.

** Ciprofloxacin and ceftazidim in combination with a drug effective against pneumococci

- depression
- and/or impairment of consciousness up to coma (CO_2 narcosis)

Indications for antimicrobial treatment of patients with moderate to severe AECOPD

Besides the severity of the AECOPD, the procalcitonin (PCT) level measured in serum is used in the treatment decisions regarding antibiotic use.

The S3 guidelines recommends the following medication (Table 10):

Antibiotic therapy is recommended (level B) for:

- moderately severe AECOPD (indication for hospitalization): antimicrobial therapy only if Stockley II (purulent sputum)
  *if PCT levels are available and the measured value is <0.1 ng/ml, antimicrobial treatment may be forgone.
- severe AECOPD (indication for intensive care): antimicrobial therapy is always indicated.

Pneumonia

Pneumonia is diagnosed in patients with new or increasing infiltrates in chest x-ray and the following clinical signs:

- body temperature >38°C (or occasionally <36°C) and/or
- leukocytosis (>10/µl) and/or
- leftward shift (>5%) and/or
- CRP>5 mg/dl

and at least 2 of the following symptoms:

- productive cough
- purulent sputum
- dyspnea, trachypnea
- chills
- fine crackles on auscultation
- thoracic pain when breathing

Classification of pneumonias is made according to the recommendations of the American Thoracic Society (ATS) and the Infectious Diseases Society of America (IDSA), taking into consideration whether the disease was community-acquired or hospital-acquired.

For community-acquired pneumonias – depending on age, risk factors, severity, and course of illness – four patient groups could be identified whose disease may be attributed with high probability to the pathogens typical for the respective groups.

The classification of nosocomial pneumonias into three groups with different treatment strategies based on risk assessment using a clinical score follows the recommendations of the PEG and DGP from 2003. Time of onset of pneumonia after hospital admission, need for ventilator support, age of the patient, comorbidities, and previous antiinfective therapy are assessed.
Supportive measures in the management of pneumonia include adequate intake of fluids (>2 L per day), appropriate antipyretics, oxygen support for hypoxia, treatment of bronchial obstruction, and in some cases the administration of glucocorticoids. All patients should receive prophylaxis against thromboembolism.

Community-acquired pneumonia

CRB-65 Score

Test for the presence of the following criteria:

- confusion
- respiratory rate (≥30/min)
- diastolic blood pressure ≤60 mmHg / systolic blood pressure <90 mmHg
- age (≥65 years)

The score is calculated by adding one point for the presence of each of the listed items.
These recommendations apply to moderate to severe CAP since mild CAP should be treated orally.

- Moderately severe community-acquired pneumonia: management in general wards (hospitalized CAP): clinical decision using the CRB-65 Score
- Severe community-acquired pneumonia: management in a monitoring ward (intensive care, intermediate care, etc.) (severe CAP): clinical decision using the CRB-65 score
  - without indication for empirical treatment effective against *P. aeruginosa* (see risk factors for *P. aeruginosa*)
  - with indication for empirical treatment effective against *P. aeruginosa* (see risk factors for *P. aeruginosa*)

Pathogen spectrum of hospitalized CAP patients

The most frequent pathogens are *S. pneumoniae*, *M. pneumoniae*, *H. influenzae*, gram-negative enterobacteriaceae and respiratory viruses. The frequency of *L. pneumophila* varies across regions, it may be as high as 6%. Enterobacteriaceae were shown to be somewhat more frequent than in CAP patients treated as out-patients.
According to the latest data from CAPNETZ, P. aeruginosa has a minor role as a CAP pathogen in Germany. Therefore for CAP treated on general wards, *Pseudomonas* coverage in initial treatment is necessary only in patients with risk factors (see risk factors for *P. aeruginosa*).

Risk factors for P. aeruginosa

- Severe chronic structural lung diseases such as severe COPD with previous antibiotic treatment or previous hospitalization, both within the last 3 months
- known colonization by *P. aeruginosa*
- bronchiectases
- cystic fibrosis

Treatment of hospitalized CAP patients

Antimicrobial therapy should be started as early as possible (recommendation level B). A delay of treatment initiation by ≥8 hours after hospital admission is associated with higher mortality. Diagnostic measures must not delay the start of treatment.
After parenteral initial therapy, an early switch to an oral treatment is appropriate if the following requirements are fulfilled (recommendation level A):

- heart rate ≤100/min
- respiratory rate ≤24/min
- systolic blood pressure ≥90 mm Hg
- body temperature ≤37.8 °C
- ability to tolerate oral nutrition
- normal level of consciousness
- no hypoxemia (pO_2≥60 mm Hg or SaO_2≥90%) and
- safe oral intake of medication

Duration of treatment

The S3 guidelines recommend (recommendation level A) (Table 11): antibiotic treatment may be stopped 48 to 72 hours after clinical improvement with reduction in body temperature, but not before completion of 5 days of therapy. A duration of treatment of more than 7 days is not generally required. A treatment duration of 8 to 15 days is recommended for proven infections with *P. aeruginosa*.
Appropriate reasons for a shorter treatment (<8 days) include:

- improvement of general health status
- ability to tolerate oral nutrition
- improvement of respiratory symptoms
- body temperature <38 °C

Management of severe community-acquired pneumonia (sCAP)

- Indication for intensified monitoring (depending on facilities, intensive care unit, intermediate care unit or intensified monitoring on a general ward): patients with acute lower respiratory tract infection with or without positive local auscultatory findings, an infiltrate in chest x-ray and
  - 1 major criterion of the modified ATS score
  - ≥2 minor criteria of the modified ATS score or
  - CRB-65 index ≥2

Table 11: Recommendations for the calculated initial therapy of hospitalized CAP patients

Substances for initial therapy	Dosage for the initial treatment (per day)	Total duration of treatment
Beta lactams		
Amoxicillin/clavulanic acid	3x2.2 g IV	5–7 days
Ampicillin/sulbactam	3x3.0 g IV	5–7 days
Cefuroxim	3x1.5 g IV	5–7 days
Ceftriaxon	1x2.0 g IV	5–7 days
Cefotaxim	3x2.0 g IV	5–7 days
with or without a macrolide*		5–7 days
or** **Fluoroquinolones***		
Levofloxacin	1x500 mg IV	5–7 days
Moxifloxacin	1x400 mg IV	5–7 days
or, for special patients**** **Carbapenems**		
Ertapenem	1x1.0 g IV	5–7 days
with or without a macrolide*		5–7 days

* Depending on the clinical decision for parenteral or oral therapy; parenteral administration is preferred (B). For oral treatment, the modern macrolides (clarithromycin, roxithromycin or azithromycin) should be chosen over the older macrolides.

** After previous treatment with antibiotics within the last 3 months, a change from the last used substance group is recommended.

*** Initial oral treatment is equivalent to parenteral therapy, an initial parenteral administration is preferable, however (B).

**** Patients with risk factors for infection with *Enterobacteriaceae* incl. ESBL-producers (except for *P. aeruginosa*) as well as patients who have recently been treated with penicillins or cephalosporins.

In particular cases one minor criterion of the modified ATS score or a CRB-65 index of 1 can also be sufficient to warrant intensified monitoring. Thorough clinical evaluation of CAP severity is essential for decision on intensive care.
Modified ATS criteria for severe pneumonia (sCAP): major criteria, determined at admission or later (positive if 1 or 2 factors are present)

1. Need for intubation and mechanical ventilation
2. Need for vasopressor use >4 hours (septic shock)

Minor criteria, determined at admission (positive if 2 or 3 factors are present)

1. Severe respiratory insufficiency (PaO_2/FiO_2<250)
2. Multilobar infiltrates in chest x-ray
3. Systolic blood pressure <90mm Hg

Pathogen spectrum in sCAP

The etiology of sCAP differs from less severe CAP forms by a wider pathogen spectrum. Approximately 10% of sCAPs are polymicrobial infections.
Determination of a potential involvement of *P. aeruginosa* is important for differential therapy.

Patients with sCAP are categorized in two risk groups:

- Patients with sCAP without risk factors for *P. aeruginosa* infection
- Patients with sCAP with risk factors for *P. aeruginosa* infection

CAP caused by *P. aeruginosa* occurs almost exclusively in patients with particular risk factors.

Treatment of severe community-acquired pneumonia (sCAP)

Calculated initial therapy

The risk of unfavourable outcomes due to inadequate therapy of infections with resistant pathogens is particularly high in sCAP. Considering the latest resistance data is crucial.
The treatment of choice for sCAP without risk factors for *P. aeruginosa* involvement, according to S3 guidelines (recommendation level B) is a combination of broad-spectrum beta-lactam antibiotic (cefotaxim, ceftriaxon, piperacillin/tazobactam, or ertapenem) and a macrolide (Table 12). Monotherapy with a fluoroquinolone covering pneumococci (levofloxacin or moxifloxacin) is a potential alternative, but should be limited to patients without septic shock or invasive ventilation.
For patients with indication for empirical therapy covering *P. aeruginosa*, the S3 guidelines (Table 13) recommend a combination of piperacillin/tazobactam, cefepim, imipenem or meropenem and a fluoroquinolone covering pseudomonas (levofloxacin or ciprofloxacin) or an

Table 12: Recommendations for calculated initial therapy of hospitalized patients with severe community-acquired pneumonia (sCAP) without risk factors of P. aeruginosa infection

Drugs for initial therapy	Dosage for initial therapy (per day)	Total duration of therapy
*Drug of choice*** **Beta lactams**		
Piperacillin/tazobactam	3x4.5 g IV	8–10 days
Ceftriaxon	1x2.0 g IV	8–10 days
Cefotaxim	3x2.0 g IV	8–10 days
Ertapemen**	1x1.0 g IV	8–10 days
plus a macrolide		8–10 days
*Alternatives** **Fluoroquinolones*****		
Levofloxacin	2x500 mg IV	8–10 days
Moxifloxacin	1x400 mg IV	8–10 days

* After previous treatment with antibiotics within the last 3 months, a change from the last used substance group is recommended.

** Patients with risk factors for infection with Enterobacteriaceae incl. ESBL-producers (except *P. aeruginosa*) as well as patients who have recently been treated with penicillins or cephalosporins.

*** For patients with septic shock and/or invasive ventilation, initial combination therapy with a beta lactam is indicated.

Table 13: Recommendations for calculated initial therapy of hospitalized patients with severe community-acquired pneumonia (sCAP) with indication for empirical therapy effective against P. aeruginosa

Drugs for initial therapy	Dosage for initial therapy (per day)	Total duration of therapy
Beta lactams active against *Pseudomonas*		
Piperacillin/Tazobactam	3x4.5 g IV	8–15 days
Cefepim	3x2.0 g IV	8–15 days
Imipenem	3x1.0 g IV	8–15 days
Meropenem	3x1.0 g IV	8–15 days
plus a fluoroquinolone		
Levofloxacin	2x500 mg IV	*
Ciprofloxacin	3x400 mg IV	*
or** plus an aminoglycoside and a macrolide		
Amikacin	15 mg/kg body weight IV***	3 days*
Gentamicin	5–7 mg/kg body weight IV***	3 days*
Tobramycin	5–7 mg/kg body weight IV***	3 days*

* After clinical response, deescalation to treatment with a beta lactam/macrolide or a fluoroquinolone is indicated, taking antibiotic susceptibility tests into account if available. In most cases aminoglycosides should not be given for longer than 3 days because of oncreased toxicity.

** After previous treatment with antibiotics within the last 3 months, a change from the last used substance group is recommended.

*** Further dosing according to plasma levels.

aminoglycoside plus a macrolide. An important differential criterion is previous therapy with an antibiotic necessitating a switch of drug class. Ceftazidim is active against *P. aeruginosa* but – unlike cefepim – inadequately effective against *S. pneumoniae* and *S. aureus*. As a rule, the treatment should be changed to monotherapy after clinical improvement and/or pathogen detection with a susceptibility test.

Duration of therapy

The S3 guidelines recommend (level B) a treatment duration of 8 to 10 days for patients without complications or 5 days after defervescence. In patients with proven *P. aeruginosa* infections, treatment should be continued for 15 days. Prolonged treatment courses are necessary for sCAP caused by *S. aureus* as well.

Nosocomial pneumonia

Nosocomial pneumonia is a hospital-acquired lung infection with onset within three days after admission to seven days after discharge of the patient. In the USA and Europe, pneumonia is the second most frequent nosocomial infection. It is the most common infection in intensive care medicine. With mortality rates of 30–50% it is the most frequently lethal hospital-acquired infection. Particularly infections with multiresistant bacteria have a poor prognosis. Early and effective treatment of nosocomial pneumonia is essential in reducing morbidity and mortality [2], [81], [106].
Risk factors predisposing patients for nosocomial pneumonia include:

- higher age (>65 years)
- previous antibiotic treatment
- immunosuppression
- coma
- prolonged intubation and ventilation
- organ failure and septic shock
- preexisting respiratory disease
- thoracic or abdominal surgery
- severe trauma
- smoking
- alcohol abuse
- drug abuse

All patients are colonized with possible pathogens in the oropharynx, have an impaired immune function and potential aspirations caused by diminished protective larynx reflexes.
The choice of initial antimicrobial therapy is based on the classification of patients into defined groups with characteristic pathogen spectra and defined treatment recommendations. Each of these three groups has its particular risk profile resulting in an overall risk score. The individual factors are weighted with 1 to 4 points (Table 14). Spontaneous breathing and artificial ventilation or severe respiratory insufficiency with early (until day 4) or late (day 5 or later) onset after the occurrence of pneumonia, age of the patient and other risk factors including previous antiinfective therapy, structural lung diseases or extrapulmonary organ failure are considered as well. The individual risk factors have divergent degrees of influence on the severity of illness and the expected pathogen spectrum. The recommendations are based on evidence of variable quality and often reflect expert opinions. This procedure is presently investigated in a retrospective chart review in several large hospitals in Germany. The recommendation to treat patients with nosocomial pneumonia according to a risk-based point system compiled in 2003 at a joint PEG and DGP consensus conference on nosocomial pneumonia remains controversial. At the current consensus conference, 34% of the participants rejected this recommendation.
Some of the listed antibiotics are not licensed for the respective indication but are recommended on the basis of the available evidence. In group 3, the combination with a fluoroquinolone has evidence level IV.
The adequacy of monotherapy is independent of disease severity. Monotherapy is indicated in pneumonia with onset within the first four days of hospitalization in the absence of risk factors. Multiresistant pathogens are less frequently found in spontaneously breathing patients.
The superiority of combination therapies for late-onset pneumonia and/or patients with risk factors is not reliably established. Combination therapy is still recommended in cases with suspected *Pseudomonas* involvement [442], [530], [562] and in patients with ventilator-associated pneumonia [126], [262], [442], [522]. The rationales of combination therapy include the extension of the antibacterial spectrum and the exploitation of possible synergies. After 2 to 3 days of treatment, the initial combination therapy should be evaluated [428], [442], [522], [542]. A decisive factor for treatment success is the early start of adequate antimicrobial therapy [74], [276] at a sufficient dosage. The duration of therapy should be not more than 8 to 10 days [101], [222], [562]. Pneumonias caused by *S. aureus* or *P. aeruginosa* require longer treatment duration [14], [224], [523], [530].

Initial calculated therapy group I: spontaneously breathing patients with ≤2 risk points

The pathogen spectrum of this patient group largely corresponds to the endogenous flora of the upper respiratory tract, that patient brought in from his environment. This includes *S. pneumoniae*, methicillin-susceptible *S. aureus*, *H. influenzae* and other gram-negative pathogens. Multiresistant bacteria are rarely present. Pneumonias occurring later than the fifths day after admission are primarily caused by gram-negative enterobacteria.
Group 2 cephalosporins or aminopenicillins/BLI are sufficient to treat mild pneumonias detected before the fifth day after admission. In severe cases, group 3a cephalosporins are preferred. Group 3 or 4 fluoroquinolones or group 2 carbapenems could also be used; they are not yet licensed in Germany for the treatment of nosocomial pneumonias but are currently being tested in clinical studies.
The initial treatment should be administered parenterally. It may be changed to an oral therapy after clinical improvement. If gastrointestinal absorption is intact, fluoroquinolones may be initiated orally if patient compliance is ensured.

Initial calculated therapy group II: non-ventilated patients with risk factors or patients on mechanical ventilation without risk factors (patients with 3 to 5 risk points)

In this patient group, an increased incidence of *Enterobacter* spp., *Serratia* spp., *Citrobacter* spp., *Pseudomonas* spp., *Acinetobacter* spp., *S. maltophilia* and anaerobes must be anticipated besides the above mentioned

Table 14: Scoring of risk factors in patients with nosocomial pneumonia and recommendations for calculated initial therapy

Risk factors			**Points**
Age>65 years			1
Structural lung disease			2
Previous antibiotic therapy			2
Pneumonia onset on 5th day in hospital or later			3
Severe respiratory insufficiency with or without ventilation (mechanical or non-invasive)			3
Extrapulmonary organ failure (shock, acute liver or kidney failure, disseminated intravascular coagulation)			4
Group I: up to 2 points			
Substances	**Daily dose parenteral**	**Evidence level**	**Recommendation level**
Ampicillin/sulbactam	3x3 g	Ia	A
Amoxicillin/clavulanic acid	3x2.2 g	Ia	A
Cefuroxim	3x1.5 g	Ia	B
Cefotaxim	3x2 g	Ia	B
Ceftriaxon	1x2 g	Ia	B
Levofloxacin	1x0.5 g	Ia	A
Moxifloxacin	1x0.4 g	Ia	A
Ertapenem	1x1 g	Ia	A
Group II: 3 to 5 points			
Substances	**Daily dose parenteral**	**Evidence level**	**Recommendation level**
Piperacillin/Tazobactam	3x4.5 g	Ia	A
Piperacillin + Sulbactam	3x4 g + 3x1 g	IV	B
Cefepim	3x2 g	Ia	A
Doripenem	3x0.5 g	Ia	A
Imipenem	3x1 g	Ia	A
Meropenem	3x1 g	Ia	A
Group III: 6 or more points			
Substances	**Daily dose parenteral**	**Evidence level**	**Recommendation level**
Piperacillin/tazobactam or	3x4.5 g	Ia	A
Piperacillin + sulbactam or	3x4 g + 3x1 g	IV	B
Ceftazidim or	3x2 g	Ia	B
Cefepim or	3x2 g	Ia	A
Doripenem or	3x1 g	Ia	A
Imipenem or	3x1 g	Ia	A
Meropenem	3x1 g	Ia	A
Each plus			
Ciprofloxacin or	3x0.4 g	IV	A
Levofloxacin or	2x0.5 g	IV	A
Fosfomycin or	3x5 g	IV	A
Aminoglycoside		Ia	C

pathogens. Therefore, antibiotics covering these pathogens in their spectra should be used for treatment. Available options include group 4 cephalosporins, acylaminopenicillins/BLI and group 1 carbapenems. Because of the resistance situation and the undesirable microbiological side effects (collateral damage) in terms of selection of antibiotic-resistant pathogens and colonization or infection with multiresistant pathogens, group 3 cephalosporins and fluoroquinolones should not be used for these patients [78], [372], [399], [566]. In the case of cephalosporins this means an increased occurrence of vancomycin-resistant enterococci (VRE), ESBL-producing enterobacteriaceae and beta-lactam antibiotic-resistant *Acinetobacter* spp. [78], [399]. When using fluoroquinolones, colonization by MRSA and the resistance situation

of *E. coli* and *P. aeruginosa* must be taken into consideration [372], [566].

Initial calculated therapy group III: patients with high risk, usually on mechanical ventilation (patients with ≥6 risk points)

In these patients, pneumonias are often caused by multiresistant pathogens. For this reason a combination treatment should be initiated [126], [262], [442], [522], [530], [562]. The options include group 3b or 4 cephalosporins, acylaminopenicillins/BLI or group 1 carbapenems in combination with an aminoglycoside (once daily), high-dose group 2 or 3 fluoroquinolones, or fosfomycin. A group 2 or 3 fluoroquinolone or fosfomycin should be preferred as combination partner for beta-lactam antibiotics [442], [530], [571].

MRSA pneumonias

From the clinical point of view, there are no substances available for the treatment of MRSA pneumonias which have been tested in clinical studies except for linezolid and the glycopeptides. Linezolid showed statistically significant advantage in a post hoc analysis of two prospective studies [582] but was not superior to vancomycin in the primary endpoint in another clinical trial [581].
The critical disadvantage of vancomycin is its poor penetration into the lungs (11% of the plasma level), which could theoretically be partially compensated by combination with MRSA-effective substances (fosfomycin, rifampicin) with good tissue penetration. However, these combinations were not tested in randomized clinical trials. Linezolid is therefore the preferred choice for pulmonary MRSA infections. Because linezolid, like vancomycin, is active against gram-positive pathogens only, it should be used in monotherapy only if the involvement of gram-negative or atypical pathogens has been ruled out.

Aspiration pneumonia and pulmonary abscess

Aspiration pneumonias are subdivided into insidious recurrent aspirations and acute aspirations of stomach contents.

- Pathogen identification is difficult.
- Polymicrobial aetiology is common (aerobic and anaerobic pathogens).
- Gram-positive pathogens are more likely in cases with community-acquired aspiration.
- Gram-negative or polymicrobial infections, some involving anaerobes, are common in patients with frequent hospitalization and antimicrobial therapies.

The pathogenesis of primary lung abscesses involves aspiration, virulence of the pathogen and immune impairment of the patient. Risk factors for aspiration include

- previous CNS diseases,
- intoxication,
- difficulty of swallowing and/or
- oesophageal pathologies.

Secondary lung abscesses are due to

- bronchial obstruction by tumors,
- bronchial obstruction by foreign bodies and poststenotic pneumonia,
- colliquation,
- super infections of infarct pneumonias,
- rarely bacteremia.

Bacterial mixed infections predominate; obligate anaerobes were detected in 20% to 90%. In a German study, *S. aureus* was found to be the most frequent pathogen in aspiration pneumonias and lung abscesses [389].
Previous aspiration is a risk factor for the involvement of enterobacteriaceae. As an additional aetiological role of anaerobic bacteriae in aspiration pneumonia is possible and as a large number of anaerobes produce beta-lactamases, penicillins should be combined with a beta-lactamase inhibitor. Alternatively, a combination of a group 3a cephalosporin (cefotaxim, ceftriaxon) with clindamycin, a group 4 fluoroquinolone (moxifloxacin) or a group 2 carbapenem (ertapenem) may be used.

Pleural infections

There is little proven data on calculated treatment of pleural infections. The evidence is based primarily on retrospective investigations and expert opinions.
Pleuritis sicca is caused mainly by viruses, *Chlamydia* spp. or *Mycoplasma* spp. Therefore, macrolides or group 3 and 4 fluoroquinolones (evidence level IV) are used as calculated treatments.
The primary goals in treatment of parapneumonic effusions include control of the infection, drainage of infected effusion, (re-)expansion of the lungs and avoidance of pleural calluses.
Basic therapy includes sufficient, pathogen-specific antimicrobial treatment aiming at the control of the underlying infection. There are no controlled clinical trials on the optimum antibiotic treatment and its duration. The calculated antimicrobial treatment should cover gram-positive cocci, gram-negative pathogens (where applicable including *P. aeruginosa*) and anaerobes. Initially, parenteral administration is preferred to ensure sufficient plasma and intrapleural concentrations. Basically, treatment should be continued at least until the infected effusion has been completely drained. Long treatment durations of several weeks are often necessary.
A basic requirement in the treatment of complicated parapneumonic effusions is the effective and complete drainage of infected fluid. The following differentiated approach is suggested:

1. No intervention
2. Thoracocentesis
3. Establishment of a thoracic suction drainage without local fibrinolysis

4. Establishment of a thoracic suction drainage with local fibrinolysis
5. Video-assisted thoracoscopy with post-intervenional thoracic suction drainage
6. Surgical exploration (thoracotomy) with or without decortication and/or rib resection

If drainage is insufficient to rapidly remove the infected pleural fluid, video-assisted thoracoscopy (VATS) in a preferred option as well as a limited attempt of local fibrinolysis if appropriate.

Risk stratification

1. Size of effusion
   A 0: Minimal effusion (<5 cm in a lateral x-ray) or thorax sonography
   A 1: Medium-large, freely discharging effusion (>5 cm and <½ hemithorax)
   A 2: Large, freely discharging effusion (>½ hemithorax), chambered effusion or effusion with thickened pleura
2. Bacteriology of exsudate
   B x: Gram stain or culture not known
   B 0: Negative culture and gram stain
   B 1: Positive culture or gram stain
   B 2: Pus
3. Clinical chemistry of exsudate
   C x: pH unknown
   C 0: pH >7.2
   C 1: pH <7.2

Additional patient risk due to pleural effusion is estimated using the following parameters: prolonged hospitalization, increased morbidity due to further interventions, prolonged physical disability, increased risk of a respiratory impairment, increased risk of local inflammation, mortality.

Treatment recommendation (recommendation B)

Category 1 (very low risk): presence of A 0, B x or C x: no drainage
Category 2 (low risk): presence of A 1, B 0 or C 0: no drainage
Category 3 (medium risk): presence of A 2, B 1 or C 1: drainage indicated
Category 4 (high risk): presence of B 2: drainage indicated
For patients of categories 3 and 4, a relief puncture appears to be insufficient in most cases. Therefore, thoracic drainage is indicated. In the case of chambered effusions, or category 4 patients, local fibrinolysis or video-assisted thoracoscopy is the most appropriate approach.

6 Infections in the ear, nose and throat or mouth, jaw and facial regions

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In daily practice, bacterial infections in the head and throat region often require the use of antibiotics. The decision for an intravenous treatment depends on the severity of the infection and the individual prerequisites for administration. However mastoiditis, malignant otitis externa, sinusitis with orbital and other complications, epiglottitis, severe odontogenic abscesses and cervical phlegmons should generally be treated with intravenous antibiotics. Even if initial treatments are mostly calculated therapies, microbiological pathogen identification is mandatory for these severe diseases. Switching to an oral preparation after the initial intravenous treatment phase is possible in some cases. Recently introduced antibiotics have extended the range of indications for oral treatments. Specifically, fluoroquinolones may be administered orally for some severe infections. If possible, oral therapy should be preferred for economic reasons. As a matter of principle, any antibiotic therapy should be reassessed after 3 or 4 days. Interestingly, despite the high incidence of these infections, systematic investigations of the pathogen spectrum have been performed only rarely. Very few randomized comparative studies with large patients numbers that may support the present recommendations are available. Current expert recommendations of medical societies for antimicrobial treatment of head and throat infections were considered in the following recommendations (Table 15) [8], [10], [167].

Malignant otitis externa

Malignant otitis externa is a very rare disease predominantly caused by *Pseudomonas aeruginosa*. In rare cases other pathogens might be involved [32], [100], [287], [485]. The infection usually affects older, male diabetes mellitus patients [214] and in rare cases patients with immunosuppression [16], [477]. The infection may spread to adjacent bone structures and requires surgical debridement of the affected area.
The disease may be lethal if left untreated. Therefore therapy must be initaited immediately upon admission to the hospital with a high-dosage intravenous antibiotic, e.g. from the group 2 fluoroquinolones (ciproflaxacin), ureidopenicillins (preferrably piperacillin), group 3b or group 4 cephalosporins (ceftazidime or cefepime, respectively), group 1 carbapenems (doripenem, imipenem/cilastatin, meropenem) or group 3 fluoroquinolones (levofloxacin) [56], [60]. In cases with insufficient response, treatment should be switched to a beta-lactam combined with an aminoglycoside.
Treatment duration should be approximately 6 weeks. If an aminoglycoside (e.g. tobramycin) is used due to a high-

Table 15: Recommendations for empirical intravenous initial antimicrobial therapy of the ear, nose and throat (ENT) and the mouth jaw and face region

Diagnosis	Most frequent pathogen	Initial therapy	Total treatment duration (intravenous and oral)	Level of evidence	Level of recommendation
Malignant otitis externa (Otitis externa maligna)	*Pseudomonas aeruginosa*	Group 2 fluoroquinolone (ciprofloxacin)	Up to 6 months (switch to oral treatment)	III	B
		Ureidopenicillin (preferably piperacillin)		III	B
		Group 3b cephalosporin (ceftazidim)		III	B
		Group 4 cephalosporin (cefepim)		III	B
		Group 1 carbapenem (doripenem, imipenem/ cilastatin, meropenem)		III	B
		Group 3 fluoroquinolone (Levofloxacin)		III	C
Mastoiditis	*Streptococcus pneumoniae* *Streptococcus pyogenes* *Haemophilus influenzae*	Aminopenicillin/BLI (ampicillin/sulbactam, amoxicillin/clavulanic acid)	Approx. 7 days	III	C
	Staphylococcus aureus *Pseudomonas aeruginosa*	Group 2 cephalosporin (cefuroxim, cefotiam)		III	C
	Escherichia coli *Proteus mirabilis*	Group 3a cephalosporin (cefotaxim, ceftraxon)		III	C
		Group 4 cephalosporin (cefepim)		III	C
Frontal bone osteomyelitis	*Staphylococcus aureus* *Streptococcus pneumoniae* *Haemophilus influenzae* *Pseudomonas aeruginosa*	Ureidopenicillin/BLI (Piperacillin/tazobactam, Piperacillin + sulbactam, Mezlocillin + sulbactam)	Approx. 6 weeks	III	C
		Aminopenicillin/BLI (Amoxicillin/clavulanic acid, Ampicillin/sulbactam)		III	C
		Carbapenem (doripenem, imipenem/ cilastatin, meropenem, ertapenem)		III	C
Orbital phlegmone	*Staphylococcus aureus*	High dosage	14 days		
		Ureidopenicillin/BLI (piperacillin/tazobactam, piperacillin + sulbactam, mezlocillin + sulbactam)		III	C
		Aminopenicillis/BLI (amoxicillin/clavulanic acid, ampicillin/sulbactam)		III	C
		Carbapenem (doripenem, imipenem/ cilastatin, meropenem, ertapenem)		III	C
		Group 3a cephalosporin (cefotaxim, ceftraxon) + clindamycin or metronidazol		III	C

(Continued)

Table 15: Recommendations for empirical intravenous initial antimicrobial therapy of the ear, nose and throat (ENT) and the mouth jaw and face region

Diagnosis	Most frequent pathogen	Initial therapy	Total treatment duration (intravenous and oral)	Level of evidence	Level of recommendation
Epiglottitis	*Streptococcus pyogenes* *Haemophilus influenzae* B	Group 3a cephalosporin (cefotaxim, ceftriaxon)	10 days	III	C
	Staphylococcus aureus *Streptococcus pneumoniae* Rarely: *Haemophilus*	Aminopenicillis/BLI (amoxicillin/clavulanic acid, ampicillin/sulbactam)		III	C
	parainfluenzae, viruses	If evidence of *S. aureus* optionally group 2 cephalosporin (cefuroxim, cefotiam)		III	C
Perichondritis	*Pseudomonas aeruginosa*	Piperacillin/BLI	10 days	III	C
	Staphylococcus aureus	Cefepim		III	C
		Imipenem/cilastatin, meropenem		III	C
Nasal furuncle	*Staphylococcus aurens*	Isoxazolyl penicillin (flucloxacillin, dicloxacillin)	5–8 days	III	C
		Cefaclor		III	C
		Aminopenicillin/BLI (ampicillin/sulbactam, amoxicillin/clavulanic acid)		III	C
Peritonsillar abscess	*Haemolytic streptococci* *Staphylococci* *Prevotella spp.* *Fusobacterium necrophorum* other Anaerobes Gram-negative pathogens	Group 1 cephalosporin (cefazolin, cefuroxim, cefotiam) + clindamycin	1–2 days parenteral, then oral treatment for 8–9 days	III	C
		Aminopenicillin/BLI (ampicillin/sulbactam, amoxicillin/clavulanic acid)		III	C
		Macrolide (erythromycin, clarithromycin, azithromycin)		III	C
Chronic purulent sinusitis	*Staphylococcus aureus* *Streptococcus* *Haemophilus influenzae* *Enterobacteriaceae* Rarely: *Pseudomonas aeruginosa* Anaerobes *Aspergillus*	Aminopenicillin/BLI (amoxicillin/clavulanic acid, sultamicillin)		II	B
		Oral cephalosporin (cefuroxim axetil, loracarbef, cefpodoxim proxetil)		II	B
		Group 3/4 fluoroquinolone (levofloxacin, moxifloxacin)		II	B
Odontogenic abcess/throat phlegmon	Streptococci Rarely: staphylococci *Prevotella spp.* *Fusobacteria* *Bacteroides spp.* *Veillonella* Peptostreptococci	Aminopenicillin/BLI (e.g. amoxicillin/clavulanic acid)	3–14 days	II	B
		Carbapenem		IV	C
		Metronidazole + ciprofloxacin		IV	C
		Clindamycin		II	B
		Moxifloxacin		II	B
Osteomyelitis	See odontogenic abscess	Clindamycin	4–6 weeks	III	C
		Penicillin		III	C

(Continued)

Table 15: Recommendations for empirical intravenous initial antimicrobial therapy of the ear, nose and throat (ENT) and the mouth jaw and face region

Diagnosis	Most frequent pathogen	Initial therapy	Total treatment duration (intravenous and oral)	Level of evidence	Level of recommendation
Acute necrotizing gingivitis and tonsillitis	Spirochetes	Penicillin + metronidazole	according to symptoms	IV	B
		Clindamycin		IV	B
Cervicofacial actinomycosis	*Actinomyces israelii*	Amoxicillin	6 weeks	II	B
		Doxycyclin		III	C
		Clindamycin		III	C
Sialadenitis	*Staphylococci* *Streptococci* *Anaerobes*	Aminopenicillin/BLI	3–10 days	III	C
		Clindamycin		III	C

resistance situation, serum levels must be monitored due to the ototoxic and nephrotoxic potential of this group of drugs. A once-daily regimen resulting in high peak and low trough levels is preferred (see chapter 3).

Mastoiditis

Mastoiditis is a common complication of acute or chronic otitis media. The pathogen that caused the primary infection should be suspected as the cause of mastoiditis. The most commonly involved pathogens in order of frequency are *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Haemophilus influenzae*, *Staphylococcus aureus*, *P. aeruginosa*, *Escherichia coli* and *Proteus mirabilis* [167], [336].

Surgical debridement is strictly required. The initial calculated therapy should be started with an aminopenicillin/beta-lactamase inhibitor (BLI) combination (ampicillin/sulbactam, amoxicillin/clavulanic acid) or a cephalosporin from group 2 (cefuroxim, cefotiam), 3a (cefotaxim, ceftriaxon) or 4 (cefepim). Alternatively, group 3 or 4 fluoroquinolones (levofloxacin or moxifloxacin, respectively), ureidopenicillins/BLI (piperacillin/BLI, mezlocillin/BLI) or group 2 carbapenems (ertapenem) may be used.

Pathogens should be identified from samples taken intraoperatively if possible. Based on the microbiology results, the antimicrobial treatment may be adjusted to obtain better pathogen targeting. The treatment duration is about 1 week.

Frontal bone osteomyelitis

Frontal bone osteomyelitis is an infection of the frontal bone that spreads from acute or chronic sinusitis or dental infections of the upper jaw *per continuitatem*. It mostly affects adolescents. Surgical debridement of the affected frontal sinus and removal of the infected part of the bone is strictly indicated. The most common pathogens are *S. aureus*, *S. pneumoniae*, *H. influenzae* and *P. aeruginosa*.

Antimicrobial therapy initially consists of high-dose ureidopenicillin/BLI or aminopenicillin/BLI (piperacillin/tazobactam, piperacillin + sulbactam, mezlocillin + sulbactam, amoxicillin/clavulanic acid, ampicillin/sulbactam) or a carbapenem (doripenem, imipenem/cilastatin, meropenem, ertapenem). If cefotaxim or ceftriaxone is used, it should preferably be combined with clindamycin or metronidazol.

In severe cases, beta-lactam antibiotics are combined with an aminoglycoside or fluoroquinolone. Samples obtained by sinus puncture, surgical drainage fluid and blood cultures should be examined microbiologically. After pathogen indentification the treatment should be adjusted to obtain more specific targeting. Treatment duration should be approximately 6 weeks.

Orbital phlegmon

Orbital phlegmon is an acute infection of the soft tissue of the ocular orbit. It usually results from an infection spreading from the paranasal sinuses. Occasionally, the root cause are odontogenic or intracranial infections. In rare cases trauma, surgery or dacryocystitis may also be the causative event. Because of a high risk of complications in terms of loss of vision or intracranial spread of infection, surgical intervention is strictly required. Potential pathogens include *S. aureus*, *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*, *K. pneumoniae*, *P. aeruginosa* and anaerobes. Fungi are detected less frequently. Polymicrobial infections are prevalent.

Antibiotic therapy should be initiated intravenously. High-dose ureidopenicillins/BLI or aminopenicillins/BLI (piperacillin/tazobactam, piperacillin + sulbactam, mezlocillin + sulbactam, amoxicillin/clavulanic acid, ampicillin/sulbactam) or carbapenems (doripenem, imipenem/cilastatin, meropenem, ertapenem) are recommended. If cefotaxim or ceftriaxone is used, it should be combined with clindamycin or metronidazol if possible.

In severe cases, an aminoglycoside or fluoroquinolone (ciprofloxacin, levofloxacin) is added to the basic treatment. A switch to oral moxifloxacin is a feasible option for sinusitis with orbital involvement. Samples obtained

by sinus puncture, surgical drainage fluid and blood cultures should be examined microbiologically. After pathogen identification the treatment should be adjusted to obtain more specific targeting. The recommended treatment duration is 14 days.

Epiglottitis

Acute epiglottitis occurs mainly in children and is quite rare in adults. Usually it is an acute and severe rapidly progressing disease. Due to the imminent risk of an airway obstruction, it must immediately be treated in a hospital intensive care unit with the option of rapid intubation or tracheotomy.
In adults, potential pathogens are *S. pyogenes*, *H. influenzae* Type B, *S. aureus*, and *S. pneumoniae*, occasionally *Haemophilus parainfluenzae* or viruses. Group 3a cephalosporins (cefotaxim, ceftriaxon), aminopenicillins/BLI (amoxicillin/clavulanic acid, ampicillin/sulbactam) or – if *S. aureus* is detected – group 2 cephalsporins (cefuroxim, cefotiam) are recommended for calculated therapy. The incidence of epiglottitis has declined in children living in Western countries due to widespread vaccination against *Haemophilus influenzae* B [205], [285].

Perichondritis

This infection usually results from an earlier injury. In the ear region, common pathogens are *P. aeruginosa* and *S. aureus* but other pathogens may be involved as well, depending on the type of trauma. Samples should be obtained for microbiological diagnosis. The antibiotic treatment should be as targeted as possible based on the microbiological results. Hospitalization may be required in severe cases. Options for initial calculated therapy include intravenous piperacillin/BLI, cefepim, imipenem/cilastatin or meropenem. Alternatively ciprofloxacin, ceftazidime or levofloxacin may be used if the involvement of *Pseudomonas* is strongly suspected.

Nasal furuncles

Nasal furuncles are painful deep infections of the hair follicles in the nasal vestibulum with a phlegmonous spread towards the tip of the nose, nasal septum, upper lip or along the root of the nose. It is caused by *S. aureus*. Out-patient therapy of mild forms is feasible. Hospitalization is necessary for complicated forms of disease which may require surgery (incision of the furuncle, drainage, ligation and transection of the angular vein) to avoid the risk of thrombosis with sepsis spreading to the cavernous sinus.
The antibiotic treatment should involve anti-staphylococcal, penicillinase-stable beta-lactams such as flucloxacillin, dicloxacillin, cefaclor, ampicillin/sulbactam or amoxicillin/clavulanic acid. Treatment should be administered intravenously if necessary (flucloxacillin, oxacillin, cefazoline).

Peritonsillar abscess

Peritonsillar abscesses occur predominantly in young adults [176], [216], [246] and rarely in children. The infection is almost exclusively unilateral. As a rule it stems from recurrent or acute exacerbated tonsillitis and blocked drainage of pus due to formation of scar tissue. Aerobic/anaerobic mixed infections are often present. Beta-haemolytic streptococci, staphylococci, *Prevotella* spp, *Fusobacterium necrophorum* [188], [209], [216], [444], other anaerobes and gram-negative aerobic pathogens [331] have been detected.
Abscesses require lancing due to the risk of spreading with formation of distant septic metastasis and a high risk of complications. In addition, antibiotic treatment is required. Out-patient treatment of mild cases is possible but hospitalization is required for severe cases or abscess tonsillectomy.
Antibiotic treatment is required in the perioperative and postoperative phase. It involves initial intravenous application of a group 1 or 2 cephalosporin (cefazolin, cefuroxim, cefotiam) in combination with clindamycin. Other options include aminopenicillins/BLI (ampicillin/sulbactam, amoxicillin/clavulanic acid), erythromycin, clarithromycin or azithromycin. A switch to a usual oral therapy used for tonsillitis (phenoxymethylpenicillin, cephalosporins, macrolides) may be feasible on the second or third day of therapy.

Chronic purulent sinusitis

Chronic sinusitis results from an incompletely cured acute sinusitis. It persists for more than 8 weeks or more than 4 episodes per year with residual symptoms. Potential causes include gradual obstruction of the sinus by increased tissue formation in the osseous parts, disruption of the mucociliary function and impaired drainage of secretions. In a substantial number of cases, odontogenic infections usually spreading from the root tips of the upper molars are responsible. Basically, it is necessary to remove the focal source of infection after the critical phase of disease has been overcome.
There are two forms of chronic sinusitis. The most frequent form is polypous-serous sinusitis. The mucous-purulent chronic sinusitis occurs less often and, as a rule, should be treated with oral antibiotics (and nasal decongestants). The most frequent pathogens are not those encountered in acute sinusitis but rather *S. aureus*, *Streptococci*, *H. influenzae*, various enterobacteriaceae, less often *P. aeruginosa*, anaerobes and in rare cases *Aspergillus* spp. [167]. Inhibitor-protected aminopenicillins (amoxicillin/clavulanic acid, sultamicillin), oral cephalosporins (cefuroxim axetil, loracarbef, cefpodoxim proxetil) or levofloxacin and moxifloxacin [546] are recommended for calculated oral antibiotic therapy. The spectrum of efficacy should include anaerobes if there is an odontogenic source of infection. Treatment may be required for up to 3 weeks. Intravenous antibiotic therapy is needed only in specific cases.

Odontogenic abscess/throat phlegmone

There are no systematic data on the resistance situation or the development of resistance in dental medicine, as most odontogenic infections can be treated orally on an outpatient basis. For uncomplicated odontogenic infections, identification of pathogens is not required in dental practices. However, it is essential to isolate the pathogens of parenterally treated severe odontogenic infections with the risk of spreading to adjacent tissues. Typical pathogens, also found in closed abscesses, include oral streptococci and less frequently staphylococci. Anaerobes or capnophilic pathogens often include *Prevotella* spp., *Fusobacteria*, *Bacteroides* spp., *Veillonella* and *Peptostreptococci* [7].

According to available date, pathogens from previously untreated abscesses have low resistance rates for penicillin and clindamycin [146], [147], [339]. On the other hand, beta-lactamase-producing pathogens were reported in about 15% to 35% of cases, particularly in complicated, previously treated abscesses which required parenteral treatment [152], [280], [412], [484], as well as sometimes critical rates of resistance against clindamycin in 25% to 45% of cases [11], [280], [412], [484]. It appears that particularly pretreatment with antibiotics results in an increase in penicillin-resistant pathogens [9], [281]. In severe odontogenic soft tissue infections, which typically have already been pretreated, higher resistance rates against penicillin and clindamycin are expected [148]. As indicated by the data discussed above, inhibitor-protected penicillins (e.g. amoxicillin/clavulanic acid) are almost universally effective against the relevant pathogens [411]. However, when judging resistance, it should be considered that the pathogenic role of the detected bacteria is not clear [390]. In life-threatening situations, carbapenems are the drugs of choice in empirical regimens [279], [412], [449]. Alternatively, metronidazole can be used in combination with a fluoroquinolone [9], [152], [280]. In the presence of allergies to beta-lacams, clindamycin as monotherapy with the above-mentioned limitations, is the established alternative. New data suggest that moxifloxacin is a potential treatment option as well [11], [565].

Osteomyelitis

The most important form is acute and secondary chronic osteomyelitis caused by bacteria (odontogenic infection, pulpal and parodontal infection, infected extraction wounds) with pus discharge, fistulation and sequestration. The pathogens are similar to those encountered in odontogenic polymicrobial abscesses [323], [413]. Colonization and infection with multiresistant gram-positive pathogens are reported, particularly after longer antibiotic pretreatment [19], [529]. Osteomyelitis is treated with a combination of surgery and antibiotics [323]. The less frequent primary chronic osteomyelitis is differentiated as a non-purulent chronic inflammation of unclear origin [323]. Special forms of inflammation in previously irradiated bones such as infected osteoradionecrosis or osteomyelitides induced by medications such as bisphosphonates [563], glucocorticoids and antineoplasic substances are not considered to be caused primarily by bacteria. Bacterial superinfections require targeted adjuvant antibiotic treatment.

The primary goal of osteomyelitis treatment is the eradication of the focus by resection of infected and necrotic bone combined with an initially empirical antibiotic treatment which is best followed by pathogen-specific antimicrobial therapy. Because of the protracted course of the disease parenteral treatment is usually necessary. For many years, locally implanted gentamicin-releasing polymethyl methacrylate (PMMA) chains have been successfully used, particularly for chronic disease [168], [202]. Any adjuvant antibiotic treatment should cover the anaerobic pathogen spectrum as well as staphylococci which are often isolated [265]. Clindamycin or penicillin are recommended for antimicrobial therapy in pretreated patients. However, the above-described limitations apply [478], as penicillin resistance is often found after previous therapy [413]. Due to the potentially long and critical course of the disease, pathogen identification should be attempted in all cases. Some authors recommend that antibiotic therapy should be administered for 4 to 6 weeks after surgery [34].

Acute necrotizing gingivitis and tonsillitis

The acute form of necrotizing gingivitis (ANUG) is often associated with other viral diseases and evolves into the disfiguring disease noma in malnourished patients [166]. Spirochetes typically appearing in ANUG can be controlled in most cases with local disinfection measures such as hydrogen peroxide or chlorhexidine mouthwash. In severe cases, additional adjuvant antibiotic treatment is recommended. Intravenous therapy is often required due to the severity of symptoms [257], [422]. The acute course of the disease and problems caused by culture evidence of spirochete involvement often means that classical pathogen identification is not reasonable. Mixed infections with fusobacteria are also reported [197], [415], [451]. Penicillin V in combination with metronidazole is the treatment of choice [478]. In allergy cases, clindamycin can also be used as an alternative. However, no comparative studies are available for these medications.

Cervicofacial actinomycosis

As a usually mixed infection with the major pathogen being *Actinomyces israelii*, this disease is treated successfully with antibiotics [483]. Depending on the severity of the findings, an additional surgical intervention may be necessary. Microbiological or at least histopathological examination of the *Actinomyces* plaques is important. Actinomycetes are typically susceptible to penicillin. In cases with allergy, doxycycline, clindamycin or a cephalosporin are recommended [478], [483]. The necessity of covering the accompanying obligatory anaerobes re-

mains controversial [457], [483]. As with other chronic infections, high-dose long-term therapy is required due to the poor penetration into granulation tissue [478]. There is no exact data on the optimum treatment duration for the cervicofacial form. Treatment of up to 6 months is considered for complicated forms. In cases with less severe disease or adequate surgical treatment, recommended treatment durations of about 6 weeks are found in the literature [320], [483].

Sialadenitis

Sialadenitis is a bacterial or viral infection of the salivary glands. A sialadenitis often occurs as a superinfection following functional impairment of the salivary glands. The submandibular glands are most often affected. Secretory dysfunction of the salivary and mucous glands causes increased viscosity of the saliva, which promotes the precipitation of inorganic substances. The resulting sialoliths may promote bacterial colonization and infection. They should be removed during the chronic phase of disease. There are acute and chronic forms of the disease. The predominant pathogens are viruses (usually mumps virus, parainfluenza viruses or CMV), and in adults staphylococci and streptococci but also anaerobes. A recent publication reports evidence of an increased incidence of infections due to *Fusobacterium necrophorum* (14%), particularly in the presence of peritonsillar abscesses (91%) [209], [444]. *F. necrophorum* may cause the Lemierre syndrome as a severe complication. In the acute phase a conservative treatment is preferred in most cases. Because of the high prevalence of systemic symptoms, intravenous therapy or surgical release is often necessary, which generally requires hospitalization. Severe bacterial infections must be treated with intravenous antibiotics while oral treatment is also acceptable for less severe infections. In older studies, a causal role of streptococci and staphylococci is reported [286]. More recent work has drawn attention to the major importance of anaerobes in purulent sialadenitis [299]. Due to frequent penicillin resistance of the pathogens use of an aminopenicillin/BLI or clindamycin is recommended [167]. There are published recommendations to use cephalosporins [167]. This group of drugs, however, is ineffective against anaerobes.

7 Intraabdominal Infections

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Indications for Antimicrobial Treatment and Duration of Treatment

Intraabdominal infections (IAI) are rather common. In Germany about 150,000 patients per year are treated for an IAI [30]. National and international databases show that every fourth case of severe sepsis or septic shock can be attributed to IAI [159], [276]. Almost 90% of all intraabdominal infections require primarily a surgical intervention to control the source of infection (e.g. closure of gastric perforation). Nevertheless, the value of antibiotic therapy versus placebo is significant in this group of diseases [579]. Inadequate initial antibiotic treatment of IAI is associated with substantially worse outcomes and results in considerable increased cost [37], [118], [150], [364].

Recommendations on antibiotic therapy of intraabdominal infections are derived from numerous prospective randomized controlled studies. As the objective of most studies is the demonstration of therapeutic equivalence, the available evidence is not sufficient to prefer any specific regimen over another [579]. When choosing the appropriate antibiotic, individual patient characteristics (e.g. immunosuppression, previous therapy), anticipated pathogen spectrum, local pathogen and resistance situation, appropriate mode of administration, low toxicity and cost should be included in the decision.

No reliable data are available on the appropriate duration of treatment for intraabdominal infections [274]. Treatment durations given below are based on durations used in randomized studies, the peculiarities of special pathogens (e.g. *Candida* spp.), the local and systemic severity of infection and the experience of the authors. In general, discontinuation of the antibiotic should be considered if clinical condition and infection parameters are significantly improved. If treatment success is not achieved after 10 days, antimicrobial treatment should preferably be discontinued and new samples taken for susceptibility testing rather than continuing a regimen that may select resistant pathogens and/or unnecessarily expose the patient to potential toxicities.

Systematically, three forms of peritonitis with different pathogenesis, pathogen spectrum, and requirement of surgical and/or antimicrobial therapy can be differentiated [274].

Primary peritonitis

Primary (i.e. spontaneous bacterial) peritonitis (SBP) accounts for approximately 1% of all peritonitis cases. Juvenile peritonitis is a hematogeneous infection caused

Table 16: Recommendations for initial antimicrobial therapy of primary peritonitis and CAPD-associated peritonitis

Diagnosis	Most common pathogens in monobacterial infection	Initial therapy	Duration of therapy	Level of evidence	Level of recommendation
Juvenile Peritonitis	Group A Streptococci Pneumococci Less common: *Haemophilus influenzae*	Aminopenicillin/BLI Ureidopenicillin/BLI Group 2 cephalosporin	7 days	A A A	III III III
Peritonitis in pts. with liver cirrhosis (mono infection)	Escherichia coli *Enterococci* *Klebsiella spp.*	Group 3a cephalosporin Group 2 fluoroquinolone Ureidopenicillin/BLI	5–7 days	A A A	Ia Ia Ib
Peritonitis in pts. with liver tuberculosis	Mycobacteria	Combination therapy after susceptibility test	>6 months		
Peritonitis in pts. with CAPD	Staphylococci *Escherichia coli* Enterococci Other Streptococci Enterobacteriaceae *Pseudomonas spp.* *Acinetobacter spp.* MRSA, VRE ESBL producers *Candida spp.*	Group 2 cephalosporin Group 2 fluoroquinolone See Table 19 See Table 19 See Table 19		A	IIa

CAPD= continuous ambulatory peritoneal dialysis, BLI= beta-lactamase inhibitor

by streptococci, pneumococci, or rarely *Haemophilus influenzae*. In adults, primary peritonitis mostly affects patients with ascites caused by hepatic cirrhosis (approximately 70%) or immune impairment (approximately 30%) [171], [432]. Usually it is a monobacterial infection. In routine practice, the pathogen is identified in only about 35% of the cases, where *Escherichia coli*, *Klebsiella* spp., staphylococci, enterococci or streptococci, and sometimes pathogenic intestinal bacteria such as *Aeromonas* spp. or *Salmonella* spp. are isolated [171]. Primary peritonitis associated with tuberculosis is caused by hematogeneous dissemination.

Only few randomized trials have been investigating treatment of SBP. Most available studies are retrospective analyses. The investigated drugs included ceftriaxone, cefotaxim, ceftazidim as well as ureidopenicillins combined with a beta-lactamase inhibitor (BLI) [102] (Table 16). Given in conjunction with albumin (to treat ascites) these therapies achieved clinically treatment success rates of about 80% [489].

Peritonitis associated with CAPD

Peritonitis associated with continuous ambulatory peritoneal dialysis (CAPD) is usually caused by a contamination of tubes or a catheter system. The most frequent pathogens are coagulase-negative staphylococci and *Staphylococcus aureus*. *E. coli*, enterococci, streptococci, *Pseudomonas aeruginosa*, anaerobes, *Enterobacter* spp. or *Candida* spp. have been less frequently identified [502]. Uncomplicated cases may be treated locally by adding antimicrobial substances to the dialysis fluid. Only in the less common severe forms, intravenous therapy is required in addition to the intraperitoneal treatment. Dosage should be adjusted for renal dysfunction as appropriate.

A group 2 cephalosporin optionally combined with ciprofloxacin is recommended for calculated therapy [302]. The treatment should be adjusted according to the results of microbiological diagnosis. The antibiotics listed in Tab. 19 may be used if there is evidence of MRSA, MRSE and enterococci (incl. VRE). If the infection remains uncontrolled after a week of therapy, the peritoneal dialysis catheter must be removed [545].

Secondary peritonitis

Comprising about 80% to 90% of all cases, secondary peritonitis due to a perforation of the gastrointestinal tract is by far the most frequent IAI. By definition surgical intervention is required to control the source of infection (e.g. appendectomy for perforated appendix). Increasingly, the preferred approach is primary surgical treatment of the infection source followed by definitive closure of the abdomen and subsequent clinical monitoring of the patient [220], [535]. Secondary peritonitis may be divided in community-acquired (approx. 70%) and postoperative (approx. 30%) forms.

Community-acquired secondary peritonitis

Community-acquired secondary peritonitis always involves mixed bacterial infection. The spectrum of pathogens originates from the gastrointestinal flora and depends on the pathogenesis and localization of the perforation

Table 17: Recommendations for the initial therapy of secondary and tertiary peritonitis

Diagnosis	Most common pathogens	Initial therapy	Duration of therapy	Level of evidence	Level of recommendation
Community-acquired localized (e.g. newly perforated appendix)	Enterobacteriaceae Enterococci Anaerobic bacteria (mostly mixed infections)	Group 2/3 cephalosporin + metronidazole Ureidopenicillin/BLI Aminopenicillin/BLI Group 2 fluoroquinolone + metronidazole Group 2 carbapenem	1–2 days	Ia Ia Ia Ia Ia	A A A A A
Community-acquired diffuse +/- risk factors (e.g. perforated faecal diverticulitis)	Enterobacteriaceae Enterococci Anaerobes (mostly mixed infections)	Ureidopenicillin/BLI Group 3a/4 cephalosporin + metronidazole Group 2/3 fluoroquinolone + metronidazole Group 1 carbapenem Group 2 carbapenem Tigecycline Group 4 fluoroquinolone	3–5 days	Ib Ib/Ib Ib/Ib Ib Ib Ib Ib	A A/B A/B A A B B
Nosocomial post-operative or post-interventional peritonitis requiring surgical source control (e.g. anastomotic leakage after bowel resection)	Enterobacteriaceae (incl. ESBL producers) Enterococci (incl. VRE) Staphylococci (incl. MRSA) Anaerobic bacteria *Candida spp.* (mostly mixed infections)	Group1 carbapenem Group 2 carbapenem Ureidopenicillin/BLI Tigecycline* Group 4 fluoroquinolone refer to Table 19	7 days	Ib Ib Ib IIa Ib	A A A A B
Nosocomial tertiary peritonitis (recurrent infection after surgical source control)	Enterobacteriaceae (incl. ESBL producers) Enterococci (incl. VRE) Staphylococci (incl. MRSA) Anaerobic bacteria *Pseudomonas spp.*	Group 1 carbapenem Ureidopenicillin/BLI Tigecycline* Group 2 carbapenem Group 3a/4 caphalosporin + metronidazole	7 days	Ib Ib IIa IV IV	A A A B B
Invasive intra-abdominal fungal infections	*Candida spp.* (fluconazole-sensitive, fluconazole-resistant)	Fluconazole Anidulafungin Caspofungin Voriconazole Amphotericin B	14 days		

BLI= beta-lactamase inhibitor
* Combination with an agent active against *Pseudomonas* is essential if appropriate

and/or leakage. The predominant pathogens are *E. coli*, *Bacteroides fragilis*, enterococci and *Candida* spp. Besides surgical interventions, calculated initial antibiotic therapy should be started preferably before surgery.

The following recommendations are based on the duration of disease and the pathogen spectrum as determined by the cause of disease [545]. Aminopenicillins/BLI, ureidopenicillins/BLI, group 2 carbapenems, or alternatively group 2 or 3a cephalosporins or a group 2 fluoroquinolone in combination with metronidazole can be used for locally confined, acute peritonitis. In the absence of risk factors, therapy can be limited to 1 or 2 days (Table 17). Group 2 fluoroquinolones and aminopenicillins/BLI should only be used if the local resistance epidemiology for major pathogens such as *E. coli* shows susceptibility rates ≥90% [486].

Drugs or combinations with a broad spectrum of efficacy should be used to treat diffuse peritonitis that already lasted more than 2 to 4 hours. Ureidopenicillins/BLI or group 1 and 2 carbapenems are used for calculated therapy. Alternatively, a combination of metronidazole with a group 2 and 3 fluoroquinolone as well as a group 4 fluoroquinolone or a glycylcycline (tigecycline) can be used. The involvement of enterococci should only be considered when choosing a drug regimen for postoperative peritonitis and severely ill patients [141], [217], [486], [550]. Aminoglycosides (even in combination with clindamycin or metronidazole) have been shown to be inferior to newer treatment regimens with beta-lactam antibiotics and fluoroquinolones and are no longer considered as drugs of choice [401]. However, aminoglycosides are useful as combination partners used together with broad-spectrum beta-lactam antibiotics (particularly carbapenems and ureidopenicillins/BLI) [194], [324]. Pharmacokinetic variability as well as ototoxicity and

nephrotoxicity require regular plasma level monitoring (see chapter 3).

Postoperative peritonitis

Postoperative peritonitis is a nosocomial secondary peritonitis defined as an intraabdominal infectious complication following a surgical intervention (e.g. leaking anastomosis after anterior rectum resection). In contrast to tertiary peritonitis, postoperative peritonitis requires surgical intervention [141], [549]. Most patients have been treated with antibiotics before the disease becomes apparent. Therefore, postoperative peritonitis is characterized by a selected spectrum of pathogens including enterococci (including VRE), multiresistant gram-negative pathogens (ESBL producers) and fungi.
Antibiotics with broad antimicrobial spectra including group 1 and 2 carbapenems, tigecycline, piperacillin/tazobacam or moxifloxacin should be used. The use of antifungals should be considered if appropriate [29], [103], [236], [314], [316], [328].

Tertiary peritonitis

In tertiary peritonitis the intraabdominal infection persists without a surgically removable focus after surgical sanitation of the source of a secondary peritonitis [103], [274], [366]. Usually low-virulence pathogens cause persistent infection, due to sustained immunosuppression of the patient. This form of nosocomial peritonitis has a shifted pathogen spectrum similar to that found in secondary postoperative peritonitis. It commonly involves enterococci (including VRE), staphylococci (including MRSA), enterobacteriaceae, anaerobes and *Candida* spp. [141]. Group 1 and 2 carbapenems, tigecycline (in combination with a drug effective against *Pseudomonas*), ureidopenicillins combined with a beta-lactamase inhibitor or group 3a cephalosporins in combination with metronidazole can be used in antimicrobial therapy (Table 17) [141], [236], [314], [328], [486]. Combination therapy is recommended if there is evidence of *Enterobacter* spp. and treatment with a carbapenem is not feasible.

Necrotizing pancreatitis with infected necrosis

Approximately 80% of all deaths due to acute pancreatitis are caused by septic complications. The translocation of pathogens from the colon into the peripancreatic tissue is the most common cause of secondary infected pancreatic necrosis [77], [572]. Infected pancreatic necrosis is assumed if fever, leukocytosis, an increase of CRP in serum and an unexpected clinical deterioration occur. Evidence of gas inclusions within the necrotic pancreas tissue in the abdominal CT is considered to demonstrate infected necrosis [35]. The conservative interventional treatment of infected pancreatic necrosis includes CT-guided endoscopic transgastric drainage. Open or minimally invasive surgical treatment is currently thought to be best performed after an interval of more than 3 weeks [61]. Recent publications and meta-analyses conclude that indiscriminate administration of antibiotics does not achieve significantly positive effects on the course of necrotizing pancreatitis but will rather select for resistant pathogens and *Candida* spp. [235], [327], [541]. International consensus conferences do not generally recommend antibiotic treatment [121], [365].
Absolute indications for antibiotic treatment of proven infected necrosis include infected pseudocysts, abscess formation, cholangitis and other extrapancreatic manifestations. The most important pathogens of infected pancreatic necrosis are enterobacteriaceae, enterococci, staphylococci, anaerobes and *Candida* spp. When choosing appropriate antimicrobials, the ability of the drug to penetrate the pancreatic tissue has to be taken into consideration (Table 18). Investigations with reliable data showing adequate tissue penetration are available for quinolones (ciprofloxacin, moxifloxacin), carbapenems (doripenem, ertapenem, imipenem/cilastatin, meropenem), metronidazole, cephalosporins (cefotaxime, ceftazidime, cefepime) and penicillins (mezlocillin, piperacillin ± tazobactam). Inadequate tissue penetration has been demonstrated for aminoglycosides [400], [545].

Secondary cholangitis

Infection of the hepatic bile ducts is usually caused by an obstruction, most commonly caused by gall stones, benign structures and tumors. Isolation of the pathogen by endoscopic retrograde cholangiopancreaticography (ERCP), intraoperative sampling or blood cultures is successful in 75% to 100% of bile duct obstruction caused by stones. The spectrum of pathogens includes enterobacteriaceae, enterococci and anaerobes as well as *Pseudomonas* spp. The key intervention for choledocholithiasis consists of endoscopic clearing of the bile ducts and subsequent laparoscopic cholecystectomy. Calculated antibiotic treatment can be started with an aminopenicillin/BLI, ureidopenicillin/BLI or a group 3 or 4 cephalosporin in combination with metronidazole. Alternatively, group 1 or 2 carbapenems or group 2 or 3 fluoroquinolones are used. Treatment duration after successful bile duct clearing is less than 3 days, it should be prolonged if the bile flow remains impaired. If *Pseudomonas* infection is suspected (e.g. case of repeated intervention or prolonged hospitalization), a combination with another agent covering *Pseudomonas* is recommended [545].

Difficult to treat and multiresistant pathogens (MRP)

In the mid 1990s, 95% to 97% of all bacterial strains isolated from patients with intraabdominal infections were still susceptible to frequently used antibiotics (group 3a cephalosporins + metronidazole, group 2 quinolones) [266]. In recent years, however, the proportion of resistant strains (MRSA, VRE, ESBL producers, multiresistant *Pseudomonas* spp.) has markedly increased worldwide,

Table 18: Calculated antimicrobial treatment for necrotizing pancreatitis and secondary cholangitis

Diagnosis	Most common pathogens	Initial therapy	Duration of therapy	Level of evidence	Level of recommendation
Infected necrotizing pancreatitis	Enterobacteriaceae Enterococci Staphylococci Anaerobic bacteria MRSA, VRE ESBL producers *Candida spp.*	Group 1 carbapenem Group 2 carbapenem Group 2 fluoroquinolone or Group 3 fluoroquinolone or Group 2 cephalosporin + metronidazole Group 4 fluoroquinolone Ureidopenicillin/BLI See Table 19 See Table 17	7–10 days	Ia Ia II III Ib III III	A A B B B B B
Secondary cholangitis	Enterobacteriaceae Enterococci Anareobic bacteria *Pseudomonas spp.*	Aminopenicillin/BLI Ureidopenicillin/BLI Group 1/2 carbapenem Group 4 fluoroquinolone Group 2 fluoroquinolone or Group 3 fluoroquinolone or Group 3a cephalosporin or Group 4 cephalosporin, each + metronidazole	3–5 days	Ib Ib Ib IIb Ib Ib Ib III	A A A B A A A B

BLI= beta-lactamase inhibitor

particularly in postoperative peritonitis and tertiary peritonitis [103], [122], [149], [267], [441]. Particularly in cases with life-threatening disease that may be caused by resistant pathogens, it is of key importance to cover the expected pathogen spectrum with the initial antibiotic treatment. If microbiological results show no evidence of resistant pathogens, treatment should be deescalated. The following sections discuss particular aspects of individual multiresistant pathogens (see Table 19).

Methicillin-resistant Staphylococcus aureus (MRSA)

Intraabdominal infections caused by MRSA is rarely found in immunocompetent patients. In most cases MRSA involvement will be a colonization of open abdomen, for example after abdominal compartment syndrome and open irrigation. Antibiotic treatment is indicated for non-immunocompromized patients only in case of local and systemic signs of infections as well as persistent detection of MRSA. In immunocompromized patients (e.g. after transplants) any indication of MRSA involvement should prompt antimicrobial therapy. Tigecycline is the only novel MRSA-effective antibiotic licensed for the treatment of intraabdominal infections [29]. It also covers other expected gram-negative and anaerobic pathogens. Vancomycin does not penetrate well into the intraabdominal compartment. Clinical data are available for treatment of intraabdominal infections with linezolid [63]. Linezolid, daptomycin and vancomycin should be combined with antibiotics effective against gram-negative pathogens [22], [141], [567].

Enterococci (including VRE)

Some controversy prevails about the role of enterococci as a primary pathogen in polymicrobial IAI as multiple evidence indicates successful treatments of IAI by means of surgical source control and use of antibiotics that do not cover enterococci [217], [374], [441]. Therapy targeting enterococci is recommended for patients with postoperative or tertiary peritonitis, severe sepsis originating in the abdomen and a risk of endocarditis (peritonitis and cardiac valve replacement) [217]. In these situations, selective pressure favouring VRE is expected particularly after previous antimicrobial therapy (Table 19). Case reports on linezolid-resistant enterococcal strains have been published [212].

ESBL producers

In the last few years the enterobacteriaceae (particularly *E. coli* and *K. pneumoniae*) have increasingly developed resistance against beta-lactam antibiotics, including group 3 and 4 cephalosporins, which are hydrolysed by extended-spectrum beta-lactamases (ESBL) [307], [576]. Surgical treatment areas focusing on the abdomen report a relevant prevalence of ESBL-producing pathogens [296]. Carbapenems are primarily indicated in infections with ESBL-producing pathogens. Depending on test results, fluoroquinolones or fosfomycin may be used as combination partners. Tigecycline and colistin are usually effective, but their activity must be tested as well [194], [324].

Table 19: Calculated antimicrobial therapy of suspected or proven intraabdominal infections with resistant pathogens

Diagnosis	Antimicrobial drug	Duration of therapy	Level of evidence	Level of recommendation
MRSA	Tigecycline Linezolid + Daptomycin + Vancomycin + Cotrimoxazole	7 days	IIa III IV IV IV	A A B B B
VRE	Tigecycline Linezolid +	7 days	IIa III	A A
ESBL producers *(E. coli, Klebsiella spp.)*	Group 1 carbapenem Group 2 carbapanem Tigecycline Fosfomycin (combination only) Colistin	7 days	III III III IV IV	A A A B C
Pseudomonas spp.	Group 2/3 fluoroquinolone Group 3b/4 cephalosporin Group 1 carbapenem Piperacillin/tazobactam Aminoglycoside Colistin	7–10 days	III III III III III IV	A A A A B C

MRSA= Methicillin-resistant *Staphylococcus aureus*, VRE= Vancomycin-resistant *Enterococcus facium or faecalis*, ESBL= extended-spectrum beta-lactamase
+ combination with an antimicriobial active against gram-negative and anaerobic bacteria

Pseudomonas spp., Acinetobacter spp.

Pseudomonas spp. is detected in about 8% of IAI. However, the percentage of causally relevant strains may be significantly lower [134], [490]. In general, group 3b and 4 cephalosporins, ciprofloxacin, group 1 carbapenems, piperacillin ± tazobactam and aminoglycosides may be used in antimicrobial therapy [139]. Combination therapy (e.g. a group 3b cephalosporin plus an aminoglycoside or plus ciprofloxacin) lowers the post-treatment resistance rate [526] but has no clinical advantage [400]. If three or four antibiotic classes are ineffective (multidrug resistance, MDR), usually only colistin can be used [194], [324]. The same applies for carbapenem-resistant *Acinetobacter* spp., where tigecycline may also be effective. In special cases, sulbactam used as monotherapy may be active as well (note test results).

Invasive intraabdominal fungal infections

Most invasive intraabdominal fungal infections (IAFI) are caused by *Candida* spp. Up to 18% of all cases of severe sepsis in Germany are caused by *Candida* spp. [159]. Antifungal therapy is not required if *Candida* is detected only once in intraoperatively acquired samples of a postoperatively stable and immunocompetent patient with community-acquired secondary peritonitis (e.g. after perforation of a gastric ulcer). From a surgical point of view, risk groups for IAFI include patients with severe postoperative peritonitis (e.g. caused by suture leakage after esophagojejunostomy) or tertiary peritonitis. In two studies with such risk groups, pre-emptive therapy with fluconazole achieved a significant reduction of the incidence of invasive fungal infections and a statistically non-significant reduction of mortality versus placebo [151], [407]. However, the necessity of pre-emptive treatment remains controversial [66].

In approximately 60% of cases, initial high-dose therapy with fluconazole is adequate (Table 17). However, the rate of *Candida* strains with reduced susceptibility to fluconazole remains high at approximately 40% in Germany [410]. Therefore, based on new multicentre studies, the use of an echinochandin (anidulafungin, caspofungin) is preferred if the patient is instable or recently received treatment or prophylaxis with an azole. For toxicity reasons, initial therapy with amphotericin B is recommended only in patients with allergy to other antifungal substances [396]. Delaying the treatment of an IAFI is associated with poor outcomes [66], [271], [343]. Due to a lack of specific controlled study data for IAFI and because of the individual clinical situation (e.g. stable vs. unstable patient), no levels of recommendation have been assigned.

8 Infections of kidneys and genito-urinary tract

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Indications for initial intravenous antimicrobial therapy

Usually infections of the kidneys and urogenital tract in adults require initial (empirical) intravenous antibiotic therapy only for cases with severe clinical course and systemic manifestations, e.g. nausea and vomiting, or suspected sepsis (see chapter 10) [199]. This generally includes severe forms of uncomplicated or complicated and/or nosocomial pyelonephritis, acute prostatitis, and less frequently acute epididymitis with or without orchitis, acute salpingitis-pelvicoperitonitis or severe abscess-forming infections in kidneys and urogenital tract. Occasionally, intravenous therapy should be empirically initiated if, in certain clinical situations, multiresistant pathogens must be anticipated for which is no oral antibiotic available and the results of microbiological tests cannot be awaited as, for example, surgery must be immediately performed (e.g. acute urinary stone obstruction).

General criteria for choosing an antibiotic

The antimicrobial agent is chosen according to the expected pathogen spectrum, taking into consideration the pharmacokinetic and pharmacodynamic properties of the drug. When treating infections of the urinary tract, sufficient renal elimination of the active drug is required [405], [557]. In addition, the collateral damage of antibiotics, e.g. side effects and development of resistance, must be taken into account (see chapter 2). Other appropriate measures may be needed but are not the subject of this article [62], [72], [514].

Acute uncomplicated pyelonephritis

The most frequently detected pathogen is *Escherichia coli*, followed by *Proteus mirabilis* and *Klebsiella pneumoniae*. Other enterobacteriaciae have been detected less frequently in the urine. There are no large epidemiological studies on antimicrobial susceptibility. Studies on uncomplicated cystitis may be used as substitute, since they have a somewhat similar pathogen spectrum and resistance situation [357]. Early initiation of effective therapy may prevent damage to the renal parenchyma. An initial (empirical) intravenous therapy with a group 3a cephalosporin, a fluoroquinolone with high renal elimination (e.g. ciprofloxacin or levofloxacin), an aminopenicillin/beta-lactamase inhibitor (BLI) or an aminoglycoside is indicated in cases with severe systemic symptoms including nausea and vomiting [33], [199], [239], [354], [409]. After improvement of these symptoms, the intravenous therapy should be changed to an oral regimen as soon as possible. An oral fluoroquinolone such as ciprofloxacin or levofloxacin, an oral group 3 cephalosporin, an aminopenicillin/BLI, cotrimoxazol or trimethoprim would be appropriate, if the pathogen tested susceptible [199], [353], [431], [511]. Treatment duration depends on the clinical course of the disease. Seven to 10 days are usually sufficient. Sometimes an elevated initial dose of a fluoroquinolone, e.g. levofloxacin 750 mg per day, can shorten the duration of therapy to 5 days [409].

Complicated and/or nosocomial urinary tract infections

Definition

A complicated urinary tract infection (UTI) is defined as an infection of the urinary tract, which is associated with a morphological, functional or metabolic abnormality resulting in renal dysfunction, impairment of urine flow and/or local or systemic disruption of immune mechanisms [65], [240], [514], [553].

Indications for initial intravenous antimicrobial therapy

As mentioned above, the indications for any initial intravenous antimicrobial treatment depend on the general condition and risk profile of the patient. The successful antibiotic treatment of complicated UTI requires elimination of the complicating or causative factors [199].

Pathogen spectrum

In general, the expected pathogen spectrum is considerably broader than in uncomplicated UTI and depends on the circumstances under which the complicated UTI was acquired [65], [240], [556]. Thus the pathogen spectrum of a community-acquired, first-time, complicated UTI, e.g. acutely evolving as a result of calcium oxalate urinary stones, in a patient without recent antibiotic treatment and catheters, is relatively similar to the spectrum of an uncomplicated acute pyelonephritis [62]. In contrast, in a nosocomial complicated UTI, pathogens must be anticipated that do not belong to the usual spectrum of pathogens seen in primary urinary tract infections because these infections rather represent secondary events resulting from selection or colonization. These pathogens may include, *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and *Providencia stuartii* [240], [556]. If a complicated UTI is suspected, sampling for urine culture is mandatory before starting an antibiotic treatment. This enables to adjust the treatment to the results of the microbiological test despite the broad pathogen spectrum and potential resistance [199].

Choice of antibiotics

The empirical initial antibiotic treatment must take into account the regional resistance situation of the expected spectrum of pathogens [240]. The following previous clinical conditions may influence the expected pathogen spectrum and susceptibility [240]:

1. Where was the UTI acquired, e.g. community, nursing home, hospital, after a diagnostic/therapeutic intervention?
2. Was there a previous antibiotic therapy (how long ago, which antibiotic)?
3. Was there a previous prolonged hospitalization?
4. Did the patient have a catheter (which, how long ago, how treated)?
5. If so, check the quality of the urine drainage and if necessary change the catheter (remove the infectious biofilm)
6. Is this a recurrence or a treatment failure?

Group 3a cephalosporins, fluoroquinolones, aminopenicillins with a BLI or a group 2 carbapenem (ertapenem) can be used as parenteral initial treatment of a first-time, community-acquired, complicated UTI [33], [199], [239], [354], [409]. In patients with nosocomial or catheter-associated UTI, multiresistant pathogens may be involved [240], [551], [553], [556]. Therefore, in empirical therapy an antibiotic should be used that covers rare and multiresistant gram-negative pathogens (see above). Group 3b or 4 cephalosporins, group 2 or 3 fluoroquinolones (check for local *E. coli* resistance!) and group 1 carbapenems (doripenem, imipenem, meropenem) can be used [199], [355], [559]. If coverage of enterococci is desired, as mixed infections with enterococci are particularly frequent in catheter-associated urinary tract infections, ureidopenicillins in combination with a BLI (e.g. tazobactam) are appropriate for empirical therapy [199], [356]. If multiresistant pathogens are suspected (due to outbreaks or high endemic resistance rates), the appropriate drugs should be used in the empirical treatment. Since carbapenemases rarely occur in the German-speaking countries yet, a group 2 carbapenem (ertapenem) can be used for enterobacteriaceae expressing extended-spectrum beta lactamases (ESBL) or a group 1 carbapenem (doripenem, imipenem, meropenem) can be used if involvement of Pseudomonas is suspected [199], [355], [559]. For ESBL, fosfomycin could also be used as intravenous initial therapy. However, few data are available for complicated UTI [358]. For infections with methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE), several very effective drugs, e.g. daptomycin or linezolid are available [352], [552], [557]. However, there are no adequate studies on urinary tract infections, so the appropriate treatment must be chosen on an individual basis.

Patients with diabetes mellitus

Urinary tract infections in patients with diabetes mellitus are problematic as they may increase the pathogenetically significant insulin resistance and therefore deteriorate the instable metabolism situation. This is particularly true for patients with an HbA1c value >9%, with a tendency for hypo- or hyperglycaemia, a BMI >30 kg/m^2 and in cases with diabetic nephropathy (stage 2: albumin excretion >200 mg/l, eGFR <60 ml/min). Glucosuria facilitates the colonization of the urinary tract with pathogens and facultative pathogenic microorganisms.
For asymptomatic bacteriuria in patients with stable diabetic metabolism situation and no obstruction or other anatomical abnormalities, an antimicrobial treatment is not necessary [179], [388]. For uncomplicated and complicated infections, the same recommendations for initial intravenous and subsequent oral treatment apply as for patients without diabetes mellitus. Note that cotrimoxazole may enhance the hypoglycaemic effect of oral antidiabetics. Other metabolic interactions of antibiotics and antidiabetics are rare.

Patients with impaired renal function or kidney transplant

No potentially nephrotoxic antibiotic, e.g. aminoglycosides or vancomycin, should be used for patients with impaired renal function, dialysis patients or kidney transplant recipients. The first dose should always be a full normal dose. The choice of subsequent dosage depends on the mode of drug elimination and renal function (Table 20) [25], [73], [463], [495], [503], [587].

Urosepsis

Urosepsis occurs after haematogenic distribution from the infected urinary tract without or after previous urological interventions. Primarily *E. coli* and other enterobacteriaceae have been detected as pathogens. Following urological interventions and in patients with indwelling catheters, multiresistant *Pseudomonas* spp., *Proteus* spp., *Serratia* spp., *Enterobacter* spp., enterococci and staphylococci must be considered (see complicated UTI) [199], [240].
The initial parenteral antibiotic therapy must be started immediately at the first suspicion of urosepsis (within the first hour) and after taking appropriate samples of urine and blood cultures [123], [124], [154], [276], [525]. Treatment recommendations are given in chapter 10. In general, the maximum possible dosage should be chosen [405], [561] in addition to intensive care for sepsis.
Urosepsis usually involves obstructive uropathy, e.g. due to urolithiasis, tumors, benign prostatic hypertrophy or abscess-forming infection, specific urological diagnostics should detect and localize the obstructive uropathy and/or the abscess with the goal of controlling the source as early as possible or bypass the obstruction (e.g. by transurethral or suprapubic catheter, ureteral stent or

Table 20: Recommendations on the empirical initial parenteral antibiotic therapy of urogenital infections

Diagnosis	Most common pathogens	Initial therapy	Total treatment duration* (parenteral and oral)	Level of evidence	Level of recommendation
Acute uncomplicated pyelonephritis	*Escherichia coli* *Proteus mirabilis* *Klebsiella peumoniae* Other Enterobacteriaceae *Staphylococcus saprophyticus*	Group 3a cephalosporins	5–7 (–10) days	Ib	A
		Group 2 fluoroquinolone		Ib	A
		Group 3 fluoroquinolone		Ib	A
		Aminopenicillin/BLI		IV	B
		Aminoglycoside		IV	B
Urinary tract infections – complicated – nosocomial – catheter-associated	*Escherichia coli* *Klebsiella spp.* *Proteus spp.* *Enterobacter spp.* Other Enterobacteriaceae *Pseudomonas aeruginosa* Enterococci Staphylococci (*Candida*)	Group 3a cephalosporin	Up to 3–5 days after source control	Ib	A
		Group 2 fluoroquinolone		Ib	A
		Group 3 fluoroquinolone		Ib	A
		Aminopenicillin/BLI		IV	B
		Group 2 carbapenem (ertapenem) If initial treatment unsuccessful and risk factors (see text)		Ib	A
		Group 3b cephalosporin		IV	B
		Group 4 cephalosporin		IV	B
		Ureidopenicillin/BLI		Ib	A
		Group 1 carbapenem (doripenem, imipenem, meropenem) (fluconazole)		Ib	A
Acute prostatitis, prostatic abscess	*Escherichia coli* Other Enterobacteriaceae *Pseudomonas aeruginosa* Enterococci Staphylococci	Group 2 fluoroquinolone	2 (–4) weeks	IV	B
		Group 3 fluoroquinolone If previous use of fluoroquinolones:		IV	B
		Group 3 cephalosporin		IV	B
		Group 4 cephalosporin		IV	B
		Ureidopenicillin/BLI		IV	B
Acute epididymitis, epididymal orchitis +/- abscess					
– men <35 years	*Chlamydia trachomatis* *Neisseria gonorrhoeae*	Group 3a cephalosporin (intramuscular; one dose) + doxycycline	10–14 days	IV	B
– men >35 years	Enterobacteriaceae	Group 2 fluoroquinolone		IV	B
		Group 3 fluoroquinolone		IV	B
		Group 3a cephalosporin		IV	B
Salpingitis, endometritis, tubo-ovarian abscess	*Chlamydia trachomatis* *Neisseria gonorrhoeae* *Prevotella spp.* *Bacteroides spp.* Peptococci Peptostreptococci	Aminopenicillin/BLI + doxycycline	(7–) 10 days	IV	B
		Clindamycin + aminoglycoside		IV	B
		Group 2 fluoroquinolone + metronidazole		IV	B
		Group 3 fluoroquinolone + metronidazole		IV	B
		Group 3 carbapenem (ertapenem)		IV	B

BLI= beta-lactamase inhibitor
* Change to oral therapy as soon as clinically appropriate

nephrostomy) ensuring unimpaired urinary flow [123], [124], [558], [560].

Acute prostatitis, prostatic abscess

The empirical treatment for acute bacterial prostatitis (ABP) follows the same considerations as for complicated urinary tract infections [199], [555]. Predominantly *E. coli* and other enterobacteriaceae are responsible for spontaneously occurring ABP. In patients with acute prostatitis following urological surgery, other gram-negative pathogens, e.g. *Pseudomonas* spp. may be detected as well. In these patients the acute prostatitis is often accompanied by abscesses which frequently involve *K. pneumoniae* as well [337].

For the empirical treatment, the chosen drug should achieve high antibiotic concentration in the urine, and sufficient concentration in the prostate tissue, prostate secretion and ejaculate [199]. Initial intravenous antibiotic therapy is necessary only for severe forms of acute bacterial prostatitis with and without abscess. The drug of choice is a group 2 or 3 fluoroquinolone [554], [555]. History of previous antibiotic therapy is particularly important as many patients have already received fluoroquinolones and are thus at risk for fluoroquinolone-resistant pathogens. Alternatively, group 3 or 4 cephalosporins or an ureidopenicillin with a beta-lactamase inhibitor may be used for acute prostatitis. Since acute prostatitis is a less common infection and early initiation of antibiotic therapy is necessary, there are no prospective randomized studies available. Treatment recommendations are therefore based mainly on expert opinions [199], [458], [555].

After the pathogen has been isolated from a urine culture (prostate massage is contraindicated in cases of acute bacterial prostatitis) and the resistance situation has been clarified, the treatment should be switched to a targeted therapy. After improvement in the clinical situation it should be continued orally for at least two (to four) weeks to avoid complications such as acute urinary retention, epididymitis, prostate abscesses or chronic prostatitis [199], [458], [555].

Acute epididymitis, epididymal orchitis, including infections with abscesses

An epididymitis in sexually active men under 35 years of age is usually caused by *Chlamydia trachomatis* or *Neisseria gonorrhoea*, or enterobacteriaceae in men having sex with men. An (often asymptomatic) urethritis is usually present [199], [99].

Generally, intravenous therapy is only necessary in severe forms with a risk of complications, e.g. abscesses, or treatment failure. The intravenous treatment should be changed to an oral regimen as early as possible. In young men, ceftriaxon in combination with doxycycline is recommended. In older men or in the case of allergies against beta-lactam antibiotics, group 2 or 3 flurorquinolones can be considered. The increasing resistance to fluoroquinolones and the increasing occurrence of ESBL-producing enterobacteriaceae must also be taken into account in older men with urinary tract infections [65], [556].

Endometritis, salpingitis, tubo-ovarian abscess, pelvicoperitonitis

In infections of the female genital organs in sexually active, premenopausal women, a broad-spectrum of potential pathogens must be expected. Besides the sexually transmitted pathogens *N. gonorrhoeae* and *C. trachomatis*, potential pathogens involve the vaginal flora and pathogens of bacterial vaginosis – and in rare cases mycoplasma or ureaplasma [233], [306], [505]. With a few exceptions only laparoscopically acquired samples are diagnostically relevant for the aetiology of ascending infections [238]. Since none of the available antibiotics covers the complete spectrum of potential pathogens, there is no consensus on the treatment of choice. However, numerous investigations with drug combinations have shown positive results. Reliable investigations of intravenous and oral treatment regimes as well as comparisons of the out-patient and hospital treatment are still pending. Therefore the decision for one of the proposed regimes must be made on an individual basis, depending on the severity of disease, patient compliance and local resistance situation. After clinical improvement, an intravenous initial treatment can be changed to an oral regimen with one of the combination partners usually being doxycycline, clindamycin or a fluoroquinolone [99]. Cephalosporins should be combined primarily with metronidazole for anaerobic coverage. Alternatively, fluoroquinolones or aminopenicillins/BLI which are characterized by their broad spectrum of activity can also be used. Group 2 or 3 fluoroquinolones in combination with metronidazole, aminopenicillins/BLI plus doxycycline or a group 2 carbapenem can be used as well. Monitoring the course of the disease for 72 hours is essential, even in primarily uncomplicated infections [99]. In case of treatment failure, the antimicrobial therapy should be adapted to the meanwhile available microbiological results and, if necessary, surgical intervention should be performed [233], [306]. In pregnant women, the embryotoxic and teratogenic potential of antibiotics must be taken into consideration.

9 Skin, soft tissue, bone and joint infections

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There is a broad spectrum of skin and soft tissue infections, ranging from harmless, superficial pyodermia to life-threatening myonecrosis with high mortality. Skin and soft tissue infections caused by viruses, bacteria, parasites or fungi are among the most frequent infectious diseases [243], [272]. In order to organize this plethora of diseases, the British microbiologist Kingston devised three levels of severity in 1990 [258]. His classification is of clinical relevance as it considers the urgency of surgical intervention (Table 21).

Table 21: Division of soft tissue infections according to the urgency for surgery – examples (according to Kingston)

Mild infections (slowly progressive)	Furunculosis
	Impetigo
	Restricted phlegmons
	Erysipelas
Infections requiring urgent surgical intervention	Paronychia
	Abscess
	Phlegmons
	Purulent bursitis
Severe soft tissue infections (rapidly progressive)	Necrotizing fasciitis
	Myonecrosis of gas gangrene
	Necrotizing mixed infection

A further clinically useful approach is the classification of complicated versus uncomplicated skin and soft tissue infections. The term complicated used by the FDA is defined by major risk factors of skin and soft tissue infections (Table 22). Complicated skin and soft tissue infections (cSSTI) or complicated skin and skin structure infections (cSSSI) formed the basis for the pivotal clinical licensing studies for new antibiotics in recent years [22], [156], [322].
Another consideration is the extent of infection in terms of local versus diffusely spread infection with sytemic symptoms [300]. Also the depth of infection, i.e. involvement of subcutaneous tissue, fascia or muscles must be considered (Table 23).

Skin infections with predominantly conservative treatment

Examples of these primarily cutaneous, superficial bacterial infections include impetigo contagiosa, boils, carbuncles, erysipelas and erysipeloids.

Indication for the use of an antibiotic is an infection with general symptoms: fever (>38.5°C), leukocytosis (>10,000/µl) and markedly increased CRP.

Impetigo/ecthyma (deep, ulcerating form of impetigo) (Streptococcus pyogenes, beta-hemolytic group C and G streptococci, Staphylococcus aureus)

A widespread impetigo requires systemic but almost never intravenous antibiotic therapy. Intravenous administration is indicated only for infections of the face and failure to respond to oral therapy. Penicillin G is recommended for ecthyma caused by streptococci and an isoxazolyl penicillin (oxacillin or flucloxacillin) for ecthyma caused by *S. aureus*.
If the pathogen is unknown, a Group 2 cephalosporin or alternatively a macrolide is recommended [465].
Boils and carbuncles also require a systemic antibiotic treatment or a parenteral treatment only for localization on the face or failure to respond to the orally administered drug.
As *S. aureus* is the most frequent pathogen, treatment should be with Group 1 or 2 cephalosporins, clindamycin or an aminopenicillin in combination with a beta-lactamase inhibitor (BLI).

Erysipeloid (Erysipelothrix rhusiopathiae)

The treatment of choice for both local infections and rare systemic forms (with fever, endocarditis or arthritis) is penicillin G. Patients who are allergic to penicillin receive cephalosporins, clindamycin or fluoroquinolones. *Erysipelothrix* is resistant to glycopeptides.

Erysipelas (S. pyogenes)

Classic erysipelas is an infection caused by *S. pyogenes* with the characteristic symptoms of overheated erythema with shiny surface, sharply defined edges and tongue-shaped offshoots, usually at some centimeters distance from the focus of infection (e.g. interdigital mycosis). Depending on the enzyme and toxin expression of the bacteria, blisters and bleeding as well as already initially systemic infection reactions (fever, chills, increasing ESR, increasing CRP, and leukocytosis (>10,000/µl) occur. The drug of choice is penicillin, also in the case of a recurrence. To date, no penicillin-resistant *S. pyogenes* strains have been detected. Aminopenicillins or penicillinase-insensitive penicillins are not the first choice due to their low activity. In patients with allergy, clindamycin is the alternative treatment. Moxifloxacin may be used in case of clindamycin failure.
Parenteral antibiotic therapy is indicated for complicated erysipelas (e.g. haemorrhagic, necrotizing or blistered erysipelas) as well as localization in the face and impaired venous or arterial blood circulation. If symptoms improve

Table 22: FDA definition of complicated skin and soft tissue infection

• The infection requires a major surgical intervention (e.g. debridement of necrotic tissue, abscess drainage, removal of infected foreign bodies, surgical incision of fascia).
• The infection process involves deep soft tissue (fascia and/or muscle).
• Preexisting disease that interferes with treatment response, e.g. – diabetes mellitus – bacteremia – cellulitis involving >3% of body surface – corticosteroid treatment (>7.5 mg/day prednisolone-equivalent) – neutropenia (granulocyte count < 500/mm^3) – hepatic cirrhosis (Child-Pugh B or C) – burns (>10% of body surface) – local or systemic radiation therapy – known history of alcohol abuse (>6 months) – organ transplant – malnutrition – immunosuppressive therapy

Table 23: Classification of postoperative wound infections

Superficial wound infection
• Infection at the incision site within 30 days after surgery and • Involvement of skin, subcutaneous tissue above the fascia and • Purulent discharge at incision site or subcutaneous drainage or • Pathogens isolated from secretion of a primarily closed wound or • Surgical opening of the wound (except if wound smear negative)
Deep wound infection
• Infection at the incision site within 30 days after surgery (for implants within one year) and • Involvement of tissue or areas on or below the fascia and • Purulent discharge from the drainage below the fascia layer or • Abscess or other signs of infection found during clinical examination, surgery or histopathological examination or • Spontaneous wound dehiscence or • Surgical wound opening if patient has fever (>38°C) and/or localized pain or • Sensitivity to pressure on the wound (except if wound smear negative) or • Diagnosis made by surgeon

after 5 to 7 days, treatment may be continued with oral penicillin V or an oral group 1 or 2 cephalosporin.

Soft tissue infections without need for immediate surgical intervention/ cellulitis/plegmons (e.g. soft tissue infections in chronic wounds)

Other than in classical erysipelas which is caused only by Streptococci, the deep forms of soft tissue infections are clinically characterized by overheated, more edematous, painful reddening and doughy swelling, by livid, dull and less distinct borders, while initial systemic signs of infection may be absent. An appropriate differentiation is desirable for therapeutic reasons, since a broad spectrum of pathogens must be expected for soft tissue infections which are not classical erysipelas.

The term cellulitis in the broadest sense describes any skin infection spreading out from a point of primary infection. In a more narrow interpretation, cellulitis is an acute infection which spreads from a pre-existing skin lesion (wound, ulcer) into the dermis and subcutaneous tissue. Pathogens are usually *S. aureus* but also *Escherichia coli*, *Klebsiella* spp., etc. However, usage of this term is not restricted to this definition in the German and English-speaking countries. It is rather used as a generic term for all cutaneous soft tissue infections including erysipelas and phlegmons [504].

The most frequent pathogen is *S. aureus*. However, infections originating from chronic wounds such as pressure sores, ulcers associated with peripheral arterial vascular disease (pAVD) or venous insufficiency are often polymicrobial (*S. aureus*, haemolytic streptococci, enterobacteriaceae).

Mild to moderately severe infections can be treated with oral clindamycin (3–4x300–600 mg/day orally). For moderately severe to severe *S. aureus* infections or critical localization (e.g. hands or face), treatment with an intravenous isoxazolyl penicillin (flucloxacillin or oxacillin 4x1–2 g/day IV) or alternatively a Group 2 cephalosporin (e.g. cefuroxim 3x0.75–1.5 g/day IV) is recommended.

Complicated chronic, usually polymicrobial infections (e.g. pressure sores, ulcers) are often caused by mixed infec-

tions of gram-positive and gram-negative pathogens and typically involve anaerobes as well. Initial therapy is preferably IV aminopenicillin/BLI (e.g. amoxicillin/clavulanic acid 3x2.2 g/day or ampicillin/sulbactam 3–4x1.5–3 g IV) or moxifloxacin. In case of treatment failure, a therapy targeted to the detected pathogen and susceptibility results should be started. he pathogen should preferably isolated from a tissue sample.

- For infections complicated by diabetes mellitus or pAVK see below.
- For infections with evidence of MRSA see below.

For septic diseases which aetiologically result from polymicrobially infected ulcers, the recommended initial therapy is an intravenous carbapenem, piperacillin/BLI or Group 2 or 3 fluoroquinolone combined with metronidazole, or moxifloxacin given as monotherapy.
The following pathogens require specific antibiotics or antifungals, respectively:

- *Aeromonas hydrophila* after exposure to fresh water and *Vibrio* spp. (*Vibrio vulnificus*, *Vibrio alginolyticus*, *Vibrio parahaemolyticus*) after exposure to salt water (see above)
- *Mycobacteria*
- *Haemophilus influenzae* in children (periorbital cellulitis)
- *Pseudomonas aeruginosa* with neutropenia
- *Cryptococcus neoformans* with disturbances of the cell-mediated immune response
- *Pasteurella* spp. and *Capnocytophaga* spp. after animal bites (see below) [155], [161], [294], [504]

Infections needing immediate surgical intervention For these infections as for abscesses, panaritium, phlegmons or suppurative bursitis, surgical intervention with adequate debridement is essential. If risk factors are present such as a complicated skin and soft tissue infection and general symptoms, oral or parenteral antibiotic treatment is indicated. Local antibiotic therapy is inappropriate. The calculated initial treatment should involve an aminopenicillin/BLI, an ureidopenicillin/BLI, a Group 1 or 2 cephalosporin, an isoxazolyl penicillin or clindamycin. Group 4 fluoroquinolones may be used for these infections because of their broad spectrum of activity [67], [193], [305]. After identification of the pathogen and testing its susceptibility, the treatment can be optimized by further targeting. Antibiotic therapy can be stopped after an improvement of fever, general symptoms, CRP and leukocytosis (to values below 8,000/µl). A 5-day antibiotic regime is equivalent to a 10-day treatment [499].

Severe, life-threatening soft tissue infections

A hallmark of these rare necrotizing soft tissue infections is the acute course of disease with early organ failure. These diseases are grouped under the designation “necrotizing skin and soft tissue infections” (nSSTI) in English-speaking countries [305]. They are often associated with agonizing pain and toxin-induced microthromboses causing pronounced tissue necrosis with decreased perfusion and hypoxia in the affected area [85].
The initial clinical presentation is often unspecific making timely and life-saving diagnosis more difficult. The typical early tissue necrosis is often detected intraoperatively or by means of biopsies. Necrosis of the skin is generally absent at the time of diagnosis and appears later in the course of disease. Immediate measures involve radical surgical debridement with antibiotic therapy started at latest during surgery and intensive medical care. The disease patterns include myonecrosis (gas gangrene), necrotizing fasciitis including Fournier’s gangrene, secondary infected injection abscess and myositis. Streptococcal toxic shock syndrome (STSS) can also be grouped into this type of diseases [82].
Aside from hematogenic dissemination, potential pathogen entry points include trivial traumatic wounds, infected surgical wounds and injection sites, less frequently infected periurethral glands or perianal infections (Fournier’s gangrene). Usually these are mixed infections with grampositive pathogens (beta-haemolytic streptococci, *S. aureus*), anaerobes (*Bacteroides fragilis*, *Prevotella melaninogenica*) and enterobacteriaceae often with a resulting synergistic increase of virulence.
Antimicrobial therapy with an ureidopenicillin/BLI or a Group 1 or 2 carbapenem is recommended. Alternatively a combination of a Group 3a cephalosporin with metronidazole or clindamycin is appropriate. Because of its broad spectrum, monotherapy with moxifloxacin is an alternative. The additional administration of clindamycin or linezolid inhibits toxic protein biosynthesis in grampositive bacteria. This alleviates septic complications of exotoxin production (e.g. superantigens). There is evidence that the combination of a penicillin with clindamycin is effective in streptococcal toxic shock syndrome [64], [499].
Certain skin and soft tissue infections require special treatment.

Bite wounds

The jaws of mammals generate bite pressures of up to 1 t/cm^2. Therefore, their teeth may inflict severe tissue distruction with accompanying contamination. For deep wounds surgical treatment and primary antibiotic therapy is indicated. An aminopenicillin/BLI or, in case of allergy, a Group 1 or 2 cephalosporin or a Group 4 fluoroquinolone is recommended [278], [510].
The pathogen spectrum generally originates from the physiological oral flora of the animal which inflicted the wound or from the bitten individual. Cat and dog bites are usually aerobic/anaerobic mixed infections of various pathogens. Pasteurella, staphylococci and streptococci are regularly found. Particularly after cat bites, the transmitted pathogens may reach deeper tissue layers due to the puncture type of the bite.
If bones or tendons are injured, chronic osteomyelitis or tendomyositis and/or tendosynovitis can result.

The most frequently isolated anaerobes after a dog or cat bite are *Bacteroides* spp., *Fusobacterium* spp., *Porphyromonas* spp., *Prevotella* spp., *Propionibacterium* spp. and *Peptostreptococcus* spp.
After rat bites, *Streptobacillus moniliformis*, the pathogen of rat-bite fever, must be expected.
Bite wounds inflicted by humans may cause acute and smoldering chronic infections. Usually there are Gram-positive (mostly *Streptococcus* spp.) and Gram-negative pathogens (e.g. *Haemophilus* spp., *Eikenella corrodens*) as well as anaerobes (*Fusobacterium*, *Prevotella* and *Porphyromonas* species).
In all cases of bite wounds, the patient's tetanus vaccination status must be checked.

Diabetic foot syndrome

Foot lesions in diabetics are the result of complex long-term neuropathic and angiopathic damage. Reduced immune reactions after trivial trauma and permanent mechanical stress often lead to painless soft tissue infections which may extend to adjacent tendons, joint capsules and bone or the entire foot. Antibiotics which are sufficiently active in soft and osseous tissue should be used.
Diabatic foot infections usually involve mutiple pathogens including staphylococci, streptococci, enterobacteriaceae, pseudomonads and/or anaerobes.
For mild infections, oral aminopenicillins/BLI or Group 2 and 3 fluoroquinolones are recommended. Moderate to severe illnesses must be treated surgically and initially parenteral antimicrobials must be administered. Here ureidopenicillins/BLI, a Group 1 or 2 carbapenem, or a combination of clindamycin with a Group 2, 3a or 4 cephalosporin or a Group 4 fluoroquinolone (moxifloxacin) is recommended. A long-term treatment over several weeks is often necessary [55], [273], [304], [538].

Decubital ulcers (bedsores)

Pressure sores may evolve even with appropriate prophylactic measures [96].
The surgical treatment depends on the sore stage of, according to the scale suggested by Campbell. Treatment with an antibiotic is usually indicated for infected sores. The responsible pathogens are Gram-positive and Gram-negative aerobic bacteria and anaerobes. Ureidopenicillins/BLI, a Group 2, 3 or 4 fluoroquinolone, or a Group 3 or 4 cephalosporin are recommended. Clindamycin or metronidazole may be added.

MRSA in skin and soft tissue infections

Skin and soft tissue infections (mostly in hospitals and long-term care facilities) may be caused by methicillin-resistant *S. aureus* (MRSA). These are most frequently postoperative or chronic wounds. As for other skin and soft tissue infections, local treatment is indicated. The decolonization is carried out locally according to the corresponding hygiene guidelines [248].
The indication for systemic use of antibiotics should be handled restrictlively (e.g. for infections with systemic reactions such as fever [>38.5 °C], leukocytosis [>10,000/µl] and marked increase in CRP). Detection of pathogens is often due to bacterial colonization rather than wound infection.
According to available data, linezolid achieves significantly higher eradication rates in MRSA monoinfections than vancomycin [567]. Daptomycin may also be used in cases of systemic infection or MRSA bacteremia [22], [450]. Tigecycline is a therapeutic alternative for polymicrobial infections involving MRSA. It is recommended to use glycopeptides (vancomycin or teicoplanin) in combination with rifampicin or fosfomycin.
In recent years, primarily in the USA, outbreaks of MRSA strains susceptible to clindamycin, cotrimoxazol and partially fluoroquinolones have occurred. These community-associated MRSA (caMRSA) occur in groups of healthy patients (military, sport clubs). Because of their high virulence mediated by toxin production (particularly panton-valentine-leukocidin), they may cause skin and soft tissue infections of all severity levels. Early diagnosis and consistent treatment currently appear to be the most effective approach to prevent severe disease. Strict hygiene measures are important to avoid outbreaks within hospitals. Wound closure should be achieved.

Mediastinitis

The most frequent forms of mediastinitis are caused by perforations of oesophagus or trachea, by descending infections from the mouth/throat, and postoperative sternum infections. The source of the infection must be surgically removed. In addition, a high-dose antibiotic therapy is indicated. The pathogen spectrum of hematogenous mediastinitis mainly includes gram-positive cocci. Primarily Gram-positive cocci, anaerobes and *Candida* spp. may be involved after perforation of the esophagus or postoperative complications following esophageal surgery. A group 1 or 2 carbapenem, an ureidopenicillin/BLI or a group 3 or 4 cephalosporin, optionally in combination with metronidazole is recommended. Moxifloxacin may be used as a monotherapy. Initially, fluconazole may be added in patients at high-risk of fungal involvement. The use of daptomycin, linezolid and tigecycline is also possible.

Postoperative wound infections

The incidence of postoperative wound infections has significantly decreased in the last two decades after the introduction of perioperative antibiotic prophylaxis. The management of postoperative wound infections depends on the stage of infection according to Cruse's wound classification and the additional risk factors (see Chapter 16) [115].

Postoperative wound infections are divided into superficial and deep wound infections defined by the Centers for Disease Control (CDC) in Atlanta, Georgia, USA [38].
Microbiological investigation to determine the pathogen should be carried out for all postoperative wound infections. The treatment of choice is to open the infected wound and treatment continuation. Treatment with antibiotics is indicated only in exceptional cases (immunosuppression, sepsis, multiple risk factors). The calculated initial treatment should complement the perioperatively administered antibiotic. Either an ureidopenicillin/BLI, a group 3 cephalosporin or a group 2, 3, or 4 fluoroquinolone is recommended. In any perioperative wound infection, the possibility of a surgical complication (suture insufficiency, infected prosthesis, foreign body left in situ) must be considered and excluded during diagnosis. In severe disease and in patients at risk of MRSA infection, the initial additional use of linezolid or daptomycin should be considered. If there is no evidence of a resistant pathogen, treatment can be de-escalated early.
A summary of the antibiotic treatments for the skin and soft tissue infections discussed here is given in Table 24.

Bone and joint infections

The course of and prognosis of bone and joint infections critically depend on early diagnosis and adequate treatment. The latter consists of extensive surgical debridement and/or synovectomy, stabilization of fracture, and treatment of a skin/soft tissue defect. Antibiotic therapy is indicated (Table 25), initially given at high-dose and via the intravenous route. A switch to oral therapy is feasible if adequate drug exposure is reached with an oral medication.

Osteomyelitis

Osteomyelitis is an infection of the bone marrow canal, which is usually caused by the hematogenous spread of endogenous pathogens. The pathogen spectrum varies according to the age of the patient. In adults, monoinfections by *S. aureus*, streptococci, *Serratia marcescens* or *Proteus* spp. are dominant pathogens. Calculated therapy is started with a Group 2 cephalosporin in combination with clindamycin or an aminopenicillin/BLI. Alternatively, a Group 2 or 3 fluoroquinolone in combination with clindamycin or moxifloxacin as monotherapy can be used. In complicated cases (e.g. severe spondylodiscitis), the combination of fosfomycin with a cephalosporin can be considered [459]. As soon as evidence of the pathogen and the results of a susceptibility test are available, the treatment should be changed to a more targeted regimen.

Posttraumatic or postoperative osteitis

Osteitis is defined as an infection of any bony skeletal structure. This generally occurs posttraumatically or postoperatively due to direct contamination during a trauma or surgery. Mixed infection with staphylococci, streptococci, enterobacteriaceae and anaerobes are common. Staphylococci dominate in postoperative osteitis. Treatment must start as soon as possible with surgical debridement, stabilization of the bone and initial calculated antibiotic therapy. An aminopenicillin/BLI, a Group 2 cephalosporin and clindamycin are recommended. In cases with high risk of multiresistant staphylococci, daptomycin, linezolid or teicoplanin or a combination with fosfomycin can be used. Rifampicin penetrates well into biofilms. In cases of chronic osteitis, the infected bone must be removed. This should be followed by a targeted antibiotic therapy [182], [247].

Sternum osteitis

Sternum osteitis is essentially caused by *S. aureus* and coagulase-negative staphylococci which are frequently multiresistant. The initial high-dose antibiotic therapy should involve an isoxazolyl penicillin or a group 2 cephalosporin combined with clindamycin or fosfomycin. In cases of MRSA or methicillin-resistant coagulase-negative staphylococci such as, for example, *Staphylococcus epidermidis*, the use of linezolid or daptomycin is recommended [461].

Bacterial arthritis

The fundamental cause of bacterial arthritis is an iatrogenic infection. With regard to the prognosis, the early infection is differentiated from the late infection. The pathogen spectrum includes mainly staphylococci and beta-hemolytic group A, B, C or G streptococci. Other pathogens such as enterobacteriaceae and gonococci are rare. Besides surgical treatment, the calculated antibiotic treatment is the same as recommended for osteitis. In rare cases of infections caused by *Salmonella* spp. or gonococci, antibiotic treatment alone is sufficient.

Prosthetic infections

Infected prostheses should preferably be removed or changed after extensive surgical debridement and antibiotic treatment at the maximum feasible dosage [325]. Only in cases of life-threatening contraindications surgical exchange of the prothesis may be omitted. The infection rarely resolves if purely conservative treatments are used.

Table 24: Recommendations for calculated antibiotic treatment of skin and soft tissue infections

Diagnosis	Bacterial pathogen	Initial therapy	Duration of therapy	Level of evidence	Level of recommendation
Erysipelas	Group A streptococci	Benzylpenicillin	2 weeks	I	A
		Group 1/2 cephalosporin	6 weeks if relapse	II	B
		Clindamycin (if allergy to beta-lactams)		I	A
Moderately severe infections	*Staphylococcus aureus* Groups A, B, C, F, G streptococci	Aminopenicillin/BLI	After sucessful surgical treatment <7 days	I	A
		Ureidopenicillin/BLI		I	A
		Group 1/2 cephalosporin		I	A
		Moxifloxacin		I	A
		Clindamycin (if allergy to beta-lactams)		I	A
		Tigecycline		I	A
Severe infections Nectrotizing infections	Mixed infections Streptococci Staphylococci Anaerobes Enterobacteriaceae	Ureidopenicillin/BLI	7 days	III	A
		Group 1/2 carbapenem		III	A
		Group 3a cephalosporin ± Metronidazole		II	B
		Moxifloxacin		II	A
		Tigecycline		II	B
		Each + clindamycin or		II	B
		Linezolid		II	C
Bite wounds	*Pasteurella multocida Capnocytophaga spp.* Others	Aminopenicillin/BLI	1–10 days	I	A
		Group 1/2 cephalosporin		II	B
		Carbapenem		II	B
		Moxifloxacin		II	B
Diabetic foot syndrome (moderate to severe)	Staphylococci Streptococci Enterobacteriaceae Anaerobes	Ureidopenicillin/BLI	1–2 weeks IV followed by 2–3 weeks oral	I	A/B
		Group 3 fluoroquinolone + clindamycin		I	A
		Moxifloxacin		I	A
		Group 3a cephalosporin + clindamycin		II	C
		Group 1/2 carbapenem		I	A
		Fosfomycin (as a combination partner if required)		II	B
MRSA in skin/soft tissue infections		Daptomycin		II	A
		Linezolid		I	A
		Tigecycline		II	A
		Glycopeptide		I	A
		Fosfomycin or rifampicin (as a combination partner if required)			
		Cotrimoxazol		III	B
Mediastinitis	Grampositive cocci Anaerobes Enterobacteriaceae	Each at high dose			
		Group 1 carbapenem		III	A
		Group 2 carbapenem		III	B
		Ureidopenicillin/BLI		III	B
		Group 3a/4 cephalosporin		III	B
		Each + metronidazole		III	B
		Moxifloxacin		III	B

Table 25: Recommendations for the calculated antibiotic therapy of bone and joint infections

Diagnosis	Bacterial pathogen	Initial therapy	Duration of therapy	Level of evidence	Level of recommendation
Hematogenous osteomyelitis	Staphylococcus aureus Groups A, B, C, G beta-haemolytic streptococci rarely Salmonella, and other Enterobacteriaceae	Isoxazolyl penicillin	1–4 weeks IV followed by 2–6 weeks oral Total duration at least 8 weeks	I	A
		Aminopenicillin/BLI		I	B
		Group 2 cephalosporin + clindamycin		I	B
		Moxifloxacin		I	B
		Fosfomycin (as combination partner)			
Posttraumatic/ postoperative osteitis	Mixed infections Staphylococci Streptococci Enterococci Enterobacteriaceae Anaerobes	Aminopenicillin/BLI	1–4 weeks IV followed by 2–6 weeks oral	I	A
		Group 2 cephalosporin		II	B
		Clindamycin		II	B
		Fosfomycin (as a combination partner)			
		Linezolid (MRSA)		II	B
		Teicoplanin (MRSA)		III	B
		Daptomycin (MRSA)		III	B
Sternum osteitis	Staphylococcus aureus Coagulase-negative staphylococci	Isoxazolyl penicillin		III	C
		Group 1 or 2 cephalosporin +		II	B
		Clindamycin or fosfomycin		III	B
		If MRSA:			
		Linezolid or		III	B
		daptomycin		III	B
Bacterial arthritis	Staphylococcus aureus Group A, B, C, G beta-hemolytic streptococci Enterococci Anaerobes Rarely enterobacteriaceae Salmonella Gonococci	Aminopenicillin/BLI		I	A
		Group 2 cephalosporin		II	A
		Clindamycin		I	B
		Moxifloxacin		II	B
		If MRSA/MRSE:			
		Linezolid or		II	B
		daptomycin		III	B

10 Sepsis

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The treatment of sepsis is one of the greatest challenges for hospital physicians [174], [184], [204], [226], [378], [427], [448], [507], [508], [570]. Particularly in intensive care medicine, sepsis and septic shock are very important due to the high mortality of 40% to 60%. A large study on the epidemiology of sepsis in German intensive care units [159] found prevalence rates of 12.4% for sepsis and 11% for severe sepsis (including septic shock), with an overall mortality of 48.4% and a hospital mortality of 55.2%. The incidence of newly diagnosed severe sepsis in Germany was 76 to 110 per 100,000 population. Fungal sepsis in non-neutropenic patients must also be taken into consideration [396]. In the German prevalence study, 17.8% of severe sepsis cases with microbiological documentation of pathogens were caused by fungi. In the USA, *Candida* spp. is the third most frequent pathogen detected in blood cultures of patients in intensive care units [575]. All immunocompromized patients, including those with tumors, diabetes mellitus, kidney and liver diseases, hematological malignant diseases, surgical intensive care (e.g. after polytrauma and burns) and high-risk surgery (e.g. organ transplants) carry an increased risk of developing sepsis. Aside from source control, effective antimicrobial therapy is the most important causal intervention which is supplemented by supportive and adjunctive intensive care measures [123], [124].
According to current knowledge, microbial sepsis appears to be best described by the definition of Schuster [469]: “Sepsis is the entirety of symptoms of life-threatening clinical diseases and pathophysiological changes occurring as reactions to pathogens and their products which spread from the point of infection into the blood stream, activating biological cascades and special cell systems

thus triggering the production and release of humoral and cellular mediators."
The generally accepted criteria for the diagnosis of sepsis include evidence of infection and at least two of the four criteria listed below [71]

1. fever >38°C or, in rare cases, hypothermia <36°C
2. tachypnea >20/min or hypocapnia with a $PaCO_2$<32 mm Hg
3. tachycardia >90/min.
4. leukocytosis >12,000/mm^3 or leukopenia <4,000/mm^3.

Sepsis as a sydrome is divided into different levels of clinical severity according to the American consensus definition:

- SIRS (Systemic Inflammatory Response Syndrome) is a general inflammatory defense reaction to various events (e.g. trauma, hypoxia, pancreatitis), which exhibits at least two of the above-listed criteria, although an infection need not be present.
- Sepsis is the systemic reaction to an infection. As with SIRS, at least two of the above-listed criteria must be present. The international consensus definition of sepsis does not include the presence of organ dysfunction.
- Severe sepsis is defined by organ dysfunction in addition to sepsis symptoms. Dysfunctions may affect: lungs (hypoxia, respiratory acidosis), kidneys (oliguria/anuria, metabolic acidosis), liver (e.g. jaundice, progressive sclerosing cholangitis), heart (heart failure, septic cardiomyopathy) but also CNS, gastrointestinal tract, bone marrow, coagulation and immune system. From the intensive care point of view and in contrast to the international consensus recommendation, the term sepsis is used if organ failure is present. Recommendations for antimicrobial therapy also refer to severely ill patients with organ dysfunction.
- Septic shock is accompanied by a persistent reduction of blood pressure despite adequate fluid supply. Refractory septic shock is present if blood pressure falls for longer than one hour and cannot be corrected by infusion of fluids and use of vasopressors.

Pathophysiological evidence indicates that sepsis is caused by a complicated network of pro and anti-inflammatory cytokines. Following the pro-inflammatory phase of SIRS, an excess of anti-inflammatory cytokines is produced. This phase is called CARS (compensatory anti-inflammatory response syndrome). The SIRS and CARS phases often overlap in patients, making for a mixed antagonistic response syndrome (MARS). Sepsis is a dynamic process with transitions from the stage of "mild" sepsis to "severe" sepsis to "septic shock" with organ dysfunction or failure but also with the development of septic organ metastases.
Sepsis research in the last 20 years has concentrated mainly on supportive (volume and circulatory treatments) and adjunctive measures (anti-inflammatory agents). Initial positive study results with newly tested interventions often could not be confirmed in large, multicentre trials. Low-dose hydrocortisone can no longer be recommended as routine treatment for patients with septic shock (increased incidence of superinfections and no reduction of mortality) [493]. Likewise an intensified intravenous insulin treatment (glucose target level ≤110 mg/dl) is generally no longer recommended (increased incidence of severe hypoglycemic events), nor are antithrombin (AT III), low-dosed dopamin, vasopressin and hydroxyethyl starch in the investigated formulations [84].
Lung-protective ventilation [23], treatment guided by haemodynamic target values (early goal-directed therapy) [433] and – for patients at high risk of lethal outcome (failures of at least two organs) and without contraindications – early administration (<48 hours) of recombinant activated protein C [59] have become established treatments.
Addendum: the use of activated protein C is no longer recommended. The failure of new therapies for the treatment of severe sepsis and septic shock is related to the lack of an early and differentiated diagnosis. Whenever sepsis is suspected, an early "aggressive" diagnostic workup (e.g. CT, BAL) is required [521].
Early, adequate antimicrobial therapy is an essential determenant of patient survival.
For septic shock patients, Kumar et al. [276] showed in a retrospective study published in 2006 that the mortality rate increases by 7.6% with every hour of delay of therapy after the onset of hypotension. In a follow-up article published in 2009 [275], these data were impressively confirmed.
The severity of illness may be determined rather simple according to clinical criteria: need for ventilation, need for catecholamine therapy (particularly vasopressors), and organ dysfunction, primarily renal impairment. However, no clinical study was performed to validate this procedure.
Due to the increased prevalence of multiresistant pathogens (MRSA, VRE, *Pseudomonas aeruginosa*, ESBL-producing pathogens, etc.), broadly active, optionally combined antimicrobial therapy must often be started in order to adequately cover the spectrum of potential pathogens. Any previous antimicrobial treatment must be considered in therapeutic decisions.
The need for antimicrobial therapy should be established at latest by day 3 [116] and re-evaluated at least every 48 hours [479]. If feasible, combination therapy should be de-escalated to a therapy with a more narrow spectrum after 3 to 5 days and after microbiological data become available.
Given the physiologically and pharmacologically complex situation and the high volume of distribution in sepsis patients, high-dose therapy on the first day is needed to rapidly establish sufficiently high plasma levels. However, there is little study data supporting this plausible notion. In the following days, dosage should be adjusted for organ (kidney and liver) function with consideration of potential drug-drug interactions.

Therapy can be guided by monitoring the procalcitonin (PCT) in the serum. In a study in severe sepsis patients [379], the duration of antibiotic therapy could be reduced by 3.5 days and the duration of stay in the intensive care unit was shortened by 2 days without any clinical disadvantages. The antibiotic was stopped when the PCT value had fallen by more than 90% of the initial value.
In order to be able to implement this strategy in the clinical routine setting, a close cooperation between the intensive care physicians and clinical infectiology and microbiology departments is required. The term "antimicrobial stewardship" [125] describes this interdisciplinary approach.

Microbiology and current resistance situation

The current recommendations for blood culture diagnostics are published within the framework of the "MIQ Guidelines" (quality standards in the microbiological-infectiological diagnostics of the German Society for Hygiene and Microbiology, DGHM). The guidelines describe procedures for blood culture sampling, choice of access site, venipuncture, as well as sample transport and processing with and without automatic detection systems. Blood cultures samples should be taken before starting antibiotic therapy. The following procedures are recommended:

- make a fresh puncture in a peripheral vein; use an indwelling catheter only for additional samples
- disinfect hands of staff
- wipe or spray an area of at least 5x5 cm with alcohol-based disinfectant, wait for 1 min
- disinfect the skin a second time from centre outwards with a sterile swab
- put on disposable gloves
- do not palpate the puncture site again
- puncture the vein and take samples of (5–) 8 to 10 ml of blood per blood culture bottle, i.e. 16 to 20 ml per blood culture set
- use at least two, better 3 blood culture sets
- wipe the stoppers of blood culture bottles with alcohol-based disinfectant
- wait until the disinfectant has dried
- inoculate the blood culture bottles with fresh syringes (not inserted!) or a closed removal system (TRBA!)
- do not ventilate the anaerobic bottles
- transport the blood culture bottles to the laboratory immediately

Sepsis may involve a broad spectrum of potential pathogens. In the SEPNET study in Germany, 55% of the cases were caused by gram-positive bacteria, 54% by gram-negative microorganisms and almost 18% by *Candida* strains; these add up to more than 100% due to polymicrobial infections [159].
In the fourth PEG Blood Culture Study, with 14 laboratories all over Germany plus 1 centre in Austria participating, the distribution of the 7,652 pathogens detected from all clinically relevant blood culture isolates collected between July 1, 2006 and June 30, 2007 was as follows: 46.1% gram-positive pathogens, 46.7% gram-negative pathogens, 1.6% anaerobes and 5.6% fungi. The most frequently detected pathogen was *Escherichia coli*, followed by *S. aureus*. Enterococci, particularly *Enterococcus faecium*, as well as fungi showed the largest increase of prevalence.
The current resistance situation in blood culture isolates in Germany was also analyzed in the fourth PEG Blood Culture Study. According to these data, the proportion of methicillin-resistant *S. aureus* strains (22.8%) has increased significantly compared to the years 2000/2001. However, there was a large cross-center variation of 8.7% to 41%.
The proportion of glycopeptide-resistant *E. faecium* strains was 5.4%, which is in the same range as the rate of 6.3% found for Germany in the European Antimicrobial Resistance Surveillance Study (EARSS) of 2008.
The proportion of fluoroquinolone-resistant *E. coli* strains has increased to 31.2%. The proportion of cefotaxime-resistance as a marker of ESBL production was 7% in the current study. The fluoroquinolone resistance rate in *Klebsiella pneumoniae* and *K. oxytoca* increased to 17% and 15%, respectively. The rate of ESBL producers in *K. pneumoniae* increased to 14%, as measured by cefotaxime resistance.
For *P. aeruginosa*, the rates of resistance to ceftazidim and meropenem have remained stable at 14.4% and 11.8%, respectively. Ciprofloxacin resistance actually decreased slightly to 23.9%.

Pharmacokinetics and Pharmacodynamics

Investigations on pharmacokinetics and pharmacodynamics of antibiotics used in patients with sepsis remain limited to date. Pharmacokinetics are influenced by complex, partially antagonistic processes making antibiotic levels difficult to predict. In many patients, the early phase of sepsis is dominated by a hyperdynamic circulatory situation which may lead to enhanced clearance of renally eliminated antibiotics as compared to in healthy individuals. Capillary leakage may cause significant expansion of the extracellular space. These two factors result in unexpectedly low plasma level of hydrophilic and renally eliminated antibiotics which applies to most beta lactams and aminoglycosides. This effect is less pronounced for antibiotics with larger volumes of distribution, i.e. mostly intracellular accumulation. If organ function – primarily renal clearance – declines in the further course of sepsis, plasma levels will increase due to decreased elimination. This may lead to accumulation of usually ineffective but potentially toxic drug metabolites [303]. In addition, antibiotics with high protein binding are dissociated from plasma proteins by other drugs or changes in pH. For these reasons antibiotics with low protein binding and low potential toxicity should be chosen (e.g. for MSSA sepsis, cephalosporins should be used rather than fluc-

loxacillin, with its high affinity to proteins (>90%) and a high risk of hepatotoxicity). Pharmacodynamics describes antimicrobial efficacy as a function of drug exposure parameters. For example beta lactams (penicillins, cephalosporins, carbapenems) are classified as time-dependent antibiotics, which means that the plasma level should remain above the MIC of the infecting pathogen as long as possible, while high plasma level spikes do not confer an advantage in terms of pathogen killing. Continuous infusions may improve the treatment results, particularly in severly ill patients with moderately susceptible pathogens [269], [312].

Group 1 carbapenems, with their postantibiotic effect against gram-negative pathogens and limited half-life at room temperature, are also suitable for prolonged infusions (3–4 hours), thus optimally exploiting the pharmacokinetic-pharmacodynamic (PK/PD) profile. In contrast, peak level dependent antibiotics such as aminoglycosides should be administered as a bolus dose once daily. This similarly applies for fluoroquinolones whose PK/PD profile is determined by the parameter AUC (area under the plasma concentration-time curve) >MIC. To allow for dose adjustments, an early measurement of plasma levels (i.e. therapeutic drug monitoring) is urgently recommended but is available only in exceptional cases.

Treatment recommendations

Almost all patients receive calculated initial antimicrobial treatment as recommended by the PEG (Paul-Ehrlich Society). For some patients, where information of pathogen susceptibility is available, the initial therapy may be modified accordingly.

The initial choice of antibiotic is influenced by the suspected source of infection, the underlying disease, the risk factors, whether an infection is community-acquired or nosocomial, the onset of the infection and whether the patient was previously treated with antimicrobials.

Table 26 shows treatment recommendations for an unknown pathogen, based on the type and origin of the infection. Table 27 lists treatment recommendations for known pathogens. The diversity of the treatment options in Table 26 and Table 27 stems from the different degrees of disease severity and various risk factors. Treatment duration should be in the range of 7–10 days. Exceptions are a slow response to treatment, failure of source control and immunosuppression [79].

Although the database is not sufficient, patients with life-threatening disease should always receive therapy with a combination regimen (Table 26). This approach is supported by the results of the Surviving Sepsis Campaign [79]. Dellinger et al. recommended the administration of one or more drugs with broad spectrum of antimicrobial activity and good tissue penetration for calculated initial therapy [123].

A combination treatment is explicitly required if a *Pseudomonas* infection is suspected or detected [79], [84], [112]. Traditionally, aminoglycosides are the preferred combination partner of beta-lactam antibiotics. The option to use fluoroquinolones as combination partners for a beta-lactam is substantiated by the work of Paul [400], [401], pharmacokinetic advantages, lower toxicity and the fact that plasma levels need not be determined regularly, while direct treatment costs are higher. In view of the increasing rates of resistance to fluoroquinolones, fosfomycin is another option as a combination partner. It achieves good tissue penetration (Table 28).

In sepsis patients, all antibiotics must be administered intravenously and at high doses. Neither intravenous to oral sequential treatment nor dose reductions have been documented in a study on this indication.

A lipopeptid (daptomycin) [116], [125], [159] or a glycopeptide should be added to the combination in high-risk patients with severe sepsis, septic shock or unknown focus of sepsis, particularly if local MRSA prevalence is high.

In sepsis with a focus in the respiratory tract, predominantly *Streptococcus pneumoniae*, various enterobacteriaceae and anaerobes from aspiration pneumonia must be anticipated. In high risk patients and those who have been hospitalized for more than 5 days, *P. aeruginosa*, *Acinetobacter* spp. and *Stenotrophomonas maltophilia* must be considered as potential pathogens. The pathogen spectrum can vary greatly from hopsital to hospital. A recent study has shown that gram-negative pathogens should be expected in patients on mechanical ventilation, even in those with shorter periods of hospitalization [187].

An oxazolidinone (linezolid) should be added to the combination for severe sepsis or septic shock in high-risk patients and in settings with high local rates of MRSA [125].

In cases of sepsis originating in the urinary tract without previous instrumental intervention, *E. coli* and *Proteus mirabilis* are the most likely pathogens. After urological surgery, other enterobacteriaceae, *P. aeruginosa*, enterococci and staphylococci must also be considered.

If the source of sepsis is the intestinal tract or a gynaecological organ, the following pathogens must be expected: enterobacteriaceae, anaerobes, enterococci, *Pseudomonas* spp., and *S. aureus*.

In a biliary sepsis, pathogen colonization of bile ducts and bacteraemia increase with the degree of bile duct obstruction. In cases with obstructive jaundice, pathogens are detected in the blood in more than 75% of patients. The spectrum of pathogen includes enterobacteriaceae, enterococci and anaerobes. Additional gram-negative pathogens including *P. aeruginosa* have been detected in postoperative bacteraemia, cholangitic sepsis, subhepatic abscesses and interventional surgery (ERCP or endoscopic papillotomy). For severe sepsis or septic shock originating in the intestines, gynaecological organs and bile ducts, a glycylcycline (tigecycline) can be added to the combination [123], [124], [125], [185].

If the focus of sepsis is located in skin or soft tissue, infections are mostly due to *Streptococcus pyogenes*, *S. aureus* (including MRSA) as well as mixed pathogens with the possilbe additional involvement of non-A strepto-

Table 26: Recommendations for treatment of sepsis caused by unknown pathogens

Infection source Most frequent pathogen	Nosocomial (+ = severe sepsis and/or enhanced spectrum)	Community acquired (+ = severe sepsis and/or enhanced spectrum)
Unknown Source of Infection Staphylococcus aureus Streptococcus spp. Escherichia coli Enterococci Klebsiella Pseudomonas	Ureidopenicillin/BLI ± Group 2/3 fluoroquinolone or fosfomycin Group 4 cephalosporin ± Group 2/3 fluoroquinolone or fosfomycin Group 1 carbapenem ± Group 2/3 fluoroquinolone or fosfomycin	Group 2/3a cephalosporin ± Group 2/3 fluoroquinolone aminopenicillin/BLI ± Group 2/3 fluoroquinolone ureidopenicillin/BLI ± Group 2/3 fluoroquinolone
	High-risk patients (mechanical ventilation, previous antibiotic treatment, major surgery, long intensive care stay) with severe sepsis or septic shock and if high local rate of MRSA: use a lipopeptide (daptomycin) [116], [125], [159] or a glycopeptide in combination (and consider the use of an echinocandin if a fungal infection is suspected)	
Respiratory tract Streptococcus pneumoniae Haemophilus influenzae Staphylococcus aureus Enterobacteriaceae Anaerobes Pseudomonads	Group 3b/4 cephalosporin + Group 2/3 fluoroquinolone or fosfomycin Ureidopenicillin/BLI + Group 2/3 fluoroquinolone or fosfomycin Group 1 carbapenem + Group 2/3 fluoroquinolone or fosfomycin	Group 2/3 cephalosporin + macrolide Ureidopenicillin/BLI + macrolide Group 3/4 fluoroquinolone Group 1 carbapenem + macrolide (especially in severe cases) (differentiation according to risk of Pseudomonas involvement)
	High-risk patients with severe sepsis or septic shock should receive an oxazolidinone (linezolid) in combination if local MRSA rates are high.	
Urinary tract Escherichia coli Proteus mirabilis Pseudomonads Other Enterobacteriaceae	Group 2/3 fluoroquinolone Group 3a/3b/4 cephalosporin Ureidopenicillin/BLI Group 1 carbapenem	Aminopenicillin/BLI Group 2/3 fluoroquinolone Group 3a cephalosporin Group 2 carbapenem
Intestinal tract, gynaecological organs Enterobacteriaceae Anaerobes Enterococci Pseudomonas spp.	Ureidopenicillin/BLI Group 3b/4 cephalosporin + metronidazole Group 2/3 fluoroquinolone + metronidazole Group 1 carbapenem	Ureidopenicillin/BLI Group 3a cephalosporin + metronidazole Group 2 carbapenem
	Patients with severe sepsis or septic shock can be treated with a combination including a glycylcycline (tigecyclin) [123], [124], [125], [185]	
Bile ducts Enterobacteriaceae Enterococci Pseudomonads Anaerobes	Ureidopenicillin/BLI Group 2/3 fluoroquinolone + aminopenicillin Group 3a cephalosporin + aminopenicillin Group 1 carbapenem	Ureidopenicillin/BLI Group 2/3 fluoroquinolone + aminopenicillin Group 3a cephalosporin + aminopenicillin Group 2 carbapenem
	Patients with severe sepsis or septic shock can be treated with a combination including a glycylcycline (tigecyclin) [123], [124], [125], [185]	
Skin/soft tissue Streptococcus pyogenes Staphylococcus aureus Anaerobes Enterobacteriaceae Pseudomonads	Group 3b/4 cephalosporin + clindamycin Ureidopenicillin/BLI ± clindamycin Group 2/3 fluoroquinolone + group 2 Cephalosporin or clindamycin Group 1 carbapenem + clindamycin	Group 1/2 cephalosporin + clindamycin
Catheter-related sepsis Coagulase-negative Staphylococci Staphylococcus aureus Gram-negative rods Corynebacterium jeikeium Propionibacteria (Caveat: Candida spp.)	Glycopeptide or lipopeptide (daptomycin) ± Ureidopenicillin/BLI or ± Group 3a/4 cephalosporin or ± Group 1 carbapenem	Glycopeptide ± ureidopenicillin/BLI or ± group 3a/4 cephalosporin or ± group 1 carbapenem

BLI= Beta-lactamase inhibitor

Table 27: Recommendations for targeted antibiotic treatment of sepsis caused by known pathogens

Pathogen	Monotherapy	Combination therapy
Staphylococcus aureus MSSA		Group 1/2 cephalosporin + rifampicin or clindamycin and/or aminoglycoside (3–5 days) Isoxazolyl penicillin + rifampicin or clindamycin and/or aminoglycoside (3–5 days)
Staphylococcus aureus MRSA		Linezolid (pneumogenic sepsis) or daptomycin (not for pneumogenic sepsis!) or glycopeptide + rifampicin or fosfomycin
Coagulase-negative Staphylococci MSSE	Group 1/2 cephalosporin Isoxazolyl penicillin	Group 1/2 cephalosporin or isoxazolyl penicillin + aminoglycoside (3–5 days) and/or rifampicin (after antibiogram) glycopeptide (+ rifampicin or fosfomycin) combination therapy for device infections, e.g. stent
Coagulase-negative Staphylococci MRSE	Daptomycin Linezolid	Daptomycin or linezolid or glycopeptide + rifampicin Combination therapy for device infections, e.g. stent
A Streptococci	Benzylpenicillin Group 1/2 Cephalosporin (if allergic to penicillin)	Benzylpenicillin + clindamycin
Pneumococci	Benzylpenicillin Group 3a cephalosporin (if allergic or resistant to penicillin) Moxifloxacin	Beta Lactam + macrolide Glycopeptide + rifampicin Linezolid (if allergic or resistant to beta-lactams)
Enterococcus faecalis	Aminopenicillin (high dose) Ureidopenicillin (high dose)	Aminopenicillin + aminoglycoside Ureidopenicillin + aminoglycoside Allergy to penicillin: Glycopeptide + aminoglycoside
Enterococcus faecium	Glycopeptide Daptomycin Linezolid	Glycopeptide + aminoglycoside
Enterococcus faecium VRE	Linezolid Daptomycin Tigecyclin (only if intraabdominal focus)	
Escherichia coli Klebsiella pneumoniae Proteus mirabilis	Aminopenicillin/BLI Ureidopenicillin/BLI Group 3a/3b/4 cephalosporin Group 2/3 fluoroquinolone Carbapenem	
ESBL-producing E. coli Klebsiella pneumoniae Proteus mirabilis	Carbapenem Colistin (not for *Proteus mirabilis*!)	Carbapenem + fosfomycin Carbapenem + tigecycline Colistin + fosfomycin
Citrobacter freundii Enterobacter spp. Serratia marcescens	Carbapenem Group 4 cephalosporin Group 2/3 fluoroquinolone	
Pseudomonas aeruginosa		Group 3b/4 cephalosporin + group 2/3 fluoroquinolone or fosfomycin or aminoglycoside Ureidopenicillin/BLI + group 2/3 fluoroquinolone or fosfomycin or aminoglycoside Group 1 carbapenem + group 2/3 fluoroquinolone or fosfomycin or aminoglycoside
Acinetobacter baumannii	Group 1 carbapenem	Group 1 carbapenem + group 2/3 fluoroquinolone or tigecyclin Colistin + tigecycline
Stenotrophomonas maltophilia (after antibiogram!)		Trimethoprim/sulfomethoxazole +group 3b/4 cephalosporin or group 3/4 fluoroquinolone
Bacteroides fragilis	Carbapenem Ureidopenicillin/BLI Metronidazole	
Clostridium perfringens	Benzylpenicillin Clindamycin Metronidazole (if allergic to penicillin)	

BLI= Beta-Lactam Inhibitor

cocci, anaerobes, enterobacteriaceae and/or *P. aeruginosa*.
The pathogen spectrum of catheter-related sepsis includes coagulase-negative staphylococci, *S. aureus*, gram-negative rods, *Candida* spp., *Corynebacterium jeikeium* and propionibacteria. The lipopeptide daptomycin is an alternative to the use of a glycopeptide [116], [159].
The recommendation to use a single-agent regimen is based on the results of well-documented randomized clinical studies corresponding to evidence level I.
In general, there is insufficient evidence from clinical studies to support recommendations for combination therapies. These recommendations are based on expert opinion and are predominantly classified as evidence level IV. This is particularly true for combination treatments involving fluoroquinolones.

Table 28: Recommendations for antibiotics used in nosocomial sepsis caused by unknown pathogens and unknown source of infection

Substances	Level of recommendation
Piperacillin/tazobactam	A
Piperacillin + sulbactam	C
Cefepim	A
Cefpirom	A
Ciprofloxacin	A
Levofloxacin	A
Imipenem/cilastatin	A
Meropenem	A
Doripenem	A
Fosfomycin	B

11 Bacterial endocarditis

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Endocarditis is an endovascular infection, mostly caused by bacteria. It affects the native heart valve or intravascularly implanted devices such as prosthetic valves or pacemaker electrodes. Despite substantial diagnostic and therapeutic advances, bacterial endocarditis is still a severe disease with a mortality rate of 20% to 30%. The exact incidence in Germany is not known. In France, it is in the range of 30 cases per million population [229]. The disease is categorized clinically according to severity as subacute or acute endocarditis. The former is more frequently caused by streptococci and enterococci, the latter by staphylococci.

Clinical diagnosis

Many cases of endocarditis are definitively diganosed and adequetely treated only after long delay of often over a month after the onset of symptoms [54]. The classical key symptoms are often difficult to assess (e.g. aggravated heart murmur), or rather unspecific (e.g. fever, loss of body weight, night sweats, exhaustion or myalgia). In many cases, the first symptoms already indicate complications, including progressive dyspnea as as sign of valvular destruction with significant regurgitation and volume overload. Septic embolisms from a heart vegetation may cause neurological conplications and are often the first symptoms.
The possibility of endocarditis must be considered in the differential diagnosis of even unspecific symptoms particularly in patients with risk factors, e.g. a prosthetic valve or intravenous drug abuse.

Echocardiography

After the clinical diagnosis endocardial involvement must be confirmed by further diagnostic workup which should include immediate transthoracic echocardiography to detect serious valve destruction or septic cardiomyopathy. Transoesophageal echocardiography (TEE) will be necessary in most cases. One single negative TEE does not rule out an infective endocarditis. If clinical suspicion remains, the TEE should be repeated after 6 to 10 days. After the diagnosis has been made, weekly echocardiography will be used to monitor the course of disease. Even in the absence of fever, local progression may result in a growth of vegetations or formation of abscesses or fistulas. In cases with clinical worsening, immediate examination is necessary to identify complications as soon as possible.

Pathogen identification

Besides echocardiographic imaging, the identification of the causative pathogen is vital for targeted therapy. It is of key importance to take blood cultures correctly before starting the antimicrobial treatment. At least three blood culture sets must be taken (aerobic and anaerobic) at different times from a peripheral freshly punctured vein after adequate disinfection. This should be carried out without regard to body temperature, as continuous bacteremia must be suspected. The most common cause for negative blood cultures is ongoing treatment with antibiotics. Therefore, in clinically stable patients who have already received an antibiotic before the diagnosis or who have had negative blood cultures, the interruption of an ongoing antibiotic therapy (>48 hours) before taking a blood culture should be considered. Another reason for a negative blood culture might be the presence of a microorganism which is difficult to culture. Therefore, it is important to notify the laboratory of the suspected diagnosis of endocarditis to ensure adequate analysis (e.g. sufficiently long incubation period). For instance, a serological analysis must be carried out for Bartonella, *Brucella* and *Coxiella* spp. Molecular biological methods to detect pathogens in EDTA blood samples using polymerase chain reaction (PCR) are available for clinical testing and could offer a workaround for the described

Table 29: Empirical therapy of culture-negative infectious endocarditis after previous antibiotic therapy and/or until blood culture results become available. An infectious disease specialist should advise on culture-negative endocarditis in patients with no previous antibiotic therapy.

Antibiotic drug	Dosage regimen	Comments	Level of evidence	Level of recommendation
Native valve endocarditis				
		If no pathogen detected: calculated therapy for 6 weeks		
Ampicillin/sulbactam, plus gentamicin if required[1]	12 g/day IV in 4 doses 3 mg/kg/day IV	Patients with negative blood cultures should be treated in consultation with an ID specialist	IV	B
Vancomycin[2] or daptomycin plus gentamicin if required[1]	30 mg/kg/day IV in 2 doses At least 6 mg/kg/day 3 mg/kg/day IV	In patients allergic to beta lactams	IV	B
Prosthetic valve endocarditis (<12 months post surgery)				
Vancomycin[2] or daptomycin plus gentamicin[1] or plus rifampicin	30 mg/kg/day IV in 2 doses at least 6 mg/kg/day 3 mg/kg/day IV 900 mg/day PO in 2 doses	If no clinical response: consider surgery and expansion of antibiotic treatment with a drug effecive against Gram-negative bacteria	IV	B
Prosthetic valve endocarditis (>12 months post surgery)				
As for native valve endocarditis			IV	B

1 Weekly monitoring of serum level and kidney function recommended.
2 Monitoring of serum level recommended. Trough level at least 15–20 mg/l.

diagnostic problems. However, their clinical validity in endocarditis has not been sufficiently evaluated to date. The microbiological testing of surgically excised heart valve material is obligatory. Other than in the analysis of blood, the PCR can deliver directive results. It should be noted that the presence of bacterial DNA does not yield any information about the activity of the infection.
Diagnostic criteria such as the Duke criteria help in the categorization of findings. Particularly in cases with negative blood cultures, their sensitivity is often sufficient for infections of prosthetic valves or pacemaker electrodes or if the right side of the heart is affected. However, they can never replace a rational clinical judgement.

Essentials of endocarditis treatment

The antibiotic therapy, surgical treatment and management of complications are the three essential treatment approaches in bacterial endocarditis. For this reason, endocarditis is always treated by a team of physicians, consisting of cardiologists, infectiologists, microbiologists and heart surgeons. The prognosis for bacterial endocarditis depends on many factors which are, among others,

- the source of the infection (nosocomial or community-acquired),
- the underlying pathogen,
- the local resistance situation, and
- the presence of foreign material.

In general, cerebral complications are less frequent in right-sided endocarditis and the success rate of conservative management is usually higher than in left-sided endocarditis. An endocarditis involving a prosthetic valve usually needs surgical intervention more urgently and earlier than a native valve endocarditis. An infection with *Staphylococcus aureus* is usually more severe than a streptococcal infection.

Antibiotic therapy

If the general condition of the patient is critical, empirical antimicrobial treatment is started immediately but always after taking blood culture samples. In native heart valve endocarditis and late endocarditis after cardiac valve replacement (>1 year after surgery), methicillin-sensitive *S. aureus* strains (MSSA), various streptococci and Enterococcus faecalis are the most frequent pathogens (Table 29). The microbiological results from the first infection may help in choosing the calculated treatment.
In early endocarditis after a valve replacement (<1 year after surgery), methicillin-resistant *S. aureus* strains (MRSA), coagulase-negative staphylococci and gram-negative bacteria are more frequently found as causative pathogens (Table 29).
Any empirical treatment should be modified as necessary when the results of pathogen identification and antibiotic susceptibility are available. Treatment regimens for endocarditis are listed in Table 30 for the most frequent pathogens. Further detailed treatment recommendations

Table 30: Overview of antibiotic regimens for infectious endocarditis with known pathogens

Microorganism	Antibiotic drug	Dosage regimen	Duration of therapy	Level of evidence	Level of recommendation
Staphylococcus spp. (methicillin-sensitive)[3]	Flucloxacillin	12 g/day in 4–6 doses	4–6 weeks IV	III	A
Staphylococcus spp. (methicillin-resistant)[3]	Vancomycin [1]	30 mg/kg/day in 2 doses	>6 weeks IV	III	A
	or daptomycin	At least 6 mg/kg/day**	6 weeks IV	Ib	A
Staphylococcus spp.[3] (prosthetic valve infection)	As above plus				
	rifampicin[4]	1200 mg/day in 2 doses	>6 weeks PO	IV	A
	and gentamicin[2]	3 mg/kg/day	2 weeks IV		
*Enterococcus faecalis**	Ampicillin	200 mg/kg/day in 3-4 doses	4–6 weeks IV	III	A
	plus gentamicin[2]	3 mg/kg/day	4–6 weeks IV		
Oral streptococci and group D streptococci (penicillin MIC <0.125 mg/l)	Penicillin G	20–30 MIU/day in 3-4 doses	4 weeks IV[5]	III	A
	or ampicillin	100 mg/kg/day in 3-4 doses	4 weeks IV[5]		
	or ceftriaxon	2 g/day in 1 dose	4 weeks IV[5]		
	If allergic to penicillin:				
	vancomycin[1]	30 mg/kg/day in 2 doses	4 weeks IV	IV	A
Oral streptococci and group D streptococci (penicillin MIC 0.125–2 mg/l)	Penicillin G	20–30 MIU/day in 3-4 doses	4 weeks IV	III	A
	or ampicillin	200 mg/kg/day in 3-4 doses	4 weeks IV		
	If allergic to penicillin:				
	vancomycin[1]	30 mg/kg/day in 2 doses	4 weeks IV	IV	A
	plus gentamicin[2]	3 mg/kg/day in 1 dose	2 weeks IV		

1 Monitoring of serum levels recommended. Trough level at least 15–20 mg/l.
2 Weekly monitoring of serum level and kidney function recommended.
3 A combination treatment with gentamicin is no longer recommended by the PEG expert committee because of the inadequate evidence of survival benefit and increased nephrotoxicity.
4 The clinical value of rifampicin is not strictly proven in this situation but its addition is still generally recommended because of its favorable penetration into biofilms.
5 Or 2 weeks using a combination with gentamicin 3 mg/kg/day in one dose. A higher dose is possibly more effective.
* Does not apply for *E. faecium*. Contact infectiologist or clinical microbiologist.
** The licensed dosage is 6 mg/kg body weight. Higher dosages are potentially more effective.

as well as advice on the management of complications, indications for surgical intervention and antibiotic therapy after surgery are given in the guidelines of the European Society for Cardiology [208].

Evaluation of recommendations for treatment of endocarditis with antibiotics given by the European Society for Cardiology (ESC) in 2009

Considerable changes appear in the newly revised European guidelines, particularly regarding the treatment of staphylococcal endocarditis. The additional treatment of native valve endocarditis with gentamicin is recommended only as an option of new data [113], [164], [400] show significantly increased nephrotoxicity and no survival advantage. In addition, the expert committee of the PEG sees insufficient evidence for recommending a combination therapy with gentamicin for native valve endocarditis caused by streptococci with penicillin MICs<0.125 mg/l. Gentamicin is usually administered once daily because kidney toxicity is reduced and efficacy increased by application of high doses in long intervals.

As increased efficacy is assumed, enterococcal endocarditis should be treated with a multiple-drug combination including an aminopenicillin. Increased efficacy is also assumed against frequently encountered strains with low-level resistance to gentamicin but not against those with high-level resistance [580].

When treating documented infections with methicillin-susceptible staphylococci, vancomycin should strictly be avoided in accordance with the ESC guidelines. Several studies showed that patients were less successfully treated with vancomycin than with a beta-lactam antibiotic [256], [501]. The beta-lactam antibiotics primarily recommended are still flucloxacillin, alternatively cefazolin or cefuroxim; a combination of aminopenicillin or ureidopenicillin plus beta-lactamase inhibitor (e.g. ampicillin/sulbactam) are not the drugs of choice for this indication.

When using potentially toxic agents such as vancomycin or gentamicin, monitoring of plasma levels and kidney function should be initiated. The revised ESC guidelines recommend a much higher therapeutic level for vancomycin than earlier guidelines (particularly for *S. aureus* endocarditis). The rationale is the prevalence of *S. aureus* strains with selectable subpopulations of bacteria showing

reduced susceptibility to vancomycin, so-called hVISA (heterogenous vancomycin-intermediate *S. aureus*) [21], [31], [351], [487]. However, it should be stressed that the recommendation of a higher trough plasma level is based on expert opinion. The vancomycin trough plasma level should be in the range of 15–20 mg/L for infectious endocarditis according to the PEG expert committee.
In the revised guidelines, daptomycin [174] at 6 mg/kg/day IV is also recommended as an alternative to vancomycin in the treatment of staphylococcal endocarditis if methicillin resistant pathogens are involved. Higher dosages, e.g. 9 mg/kg/day, may be more effective but are not licensed.
In the current revision of the European guidelines, amoxicillin and ampicillin are often recommended almost as synonyms. Amoxicillin in contrast to ampicillin is not available as a monosubstance for IV administration in Germany. When given in combination with clavulanic acid, the high dosage level of amoxicillin recommended for enterococci endocarditis cannot be reached due to possible hepatotoxicity of clavulanic acid [4]. Thus, ampicillin at the appropriate high dosage level remains the drug of choice. The revised European guidelines also open the possibility of an IM (intramuscular) administration of an antibiotic. This is not recommended in Germany. The treatment should be administered strictly intravenously and patients should be hospitalized during initial treatment.
An out-patient treatment may be considered after 2 weeks of treatment in hospital and only for restricively chosen patients with clearly defined indication. The reason for this recommendation is that complications frequently occur in the first two weeks after starting antibiotic treatment and close monitoring must therefore be recommended even in an apparently favourable course of disease [15].

Surgical treatment and postoperative care

In general a surgical treatment should be an integral part of the therapeutic concept and not as a fall-back approach after failure of the antibiotic therapy. Conversely, eradicating bacteria in vegetations is often unfeasible before surgery and attempts to do so should not lead to a delay of surgical intervention in cases with a clear indication for an operation (e.g. abscess formation, progressive heart failure). Oral follow-up therapy after intravenous treatment according to guideline recommendations does not appear appropriate. Blood cultures are not only useful for diagnosis but also for monitoring therapeutic success. Blood culture samples should again be collected 2–4 weeks after after the end of antimicrobial therapy, with high vigilance for the occurrence of fever in the meantime.

12 Bacterial meningitis

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Acute bacterial meningitis is characterized by the clinical key symptoms of fever, headache and meningeal irritation (meningism). In addition confusion, reduced vigilance or coma may define the clinical picture [69], [143], [418], [421]. Acute bacterial meningitis is differentiated from viral meningitis. Overall, the incidence of acute bacterial meningitis is 5 to 10 cases per 100,000 population per year [467]. The pathogen spectrum depends on age, the most common pathogens in adults being pneumococci and meningococci. Since the introduction of active vaccination against Haemophilus influenzae type b, the formerly dominant pathogen of bacterial meningitis in children is declining [143], [467]. Other less frequent pathogens of acute bacterial meningitis include *Listeria monocytogenes* and, in meningitis associated with CSF-drainage and prior surgery, staphylococci, enterobacteriaceae and *Pseudomonas* spp. Meningitis due to a spread from craniofacial infections is caused primarily by pneumococci and other streptococci. Other infectious diseases with septic manifestations may also lead to CNS manifestation, e.g. *Leptospira* or *Borrelia burgdorferi* infections. Subacute or chronic meningitis syndrome is caused primarily by mycobacteria, *Candida*, *Cryptococcus neoformans*, *Coccidioides immitis* and *Treponema pallidum*. In patients with severe immunosuppression, atypical and rather subacute forms of meningitis may occur.

Diagnostics

Blood culture sample must be collected from all patients. Depending on the localization of a coexisting infection, it is essential to take throat swabs, samples of bronchial secretions, urine samples or wound smears.
The diagnosis of bacterial meningitis is confirmed by lumbar puncture and examination of cerebrospinal fluid (CSF). A granulocytic pleocytosis above 1,000 cells/µl, CSF protein levels above 100 mg/dl, lactate above 3.5 mmol/l and a liquor-serum-glucose quotient below 0.3 are potential indicators of meningitis. Methylene blue test and gram stains of the CSF sediment may provide evidence of the type of pathogen (gram-negative rods or cocci, gram-positive rods or cocci).
Helpful supplementary diagnostics include antigen detection from the spinal fluid, serum and urine (e.g. [319]), PCR from CSF (particularly tuberculous meningitis and/or evidence or exclusion of viral CNS infection), CRP/PCT determination in serum and differential blood analysis. Evidence of pathogen-specific antibody synthesis by determination of the CSF/serum antibody index is very important in subacute meningitis and encephalitis, particularly in neuroborreliosis [425].
In patients without impairment of consciousness and without focal neurological deficits, CSF and blood samples

Table 31: Calculated antibiotic therapy for bacterial meningitis in adults [264], [406], [418], [421], [466]

Bacterial meningitis	Most frequent pathogen	Antibiotic treatment	Duration of treatment	Evidence level	Recommendation level
Community-acquired	Neisseria meningitidis Streptococcus pneumoniae Listeria monocytogenes Haemophilus influenzae type b	Cefotaxime 3x2 g or ceftriaxone 2x2 g + ampicillin 3x5 g	>7 days for N. meningitidis >10 days for other pathogens	Ib	A
Nosocomial (post-operative/shunt infection)	Enterobacteriaceae Pseudomonas aeruginosa Staphylococci	Vancomycin 2x1 g + meropenem 3x2 g or ceftazidime 3x2 g	>10 days	IV	B
Tuberculous meningitis	Mycobacterium tuberculosis	Isoniazid + rifampicin + pyrazinamide + ethambutol and/or streptomycin	1 year (months 4–12 for fully susceptible pathogen: isoniazide + rifampicin)	IV	A

should be collected before the immediate start of antibiotic therapy [219], [264]. Subsequent imaging (cranial CT or MRI) and examination in collaboration with an ENT specialist help to localize the source of infection in the CNS region (e.g. sinuses, mastoid) and to recognize early intracranial complications. In patients with impairment of consciousness or focal neurological deficits, CSF samples should not be taken before cerebral imaging. However, blood cultures, urine samples, throat swabs and/or bronchial secretions (for evidence of pneumococci and meningococci) should be collected before an immediate start of antibiotic therapy [264].

Treatment

A delay in antibiotic treatment initiation is strongly associated with poor prognosis [24], [27]. Due to the pathogen spectrum of community-acquired bacterial meningitis, calculated initial therapy should be started (Table 31) with a group 3a cephalosporin [406], [466] in combination with ampicillin (which is effective against *Listeria monocytogenes*). For nosocomial bacterial meningitis and infected CSF drainage devices, the empirical initial treatment should consist of vancomycin plus meropenem or vancomycin plus ceftazidim. If the pathogen can be identified, the treatment should be readjusted according to the results of the microbiological examination (Table 32). As a rule, any infected drainage device must be removed and replaced by an external device. The minimum duration of treatment for unknown pathogens, *H. influenzae* or *Streptococcus pneumoniae* should be at least 10 days, and 7 days for meningococci. The antibiotic treatment of patients with meningitis due to *Listeria*, *Staphylococcus aureus*, *Pseudomonas aeruginosa* or enterobacteriaceae should last for 3 weeks.

The success of the antimicrobial treatment, except in meningitis caused by meningococci, should preferably be aided by a control puncture at latest after 48 hours [293]. Fever or an increase in pleocytosis in sterile CSF should not prompt changes in treatment. A final lumbar puncture at or after the end of treatment is not necessary if no complications occurred.

For pathogens with reduced susceptibility to antibiotics, an intraventricular antibiotic treatment might be necessary to eliminate the pathogens from the CNS. In Germany, no antibiotics are currently licensed for intraventricular administration and there are no randomized clinical studies showing an improvement in treatment results by intraventricular administration. The intraventricular administration of antibiotics is an experimental treatment. Table 33 shows antibiotics with published experience where intraventricular administration would be rational because of low CSF penetration and high systemic toxicity. Therapeutic monitoring via determination of CSF drug concentrations is recommended [586].

Adjuvant therapy with dexamethasone [421], [460], [466] improves the prognosis in community-acquired bacterial meningitis in adults, primarily in pneumococcal meningitis. In countries with high standards of medical care (diagnostics and therapy), dexamethasone is recommended to reduce mortality and to avoid long-term damage, particularly hearing loss [119], [532]. A 10 mg dose of dexamethasone (adults) is given 20 minutes or immediately before or with the first administration of an antibiotic and then every 6 hours for 4 days. In countries with low standards of medical care, the adjuvant treatment with dexamethasone is not recommended [341], [456]. As there are no data available for patients with nosocomial meningitis or for immunosuppressed patients with bacterial meningitis, the adjuvant treatment with dexamethasone is not recommended in these groups. There is insufficient experience for adults with other adjuvant strategies which were effective in animal experiments.

It has been shown that adjuvant use of corticosteroids improves the treatment results, particularly in severe tuberculous menigitis [419], [519]. Depending on the neurological deficits, adults and adolescents receive dexamethasone for 4 or 8 weeks (stage 2 or 3) as follows: 0.4, 0.3, 0.2 and 0.1 mg/kg IV per day in weeks 1, 2, 3 and 4, respectively, followed by 4, 3, 2, and 1 mg per day

Table 32: Targeted antibiotic treatments for bacterial meningitis in adults (modified according to the guidelines of the German Society for Neurology [http://www.dgn.org])

Bacterial pathogen	Usually effective antibiotic regimens[1]
Neisseria meningitidis	Penicillin G, ceftriaxone (or cefotaxime), ampicillin, rifampicin[3]
Streptococcus pneumoniae, penicillin-susceptible	Penicillin G, ceftriaxone (or cefotaxime)
Streptococcus pneumoniae, penicillin-intermediate (MIC 0.1–1 mg/l)	Ceftriaxone (or cefotaxime), meropenem
Streptococcus pneumoniae, penicillin-resistant (MIC>1 mg/l)	Cefotaxime (or ceftriaxone) + vancomycin or cefotaxime (or ceftriaxone) + rifampicin[2]
Haemophilus influenzae	Ceftriaxone (or cefotaxime), ampicillin + chloramphenicol
Group B streptococci (*Streptococcus agalactiae*)	Penicillin G (+ gentamicin), ceftriaxone, ampicillin (+ gentamicin), vancomycin
Enterobacteriaceae (e.g. *Klebsiella spp., E. coli, Proteus spp.*)	Ceftriaxone (or cefotaxime), meropenem
Pseudomonas aeruginosa	Ceftazidime + aminoglycoside, meropenem + aminoglycoside, ciprofloxacin
Staphylococci (methicillin-susceptible)	Cefazoline (or flucloxacillin), fosfomycin[3] (in combination with cefazoline), rifampicin[3] (in combination with cefazoline)
Staphylococci (methicillin-resistant)	Vancomycin, linezolid[2,] Vancomycin in combination with fosfomycin[3] or rifampicin[3]
Listeria monocytogenes	Ampicillin + gentamicin, cotrimoxazole, meropenem
Mycobacterium tuberculosis	Start treatment with combination of four drugs: isoniazide + rifampicin + pyrazinamide + ethambutol Alternatives if resistance: streptomycin, protionamide, moxifloxacin, etc.

1 The choice of the antibiotic depends on the results of susceptibility testing.
2 Do not use as monotherapy because of rapid resistance development.
3 Linezolid has an efficacy spectrum similar to vancomycin and effectively penetrates the CNS. To date there are few reports on the use of linezolid in staphylococcal infections of the central nervous system [443].

Table 33: Intraventricular antibiotic therapy – adult doses according to [418], [586]; usually simultaneous systemic therapy is required

Antibiotic	Dose	Important side effects
Gentamicin	5 mg every 24 hours	(Temporary) hearing loss, epileptic seizures, aseptic meningitis, CSF eosinophilia
Tobramycin	5 mg every 24 hours	Similar to gentamicin
Amikacin	30 mg every 24 hours	Similar to gentamicin
Streptomycin	1 mg/kg every (24–) 48 hours	Hearing loss, epileptic seizures, radiculitis, transverse myelitis, arachnoiditis, paraplegia
Vancomycin	20 mg every 24 hours	Hearing loss
Colistin (colistin methane sulfonate sodium)	1st day 20,000 IU maintenance dose 20,000 (to 100,000 IU) Treat until CSF is sterile.	Meningeal irritation at high doses, epileptic seizures, loss of appetite, excitability, eosinophilia, edema, pain
Amphotericin B	0.1–0.5 mg every 24 hours	Tinnitus, fever, chills, Parkinson's disease

orally in weeks 5, 6, 7, and 8, respectively. Alternatively, prednisone may be started at 60 to 80 mg/day and tapered out over 4 to 6 weeks. To date, experience and studies also indicate a trend towards an improvement of results in children and immunosuppressed patients (HIV). However, the available data do not yet justify a general recommendation. Low-dose heparin is recommended for prophylaxis against thromboembolism and proton-pump inhibitors are used for gastric protection.

Prophylaxis

The most frequent pathogen causing meningitis after splenectomy is *S. pneumoniae*, followed by other encapsulated bacteria. Therefore, active vaccination against pneumococci, *H. influenzae* type b and meningococci should be provided before splenectomy (in patients with emergency surgery after the operation). With regard to other indications for vaccination against *Haemophilus*, pneumococci and meningococci, refer to the homepage

of the Permanent Commission on Vaccination of the Robert Koch Institute (http://www.rki.de/nn_199596/DE/Content/Infekt/Impfen/impfen.html). Based on current resistance data, people in close contact to patients with meningococcal meningitis acquired in Germany should receive an antimicrobial prophylactic treatment. The prophylaxis can be administered up to ten days after the last contact with the patient. Recommended antibiotics are ciprofloxacin, rifampicin or ceftriaxone (http://www.meningococcus.uni-wuerzburg.de/startseite/berichte/daten_2008) [177]. Adults (except when pregnant) receive ciprofloxacin (a single dose of 500–750 mg orally) or alternatively rifampicin 600 mg every 12 hours for 2 days. Pregnant women receive ceftriaxone (a single dose of 250 mg IM). Children receive rifampicin (10 mg/kg body weight every 12 hours for 2 days orally). Rapid development of resistance to rifampicin (even in prophylactic treatment) has been reported [177]. Resistance to ciprofloxacin appears to increase in *N. meningitidis* isolated from patients from Southern and Western Europe and Southeast Asia [5], [480], [482]. If there is at least one unvaccinated child or a person with a relevant immunodeficiency among a group of people around a close contact to a patient with *H. influenzae* meningitis, they should receive antimicrobial prophylaxis up to 7 days after the last contact to the patient (https://www.rki.de/DE/Content/Infekt/EpidBull/Archiv/2002/Ausgabenlinks/30_02.pdf?__blob=publicationFile): adults (unless pregnant) receive rifampicin 600 g every 24 hours for 4 days orally; infants and children receive rifampicin 10 and 20 mg/kg body weight, respectively, every 24 hours for 4 days orally.

Addendum

In a recently published meta-analysis, the efficacy of adjuvant dexamethasone in bacterial meningitis was not confirmed [533].

13 Eye infections

Wolfgang Behrens-Baumann, Hermann O. C. Gümbel, Michael Kresken

Infections in ophthalmology affect the eyelids, orbita, conjunctiva, cornea, and the interior of the eyeball, as endophthalmitis, or more specifically retinitis or chorioiditis. *Infections of the surface of the eye* are best treated with topical antiinfectives for pharmacokinetic reasons. However, in cases of conjunctivitis caused by *Chlamydia* spp. and *Haemophilus* spp. it is often preferable to use a systemic antibiotic in addition to the topical therapy as these pathogens also colonize the urogenital tract and the nose and throat region [48].

Endophthalmitis is an inflammatory reaction to an intraocular infection by bacteria, fungi or (rarely) parasites. Inoculation occurs exogenously (postoperative, posttraumatic, spread from neighbouring tissues) or endogenously (bacteremia). The PEG recommendations follow the guidelines of the German-speaking Society for Intraocular Lens Implantation and Refractive Surgery [51], which formed the basis of the guidelines on prevention, investigation and management of postoperative endophthalmitis of the European Society of Cataract and Refractive Surgeons (ESCRS) [39].

The spectrum of pathogens encountered in eye infections is broad (Table 34). Therefore, a *diagnostic pars plana vitrectomy* (ppV) is recommended [39]. This can be performed simultaneously to the injection of an intravitreal antibiotic. This mode of application yields the highest drug concentration directly at the site of infection and is therefore indispensable. However, sufficient concentrations of the active substance are maintained for a limited period of time only. While injection of antibiotics may be successful per se [402], it is often combined with a ppV.

A dose of 1 mg/0.1 ml of vancomycin is recommended for infections caused by gram-positive pathogens [317]. This dosage results in concentrations above the MIC_{90} of *Staphylococcus epidermidis* for >48 hours [210]. Using 0.2 mg/0.1 ml vancomycin, therapeutically useful levels are maintained for about 3 to 4 days [181]. With regard to Gram-negative pathogens, it is increasingly recommended not to use aminoglycosides (due to their comparatively narrow antibacterial spectrum and the risk of retinotoxicity) [180], [237] but instead prefer 2 mg/0.1 ml of ceftazidime [97], [180], [237].

Although the Early Vitrectomy Study (EVS) [158] apparently indicates that systemic antibiotic treatment is unnecessary, it should nevertheless be performed. EVS tested the efficacy of intravenous ceftazidime plus amikacin for 5 to 10 days but no antibiotic with higher activity against gram-positive pathogens, e.g. vancomycin, was included. However, 38% of eyes with a final visual acuity of <5/200 were infected with Gram-positive bacteria. It is widely known that ceftazidime is less effective against Gram-positive bacteria than vancomycin [104], and amikacin does not penetrate into infected rabbit eyes [157]. All in all, based on the study design, the EVS cannot answer the question whether intravenous antibiotic treatment is useful [142], [498]. In fact, answering this question was not intended in the study, as its name already indicates (see [158]). Therefore Sternberg and Martin state: “intravenous antibiotic therapy is considered the standard of care” [498].

The main rationale of using additional systemic antibiotics is that sufficiently high levels of active drug are maintained for only a limited period of time after intravitreal injection. Since the clearance of antibiotics in the human vitreous has not been systematically investigated, systemic administration makes sense. Alternatively, intravitreal injection may be given every one to three days, according to animal studies [136].

In parallel to the intravitreal treatment, the same antibiotic could be administered intravenously, corresponding to level III of the Magdeburg Three Level Plan [49], [50] (Table 35). This treatment scheme for infections with

Table 34: Pathogen spectrum of eye infections

Postoperative endophthalmitis (e.g. after cataract surgery) [1], [137], [213], [338], [577]	
33%–77%	Coagulase-negative staphylococci
10%–21%	Staphyloccus aureus
9%–19%	Streptococcus spp.
6%–22%	Gramnegative bacteria
Up to 8%	Fungi
Delayed postoperative (cataract surgery with IOL implantation) endophthalmitis	
Often	Propionibacterium acnes or fungi
Postoperative (glaucoma surgery) endophthalmitis [387], [420]	
Up to 67%	Coagulase-negative staphylococci
Delayed postoperative (glaucoma surgery) endophthalmitis [108], [201]	
Often	Streptococcus spp.
Often	Gram-negative bacteria (primarily Haemophilus influenzae)
Postoperative endophthalmitis (pathogen determined 62%–65%, mixed infection 12%–42%) [80], [277], [464], [517]	
16%–44%	Coagulase-negative staphylococci
17%–32%	Bacillus spp.
10.5%–18%	Gram-negative bacteria
8%–21%	Streptococcus spp.
4%–14%	Fungi
4%–8%	Corynebacterium spp.
Endogenous endophthalmitis [28], [338], [383], [578]	
24%–60%	Fungi: 33%–100% Candida albicans, up to 66% Aspergillus spp.
4.5%–30%	Streptococcus spp.
4.5%–20%	Gram-negative bacteria
Up to 28%	Staphyloccus aureus
Up to 25%	Propionibacterium acnes
Up to 8%	Bacillus spp.
Up to 8%	Klebsiella spp. (in Asia up to 75%)
IOL: Intraocular lens	

unknown pathogens, has become an established standard in the German-speaking countries and is regularly updated [50]. If there are contraindications to the drugs listed in level III, antibiotics from level II may be used. The antibiotics of levels II and III should always be given intravenously because of better pharmacokinetics and tolerability. Using high dosages is also recommended to overcome potential low-level resistance mediated by efflux pumps [471]. Due to the resistance situation in nosocomial infections, the fluoroquinolones are not used in the primary therapy of unknown pathogens (see chapter 2). If there is evidence of vancomycin-resistant enterococci (VRE), methicillin-resistant staphylococcus aureus (MRSA) or methicillin-resistant staphylococcus epidermidis (MRSE), daptomycin is available as a back-up alternative antibiotic [22], [395]. Ceftobiprole is a new treatment option, which albeit is available in Switzerland only [242], [380]. (Note added in the translated version: ceftobiprole had been introduced in Canada and Switzerland. Currently (November 2013), the drug is no longer available worldwide.) If the anterior eye chamber is involved in endophthalmitis, the use of group 3 and 4 fluoroquinolones (levofloxacin or moxifloxacin) eye drops every 30–60 minutes appear useful [52].

Glucocorticoids. Endophthalmitis is often characterized by invasion of leukocytes and monocytes from the peripheral blood mainly into the vitreous. These cells secrete proteases, cations and cytokines stimulating strong exsudation and infiltration, leading to “immune-associated damage” [245], [417]. This damage continues even after the pathogen has been eradicated. Glucocorticoids have cytoprotective effects including the inhibition of phospholipase activity, cytokine expression and monocyte adhesion. Therefore, steroids should be used in endopthalmitis (e.g. prednisone 200 mg/70 kg body weight). Dexamethasone (0.4 mg in 0.1 ml) is commonly injected intravitreally during the initial treatment.

Late endophthalmitis (after >2 weeks to several years) after a cataract operation is often caused by *Propionibacterium acnes*, less frequently by a fungus. The pathogens are usually localized within the intraocular lens (IOL) inside the cicatrized capsular sack. Thus, diagnostic and therapeutic access is difficult. A treatment attempt with systemic clarithromycin can be successful [384] and ap-

Table 35: Magdeburg three-level plan for systemic antibiotic treatment according to Prof. Behrens-Baumann (1991/2001), for infections with unknown pathogen [49, 50]

Level I		
Antibiotic	Cefuroxime	Cefuroxime axetil
Daily dose	3x1500 mg IV	2x500 mg oral
Level II		
Antibiotic	Imipenem/cilastatin	+ ciprofloxacin
Daily dose	3x1 g IV	3x400 mg IV
Antibiotic	Clindamycin	+ ciprofloxacin
Daily dose	3x600 mg p.o.	2x750 mg p.o.
Level III		
Antibiotic	Vancomycin	+ ceftazidime
Daily dose	2x15 mg/kg body weight IV	3x2 g IV
Antibiotic	If resistant pathogen: daptomycin	
Daily dose	6 mg/kg body weight IV	
The duration of the treatment depends on the individual situation (usually 7–14 days) ***Indication*** Level I Non-threatening infection, no suspected involvement of *Pseudomonas* (not for endophthalmitis) Level II Threatening, severe infection (as an alternative to level III, if contraindiactions against the drugs used in level III) Level III Maximum therapy (e.g. for endophthalmitis) These recommendations are valid for calculated therapy, i.e. infections with unknown pathogens. Targeted regimens should be used if the pathogen has been identified.		

pears rational as the initial, less invasive measure. A dose of 2x500 mg per day is recommended. If the condition recurs, a ppV with opening of the posterior lens capsule is recommended [127]. Although flushing the capsule with vancomycin solution can be successful [6], [241], [462], many cases require surgical removal of the IOL and the capsular sack [6], [105].

The incidence of *traumatic endophthalmitis* (TE) is in the range of 5–14% [3], [429]. The symptoms of TE are the same as those observed in postoperative endophthalmitis. Immediate tissue sampling (vitreous) is required and samples sent for microbiological examination in the case of an open eyeball injury. In doing so, the microbiological-infectiological quality standards on microbiological diagnostics in eye infections must be observed [569].

Open eyeball traumas are associated with a particularly high risk of traumatic endophthalmitis. Therefore, antiseptic treatment and antibiotic prophylaxis – both topically and systemically – is clearly required, as periorbital structures (tear ducts, sinuses, etc.) which are not reached by antibiotic drops and creams are often affected by the trauma [46].

Based on a study carried out by Narang et al. in 70 patients with open eye injuries, the intravitreal administration of 1 mg/0.1 ml of vancomycin plus 2.25 mg of ceftazidime appears to be reasonable [360]. An international randomized study is currently investigating the role of these intravitreal injections as adjuvant treatment added to the systemic administration of intravenous moxifloxacin in low-risk (e.g. metal foreign objects) and high-risk (e.g. injuries in the agricultural industry, organic foreign material) patients [539].

The antibiotic treatment of acute traumatic endophthalmitis after primary wound closure follows level III of the Magdeburg three-level plan,

Endogenous endophthalmitis should be treated with targeted systemic antibiotic therapy (according to the result of blood culture diagnostics) in order to control the source of infection and bacteremia.

14 Antibiotic therapy in elderly patients

Peter Walger

Even if chronological age is of limited value to describe the probability of health problems, multimorbidity, the need for care and rates of dementia increase significantly beyond the age of 80 to 85 years. In general, the elderly or seniors are defined as people in the age of at least 65 years, while the aged or very old people are those of 85 years and beyond. While aging and illness are two separate phenomena, age-related health deterioration and age-correlated diseases are mutually interacting processes. Diseases with long latency, illnesses manifest-

ing after decades of exposure to various risk factors, or chronic diseases aging with their carriers shape the medical implications of age as much as acute illnesses which are more frequent, have divergent symptoms and are more hazardous in old age.

Biological-physiological, medical and psychosocial parameters change with increasing age. Impaired immune function, reduced mobility, malnutrition, exsiccosis, and multiple chronic comorbidities commonly result in polypharmacotherapy with a high risk of drug interactions and increasing non-adherence.

Both the morbidity and the mortality of numerous infectious diseases increase with advancing age. Community-acquired pneumonia (CAP) is the most frequent infection-related cause of death in patients beyond 65 years of age. The incidences of many other infections such as urinary tract infections, sepsis, skin and soft tissue infections, bacterial endocarditis, cholecystitis and diverticulitis are elevated as well. Atypical clinical manifestations, e.g. reduced fever reaction, unspecific general symptoms or early impairment of brain functions impede the diagnosis leading to delays of adequate therapy [68], [196], [326].

Frequent side effects of antibiotics in the elderly

More than 30% of people >70 years of age have at least five chronic diseases [326], [342]. Extensive use of prescription and over-the-counter drugs as well as plant-based medicines is common in elderly people. In the USA, 25% of women in the age group of >65 years take 5 prescription drugs, 12% take at least 10.

Data for Germany are similar. People in the age group of >70 years take on average 3 different medicines per day. The 80–85-year-old individuals receive the highest number of drugs on a daily basis; 35% of the >70-year-old people take 5–8 and 15% take >13 different medications [195]. Polypharmacotherapy increases with age. Additionally, herbal medications or nutritional supplements are taken by 14% (1998) [250] or 26–27% (2002) [253], [359], respectively. According to treatment guidelines (USA 2005), a ficticious 79-year-old patient with five of the most common comorbidities (COPD, Type 2 diabetes mellitus, hypertension, osteoporosis, and osteoarthritis) receives 12 medications daily in a complicated regimen, with unpredictable interactions of diseases and/or medications, and with numerous adverse drug effects [76].

In general, side effects of medications are up to three times more prevalent in the elderly than in younger adulty around the age of 30 years [537]. Taking up to 5 medications entails a risk of adverse drug reactions (ADRs) in the range of 4%, 6–10 medications are associated with an ADR risk of 10%, and taking 11–15 medications increases the ADR risk to 28% [362]. Overall, ADRs occur in 15–35% of elderly patients. Adverse drug reactions cause 20–25% of geriatric hospital admissions. Anticoagulants, non-steroidal anti-inflammatory drugs (NSAIDs), antidiabetics, diuretics and digitalis glycosides are the drugs most commonly associated with ADRs leading to hospitalization [518]. Interactions play a role in approximately 40% of the ADRs. Low body weight in particular is frequently associated with ADRs. More than 80% of hospitalizations associated with ADRs are avoidable [53], [416].

Prevalence of inappropriate drug prescriptions

Data from the USA, Canada and Europe indicate a high rate of inappropriate use of medications in elderly patients; e.g. in the US the rate was 23.5% in 1994, 20% in 1996 (3% of these drugs were on the Beers list of 11 “always avoid” medications with increased risk of hospitalization and death), an 19% in 2002; in Europe approximately 20% in 2005. The typical patient receiving polypharmacotherapy with a high rate of inappropriate medications is a >85-year-old female, who lives alone, has a low health and social status [439], [583].

The Beers Criteria [44] provide a list of inappropriate medications categorized in three groups: “always avoid” (11 drugs), “rarely appropriate” (8 drugs) and “some indication but often misused” (14 drugs). Based on the criteria, a number of revised PIM lists (PIM= potencially inappropriate medications) were published in the USA, France, the Netherlands and Canada [43], [170], [290], [330]. The risk of adverse drug reactions leading to the hospitalization of elderly patients is strongly increased if several drugs are taken concomitantly (high risk of interactions). Polypharmacotherapy and prescription of neuroleptics or anti-dementia drugs are significant risk factors for ADRs in people living in retirement homes [215]. A list adapted to the situation in Germany „Potentially inadequate medications for elderly people“ is being prepared in cooperation with the Drug Commission of the German Medical Association [231].

The treatment of elderly patients with bacterial infections therefore typically means adding an antibiotic – with its own side effects and interaction potential – to a long list of various medications with partially unclear interaction potential and diverse side effects.

Prescribing antibiotics for the elderly

The available classes of antibiotics (or individual drugs) have been assessed according to specific aspects and risks:

1. Risk of selection for *Clostridium difficile*
   Hazardous antibiotics: cephalosporins, fluoroquinolones, ampicillin, amoxicillin, clindamycin.
2. Neuropsychiatric side effects (encephalopathy, seizures, ototoxicity) and interactions with psychopharmacons
   Hazardous antibiotics: fluoroquinolones, metronidazole, carbapenems (particularly imipenem), high-dose penicillins (particularly penicillin G), cephalosporins (particularly cefazolin), linezolid (serotonin

syndrome), sulfamethoxazole, clarithromycin (psychoses), gentamycin, tobramycin, streptomycin, isoniazide. The neurotoxicity of aminoglycosides is actually a cochlear and vestibular toxicity, more rarely a neuromuscular blockade. The ototoxicity is enhanced by comedication with loop diuretics and vancomycin but also by loud ambient noise. Age is an important risk factor per se. For QT prolongation, see point 4).

3. Interactions with other important drugs
   Potentially hazardous antibiotics
   – Anticoagulant therapy with phenprocoumon: cephalosporins, amoxicillin/clavulanic acid, cotrimoxazole, clarithromycin; ADR: increased INR
   – Lipid reduction with CSE inhibitors (statins): macrolides (CYP-3A4 inhibition); ADR: rhabdomyolysis
   – Antihypertensive therapy with calcium antagonists (dihydropyridines): macrolides (CYP-3A4 inhibitors); ADRs: hypotension, reflex tachycardia
   – Bronchodilator therapy with theophyllin or caffeine: fluoroquinolones (CYP-1A2 inhibition); ADR: increased CNS stimulation
   – Diuretic therapy with loop diuretics, anti-inflammatory treatment with NSAIDs, therapy with cisplatin or amphotericin B: enhaced nephrotoxicity of aminoglycosides, glycopeptides and beta-lactam antibiotics, enhanced ototoxicity of aminoglycosides and erythromycin
   – Enzyme induction of hepatic CYP450 isoenzymes by rifampicin leads to decreased efficacy of calcium channel blockers, theophyllin, phenoprocoumon, contraceptives and phenytoin
   – Erythromycin and clarithromycin inhibit the hepatic CYP3A system, potentially causing hazardous enhancement of toxicity of various drugs by inhibition of hepatic drug metabolism. This particularly affects many psychotropic drugs such as risperidon, clozapin and clomipramin; antiepileptics such as phenytoin, carpamazepin and valproic acid, as well as simvastatin and other statins, theophyllin, warfarin and some anti-HIV drugs. Azithromycin has the smallest interaction potential among the macrolides.
4. QT prolongation
   Potentially hazardous antibiotics: fluoroquinolones, macrolides and metronidazole, particularly in polypharmacotherapy in combination with beta-blockers, antiarrhythmic drugs, psychotropic drugs and phenytoin
5. Nephrotoxicity
   Potentially hazardous antibiotics: aminoglycosides, glycopeptides, cotrimoxazole, and nitrofurantoin. All beta-lactam antibiotics, particularly penicillins and cephalosporins, may cause interstitial nephritis in <1% of patients. Dosage levels of most antibiotics must be adjusted to impaired renal function; among the fluoroquinolones, ofloxacin/levofloxacin need dose-adjustements at a creatinine clearance of <50 ml/min, and ciprofloxacin at <30 ml/min
6. Ototoxicity
   Potentially hazardous antibiotics: aminoglycosides, erythromycin, less frequently clarithromycin (transient hearing loss due to high dosage or use in patients with renal impairment)
7. Hepatotoxicity
   Potentially hazardous antibiotics: rifampicin, combinations with clavulanic acid, isoxazolyl penicillins, erythromycin. In 1% to 10% of patients, fluoroquinolones cause a small increase in transaminases, which in most cases does not require treatment discontinuation or dose reduction. Due of a few severe, sometimes lethal hepatic complications, oral moxifloxacin was downgraded in 2008 to a reserve status after failure of other antibiotics in non-life-threatening infections such as bronchitis, sinusitis or community-acquired pneumonia. Therefore, monitoring liver enzyme levels is essential in patiens receiving fluoroquinolones. For some antibiotics, dose adjustments are only required in patients with severe liver dysfunction, these include macrolides, clindamycin, ciprofloxacin, minocyclin, metronidazole, linezolid, and tigecycline
8. Drug rash, allergic reactions, hypersensitivity
   50% of all allergic skin reactions to medications in hospitalized patients are caused by beta-lactam antibiotics. Depending on the time of appearance, these are divided into immediate (0–1 hour), delayed (1–72 hours) and late (>72 hours) [297]. The classification of Gell and Coombs [189] differentiates four immunopathological reactions: type I is mediated by IgE (anaphylaxis), type II is mediated by IgG or IgM (cytotoxic, cytolytic), type III is mediated by soluble immune complexes (immune-complex disease) and type IV is mediated by T-lymphocytes (delayed or T-cell-dependent hypersensitivity). In addition, there are other “idiopathic” types with unknown pathogenesis (e.g. maculopapular rash, Stevens-Johnson syndrome, and exfoliative dermatitis) [414].
9. Malnutrition, nutritional deficiency and exsiccosis
   Dose adustments according to renal function and physiological parameters
10. Multiresistance induction or selection (collateral damage)
    Hazardous antibotics if overused: cephalosporins, fluoroquinolones, carbapenems
11. Rare side effects associated including those with high risk of morbidity
    Hazardous antibiotics: fluoroquinolones (Achilles tendon rupture), linezolid (serotonin syndrome) if concomitant use of selective serotinin reuptake inhibitors (SSRI), monoamine oxidase inhibitors (MAOI), specific antidepressants, valproic acid, tryptophan, lithium salts, ritonavir [497].

Evaluation of kidney function in the elderly

The average renal blood flow decreases by about 10% per decade of age from 600 ml/min per 1.73 m^2 in the fourth decade to about 300 ml/min per 1.73 m^2 in the ninth decade. Accordingly, the glomerular filtration rate as well decreases by about 10% per decade. However, as the production of creatinine decreases with progressive loss of muscle mass with age, the serum creatinin level remains constant. Therefore creatinine levels in the upper normal range already indicate a reduced renal function. Increase in creatinin should be a critical factor when choosing the dosage of antibiotics. Many laboratories report the glomerular filtration rate based on the MDRD formula (MDRD= Modification of Diet in Renal Disease Study). However, this formula was not validated for people over 70 years of age in the MDRD study. The calculation of GFR by the Cockcroft-Gault formula also has significant limitations regarding higher age and large variations in body weight. In comparative studies, the most reliable GFR estimates were obtained by 24-hour collection of urine, even though there was a trend towards false high values. However, in practice, collection errors severely limit the utility of the method. Another alternative is the determination of cystatin C, which is independent of age and muscle mass. This method appears to be most reliable for incipient renal dysfunction without a detectable increase of creatinin levels. As all available methods of renal monitoring have significant limitations in elderly people, a potential overestimation of glomerular filtration rate should be compensated for by a restrictive use of potentially nephrotoxic substances [573].

Antibiotic resistance in the elderly

All risk factors promoting the colonization or infection by multiresistant pathogens become more prominent with age. Multimorbidity and specific comorbidities such as diabetes mellitus or COPD, prior antibiotic therapy, previous hospitalizations, care in nursing homes, rehabilitation facilities and other tertiary healthcare structures, presence of invasive devices, e.g. gastric feeding tubes, central intravenous catheters, tracheal cannula and urinary catheters. Other nosocomial risks such as dialysis, treatment of chronic ulcers and other long-term care requirements and pre-existing colonizations also accumulate with increasing age. The risk of multiresistance represents a major challenge in the selection of an adequate antimicrobial regimen, i.e. the choice of a broad-spectrum antibiotic or appropriate combinations. Any inappropriate treatment carries the risk of prolonged hospitalization, increased costs and, ultimately, increased hospital mortality [70], [263].

Summary

In principle, antibiotics can be used in the elderly following the same principles as in younger adults. No antibiotic must be generally regarded as inappropriate for older people.
However, the choice and the dosing of antibiotics must be adapted to the general medical problems and physiological changes of old age. At the same time the increased risk of resistant and multiresistant pathogens in the context of multiple hospitalizations and previous antibiotic therapies has become increasingly important during the last few years.
Because of the higher frequency and potentially serious consequences of antibiotic side effects in the elderly versus younger adults, the following measures are essential for treatment optimization: restrictive indication; choice of the optimal antibiotic, with respect to rare but harzardous side effects, choice of dosage, dosing interval and duration of treatment appropriate for the physiological status of the patient; and monitoring of efficacy and toxicity aiming at the early detection of expected and unexpected side effects. Any recommendations must reflect the special requirements of antibiotic therapy in elderly patients.

15 Pharmacoeconomics

Eva Susanne Dietrich, Egid Strehl, Katja de With, Wolfgang Kämmerer, Michael Wilke

The total expenditures of the German statutory health insurances in 2008 were €160 billion. Of that amount, €29 billion (18%) was paid for drugs used in out-patients and about €3 billion was for drugs used in hospitalized patients.
The price disparity between generics, established products and newly licensed medications is becoming ever larger while the evidence for patient-relevant use is heterogeneous.
In order to allocate the available financial ressources with the maximum possible effect on quality of care, avoid hidden rationing, and keep the available ressources and expeditures in balance, the decision-makers on the level of healthcare suppliers, insurance companies and administrations are increasingly looking for rationalization possibilites.
Important instruments are benefit and cost-benefit analyses of treatments and workflows, budget and health-impact analysis, as well as process optimization.
While treatment guidelines are based mainly on these aspects, doctors, lawyers and scientists are still debating whether or not economic evaluations of individual medications should be included in guidelines. Therefore the following recommendations do not focus on individual medications but rather on general measures to optimize treatments and processes.

Implementation of recommendations

Besides improving care and the compliance, guideline-based prescription may help to reduce the total cost of therapy and increase cost-effectiveness. This is particularly true in hospitals where numerous studies have produced evidence in favor of this approach (e.g. [133], [332]). In the office-based sector, there is considerable evidence of additional costs [131]. In many cases, extra costs are induced through increased treatment quotas (by lowering the intervention threshold), higher dosages, and better compliance of patients with chronic diseases. Cost savings may stem from avoidance of polypharmacotherapy and from adequate treatment duration in acute diseases.

Calculated antibiotic therapy

Microbiological diagnostics

Compared to the total cost of treatment in a hospital, the cost of microbiological diagnostics is small. Therefore a reduction in microbiological investigations should not be a primary target for cost-saving efforts, particularly in hospitals. For example, a rapid antibiotic susceptibility test may help to significantly reduce the costs of antibiotics as well as entire treatment costs while reducing mortality through early adjustment of antimicrobial therapy according to the test results [135]. In studies, 8–20% of patients with sepsis did not receive appropriate antibiotic therapy, even though the culture results including an antibiogram were fully available [75], [107]. Active communication of blood culture results with meaningful interpretation of the antibiogram by microbiologists or infectious disease specialists may improve the prescribing quality of antimicrobial treatment and thereby reduce costs and length of hospitalization [75], [94], [172].

Step-down therapy

Effective oral antibiotics enhance the opportunity to switch patients from parenteral to oral treatment (step-down therapy) even in hospitalized patients and enable continuation of treatment as an oral follow-up out-patient treatment after discharge. In principle the oral follow-up antibiotic is not necessarily identical to the parenteral drug or even from the same substance group. The choice rather depends on the indication and the expected pathogen spectrum. High bioavailability of the oral drug is particularly advantageous.
Compared to the oral only treatment, the step-down therapy has the advantage of rapidly reaching high drug levels by initial IV administration. Depending on the clinical course of infection, the treatment may already be changed to a less expensive oral follow-up therapy after 1 to 3 days.
Numerous clinical and economic studies have shown that a step-down therapy and fully intraveneous therapy are equivalent in many indications, while the step-down approach is significantly more economical (e.g. [206], [333], [355], [392], [547]).
An early switch to oral therapy effectively shortens the length of hospitalization [234], [329], [430]. This is very important given the current paradigm of hospital financing of lump payments according to diagnosis-related groups (DRG) in Germany and other countries.
Other reasons for the economical advantage of step-down therapy versus fully parenteral administration include:

- lower antibiotic costs
- lower staff costs for preparation and administration
- earlier mobilization of patients and shorter hospitalization
- fewer complications by intravenous injections application.

In cases with pharmacokinetically equivalent formulations and adequate absorption, the oral application should be preferred over parenteral use. If an oral therapy is prescribed, equivalent drugs with longer half-life are preferred because of the better compliance.
Switching to an oral administration requires the following:

- reduction of infection parameters, particularly fever for 24–48 hours, CRP, leukocytosis with leftward shift
- reduction in clinical signs, e.g. reduction in coughing, sputum production and thoracic pain in respiratory infections
- significant improvement of general health condition
- appropriate oral treatment available
- abiity to swallow and tolerate oral medication
- no impairment of intestinal absorption.

De-escalation

Besides step-down therapy, de-escalation may contribute to the optimization of the clinical-economical balance. The principle of this treatment strategy is the initial calculated use of a highly effective broad-spectrum antibiotic followed by an equally effective but more targeted therapy with a narrower spectrum after availability of microbiological findings. De-escalation should minimize the selection pressure with respect to multiresistant bacteria (e.g. *Klebsiella* spp. with extended-spectrum beta-lactamases (ESBL), *Stenotrophomonas maltophilia*, *Bacteroides* spp. producing metallo-beta-lactamases) or fungi [440].
Reducing the spectrum of therapy is usually associated with a reduction of cost. Prerequisites for de-escalation include:

- availability of specific microbiological results,
- clinical improvement (see above).

There is good evidence for the equivalence of a de-escalation treatment and other treatment concepts (e.g. [145], [476]).

Monotherapy

As studies on various indications have shown, monotherapies with modern substances are as effective as com-

bination therapies which often result from polypragmatism (e.g. [138], [408]). Monotherapies have the following advantages:

- fewer side effects
- exclusion of potential antagonism between antiinfectives
- fewer pharmacokinetic interactions
- lower drug and subsequent costs.

Once-daily dosage

Antibiotics with a long biological half-life (4 to 6 hours) and a long-lasting postantibiotic effect enable once-daily dosage, potentially saving costs for staff and materials. In addition, side effect rates could be lower.

Antibiotic cycling and diversity

Increased use of antibiotics may cause increased selection pressure resulting in the development of resistance which in turn leads to increased costs. Cycling strategies try to minimize the selection pressure thereby reducing or preventing the development of resistance by transient removal and re-introduction of a given antimicrobial drug or class. Studies testing cycling strategies are difficult to implement. Due to the complexity of study protocols and the related difficulty of consistant implementation, only one substance or antibiotic class is switched by schedule. The mathematical results of published studies on the effects of cycling strategies on costs or use of drug as well as mortality, duration of hospitalization and resistance rates are scantly meaningful or poorly reliable for the above reasons. Consequently, it remains unclear whether this treatment concept is able to favorably influence resistance development and subsequent costs. In addition, models on the minimization of resistance development show that cycling strategies are probably less effective than antibiotic diversity, i.e. the simultaneous use of different antimicrobials in terms of heterogeneous prescribing on the same ward.

Therapeutic drug monitoring (TDM)

Therapeutic drug monitoring may have various goals:

- establish a rational basis for a formerly empirical dosage [527]
- identify reasons for failure of a rational therapy in a specific case
- avoid severe and/or persistent side effects (with respect to morbidity/mortality) of drugs with a narrow therapeutic range
- avoid unnecessary drug expenses and other follow-up and incidental costs within the DRG reimbursement system by determining the optimal dose and treatment duration for expensive drugs (e.g. parenteral antifungals) thus saving additional cost of underdosing, overdosing (in this case mostly harmless) or unnecessarily long duration of treatment [397].

Drug monitoring should absolutely be cost-effective. That means that any savings derived from the reduction of drug consumption and the reduction of side effects and their treatment must be greater than the total cost of equipment, substances and staff time used in drug monitoring [524].
The following aspects should be kept in mind when considering TDM:

- What percentage of patients remain free of side effects with a suitable TDM?
- What percentage of samples for a TDM are taken at exactly the optimal time?
- In what percentage of patients can the serum concentration level be adjusted and maintained at a predefined therapeutic target range by means of TDM?

There is high-level evidence that TDM is cost-effective even in treatments with the relatively low-priced aminoglycoside antibiotics [534].
With a lower level of evidence, it has also been shown that a TDM of vancomycin is cost-effective by reducing the nephrotoxicity e.g. for patients in intensive care or with malignant diseases or those simultaneously taking potentially nephrotoxic medications [117].
Prolonged infusion instead of bolus administration or short infusion of meropenem and other carbapenems may be more costeffective and advantageous in achieving adequate penetration in the respiratory tract as necessary, for example, in cystic fibrosis patients. Here a TDM will result in both economic and therapeutic benefits [527].

Optimization of procedures and costs

An important instrument in the optimization of procedures and costs is the establishment of clinical treatment protocols and/or of standard operating procedures (SOP). As part of the treatment protocol, standards of medication use must be developed, established and evaluated. Because of their impact on cost but also on the quality and success of patient care, antiinfectives are a very important drug group to be considered in treatment standards and SOPs.
An important criterion for the choice of appropriate antiinfectives for the treatment protocol/procedure is an economic-pharmacoeconomic analysis of treatment alternatives from the hospital perspective. This analysis should include an examination of the procedure costs of an antiinfective treatment from purchase to application in the patient. Another important question is to what degree the administered antiinfective fulfills the aspects of quality management and assurance, procedure management, patient orientation and staff orientation. Besides the purchase price of relevant alternatives, the following parameters must be included in the procedure analysis:

- Staff time and expenditure per administration, as a reduction in dosing frequency is favorable under DRG conditions (higher performance, less staff time). The key parameter is the staff cost per administration

Table 36: Influence of antibiotic treatments on the total cost of therapy

Influence factor	Consequence
Less effective and/or less well tolerated antibiotic	Reduction in treatment cost per day Dramatic increase in total cost of therapy
Higher efficacy	Shorter duration of therapy Less hospitalization Earlier transfer from ICU to general ward Earlier discharge from hospital
Good tolerability	Less side effects/comorbidity Less drug monitoring
Short term therapy Oral therapy Step-down therapy	Shorter hospitalization Potential of earlier switch to outpatient treatment
Favorable pharmacokinetics Longer half-life	Less staff and material costs by longer dose intervals Potential of outpatient intravenous therapy (OPAT)
Earlier start of therapy	Shorter hospitalization Less infection-related complications Reduced risk of transmitting infection
Adequately high dose	Shorter hospitalization Less infectious complications
Adequate duration of therapy (as short as possible, as long as necessary)	Less side effects Less selection of pathogens or resistance Less drug costs
Antibiotic diversity (and cycling)	Minimization or avoidance of selecting resistant pathogens
Lower drug acquisition cost, rebates	Reduction of daily treatment cost with unchanged efficacy and tolerability
Tracing of costs of application, storage etc. (= process cost)	Insights on actual total costs of antibiotic therapy
Tracing process costs (application-related staff costs, applications aids, monitoring)	Insights on actual total costs of antibiotic therapy
Process analysis (QM) (risk of confusion, preparation steps, avoidance of errors)	Increased drug safety, error management

which in the literature ranges between 2 to 4 Euros or US Dollars per dose [476], [536].

- The cost of drug application material such as needles, catheters, infusion equipment, etc. These costs range from as €1 to €4 by type of administration in the literature [536].
- A lower error rate. Investigations and the resulting recommendations for Anglo-Saxon countries showed that a lower dosing frequency and simpler preparation reduce the probability of errors in the use of a drug [114]. The number of preparation steps should also be taken into account. Therefore, whenever possible, ready-to-use preparations should be employed.
- The risk of confusion/mix-ups.
- The cost of necessary monitoring.

Table 36 shows key properties of antibiotic therapies affecting the total costs of treatment.

Useful literature

Cost-effectiveness, budget-impact and health-impact analyses are valuable decision aids to identify the best treatments among the numerous options from both a patient and a budget perspective.

Both physicans and pharmacists are increasingly confronted with pharmacoeconomic studies reporting positive results for new products. It is therfore necessary to evaluate the quality of these investigations, e.g. based on the suggestions for planning, conduct and publication of pharmacoeconomic evaluations of antiinfectives given by the working group “Pharmacoeconomics of Antiinfectives” [132].

Alternatively, information on the evaluation of drugs (e.g. health-technology assessments) may be obtained from recognized institutions such as the National Institute for Health and Clinical Excellence (http://www.evidence.nhs.uk/default.aspx), the Institute for Quality and Cost-effectiveness in Health Care (http://www.iqwig.de/publikationen-des-iqwig.114.html) or the Canadian Agency for Drugs and Technologies in Health (http://www.cadth.ca/en/products/health-technology-assessment). Besides detailed presentation of available evidence and assessment of its quality, these institutions usually provide evaluations of the cost-effectiveness of medications under consideration, in part based on their own economic studies. Because of the increased networking among international HTA agencies and an advanced standardization of methods, it is increasingly rare that the conclusions of the HTAs differ.

Information on pharmacoeconomics as well as individual clinical trials and HTAs can be obtained from the databank of the NHS Centre for Review and Dissemination (http://www.crd.york.ac.uk/crdweb/). Here, the studies are described in much more detail than on Medline. Based on a comprehensive table of approximately 30 criteria, study goals, design of clinical and economic parts of the studies as well as their clinical and economic results are presented clearly and in detail. In addition, a short evaluation of the quality of the study is provided.

Future prospects

Pharmacoeconomic analyses are an important basis for benefit-dependent reimbursement in many countries and thereby set the legal framework for physician therapeutic decisions. Future clinical practice guidelines will increasingly consider the economic and legal framework and critically deal with the cost-effectiveness of drugs. This will differentiate them from systematic reviews or textbooks that evaluate the evidence with respect to quality and efficacy.
Furthermore, pharmacoeconomic analyses also offer an opportunity, as they combine a critical, evidence-based evaluation of the patient-relevant benefit with economic considerations thus rendering these aspects inseparable. If these analyses are more strongly involved in decision making, the outcome will be an enhanced selection of high-quality medications which are better adapted to patient needs.

16 Perioperative antibiotic prophylaxis

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Perioperative prophylaxis in surgical interventions is usually a short-term, single-shot administration of an antibiotic shortly before, at the start of or at latest during the intervention to avoid postoperative wound complications. The prevention of other types of postoperative infections such as sepsis, pneumonia, urinary tract infections (except for urological surgery) or meningitis has been targeted and differentially examined in only a few studies to date. Data on these infections have been mostly derived from studies conducted with the goal of investigating the effects on wound infection rates. Antibiotic prophylaxis is complementing rather than replacing evidence-based hygiene measures for the prevention of postoperative infections.
The indication for perioperative prophylaxis is based on the wound classification and additional risk factors of the patient. It is carried out for all patients with “contaminated” or “dirty” wounds, independent of other factors. The administration of antibiotics is also established in aseptic surgery with implantation of foreign material. In “clean” or “clean-contaminated” surgery or wounds, the indication should be validated by the presence of risk factors. Antibiotic prophylaxis is recommended in surgical interventions where infectious complications have particularly severe consequences (e.g. intracranial surgery) independent of risk factors and scientific evidence from clinical studies.
The essential features of perioperative prophylaxis are summarized as follows:

- Antibiotic prophylaxis and its indications are established along with measures of asepsis.
- The primary goal of perioperative prophylaxis is the reduction of wound infection rates. The secondary goal is avoidance of local and systemic postoperative complications due to infection.
- Prophylaxis should be customized to the individual patient and the involved risks.
- The risk begins with the operation. Effective levels of the antibiotic agent should be ensured for the duration of the risk period. In cases with persistent risk, the drug level must therefore be maintained according to the pharmacokinetic properties.
- Premature application of an antibiotic is useless. The continuation of prophylaxis beyond the operation as a preventative treatment requires special indications.
- The risk profile and regional epidemiology must be taken into consideration when choosing the antibiotic. Special attention must be given to possible secondary infections, particularly those caused by gram-negative pathogens.
- Only substances which have been proven effective in the relevant indications should be used. The broadest experience is available for beta-lactam antibiotics.
- The choice of the prophylactic drug should be based primarily on the pathogen spectrum, the pharmacokinetics and the licensing status.
- For the individual patient, the risk of resistance development is small. However, this is not true for the entire patient population of a hospital.
- The economic aspects are important, even if the cost of antibiotic prophylaxis is less than the cost of postoperative infectious complications.

Table 37 gives an overview of recommendations for perioperative prophylaxis in selected surgical indications. A detailed account is given in the full version of this chapter in the Chemotherapy Journal [548].
The listed substance groups and substances have been shown to be effective in clinical studies. Because of the large number of choices in some substance groups, individual evidence grades were not assigned for each single option and in individual cases analogous conclusions were allowed.
Available meta-analyses and prospective randomized studies on antibiotic prophylaxis in surgery often vary in quality and sometimes group different surgical interventions under the general term of abdominal surgery and allow for different substances, with the effect of some-

Table 37: Overview of recommendations for antibiotic prophylaxis in surgery

Type of surgery	Most common pathogens	Drugs of choice	Level of evidence	Level of recommendation
Liver Pancreas Esophageal resection	Enterobacteriaceae Anaerobes Enterococci Staphylococci	Cephalosporin group 2 + metronidazole *Allergy against beta-lactams:* Clindamycin + aminoglycoside Fluoroquinolone group 2/3 + metronidazole *Risk patients:* Cephalosporin group 3a + metronidazole Acylaminopenicillin/BLI	Ib III III Ib Ib	A B C C C
Stomach	Enterobacteriaceae Anaerobes Staphylococci	Aminopenicillin/BLI Cephalosporin gr. 1/2 *Allergy against beta-lactams:* Clindamycin + aminoglycoside *Risk patients:* Acylaminopenicillin/BLI Cephalosporin group3a + metronidazole Carbapenem group 2	Ib Ib III Ib Ib Ib	A A B B B C
Bile duct	Enterobacteriaceae Enterococci Anaerobes (Staphylococci)	*Only in patients with risk factors:* Aminopenicillin/BLI Acylaminopenicillin Cephalosporin group 1/2 *Allergy against beta-lactams:* Clindamycin + aminoglycoside Fluoroquinolone group 2/3 + metronidazole *Risk patients:* Cephalosporin group 3a + metronidazole Acylaminopenicillin/BLI Carbapenem group 2	 Ia Ia Ia III III Ia Ia Ia	 A A A B C B A C
Colorectal	Anaerobes Enterobacteriaceae Enterococci	Aminopenicillin/BLI Cephalosporin group 1/2 + metronidazole *Allergy against beta-lactams:* Clindamycin + aminoglycoside Fluoroquinolone group 2/3 + metronidazole *Risk patients:* Cephalosporin group 3a + metronidazole Acylaminopenicillin/BLI Carbapenem group 2	Ia Ia III III Ia Ia Ia	A A B C B A C
Appendectomy	*Escherichia coli* *Bacteroides fragilis*	*Only in patients with risk factors:* Aminopenicillin/BLI Cephalosporin group 1/2 + metonidazole *Allergy against beta-lactams:* Clindamycin + aminoglycoside Fluoroquinolone group 2/3 + metronidazole	 Ia Ia III III	 A A B C
Groin/abdominal wall	Staphylococci	*Risk patients:* Aminopenicillin/BLI Cephalosporin group 2	 Ia Ia	 A A
Neurosurgery	Dependent on localization: Staphylococci Streptococci Propionibacteria	Cephalosporin group 1 Aminopenicillin/BLI	Ia Ia	A A
Gynecology Hysterectomy	Enterobacteriaceae *Staphylocccus aureus* Anaerobes STD pathogens	Cephalosporin group 2 + metronidazole *Allergy against beta-lactams* Clindamycin + aminoglycoside	Ia Ia	A C
Cesarean section		Aminopenicillin Cephalosporin group 1/2	Ia Ia	A A

* consider local *E. coli* resistance situation

(Continued)

Table 37: Overview of recommendations for antibiotic prophylaxis in surgery

Type of surgery	Most common pathogens	Drugs of choice	Level of evidence	Level of recommendation
Urological surgery with opening of bowel segments	Enterobacteriaceae Enterococci Anaerobes Staphylococci	Aminopenicillin/BLI Cephalosporin group 2 + metronidazole *In patients pretreated with antibiotics or with previous permanent urinary catheters:* Cephalosporin group 3/4 Acylaminopeniciillin/BLI	IV IV IV IV	A A B B
Urological surgery with opening of bowel segments and without evidence of bacteruria	Enterobacteriaceae Enterococci Staphylococci	*In risk patients only:* Fluoroquinolone* with high levels in urine Cephalosporin group 2 Aminopenicillin/BLI *In patients pretreated with antibiotics or with previous permanent urinary catheters:* Cephalosporin group 3/4 Acylaminopeniciillin/BLI	 IV IV IV IV IV	 A A A B B
Use of implants/reconstructive genital surgery	Staphylococci	*In patients with secondary care or increased risk of infection:* Cephalosporin group 1/2	 IV	 A
Other surgery outside the urinary tract	Staphylococci	*In patients with increased risk of infection:* Cephalosporin group 1/2	 IV	 A
Endoscopic surgery including ESWL	Enterobacteriaceae Enterococci Staphylococci	*In risk patients only:* Cephalosporin group 2 Aminopenicillin/BLI Fluoroquinolone* with high levels in urine *In patients pretreated with antibiotics or with previous permanent urinary catheters:* Cephalosporin group 3/4 Acylaminopeniciillin/BLI	 IIIb IIIb IIIb IIIb IIIb	 A A A B B
Prostatectomy	Enterobacteriaceae Enterococci Staphylococci	Fluoroquinolone* with high levels in urine Cephalosporin group 2	Ib Ib	A A
Transrectal prostatectomy	Enterobacteriaceae	Aminopenicillin/BLI Cephalosporin group 2 Aminoglycoside Fluoroquinolone* with high levels in urine	Ib Ib Ib Ib	B B B A
Cardiac, vascular, implant surgery	Staphylococci *Corynebacterium spp.* *Propionibacterium spp.*	Cephalosporin group 1/2 *Allergy against beta-lactams:* Vancomycin, teicoplanin	Ia IV	A A
Trauma surgery	Staphylococci Broad spectrum of pathogens depending on exposure by trauma	Aminopenicillin/BLI Cephalosporin group 1/2 + metronidazole *Allergy against beta-lactams:* Clindamycin + aminoglycoside	Ia Ia IV	A A B
Orthopedic surgery	Staphylococci Caveat: Increasing prevalence of *Staphylococcus epidemidis*	Aminopenicillin/BLI Cephalosporin group 1/2 *Allergy against beta-lactams:* Clindamycin + aminoglycoside	Ia Ia IV	A A B
Plastic surgery Hand surgery	Staphylococci	Cephalosporin group 1/2 *Allergy against beta-lactams:* Clindamycin	Ib III	A B
Oropharynx Larynx	Staphylococci Enterobacteriaceae Oral streptococci Oral anaerobes	Aminopenicillin/BLI Cephalosporin group 1/2 + metronidazole *Allergy against beta-lactams:* Clindamycin Fluoroquinolone group 4	Ib Ib III III	B B B B

BLI= beta-lactamase inhibitor

times less definitive recommendations. Therefore apparently equivalent studies were given recommendation levels ranging from A to C by the experts.

Notes

Origin

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