Antibiotic Therapy

7

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Alongside rational considerations and scientific evidence, local factors and personal experience frequently dictate the choice of antibiotic therapy. This explains why there is not always an internationally uniform standard for a specific infectious disease. In principle, the chosen antibiotic or combination of antibiotics must be effective against the suspected or demonstrated bacteria. However, it is often unclear whether one or other theoretically effective antibiotic therapies are comparatively more effective and what the minimum treatment duration should be.

A distinction must be made as to whether the treatment concerned involves prophylactic antibiotics administration, untargeted (also called empirical or calculated) antibiotic therapy for a suspected infection, or targeted antibiotic therapy of a proven infection with a known pathogen. The patient's clinical condition also plays a decisive role, particularly in untargeted antibiotic therapy. If they have a severe disease, it is preferable to start with the most potent and broadest antibiotic therapy possible (and later de-escalate or adapt specifically, as needed). If the disease is a milder, the opposite strategy can be adopted initially.

Not only is the choice of the correct drug essential for the success of antibiotic therapy, but the dose and method of administration also play important roles. When combining antibiotics, synergistic effects can be utilized, e.g., combination of a beta-lactam antibiotic and aminoglycoside. On the other hand, mechanisms that increase the selective pressure for resistance need to be borne in mind, e.g., the

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combination of carbapenems with a beta-lactam increases the probability of extended-spectrum beta-lactamase (ESBL)-producing strains.

In the method of administration, a distinction is drawn, for example, between whether the effect of a product is more time-dependent or concentration-dependent. When time-dependent drugs are administered, the maintenance of a minimum inhibitory concentration (MIC) over a long period is a determining factor. The dose and administration must therefore be selected accordingly (e.g., multiple doses over the day or continuous drip infusion). This group includes beta-lactam antibiotics among others (e.g., vancomycin). In practice, determination of the blood concentration of the administered antibiotic is impractical but should be considered. In exceptional cases, the dose has to be adjusted to stay above the MIC. By contrast, the highest possible dose or tissue concentration is important for the mode of action of when administering concentration-dependent drugs. This group includes aminoglycosides, where administration of the whole daily dose at one time has become established practice.

The molecular properties of the antibiotic also affect how well it can penetrate a specific tissue and thus reach a possible focus of infection. Since glycopeptides, for instance, are rather large molecules, the dose must be increased in the treatment of meningitis in order to ensure a sufficient tissue concentration. Aminoglycosides, by comparison, are ineffective in an acidic medium, as in an abscess. Only lipophilic substances can exert an intracellular effect (e.g., macrolides, quinolones).

As all antibiotics can have considerable adverse drug reactions (ADR), toxicity must naturally be taken into account, and the dosages or intervals between doses must be adapted to the metabolic and excretory functions of the body. The glomerular filtration rate (GFR) of the kidney or the effluent rate (= clearance rate) in renal replacement therapy (RRT) is of particular importance here (see also Chap. 4).

Irrespective thereof, all antibiotic therapies run the risk of promoting bacterial resistance by selective pressure. Unfortunately, the burden of multiresistant microorganisms has increased considerably in recent years in pediatric intensive care units.

7.1 Perioperative Prophylaxis in Open-Heart Surgery

Perioperative administration of antibiotics primarily serves to prevent surgically related infectious complications. However, in addition, the exacerbation of previously undiscovered (or latent) infections can occur in the course of elective surgery (e.g., respiratory tract infection). Lastly, infections due to inserted foreign material (e.g., cannulas, allograft, artificial tissue) or even open wound surfaces (e.g., “open chest”) are possible.

In principle, antibiotics that are effective against gram-positive skin microorganisms are candidates for perioperative antibiotic prophylaxis in elective heart surgery (e.g., cefazoline and cefuroxime). Current recommendations advocate the shortest possible use (<72 h) to prevent resistance formation. By contrast, prolonged prophylactic antibiotic administration has become established practice at our center in Giessen (duration,

5–14 days). Our own experiences with fairly low postoperative infection rates following open-heart surgery play a role here. In addition, the authors consider extended antibiotic therapy of open-chest patients (mostly neonates and small infants who have undergone complex and usually lengthy surgery under hypothermia) and patients with ECMO or at the beginning of Berlin Heart therapy to be advisable.

7.1.1 Standard Prophylaxis with Cefuroxime

For routine *standard perioperative prophylaxis*, *cefuroxime* is used as a 2nd-generation cephalosporin effective against staphylococci in all patients at our center in Giessen (see below).

Exceptions:

- Neonates with a history of infections and neonatal infection: ampicillin/gentamicin
- Preexisting antibiotic therapy on other wards/in other hospitals
- Preexisting antibiotic therapy on the present ward

Cefuroxime treatment is usually sufficient and is discontinued after removal of the CVC in cases of uncomplicated surgery, unremarkable wounds, and following a reduction of existing inflammatory markers.

7.1.2 Extension of Standard Prophylaxis

Extension of the standard prophylaxis must be considered if an infection is suspected (see Table 7.1) or there are additional specific risk factors.

This sort of situation is present, for example, in the following circumstances:

- Raised CrP on the 2nd/3rd postoperative day >150–200 mg/L
- Clinical signs of infection (e.g., infiltrates on chest X-ray, abnormal tracheal aspirate, fever, etc.)
- Open wound surfaces (e.g., open chest)
- Implanted foreign material with contact to the outside (e.g., ECMO, Berlin Heart)
- Patients at particular risk (Table 7.2).

This requires a targeted search for further indicators of infection (see Sect. 7.2) and initially an untargeted extension of perioperative antibiotic therapy.

On *suspicion of a respiratory infection, combination therapy with cefuroxime and tobramycin* has become established practice at our center in Giessen.

On *suspicion of sepsis, with an open chest, or with implanted foreign material with contact to the outside,* we prefer a combination of *teicoplanin and ceftazidime*, or alternatively meropenem (for teicoplanin, see Sect. 7.9.13; for ceftazidime, see Sect. 7.9.6; for meropenem, see Sect. 7.9.7).

Table 7.1 Signs of infection

Appearance	CrP, etc.	Leukocytosis	Fever	Ventilation	Wound	Ultrasound
Dirty grayish	Increases after more than 36 h	Over 20,000/μL	With good hydration	O_2 requirement ↑	Red/protruding	Poorer function
MC impaired	Increases above 150 mg/L	Increases secondarily	Over 39 °C	Auscultation findings	Painful	Vegetations
Hypercirculation (rare in children)	Increases secondarily		Increases secondarily	Radiographic findings	Fluctuating	Intrathoracic hematoma
Cool periphery	Liver function parameters, lactate		May be seen after homograft implantation (without infection)	Tracheal secretion abnormal	CVC puncture site infected	
Liver enlarged						

Table 7.2 Patients at risk of infection

Neonates	Patient-related	Surgery-related	Wart-related
Long CVC	Catch 22, etc.	Emergency surgery	Preoperatively in ICU, long-stay patient
Asphyxia	Trisomy 21	Open chest	Previous antibiotic therapy (too many, too long)
Compromised GI perfusion, HLHS, aortic isthmus stenosis, PDA closes	Mental retardation with risk of aspiration	Long machine time, deep hypothermia	Many foreign bodies (e.g., central venous line, Foley catheter, drains, etc.)
	Previously sick lung, status post recurrent pneumonia	Critically ill patient	Insufficient hygiene measures under stress (e.g., forgot to disinfect hands)
	Status post resuscitation	Dialysis, ECMO, VAD	
	Status post endocarditis, status post-CPB surgery	Synthetic material (valves), homografts, etc.	

CPB cardiopulmonary bypass, *GI* gastrointestinal, *VAD* ventricular assist device

7.2 Investigations on Suspicion of Infection

In the workup following a clinical suspicion of infection, there are three principal approaches:

1. Laboratory changes (or laboratory profile):
   - Blood count (leukocytosis or leukopenia; ratio of immature to total neutrophiles)
   - CrP, procalcitonin (more effective than CrP in differentiating from SIRS), IL6

- Coagulation parameters, platelets, and D-dimers (particularly on consumption).
- Acute phase proteins (e.g., increase in fibrinogen)
- Organ functions (e.g., creatinine, urea, gas exchange, etc.)

2. Microbiological detection:
   - Blood culture (from CVC and peripherally, repeated where applicable)
   - Endotracheal secretion collection (bronchoscopic sample collection, where applicable)
   - Urine culture
   - Culture of pleural effusions and ascites, where applicable
   - Wound smears (where applicable pus, where applicable surgical revision)
   - Samples of surgically inserted foreign materials (e.g., allografts, vascular prostheses, artificial valves, etc.)
   - Rare: CSF, stool samples (e.g., clostridial toxins), biopsies
3. Imaging:
   - Chest X-ray (e.g., pneumonia, aspiration, etc.)
   - CT (e.g., sinusitis, abscesses, pneumonia, septic emboli, etc.)
   - Echocardiogram (e.g., endocarditis, pericarditis, effusions, vegetations, valve incompetence, thrombi, etc.)
   - Abdominal ultrasound (e.g., ascites, liver size, biliary tract changes, urinary tract changes, etc.)
   - Rare: leukocyte scintigraphy or PET/CT scan (PET = positron emission tomography)

7.3 Postoperative Infections

Postoperative infections are usually pulmonary (e.g., lobar pneumonia, bronchopneumonia, aspiration pneumonia, septic emboli, pulmonary sequester, etc.), some of which were preexistent and are exacerbated following cardiopulmonary bypass (CPB) surgery. The second most common forms of infection are catheter infections, while wound infection, mediastinitis, endocarditis, urinary tract infection, or infections from inserted foreign material occur more rarely. In many cases, a focus cannot be identified (e.g., failure of microbiological detection during ongoing antibiotic therapy, difficult diagnosis, systemic inflammatory response syndrome (SIRS), occult infection). In the case of negative blood cultures (e.g., after prior antibiotic treatment), prokaryotic PCR (polymerase chain reaction from blood or secreta) can sometimes still provide evidence of bacterial infection.

Depending on the clinical suspicion, the following microbiological examinations should be performed to identify the focus of infection.

Nosocomial infections after cardiac surgery in children:

- Catheter sepsis → blood cultures (central and peripheral), dispatch of catheter tip (after removal)
- With drains → drainage fluid, drainage material
- Respiratory tract infection → tracheal secretion, bronchial secretion, where applicable bronchial secretion by bronchoscopy, chest X-ray, in exceptional

cases: chest CT, serology, or PCR on suspicion of *Mycoplasma*, *Chlamydia*, *Legionella*, or viruses, etc.
- Wound infections→ smears, revision by surgeons
- Urinary tract infection, particularly with indwelling bladder catheter→ urinstix, urine culture, ultrasound where applicable
- Endocarditis → blood cultures (at least 5–6), transthoracic ultrasound, or TEE (transesophageal echocardiography)
- In rare cases: LP (lumbar puncture) where applicable; stool culture where applicable (particularly *Clostridium* difficile toxin); on suspicion of osseous spread: X-ray, PET-scan; on suspicion of cerebral spread (brain abscesses): cCT (cranial computed tomography)/MRI, etc.

A distinction must be drawn between:

- Increase of inflammatory markers without clinical change/deterioration (nonspecific reaction)
- Increase of inflammatory markers with clinical change/deterioration (suspicion of infection)
- Systemic inflammatory response syndrome (general change without demonstration of infection)
- Manifest infection or sepsis

7.4 Systemic Inflammatory Reaction (SIRS) vs. Sepsis

Following open-heart surgery, a clinical picture can develop associated with laboratory signs of inflammation, hypotension, capillary leakage, increased volume and catecholamine requirement, deterioration of organ functions, temperature instability, and metabolic disorders (e.g., hyperglycemia). By definition, the distinction between a systemic inflammatory response syndrome (SIRS) and sepsis depends purely on the detection of an infectious focus or bacteremia. Since this detection is frequently unsuccessful in everyday practice and it therefore remains unclear whether the changes are due to the CPB surgery (please see Chap. 10 on ECMO and CPB also) or are in fact caused by bacteria, we will advocate a fairly practical approach here.

Once microbiological studies have been performed (see Sects. 7.2 and 7.3), broad-spectrum antibiotic therapy must be initiated immediately under all circumstances (e.g., teicoplanin or vancomycin, combined with ceftazidime or meropenem). In addition, symptomatic treatment must be given to maintain organ function as adequately as possible (see also Sect. 7.8).

Fulminant septic conditions are fairly rare in postoperative intensive care medicine. This is because most surgery is elective and is usually undertaken on infection-free children and all procedures are performed under strictly sterile conditions and the patients receive antibiotic treatment perioperatively. As mentioned earlier, differentiation from CPB-mediated SIRS is difficult, particularly in the first 48 h after

surgery. Immunosuppressed patients (e.g., congenital or acquired immunodeficiency, administration of immunosuppressive agents), premature infants/neonates, and children with chronic or occult infections (e.g., ciliary dysfunction, cystic fibrosis, etc.) represent a particular risk group. Patients with trisomy 21 are also frequently prone to infection.

Postoperative SIRS frequently lasts no more than 72–96 h at most, i.e., it resolves without any further specific measures. If, however, a focus of infection can be identified, confining this is the main priority. Antibiotic therapy (dose, combination, intervals, etc.) must be adapted in such a way that limitations due to defective penetration into bradytrophic tissue or areas with poor blood supply are compensated. Examples of this include infected (chest) hematomas, infected catheters and foreign surfaces, infected sternum wounds, poorly ventilated infected areas of the lung, necrotizing enterocolitis (e.g., in bowel ischemia), and postoperative endocarditis. Infected dead tissue must be surgically debrided, as otherwise it is insufficiently accessible to antibiotic therapy. Infected foreign materials (e.g., CVCs, cannulas, artificial valves, prostheses, allografts, etc.) must be exchanged, if this is possible.

7.5 Pneumonia or Ventilation-Associated Pneumonia (VAP)

Infections of the respiratory tract, including the lung, are fairly common in children and may be "brought into surgery" undetected. In terms of the microbial spectrum, "community-acquired pneumonia" (e.g., due to pneumococci, streptococci, *Haemophilus influenzae*, etc.) is the usual culprit. Treatment with cefuroxime is usually sufficient.

If a pulmonary infection occurs after a ventilation duration of >48 h, this is then referred to as ventilator-associated pneumonia (VAP) (Table 7.3).

The diagnosis is made on the basis of microbiological findings: endotracheal or bronchial secretion (where necessary, bronchoalveolar lavage [= BAL]), infiltrations on the X-ray film, and clinical signs (deterioration of lung function). In this scenario, gram-negative microorganisms are more likely to be the causative agents of infection. Therefore, antibiotic therapy should be extended to include an aminoglycoside. Antibiotic therapy should only be adapted on the basis of microbiological resistance testing if special problem microorganisms are detected (e.g., *Pseudomonas*, extended-spectrum beta-lactamase (ESBL) producers, etc.).

Further therapeutic measures include the avoidance or reopening of atelectatic areas and good bronchial hygiene. The possibilities for (prone)-positioning the patient (intended to drain and open up lung segments) are frequently limited in postoperative therapy. In the case of sonographically or radiologically demonstrated atelectasis, recruitment maneuvers and ventilation strategies with higher PEEP can be used (see Chap. 2). Improvement of mucociliary clearance can be obtained with mucolytics (NAC at an appropriate dose), inhalation (e.g., 3% NaCl), and intensive physiotherapy.

Table 7.3 Memory card on antibiotic therapy

Cardiac surgery	Signs of infection without SIRS	Signs of infection with SIRS	Open chest	Extracorporeal circulation
Cefuroxime	Cefuroxime + tobramycin	Vancomycin, ceftazidime	Initially: Vancomycin, ceftazidime	Initially: Vancomycin, ceftazidime
		Escalation pneumonia	Escalation gr^+	Escalation gr^- (see SIRS)
		Vancomycin, ceftazidime, + tobramycin, or ciprofloxacin	Consider linezolid, rifampicin, or clindamycin. Close chest as soon as possible	Extracorporeal circulation, escalation gr^+ (see open chest, escalation gr^+)
		Alternative: Vancomycin, carbapenem, and tobramycin	In difficult cases with suspected mediastinitis, tigecycline may be considered	In all cases of suspected or proven infection during extracorporeal circulation (e.g., ECMO) or assist (e.g., berlin heart), consider explantation as soon as possible
		In special cases: Switch tobramycin to amikacin		In difficult cases with suspected mediastinitis, tigecycline may be considered
			Teicoplanin may be used instead of vancomycin	

SIRS systemic inflammatory response syndrome

If more extensive antibiotic therapy is required, the following antibiotics may be proposed:

- Ceftazidime (see also Sect. 7.9.6): gram-negative problem microorganisms, including *Pseudomonas*, *Serratia*, and *Acinetobacter*.
- Quinolones (see also Sect. 7.9.10): effective against *Enterobacteriaceae*, *H. influenzae*, and *Legionella* and weaker against staphylococci, streptococci, enterococci, *Chlamydia*, and *Mycoplasma*. Ciprofloxacin is very effective against *Pseudomonas* but ineffective in pneumococci. In our view, there is no longer a general reticence about the use of quinolones in children (administration usually <14–21 days).
- Carbapenems (see also Sect. 7.9.7): broad spectrum of action in the gram-negative and gram-positive range, beta-lactamase-stable. However, multiresistant nonfermenters (MNF) such as *Stenotrophomonas maltophilia* can be selected.
- Erythromycin or clarithromycin (see also Sect. 7.9.12): in suspected "atypical pneumonia" due to *Mycoplasma*, *Chlamydia*, or *Legionella* (a quinolone could also be used instead).
- Combination therapies may offer certain advantages (synergies, extended spectrum of action, etc.). Thus, beta-lactam antibiotics combine well with aminogly-

cosides or quinolones. In unclear situations of pneumonia and sepsis in which it is decided to use a carbapenem (e.g., meropenem) and in which previous combination therapy has been given (e.g., glycopeptide plus ceftazidime plus aminoglycoside), ceftazidime should be replaced by the carbapenem. Where applicable, administration of the aminoglycoside can also be discontinued during meropenem therapy.

7.6 Treatment of Infections with Resistant Staphylococci (Coagulase-Negative Staphylococci, MRSA)

Patients with barrier disorders, open chest, indwelling foreign bodies (e.g., central venous catheter), and extracorporeal circulatory support (e.g., ECMO, Berlin Heart) are particularly prone to staphylococcal infections.

Coagulase-negative staphylococci are not uncommon on microbiological testing. They occur physiologically on human skin and are usually resistant to beta-lactam antibiotics. The question as to whether the sample is contaminated or there is an infection can frequently only be answered clinically. Infections with coagulase-negative staphylococci can be sufficiently treated, for example, by means of glycopeptides. However, the characteristic feature of these bacteria is that they form a biofilm on foreign surfaces that protects them from the action of antibiotics. For this reason, effective debridement is usually only possible by removing or exchanging the foreign materials, after having weighed the risks and benefits.

Colonizations or infections with methicillin-resistant *Staphylococcus aureus* (MRSA) constitute an increasing problem in hospitals. Compared with the intensive care treatment of adults, however, infections due to MRSA are still the exception in most pediatric intensive care units. MRSA are resistant to all beta-lactam antibiotics but can be treated with glycopeptides (vancomycin, teicoplanin; see also Sect. 7.9.13) or linezolid (see also Sect. 7.9.11) (depending on antibiotic susceptibility testing, rifampicin, fosfomycin, clindamycin, or gentamicin is also possible).

In selected cases, switching from a glycopeptide to linezolid, which inhibits protein biosynthesis, can be considered. The determinants here are the good efficacy of linezolid against gram-positive microorganisms and its excellent tissue penetration – even after oral administration, it shows an almost 100% bioavailability. Nevertheless, experience with this drug in pediatrics is still limited.

7.7 Treatment for Suspected Necrotizing Enterocolitis

Unlike in premature infants, necrotizing enterocolitis usually does not occur in neonates without an identifiable cause. Compromised bowel perfusion associated with a heart defect and following resuscitation, circulatory shock, and severe asphyxia are the primary features. The leading cause is usually ductal closure in PDA-dependent systemic perfusion (hypoplastic left heart syndrome (HLHS), critical aortic stenosis, and critical aortic isthmus stenosis (synonym: coarctation of the aorta).

About 1–3 days after the initially successful circulatory stabilization, deterioration occurs in the "abdominal compartment" with a subsequent septic reaction. For this reason, with the previous history mentioned above, only a very careful nutritional buildup is possible, if at all, in addition to which increased attention must be paid to any clinical changes in the abdomen.

The combination of vancomycin and meropenem (with or without metronidazole) has become established practice as antibiotic therapy for necrotizing enterocolitis (alternatively: ampicillin, gentamicin, and metronidazole).

As with all severe bacterial infections, impairment of all organ functions can occur in the course of necrotizing enterocolitis, including disseminated intravascular coagulation (DIC). A daily surgical consultation with an assessment of the situation is essential. Indications for laparotomy and/or laparoscopy in our view include:

- Signs of perforation on the plain abdominal X-ray (free air)
- Indications of migratory peritonitis with laboratory and clinical deterioration
- A "fixed" loop with clinical signs of ileus
- Demonstrated or suspected intra-abdominal abscess or an intra-abdominal compartment syndrome (IAP > 15–20 mmHg).

Otherwise, a "conservative" strategy (without surgery) can also be promising (Table 7.4).

Table 7.4 Necrotizing enterocolitis in mature neonates

History	Caution	Clinical features abdomen	Clinical features body	Diagnostic features	Treatment
Resuscitation?	Examine the abdomen several times daily	Transport disorder? Paralytic ileus?	Apnea?	Clinical appearance	Gastric decompression (e.g., open gastric tube)
Asphyxia?	Cautious (slow) dietary buildup	Abdomen distended, painful? Fixed loop? Masses present? Resistances?	Circulation worse?	X-rays: Pneumatosis, football sign, perforation, persistent loop, intestinal gas distribution?	Fasting
Heart defect with impaired circulation in lower half of body?		Resistance, shiny abdominal skin, persistent loops?	Impaired lung function?	Ultrasound: Free fluid, gas bubbles in portal vessels, ascites?	Antibiotics

Table 7.4 (continued)

History	Caution	Clinical features abdomen	Clinical features body	Diagnostic features	Treatment
		Bloody diarrhea?	Impaired kidney function?	Laboratory parameters: Blood count, coagulation, CrP, liver, lactate by Astrup method (metabolic acidosis), blood corpuscles, stool culture?	Surgical intervention
			Disseminated intravascular coagulation (DIC)?		Supportive, circulation, ventilation, kidney
			Metabolism, disorder of carbohydrate metabolism, lactate formation, impaired hepatic function?		Blood glucose balancing, total parenteral nutrition, coagulation therapy

CrP C-reactive protein

7.8 Septic Shock

The term "septic shock" usually covers a complex of symptoms in intensive medicine that involves an underlying dysregulation of the immune response and that by definition is caused by a demonstrable infection. The hallmark clinical features are the changes already described in Sect. 7.4, which may be potentially life-threatening (see Table 7.5).

While only few septic clinical pictures exhibit a relatively standard phenotype, such as meningococcal sepsis with purpura fulminans, the cause is initially unclear in most of the cases. The causative pathogen must be identified as rapidly as possible (for workup, see Sect. 7.2), and broad-spectrum, untargeted antibiotic therapy must be initiated immediately even before the microbiological results are received. In other words, "hit hard and early."

The treatment of sepsis involves relatively unspecific, fairly symptomatic measures, such as stabilization of the circulation, as well as pathogen-specific approaches. The latter would include targeted antibiotic therapy and debridement of the focus of infection (e.g., abscess drainage, removal of infected foreign bodies, etc.), as well as administration of immunoglobulins in toxic shock syndrome

Table 7.5 Sepsis-induced multi-organ failure

Lung	Circulation	Kidney	Coagulation	Heart	Liver	Brain
Development of ARDS	Hypotension	Diversion of intrarenal blood flow away from the renal cortex	Disseminated intravascular coagulation (DIC)	Initially compensation by hypercirculation	Glycogen consumption Gluconeogenesis inhibited Mitochondrial disorder	Agitation, apathy
Development of effusions	Endothelial damage	Glomerular necrosis	Platelet consumption	Contractility disorder	Lactic acidosis	Energy deficiency, vasoplegia in acidosis
Intrapulmonary shunt	Microthrombosis, terminal capillary vessels	Excretion disorder	Factor consumption	Ventricular dilation	Protein catabolism	Cell swelling, microhemorrhage
PHT	Generalized edema	Swelling	Microthrombosis, terminal capillary vessels	RV failure	NH_3 and bilirubin increase	Increasing loss of consciousness
Lung failure	Catecholamine-refractory shock	Renal failure	Generalized bleeding tendency	Circulatory arrest	Liver failure	Coma

NH_3 ammonia, Bili = bilirubin

(streptococcal or staphylococcal toxic shock syndrome). In our opinion, the replacement of protein C can be useful in the case of purpura fulminans (target: protein C levels >80%). However, care has to be taken, since official guidelines recommend against the use of protein C in pediatric sepsis (due to the risk of bleeding complications). Although initial results may point in this direction, it remains to be proven whether cytokine- or endotoxin-reducing measures (e.g., by specific dialysis filters or hemadsorption) exert a demonstrably positive effect on the disease course.

The pathophysiology of septic shock is extremely complicated and complex. The bacteria and/or bacterial toxins activate granulocytes (polymorphonuclear neutrophils, PMN) and macrophages, which in turn produce cytokines and activate a series of endogenous mediator or effector systems (e.g., complement system, coagulation system, etc.). In simplified terms, the path may be depicted as follows: noxae → activation of the body's defenses → microcirculatory disorder → cell dysfunction → organ failure (including PMN/macrophage activation, mediator release↑, complement [etc.], mediator release ↑, coagulation activation, and hyperfibrinolysis). The focal point is therefore the massive disorder of the terminal capillary vessels ("microcirculatory disorders"), including permeability of the capillary membrane (capillary leakage), endothelial dysfunction, and peripheral "vascular failure" (refractory hypotension). In addition, a "mediator-induced mitochondrial cell function disorder" results in a generalized metabolic crisis with lactate formation (not just from impaired perfusion) and a glucose utilization resistance.

In the treatment of septic shock, the principal options for safeguarding the circulation and O_2 supply are fluid volume administration and catecholamine therapy (α-adrenergic in vascular failure, β-adrenergic in myocardial contraction weakness) (early goal-directed therapy). In respiratory failure, this also includes invasive ventilation (or preferably noninvasive ventilation, if feasible).

Close monitoring by echocardiography should always be undertaken in all patients (from neonates to adolescents) in addition to the usual monitoring (including invasive blood pressure and CVP) in order to be able to obtain an impression of the patient's filling status and myocardial function and to enable the treatment to be adapted accordingly.

Primary goals are a sufficient arterial blood pressure (in line with the age-commensurate lower limit of normal) to maintain organ perfusion (e.g., urine output >1 mL/kg/h, GCS 13–15) and an appropriate O_2 supply to the body (appropriate cardiac output, $SvO_2 > 70\%$, CVP = 8–12 mmHg, Hb > 8 g/dL, $SpO_2 > 90\%$, lactate <5 mmol/L, BE > −8 mmol/L).

If cardiac output is massively reduced as a result of septic cardiomyopathy (cold shock), milrinone (where necessary levosimendan) can be tried additionally, or ECMO treatment may even be necessary. In the event of massive vasodilation with severe hypotension and organ failure (warm shock or vasoplegic shock), at noradrenaline doses >1.0 µg/kg/min, additional treatment with vasopressin (e.g., 0.0002–0.0008 IU/kg/min) or terlipressin (e.g., 10 µg/kg every 4–6 h i.v.) can be helpful.

Since impairment of lung function often occurs in association with volume therapy and a general barrier disorder, controlled ventilation must be considered at an

early stage (to ensure gas exchange and reduce work of breathing). On intubation, induction agents (e.g., ketamine, etomidate, rocuronium) must be dosed very carefully and syringes kept available for additional catecholamine administration, since there is the risk of an acute circulatory collapse. If etomidate is chosen, hydrocortisone replacement should be considered for at least 24 h.

In right heart overload due to increased pulmonary resistance, consideration must be given to a protective form of ventilation (PEEP 5-(10) cmH_2O, driving pressure < 14-(18) cmH2O, Vt 4–6 ml/kg) and the administration of NO (20(−40) ppm).

At a volume replacement of more than 40–60 mL/kg, the transfusion of red blood cell concentrates is often necessary to maintain Hb >8 g/dL.

In oliguria, after optimization of cardiac output and perfusion pressure, a long-term furosemide drip (at our center in Giessen, combined with low-dosed theophylline) can be tried in order to increase urine output and to achieve fluid balance in the patient. If acute renal failure occurs (urine output <0.5–1.0 mL/kg/h for >24 h with an increase in retention parameters), renal replacement therapy (RRT) should be initiated early in the context of sepsis (effluent rate = clearance dose >35 mL/kg/h seems beneficial, a "cytokine-eliminating" filter may also be considered).

Other measures:

- Treatment of coagulation disorder and thrombocytopenia.
- Cutoff values for platelets:
  - Without bleeding >10,000–30,000/μL
  - Before surgery or catheter placement at a noncompressible site >50,000/μL
- Platelet transfusion: In the event of bleeding, high risk, or platelets <10,000/μL.
- No routine AT-III administration.
- No routine administration of fresh frozen plasma (except with active bleeding).
- Heparin (UFH: 50–300 IU/kg BW/d or LMWH, low-molecular-weight heparin):
  - In DIC with signs of peripheral circulatory disorders (e.g., purpura fulminans)
  - If no active bleeding, PTT < 50 s and/or INR < 2.0
- Stress ulcer prophylaxis (in children, only with steroid therapy).
- Whenever possible, enteral nutrition (otherwise parenteral nutrition with sufficient calories (hyperglycemia with BG > 200 mg/dL and triglyceridemia with triglycerides >300 mg/dL must be avoided).
- NaBic only if pH < 7.1, or BE < −10 mmol/L, or massive PHT (CO_2 must be able to be expired).
- Monitoring of organ perfusion by regular SvO_2, lactate determination, and NIRS (where applicable).
- Hydrocortisone administration: In the absence of an adequate response to catecholamines (catecholamine-refractory shock), steroids can both reduce the catecholamine requirement and in some cases improve lung function. An examination for corticoadrenal insufficiency (relative or absolute) is recommended before the beginning of therapy, but in our view is usually too time-consuming.

  - Hydrocortisone dose: Initially up to 10–(50) mg/kg BW i.v. and then 1–(10) mg/kg BW every 6 h (depending on the severity of the circulatory instability – standard dosage, see Chap. 19). Treatment should be stopped again after 3–4 days (or depending on the clinical picture). It is not absolutely necessary to taper off treatment after a treatment duration of <7 days.
- Immunoglobulins: In severe sepsis, administration of immunoglobulins (usually IgG) can be considered as a supportive measure: Dose 0.5 g/kg BW/day, e.g., on 2 successive days. It is not definitively established whether administration of IgM has benefits over that of IgG.

Detailed recommendations on the treatment of sepsis in children can be found in the recommendations of the "Surviving Sepsis Campaign," most recently published in 2016.

7.9 Frequently Used Antibiotics in the Intensive Care Unit

7.9.1 Penicillin

Sensitive: *Pneumococci, beta-hemolytic and viridans streptococci*, beta-lactamase-negative staphylococci, *Corynebacterium diphtheriae*, *Bacillus anthracis*, beta-lactamase-negative gonococci, *meningococci*, *Pasteurella multocida*, anaerobes (e.g., *Fusobacteria*, peptostreptococci, clostridia [except difficile]), *Bacteroides* (except fragilis), actinomycetes, *Treponema*, *Borrelia*, *Leptospira*.

Resistant: *Enterobacteriaceae*, nonfermenters (*Pseudomonas aeruginosa*, *Stenotrophomonas*, and *Acinetobacter*), beta-lactamase-forming gram-negative pathogens (gonococci (>20%), *Haemophilus*, *Moraxella*), enterococci, beta-lactamase-producing staphylococci (>90%), MRSA, *Clostridium difficile* and *Bacteroides fragilis*, *Mycoplasma*, *Chlamydia*, *Legionella*.

Indications: Streptococcal, pneumococcal, meningococcal infections, syphilis, borreliosis, scarlet fever, tonsillitis, erysipelas, rheumatic fever, subacute bacterial endocarditis.

Dosage: 0.25–0.5 million IU/kg BW/day i.v. in 4–6 single doses or 30–50 mg/kg BW i.v. every 4–6 h.

Penicillin G (benzylpenicillin): 1 µg = 1.67 IU; 1 IU = 0.6 µg.

Adjustment in RI (depending on GFR in mL/min):

- GFR > 50: normal dosage
- GFR 10–50: 50,000–100,000 IU/kg every 8 h
- GFR < 10: 50,000–100,000 IU/kg every 12 h
- PD: 50000–100,000 IU/kg every 12 h
- HF: 50000–100,000 IU/kg every 8 h

Adverse drug reactions: Allergic reactions can occur with all beta-lactam antibiotics (e.g., skin reactions, eosinophilia, bronchospasm, anaphylactic shock); hemolytic

anemia, leukopenia, thrombocytopenia, drug fever; neurotoxic reactions in patients on high-dose therapy with a predisposition to seizures or renal impairment.

Caveat Cross-allergy with other beta-lactam antibiotics!

7.9.2 Ampicillin

Sensitive: as penicillin.

Additionally: *Proteus mirabilis*, *Salmonella*, *Shigella*, *E. coli* (40%), *Haemophilus*, *Moraxella catarrhalis*, *enterococci* (except *E. faecium*), *Listeria*.

Resistant: As penicillin.

Indication: Neonatal infection without microorganism detection, enterococcal endocarditis, listeriosis.

Dosage: 100–200 mg/kg BW/day i.v. in 3–4 single doses.

Adjustment in RI (depending on GFR in mL/min):

- GFR > 50: normal dosage
- GFR 10–50: 50 mg/kg every 8 h
- GFR < 10: 50 mg/kg every 12 h
- PD: 50 mg/kg every 12 h
- HF: 50 mg/kg every 8 h

ADR: allergic and anaphylactic reactions (drug fever, bronchospasm, fall in blood pressure, etc.), gastrointestinal disorders, such as pseudomembranous enterocolitis, blood count changes (granulocytopenia, thrombocytopenia, anemia)

Caveat Contraindicated on suspicion of infectious mononucleosis (rash)

7.9.3 Piperacillin/Tazobactam (Ratio 80:10)

Sensitive: like ampicillin.

Additionally: *Pseudomonas aeruginosa*, beta-lactamase-forming *Haemophilus*, gonococci and *Moraxella*, beta-lactamase-forming staphylococci, anaerobes extended to include *Bacteroides fragilis*, *Enterobacteriaceae* (incl. *Serratia*, *Citrobacter*, *Proteus vulgaris*, *Morganella morganii*, *Providencia*) – depending on susceptibility testing.

Resistant: *Stenotrophomonas*, *Burkholderia cepacia*, *Enterococcus faecium*, MRSA, *Mycoplasma*, *Chlamydia*, *Legionella*.

Indication: Severe intra-abdominal infections (here authorized also in children), urinary tract, genital tract, and biliary tract infections; infections due to susceptible gram-negative rods, *Pseudomonas* infections, severe general infections, mixed infections – can readily be combined with an aminoglycoside.

Dosage: 300–400 mg/kg BW/day i.v. in 3–4 single doses.
Adjustment in RI (depending on GFR in mL/min):

- GFR > 50: normal dosage
- GFR 10–50: 50–75 mg/kg every 8 h
- GFR < 10: 50 mg/kg every 12 h
- PD: 50 mg/kg every 12 h
- HF: 50 mg/kg every 8 h

7.9.4 Cefuroxime

Sensitive: *Streptococci, pneumococci*, beta-lactamase-forming *staphylococci*, *E. coli*, *Klebsiella*, *Salmonella*, *Shigella*, *Proteus mirabilis*, other *Enterobacteriaceae* (after susceptibility testing), gonococci, meningococci, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Fusobacteria*, *Prevotella*, *Porphyromonas*, anaerobes.

Resistant: Nonfermenters (*Pseudomonas aeruginosa*, *Acinetobacter*, *Stenotrophomonas*), Enterobacter, *Proteus vulgaris*, *Providencia*, *Morganella morganii*, *Serratia*, *Citrobacter*, *enterococci*, MRSA, MRSE, *Listeria*, *Bacteroides fragilis*, *Mycoplasma*, *Chlamydia*, *Legionella*. Cefuroxime is extensively beta-lactamase-resistant but can be hydrolyzed by extended-spectrum beta-lactamases (ESBL).

Indications: community-acquired pneumonia, urinary tract infection (UTI), perioperative prophylaxis.

Dosage: 100–150 mg/kg BW/day in 3 single doses i.v.
Adjustment in RI (depending on GFR in mL/min):

- GFR > 50: normal dosage
- GFR 10–50: normal dosage
- GFR < 10: 30–50 mg/kg every 12 h
- PD, HF: 30–50 mg/kg every 12 h

ADR: allergic reactions, rarely circulatory reactions, allergic neutropenia (reversible on discontinuation), bleeding tendency with impaired renal function, increase in transaminases, immune hemolysis.

7.9.5 Cefotaxime

Sensitive: as cefuroxime.

Additionally: many *Enterobacteriaceae* (after susceptibility testing – e.g., *Acinetobacter*), beta-lactamase-forming staphylococci (less good than cefazoline or cefuroxime), particularly good against *E. coli* and *Klebsiella pneumoniae.*

Resistant: as cefuroxime.

Indications: Empirical first-line treatment in intensive care patients for sepsis, pneumonia (particularly postoperative pneumonia with suspected involvement of problem microorganisms), peritonitis, phlegmon, abscesses, meningitis and ventriculitis, and hospital-acquired infections with severe underlying conditions; for neuroborreliosis, however, in contrast to ceftriaxone, three daily doses required.

Dosage: 25 mg/kg BW i.v. every 6–8 h (max. 1 g/dose); in meningitis: 50 mg/kg BW i.v. every 6 h (max. 2–3 g/dose) – good CSF penetration.

Adjustment in RI (depending on GFR in mL/min):

- GFR > 50: normal dosage
- GFR 10–50: normal dosage
- GFR < 10: 25 mg/kg every 8 h
- PD: 25 mg/kg every 12 h
- HF: 25 mg/kg every 8 h

7.9.6 Ceftazidime

Sensitive: as cefotaxime.

Additionally: *Pseudomonas aeruginosa*, *Acinetobacter*, *Enterobacter cloacae*, *weaker* against staphylococci.

Resistant: as cefuroxime.

Dosage: 100–150 mg/kg BW/day i.v. in three single doses.

Adjustment in RI (depending on GFR in mL/min):

- GFR > 50: normal dosage
- GFR 10–50: 30–50 mg/kg every 12 h
- GFR < 10: 30–50 mg/kg every 12 h
- PD: 30 mg/kg every 24 h
- HF: 30–50 mg/kg every 12 h

7.9.7 Meropenem

Sensitive: *Almost all gram-positive, gram-negative, and anaerobic microbes* (compared with imipenem/cilastatin somewhat better in the gram-negative and somewhat weaker in the gram-positive range).

Resistant: *Stenotrophomonas maltophilia*, carbapenemase-formers (enterobacteria, *Klebsiella pneumoniae*, *E. coli*, *Serratia marcescens*, *Citrobacter freundii*, *Enterobacter cloacae*, *Morganella morganii*, and nonfermenters, *Pseudomonas aeruginosa*, *Acinetobacter baumannii*), *Burkholderia cepacia*, *Enterococcus faecium* and *faecalis* (susceptibility testing), *MRSA*, MRSE, *Corynebacterium jeikeium*, *Clostridium difficile*, *Mycoplasma*, *Chlamydia*, *Legionella*.

Indications: nosocomial and severe infections (e.g., peritonitis), particularly in immunodeficiency, in sepsis, and in infections due to microorganisms resistant to other antibiotics.

Dosage: 60–120 mg/kg/d i.v. in 3–4 single doses.

Adjustment in RI (depending on GFR in mL/min):

- GFR > 50: normal dosage
- GFR 10–50: 20–40 mg/kg every 12 h
- GFR < 10: 10–20 mg/kg every 24 h
- PD: 10–20 mg/kg every 24 h
- HF: 20–40 mg/kg every 12 h

ADR: gastrointestinal reactions; in 1–2% CNS (dose-dependent) ADR (tremor, myoclonus, seizures, confusional states, somnolence, dizziness), particularly in the case of renal impairment or previous CNS injury; increase in transaminases (usually insignificant), allergic reactions, eosinophilia, leukopenia, thrombocytopenia, fall in Hb, immune hemolysis, temporary prolongation of PTT, rarely renal impairment/urine discoloration (red), seizures in combination with ganciclovir

Caveat Carbapenems exhibit relatively poor penetration into CSF! No combination therapy with beta-lactam antibiotics: carbapenems induce the production in gram-negative bacteria of chromosomally coded beta-lactamases, which inactivate other beta-lactam antibiotics (other than carbapenems). Beta-lactam antibiotics can be reinstated 12 h after discontinuation of carbapenems.

7.9.8 Clindamycin

Sensitive: *Staphylococci, streptococci, pneumococci, Corynebacterium diphtheriae*, *Bacillus anthracis*, almost all *anaerobes* (incl. *Bacteroides fragilis*), *Mycoplasma hominis*, *Pneumocystis jiroveci*, *Toxoplasma gondii.*

Resistant: *Enterobacteriaceae*, nonfermenters, *Haemophilus influenzae*, gonococci, meningococci, enterococci, some clostridia, *Mycoplasma pneumoniae*, *Ureaplasma urealyticum.*

Indications: alternative in staphylococcal infections and infections due to gram-positive cocci in the event of an allergy to beta-lactam antibiotics, bone and soft tissue infections, MRSA infections.

As a combination antibiotic to inhibit toxin formation in severe staphylococcal and streptococcal infections (toxic shock).

Anaerobe infections, particularly due to *Bacteroidaceae* or *Fusobacteria.*

Dosage: 10–20 mg/kg BW/day i.v. in 3–4 single doses.

Adjustment in RI:

- None (according to dosing.de)
- GFR <10 ml/min: where necessary 10 mg/kg every 12 h

- PD: where necessary 10 mg/kg every 24 h
- HF: where necessary 10 mg/kg every 12 h (clindamycin is not dialyzable)

Adverse drug reactions: *allergic*: skin reactions, rash, anaphylaxis; *toxic*: 10–30%, predominantly gastrointestinal disorders, not dose- and time-dependent, rare in children, diarrhea; pseudomembranous colitis.

Clindamycin is particularly suitable in bone and soft tissue infections because of its good tissue and bone penetration and is also well suited for use in severe staphylococcal/streptococcal and anaerobe infections.

7.9.9 Tobramycin

Sensitive: *Pseudomonas aeruginosa*, *enterobacteria*, *Yersinia*, *Campylobacter fetus*, *Pasteurella*, *Brucella*, *staphylococci*.

Compared with gentamicin, better against: *Pseudomonas aeruginosa.*

Resistant: *Enterococci, streptococci, pneumococci*, *Stenotrophomonas maltophilia*, *Burkholderia cepacia*, *all anaerobes*, *Providencia.*

Synergism exists with:

- Piperacillin/Tazobactam: *Pseudomonas*
- Ampicillin: *Listeriae*, enterococci
- Penicillin G: streptococcus viridans
- Cephalosporins: *Klebsiella*

Indications: *Pseudomonas infections* (combination with piperacillin, cephalosporin, carbapenem, or gyrase inhibitors). As part of the described escalation regimens but also as first line in peritonitis and (uro-)sepsis. Endocarditis treatment in combination with a beta-lactam antibiotic and/or a glycopeptide. *No monotherapy*. Poor penetration of abscesses and weak tissue penetration

Dosage: 3–5 mg/kg BW/day i.v. as a single dose.

Adjustment in RI:

Initial administration with normal dose and then extension of the interval depending on levels (target trough level, < 2 mg/L)

Adverse drug reactions: inner ear damage, nephrotoxicity

7.9.10 Ciprofloxacin

Sensitive: *Pseudomonas aeruginosa*, *Acinetobacter*, *Enterobacteriaceae*, *Campylobacter*, *Pasteurella*, *Haemophilus influenzae*, *Moraxella catarrhalis*, gonococci, meningococci, *staphylococci*, *Legionella*, mycobacteria.

Moderately to poorly effective in: Pneumococci, streptococci, enterococci, *Mycoplasma*, *Chlamydia*, *Rickettsia*, *Stenotrophomonas maltophilia*.

Resistant: *Enterococcus faecium*, anaerobes, *Listeria*.

Indication: hospital-acquired pneumonia (e.g., VAP), suspected *Pseudomonas* infection, in severe infections in combination with beta-lactam antibiotics instead of aminoglycosides, urinary tract infections. Prophylaxis for meningococci (adults).

Dosage: 20–30 mg/kg/d i.v. in 2 single dose.

Adjustment in RI (depending on GFR in mL/min):

- GFR > 50: normal dosage
- GFR 10–50: 10 mg/kg every 12 h
- GFR < 10: 5 mg/kg every 12 h
- PD: 5 mg/kg every 12 h
- HF: 10 mg/kg every 12 h

ADR: gastrointestinal reactions, central nervous systems disorders (seizures, psychotic states, vigilance disorders, taste disorders), rash, circulatory disorders, phototoxicity, Achilles tendon rupture, arthropathies.

Interactions: Increased theophylline levels, cyclosporine; increased tendency to seizures in combination with NSAIDs (not with aspirin); reduced absorption following administration of mineral antacids.

7.9.11 Linezolid

Sensitive: *Staphylococci* (*S. aureus*, *S. epidermidis, MRSA, MRSE, coagulase-negative staphylococci), streptococci, enterococci (faecalis, faecium, VRE)*, corynebacteria, *Listeria*, *Bacillus*, *Pasteurella*, gram-positive anaerobes (*Clostridium perfringens*, *Peptostreptococcus*), *Mycobacterium tuberculosis* complex, *Mycobacterium avium* complex.

Resistant: aerobic gram-negative rod bacteria, gram-negative anaerobes.

Indication: Reserve antibiotics following detection of abovementioned gram-positive microorganisms (especially VRE), soft tissue infections due to gram-positive microorganisms.

Dosage: 20–30 mg/kg/d i.v. in 2–3 single doses.

Adjustment in RI:

– *None* (according to Zyvoxid® product information)
– Adverse drug reactions: raised blood pressure, hyperthermia, CNS disorders (headache, dizziness), *thrombocytopenia*, sometimes pancytopenia, gastrointestinal disorders

7.9.12 Erythromycin and Clarithromycin

Erythromycin

Sensitive: *Mycoplasma* (other than hominis), *Chlamydia* (other than psittaci), *Legionella*, *Ureaplasma*, streptococci, staphylococci, pneumococci, *Bordetella pertussis*, *Corynebacterium diphtheriae*, *Listeria*, gonococci, meningococci, *Haemophilus*

influenzae, *Moraxella catarrhalis*, *Campylobacter*, *Helicobacter pylori*, clostridia, peptostreptococci, propionibacteria, actinomycetes, *Borrelia*, *Treponema*, some atypical mycobacteria.

Resistant: *Enterobacteriaceae*, *Pseudomonas*, *Acinetobacter*, many enterococci (> 50%), MRSA, MRSE, gram-negative anaerobes, *Mycoplasma hominis*, *Nocardia*, *Mycobacterium tuberculosis.*

Indications: atypical and community-acquired pneumonia, whooping cough, meningitis due to mycoplasmas, to increase bowel motility.

Dosage: 40 mg/kg/d i.v. in four single doses; to increase bowel motility, 10–15 mg/kg/d in three single doses p.o. or i.v.

Adjustment in RI (depending on GFR in mL/min):

- GFR > 50: normal dosage
- GFR 10–50: 5–10 mg/kg every 8 h
- GFR < 10: 5–10 mg/kg every 12 h
- PD: 5–10 mg/kg every 12 h
- HF: 5–10 mg/kg every 8 h

Adverse drug reactions: Because of the *triggering of arrhythmias* and *hepatotoxicity*, erythromycin is used reticently in intensive care therapy as a prokinetic in gastroparesis.

Caveat May increase theophylline and cyclosporine A blood levels and enhanced effect of anticoagulants; do not use in long QT syndrome!

Clarithromycin

Sensitive/resistant: as erythromycin.

Indications: atypical and community-acquired pneumonia, whooping cough, meningitis due to mycoplasmas.

Dosage: 15–20 mg/kg/d p.o. in two single doses (good oral availability).

Adjustment in RI (depending on GFR in mL/min):

- GFR > 50: normal dosage
- GFR 10–50: normal dosage
- GFR < 10: 7.5 mg/kg every 12 h
- PD: 7.5 mg/kg every 24 h
- HF: 7.5 mg/kg every 12 h

7.9.13 Vancomycin and Teicoplanin

Vancomycin

Sensitive: all gram-positive pathogens (incl. MRSA) and gram-positive anaerobes (incl. *Clostridium difficile*); compared with teicoplanin, better against

staphylococci and worse against streptococci, pneumococci, enterococci, *Clostridium difficile.*

Resistant: all gram-negative pathogens, glycopeptide-resistant staphylococci and enterococci (e.g., VRE), intracellular pathogens.

Indications: severe infections with beta-lactam-resistant gram-positive pathogens (MRSA, coagulase-negative staphylococci, *Enterococcus faecium*), primarily catheter sepsis, infections due to MRSA, infection due to clostridia (then oral use).

Dosage: 40–60 mg/kg BW/day i.v. in four single doses.

Intraperitoneal administration on peritoneal dialysis (see Chap. 4) and intrathecal therapy for shunt infections are also possible (e.g., 10–20 mg intrathecally every 24–48 h and then clamp off external ventricular drain for 4 h). In *Clostridium*-induced pseudomembranous colitis, oral administration (no enteral absorption) is used (e.g., 4 x 20–40 mg/kg p.o.).

Adjustment in RI (depending on GFR in mL/min):

- GFR > 50: 10 mg/kg every 6–8 h
- GFR 10–50: 10 mg/kg every 12–24 h
- GFR < 10: 10 mg/kg every 24–96 h
- PD: 10 mg/kg every 24–96 h
- HF: 10 mg/kg every 12–24 h (vancomycin is hemofiltered but not dialyzed)

Dose reduction in RI according to levels (target trough level < 15 mg/L); drug level monitoring where necessary before next administration.

Adverse drug reactions: allergies, red-man syndrome (flushing symptoms), sometimes nephrotoxicity in combination therapies, ototoxicity.

"Change of doctrine with vancomycin?" The (putative) nephrotoxicity was traditionally the focus of attention in treatment with vancomycin. Therefore, consideration was always given when dosing to ensuring that trough levels did not exceed 15 mg/L. On the basis of new findings in the last 10–15 years, the recommendations for the treatment of invasive staphylococcal infections in adults (incl. MRSA) have changed. To guarantee effective treatment and prevent resistance formation, target levels of 15–20 mg/L (before the next dose) are now recommended (i.e., the dose would be increased at trough levels of 10 mg/L).

As this procedure has not yet become established practice in German pediatrics (to our knowledge) and also good results can be achieved with the traditional regimen (in our experience), the recommendations of the "Infectious Diseases Society of America" have (as yet) not been implemented in our practice.

Teicoplanin

Sensitive/resistant: see under vancomycin.

Indications: see vancomycin (benefits over vancomycin: single daily dose, no levels strictly required); almost no CSF penetration.

Dosage: 8–10 mg/kg/d i.v. in one single dose (initially: as necessary 16–20 mg/kg/d i.v. in two single doses).

Adjustment in RI (depending on GFR in mL/min):

- GFR > 50: 8 mg/kg every 24 h
- GFR 10–50: 8 mg/kg every 48 h
- GFR < 10: 8 mg/kg every 72 h
- PD: 8 mg/kg every 72–96 h
- HF: 8 mg/kg every 24–48 h

Dose reduction in RI where necessary, based on drug levels (target trough level < 10–15 mg/L).

Adverse drug reactions: Teicoplanin is usually well tolerated. Ototoxicity and nephrotoxicity can sometimes be potentiated in combination with other ototoxic and nephrotoxic substances.

7.9.14 Metronidazole

Sensitive: *all anaerobes* (except *Propionibacterium*, actinomycetes), *Campylobacter fetus*, *Helicobacter pylori*, *Gardnerella vaginalis*, lamblia, *Trichomonas*, *Entamoeba histolytica.*

Resistant: all aerobic and facultative aerobic bacteria, propionibacteria, actinomycetes.

Indications: infections due to anaerobes in combination with a beta-lactam antibiotic, infections due to gas-formers, infections due to *Clostridium difficile* (if vancomycin cannot be given p.o.), amebic dysentery.

Dosage: 30 mg/kg/d iv in three single doses.

Adjustment in RI: *none* (according to manufacturer).

Adverse drug reactions: primarily gastrointestinal ADR, at higher doses possibly neuropathies and central nervous system disorders.

7.9.15 Tigecycline

Sensitive (practically all): gram-positive, including MRSA and VRE, gram-negative (incl. ESBL, *Klebsiella*), anaerobes, and atypical microorganisms.

Resistant: *Pseudomonas aeruginosa*, *Burkholderia cepacia*, *Proteus*, *Providencia*, *Morganella.*

Indications: severe skin and soft tissue infections (e.g., necrotizing fasciitis, mediastinitis), severe mixed infections, severe intraabdominal infections. Preferably not in pulmonary and urinary tract infections.

Dose: Initially 2 mg/kg i.v. (Ad. 100 mg/dose) and then 1 mg/kg (Ad. 50 mg/dose) i.v. every 12 h.

According to our microbiology, the manufacturer's stated dose should be doubled.

Halving of the dose in severe hepatic impairment (Child-Pugh C).

Adjustment in RI: *none* (see dosing.de or manufacturer's information).

Adverse drug reactions: Tigecycline is usually well tolerated; occasionally abdominal symptoms, slight increase in transaminases, allergic reactions, blood count changes.

Remark on the information in this chapter about dose adjustments in renal impairment (RI) The authors assume no liability for the information on dose adjustments in RI. It is intended to serve as a guide and should be checked in each individual case (please also see for example: https://kdnet.kdp.luoisville.edu/drugbook/pediatric/).

Remark on liver conditions emergent on antibiotic therapy (in particular, increases in transaminases, cholestasis) Many antibiotic therapies can cause an elevation in transaminases without necessarily being a sign of liver damage (a classic example of this is meropenem). Some antibiotics, however, are directly hepatotoxic (e.g., rifampicin). By contrast, cholestasis of varying degrees of severity can occur infrequently on antibiotic therapy; classic examples of this are penicillins, cephalosporins, and macrolides. The website "LiverTox" (https://livertox.nih.gov/) of the National Library of Medicine can provide guidance.

In case of doubt, the suspect medications must be discontinued or exchanged.

7.10 Management of Multiresistant Microorganisms

The "problem" microorganisms in hospitals can be divided into three main groups: (1) methicillin-resistant *Staphylococcus aureus* (MRSA), (2) vancomycin-resistant enterococci (VRE), and (3) multiresistant gram-negative (MRGN) pathogens.

While MRSA isolates have decreased slightly in recent times, those from MRGN pathogens have been on the constant rise. Although the patients themselves usually bring microorganisms into the hospital, they can obviously also become contaminated or infected in the hospital or "develop" a resistant microorganism on antibiotic therapy.

7.10.1 Methicillin-Resistant *Staphylococcus aureus*

Methicillin-resistant *Staphylococcus aureus* (MRSA) predominantly colonize the nasopharyngeal cavity but can also be found in chronic wounds and the perianal region. Transmission of MRSA occurs primarily by hands and also as a droplet infection. However, MRSA can also remain contagious for months on contaminated surfaces and objects (e.g., stethoscope). Most MRSA carriers can be identified by systematic screening procedures on admission to the ward (smears from both nasal vestibules and where necessary from the throat or from wounds).

Basic hygiene measures (see Table 7.6) and personally assigned materials (e.g., patient-specific stethoscope) are effective in preventing transmission. In the event of proven or known MRSA colonization of the patient, *single room isolation* and *MRSA-reducing treatment* are also recommended. The "decolonization plan" includes the use of mupirocin nasal ointment, washing the skin and hair with an

Table 7.6 Hospital hygiene measures

Pathogens	Single room	Cohorting	Protective gown and disposable gloves	Face mask
MRSA	Yes	Yes	Yes	Yes
2MRGN2 NeoPed	No	Yes	Yes	No[a]
3MRGN and 4MRGN[b]	Yes	Yes	Yes	Yes
VRE	Yes	Yes	Yes	No
P. aeruginosa *S. Marcescens* (without MRGN properties)	No	Yes	Yes	No[a]

After http://dgpi.de/go/wp-content/uploads/2014/08/MRGN_DGPI_PaedIC-Empfehlung_HygMed.20141.pdf

[a]Only in activities with an increased risk, e.g., when aspirating the nasopharynx, in ventilated children requiring open aspiration

[b]In patients colonized or infected with 4MRGN bacteria, a sufficient number of nursing staff should be assigned to ensure other patients not colonized with those pathogens are not treated at the same time

antimicrobial washing lotion, and mouth rinses (see www.gosh.nhs.uk/health-professionals/clinical-guideline/meticillin-resistant-staphylococcus-mrsa-control-and-mangement).

7.10.2 Vancomycin-Resistant Enterococci

Vancomycin-resistant enterococci (VRE) constitute a particular problem as they can transfer the glycopeptide resistance gene to staphylococci, for example. *Enterococcus faecium* in particular already possesses a broad spectrum of intrinsic resistance. VRE usually occur perianally or around colostomies. Contamination occurs by direct contact with secreta (droplet or smear infection). Dried isolates can remain viable for many months. The recommendations for infection prophylaxis in VRE (see Table 7.6) are to a large extent identical to those for MRSA (with the exception of a decolonization plan). Restrictive use of glycopeptides can help prevent the development of VRE.

7.10.3 Multiresistant Gram-Negative Pathogens (MRGN)

Pathogens collectively referred as multiresistant gram-negative (MRGN) differ in the group of antibiotics they are resistant to. Of mention here are *E. coli*, *Klebsiella*, *Serratia*, *Pseudomonas*, *Acinetobacter*, and other gram-negative rod bacteria. These microorganisms are usually found in the gastrointestinal or urogenital tract. Colonization with MRGN bacteria therefore mainly occurs perianally but can also be present in pharyngeal or tracheal secretions. As with vancomycin-resistant enterococci (VRE), transmission usually involves a droplet or smear infection. The pathogens of the MRGN group are divided according to the presence of resistance

to 2–4 of the relevant antibiotic drug classes, acyl-ureidopenicillins (piperacillin), 3rd−/4th-generation cephalosporins (e.g., cefotaxime, ceftazidime), carbapenems (e.g., meropenem), and fluoroquinolones (ciprofloxacin), into either 2MRGN, 3MRGN, or 4MRGN. While 2MRGN do not play any role in terms of hygiene measures on adult wards, they must be given due consideration in the risk area of a pediatric intensive care where neonates and sometimes premature infants are also cared for. If 2MRGN are present, glove and gown nursing is usually sufficient. From 3MRGN, the patient should receive barrier nursing as well (preferably an isolation room), in addition to which a face mask should be worn. A patient with a 4MRGN must always be isolated in a single room (see Table 7.6). Decolonization measures are also of no relevance here.

Generally, all measures to protect the patient against iatrogenic infections must be implemented. Above all, the following should be mentioned:

- Disinfect hands as well as instruments, stethoscope, etc.
- Comply with the specified hygiene measures (in accordance with institutional hygiene plan)
- Comply with special hygiene measures in immunosuppressed patients (e.g., reverse isolation of patients)

Suggested Reading

1. Algra SO, et al. Bedside prediction rule for infections after pediatric cardiac surgery. Intensive Care Med. 2012;38(3):474–81.
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