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Analysis of Antibiotic Usage in the Children's Hospital Munich Schwabing: Identifying Interventions for an Optimized Antibiotic Therapy

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Contents

1 Introduction

1.1 History

In the first section significant moments in the history and development of antibiotics are being presented.

1.1.1 Discovery of Penicillin

In 1929, Alexander Fleming published a paper about his discoveries on the antibacterial effects of a penicillium mould [1]. Initially, he was working with *Staphylococcus* cultures, of which some got contaminated with different microorganisms. Examining his cultures, he accidently discovered a penicillium mould on his agar plate. In a circumscribed circle around it no *Staphylococcus* was growing. Fleming drew the conclusion that the mould had to produce a certain agent that inhibited the growth of *Staphylococcus*. This agent, which he named penicillin, was the pioneer substance of the antibiotic timeline [2].
The following experiments, Fleming conducted with penicillin, were described in his paper: The fact that penicillin had bactericidal effects on *Staphylococcus* but not on *Bacillus influenza*e (syn. *Haemophilius influenzae*) made him able to isolate or unmask certain bacteria. Furthermore, he addressed the problem of toxicity as a crucial quality of an agent potentially used on humans. However, he did not find any toxic symptoms in animals after intravenous injection of penicillin. All in all, he pointed out that penicillin could be adopted in the treatment of bacterial infection with a better outcome than chemical antiseptics used so far.
10 years later, the Oxford Group with its leading members Ernst Chain and Howard Florey picked up research on penicillin. They made further investigations on the characteristics of penicillin concerning its therapeutic effects on infected animals. Focusing on dosage and the interval of treatment Chain and Florey added more clinical aspects to the research of Fleming [3]. Finally, in 1941 the 2 scientists developed a method to isolate and produce penicillin, which paved the way for its industrial fabrication [4]. In 1945, Alexander Fleming, Ernst Chain, and Howard Florey received the Nobel Prize in Physiology or Medicine "for the discovery of penicillin and its curative effect in various infectious diseases" [5].
The awarded scientists highly impacted the future of human medicine with their discoveries: During the following decades antibiotics were decisive for successful therapy and containment of infectious diseases [6].

1.1.2 First Successes with Antibiotics

At the end of the 20th century, Gregory L. Armstrong and colleagues published „Trends in Infectious Disease Mortality in the United States during 20th Century" in the Journal of the American Medical Association (JAMA). Analyzing and interpreting data on causes of death and mortality statistics provided by the Division of Vital Statistics of the Centers for Disease Control and Prevention's (CDC) National Center for Health Statistics (NCHS), they presented the development of mortality due to infectious diseases from 1900 to 1996: Whereas it showed an annual decrease of 2.8% in the period from 1900 to 1937, the rate declined by 8.2% per year in the following 15 years [7]. Furthermore, the mortality rate of the venereal disease syphilis dropped significantly to less than 0.2 per 100,000 in the years around 1940. Certainly, that is owed to the change in syphilis therapy from arsephenamine, the first chemotherapeutic drug discovered by Paul Ehrlich, to penicillin. Its overall advantages were a shorter duration of therapy, the efficacy against neurolues and less side effects. As patients with syphilis were socially stigmatized, that can be considered a crucial success [8]. Beside the pharmacological benefits of penicillin, it is assumed that its wide spread use led to less cases due to unnoticed infections and less diagnoses [9].
Amongst other reasons, such as improvements in human living conditions and sanitary facilities, the development of penicillin and in the following other antibiotics were definitely decisive factors for the decrease of mortality due to infectious diseases [7]. In fact, infectious diseases were thought to be defeated and chronic diseases were considered to be the medical challenge of the future [10].

1.2 Most Important Antibiotic Classes

In the following, important facts in terms of antibiotic therapy are explained. In addition, most relevant antibiotics for this study are outlined.

1.2.1 Definitions

Antiinfective pharmaceuticals are substances with the ability to eradicate microorganisms in human beings. In particular, they are effective in a concentration which humans still tolerate without any toxic effects. Antiinfectives are used in the therapy against bacteria, fungi, parasites, and viruses.
In former times, antiinfectives used to be subdivided into antibiotics and so called "chemotherapeutics". Unlike antibiotics, which were naturally produced by microorganisms like fungi, chemotherapeutics were chemically synthesized. Meanwhile, many antibiotics are produced synthetically as well. Therefore, the terms

"antibiotics" and "chemotherapeutics" merge. In the following, "antibiotics" is the consistently used term.
The spectrum of activity of antibiotics specifies the bacteria affected by the antibiotic in vitro. Broad-spectrum antibiotics are hence effective against numerous bacteria.
Concerning the mechanism of antibiotic effectiveness, there are bacteriostasis and bactericidy. Whereas bacteriostatic antibiotics just stop the growth of bacterial cells without destruction, bactericidal antibiotics attack and actively kill bacterial cells. In the process of bactericidy, the efficacy of antibiotics is either depending on the concentration achieved at the site of infection, and on the amount of time they remain at a therapeutic concentration. Relating thereto is the minimal inhibitory concentration. This is the concentration of an antibiotic which is at least necessary to prevent visible growth of bacteria *in vitro*.
In general, antibiotics interfere with one of the following structures or processes in the bacterial cell: the cell wall, the cell membrane, the protein synthesis or the synthesis of nucleic acid [11].

1.2.2 Principles of Antibiotic Therapy

Antibiotic therapy requires the adherence to some principals: The antibiotic and its dosage have to be chosen according to the most probable pathogen in empiric therapies and according to susceptibility and resistances in targeted therapies. Antibiotic therapy should be reconsidered regularly. Important aspects are way of application, the duration of therapy, side effects, and pharmacological properties of the antibiotic. Furthermore, patient characteristics like weight and renal or liver function need to be respected [12].

1.2.3 Overview of the Most Common Antibiotics

In the following, the most important classes of antibiotics and the basics of antibiotic therapy are summarized. It was focused on antibiotics for systemic administration.

1.2.3.1 β-lactam Antibiotics

The β-lactam antibiotics comprise penicillins, cephalosporins, monobactams, and carbapenems. What they all have in common is a structural component, the β-lactam ring, and their mechanism of action: β-lactam antibiotics interfere with an enzyme responsible for the synthesis of the cell wall. In detail, that enzyme is called transpeptidase and catalyzes the last reaction of the peptidoglycan synthesis. The latter is the main element in the bacterial cell wall. Due to similarity in

the molecular structure between β-lactam antibiotics and the transpeptidase's substrates, the antibiotics are able to bind on the active center of transpeptidase and block it. This leads to mistakes in the construction of the cell wall and therefore to bacteriolysis. It is important to know that β-lactam antibiotics only affect proliferating pathogens, as only these show cell wall synthesis [13].
As penicillins and cephalosporins are the most important β-lactam antibiotics for the present study, they are described in more detail in the following.

1.2.3.1.1 Penicillins

According to their spectrum of activity there are different subclasses of penicillins. Also, they are subdivided by their sensitivity towards penicillinases. These enzymes are able to cut the β-lactam ring and thereby inactivate the antibiotics.
Penicillinase-sensitive penicillins are benzylpenicillin and phenoxymethylpenicillin. Their spectrum of activity covers gram-positive *Cocci*, gram-positive rod-shaped bacteria, gram-negative *Cocci* and *Spirochetes*. Whereas benzylpenicillin is acid-labile and has to be administered intravenously, phenoxymethylpenicillin can be given orally.
Penicillinase-stable are oxacillin and flucloxacillin. They are mainly used in the treatment of infections caused by *Staphylococci* but show nearly no efficacy against gram-negative bacteria.
The aminopenicillins ampicillin and amoxicillin show a broader spectrum of activity due to a slightly different molecular structure. In addition to the spectrum of benzylpenicillin, ampicillin and amoxicillin are effective against numerous gram-negative bacteria, like *Haemophilus influenzae*, *Escherichia coli (E. coli)* and *Proteus mirabilis*. Amoxicillin is better absorbed (by the human body) and can thus be used for oral treatment unlike ampicillin.
Another group of broad spectrum penicillins are acylaminopenicillins such as mezlocillin and piperacilline. They show, for example, activity against *Pseudomonas* or *Proteus species* and are therefore the most effective penicillins concerning gram-negative bacteria. They are used to treat acute, severe bacterial infections.
Aminopenicillins as well as acylaminopenicillins are sensitive towards penicillinase and can be administered in combination with β-lactamase inhibitors (BLI) like clavulanic acid, sulbactam or tazobactam [14].

1.2.3.1.2 Cephalosporins

Similar to penicillins, cephalosporins are subdivided due to their spectrum of activity.
Group 1 comprises cefazolin, cefaclor, cafadroxil, and cefalexin. They show efficacy against gram-positive bacteria.

Group 2 includes cefuroxime and its oral equivalent cefuroxime axetil. They also show high activity against gram-positive bacteria, but also affect gram-negative pathogens, e.g. *Haemophilus influenzae.*
An even more extended spectrum against gram-negative bacteria show cephalosporins of the third group (cefotaxime, ceftriaxone, cefpodoximproxetil, ceftibuten, ceftazidime). However, in comparison to group 1 and 2, they have reduced activity against gram-positive bacteria. Ceftazidime is the only group 3 cephalosporin which is effective against *Pseudomonas*.
Group 4 cephalosporins (cefepime) contain activity against *Pseudomonas* and otherwise have the same spectrum as group 3. On top of that, they can be used against β-lactamase producing *Enterobacteriaceae* [15].

1.2.3.2 Glycopeptides

Glycopeptides such as vancomycin, teicoplanin, and telavancin inhibit the cell wall synthesis with another mechanism than β-lactam antibiotics. They bind the substrates of transpeptidase so that transpeptidase is unable to process them. Their spectrum only covers gram-positive bacteria and usually glycopeptides are reserved for application against multi-resistant *Staphylococcus* and *Enterococcus* strains. Furthermore, they can be used for the oral treatment of infections with *Clostridium difficile* [16]. Currently there are new agents in the development and some are already approved [17].

1.2.3.3 Aminoglycosides

Aminoglycosides such as tobramycin, gentamicin, amikacin, and streptomycin impact the protein synthesis by interfering with a subunit of the ribosome. As a result of their characteristics, e.g. broad spectrum of activity, strong bactericidal activity, fast onset and synergic effect with β-lactam antibiotics, aminoglycosides are useful agents against severe septic and nosocomial infections caused by gram-negative and gram-positive germs. Disadvantages are the little therapeutic range and high toxicity. Due to nephro- and ototoxicity serum concentrations must be monitored [18].

1.2.3.4 Macrolides

Similar to aminoglycosides, macrolides affect a subunit of the bacterial ribosome leading to damaged protein synthesis. The most common applied macrolides are erythromycin and the newer clarithromycin and azithromycin. They can be used to treat respiratory tract infections and as an alternative to penicillin in case of penicillin allergy. Due to only few adverse events, which are mainly gastrointestinal symptoms, macrolides are popular in pediatrics. Furthermore, they are part

of the eradication protocols in the treatment of *Helicobacter pylori*. Clarithromycin and azithromycin show a better bioavailability and have higher concentrations at their site of activity compared to the precursor substance erythromycin. Also, it is necessary to administer them once or twice a day because of better pharmacokinetic characteristics.
Macrolides are metabolized by hepatic Cytochrom-P450 (CYP) enzymes and thus interact with a lot of other drugs. Dose reduction and alternatives should be considered in patients with certain co-medication. Furthermore, *Streptococcus pneumoniae* (*S. pneumoniae*) shows high resistance rates against macrolides [19].

1.2.3.5 Oxazolidinones

The most common oxazolidinone is linezolid. It is effective against gram-positive bacteria due to inhibition of the protein synthesis at an early step involving the binding of N-formylmethionyl-tRNA to the ribosome. It is mainly used in the treatment of infections of lung, skin or soft tissue. Furthermore, it is a reserve antibiotic in the defense of multiresistant bacteria like *methicillin-resistant Staphylococcus aureus* (*MRSA*), penicillin-resistant streptococci, or *vancomycin-resistant enterococci* (*VRE*). Adverse events manifest in gastrointestinal symptoms, in changed blood counts or in elevated liver enzymes. Due to efficacy as inhibitor of monoamine oxidase the combination with antidepressants should be avoided [20].

1.2.3.6 Tetracyclines and Glycylcyclines

The most common tetracyclines are tetracyclin, doxycyclin, and minocyclin. They affect the protein synthesis by preventing the attachment of aminoacyl-tRNA to the ribosomal acceptor site. Tetracyclines show a broad-spectrum efficacy against gram-positive and gram-negative bacteria. However, *Pseudomonas, Proteus* and *Mycobacteria* are resistant. Tetracyclines work in infections with *Chlamydia, Mycoplasma* or *Borrelia* for example. Unfortunately, resistance rates against tetracyclines are rising [21]. The 2005 approved glycylcycline tigecycline is a tetracycline analogue. Due to molecular structures most bacteria are unable to develop resistance against tigecycline. Furthermore, it shows a broader spectrum including multi-resistant bacteria. Still, *Pseudomonas* is naturally resistant against tigecyclin. It can only be administered parenterally and is used for complicated infection of the abdomen, the skin, and soft tissue. The high amount of adverse events, which are mainly nausea and vomiting, have to be taken into account [22].

1.3 Resistances and Ways of Containing Them

The following section is about the problem of antibiotic resistances in bacteria. Causes and impacts of resistant bacteria as well as attempts to control them are mentioned.

1.3.1 Bacterial Mechanisms of Antibiotic Resistance

The success of antibiotics led to widespread use, which resulted in a high selective pressure for the bacteria. Thus, after a short amount of time, the first bacteria developed resistance against penicillin and its derivatives: *Staphylococcus aureus*, which was of the first microbes attacked by antibiotics, learnt to produce penicillinase. This enzyme destroys the therapeutic power of penicillin by cutting its β-lactam ring. Resistances also developed rapidly against Streptomycin, which was discovered right after penicillin and was commonly used in combination with penicillin. Therefore, it was used less and less, so that the treatment of tuberculosis is today almost the only indication for streptomycin [23].
Bacterial resistance is based on genetic changes, including altered gene expression, gene mutation, or acquisition of genetic material [24]. Genes can be transferred from one cell to another by *plasmids* (independently reproducing, circled DNA fragments), a process called horizontal gene transfer. Other examples of mobile DNA pieces using horizontal gene transfer are *transposons* and *integrons* [25]. Genetic changes result in 4 main mechanisms of bacterial resistance [26]. The first is enzymatic inhibition, and, for example, established in penicillinase producing pathogens. A group of enzymes, called β-lactamases, cut the amide bond of the β-lactam ring, which is the essential structure for the effect of the β-lactam antibiotics as described above. The second common mechanism to achieve resistance is a molecular change in the antibiotics' target. The latter be modified in a way that prevents antibiotics from binding. Thirdly, antibiotic resistant bacteria may alter the structure of transmembrane proteins called *porins*. These are responsible for the cell’s exchange with the environment. Structurally large antibiotics cannot pass through smaller *porins*, for example, and the production of efflux proteins leads to a decline of the intracellular antibiotic concentration. The 4th mechanism of bacterial resistance is the adaption of their metabolism to the antibiotic effect. Some antibiotics target certain metabolic molecules, e.g. enzymes responsible for the production of amino acids. Substances like amino acids are normally essential to maintain an adequate cell function. However, bacteria can be able to replace some of those substances or change their metabolism and can thus handle the antibiotics' effect [27].

1.3.2 Resistant Bacteria as a Threat to the Health Care System

In 2014, the World Health Organization (WHO) attended to the problem of resistant bacteria and published a global report on this topic [28]. The report points out that “A post-antibiotic era-in which common infections and minor injuries can kill-is a very real possibility for the 21st century” [24, p. 3]. This statement is underlined by data provided by the member states of the WHO. It shows, for example, the increased rates of cephalosporin resistance in *E. coli* and *Klebsiella* and increased rates of penicillin resistance in *S. pneumoniae*. The use of last resort antibiotics, which are necessary for the treatment of infections caused by these microbes, leads to higher costs and more side effects for the patient. Despite its natural susceptibility to β-lactam antibiotics *E. coli*, typically causing urinary tract infections, especially in children, shows rates of 41% to 100% ampicillin resistance depending on the country [29].

The higher resistance rates are mainly linked to poverty in the according areas. In developing countries antibiotics are either not available due to their price or produced locally and thus are of lower quality. Furthermore, there are no restrictions concerning the usage of antibiotics. People can buy their medication over the counter without prescription and subsequently may take it in a wrong way. Consequently, developing countries are faced by multidrug-resistant bacteria, for which they would need but could never afford the necessary last resort antibiotics. Keeping in mind that about 80% of the world’s population live in developing countries the impact of this problem becomes even more evident [30].

It is self-explanatory that in times of globalization, international travel, migration and import of agricultural products the situation in developing countries also affects industrial countries, as resistant bacteria can easily cross borders. That makes them a global problem for the treatment of infectious diseases [31]. Thomas Tängdén and colleagues further investigated that issue in 2010. They detected foreign travel as a major risk factor for colonization with resistant bacteria by investigating rectal swabs of travelers before and after a journey out of northern Europe [32].

Unfortunately, the development of new drugs against resistant strains is not as fast as the development of bacterial resistances [33] [34]. Especially multidrug-resistant gram-negative bacteria cannot be fought if there is no significant progress in antibiotic research [35]. One reason for the stagnation is that there are only a few pharmaceutical companies left today doing research on antibacterial agents. Many of the companies moved on to research in the area of lifestyle drugs or therapeutic agents for chronic diseases. Furthermore, the balance between the effort for developing a safe and effective antibiotic and the economic profit

through selling it is uneven [36]. In summary, the bacteria are simply faster in gaining resistance than humans are in fighting it [37]

Another consequence of the development of resistances is increasing costs to be covered by the healthcare system. In 2009, an investigation of the European Union (EU) on the costs caused by multidrug-resistance and its consequences found that an additional 900 million Euro per year had been spent in the EU, Norway and Iceland due to a higher number of hospital days and increased in-hospital costs [38]. It is no surprise that the issue of antibiotic resistance has already found its way into politics. In 2011, Germany changed its law on the prevention and control of infectious diseases containing now compulsory elements in hospital hygiene aiming at preventing infections and resistant pathogens [39]. This was followed by a 10-point plan to avoid spreading resistances presented by the German health minister in 2015 [40]. Also in 2015, the President of the United States of America (USA) Barack Obama published a “National action plan for combating antibiotic-resistant bacteria” [41], which completes the image of antibiotic resistance as an important global topic.

1.3.3 Use of Antibiotics in Veterinary Medicine – Contribution to the Development of Resistances

There are several reasons why antibiotics are used in agriculture and food animal production. One of them is the use of antibiotics as *growth promotors*. In the years around 1950, it was discovered that subtherapeutic dosages in animals drinking water or food makes them grow [42]. The underlying mechanisms are still not completely clear. Possible factors contributing to the effect might be interactions between antibiotics and microbes in the intestine that result in a thinner intestine wall and thus better resorption of nutrients as well as fewer opportunistic pathogens [43]. As the dosage used in growth promoters is too low to eradicate bacteria, the continuous non-therapeutic application of antibiotics leads to the development of resistances in the bacteria colonizing the animals, which was proved by an investigation on the resistance rates of *E. coli* in cattle [44]. Consequently, the use of antibiotic growth promotors in animal food was forbidden in 2006 by the European Union [45]. However, antibiotics are also used as therapeutic agents in veterinary medicine and food animal production in order to control or prevent infectious diseases. Apart from individual treatment, which is mostly used for domestic animals and is similar to the treatment of humans, a common concept in livestock production is metaphylaxis. Once one or a few animals show symptoms of infection, the whole group gets treated by adding antibiotics to water or food. The aim is to avoid illness of the whole herd or flock and thereby reduce

treatment costs. Thirdly, antibiotics are used, like in humans, as prophylaxis to prevent mastitis in dairy cows for example. Prophylactic antibiotic administration is also made use of in order to contain the spread of respiratory or enteric diseases when different species get mixed [46]. It stands to reason that some of the applications are necessary, but still the use of antibiotics in animals again raises the selective pressure on bacteria.
All in all, estimates indicate that the use of antibiotics in veterinary medicine and livestock production is twice as high as in human medicine and will keep on rising [47]. Due to the increasing demand of food producing animals and a shift towards intensive farming systems the consumption of antibiotic agents in livestock production will reach an increment of 67% by 2030 according to a study conducted by Thomas P. van Boeckel and colleagues [48].
It is obvious that the use of antibiotics in livestock production and veterinary medicine also affects humans, in particular through direct contact, especially between farmers and animals, or through the food chain as resistant bacteria can spread from animal to man or pass on resistance transferring plasmids [49]. This leads to the colonization of humans with resistant strains of e.g. *E. coli*, *Campylobacter* or *Salmonella*. Thus, it is crucial to question the comprehensive application of antibiotics in animals [50] [51].

1.3.4 Strategies against Resistant Bacteria: Antibiotic Stewardship (ABS)

In order to control the development of resistant bacteria, strategies concerning the use of antibiotics have become an urgent necessity [52]. Those strategies normally comprise different interventions which are part of a so-called antibiotic stewardship (ABS) program. Several studies investigate the effect of different ABS interventions on antibiotic prescription. Hence, the societies for infectious diseases of many countries have developed guidelines for the rational use of antibiotics in hospitals. The following is retrieved from the guidelines of the German Society for Infectious Diseases [53]. 4 points were highlighted as core elements of each ABS program:

1. “Application of local treatment guidelines/pathways, hospital antiinfective formulary, formulary restrictions, and approval requirements” [44, p. 399]
2. “Design and implementation of education, training, and information” [44, p. 400].
3. “Conducting proactive audits of antiinfective use” [44, p.400].
4. “Quality indicators” [44, p.400].

These points indicate that basic knowledge referring to the ABS interventions should be provided to the medical staff participating in the ABS program, that re-evaluation and critical discussion of any administered therapy with the ABS team is recommended, and that ABS programs should be implemented as part of the clinic's quality management.
In order to be able to establish an effective ABS program, hospitals have to fulfill the following conditions: First, the interventions need to be implemented by an ABS team distinguished by professional knowledge about infections, effects of antibiotics and their pharmacological attributes. At best, the ABS team includes an infectious disease physician, a clinical pharmacist, and a microbiologist. Secondly, the hospital should at least annually collect data on pathogens, resistance patterns, and antibiotic prescription to provide basic statistics on which the ABS program can be built.
Beside the above-mentioned main elements of ABS programs, the German guideline lists several items which can be added. Those are for example precocious de-escalation and reduced duration of therapy, switching form intravenous to oral administration at an early stage and computer-aided prescription tools, as well as improvement of dosing.
The corresponding American guideline [54] mentions similar interventions in the establishment of ABS programs but focuses on only 2 fundamental elements:

1. "Prospective audit with intervention and feedback" [45, p.164].
2. "Formulary restriction and preauthorization requirements for specific agents" [45, p.164].

In other words, retrospective audits are recommended after antibiotic prescription and should include a thorough discussion with the ABS team with critical assessment regarding dosage, length of therapy and way of application. Moreover, in the case of specific agents, the physician has to confer with the ABS team prior to its clinical use to confirm its indication.
Strategies like local guidelines and education are listed as accessory items of any ABS program. In general, the involvement of infectious disease specialists in ABS programs and in the treatment of inpatients with bacterial infections is strongly recommended as they can contribute important clinical knowledge about infections and ABS to recommendations provided by pharmacists and microbiologists. The consultation of infectious disease specialists should thus be a fundamental part of patient care in every hospital. However, in many countries the employment of infectious disease specialists is unfortunately not established yet [55].

An increasing number of studies document the positive effects of ABS interventions. In 2013, a Cochrane review of 89 studies suggested that ABS interventions can improve clinical outcome and reduce antibiotic resistance as well as nosocomial infections [56]. While there is only limited information on pediatric ABS programs, Araujo-da Silva summarized the available studies confirming the above-mentioned Cochrane review [57].

1.4 Aim of this Study

The aim of the present study was to identify targets for an ABS program in the Children's Hospital Munich Schwabing which represents both a tertiary care pediatric reference center and a university hospital. The antibiotic usage of inpatient cases on several wards was documented and analyzed for certain parameters including appropriate indication and dosages. By comparing it to the current guidelines and literature, the use of antibiotics was being questioned and possibilities for optimizing antibiotic therapy have been identified. Furthermore, a comparison of our own data with data on antimicrobial usage in another local university children's hospital was provided. The present thesis was part of a concerted project in order to establish ABS programs at Munich children hospitals.

2 Material and Methods

2.1 Settings of the Study

The Children's Hospital Munich Schwabing belongs to both the Munich Municipal Hospital Group (MMHG) [German: Staedtisches Klinikum Muenchen (StKM) GmbH, syn. Muenchen Klinik (MueK)], the largest comprehensive care provider in Southern Germany, and the Klinikum rechts der Isar (MRI) of the Technische Universitaet Muenchen (TUM), one of the two Munich university hospitals. As such the children's hospital represents both a communal tertiary care center and a university hospital. Unlike the main part of MRI, it is located in northern Munich on the campus of the Munich Municipal Hospital Schwabing (Klinikum Schwabing, KS). During the study period, in total, the children's hospital had 97 beds for general pediatric care and 9 beds for intensive care of neonates and older children. In 2015, 4420 patients were admitted to general wards, while 236 neonates and 363 older children were admitted to the intensive care unit.
The study was conducted on the neonatal ward (named here ward 1, including neonates and infants) and on 3 general pediatric wards (named here ward 2, 3 and 4). Ward 2 and 3 both were general pediatric wards with a focus on neurological or metabolic diseases and infectious diseases, respectively. Ward 4 included 2 units cared for by general pediatricians and pediatric surgeons, respectively.

2.2 Study Design

2.2.1 Data Collection and Documentation

In order to collect the data on antimicrobial therapy, the record of any patient discharged from the selected wards was checked on the day of discharge and the medical reports were analyzed as soon as available. If these documents were not comprehensive enough to answer all study questions the doctors in charge were contacted. The data was collected in 2 separated data banks based on Excel tables. The first one included personal data such as name, date of birth, sex, and insurance status. The second one contained pseudonymized research data regarding the duration of hospitalization, body weight, body height, diagnosis, type, and dosage of antibiotics, duration of antibiotic therapy, microbiology and clinical chemistry results, any additional medications, and presence of fever (yes/no). In line with data protection regulations, the personal data bank was locked in the study center and only accessible for authorized personnel.

Each case (n=339) of antibiotic treatment was referred to by an individual identification code (ID) which included an acronym for this antibiotic stewardship study (abs), a serial number (001-xxx), the number of the individual ward (1-4) and an acronym indicating whether the patient was treated by pediatricians (i) or pediatric surgeons (c), which was most relevant for ward 4. The ID "abs020/3i", for example, indicated the twentieth recorded case with antibiotic therapy, which was discharged from ward 3 and cared for by pediatricians. Patients who stayed twice at the hospital during that study period received 2 IDs, each indicating an individual case of antibiotic treatment.

2.2.2 Inclusion and Exclusion Criteria

Included were all patients with antibiotic therapy treated in the field of general pediatrics, pediatric surgery or neonatology on one of the above-mentioned wards. Thus, oncology patients were not included, and antibiotic therapy given on intensive care unit was not considered. For example, if a patient changed from normal ward to intensive care unit, the antibiotic therapy was deemed to have ended and was continued when the patient was transferred to normal ward again. Furthermore, only patients with systemic antibiotic therapy were included. Patients with topical, e.g. intraperitoneal antibiotic treatment, were excluded, since this study focused on systemic administration.
Moreover, exclusive prophylactic antibiotic treatment was not considered, except for perioperative antibiotic prophylaxis (PAP). If patients received antibiotics for any therapeutic purpose in addition to ongoing antibiotic prophylaxis, the therapeutic treatment was evaluated exclusively.

Generally excluded were patients older than 18 years and patients with tuberculosis or cystic fibrosis.
Furthermore, patients with “long-term” hospitalization, defined as a stay of at least 50 days on general pediatric or pediatric surgery wards were excluded. This exclusion was not applied for neonatal patients.
When antibiotic treatment of distinct infectious diseases was analyzed, in addition patients with rare underlying diseases, such as childhood cancer, congenital syndromes or malformations, congenital metabolic diseases, or anatomical conditions which predispose to infectious diseases were excluded. However, these patients did contribute to the analysis of given antibiotics in general.

	Inclusion Criteria	Exclusion Criteria
Wards	*1, 2, 3, and 4*	*Intensive care unit* *Oncology unit*
Diseases		*Tuberculosis* *Cystic Fibrosis*
Antibiotic Therapy		*Topical* *Prophylaxis other than PAP*
Age		≥ *18 years*
Length of stay		*> 50 days in general pediatrics or pediatric surgery*

Table 2.1: General Inclusion and Exclusion Criteria

2.2.3 Study Period and Ward Restriction

The study was conducted in 2016 during a period of 4 months from August 1st until November 30th. In order to make sure that only wards 1-4 contributed to the analysis, only the days the patient spent on those wards were counted. The day a patient changed wards was set as the last day of therapy, even if the antibiotics were continued at another ward. The same approach was used by our colleagues for generating data on antibiotic treatment in the other Munich children hospital [58]. Also, the days of therapy before 1st of August or 30th of November did not count in this study. As a result, in some cases the anti-infective therapy was only partially included in this analysis. However, this approach was selected since it provided a clearer picture of the pattern of antibiotic treatment on the wards and during the time period of interest. The numbers of partially documented antibiotic treatments have been indicated and are being discussed below.

2.3 Parameters Analyzed

2.3.1 Days of Therapy (DoT) and Length of Therapy (LoT)

The most common parameter used to measure antibiotic consumption is the "defined daily dose" (DDD) implemented by the World Health Organization (WHO) to describe the assumed average maintenance dose per day for a drug used for its main indication in adults weighing 70 kg [59]. A DDD is provided for all drugs with an anatomical therapeutic chemical (ATC) code. However, DDDs are not

similarly useful in pediatrics, as antibiotic doses have to be adapted to the children's bodyweight. Thus, DDDs do not reflect the assumed average maintenance dose per day for an antibiotic used for one of its main indications in children. Therefore, comparing the intensity of antibiotic treatment in pediatrics is a challenge [60]. Alternative measures used in pediatric studies are "days of therapy" (DoT) [61] and "length of therapy" (LoT) [62]. The acronym DoT refers to the sum of days every single antibiotic is used. A therapy with 5 days of ampicillin and 5 days of ceftazidime, for example, results in a DoT of 10, even if the administration periods of the 2 antibiotics overlap. The LoT indicates the number of days in which any antibiotic was used and is thus a measure of the total duration of antibiotic therapy regardless of the number of antibiotics used. A therapy with ampicillin and ceftazidime from August 1st until August 8th, for example, makes a LoT of 8. It does not matter whether ampicillin and ceftazidime are given together for the whole period of 8 days or whether each antibiotic is given for 4 days one after another without any overlap [50]. DoT and LoT were set in relation to patient-days (PD). This parameter was calculated for each ward by the medical controlling team and indicated the sum of hospitalization days of all patients on the ward during the study period. Defining antibiotic usage as DoT or LoT per 1000 PD facilitated the comparison between different wards or institutions.

2.3.2 Microbiological Testing of Urine Samples

With all urine samples microbiological diagnostics were performed. In general, colony forming units (CFU) of more than 10^5 per ml are considered to be significant. Depending on the kind of urine sample, the number of pathogens and the proof of antibacterial substances in the urine, microbiological testing differs. In case of antibacterial substances in the urine, CFU of more than 10^3 – 10^4 already count as significant. In midstream urine standard flora is in summary declared in the laboratory results, but not tested as infection causing pathogens. Microbiological testing in this study conformed to the microbiological-infectious quality standards of the German Society for Hygiene and Microbiology (DGHM) [63].
Concerning multi-resistance, the German Commission for Hospital Hygiene and Infectious Disease Prevention [German: Kommission für Krankenhaushygiene und Infektionsprävantion (KRINKO)] of the Robert-Koch-Institute (RKI) defined the following classification [64]: Multi-resistance depends on resistances against 4 different groups of antibiotics, which are mainly used for treatment against severe bacterial infections. These are aminopenicillins (lead substance piperacillin), 3rd or 4th generation cephalosporins (lead substances cefotaxime and/or ceftazidime), carbapenems (lead substances meropenem and/or imipenem) and

fluorchinolones (lead substance ciprofloxacin). Pathogens with resistances against 3, or 4 of these groups are called “3MRGN” (*m*ulti-*r*esistant *g*ram-*n*egative rod-shaped bacteria with resistances to 3 of the 4 groups), or “4MRGN”, respectively. 2MRGN bacteria are not multi-resistant per definition, but can be relevant, if therapeutic options are nevertheless limited, when one of the effective substances is contraindicated (e. g. use of fluorchinolones in children).

2.3.3 Accordance to the current German Guidelines

Accordance of antibiotic treatment of study cases with the current German guidelines was analyzed with respect to type, dosage, changes, and duration of antibiotic therapy as well as to timing, and results of microbiological investigations. These aspects were evaluated for patients with pneumonia, urinary tract infection (UTI), neonatal infection, and patients with PAP. The accuracy of antibiotic treatment was judged primarily by the accordance to the “handbook” of the German society of pediatric infectious diseases [German: Deutsche Gesellschaft für Pädiatrische Infektiologie (DGPI)], which represents a comprehensive German guideline for the treatment of infections in children and adolescents [65]. For PAP the current German guideline Form 2012 provided by the AWMF (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften, e.V.) was used [66]. In addition, the accordance with more recent German as well as European and/or international guidelines was discussed and compared to recommendations in 2 American standard manuals, the Harriet Lane “handbook” [67] and the “Nelson´s pediatric antimicrobial therapy” [68].

2.4 Comparison to another University Hospital

An increasing number of pediatric hospitals have already developed an ABS program or are aiming at doing so [69]. Even though it has been shown, that in both adult and pediatric hospitals ABS programs were able to reduce antimicrobial usage [70], only a few studies were available which addressed the specific characteristics and requirements of ABS programs in pediatrics [57].

The Dr. von Hauner Children’s Hospital of the Ludwig-Maximilians University (LMU), another local tertiary care pediatric reference center, implemented an ABS program in 2012. In order to measure the effect of the established interventions, they evaluated data on antimicrobial use before and after its implementation [58]. The data collected from the Children’s Hospital Schwabing in this study were compared to pre-intervention data on antibiotic use kindly provided be the team of the Dr. von Hauner Children’s Hospital, headed by Prof. Hübner.

3 Results

3.1 General Features of Study Cases

3.1.1 Case Frequency and Allocation to Wards

In total, 1410 hospitalized cases with or without antibiotic therapy were reported by the hospital administration for the 5 wards analyzed in this study during the study period, with 74, 515, 336, 41, and 444 hospitalized cases on ward 1-3, 4i, and 4c, respectively. Amongst them 339 cases were study cases as defined by inclusion and exclusion criteria. As 8 patients stayed in the hospital twice during the study period the 339 cases referred to 331 patients (Fig. 3.1).

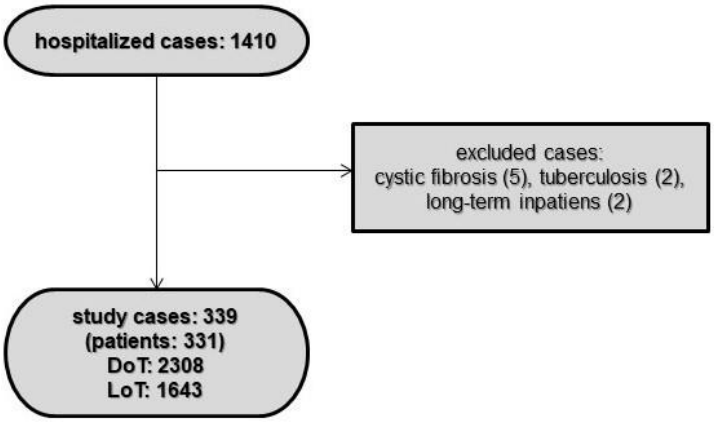

Figure 3.1: Number of Study Cases and Patients, Days (DoT) and Length (LoT) of Therapy

23, 59, 100, 12, and 145 study cases were recruited from ward 1, 2, 3, 4i, and 4c, respectively. The frequency of study cases amongst hospitalized cases thus was 24% in total and 31%, 11%, 30%, 29%, and 33% on ward 1, 2, 3, 4i, and 4c, respectively (Fig. 3.2). However, the wards did not strictly stick to their disciplines for logistical reasons. To the general pediatric ward, for example, also a few neonates and infants were admitted. Cases were therefore assigned to the most suitable discipline, resulting in 842, 450, and 118 cases hospitalized in general pediatrics (”gp"), pediatric surgery (”ps"), and neonatology ("neo"), respectively, during the study period. Amongst them there were 159, 145, and 35 study cases in gp, ps, and neo, respectively. Thus, 19%, 32%, and 30% of all cases in gp, ps, and neo, respectively, were study cases (Fig 3.2). In the following, the term "case" was used for study cases and given numbers exclusively referred to study cases.

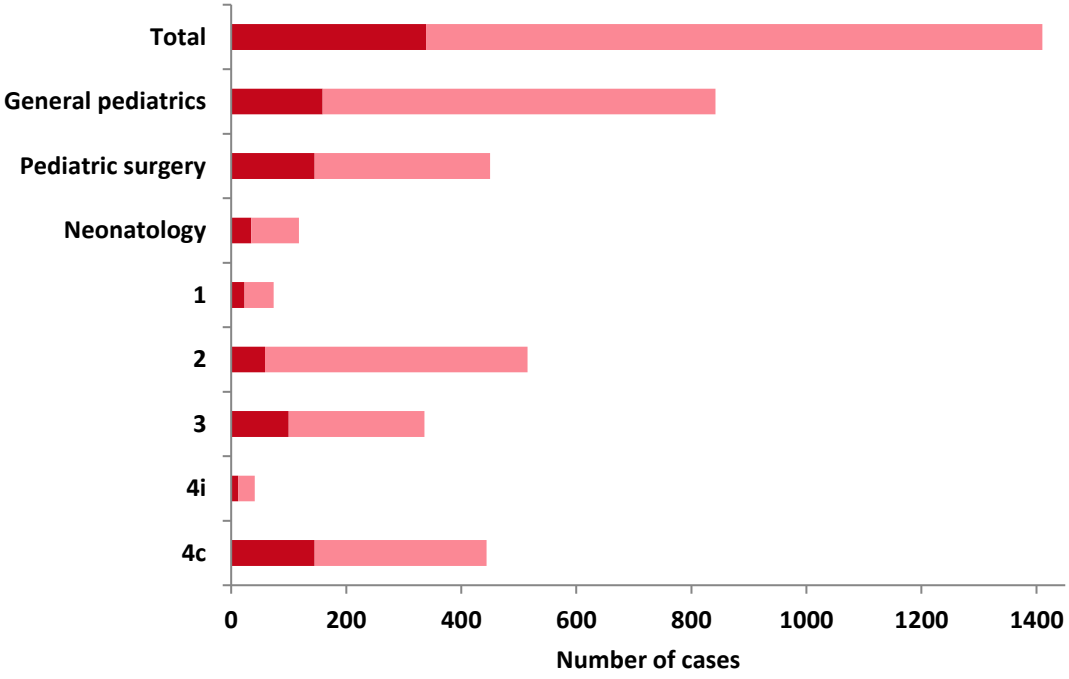

Figure 3.2: Study Cases in Relation to Hospitalized Cases

Dark plus light red: number of hospitalized cases. Dark red: number of study cases ("cases")

3.1.2 Patient Number, Age and Sex Distribution

During the 4 months period of data collection 339 cases with a defined cycle of antibiotic treatment were identified on the 5 wards, with 159, 145, and 35 cases in gp, ps, and neo, respectively. These cases resulted from the treatment of 331 patients because 4 patients of gp and 4 patients of ps were treated at the hospital twice, respectively.

For quantitative parameters such as age and duration of hospital stay the median, interquartile range (IQR), minimum (min), and maximum (max) were indicated in the following. The median age of all cases was 3 years (IQR = 0−9, min = 0, max = 18), with a median age of 3 (IQR = 0 − 7, min = 0, max = 18) and 7 years (IQR = 2 − 12, min = 0, max = 18) in gp and ps. In neo the median age at admission was 3 days (IQR = 1 − 11, min = 1, max = 138) (Tab 3.1).

The sex of the patients was male and female in 193 (57%) and 146 (43%) of all cases, respectively. It was male in 83 (52%), 83 (57%), and 27 (77%) cases and female in 76 (48%), 62 (43%), and 8 (23%) cases from gp, ps, and neo, respectively (Tab. 3.1).

3.1.3 Duration of Hospital Stay and Insurance Status

The median duration of hospital stay was 6 days (IQR = 4−8, min = 1, max = 70), with a median of 6 (IQR = 4 − 8, min = 1, max = 30), 5 (IQR = 4 − 8, min = 1, max = 52), and 8 days (IQR = 6, 5 − 29, min = 2, max = 79) in gp, ps, and neo, respectively (Tab. 3.1).

The insurance status was statutory or private in 299 (88%) and 40 (12%) of all cases, respectively. It was statutory in 152 (96%), 112 (77%), and 35 (100%) cases and private in 7 (4%), 33 (23%), and 0 (0%) cases in gp, ps, and neo, respectively (Tab. 3.1).

Variable	Total (n=339)	General Pediatrics (n=159)	Pediatric Surgery (n=145)	Neonatology (n=35)
Sex [n (%)]				
Male	193 (56.9)	83 (52.2)	83 (57.2)	27 (77.1)
Female	146 (43.1)	76 (47.8)	62 (42.8)	8 (22.9)
Age [median (IQR)]	3 (0-9) y	3 (0-7) y	7 (2-12) y	3 (1-11) d
Insurance [n (%)]				
Statutory	299 (88.2)	152 (95.6)	112 (77.2)	35 (100)
Private	40 (11.8)	7 (4.4)	33 (22.3)	0 (0)
Duration of Hospital Stay [median (IQR)]	6 (4-8) d	6 (4-8) d	5 (4-8) d	8 (6.5-29) d

Table 3.1: General Characteristics of Study Cases

y = years, d = days, IQR = interquartile range

3.2 Features of Antibiotic Treatment

3.2.1 Indications for Antibiotic Treatment

In the following, the different indications for antibiotic therapy are provided (Fig. 3.3). The indications were taken from the diagnoses mentioned in the medical records and were not checked for medical appropriateness.

In 92 (27.1%) cases the indication was PAP, with all 92 cases from ps.

In 43 (12.7%) cases the indication was urinary tract infection (UTI), with 36 (83.7%), 4 (9.3%), and 3 (7.0%) cases from gp, ps, and neo, respectively.

In 28 (8.3%) cases the indication was community acquired pneumonia (CAP), with all 28 cases from gp. In 28 (8.3%) cases the indication was newborn infection, with 3 (10.7%) and 25 (89.3%) cases from gp and neo, respectively.
In 16 (4.7%) cases the indication was phlegmon or erysipelas, with 7 (43.8%) and 9 (56.2%) cases from gp and ps, respectively.
In 15 (4.4%) cases the indication was upper respiratory tract infection (including bronchitis), with 13 (86.7%), 1 (6.7%), and 1 (6,7%) case(s) from gp, ps, and neo, respectively.
In 11 (3.2%) cases the indication was tonsillopharyngitis, with 10 (90.9%) and 1 (9.1%) case(s) from gp and ps, respectively.
In 10 (2.9%) cases the indication was cervical lymphadenitis, with all 10 cases from gp. In 8 (2.4%) cases the indication was abscess, with 1 (12.5%), 6 (75.0%), and 1 (12.5%) case(s) from gp, ps, and neo, respectively.
In 7 (2.1%) cases each the indication was aseptic skin lesion (all 7 cases from ps), feverish infection (all 7 cases from gp), or otitis media [with 6 (85.7%) and 1 (14.3%) case(s) from gp and ps], respectively.
In 6 (1.8%) cases each the indication was infected skin lesions/cysts (all 6 cases from ps) or gastroenteritis (all 6 cases from gp).
In 5 (1.5%) cases each the indication was nephropathy (all 5 cases from gp) or osteomyelitis [with 2 (40.0%) and 3 (60.0%) cases from gp and ps]. Nephropathies included: hemolytic-uremic syndrome (n=2) with renal failure in 1 case, state after kidney transplant secondary to nephronophthisis (n=1), membranoproliferative glomerulonephritis with renal insufficiency (n=1), nephrolithiasis with disorder of the urine flow II-III° (n=1).
In 4 (1.2%) cases each the indication was meningitis (all 4 cases from gp), periorbital cellulitis (all 4 cases from gp), or appendicitis (all 4 cases from ps), respectively.
In 3 (0.9%) cases the indication was sepsis, with all 3 cases from gp. 30 (8.8%) cases with rare diagnoses (less than 3 cases) were assigned to the group of "other indications" with 14 (46.7%), 11 (36.7%), and 5 (16.7%) cases from gp, ps, and neo, respectively.
“Other indications” from gp included: suspected mycoplasma infection (n=2), perichondritis (n=1), infectious cholangitis (n=1), superinfected scabies (n=1), atypical Kawasaki disease (n=1), malaria tropica (n=1), complicated feverish seizure (n=1), chlamydia conjunctivitis of a newborn (n=1), suspected eosinophil fasciitis (n=1), pharyngitis with suspected PFAPA syndrome (periodic fever, aphthous stomatitis, pharyngitis and adenitis, n=1), chest pain (n=1), and vulvovaginitis (n=1).

"Other indications" from neo included: umbilical infection (n=1), pertussis (n=1), complicated preterm birth (without definite diagnosis of an infection, n=2), as well as mature newborn with intrauterine hypoxemia, encephalomalacia, arterial hypotension and symptomatic focal epilepsy (n=1).
"Other indications" from ps were: infected osteosynthesis (n=1), vaginal germ cell tumor (n=1), superinfected herpes simplex infection (n=1), tonsillectomy with post-operative bleeding (n=1), septic arthritis of the knee joint (n=1), burns (n=2), balanoposthitis (n=1), Meckel's diverticulitis with perforation (n=1), ileocolic invagination (n=1), and acute cholecystitis (n=1).

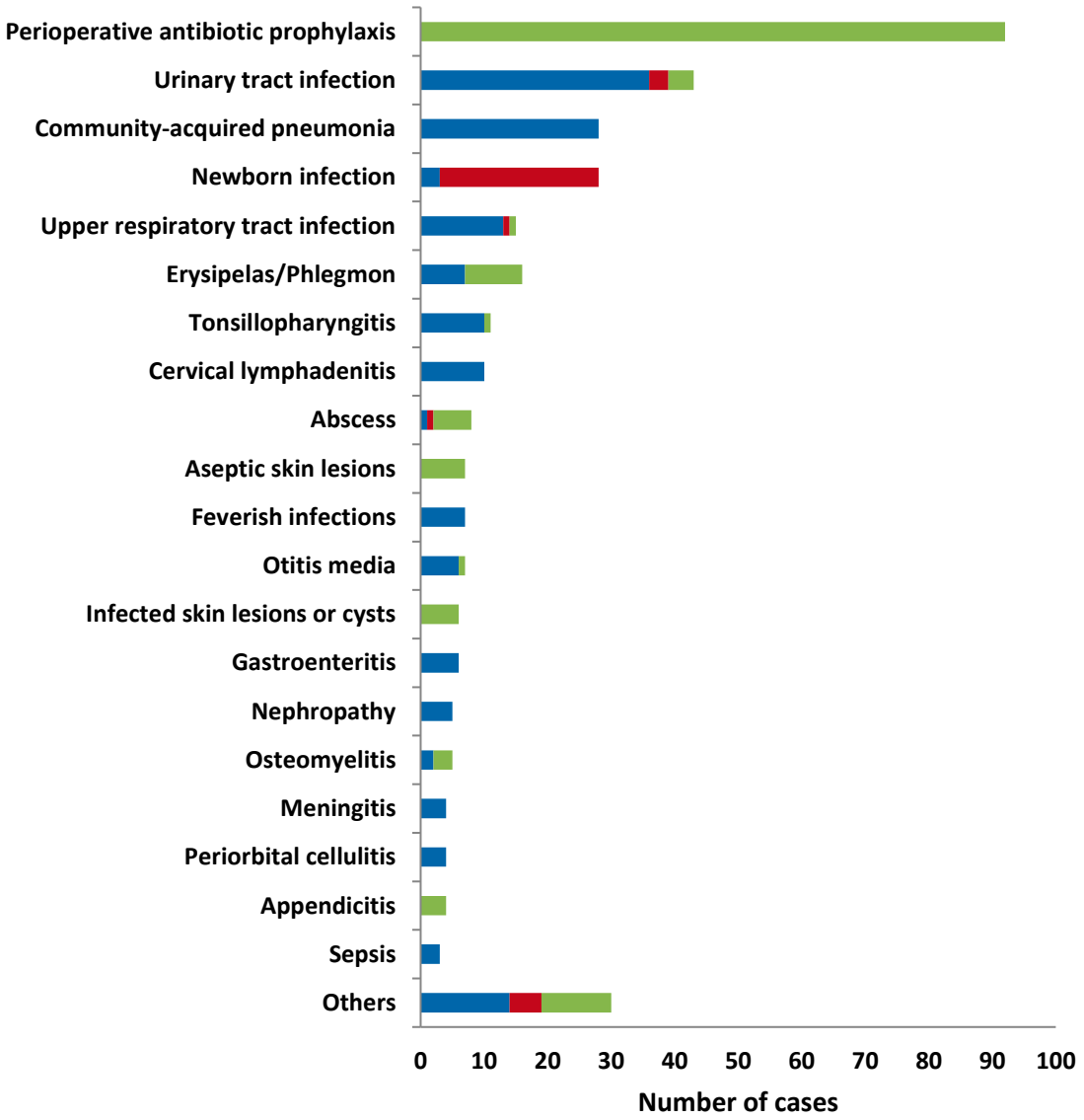

Figure 3.3: Indications for Antibiotic Treatment

Blue: general pediatrics. Red: neonatology. Green: pediatric surgery.

3.2.2 Duration of Treatment

In the following, the duration of treatment represented as DoT and LoT was analyzed (Fig. 3.4).
The LoT was 1643 with 877, 553, and 213 in gp, ps, and neo, respectively. The median LoT was 4 (IQR = 2-6, min = 1, max = 28) days, with a median of 5 (IQR = 3-7, min = 3, max = 16), 3 (IQR = 1-5, min = 1, max = 28), and 5 (IQR = 3.75-7, min = 2, max = 15) days in gp, ps, and neo, respectively.
LoT/1000 PD was 258.3 in total, 293.1 in gp, 323.0 in ps, and 128.5 in neo, respectively.
In total, 2308 DoT were documented with 1222, 700, and 386 DoT in gp, ps, and neo, respectively. The median DoT was 5 (IQR = 2-9, min = 1, max = 50), with a median of 6 (IQR = 3-10, min = 1, max = 33), 3 (IQR = 1-6, min = 1, max = 50), and 10 (IQR = 7.15, min = 2, max = 28) in gp, ps, and neo, respectively (Fig. 3.4).
DoT/1000 PD was 362.8 in total, 408.4 in gp, 408.9 in ps, and 233.0 in neo, respectively.

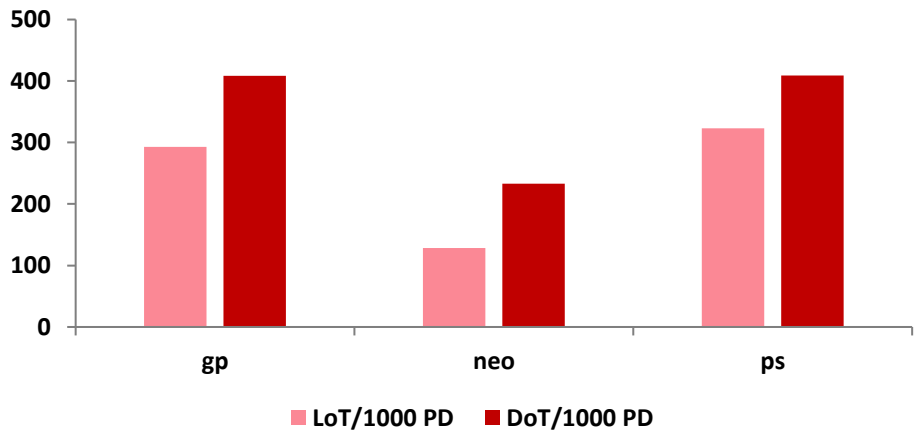

Figure 3.4: Days of Therapy/1000 Patient-days and Length of Therapy/1000 Patient-days

Gp: general pediatrics. Neo: neonatology. Ps: pediatric surgery.

3.2.3 Type of Antibiotics

In the following, the DoT is provided with regard to the types of antibiotics used. For this purpose, antibiotics were attributed to 10 different groups.

- cephalosporins (including substances of 1st, 2nd and 3rd generation)
- penicillins (including all penicillins and the combinations with BLI)
- macrolides
- glycopeptides
- sulfonamides

- aminoglycosides
- metronidazole
- meropenem
- clindamycin
- doxycyclin
- others (including rifampicin, nitrofurantoin, ciprofloxacin)

3.2.3.1 Days of Therapy with Distinct Types of Antibiotics

The results for DoT with distinct types of antibiotics are summarized in Fig. 3.5. From all 362.8 DoT/1000 PD 175.3 (48.3%), 111.1 (30.6%), 19.5 (5.4%), 15.9 (4.4%), 15.7 (4.3%), 9.4 (2.6%), 6.9 (1.9%), 4.4 (1.2%), 2.5 (0.7%), 1.1 (0.3%), and 0.9 (0.3%) DoT/1000 PD were related to cephalosporins, penicillins, macrolides, metronidazole, clindamycin, meropenem, aminoglycosides, glycopeptides, sulfonamides, others, and doxycyclin, respectively.
From 408.4 DoT/1000 PD in gp 168.8 (41.3%), 140.4 (34.4%), 40.8 (10.0%), 21.4 (5.2%), 16.0 (3.9%), 9.0 (2.2%), 5.0 (1.2%), 2.3 (0.6%), 2.0 (0.5%), 1.7 (0.4%), and 1.0 (0.2%) DoT/1000 PD were related to cephalosporins, penicillins, macrolides, clindamycin, meropenem, metronidazole, glycopeptides, others, doxycyclin, aminoglycosides, and sulfonamides, respectively.
From 408.9 DoT/1000 PD in ps 270.4 (66.1%), 64.8 (15.9%), 43.2 (10.6%), 21.0 (5.1%), 7.6 (1.9%), and 1.8 (0.4%) DoT/1000 PD were related to cephalosporins, penicillins, metronidazole, clindamycin, sulfonamides, and aminoglycosides, respectively.
From 233.0 DoT/1000 PD in neo 106.2 (45.6%), 88.7 (38.1%), 21.7 (9.3%), 7.8 (3.4%), 7.2 (3.1%), and 1.2 (0.5%) DoT/1000 PD were related to penicillins, cephalosporins, aminoglycosides, glycopeptides, meropenem, and macrolides, respectively.

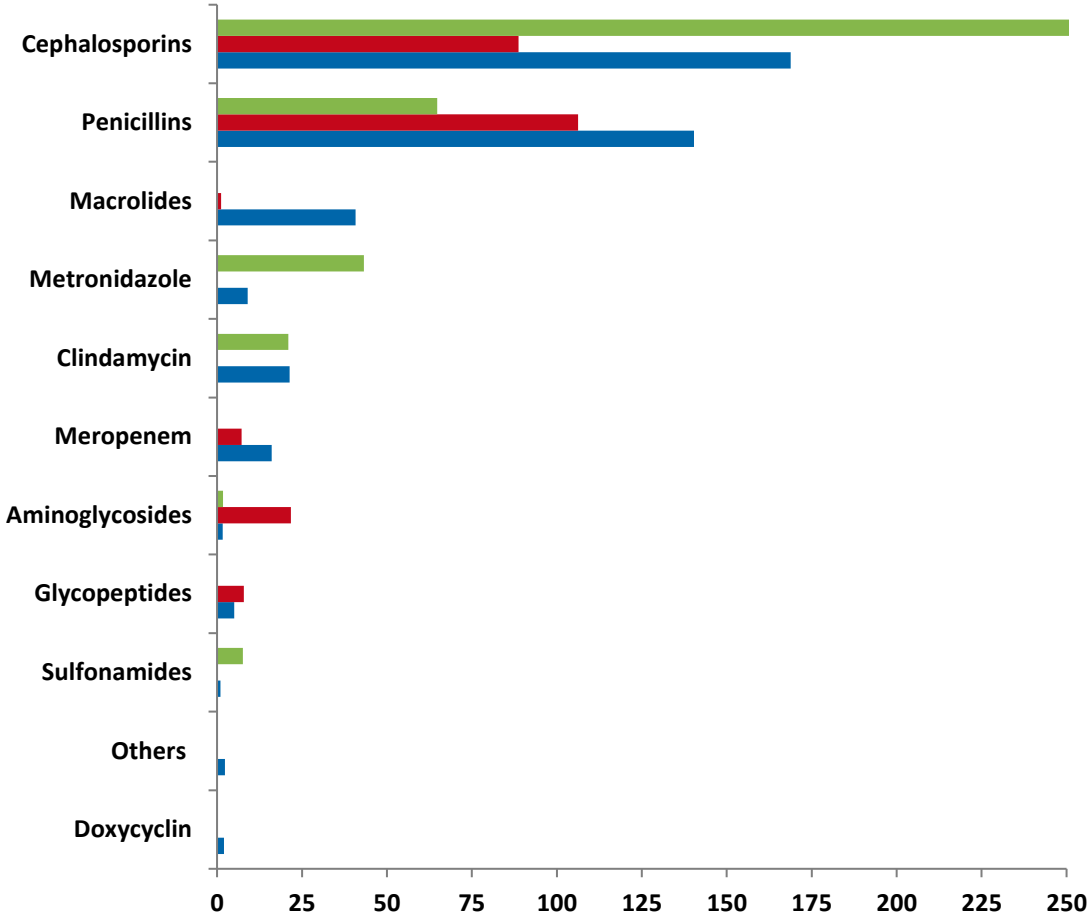

Figure 3.5: Days of Therapy/1000 Patient-days with Distinct Types of Antibiotics

Blue: general pediatrics. Red: neonatology. Green: pediatric surgery.

3.2.3.2 Days of Therapy with Cephalosporins

Detailed results for DoT with cephalosporins are summarized in Fig. 3.6.
From 1115 DoT with cephalosporins 50 (4.5%), 605 (54.2%), and 460 (41.3%) DoT were related to substances of the 1st, 2nd, and 3rd generation, respectively. 50 DoT with cephalosporins of the 1st generation split up into 1 (2.0%), 49 (98.0%), and 0 (0.0%) DoT in gp, ps, and neo, respectively. 605 DoT with cephalosporins of the 2nd generation split up into 226 (37.4%), 372 (61.5%), and 7 (1.2%) DoT in gp, ps, and neo, respectively. 460 DoT with cephalosporins of the 3rd generation split up into 274 (60.4%), 42 (9.1%), and 140 (30.4%) DoT in gp, ps, and neo, respectively. Cephalosporins of the 3rd generation were subdivided into generation 3A (cefotaxime and ceftriaxone) and generation 3B (ceftazidime). From 460 DoT with 3rd generation cephalosporins 248 (53.9%) and 212 (46.1%) DoT were related to 3A and 3B, respectively. 248 DoT with generation 3A cephalosporins consisted of 130 (52.4%), 10 (4.0%), and 108 (43.5%) DoT in gp, ps,

and neo, respectively, and split up in 244 (98.4%) and 4 (1.6%) DoT with cefotaxime and ceftriaxone, respectively. 212 DoT with generation 3B cephalosporins consisted of 148 (69.8%), 32 (15.1%), and 32 (15.1%) DoT in gp, ps, and neo, respectively.

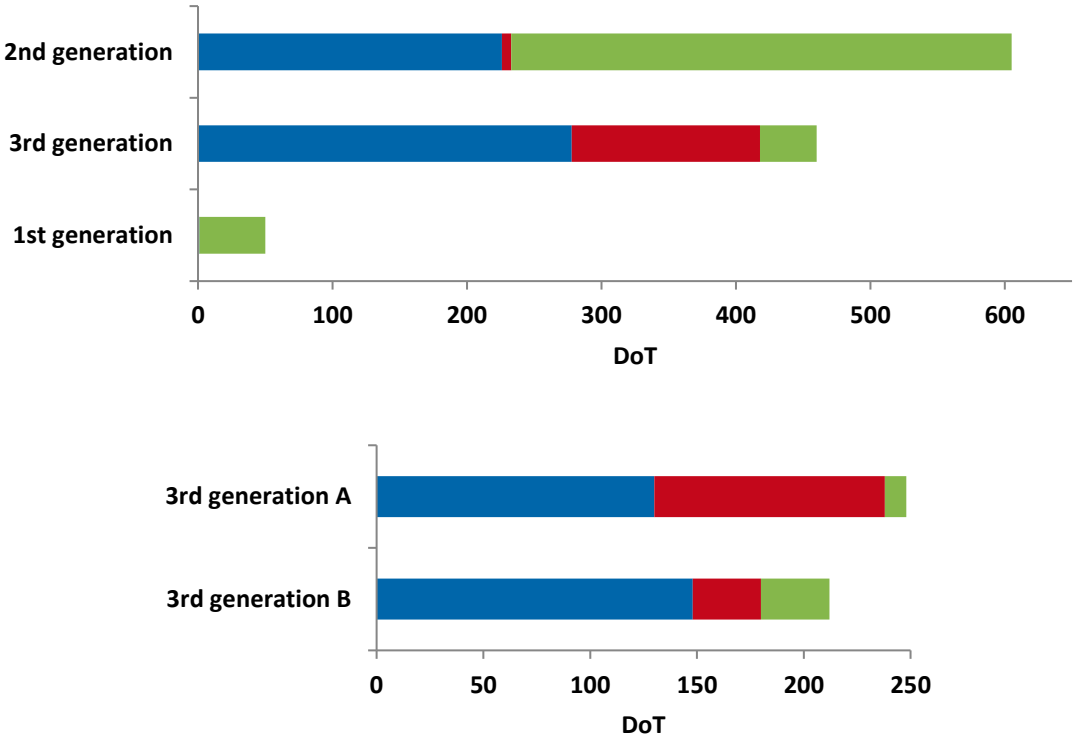

Figure 3.6: Days of Therapy (DoT) with Cephalosporins

Blue: general pediatrics. Red: neonatology. Green: pediatric surgery.

3.2.3.3 Days of Therapy with Penicillins

Detailed results for DoT with penicillins are summarized in Fig. 3.7.
From 707 DoT with penicillins 465 (65.8%), 192 (27.2%), 41 (5.8%), and 9 (1.3%) DoT related to penicillins with extended spectrum (ampicillin, amoxicillin), other penicillins plus BLI (ampicillin/amoxicillin plus BLI), piperacillin plus enzyme inhibitor, or β-lactamase-sensitive penicillins, respectively.
465 DoT with extended spectrum penicillins consisted of 273 (58.7%), 40 (8.6%), and 152 (32.7%) DoT in gp, ps, and neo, respectively. 192 DoT with penicillins in combination with BLI consisted of 105 (54.7%), 63 (32.8%), and 24 (12.5%) DoT in gp, ps, and neo, respectively. 41 DoT with piperacillin plus enzyme inhibitor

consisted of 34 (82.9%), 7 (17.1%), and 0 (0.0%) DoT in gp, ps, and neo, respectively. 9 DoT with β-lactamase-sensitive penicillins consisted of 8 (88.9%), 1 (11.1%), and 0 (0.0%) DoT in gp, ps, and neo, respectively.

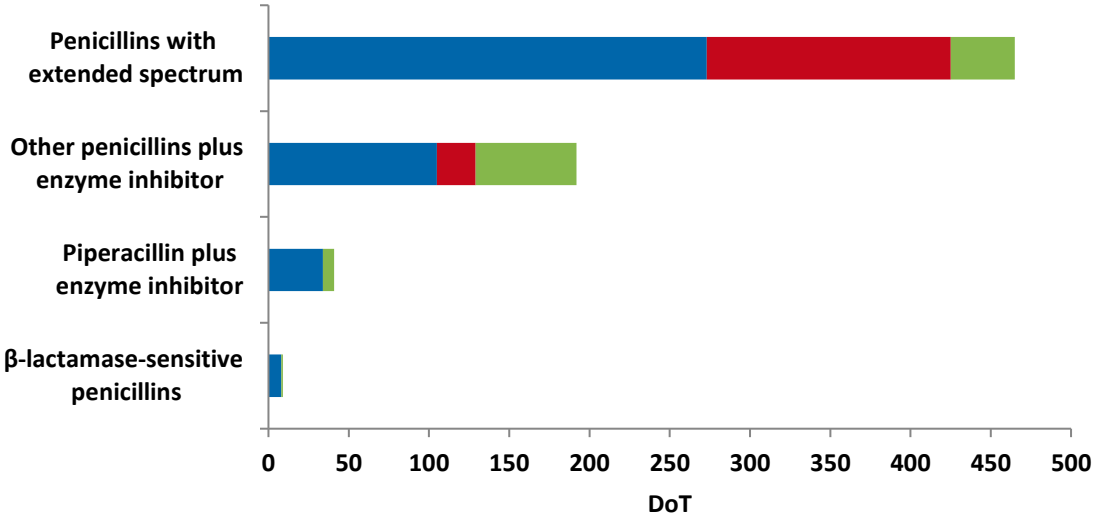

Figure 3.7: Days of Therapy (DoT) with Penicillins

Blue: general pediatrics. Red: neonatology. Green: pediatric surgery.

3.2.4 Number of Courses with Distinct Antibiotics and Number of Antibiotics per Case

When the different types of antibiotics were analyzed separately, 538 courses with distinct antibiotics were given in total, with 271 (50.4%), 194 (36.1%), and 73 (13.6%) courses of antibiotics given in gp, ps, and neo, respectively (Fig. 3.8). The median number of antibiotics given per case was 1 (IQR = 1-2, min = 1, max = 5) with a median of 1 (IQR = 1-2, min = 1, max = 5), 1 (IQR = 1, min = 1, max = 5), and 2 (IQR = 2, min = 1, max = 4) in gp, ps, and neo, respectively.

Figure 3.8: Number of Courses with Distinct Antibiotics

Blue: general pediatrics. Red: neonatology. Green: pediatric surgery.

3.3 Antibiotic Treatment of Urinary Tract Infection (UTI) and Accordance with the DGPI Guideline

3.3.1 Antibiotic Treatment of Urinary Tract Infection

In 43 cases the indication for antibiotic treatment was UTI. To evaluate the adherence to guideline recommendations for antibiotic therapy 6 cases with UTI were excluded due to known underlying diseases or complicating factors. The latter included: spina bifida with neurogenic micturition disturbance (n=3), cystic kidney disease of unknown etiology (n=1), VACTERL association (n=1), and Alagille syndrome (n=1), respectively. Of these 6 cases 4, 1, and 1 were treated with ampicillin plus ceftazidime, cefuroxime only, or cefotaxime only, respectively.
Of the remaining 37 regular cases with UTI 31 (83.8%), 3 (8.1%), and 3 (8.1%) were from gp, ps, and neo, respectively.

3.3.1.1 Type of Antibiotic Used for Initial Treatment in Regular Cases

The types of antibiotics used for initial treatment in the 37 regular cases are summarized in Fig. 3.9. In 20 (54.1%) cases the initial therapy was ceftazidime plus ampicillin, with 18 (90.0%) and 2 (10.0%) cases from gp and neo, respectively. In 3 (8.1%) cases each initially cefotaxime or cefuroxime was used, respectively, and all 6 cases were from gp. In 2 (5.4%) cases piperacillin/tazobactam was used, with both cases from gp. In 2 (5.4%) cases ceftazidime was used, with 1 case each from gp and neo, respectively. In 2 (5.4%) cases cotrimoxazole was used, with 1 case each from gp and ps, respectively. The remaining 5 cases showed initial treatment with different antibiotics, including ampicillin plus cefotaxime (n=1, gp), ampicillin plus clindamycin (n=1, ps), ampicillin plus sulbactam (n=1, ps), cefpodoxime (n=1, gp), and meropenem (n=1, gp), respectively.

3.3.1.2 Antibiotic Prophylaxis or Pre-Treatment prior to Hospital Admission

Of the 37 regular cases 5 cases had received antibiotics prior to hospital admission for either UTI prophylaxis (n=2) or UTI therapy (n=3). Oral prophylaxis had been performed with trimethoprim (n=1) or cefaclor (n=1) due to anatomical abnormalities of the urinary tract. Both cases with oral prophylaxis were from gp and after hospital admission received ampicillin plus ceftazidime in addition to the pre-established antibiotic prophylaxis. Oral pre-treatment had been performed with trimethoprim (n=1), cefuroxime (n=1), or amoxicillin plus clavulanic acid (n=1). All 3 cases with antibiotic pre-treatment were from gp and after hospital admission received cefotaxime, ampicillin plus ceftazidime, or cefuroxime instead of the preceding treatment, respectively.

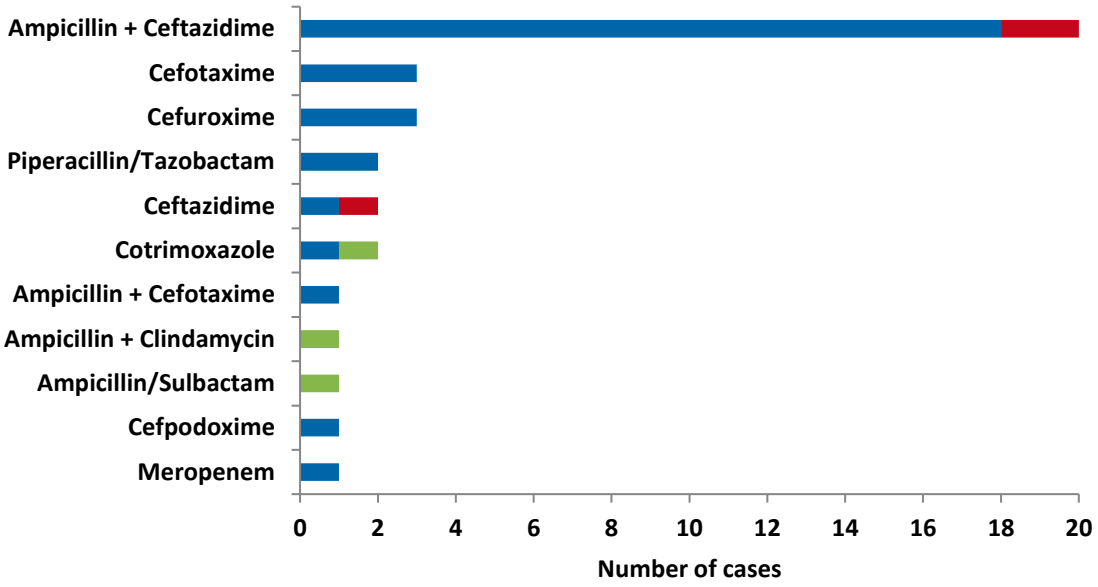

Figure 3.9: Initial Antibiotic Therapy of Urinary Tract Infection (UTI)

Blue: general pediatrics. Red: neonatology. Green: pediatric surgery.

3.3.1.3 Number of Courses with Distinct Antibiotics and Number of Antibiotics per Case

In the 37 regular cases 74 courses of treatment with a distinct antibiotic were documented during the hospital stay excluding substances used for prophylaxis. On average, 2.0 different antibiotics were used per case for therapy during the hospital stay, indicating that in a significant number of cases a second substance was added for the same indication during the course of disease, or that initial therapy was started with 2 substances at once.

3.3.1.4 Route of Application of Antibiotic Treatment

Of 74 courses of treatment with a distinct antibiotic 9 (12.2%) were given orally and 65 (87.3%) were given intravenously. Oral treatment was established in 3 cases as initial therapy (cefpodoxime in 1 case and cotrimoxazole 2 cases) and in 6 cases used as follow-up treatment after initial intravenous therapy. The following substances were used for follow-up treatment: cefuroxime (n=3), amoxicillin (n=2), or nitrofurantoin (n=1), respectively.

Among the 37 regular cases with UTI 6, 3, and 28 cases showed either combined oral and intravenous treatment (n=6), exclusively oral treatment (n=3), or exclusively intravenous treatment (n=28) during their hospital stay, respectively.

For 20 of the 28 cases with exclusively intravenous treatment a recommendation for an oral continuation of antibiotic treatment (n=16) or for oral prophylaxis (n=4) was made in the medical record at the time of discharge from the hospital.

3.3.1.5 Days and Length of Antibiotic Therapy

In total, the 37 regular UTI cases contributed to 380 DoT with 299, 37, and 44 in gp, ps, and neo, respectively. The median DoT was 4 (IQR = 3-6, min = 1, max = 20), with a median of 3 (IQR = 3-5, min = 1, max = 16), 6 (IQR = 5.75-9.5, min = 5, max = 20), and 3 (IQR = 3.5-7.5, min = 2, max = 14) DoT in gp, ps, and neo, respectively. DoT/1000 PD was 59.7 in total, 99.9 in gp, 21.6 in ps, and 26.6 in neo, respectively.
The LoT of all 37 cases was 304, with 241, 32, and 31 LoT in gp, ps, and neo, respectively. The median LoT was 5,5 (IQR = 4-10,75, min = 1, max = 20), with a median of 5 (IQR = 4-8,5, min = 1, max = 16), 6 (IQR = 5.5-13, min = 5, max = 20), and 14 (IQR = 8.5-14, min = 3, max = 15) LoT in gp, ps, and neo, respectively. LoT/1000 PD was 47.8 in total, 80.5 in gp, 18.7 in ps, and 18.7 in neo, respectively.

3.3.2 Method of Urine Sampling and Detected Pathogens

According to the DGPI guideline, the diagnosis of UTI results from the trias of clinical symptoms, leukocyturia, and microbiological evidence of significant bacteriuria [71]. However, different ways to collect urine samples have been established, and - due to the lack of micturition control by young children - pediatric methods of urine sampling are more complex than those applied to adult patients. They include the collection of urine from midstream as well as the collection by a bag, “clean-catch”, bladder punction, and transient or permanent catheterization, respectively.

3.3.2.1 Methods of Initial Urine Sampling

The methods used in the 37 study cases for the initial urine sample before inpatient antibiotic therapy are depicted in Fig 3.10. In 18 (48.6%) cases a transient disposable catheter was used, with 17 (94.4%) cases from gp and 1 (5.6%) case from neo. In 8 (21.6%) cases midstream urine was collected, with 6 (85.7%) cases from gp and 1 (14.3%) case from neo. In 5 (13.5%) cases a urine bag was used with 3 (60.0%) cases from gp and 2 (40.0%) cases from ps. In 2 (5.4%) cases a permanent catheter was used with 1 (50.0%) case each from ps and neo. In 1 (2.7%) case from gp both a urine bag and a disposable catheter were used

on the same day with the same result. In 3 (8.1%) cases no urine diagnostics were performed in the hospital. However, in 2 of the 3 cases the urine sample was collected by the local pediatrician by an unknown method. In the 5 cases with oral prophylaxis or pre-treatment urine sampling was performed with disposable catheter (n=4) or midstream urine (n=1).

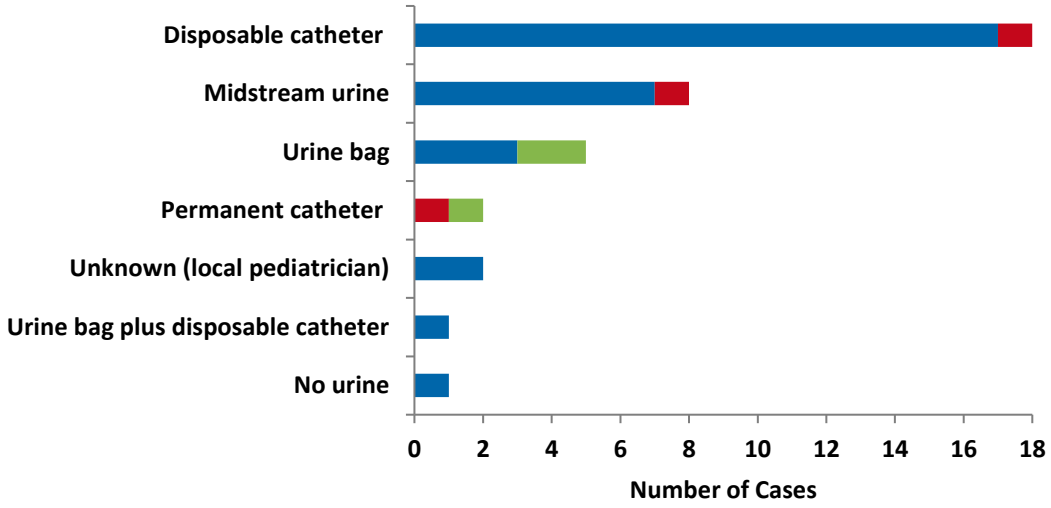

Figure 3.10: Methods of Initial Urine Sampling

Blue: general pediatrics. Red: neonatology. Green: pediatric surgery.

3.3.2.2 Pathogens in Initial Urine Samples

In the 34 urine samples collected initially in the hospital, bacteria were found at significant concentrations (> 10^5 CFU per ml) (Fig. 3.11). In 16 (47.1%) samples *E. coli* was detected exclusively. In 4 (11.8%) samples *E. coli* and *Enterococcus faecalis*, and in 3 (8.8%) samples only *Enterococcus faecalis* were detected. In 2 (5.9%) samples each *Pseudomonas aeruginosa* or *Klebsiella pneumoniae* were detected, respectively. The following bacteria or combinations of bacteria were found in only 1 (2.9%) sample each:

- *E. coli* and *Streptococcus pseudoporcinus*
- *E. coli*, *Enterococcus faecium,* and *Pseudomonas aeruginosa*
- *Klebsiella pneumoniae* and *Enterobacter cloacae*
- *Enterococcus faecalis* and *Staphylococcus aureus*
- *Enterobacter cloacae*

In 2 (5.9%) samples the urine cultures did not show any significant bacterial growth. The number of different bacteria detected in urine samples was 40, with

E. coli as the leading pathogen, detected in a total of 22 (52.5%) samples and as single pathogen in 16 (47.1%) samples.

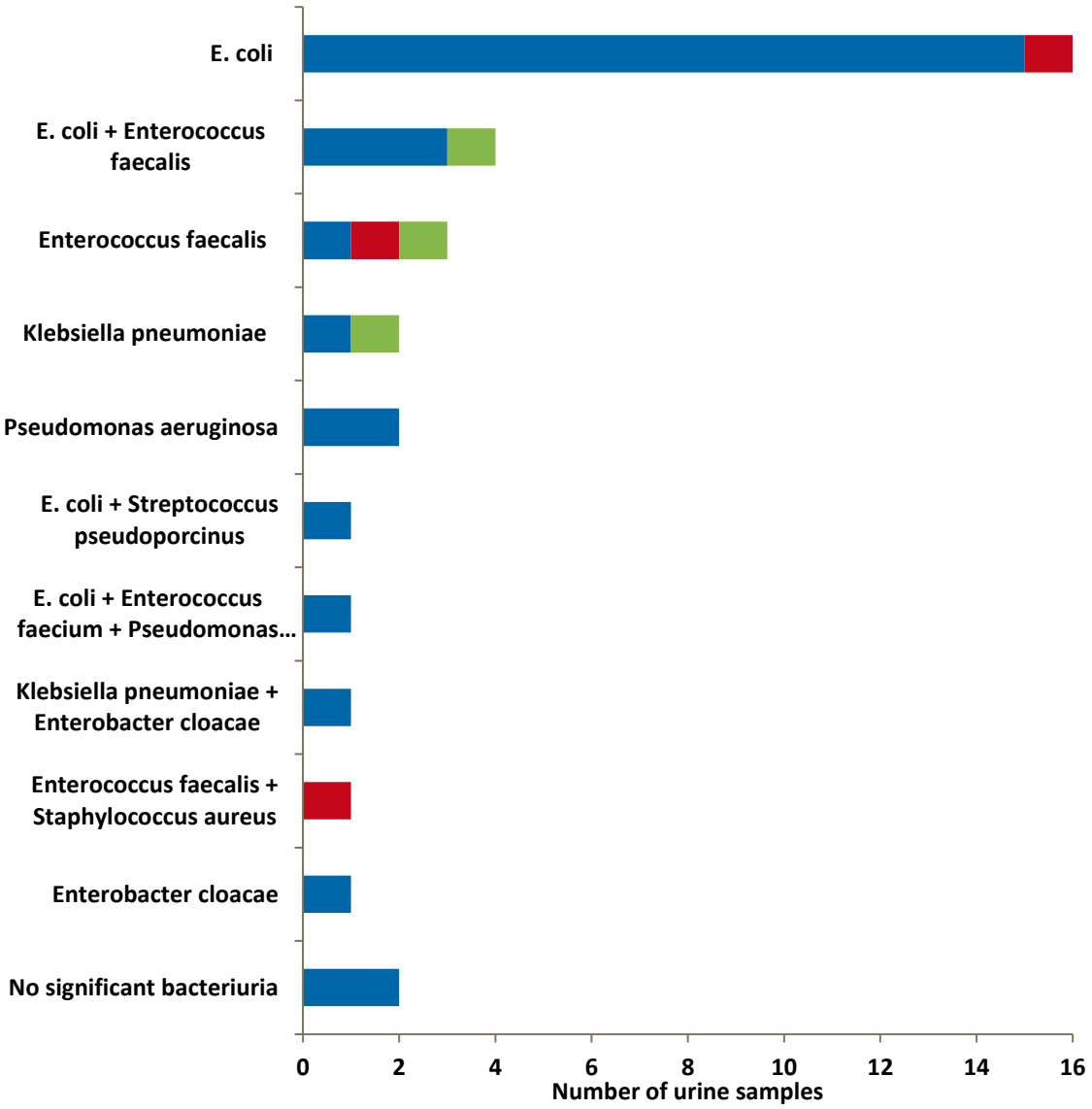

Figure 3.11: Type of Bacteria Detected in Urine Samples

Blue: general pediatrics. Red: neonatology. Green: pediatric surgery

3.3.2.3 Pathogens in Follow-up Urine Samples

In 8 (21.6%) cases follow-up urine samples were collected during antibiotic treatment. In 3 (37.5%) cases first follow-up urine sample was negative. These samples were collected 4 (n=2, midstream urine) and 6 (n=1, midstream urine) days after initial urine sampling. In 4 (37.5%) cases second follow-up was negative. These second follow-up samples were collected 7 (n=1, disposable catheter), 8 (n=2, midstream urine), and 15 (n=1, midstream urine) days after initial urine

sampling. In 1 (12.5%) case midstream urine collected 4 days after initial urine sampling showed significant growth of another bacterium (*E. coli* in initial urine sample, *Klebsiella* in the follow-up sample).

3.3.2.4 Antimicrobial Resistance Patterns of Escherichia coli in Urine Samples

In Table 3.2 antimicrobial resistance patterns of *E. coli* detected in urine samples were presented. *E. coli* was found at significant concentrations in 22 cases. Laboratory resistance tests for rod-shaped bacteria normally contained a distinct set of antibiotics (ampicillin, ampicillin/sulbactam, piperacillin, piperacillin/tazobactam, cefuroxime, ceftriaxone, cefotaxime, ceftazidime, meropenem, gentamicin, and ciprofloxacin). However, additional antibiotics were tested in selected cases.

Number of samples	***6***	***6***	***2***	***1***	***1***	***1***	***1***	***1***	***1***	***1***	***1***
Ampicillin	*S*	*R*	*S*	*R*	*R*	*R*	*R*	*R*	*R*	*R*	*R*
Ampicillin/Sulbactam	*S*	*I*	*S*	*I*	*I*	*R*	*I*	*R*	*R*	*R*	*R*
Piperacillin	*S*	*R*	*S*		*R*	*R*	*R*	*R*	*R*	*R*	*R*
Piperacillin/Tazobactam	*S*	*S*	*S*	*S*	*S*	*I*	*S*	*R*	*R*	*R*	*R*
Cefuroxime	*S*	*S*	*S*	*S*	*S*	*S*	*S*	*R*	*R*	*R*	*R*
Ceftriaxone	*S*	*S*	*S*	*S*	*S*	*S*	*S*	*R*	*R*	*R*	*R*
Cefotaxime	*S*	*S*	*S*	*S*	*S*	*S*	*S*	*R*	*R*	*R*	*R*
Ceftazidime	*S*	*S*	*S*	*S*	*S*	*S*	*S*	*R*	*R*	*R*	*R*
Meropenem	*S*	*S*	*S*	*S*	*S*	*S*	*S*	*S*	*S*	*S*	*S*
Nitrofurantoin										*S*	*S*
Gentamicin	*S*	*S*	*S*	*S*	*S*	*S*	*R*	*S*	*S*	*S*	*R*
Ciprofloxacin	*S*	*S*	*S*	*R*	*S*	*S*	*S*	*S*	*S*	*R*	*R*
Moxifloxacin			*S*						*S*		*R*
Trimethoprim/Sulfamethoxazole	*S*	*S*	*R*	*R*	*R*	*R*	*R*	*S*	*S*	*R*	*R*

Table 3.2: Resistance Patterns of Escherichia coli in Urine Samples

S: sensitive, R: resistant, I: intermediate

In 6 (27.3%) cases no resistances were found. In 16 (72.7%) cases *E. coli* showed resistances against 1-8 antibiotics tested. In 4 of these 16 cases *E.coli* were identified as MRGN, including 2 2MRGN and 2 3MRGN, as defined by the KRINKO of the RKI [64]. Resistances were observed against the following combinations of antibiotics:

- ampicillin and piperacillin (n=6)
- cotrimoxazole (n=2)

- ampicillin, ciprofloxacin, and cotrimoxazole (n=1)
- ampicillin, piperacillin, and cotrimoxazole (n=1)
- ampicillin, ampicillin/sulbactam, piperacillin, and cotrimoxazole (n=1)
- ampicillin, piperacillin, and gentamicin (n=1)
- ampicillin, ampicillin/sulbactam, piperacillin, piperacillin/tazobactam, cefuroxime, ceftriaxone, cefotaxime, ceftazidime (2MRGN, n=2)
- ampicillin, ampicillin/sulbactam, piperacillin, piperacillin/tazobactam, cefuroxime, ceftriaxone, cefotaxime, ceftazidime, ciprofloxacin, and cotrimoxazole (3MRGN, n=1)
- ampicillin, ampicillin/sulbactam, piperacillin, piperacillin/tazobactam, cefuroxime, ceftriaxone, cefotaxime, ceftazidime, gentamicin, ciprofloxacin, moxifloxacin, and cotrimoxazole (3MRGN, n=1)

3.3.3 Accordance with the German Guideline

Treatment recommendations for UTI differ, depending on the diagnosis of systemic (pyelonephritis) or local (cystitis) disease (Tab. 3.3) [72]. For the treatment of pyelonephritis in children aged of up to 6 months the DGPI recommends ceftazidime plus ampicillin or ampicillin plus an aminoglycoside. For children older than 6 months with pyelonephritis a 3rd generation cephalosporin is recommended and prioritized over ampicillin plus aminoglycoside. Oral and parental therapy are judged as equally effective, depending on the age of the patient and the severity of disease. Indications of intravenous treatment include age below 6 months, urosepsis, insufficient oral intake, vomiting, diarrhea, non-compliance, high-grade urinary retention, or renal abscess.

For the treatment of cystitis in children at any age, the DGPI recommends trimethoprim or amoxicillin plus clavulanic acid or a 2nd or a 3rd generation cephalosporin in regions with high resistances rates of *E. coli* against trimethoprim. In case of contraindications to the latter, nitrofurantoin is named as an alternative. The combination of trimethoprim plus sulfamethoxazole is not indicated according to the DGPI as sulfamethoxazole is not necessary for efficient treatment.

Age	**0 - 6 months**	**> 6 months**
Pyelonephritis	*ampicillin + aminoglycoside* ***or*** *ceftazidime + ampicillin*	*3rd generation cephalosporin*
Cystitis	*Trimethoprim* ***or*** *amoxicillin plus clavulanic acid* ***or*** *2nd or 3rd generation cephalosporin*	

Table 3.3: German Guideline Recommendations for Age-dependent Treatment of Urinary Tract Infections (UTI) in Children [72]

Of all 37 regular UTI cases 1 (2.7%) case was cystitis. The initial antibiotic treatment was cotrimoxazole, which was not in accordance with the DGPI recommendations. In 20 (54.1%) cases the initial therapy was ampicillin plus ceftazidime. In 15 (75.0%) of the 20 cases the patient's age was less than 6 months, and thus the choice of antibiotics was in accordance with the DGPI guideline. In 6 (16.2%) cases the initial therapy was a 3rd generation cephalosporin. In 5 (83.3%) of the 6 cases the patient was older than 6 months, and thus the treatment was in accordance with the DGPI guideline. 10 (27.0%) cases did not meet guideline recommendations in terms of selected substance. Instead, cefuroxime (n=3), piperacillin/tazobactam (n=2), meropenem (n=1), ampicillin plus cefotaxime (n=1), cotrimoxazole (n=1), clindamycin plus ampicillin (n=1), or ampicillin/sulbactam (n=1) were used, respectively. However, in 1 of the 10 cases the patient had already received an antibiotic from the local pediatrician and therefore guideline accordance cannot be evaluated properly.

In total, the treatment in 20 of 37 regular UTI cases (54.1%) was in accordance with the DGPI guideline, including 18 (90.0%) cases from gp and 2 (10.0%) cases from neo. However, in 17 of the 37 UTI cases treatment was not in accordance with this guideline. In 16 cases no plausible reason was identifiable for the deviation from guideline recommendations, while in 1 case initial therapy most likely differed from guideline recommendations due to antibiotic pre-treatment before admission for the same indication.

3.4 Antibiotic Treatment of Community Acquired Pneumonia (CAP) and Accordance with the DGPI Guideline

3.4.1 Initial Antibiotic Therapy

In 28 cases the indication for antibiotic treatment was CAP. Of these 28 cases 6 cases were excluded due to underlying diseases or complicating factors, including trisomy 21 (n=1), metachromatic leukodystrophy (n=1), Angelman syndrome (n=1), molybdenum cofactor deficiency (n=1), aristaless-related homeobox (ARX) gene mutation (n=1), and prematurity with short bowel syndrome, central venous catheter, and percutaneous endoscopic gastrostomy (n=1), respectively. Of the 6 excluded cases 3 (50.0%) were initially treated with ampicillin and 1 each (16.7%) with cefuroxime, clarithromycin, and piperacillin/tazobactam, respectively.

3.4.1.1 Type of Antibiotic Used for Initial Treatment in Regular Cases

The remaining 22 cases were all from gp. Their initial therapy was presented in Fig. 3.14. In 8 (36.4%) cases the initial antibiotic was clarithromycin. In 6 (27.3%) cases the initial antibiotic was ampicillin. In 3 (13.6%) cases the initial antibiotics were clarithromycin plus cefuroxime. In 2 (9.1%) cases the initial antibiotics were ampicillin plus sulbactam combined with a macrolide (clarithromycin and azithromycin in 1 case each). In 1 (4.5%) case each of 3 additional cases the initial therapy consisted of cefuroxime, ampicillin plus clarithromycin, or doxycycline, respectively.

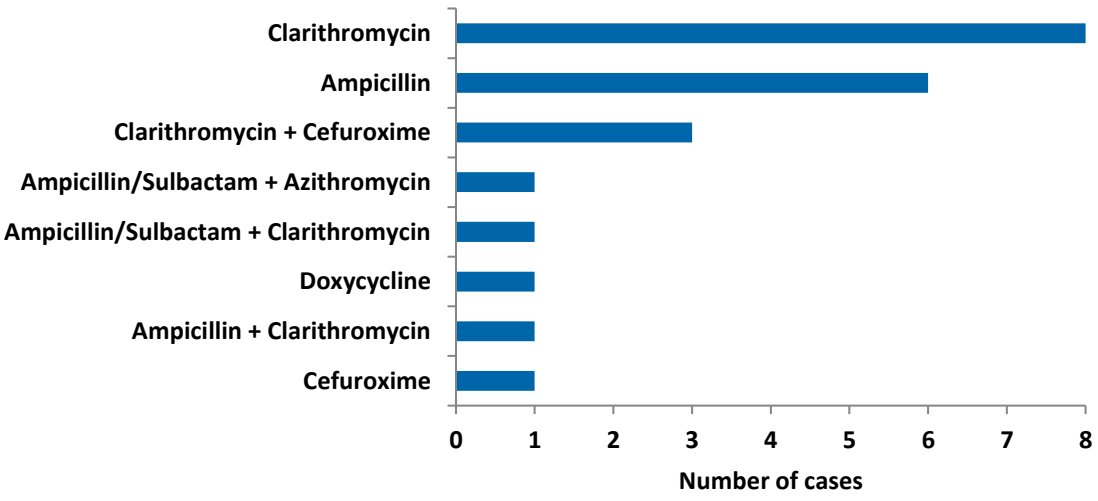

Figure 3.12: Initial Antibiotic Therapy of Community Acquired Pneumonia (CAP)

3.4.1.2 Antibiotic Pre-Treatment prior to Hospital Admission

Of 22 regular cases with CAP 6 cases showed antibiotic pre-treatment for the same indication prior to hospital admission: In 2 (33.3%) cases amoxicillin was given by the local pediatrician and was switched in the hospital to either ampicillin/sulbactam plus clarithromycin or to clarithromycin alone, respectively. In 1 (16.7%) case erythromycin was given prior to admission and was switched in the hospital to ampicillin due to suspected drug intolerance (urticarial). In 1 (16.7%) case erythromycin and cefaclor were given prior to admission and were switched to clarithromycin in a patient with known penicillin allergy and antibiotic treatment 4 weeks prior to hospital admission due to streptococcal tonsillitis. In 1 (16.7%) case (16.7%) ceftriaxone was prescribed from the local pediatrician due to suspected meningitis and was switched to doxycycline in the hospital after exclusion of meningitis. In 1 (16.7%) case cefixime was given prior to admission and was switched to ampicillin in the hospital.

3.4.1.3 Number of Courses with Distinct Antibiotics and Number of Antibiotics per Case

In total, 40 courses of treatment with a distinct antibiotic were documented for the 22 cases. On average, 1.8 different antibiotics were used per case, indicating that in a significant number of cases a second substance was added for the same indication during the course of disease or initial therapy was started with 2 substances.

3.4.1.4 Route of Application of Antibiotic Treatment

The routes of antibiotic application were outlined in Fig. 3.15. Of 40 courses with distinct antibiotics 17 (42.5%) were given orally and 23 (57.5%) were given intravenously. In 6 (27.3%) cases oral antibiotics (clarithromycin) were used exclusively. In 1 of the 6 cases clarithromycin was changed to oral azithromycin as the patient refused clarithromycin. In 9 (40.9%) cases antibiotics were applied both intravenously and orally. In 4 (44.4%) of the 9 cases oral clarithromycin was initially given together with intravenous cefuroxime (n=3) or ampicillin/sulbactam (n=1). In 1 of that 4 cases initially given cefuroxime was switched to oral cefuroxime during the course of disease. In 3 (33.3%) of the 9 cases the initially intravenously given antibiotic (which was clarithromycin, ampicillin, or doxycycline, respectively) was switched to oral administration of the same antibiotic. In 1 (11.1%) case oral clarithromycin was the initial antibiotic followed by intravenous ampicillin. In 1 (11.1%) case an initial intravenous therapy with ampicillin was extended

with oral clarithromycin, intravenous clindamycin, and intravenous ampicillin/sulbactam, respectively, due to lack of clinical improvement. In 7 cases the treatment consisted of only intravenous antibiotics. In all of these cases it was recommended to continue the therapy orally.

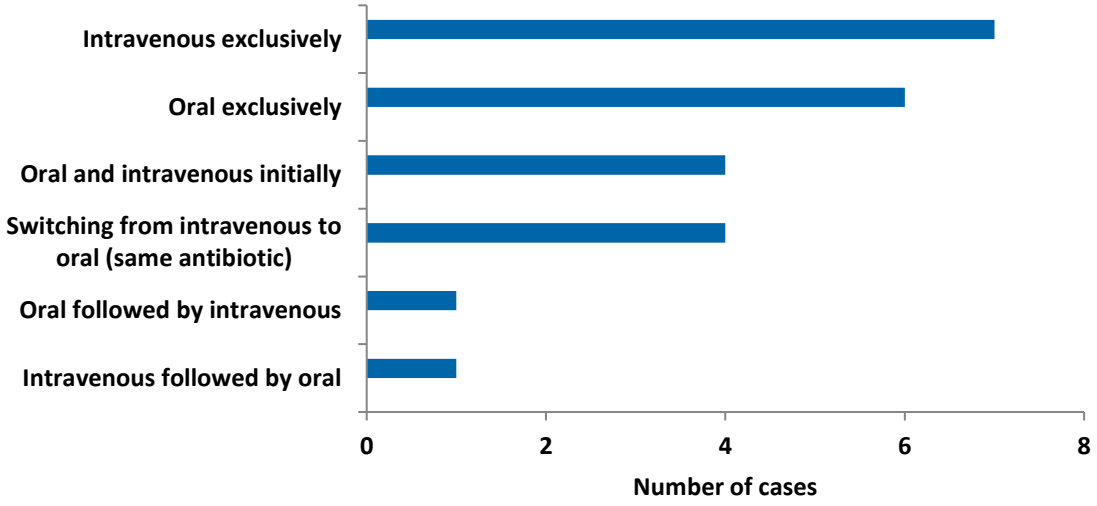

Figure 3.13: Routes of Application of Antibiotic Treatment

In 1 case both "oral and intravenous initially" and "switching from intravenous to oral (same antibiotic) occur. Thus, the sum of cases here is 23 instead of 22 real cases.

3.4.1.5 Days and Length of Antibiotic Therapy

In total, the 22 CAP cases contributed to 140 DoT (22.0 DoT/1000 PD). The median DoT was 3 (IQR = 2-5, min = 1, max = 8). The total LoT was 102 (16.0 LoT/1000 PD) and the median LoT was 4 (IQR = 3-5.75, min = 2, max = 8).

3.4.2 Criteria for Admission to the Hospital

According to the DGPI [73] different criteria have been developed for patients with CAP that suggest and justify hospitalization. The criteria include: shortness of breath or a breathing rate > 70/min (for children younger than 12 months) or > 50/min (for children older than 12 months), oxygen saturation of less than 92%, intermittent apnea, capillary refill time of more than 2 seconds, comorbidities, dehydration or refusal of food, and doubtful compliance, respectively. The DGPI experts state that a patient might be treated as outpatient if none of these criteria was fulfilled.

An admission to the intensive care unit was recommended if the parameters worsen. The novel German guideline for children and adolescents with CAP from 2017 was not available during the study period and is thus discussed later [74].

All medical reports referring to cases with CAP were scanned for statements about the above-mentioned criteria which suggest and justify a patient's admission to the hospital:
In 18 (81.8%) of the regular 22 cases at least 1 of the criteria "oxygen saturation of less than 92%", "oxygen supply", and "tachypnea" was documented, respectively, and justified the admission to the hospital. In the remaining 4 (18.2%) cases none of the latter criteria was provided.
In 12 (54.5%) of the 22 cases tachypnea was documented. In 8 (66.7%) of the 12 cases oxygen saturation was documented as lower than 92%, in 1 (8.3%) case it was documented as higher than 92%, and in 3 (25.0%) cases it was not documented.
Oxygen supply was documented in 6 cases. In 1 (16.7%) of the 6 cases oxygen saturation was documented as lower than 92%, in 4 (66.7%) cases it was documented as higher than 92%, and in 1 (16.7%) case it was not documented.
Oxygen saturation was documented in 15 (68.2%) of the 22 regular cases. In 8 (53.3%) of the 15 cases it was documented as lower than 92% and in 7 (46.7%) cases it was documented as higher than 92%.

3.4.3 Accordance with the German Guideline

The DGPI provides recommendations according to age groups [73]. They are summarized in Tab. 3.3. Recommendations of other guidelines are discussed in chapter 4.

Age	Recommendation
Newborn (1-28 days)	*aminopenicillin + aminoglycoside*
3 weeks - 3 months	*cefuroxime +/- macrolide*
4 months - 5 years	*aminopenicillin +/- macrolide*
> 5 years	*aminopenicillin +/- macrolide*

Table 3.4: German Guideline Recommendations for the Age-Dependent Treatment of Community Acquired Pneumonia (CAP) in Children [73]

Addition of a macrolide antibiotic was recommended if no clinical improvement occurred or if there was any evidence of atypical pneumonia. It can be added initially if the patient's age suggests a higher risk of atypical pathogens (> 4 years).

The route of administration was recommended to be chosen according to the severity of disease: mild diseases could be treated orally, whereas patients at increased risk had to be treated with intravenous antibiotic therapy [73].
In 6 (27.3%) of the 22 cases (aged 9 months to 4 years) initial treatment was ampicillin, in accordance to the DGPI guideline. In 2 of the 6 cases additional antibiotics were added (clarithromycin, ampicillin/sulbactam, clindamycin in 1 case, and cefotaxime, ampicillin/sulbactam, clindamycin in the other case, respectively, due to lack of clinical improvement). In 1 of the 6 cases ampicillin was switched to oral amoxicillin on the second day of therapy. In 3 of the 6 cases the patients were discharged after 2, 3, or 4 days of intravenous therapy with ampicillin, respectively, and it was recommended to continue oral therapy with amoxicillin for 4 to 5 days.
In 1 (4.5%) of the 22 cases (aged 5 years) the initial treatment was a combination of ampicillin and clarithromycin, again in accordance with the DGPI guideline.
The remaining 15 cases (aged 9 months to 15 years) did not meet the DGPI guideline recommendations, as none of the above listed substances was used as initial therapy. Instead, the following antibiotics were used: clarithromycin (n=8), cefuroxime plus clarithromycin (n=3), ampicillin/sulbactam plus clarithromycin (n=1), ampicillin/sulbactam plus azithromycin (n=1), doxycycline (n=1), or cefuroxime (n=1), respectively. However, in 4 of the 15 cases (4 of 22 cases, 18.2%) the patient had already received antibiotics from the local pediatrician.
In total, in 7 (31.2%) of 22 cases the initial treatment was in accordance with the DGPI guideline, and in 15 (68.1%) it was not. In 11 cases (50.0%) no plausible reason was identifiable for the deviation from guideline recommendations, while in 4 (18.2%) cases initial therapy most likely differed from guideline recommendations due to antibiotic pre-treatment for the same indication.

3.5 Antibiotic Treatment of Newborn Infection and Accordance with the German Guideline

3.5.1 Initial Antibiotic Therapy

In 26 cases the indication for antibiotic therapy was newborn infection. On the first day of therapy 13 (50.0%) cases were maximum 5 days old and 13 (50.0%) cases were older than 5 days. All cases were from neo.

3.5.1.1 Type of Antibiotic Used for Initial Treatment

Initial antibiotic therapy of the 26 cases with newborn infection is presented in Fig. 3.16. In 21 (80.8%) cases the initial therapy was ampicillin plus cefotaxime,

with 9 (42.9%) cases older and 12 (57.1%) cases younger than 5 days. In 2 cases (7.7%) the initial therapy was vancomycin, with both cases older than 5 days. In 3 cases ampicillin plus meropenem (n=1, > 5 days), ceftazidime plus tobramycin (n=1, > 5 days), or ampicillin plus tobramycin plus cefotaxime (n=1, ≤ 5 days) was used, respectively.

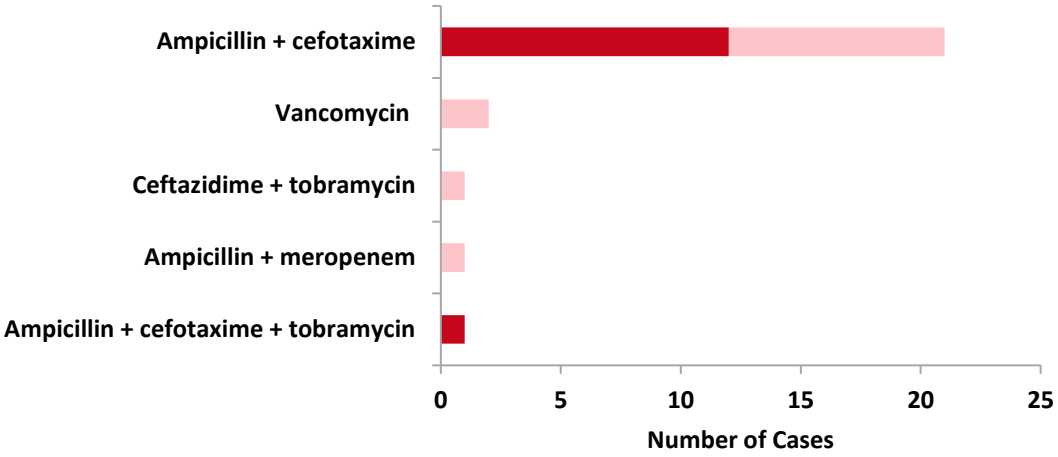

Figure 3.14: Initial Antibiotic Therapy of Newborn Infection

Red: cases younger than 5 days. Pink: cases older than 5 days.

3.5.1.2 Antibiotic Pre-Treatment prior to Hospital Admission

1 (3.8%) case was diagnosed with newborn infection in another hospital and had already received antibiotic treatment when transferred. The patient was younger than 5 days and received piperacillin/tazobactam in the other hospital. After admission to the Children's Hospital Munich Schwabing the antibiotic therapy was switched to ampicillin plus cefotaxime.

3.5.1.3 Number of Courses with Distinct Antibiotics and Number of Antibiotics per Case

In total, 55 courses of treatment with a distinct antibiotic were documented for the 26 cases. On average, 2.1 different antibiotics were used per case, which is in accordance with the results from section 3.5.1.1, as in 23 of the 26 cases initial therapy already included 2 antibiotics. Additionally, in 3 cases tobramycin was added to the initial therapy with ampicillin plus cefotaxime and in 1 case initial therapy of ceftazidime plus tobramycin was switched to ampicillin/sulbactam after 2 days.

3.5.1.4 Route of Application of Antibiotic Treatment

All antibiotics were administered intravenously.

3.5.1.5 Days and Length of Antibiotic Therapy

In total, the 26 newborn infection cases contributed to 285 DoT. The median DoT was 5 (IQR = 3-6, min = 1, max = 15). The total LoT was 146 and the median LoT was 5 (IQR = 4-6.75, min = 2, max = 14).

3.5.2 Results of Laboratory Diagnostics

Documented criteria to start antibiotic therapy in cases with newborn infection was most often "clinical and laboratory suspicion". Furthermore, certain risk factors such as green amniotic fluid, premature rupture of membranes, maternal colonization with *group B streptococci (GBS)* or amniotic infection syndrome were documented. Laboratory parameters of interest were C-reactive protein (CRP), leukocytes and interleukin-6 (Il-6).

3.5.2.1 Level of C-Reactive Protein in Cases with Newborn Infection

In Fig. 3.17 maximum values of CRP during the course of disease of the 26 cases are presented. The unit was mg/dl. In 4 (15.4%) cases the maximum CRP value was 1,0. In 5 (19.2%) cases it was below 10.0 and in 13 (50.0%) cases it varied between 10.0 and 40.0. In 1 (3.8%) case each maximum CRP was 88.0, 90.0, 99.0, or 160.0 respectively.

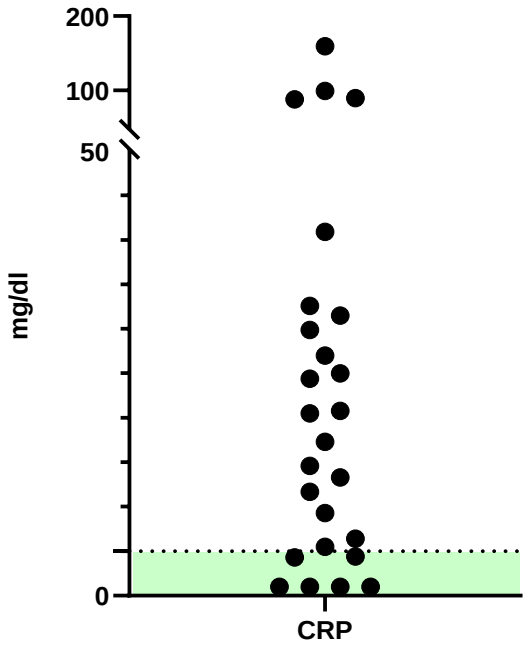

Figure 3.15: Level of C-reactive Protein in Infants with Newborn Infection

Green: normal range (< 5.0 mg/dl)

3.5.2.2 Level of Interleukin-6 in Cases with Newborn Infection

Maximum Il-6 values (pg/ml) of the 26 cases during the course of disease are shown in Fig. 3.18. In 3 (11.5%) cases the maximum value was within the range of 4.0 and 7.0. In 6 (23.1%) cases it was within the range of 18.0 to 80.0. In 12 (46.2%) cases Il-6 was between 100.0 to 800.0 pg/ml. In 1 (3.8%) case each the maximum value was 1376.0, 1606.0, 1750.0, 2165.0, or 4468.0, respectively.

3.5.2.3 Leukocyte Counts in Cases with Newborn Infection

In Fig. 3.19 maximum leukocyte counts during the course of disease of the 26 cases are presented. In 7 (26.9%) cases the leukocyte count was around 7,000. In 18 (69.2%) cases it was between 10,000 and 25,000 and in 1 (3.8%) case it was 37,000.

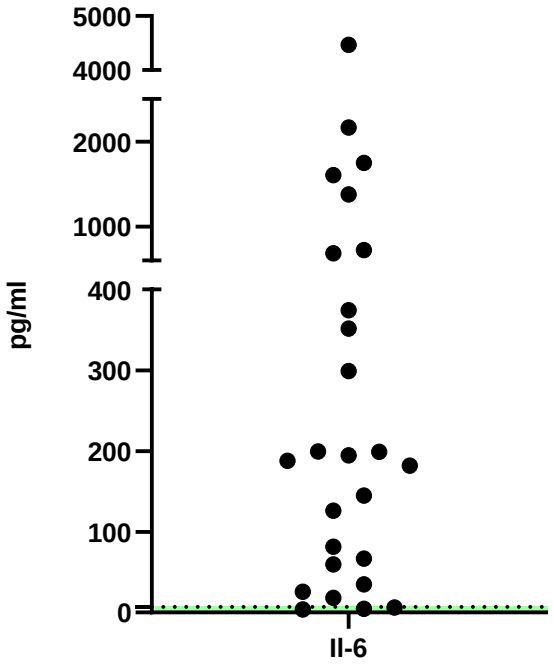

Figure 3.16: Maximum Values of Interleukin-6 in Infants with Newborn Infection

Green: normal range (< 7.0 pg/ml)

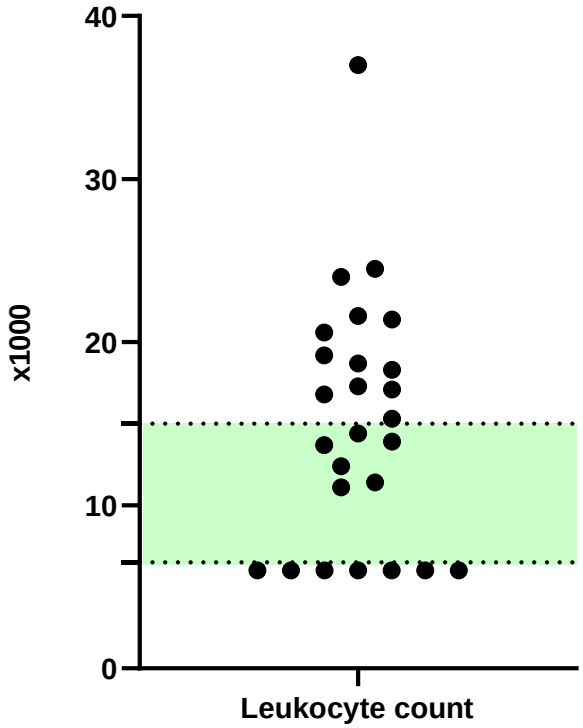

Figure 3.17: Leukocyte Counts in Infants with Newborn Infection

Green: normal range (6.6 – 15.0)

3.5.2.4 Combination of Inflammatory Markes in Cases with Newborn Infection

Combining CRP, Il-6, and leukocyte counts according to each case, respectively, it was found that in 1 (3.8%) case none of the parameters was elevated. In 2 (7.7%) cases 2 parameters were not elevated and in 6 (23.1%) cases 1 parameter was not elevated. However, in 16 (61.5%) cases all 3 parameters were elevated.

3.5.2.5 Blood Cultures in Cases with Newborn Infection

Blood cultures were extracted in 22 of the 26 cases. In 3 cases (13.6%) bacteria were found. In these 3 cases patients were older than 5 days. The following bacteria were found:

- *Staphylococcus aureus* (no resistances)
- *GBS* (resistant to doxycyclin, erythromycin, and clindamycin)
- *Staphylococcus aureus* (resistant to penicillin G, ampicillin) and *Staphylococcus epidermidis* (resistant to penicillin G, ampicillin, and doxycyclin)

3.5.3 Accordance with the German Guideline

As the spectrum of pathogens most likely causing newborn infection differs according to the age the DGPI recommended different antibiotic treatments for newborns aged 1-5 days and newborns older than 5 days (Tab. 3.4) [75].
For newborn infections within the first 5 days of life the choice of antibiotics should either consider ampicillin plus cefotaxime or ampicillin plus tobramycin or gentamicin. Furthermore, the DGPI mentions the option of adding tobramycin to the combination of ampicillin and cefotaxime.
For newborns older than 5 days at the time of diagnosis ceftazidime plus an aminoglycoside, ceftazidime plus vancomycin, or meropenem plus vancomycin should be used, respectively.
In general, antibiotic treatment was recommended to be installed upon first clinical suspicion after collection of blood cultures as infants with infection or even sepsis often do not show specific symptoms. As soon as sepsis can be ruled out due to clinical improvement or laboratory results antibiotic treatment should be stopped. Otherwise, duration of therapy should be 7-10 days for sepsis with positive blood culture and 2-3 weeks for meningitis depending on the causing pathogen. For clinically uncomplicated patients with negative blood culture the DGPI recommends a duration of 5-7 days.

Age at the time of diagnosis	Antibiotic treatment
≤ 5 days	*ampicillin + cefotaxime (+ tobramycin)* ***or*** *ampicillin + tobramycin*
> 5 days	*ceftazidime + aminoglycoside* ***or*** *ceftazidime + vancomycin* ***or*** *meropenem + vancomycin*

Table 3.5: German Guideline Recommendations for the Age-dependent Treatment of Newborn Infection

In 13 (50.0%) cases the newborns were younger than - or at most 5 days old. In 12 (92.3%) of the 13 cases initial treatment was ampicillin plus cefotaxime and in 1 (7.7%) case it was ampicillin plus cefotaxime plus tobramycin which is all in accordance with the DGPI guideline.

In 13 (50.0%) cases the newborns were older than 5 days. In 9 (69.2%) of the 13 cases the initial therapy was ampicillin plus cefotaxime. In 2 (15.4%) cases it was vancomycin and in 1 (7.7%) case each it was ceftazidime plus tobramycin (n=1) and ampicillin plus meropenem (n=1). Thus, the treatment of 1 case was in accordance with the DGPI guideline (ceftazidime plus tobramycin), the treatment of 12 cases were not. No plausible reason was identifiable for the deviation from guideline recommendations. However, 9 of 12 cases (75.0%) which were not treated according to the guideline were treated as newborn infections within the first 5 days of life.
In conclusion, the treatment of newborn infections was consistent concerning the used substances (ampicillin plus cefotaxime in 21 of 26 cases) disregarding the age differences. Further investigations are needed to evaluate the outcome of newborns treated with different substances according to their age. During study period there were no deaths due to newborn infection.

3.6 Antibiotics for Perioperative Antibiotic Prophylaxis (PAP) and Accordance to the German Guideline

The purpose of PAP is to prevent surgical site infections (SSI). However, with regard to increasing antibiotic resistance and other negative side effects, it is important to carefully select patients with increased risks of perioperative infections and to reasonably restrict the antibiotic treatment with respect to the duration of treatment and the spectrum of activity. To facilitate a proper implementation of PAP several guidelines have been established worldwide. Here, the guideline of the AWMF from 2012 will be used to evaluate the appropriateness of PAP in study cases [66].

3.6.1 Surgical Procedures with Perioperative Antibiotic Prophylaxis (PAP)

92 cases of PAP were identified in this study. 11 of these cases were excluded due to the fact, that they underwent surgery in another hospital and were admitted for post-operative monitoring. Thus, instructions concerning PAP came from other doctors. After exclusion of these 11 cases 81 cases with PAP remained, with all cases from pediatric surgery. PAP was given in the context of the following surgical procedures (Fig. 3.20):
16 (19.8%) cases received PAP in the context of urological procedures, including laparoscopic pyeloplasty or nephrectomy, urethroplasty for the correction of hypospadias, antireflux plastic, urethrocystoscopy, and surgical treatment of

ureteropelvic junction stenosis. In 13 (16.0%) cases patients underwent plastic surgery, including mastectomy, scar revision, syndactyly release, and flap reconstructions for skin injuries. In 13 (16.0%) cases patients underwent an open appendectomy. In 10 (12.3%) cases bone fractures were treated with closed reduction. In 7 (8.6%) cases PAP was given due to surgical wound management. In 6 (7.4%) cases patients underwent laparoscopic appendectomy. In 5 (6.2%) cases patients received PAP due to insertion or removal of metallic foreign bodies (e.g. skin expanders). In 5 (4.9%) cases bone fractures were treated with open reduction. In the remaining 6 (7.4%) cases patients received PAP due to the following surgical procedures: closure of an incisional hernia, rectum resection, abscess incision, extirpation of a lateral neck cyst, inguinal herniotomy, and laparoscopic cholecystectomy, respectively. These cases were summarized in the group "others".

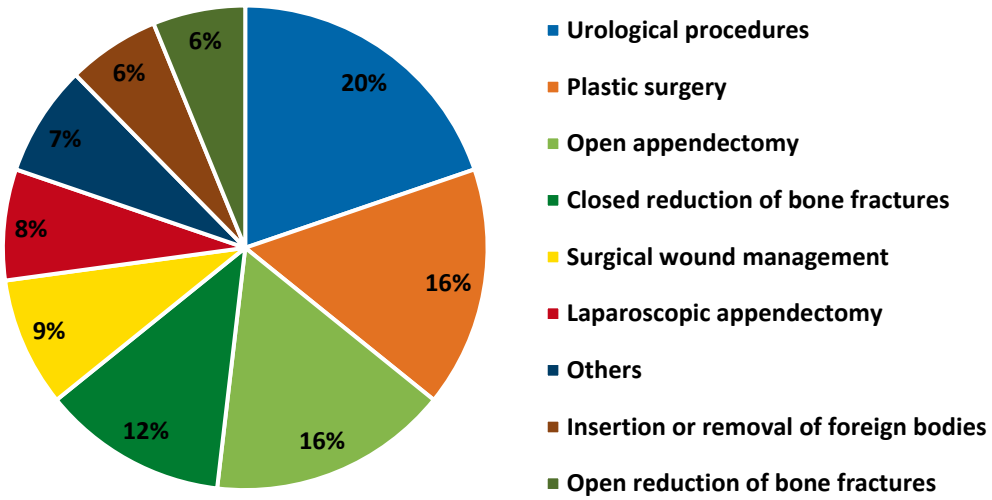

Figure 3.18: Surgical Procedures with Perioperative Antibiotic Prophylaxis (PAP)

3.6.2 Indication of Perioperative Antibiotic Prophylaxis (PAP) and Accordance to the German Guideline

The AWMF guideline for PAP from 2012 defined 5 types of risk factors that justify the indication of PAP [66]. These included

1. evidence of surgical site contamination (e.g. abscess),
2. distinct individual patient characteristics (e.g. contamination with *MRSA*),
3. distinct pre-operative conditions (e.g. emergency surgery),
4. distinct intra-operative conditions (e.g. perforation of surgical gloves), or

5. distinct post-operative conditions (e.g. drainages or catheters).

Moreover, the AWMF guideline stated that a PAP was generally not indicated in the case of exclusive

1. insertion or removal of vessel or urinary catheters or and wound drainages,
2. aseptic wound management and aseptic interventions, or
3. locally controllable risk of infection.

The indications of PAP in study cases were evaluated with regard to all types of risk factors suggested by the AWMF guideline, including the 4 classes of surgical site contamination [clean (aseptic) (class 1), clean-contaminated (class 2), contaminated (class 3), and dirty (infected) (class 4)], of which per se only class 2, 3, and 4 provided an indication of PAP.
16 (19.8%), 8 (9.9%), and another 8 (9.9%) cases were assigned to the contamination classes 2, 3, and 4, respectively. The indications of PAP in these 32 cases were thus in accordance with the guideline.
In 26 (32.1%) cases insertions or removals of foreign bodies were performed which justify PAP according to the guideline.
In 12 (14.8%) cases justification of PAP was provided by underlying conditions such as vesicoureteral reflux (VUR) (n=5), disorder of the urine flow (n=1), congenital ureteropelvic junction obstruction (n=1), open fractures (n=3), or open reductions of displaced fractures (n=2).
11 (13.6%) cases were assigned to the contamination class 1 of clean interventions and no specific risk factors justifying PAP were found, indicating inappropriate indication of PAP.

3.6.3 Number of Doses and Duration of PAP and Accordance to the German Guideline

According to the German AWMF guideline from 2012 [66], regular PAP was recommended to be given in a single shot about 30 to 60 minutes prior to surgery and should not exceed 24 hours. The AWMF guideline stated that there was no data proving better outcomes if the antibiotics were given longer than 24 hours (48 hours in cardiac surgery). There were few exceptions in which PAP might be continued for more than 24 hours. These were strong bacterial contamination of the operation area (e.g. peritonitis) with high risk of infection. In such cases indication of PAP can be replaced by indication of antibiotic therapy. The AWMF guideline, moreover, pointed out that the drug level must be high enough at the

beginning of the surgical procedure to be effective, and that this can only be achieved by an administration of the antibiotic prior to (best 30 to 60 minutes before) skin incision.

The number of doses and the duration of PAP in the 81 study cases is summarized in Fig. 3.21: In 43 (53.1%) cases PAP was given as single shot prior to surgery. In only 2 (2.5%) cases, PAP was given in several doses, but did not exceed 24 hours.

In 29 (35.8%) cases antibiotic treatment was continued for longer than 24 hours with the same substance. In 2 of the 29 cases, the diagnosis was occult perforated appendicitis or appendicitis with localized peritonitis, which both justified the continuation of PAP or rather the replacement of PAP by antibiotic treatment. In 1 of the 29 cases the patient suffered from Hirschsprung's disease and underwent rectum resection, which also justified the continuation of PAP. In 8 of the 29 cases, patients showed urogenital risk factors, including vesicoureteral reflux (n=4), ureteropelvic junction obstruction (n=3), or disorder of the urine flow (n=1), which justified single shot PAP. In 8 of the 29 cases the surgical procedure involved insertion or removal of foreign bodies, which justified single shot PAP. In 5 of the 29 cases wound classification justified PAP as single shot. In none of the latter 21 cases appropriate indication for prolonged PAP or replacement of PAP by antibiotic treatment was found. In 5 of the 29 cases no appropriate justification at all was found for PAP.

In 7 (8.6%) cases, PAP was continued for longer than 24 hours and the antibiotic substance was changed, or additional antibiotics were given. In 2 of the 5 cases indication was appropriate (appendicitis with generalized peritonitis and perforated appendicitis, respectively, which justified both PAP and antibiotic treatment). In 2 of the 5 cases indication for PAP could be identified, however there was no identifiable reason for antibiotic treatment in the following. In 3 of the 5 cases no reason for PAP was identified.

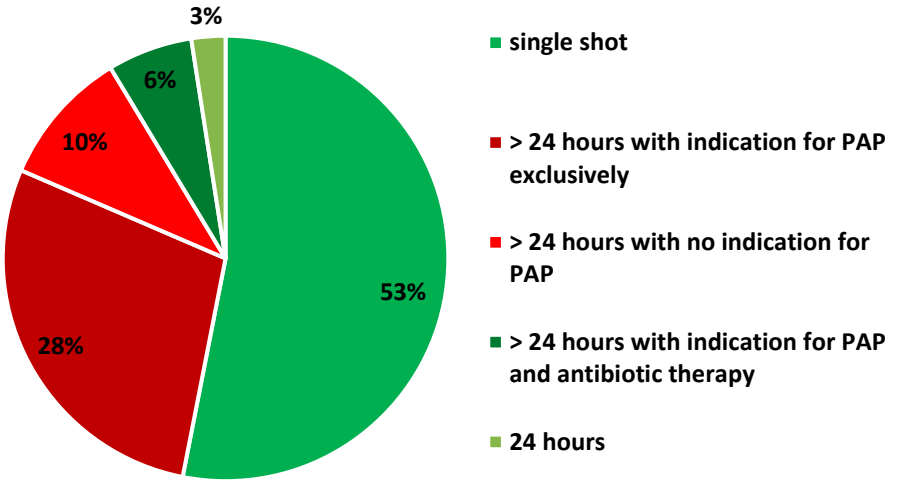

Figure 3.19: Duration of Perioperative Prophylaxis (PAP)

Green: in accordance with the German guideline.

Red: not in accordance with the German guideline

3.6.4 Type of Antibiotic Substances Selected for PAP

The AWMF guideline from 2012 [66] provided no specific recommendations about the type of antibiotic which should be given for PAP. It pointed out that the ideal substance should be bactericidal, should have few side effects and should cover pathogens most likely causing SSI. Moreover, antibiotic treatment prior to surgery and local resistances should be considered [70, p.5]. The guideline also referred to the recommendations of the Paul-Ehrlich-Society [76] as well as to the recommendations of the specific surgical subdisciplines [77-87].

5 different antibiotics and combinations thereof were used for PAP in this study cohort for 9 groups of surgical procedures (Fig 3.22., Tab 3.5). They included:

- cefuroxime (n=34) (42.0%)
- cefazolin (n=30) (37.0%)
- cefuroxime plus metronidazole (n=9) (11.1%)
- cefazolin plus metronidazole (n=6) (7.4%)
- trimethoprim (n=1) (1.2%)
- and ampicillin/sulbactam (n=1) (1.2%)

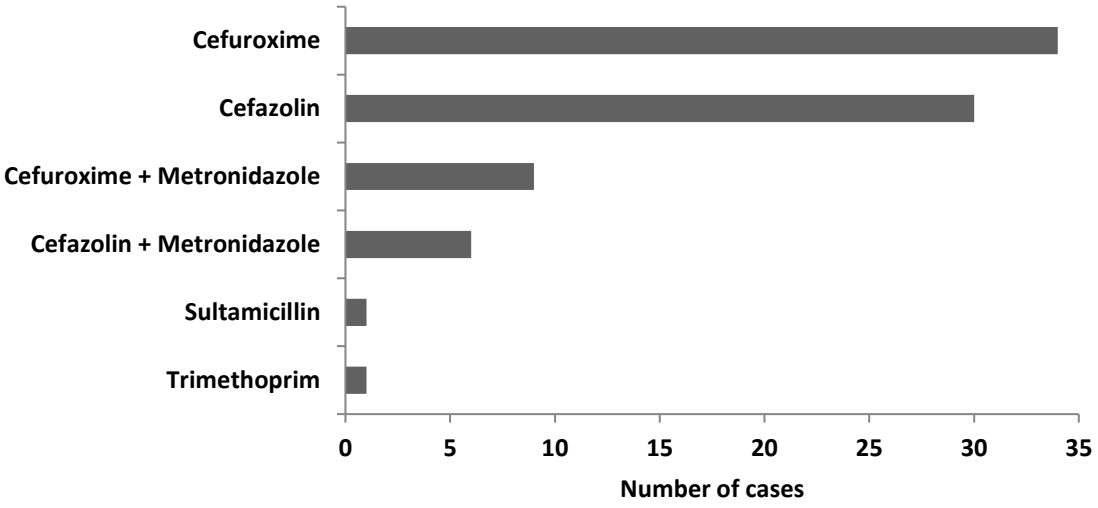

Figure 3.20: Antibiotics Used for Perioperative Antibiotic Prophylaxis (PAP)

Cefuroxime was used in 13 (38.2%) cases for urological and in 8 (23.5%) cases for plastic surgery. In 2 (5.9%) cases each it was used for open appendectomy, surgical wound management, open reduction of bone fractures, or insertion/removal of metallic foreign bodies, respectively. In 1 (2.9%) case each it was used for closed reduction of bone fractures, or laparoscopic appendectomy, respectively. In 3 (8.8%) cases it was used for “other” procedures such as inguinal herniotomy, extirpation of a lateral neck cyst, or abscess incision, respectively.
Cefazolin was used in 9 (30.0%) cases for closed reduction of bone fractures. In 5 (16.7%) cases each it was used for surgical wound management or plastic surgery. In 3 (10.0%) cases each it was used for open reduction of bone fractures or insertion/removal of metallic foreign bodies. In 2 (6.7%) cases each it was used for urological procedures or open appendectomy, and in 1 (3.3%) case it was used for laparoscopic appendectomy.
Cefuroxime and metronidazole were used for open appendectomy in 6 (66.7%) cases and for laparoscopic appendectomy in 1 (11.1%) case. In 2 (22.2%) cases this combination was used for “other” surgeries such as rectum resection or laparoscopic cholecystectomy.
Cefazolin and metronidazole were used in 3 (50.0%) cases each for open surgical or laparoscopic appendectomy.
Ampicillin/sulbactam was used in 1 case for the closure of an incisional hernia, and trimethoprim was used in another case for the correction of hypospadia by urethroplasty.

	Cefuroxime	Cefazolin	Cefuroxime + metronidazole	Cefazolin + metronidazole	Total
Surgical procedure					
Urological procedures	***13***	*2*	*-*	*-*	***15***
Plastic surgery	***8***	***5***	*-*	*-*	***13***
Open appendectomy	*2*	*2*	***6***	***3***	***13***
Closed reduction of bone fractures	*1*	***9***	*-*	*-*	***10***
Surgical wound management	*2*	***5***	*-*	*-*	***7***
Laparoscopic appendectomy	*1*	*1*	*1*	***3***	***6***
Others	*3*	*-*	*2*	*-*	***5***
Open reduction of bone fractures	*2*	*3*	*-*	*-*	***5***
Insertion/removal of foreign objects	*2*	*3*	*-*	*-*	***5***
Total	***34***	***30***	***9***	***6***	***79***

Table 3.6: Antibiotics Used for Different Surgical Procedures

Most frequently (in 79 of 81 cases) used antibiotics for perioperative antibiotic prophylaxis (PAP). Red: highest numbers.

Table 3.7: Overview of All Cases with Perioperative Antibiotic Prophylaxis (PAP)

Green: indication and duration in accordance with the German guideline. Red: not in accordance with the German guideline. White: either indication or duration not in accordance with the German guideline. n = Number of cases.

	Procedures	**PAP Indication**	**PAP Duration**	**Antibiotic(s)**
n =16	***Urological procedures***			
	laparoscopic nephrectomy, ureterectomy, circumcision	*clean-contaminated*	*single shot*	*cefazolin*
	reconstruction of the urethra with urethra stent	*foreign body*	*6 days*	*cefuroxime*
	laparoscopic pyeloplasty (with ureteral stent)	*foreign body*	*6 days*	*cefuroxime*
	urethra reconstruction (hypospadias)	*foreign body*	*7 days*	*trimethoprim*
	correction of VUR	*risk factor (VUR)*	*3 days*	*cefuroxime*
	correction of VUR	*risk factor (VUR)*	*3 days*	*cefuroxime*
	laparoscopic pyeloplasty	*risk factor (congenital ureteropelvic junction obstruction)*	*8 days*	*cefuroxime*
	urethra reconstruction (hypospadias), circumcision	*foreign body*	*8 days*	*cefuroxime*
	urethrocystoscopy, incision of ureterocele	*risk factor (disorder of urine flow)*	*single shot*	*cefuroxime*
	correction of VUR	*risk factor (VUR)*	*3 days*	*cefuroxime*
	correction of VUR	*risk factor (VUR)*	*3 days*	*cefuroxime*
	insertion of ureteral stent	*foreign body*	*3 days*	*cefuroxime*
	cystoscopy, surgical excision of bladder diverticulum	*clean-contaminated*	*single shot*	*cefuroxime*
	reconstruction of the urethra (hypospadias)	*foreign body*	*single shot*	*cefazolin*
	urethrocystoscopy, correction of VUR	*risk factor (VUR)*	*2 days*	*cefuroxime*

	reconstruction of urethra (hypospadias), circumcision	*foreign body*	*single shot*	*cefuroxime*
n =13	***Plastic surgery***			
	mastectomy (gynecomastia)	*- (aseptic)*	*single shot*	*cefazolin*
	correction of scar	*- (aseptic)*	*9 days*	*cefuroxime*
	correction of syndactyly and polydactyly	*- (aseptic)*	*3 days*	*cefazolin as single shot* *continued with: cefuroxime*
	suture of a nerve, flap plasty	*contaminated (traumatic wound)*	*2 days*	*cefuroxime*
	local flap plasty, z-plasty	*- (aseptic)*	*single shot*	*cefazolin*
	flap plasty of oral mucosa	*clean-contaminated*	*4*	*cefuroxime*
	transposition flap plasty	*- (aseptic)*	*7 days*	*cefazolin for 4 days* *continued with: cefuroxime*
	reconstruction of tendons	*- (aseptic)*	*single shot*	*cefuroxime*
	correction of syndactyly (osteotomy, flap plasty)	*foreign body (osteosynthesis)*	*single shot*	*cefuroxime*
	reconstruction of fingertip (flap plasty, osteosynthesis)	*foreign body (osteosynthesis)*	*single shot*	*cefuroxime*
	correction of scar	*- (aseptic)*	*single shot*	*cefuroxime*
	correction of syndactyly	*- (aseptic)*	*4 days*	*cefazolin for 2 days* *continued with: cefadroxil*
	correction of scar with insertion of skin expander	*foreign body*	*6 days*	*cefuroxime*
n =13	***Open Appendectomy***			
		dirty (peritonitis)	*single shot*	*cefazolin plus metronidazole*
		dirty (perforation)	*single shot*	*cefazolin plus metronidazole* *continued with antibiotic therapy*

	dirty (occult perforation)	*6 days*	*cefuroxime plus metronidazole*
	dirty (localized peritonitis)	*8 days*	*cefuroxime plus metronidazole*
	clean-contaminated	*single shot*	*cefuroxime*
	clean-contaminated	*single shot*	*cefuroxime plus metronidazole*
	dirty (localized peritonitis)	*single shot*	*cefazolin*
	clean-contaminated	*2 days*	*cefuroxime plus metronidazole*
	clean-contaminated	*single shot*	*cefuroxime*
	clean-contaminated	*single shot*	*cefazolin plus metronidazole*
	clean-contaminated	*2 days*	*cefuroxime plus metronidazole*
	clean-contaminated	*single shot*	*cefazolin*
	clean-contaminated	*single shot*	*cefuroxime plus metronidazole*
n =10 Closed reduction of bone fracture			
	foreign body (Kirschner's wire)	*single shot*	*cefazolin*
	foreign body [Elastic stable in-tramedullary nailing (ESIN)]	*single shot*	*cefazolin*
	foreign body (wire)	*single shot*	*cefazolin*
	foreign body (nailing)	*single shot*	*cefazolin*
	foreign body (Kirschner's wire)	*single shot*	*cefazolin*
	foreign body (Kirschner's wire)	*single shot*	*cefazolin*
	foreign body (ESIN)	*single shot*	*cefazolin*
	foreign body (ESIN)	*single shot*	*cefazolin*

		foreign body (ESIN)	*single shot*	*cefazolin*
		risk factor (open fracture)	*24 hours*	*cefuroxime*
n=7	***Surgical wound management***			
	suture of tendon and skin	*contaminated*	*single shot*	*cefazolin*
	intraoral surgical wound management	*contaminated (open wound)*	*2 days*	*cefuroxime*
	suture of tendons	*foreign body*	*2 days*	*cefazolin*
	aseptic wound management	*contaminated*	*4 days*	*cefuroxime*
	management of a foot cut	*contaminated (traumatic wound)*	*24 hours*	*cefazolin*
	management of an arterial cut	*contaminated*	*single shot*	*cefazolin*
	management of an arterial cut	*contaminated (traumatic wound)*	*2 days*	*cefazolin as single shot* *continued with: cefuroxime*
n =6	***Laparoscopic appendectomy***			
		dirty (peritonitis)	*single shot*	*cefuroxime* *continued with antibiotic therapy*
		dirty (phlegmonous appendicitis)	*single shot*	*cefazolin*
		clean-contaminated	*single shot*	*cefazolin plus metronidazole*
		clean-contaminated	*single shot*	*cefazolin plus metronidazole*
		clean-contaminated	*single shot*	*cefazolin plus metronidazole*
		clean-contaminated	*single shot*	*cefuroxime plus metronidazole*
n =5	***Insertion or removal of foreign bodies***			
	removal of skin expander	*foreign body*	*8 days*	*cefazolin as single shot* *continued with: cefuroxime*

	removal of metal (after skull fracture)	*foreign body*	*single shot*	*cefazolin*
	insertion of skin expander	*foreign body*	*6 days*	*cefuroxime*
	removal of skin expander	*foreign body*	*7 days*	*cefazolin as single shot continued with: cefuroxime*
	removal of osteosynthesis material	*foreign body*	*single shot*	*cefuroxime*
n = 5	***Open reduction of bone fracture***			
	radius fracture	*risk factor (open fracture)*	*single shot*	*cefazolin*
	osteosynthesis on lumbar spinal column	*foreign body (osteosynthesis)*	*single shot*	*cefazolin*
	fracture of the big toe	*risk factor (open fracture)*	*3 days*	*cefuroxime*
	displaced fracture of the clavicle	*risk factor (open fracture, elastic stable intramedullary nailing)*	*single shot*	*cefazolin*
	humerus fracture	*risk factor (open fracture and Kirschner's wire)*	*3 days*	*cefuroxime*
n =6	***Others***			
	closure of incisional hernia	*- (aseptic)*	*6 days*	*ampicillin/sulbactam*
	rectum resection (Hirschsprung's disease)	*clean-contaminated*	*7 days*	*cefuroxime plus metronidazole*
	abscess incision	*dirty*	*single shot*	*cefuroxime*
	extirpation of lateral neck cyst	*contaminated*	*single shot*	*cefuroxime*
	herniotomy of inguinal hernia	*- (aseptic)*	*2 days*	*cefuroxime*
	cholecystectomy (gallstones without inflammation)	*- (aseptic)*	*single shot*	*cefuroxime plus metronidazole*

3.7 Dosages

3.7.1 Dosages of Different Antibiotics

In pediatrics medication has to be adapted to the patients' body weight. Therefore, dosages have to be calculated for every distinct case.
In this chapter the dosages (mg/kg/d) of frequently used antibiotics were analyzed and judged with regard to the route of administration (oral or intravenous) as well as to the relevant age group (younger or older than 12 months). Dosages of antibiotics used for PAP were studied separately.
The dosages of the following antibiotics were analyzed:

- cefazolin for PAP (n=32)
- cefuroxime for PAP (n=20)
- cefuroxime intravenously for cases > 12 months (n=94)
- cefuroxime intravenously for cases < 12 months (n=19)
- ampicillin for cases > 12 months (n=30)
- ampicillin for cases < 12 months (n=56)

3.7.1.1. Dosages of Cefazolin for Perioperative Prophylaxis (PAP)

Dosages of cefazolin for PAP were presented in Fig. 3.23. The median dosage was 30 mg/kg/d (IQR = 28.47-32.76, min = 2.7, max = 66.67) (n =32). The 2 lowest dosages were 2.7 and 4.29 mg/kg/d. 1 of the 2 cases with very low dosages was a 12-year-old boy of 37 kg body weight who was operated due to a forearm fracture and received 100 mg cefazolin as a single shot (2,7 mg/kg/d). The other case was an 8-year-old boy of 35 kg body weight who underwent surgical wound management and received 150 mg cefazolin as a single shot (4.28 mg/kg/d). The highest dosage was 66.67 mg/kg/d. This dosage was given to a 10-year-old girl of 30 kg body weight who received 2,000 mg cefazolin prior to a surgery of a radius fracture. There were no identifiable reasons for the extreme dosages. However, the highest dosage was equivalent to the adults' dosage and did probably not cause any harm in this pediatric patient.

3.7.1.2. Dosages of Cefuroxime for Perioperative Prophylaxis (PAP)

Dosages of intravenous cefuroxime for PAP were presented in Fig. 3.24. The median dosage of cefuroxime for PAP was 30.0 mg/kg/d (IQR = 28.7-30.3, min = 20.0, max = 34.8) (n= 20). There were no upward or downward outliers.

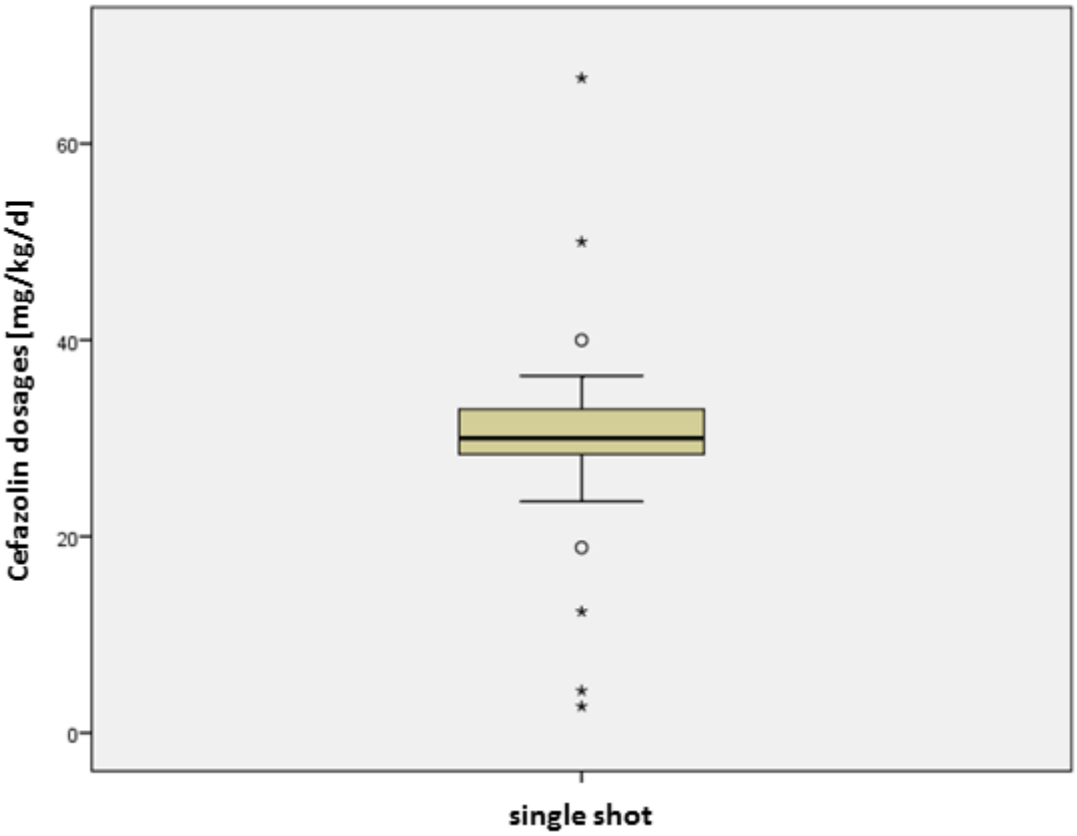

Figure 3.21: Dosages of Cefazolin for Perioperative Prophylaxis (PAP)

3.7.1.3. Dosages of Intravenous Cefuroxime for Treatment of Infectious Diseases

Dosages of intravenous cefuroxime were also presented in Fig. 3.24.
The median dosage of cefuroxime for cases < 12 months was 100.0 mg/kg/d (IQR = 96.96-105.67, min = 85.71, max = 147.89). In 2 cases dosages were 147.89 and 129.03 mg/kg/d. 1 of the 2 cases was a 5-month-old girl with 7.1 kg who suffered from a feverish respiratory tract infection along with conjunctivitis and was treated with 3 x 350 mg cefuroxime per day (147.89 mg/kg/d). The other case was a 10-months-old girl with 9.3 kg body weight diagnosed with pyelonephritis who received 3 x 400 mg cefuroxime per day (129 mg/kg/d). Even though these dosages stood out, they could still be considered as appropriate.
The median dosage of intravenous cefuroxime for cases > 12 months was 99.5 mg/kg/d (IQR = 90.0-102.4, min = 30.0, max = 150.0). The case with the minimum dosage was a 20-month-old boy of 13 kg body weight suffering from a perforated Meckel's diverticulum along with peritonitis, appendicitis, and a mechanical ileus. He received 3 x 130 mg cefuroxime per day (30 mg/kg/d). The 4 cases with the highest values were the following: A 2-year-old boy of 12.2 kg body weight with pneumonia treated with 3 x 600 mg cefuroxime per day (147.54 mg/kg/d). A 14-

year-old girl with 31.5 kg body weight and osteomyelitis was treated with 3 x 1,500 mg cefuroxime per day (142.86 mg/kg/d). A 4-year-old boy of 16 kg body weight with pneumonia was treated with 3 x 800 mg cefuroxime per day (150 mg/kg/d). His underlying disease was metachromatic leukodystrophy. A 4-year-old girl of 13.0 kg body weight with a feverish infection of the upper respiratory tract was treated with 3 x 650 mg cefuroxime per day (150 mg/kg/d). Her underlying disease was a Pallister-Hall syndrome.

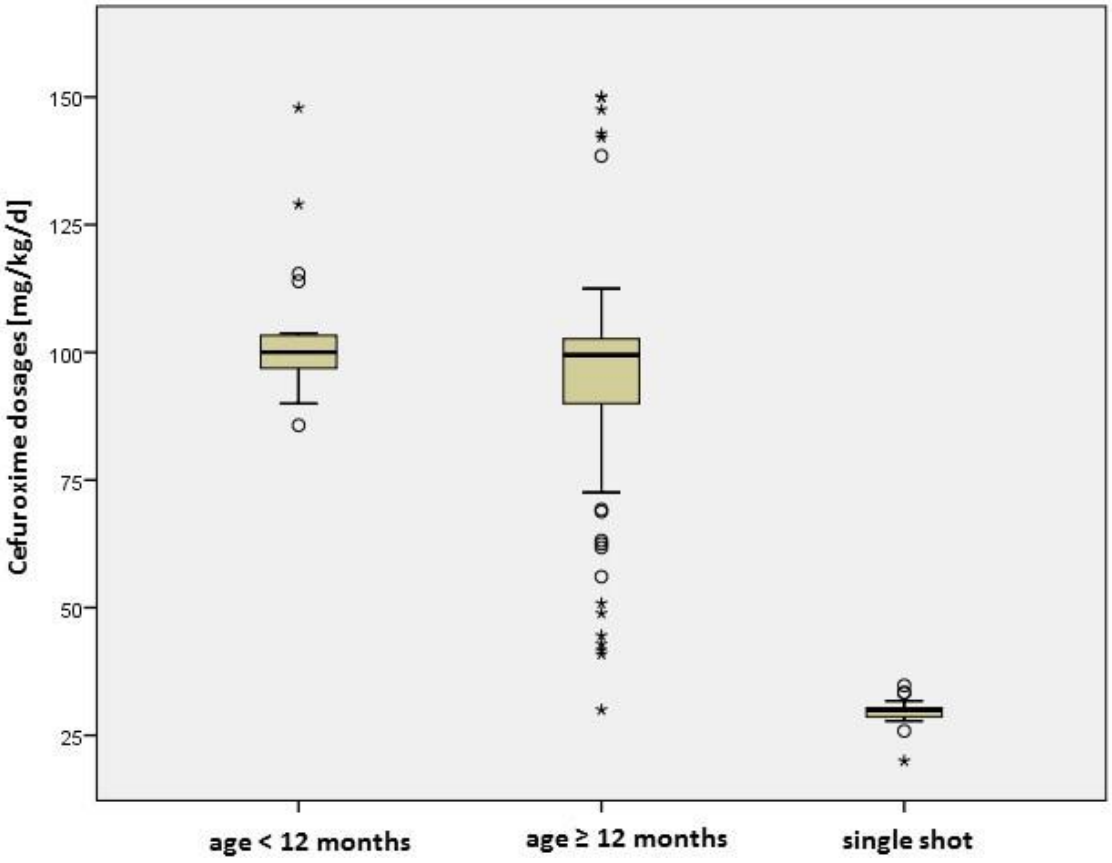

Figure 3.22: Dosages of Cefuroxime

Left and middle: antibiotic treatment. Right: perioperative prophylaxis (PAP)

3.7.1.4. Dosages of Intravenous Ampicillin for Treatment of Infectious Diseases

Dosages of ampicillin used for treatment of infectious diseases were presented in Fig. 3.25. The median dosage of ampicillin for cases < 12 months was 148.1 mg/kg/d (IQR = 139.3-152.1, min = 69.2, max = 300.0). The case with the minimum dosage of 69.2 mg/kg/d was a 7-month-old infant with renal arterial hypertonia and dysplastic-cystic kidney. The administered dosage was adapted on the renal function and therefore disproportionally low. The 4 cases with the highest

dosages were the following: A 9-month-old boy of 8.2 kg body weight with a feverish infection of the upper respiratory tract and suspicion of meningitis treated with 3 x 800 mg ampicillin per day (292,68 mg/kg/d). The suspicion of meningitis explained the high dosage. Two 3-4-month-old patients with body weights of 5.5 and 6.5 kg and pyelonephritis were treated with 3 x 500 mg and 3 x 370 mg ampicillin per day (272.73 and 170.77 mg/kg/d, respectively). A newborn boy with 4.0 kg body weight and status epilepticus after intra-amniotic infection was treated with 3 x 400 mg ampicillin per day (300 mg/kg/d) due to the suspicion of meningitis.

The median dosage of ampicillin for cases > 12 months was 113.7 mg/kg/d (IQR = 100.0-149.7, min = 76.1, max = 198.4). There were no upward or downward outliers.

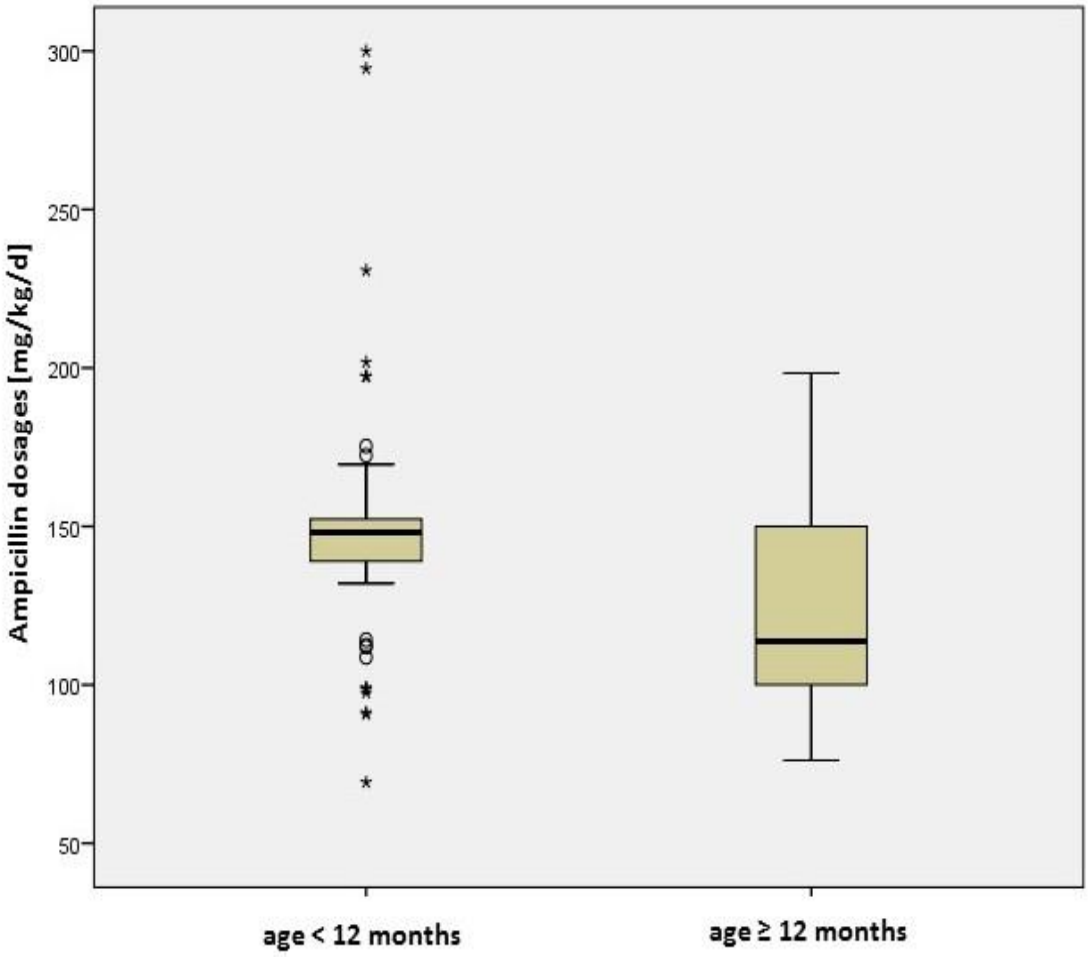

Figure 3.23: Dosages of Ampicillin

3.7.2 Accordance with the Guideline

In the following the dosages of cefuroxime and ampicillin are analyzed with regard to German guideline accordance (Fig. 3.26). PAP was not considered, as the German DGPI handbook, which does not give any recommendations about dosages for PAP, was used as reference [88]. Additionally, the recommendations of a commonly used German dosage book called "Medikamente in der Pädiatrie" (MidP) was used to assess whether the administered dosages were appropriate [89].
Overall, the antibiotic dosages of 199 cases were analyzed (86 cases with ampicillin and 113 cases with cefuroxime). 175 (87.9%) of these were in accordance with the guideline (MidP and DGPI), while 21 (10.6%) were too low and 3 (1.5%) too high.

3.7.2.1. Guideline Accordance of Intravenous Cefuroxime Dosages

Regarding intravenous cefuroxime the MidP booklet recommends 20-60 mg/kg/d for newborns and 75-150 mg/kg/d for infants at the age of 3-12 months as well as for children up to 12 years. The recommended dosage for young people and adults is 2.25-4.5 g/d. The DGPI handbook does not consider newborns, but recommends the same dosages for infants, children and young people and adults.
113 cases with intravenous cefuroxime were analyzed. 3 (2.7%) of the 113 cases were newborns. The dosages for all of them were higher than the recommendation in the MidP booklet. In 110 (97.3%) cases patients were older than 28 days. In 13 (11.8%) of the 110 cases the dosage was below 75 mg/kg/d. However, the upper limit of 150 mg/kg/d was not exceeded.
In total, in 16 (14.2%) of 113 cases the dosage of cefuroxime was not in accordance with the guideline.

3.7.2.1. Guideline Accordance of Intravenous Ampicillin Dosages

Concerning ampicillin dosages, the MidP booklet recommends 100-200 mg/kg/d for newborns, 100-300 mg/kg/d for infants at the age of 3-12 months and 80-300 mg/kg/d for children up to 12 years. For newborns with suspected meningitis the recommendation is 300 mg/kg/d. The DGPI handbook recommends 100-400 mg/kg/d for infants and children up to 12 years and 3-6 g/d for young people and adults.

86 cases with intravenous ampicillin were analyzed. 27 (31.4%) of the 86 cases were newborns. In 22 (81.5%) of the 27 cases the dosages were in the recommended range of the MidP booklet, in 4 (14.2%) cases they were lower. In 1 of the 4 cases this was due to impaired renal function and thus correct. In 1 (3.7%) of the 27 case the dosage was higher (300 mg/kg/d) due to suspicion of meningitis and therefore also in accordance with the MidP booklet.
59 (68.6%) of all 76 cases which received ampicillin were older than 28 days. 29 (49.2%) of these were at the age of younger than 12 months. In 3 (10.3%) of these 29 cases the dosage was below 100 mg/kg/d. In 26 (89.7%) cases the dosage was in the recommended range of the MidP booklet as well as the DGPI handbook. 30 (50.8%) of the 59 cases older than 28 days were at the age of 12 months or more. In 2 (6.7%) of these 30 cases the dosages were below 80 mg/kg/d, in 28 (93.3%) cases the dosages were in the recommended range of the MidP booklet and the DGPI handbook.
In total, in 8 (9.3%) of 86 cases the dosage of ampicillin was not in accordance with the guideline.

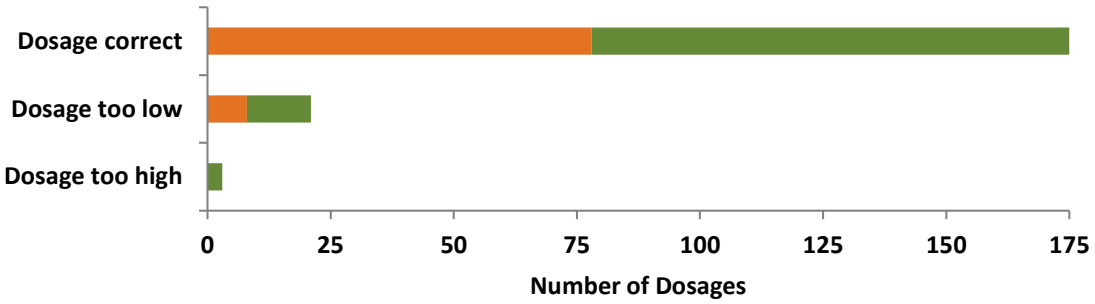

Figure 3.24: Guideline Accordance of Dosages of Cefuroxime and Ampicillin

Green: Cefuroxime. Orange: ampicillin

3.8 Comparison of Antibiotic Use in this Study Cohort to Data from the Dr. von Hauner Children's Hospital

In this chapter the data on the antibiotic use in the Children's Hospital Munich Schwabing was compared to the data kindly provided by the colleagues from the Dr. von Hauner Children's Hospital (Tab. 3.7, Tab. 3.8). The comparison was focused on the antibiotic use in general pediatrics and to the pre-intervention data form the Dr. von Hauner Children's Hospital. To provide comparability the DoT were related on 1,000 patient-days (DoT/1,000 PD).

In total, the antibiotic use was 483.6 DoT/1,000 PD in the pre-intervention period in the Dr. von Hauner Children's Hospital and 345.9 DoT/1.000 PD in the Children's Hospital Munich Schwabing. In the post-intervention period, the antibiotic use decreased from 483.6 to 432.9 DoT/1,000 PD in the Dr. von Hauner Children's Hospital, which is equivalent to a decrease of 10.5%.

The pre-intervention use in the Dr. von Hauner Children's Hospital of penicillins was 163.2 compared to 128.2 DoT/1,000 PD in the Children's Hospital Munich Schwabing. Marked differences were discovered for piperacillin plus BLI with a more frequent use in the Dr. von Hauner Children's Hospital (105.5 *versus* 7.3 DoT/1,000 PD) and in penicillins with extended spectrum (35.5 *versus* 91.4 DoT/1,000 PD), mostly ampicillin and amoxicillin, with a more frequent use in the Children's Hospital Munich Schwabing. In the post-intervention period, the use of penicillins increased from 163.2 to 187.6 DoT/1,000 PD in the Dr. von Hauner Children's Hospital, which is equivalent to an increase of 15.0%.

Substance	DoT/1,000 PD			
	Hauner pre	Schwabing		
		total	internal	surgical
Penicillins	**163.2**	**111.1**	**128.2**	**64.8**
Piperacillin + BLI	105.5	6.4	7.3	4.1
Other penicillins + BLI	17.1	30.2	27.7	36.8
Beta-lactamase resistant penicillins	0.9	-	-	-
Penicillins with extended spectrum	35.5	73.1	91.4	23.4
Beta-lactamase sensitive penicillins	4.2	1.4	1.7	0.6
Cephalosporins	**161**	**175.3**	**140.2**	**270.4**
1st generation cephalosporins	8.2	7.9	0.2	28.6
2nd generation cephalosporins	108.9	95.1	50.1	217.3
3rd generation cephalosporins	43.9	72.3	89.9	24.5
Fluorquinolones	**31.9**	**0.5**	**0.6**	**-**
Ciprofloxacin	20	0.5	0.6	-
Levofloxacin	-	-	-	-
Moxifloxacin	12	-	-	-
Nitroimidazoles (Metronidazol)	**27.1**	**15.9**	**5.8**	**43.2**
Macrolides	**24.8**	**19.5**	**26.7**	**-**
Glycopeptides	**23.5**	**4.4**	**6.0**	**-**
Vancomycin	20.4	4.2	5.8	-
Teicoplanin	3.1	0.2	0.2	-
Carbapenems	**16.6**	**9.4**	**12.9**	**-**
Lincosamides (Clindamycin)	**16.2**	**15.7**	**13.8**	**21.0**
Others	**12.2**	**4.1**	**2.8**	**7.6**
Aminoglycosides	**4.7**	**6.9**	**8.8**	**1.8**
Polymyxine (Colistin)	**2.4**	**-**	**-**	**-**
Total	**483.6**	**362.8**	**345.9**	**408.9**

Table 3.8: Comparison of the Antibiotic Use (DoT/1,000 PD) in this Study Cohort to Data from the Dr. von Hauner Children's Hospital

Hauner pre: pre-intervention data from the Dr. von Hauner Children's Hospital

Schwabing: Children's Hospital Munich Schwabing

The pre-intervention usage of cephalosporins in the Dr. von Hauner Children's Hospital was 161.0 compared 140.2 DoT/1,000 PD in the Children's Hospital Munich Schwabing. Differences in the antibiotic use were discovered for all generations of cephalosporins, with 8.2 *versus*. 0.2 DoT/1,000 PD in the 1st generation, 108.9 *versus* 50.1 DoT/1,000 PD in the 2nd generation, and 43.9 *versus* 89.9 in the 3rd generation, respectively. In the post-intervention period, the usage of cephalosporins declined from 161.0 to 103.9 DoT/1,000 PD in the Dr. von Hauner Children's Hospital, which is equivalent to a decrease of 35.0%.

Moreover, during the pre-intervention period in the Dr. von Hauner Children's Hospital more nitroimidazoles (27.1 vs. 5.8 DoT/1,000 PD), more glycopeptides (23.5 vs. 6.0 DoT/1.000 PD), less aminogylcosides (4.7 vs. 8.8 DoT/1,000 PD), and more other antibiotics (12.2 vs. 2.8 DoT/1,000 PD) have been used compared to the study cohort of the Children's Hospital Munich Schwabing.

Compared to the antibiotic use in internal pediatrics the total antibiotic use in pediatric surgery in the Children's Hospital Munich Schwabing was remarkably high, with 408.9 compared to 345.9 DoT/1,000 PD. The total use in the Dr. von Hauner Children's Hospital was 483,6 DoT/1,000 PD, which was not that much more than the antibiotic use in pediatric surgery of the Children's Hospital Munich Schwabing. The most frequently used antibiotics in pediatric surgery included cephalosporins, nitroimidazoles, and lincosamides, with 270.7, 43.2, and 21.0 DoT/1,000 PD, respectively. By contrast, penicillins were used in pediatric surgery at only 64.8 DoT/1,000 PD.

Substance	DoT absolute			
	Hauner pre	Schwabing		
		total	internal	surgical
Penicillins	**736**	**707**	**596**	**111**
Piperacillin + BLI	476	41	34	7
Other penicillins + BLI	77	192	129	63
Beta-lactamase resistant penicillins	4	-	-	-
Penicillins with extended spectrum	160	465	425	40
Beta-lactamase sensitive penicillins	19	9	8	1
Cephalosporins	**726**	**1,115**	**652**	**463**
1st generation cephalosporins	37	50	1	49
2nd generation cephalosporins	491	605	233	372
3rd generation cephalosporins	198	460	418	42
Fluorquinolones	**144**	**3**	3	-
Ciprofloxacin	90	3	3	-
Levofloxacin	-	-	-	-
Moxifloxacin	54	-	-	-
Nitroimidazoles (Metronidazol)	**122**	**101**	**27**	**74**
Macrolides	**112**	**124**	**124**	**-**
Glycopeptides	**106**	**28**	**28**	**-**
Vancomycin	92	27	27	-
Teicoplanin	14	1	1	-
Carbapenems	**75**	**60**	**60**	**-**
Lincosamides (Clindamycin)	**73**	**100**	**64**	**36**
Others	**55**	**26**	**13**	**13**
Aminoglycosides	**21**	**44**	**41**	**3**
Polymyxine (Colistin)	**11**	**-**	**-**	**-**
Total	**2,181**	**2,308**	**1,608**	**700**

Table 3.9: Comparison of Antibiotic Use (DoT absolute) in this Study Cohort to Data from the Dr. von Hauner Children's Hospital

Hauner pre: pre-intervention data of the Dr. von Hauner Children's Hospital

Schwabing: Children's Hospital Munich Schwabing

4 Discussion

4.1 Antibiotic Treatment of Urinary Tract Infection

4.1.1 International Guidelines During Study Period

In the following, the results of the present study concerning antibiotic treatment of UTI are compared to international guidelines which were available during the study period.

The clinical practice guideline of the American Academy of Pediatrics (AAP) from 2011 referred to the management of the initial UTI in febrile infants and children at the age of 2 to 24 months and recommended a cephalosporine alone, ampicillin plus clavulanic acid, or trimethoprim-sulfamethoxazole for initial oral therapy. For initial intravenous therapy this guideline recommended single antibiotic treatment with either ceftriaxone, cefotaxime, ceftazidime, piperacillin, or aminoglycosides. Oral treatment was preferred, and intravenous therapy was suggested for patients which were not compliant, unable to keep oral medication, or septic. This AAP guideline suggested that oral treatment should follow initial intravenous therapy in the case of sufficient clinical response at 1 to 2 days after the beginning of treatment. Duration of therapy was recommended for 7 – 14 days [90] (Tab. 3.9). In 2016 the AAP published an reaffirmation of the 2011 guideline, which stayed with the same recommendations [91]. A next version of the guideline is expected for 2021.

The Harriet Lane Handbook of the Johns Hopkins Hospital in the USA (20th edition, 2015) [92] suggested ceftriaxone alone or ampicillin plus gentamicin for uncomplicated and cefepime alone or piperacillin plus tazobactam for complicated pyelonephritis in children independent of age, both for 7 - 14 days (Tab. 3.9). For cystitis the same text book suggested cotrimoxazole or cefixime as oral treatment (as alternative: nitrofurantoin or ciprofloxacin) for 7 - 14 days and cefotaxime alone, ceftriaxone alone, or ampicillin plus gentamicin, respectively, for intravenous treatment [92]. The 20th edition (2015) of this handbook suggested that dehydrated or septic children as well as children unable to tolerate oral medication and newborns should be treated intravenously [92].

The guideline of the European Association of Urology (EAU) from 2015 suggested ampicillin plus an aminoglycoside or a 3rd generation cephalosporine for the treatment of UTI. Concerning the route of administration, it recommended to consider different factors, such as age, clinical suspicion of urosepsis, and severity of illness. In the case of initial intravenous treatment a switch to oral treatment

for 7-14 days was recommended as soon as the child was afebrile [93] (Tab. 3.9). In contrast to the German DGPI guideline (6th edition, 2013), international guidelines did not differ between age groups. In addition, international guidelines showed differences concerning the types of the recommended antibiotics. The combination of ampicillin with ceftazidime, most often used in cases of this study (20/37) and recommended by the DGPI handbook (6th edition, 2013) for children younger than 6 months, was not listed in any of the abovementioned international guidelines. However, the combination of ampicillin plus an aminoglycoside, which is recommended by the DGPI guideline (6th edition, 2013) as alternative treatment of infants younger than 6 months, and 3rd generation cephalosporins alone, recommended by the DGPI (6th edition, 2013) for children older than 6 months, was also recommended by international guidelines.

Two cases of this study would have been in accordance with the Harriet Lane Handbook (20th edition, 2015), which recommended oral cotrimoxazole. Six cases who had received a 3rd generation cephalosporine alone as initial therapy were treated in accordance with the recommendations of the AAP (2011), EAU (2015) and the Harriet Lane Handbook (20th edition, 2015). The rest of the cases, which did not meet German recommendations concerning the selected substance were neither in accordance with international guidelines.

4.1.2 Changes in International and National Guidelines since the Study Period

In 2018 the 21st edition of the Harriet Lane Handbook was published. In comparison with the 20th edition from 2015, the latest edition narrowed its recommendations down to ceftriaxone for uncomplicated and cefepime for complicated pyelonephritis for 7 days. For cystitis it (21st edition, 2018) suggested cephalexin or cotrimoxazole as oral treatment for 5 days. In contrast to the 20th edition (2015) the latest edition of this handbook did not recommend any intravenous treatment for cystitis [94] (Tab. 3.9). Since the conduction of this study there were no updates of the guidelines from the AAP or the EAU.

Also in 2018 the DGPI published a 7th edition of the DGPI handbook [95]. It showed some differences compared to the 6th edition. Concerning pyelonephritis, the experts now recommended a differentiation between infants aged less than 3 months and older children. In the 6th edition the cut-off was at an age of 6 months. In the first 3 months of life the 7th edition recommended an aminoglycoside plus ampicillin or ceftazidime plus ampicillin (similar to the 6th edition for infants of an age less than 6 months). For older children it recommended a 3rd

generation cephalosporine alone, amoxicillin plus clavulanic acid, or ampicillin plus an aminoglycoside, respectively (6th edition: only 3rd generation cephalosporin alone). The experts now stressed that oral treatment is equally effective as intravenous treatment but suggested (as did the 6th edition) an initial intravenous treatment for all newborns due to higher incidence of sepsis and bacteriuria. For the treatment of cystitis it was new in the 7th edition that the DGPI experts recommended oral fosfomycin (for children older than 12 years) or nitroxoline (for children older than 3 months) as an alternative to the substances already named in the 6th edition (trimethoprim, cotrimoxazole, nitrofurantoin alone, amoxicillin plus clavulanic acid, or an oral cephalosporine) (Tab. 3.9). Furthermore, it was clearly recommended to avoid reserve antibiotics such as ciprofloxacin or a 3rd generation cephalosporine for the treatment of an uncomplicated cystitis. There were no differences concerning the duration of therapy [96]. In conclusion, a reasonable target for future studies on antibiotic therapy of UTI would be the consequent establishment of oral therapy. Substances should be chosen according to the 7th edition of the DGPI handbook. Reserve antibiotics, however, should be restricted.

4.1.3 Antibiotic Stewardship in Pediatric Urinary Tract Infection

There are only few studies on antibiotic stewardship for UTI in children. Furthermore, it was observed that the existing studies on pediatric UTI were not consistent with respect to inclusion criteria or end points. Guidance on conducting trials on pediatric UTI will thus be necessary [97].

There are some studies which focused on oral *versus* intravenous antibiotic treatment of acute pyelonephritis (in two studies fever was an obligate inclusion criteria [98] [99], in one study diagnosis related on urinalysis and urine culture [100]). They measured the effect of the treatment by using scintigraphy to asses renal scarring after UTI, which can be discovered as a result of UTI in some children [101]. All studies showed that the amount of renal scarring did not differ significantly in children who received oral treatment exclusively compared to children who received oral antibiotics after initial intravenous treatment [98] [99] [100], suggesting that oral treatment can be established initially without worries of worse outcome. In the present study, only 3 cases were treated with oral antibiotics exclusively, 28 cases received an exclusive intravenous therapy, and 6 cases were treated both intravenously and orally. However, with a median of 6 months the children of this study were younger than the children in the cited studies which might explain the higher rate of intravenous treatment.

Harriet Lane (2015)	***Cystitis*** *oral:* *cotrimoxazole or cefixime (7-14 d)* *intravenous:* *cefotaxime alone, ceftriaxone alone, or ampicillin plus gentamicin (7-14 d)*	***Uncomplicated Pyelonephritis*** *ceftriaxone alone or ampicillin plus gentamicin (7-14 d)*	***Complicated Pyelonephritis*** *piperacillin plus tazobactam or cefepime alone (7-14 d)*
Harriet Lane (2018)	***Cystitis*** *oral:* *cotrimoxazole or cephalexin (7 d)*	***Uncomplicated Pyelonephritis*** *ceftriaxone (7 d)*	***Complicated Pyelonephritis*** *cefepime*
AAP (2015)	***Oral*** *Cephalosporine alone, ampicillin plus clavulanic acid, or cotrimoxazole alone*		***Intravenous*** *Ceftriaxone alone, cefotaxime alone, ceftazidime alone, piperacillin, alone or aminoglycosides.*
EAU (2011)	*Ampicillin plus aminoglycoside, or 3rd generation cephalosporine*		
DGPI (2013)	***Cystitis*** *Trimethoprim alone or amoxicillin plus clavulanic acid or 2nd or 3rd generation cephalosporin alone*	***Patient age < 6 months*** *ampicillin plus aminoglycoside or ceftazidime plus ampicillin*	***Patient age > 6 months*** *3rd generation cephalosporin*
DGPI (2018)	***Cystitis*** *trimethoprim alone* *cotrimoxazole* *amoxicillin plus clavulanic acid* *oral cephalosporin* *fosfomycin* *nitroxiline*	***Patient age < 3 months*** *ampicillin plus aminoglycoside or ceftazidime plus ampicillin*	***Patient age > 3 months*** *3rd generation cephalosporin or amoxicillin plus clavulanic acid or ampicillin plus aminoglycoside*

Table 4.1: International Guideline Recommendations for Urinary Tract Infection

Compared to the German Guidelines from the DGPI Handbook

There was only one study found which conducted a pre- and post-intervention investigation on antibiotic stewardship for UTI. After the intervention (education on guidelines and local resistance patterns) the rate of empirical treatment in accordance with the guideline increased from 44.8% to 83.0% [102]. This study was published in 2015 and conducted with adult patients. However, the results indicate that UTI might be a reasonable target disease for ABS, especially because it was the most frequent indication for antibiotic therapy in gp in this study.

4.2 Antibiotic Treatment of Community Acquired Pneumonia

4.2.1 International Guidelines during Study Period

In 2011 the Pediatric Infectious Disease Society (PIDS) and the Infectious Disease Society of America (IDSA) published a guideline on the management of CAP [103]. Concerning anti-infective treatment, the guideline stated that not every child with CAP needs to be treated with antibiotics due to high probability of viral pathogens. In cases where antibiotic treatment was indicated amoxicillin or ampicillin were recommended for initial therapy.

The 20th edition of the Harriet Lane Handbook (2015) recommended ampicillin for 10 days for children at the age of less than 5 years. The option of adding azithromycin was mentioned, but it was stressed that atypical pathogens causing CAP were not likely in that age group. For children at the age of more than 5 years ampicillin plus azithromycin for 7 – 10 days was recommended. As alternative the Harriet Lane handbook (2015) recommended ceftriaxone plus azithromycin in both cases [92].

Nelson's Pediatric Antimicrobial Therapy published in 2016 by the AAP also recommended initial ampicillin, or ceftriaxone in regions with high resistance rates against penicillins. Moreover, it suggested to consider the addition of azithromycin for school-aged children and to switch the route of administration from intravenous to oral when clinical improvement had occurred (fever decrease, no oxygen needed). Concerning the dose of ampicillin, higher concentrations were recommended by theses authors (200 mg/kg/day) [104].

The following differences were striking between American and German recommendations: Concerning substances, the American recommendations did not list cefuroxime which was suggested in the DGPI handbook for patients aged between 3 weeks and 3 months. Instead, they name ceftriaxone as alternative to

ampicillin, whereas the DGPI listed cefotaxime as alternative to ampicillin. Furthermore, for the treatment of atypical pathogens American guidelines specifically recommend azithromycin, whereas German recommendations remain vague by not suggesting a distinct macrolide.
In this present study the cases which met German guidelines recommendations were also in accordance with international guidelines (6 cases with initial treatment with ampicillin, 1 case of a 5-year-old with initial treatment of ampicillin plus clarithromycin), even though American guidelines preferred azithromycin. However, the substances used in the 15 cases which were not in accordance with the DGPI Handbook, do neither meet the above listed American guidelines.

4.2.2 Changes in International and National Guidelines since the Study Period

In the latest edition (21st edition, 2018) the Harriet Lane handbook abandoned the classification of age groups younger and older than 5 years. Instead, it provided recommendations for neonatal pneumonia (ampicillin plus gentamicin for CAP most likely caused by *E. coli, GBS,* or *Listeria monocytogenes*; erythromycin or azithromycin for CAP most likely caused by *Chlamydia trachomatis*) and for pneumonia in children older than 3 months. For the latter ampicillin was recommended as inpatient treatment for 10 days with the suggestion to add azithromycin if atypical pathogens were likely which is most often the case in children older than 5 years. As an alternative ceftriaxone plus azithromycin was suggested [94].
In the latest edition of the DGPI handbook (7th edition, 2018) [95] the recommendations within the chapters about antibiotic treatment of CAP differed [105]. Before listing the recommended substances, the 7th edition of the DGPI handbook dedicated some sentences to the indication of antibiotic therapy in general. It clearly stated that not every CAP needed to be treated antibiotically. If bronchial obstruction was the leading symptom it stated that CAP was most likely due to a viral infection and therefore no antibiotic therapy was needed. If the clinical presentation suggested a bacterial infection, an antibiotic could be added to the therapy, but should be stopped at any time if suspicion of bacterial involvement was dropped. It was notable that the emphasis was placed on a strict indication for any antibiotic therapy for CAP.
The recommendation for newborns with CAP was ampicillin plus an aminoglycoside in the 7th edition of the DGPI handbook, as it was in the 6th edition. In contrast, single amoxicillin or ampicillin was recommended regardless of age in the 7th edition. Only patients with penicillin allergy were recommended to be treated with a cephalosporin. In suspicion of atypical pathogens or severe CAP without

improvement a macrolide was allowed to be added for children under 9 years of age, and doxycycline for children over 9 years of age (7th edition, 2018). Concerning the route of administration, it was stated that initial therapy could be given orally, and an initial intravenous therapy should be switched to oral antibiotics after 2-3 days. In conclusion, the changes in comparison to the 6th edition were the age-independent recommendations, doxycycline for children over 9 years of age in case of atypical pathogens, and the emphasis on restricted use of antibiotics. These recommendations correspond to the latest AWMF guidelines on CAP which was published in 2017 [74].

Given the fact that a lot of different substances were used in the study cases, even though international and national guidelines clearly recommended the use of ampicillin, the standardization of antibiotic therapy of CAP with ampicillin should definitely be a target of future ABS activities, and educational interventions should raise awareness about the available guidelines.

4.2.3 Antibiotic Stewardship in Pediatric Community-acquired Pneumonia

There were several studies investigating the impact of ABS on the treatment of CAP, most of them from the USA. Especially after the release of the IDSA guideline different approaches were established to analyze its effect on antibiotics used for the treatment of CAP. Neuman and colleagues investigated the management of CAP prior to the guideline in children presenting with CAP in the emergency department. Amoxicillin and ampicillin were used in only 21% of children, whereas macrolides were the most often applied antibiotics followed by cephalosporins [106]. In 2014 Ross and colleagues observed a significant increase in ampicillin and amoxicillin prescription and a decrease in macrolide prescription in 43 children's hospitals in the USA, which was both attributable to the guideline publication. Nevertheless, the use of ampicillin and amoxicillin was still only 43% 1.5 years after the implementation of the guideline [107]. Similar observations were made in the UK by comparing data prior and after the publication of a guideline in 2002 [108]. Obviously, the publication of guidelines raises awareness about the suggested empirical treatment of CAP. However, the absolute numbers of ampicillin usage after guideline publication were not convincing. Apparently, the accordance to the guidelines can be increased more effectively by implementing its recommendations through ABS which was recognized by Williams and colleagues in 2015 [109]. They discovered that accordance with the guideline was higher in institutions with ABS programs. Furthermore, Ambroggio and colleagues were able to increase the amount of appropriate antibiotics from 30% to

90% by implementing the PIDS guideline through measures as educational seminars, an index card and the installation of a hyperlink to the guideline in their computer system [110]. There are several other studies showing that use of ampicillin and amoxicillin for children with CAP can be increased by ABS [111] [112] [113].
In this study the initial antibiotic was ampicillin in only 6 of 22 cases (27.3%) and antibiotics were given only orally in 6 cases (27.3%). These results are similar to the pre-intervention data of Ambroggio and colleagues [110] and the data prior to the guideline implementation of Neuman and colleagues [106] indicating that also in this setting the treatment of CAP is a worthwhile aim for an ABS program. The AWMF guideline published in 2017 [74] can be used to create appropriate ABS interventions for antibiotic use in the treatment of CAP.

4.3 Antibiotic Treatment of Newborn Infection – Accordance with International Guideline

4.3.1 International Guidelines During Study Period

In 2012 the AAP published a guideline about the “Management of Neonates with Suspected or Proven Early-Onset Bacterial Sepsis” [114]. This guideline recommended ampicillin plus an aminoglycoside like gentamicin as initial therapy for newborns with early-onset sepsis. De-escalation or adjustment of therapy was suggested when the causing pathogen was isolated.
The guideline of the National Institute for Health and Clinical Excellence (NICE) in the United Kingdom (UK) from 2014 [115] suggested benzylpenicillin plus gentamicin as treatment for newborns with early-onset sepsis.
The 20th edition of the Harriet Lane handbook (2015) suggested ampicillin plus gentamicin for pneumonia of newborns and ampicillin plus cefotaxime for meningitis. For newborn sepsis which could be considered as the correlate of the German term “newborn infection” the recommended initial antibiotic therapy was ampicillin plus gentamicin or ampicillin plus cefotaxime [92]. These recommendations did not change in the latest 21st edition [94].
Nelson’s pediatric antimicrobial therapy (2016) recommended ampicillin plus gentamicin or ampicillin plus cefotaxime for neonatal sepsis and meningitis as initial therapy in cases with unknown causing pathogen [116].
In conclusion, the American guidelines were consistent concerning the treatment recommendations for newborn early-onset sepsis which was ampicillin plus gentamicin (or cefotaxime). The UK guideline used benzylpenicillin instead of gen-

tamicin. The combinations of ampicillin plus cefotaxime or ampicillin plus an aminoglycoside was also recommended in the German guidelines. The only difference in the German guideline was the use of tobramycin instead of gentamicin regarding the combination of ampicillin plus an aminoglycoside.
In this study 12 cases of early-onset newborn infection were initially treated with ampicillin plus cefotaxime and therefore were in accordance with the Harriet Lane handbook and Nelson's Pediatric Antimicrobial Therapy. In 1 case the initial therapy was ampicillin plus cefotaxime plus tobramycin. This triple combination was neither mentioned in the American nor in the UK guideline. In contrast, the combination of ampicillin plus gentamicin, which was recommended by the American guidelines, was not established in any of the study cases. The cases of late-onset newborn infection of this study were not attributable to the international guidelines for early-onset sepsis.

4.3.2 Changes in International and National Guidelines Since Study Period

In the 7th edition of the DGPI handbook (2018) the treatment recommendations differed for newborns of the age of 1 – 3 days (early-onset) and newborns older than 3 days (late-onset). For early-onset newborn infection the recommendation was ampicillin (or piperacillin) plus an aminoglycoside and for late-onset it was ampicillin plus cefotaxime (plus an aminoglycoside) [117]. The recommendations were not completely new compared to the 6th edition. However, there were two separate recommendations for early-onset and late-onset newborn infections in the 7th edition. Instead the 6th edition recommended a range of different initial therapies. Recommendations concerning start of therapy and duration of therapy did not show any difference between the 6th and the 7th edition. The German AWMF guideline published in 2018 stated that it was not possible to give one specific and universally valid recommendation for newborn infection due to numerous aspects relevant to the choice of the initial therapy. However, they named the combination of penicillin G or ampicillin plus an aminoglycoside as often used initial therapy for early-onset newborn infection [118].
The recommendations of the Harriet Lane handbook did not change from the 20th to the latest 21st edition of 2018.
In summary, it can be stated that the latest German treatment recommendations of early-onset newborn infections focused on the combination of ampicillin plus an aminoglycoside. As this study took place prior to the publication of the AWMF guideline and of the 7th edition of the DGPI handbook, no case showed any initial therapy with ampicillin plus an aminoglycoside. The change to ampicillin plus

gentamicin as initial therapy for newborn infection should thus be enforced by ABS interventions.

4.3.3 Antibiotic Stewardship in Neonatology

Infections in the neonatal period are common diseases and are correlated with high mortality and morbidity, up to 11% are fatal [119]. Most common pathogens causing infections in neonates are *GBS* and *E. coli.* The rate of early-onset newborn infections caused by *GBS* has already declined due to antibiotic prophylaxis for pregnant women with *GBS* positive swab. However, this prophylaxis and the use of 3rd generation cephalosporins might increase resistances in *E. coli.* That is why cephalosporins should only be used in suspicion of meningitis [119] and why ABS should be established to reduce extensive use of antibiotics in neonatology. Most ABS studies were conducted in neonatal intensive care units, there are only few for regular neonatal units. In 2015, a point prevalence survey evaluated antibiotic usage in six neonatal units in Australia. Sepsis was the most frequent indication for antibiotic therapy. Most often prescribed antibiotic was penicillin and only few prescriptions were not in accordance with the guideline. Yet, the dose of the administered antibiotic varied widely and guideline accordance was worse for the treatment of late-onset sepsis [120]. Treatment of early-onset sepsis was mostly consistent and in accordance with the guideline, whereas the treatment of late-onset sepsis was performed with different antibiotics.
In 2018 McCarthy and colleagues conducted an ABS study in the neonatal unit in Ireland with pre- and post-intervention analysis. The intervention included educational presentations, analysis of mistakes in the pre-intervention period, re-evaluation of the antibiotic therapy every day in the morning round and prescribing restriction with the effect that initial prescription of antibiotic automatically stopped after 36 hours. Between September 2016 and March 2017 DoT/1000PD were reduced from 572 to 417 (27%). The DoT accounting for prolonged duration of therapy declined from 82 to 7.5 [121], showing that the electronic restriction of prescription of antibiotics can effectively reduce antibiotic usage and could also be used as ABS tool in the setting of this study. Other elements important for ABS in neonatology were analyzed by Cantey and colleagues in 2016. They recommended to use a special antibiogram for pathogens isolated from neonatal patients. Moreover, they stated that empirical therapy should be adjusted to the most common antibiograms in neonatal wards and should be stopped, de-escalated, or changed to specific therapy as soon as possible, since prolonged dura-

tion was one of the major problems in antibiotic therapy for newborns [122]. Furthermore, they recommended to reserve cephalosporins for the treatment of newborns with suspected meningitis.
In this setting of this study, ABS for the neonatal ward should focus on the reduction in the use of cephalosporins, as they represented the most frequently chosen antibiotics for newborn infection. Additionally, treatment for late-onset sepsis should be monitored and hospital-specific recommendations should be established, as the therapy of late-onset sepsis varied widely with regard to the choice of antibiotic substances.

4.4 Perioperative Antibiotic Prophylaxis – International Guidelines and Antibiotic Stewardship Interventions

4.4.1 Overview of International Guidelines for Perioperative Antibiotic Prophylaxis

In 2017 the WHO published “global guidelines for the prevention of surgical site infection” [123], the first comprehensive guideline with general recommendations to reduce SSI. In accordance with the German AWMF guideline [66] it states that the chosen antibiotic should be administered within 2 hours prior to skin incision and that there normally was no reason for prolonged application of PAP. However, for clear recommendations concerning the choice of antibiotic it relegates to guidelines of the particular subdisciplines. The American “clinical practice guideline for antimicrobial prophylaxis in surgery”, published by Bratzler and colleagues in 2013 [124], designates cefazolin as a substance being suitable for most procedures. In this study cefazolin was used exclusively or in combination in 36 of 81 cases (44.4%). The NICE guideline [125] recommends a single shot administration of PAP on the start of anesthesia. According to the Royal College of Physicians of Ireland [126] PAP should be given 60 minutes prior to skin incision in a single dose (for uncomplicated surgery) and for at most 48 hours in open heart surgery. The Scottish guideline “antibiotic prophylaxis in surgery” from the Scottish Intercollegiate Guidelines Network provides an extra chapter concerning PAP for children but refers only to the indication for PAP in different surgical procedures and not to the choice of antibiotics.
In conclusion, the above-mentioned guidelines all provide consistent recommendations concerning the time and the duration of antibiotic administration, but do not suggest distinct antibiotic substances. The guidelines of the different surgical subdisciplines [77-87], however, as well as all cited documents refer to adults and state a lack of evidence for clear recommendations for the pediatric population.

The data of this study show that PAP was given in a single shot prior to surgery in 43 cases (53.1%), in 2 cases (2.5%) it was more than one administration but did not exceed 24 hours and in 5 cases (6.2%) PAP was given longer than 24 hours with clear indication for prolonged therapy. In 31 (38.3%) cases PAP was given longer than 24 hours with no indication for prolonged administration (in 8 of these cases there was not even a documented indication for PAP). In the cases with single shot PAP prior to surgery further investigations concerning the exact interval between administration and skin incision are necessary. Furthermore, due to the lack of guidelines for PAP in pediatric surgery [127], the implementation of hospital-specific guidelines and rules is of special importance.

4.4.2 Antibiotic Stewardship for Perioperative Antibiotic Prophylaxis in Pediatric Surgery

As already pointed out in chapter 4.4.1 there is a lack of evidence-based recommendations for PAP in pediatric surgery. Correctness of PAP, however, is of great importance concerning reduction of SSI in pediatric patients, which was shown by Shah and colleges (USA) [128] as well as Khoshbin and colleges (Canada) [129]. The need for ABS interventions concerning PAP in children was also underlined by the results of a retrospective study conducted in 4 pediatric hospitals in Italy: PAP was only administered appropriately indicated or not indicated in 72.6% of the study cases, respectively. Complete accordance with the guidelines in all components of PAP, including the choice of antibiotic, the route of administration, the timing, and the duration of treatment, however, was observed in only 1.6% [130] and prolonged duration of PAP was identified as major factor in inappropriateness of PAP. In the Munich study presented here, PAP was administered with clear indication in 86.4%, and in only 55.6% PAP was in accordance with the guideline concerning both indication and duration. Therefore, also in the setting of this study prolonged duration of PAP seems to be a critical factor with regard to guideline-adherence.

Implementing guidelines in surgical disciplines, according to published reports, faces difficulties due to sociocultural factors amongst surgeons, including fear of postoperative infection and being responsible for consequences, lack of confidence in existing guidelines, and low priority of PAP in the operating room [131]. Despite this, there are pre- and post-intervention studies conducted in pediatric surgery which show significant improvement of PAP [132] [133]. An Italian study from 2017 observed an increase of procedures with appropriate indication of PAP from 82.0 to 86.6%. Their ABS interventions consisted of local guidelines, feedback in pre-intervention data, and structured education concerning the rationale

and operational aspects of PAP, involving surgeons, anesthesiologists, and nurses [132]. A Canadian study [133] established PAP as a mandatory point on the team-time-out checklist which is completed by the operating team prior to each surgery. Furthermore, they implemented an alert in their database system, which appeared whenever a doctor intended to prescribe antibiotics in cases with no indication for PAP. In addition, they also developed local guidelines and distributed them to the personnel in the operating room. By these interventions they achieved an improvement with regard to the appropriateness of PAP from 81.0 to 94.0%. Remarkably, pre-intervention data of both studies were similar to the percentage of appropriateness of PAP in this Munich study (86.4%).

Crucial factors for successful implementation of local guidelines in surgery, according to published data, are enough time for the intervention, educational feedback on the pre-intervention data, as well as cooperation with anesthesiologists and overall presence of the guidelines. It seems to be essential to involve different tools in an ABS intervention as observed by a university hospital in Latvia investigating the effect of a hospital-specific guideline on PAP in the context of appendectomy of children. Even though the guideline was developed in cooperation with the surgeons and was introduced during a period of 2 months, it had only few effects [134], suggesting that more ABS intervention tools would have been necessary.

All in all, ABS interventions in pediatric surgery should include detailed and clear guidelines, which need to be introduced for a long enough period of time. Furthermore, they should be implemented using different methods involving the anesthesia team and other staff working in the operating room. Junior doctors should be supported by their seniors and instructed to follow the guidelines.

4.4.3 Perioperative Antibiotic Prophylaxis in Adult Medicine

In adult medicine there is a lot more data available about PAP. Similar to this study several studies investigated appropriateness of PAP retrospectively by checking medical records. In 2005 Bratzler and colleagues conducted a big retrospective cohort study about PAP in adult surgery. In total, they checked 34,133 cases from 2,965 hospitals in the U.S.A. Mean age of the patient was 73.3 years and PAP was appropriate with regard to indication, timing, and duration in 92.6%, 55.7%, and 40.7%, respectively. Only 0.7% of all cases did not receive PAP [135]. A study from Greece observed 898 patients undergoing general surgery procedures of which 97.5% received PAP. It was appropriate concerning indication, timing, and duration in 70%, 100%, and 36.3%, respectively [136]. In 2014 a Ma-

laysian study observed appropriateness of PAP concerning right choice of antibiotic substances, timing, and duration in 78.2%, 75.9%, and 77%, respectively. However, their reference guideline was the Malaysian one, which listed a third generation cephalosporin as first choice for PAP [137]. In fact, performance of PAP is worse in developing countries which is underlined by a study from Palestine, showing appropriateness of PAP in only 2.0% relating to the American guidelines [138]. A retrospective data analysis done in Qatar reviewed 101 cases. They only included surgical procedures which had clear instructions for PAP. Compliance with these instructions was observed in only 46.5% [139].

There is obviously great variation in appropriate use of PAP depending on the country. Taking the study from Bratzler and colleagues [135] the rate of correct indication of PAP was higher than in this Munich study (86.4%). However, the data from adult medicine also show that there is lack of guideline appropriateness concerning special factors of PAP such as timing and duration of PAP. Additionally, the rate of procedures in which PAP is performed is very high (99.3% in the study of Bratzler and colleagues). In the setting of this Munich study further investigations involving all surgical procedures instead of only those with PAP would be important to investigate whether PAP is applied more restrictively in children. Furthermore, more precise investigation concerning the timing of PAP would be interesting and education with regard to proper documentation of the timing of PAP seems reasonable.

4.4.4 Antibiotic Stewardship for Perioperative Antibiotic Prophylaxis in Adult Surgery

Just like in pediatric surgery most common ABS studies in adult surgery are pre-*versus* post-intervention investigations. A South African study conducted in 2017 showed an increase in PAP appropriateness from 66.8% to 92.3% and a decrease in the rate of SSI from 19.7% to 1.97% [140]. The study involved 34 hospitals and the main ABS element was audit and feedback by pharmacists. A study from Italy focused on the reduction of cefazolin consumption and cost for PAP [141]. The intervention included the development of hospital-specific guidelines, educational meetings, and the discussion of the pre-intervention data, where PAP was appropriate in only 48.1% (according to the NICE guidelines). In the post-intervention phase usage of cefazoline was reduced by 21.5% being equivalent to a reduction of costs by 22.9%. Interestingly, an American study discovered an increase in appropriateness of PAP only by increasing the awareness of PAP guidelines. Appropriateness of timing and type of antibiotics were raised from 71.0 to 85.0%, and from 52.0 to 75.0%, respectively. However, increasing the

awareness of PAP guidelines had no effects on the duration of PAP [142]. Interestingly, in these studies on adult patients pre-intervention appropriateness of PAP was lower than in the studies conducted in pediatric surgery (chapter 4.4.2). However, the published interventions in most cases were quite effective, even though they often only included few measures [139, 141]. In adult surgery reduction of PAP resulted in lower costs [140] whereas the costs were not focused on in studies in pediatric surgery. Presumed that higher appropriateness of PAP in pediatric surgery would have the same effect, the reduction of costs would be an additional argument for ABS of PAP. In published studies on PAP in pediatric as well as adult surgery it was observed that prolonged duration was a major factor for low guideline accordance in line with the findings of this Munich study.

4.5 Conclusion and Outlook

4.5.1 Antibiotic Stewardship for General Pediatrics and Neonatology

In summary, initial therapy in the study cohort often was not in accordance with the current German guideline, and in some cases not in accordance with any of the international guidelines available during the study period. Moreover, significant variation in the type and dose of antibiotics as well as in the route of administration contributed to non-adherence with the relevant guidelines. The fact that the second most often used antibiotics were 3rd generation cephalosporins very well reflected the great potential for improvement with regard to guideline adherence. Since ABS programs proved very efficient in published studies, it should be established in the setting of this study as well.

However, there are some challenges of ABS programs that need to be considered. First of all, an ABS team has to be selected that creates and implements the interventions. An ABS team, in general, should include an infectious disease specialist as well as a microbiologist and a pharmacist. In the setting of this study it might be reasonable to additionally include a pediatric surgeon and a neonatologist to allow for efficient implementation of the interventions in these specific areas. Moreover, the ABS program needs a specific mandate by the head of the departments, and seniors should support junior doctors in following the ABS interventions. Especially in surgery it has been published that this impacts significantly on the success of ABS programs.

The ABS program should not only consist of clear, hospital-adapted guidelines based on a consensus of the whole team but, moreover, include educational meetings and items like a pocket card with short instructions for antibiotic therapy.

Educational meetings could take place weekly after morning and noon conferences in the surgery and pediatric departments of this hospital, respectively. It seems also promising to integrate ABS into the SAP patient management system to facilitate electronic prescription, treatment monitoring and modification, and link diagnoses with hospital-specific guidelines. Another element for a successful ABS program could be a prospective audit with feedback which means the regular discussion of all antibiotic therapies and adjustments if necessary. Another pediatric Munich ABS team already showed that an ABS program can be very effective in a similar pediatric setting. The ABS interventions of this team included weekly ward rounds with an infectious disease specialist, daily reviews of the charts of children with antibiotic therapy, a consultation service provided by an infectious disease specialist, a pocket card with hospital intern guidelines, and a prior authorization for several antibiotics [58]. This ABS program could be used as a promising blueprint for an effective ABS program in the hospital investigated in this study.

4.5.2 Antibiotic Stewardship for Perioperative Antibiotic Prophylaxis

Concerning pediatric surgery there is a lack of evidence-based guidelines for PAP which leads to inappropriateness of PAP concerning timing, indication and duration. There are guidelines for PAP in adult surgery. However, there is lack of compliance to these guidelines as well. A major result of that is prolonged duration of PAP.

Reasons for low accordance to guidelines are complex and involve psychosocial and sociocultural factory. Furthermore, there seems to be low awareness about the impact of incorrect PAP concerning length of hospital stay, rate of SSI, and readmission rate, respectively [143].

In pediatric surgery as well as in adult surgery the rate of cases where PAP is given without clear documented indication is higher than the rate of cases where PAP is not given even though there was an indication [144]. Therefore, PAP is an important target for ABS and antibiotic use is inappropriately high in this field. There are different pre- and post-intervention studies which support appropriateness of PAP. The interventions involve different measures, but there is no consistent concept to it. Still, there are some factors which should be taken care of in any case: ABS interventions should not only involve surgeons but also anesthesiologists and additional staff in the operating room. Educational interventions are crucial to increase awareness of the importance of PAP. Junior doctors need to be supported by seniors in order to encourage reduced use of PAP.

In this study the major factor for inappropriateness of PAP was prolonged duration of PAP which occurred with no identifiable reason in 26 cases (32.1%). Furthermore, in 13.6% of all cases the procedure was clean which *per se* is no indication for PAP. Therefore, clear instructions and guidelines with regard to the duration of PAP and to clean procedures might be effective tools to address critical points by an ABS program in pediatric surgery. In a second step, guidelines for all clean-contaminated, contaminated and dirty procedures should be developed. Especially for clean-contaminated procedures, in which the use of PAP might not be appropriate, clear hospital-specific instructions are needed. Also, timing of PAP should be a point of further investigation as it is also a crucial factor with regard to SSI [145]. In this study, timing of application of PAP was not evaluated. Additionally, further investigations concerning all surgical procedures, not only those with PAP, would be interesting, as this study is not able to make a statement about guideline accordance of procedures where no PAP was performed.

4.6 Limitations

This study was a single center study. Therefore, the results might differ from those of other institutions, and ABS interventions which are reasonable in this setting might not be applicable to other hospitals. The period of data collection was four months which is a rather short period of time. Results might be influenced by different factors such as seasonal differences in frequency of different diseases. Furthermore, only antibiotic therapy on the wards of interest were analyzed. When patients were transferred to different wards they were not followed anymore. That could lead to an underestimation of antibiotic usage. Furthermore, it was not investigated whether the antibiotic therapy was de-escalated or switched after the transfer of the patient. Moreover, the intensive care and oncology units were not included in the analysis and should thus be part of further investigations.

The chart review was retrospective. Therefore, possible oral information and agreements with regard to antibiotic usage were not available and accordance or reasons for deviation from guidelines might not have been adjudicated appropriately.

The present analysis only checked appropriateness of antibiotic therapy but did not question the diagnosis, which is also part of the management of infectious diseases. The correctness of diagnoses should be part of further investigations.

Only cases with antibiotic therapy were documented. There is no comparison to cases with the same diagnosis which did not receive antibiotic therapy. This comparison would be interesting to be able to make statements about a lack of antibiotic usage in cases with clear indication and on the patients' outcome with and without antibiotic treatment or PAP, respectively. Especially in PAP the evaluation of two groups with and without PAP might have been more informative with regard to the need of antibiotic use. Additionally, the exact time of administration of PAP was not recorded in the study, even though it is essential to establish correct timing of PAP.

Despite these limitations, the present study gives a clear overview about the use of antibiotics in a pediatric setting and presents a valid starting point to develop an efficient ABS program

5 Summary

This present study was conducted to analyze the usage of antibiotics at the Children's Hospital Munich Schwabing which belongs to the Munich Municipal Hospital Group (MMHG) as well as to the Medical Faculty of the Technical University Munich (TUM) from August 1st until November 30th in 2016. 339 patients with systemic antibiotic therapy or perioperative antibiotic prophylaxis (PAP) were included, with 159 patients of general pediatrics (gp), 145 patients of pediatric surgery (ps), and 35 patients of neonatology (neo), respectively. Patients older than 18 years and patients suffering from cystic fibrosis, tuberculosis, or other complex underlying diseases were excluded. Antibiotic usage was measured in days and length of therapy (DoT, LoT) which were set in relation to 1,000 patient-days (PD). The treatment of urinary tract infections (UTI), community-acquired pneumonias (CAP) and newborn infections was analyzed in detail and accuracy of treatment was judged by comparing it to the guidelines of the DGPI (Deutsche Gesellschaft für Pädiatrische Infektiologie). In pediatric surgery, PAP was analyzed with regard to indication, timing, and duration according to the guideline from 2012 provided by the AWMF (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften, e.V.). The study aimed at analyzing the current state of antibiotic usage in order to suggest hospital-specific interventions for an antibiotic stewardship (ABS) program. The data was also compared to the pre-intervention data collected at another university children's hospital, which implemented an ABS program in 2012.

The study population consisted of 56.9% male and 43.1% female patients with a median age of 3 years. During the study period 362.8 DoT/1,000 PD were documented with 408.4 in gp, 408.9 in ps, and 233.0 in neo, respectively. The most frequently used antibiotics were cephalosporins followed by penicillins and macrolides. 41.3% of the administered cephalosporins belonged to the 3rd generation which, due to the risk of inducing resistances, is being abandoned in many of the current guidelines. The most frequent indications for antibiotic therapy were urinary tract infections (UTI), community-acquired pneumonia (CAP), newborn infections, and perioperative prophylaxis (PAP) in gp, neo, and ps, respectively. The type of antibiotic chosen for initial therapy of either UTI or CAP was not uniform, and oral antibiotics were rarely used. For UTI or CAP oral antibiotics were used exclusively in 3/37 (8.1%) and 6/22 (27.3%) cases, respectively. The choice of antibiotics for initial treatment of UTI or CAP was in accordance with the DGPI guideline of 2016 in 20/37 (54.1%) and 7/22 (31.8%) cases, respectively. The initial treatment of newborn infection was more consistent with 21/26 (80.8%) cases treated with ampicillin plus cefotaxime which is recommended by the DGPI

for infections in newborns younger than 5 days (here 12 of the 21 cases). PAP was used for urological procedures, plastic surgery, and open appendectomy in more than 50.0% of the cases (42/81). Its indication was clear in 70/81 (86.4%) cases with regard to contamination class or other distinct conditions. However, duration of PAP was appropriate in 50/81 (61.7%) cases which makes prolonged treatment the major factor contributing to non-accordance with the guideline. Compared with the data of another university children's hospital in this study less penicillins were used (163.2 *versus* 128.2 DoT/1000 PD) and the amount of administered 3rd generation cephalosporins was nearly twice as high (43.9 *versus* 89.9 DoT/1000 PD) in patients from gp and neo.

Any changes of the national or international recommendations in more recent disease-specific guidelines are being discussed and targets as well as challenges of future ABS programs identified. A future ABS program should specifically encourage oral treatment and very restrict indication of 3rd generation cephalosporins to achieve guideline-accordant treatment. The program should include different measures and involve not only doctors but also other hospital personnel such as nurses and personnel in the operating room. It will be essential to establish the ABS program as a routine procedure within the hospital and to consider communication and sociocultural factors between groups subordinated to different authorities.

Taken together, this study indicated a clear need of future ABS interventions and outlines specific strategies for improving future antibiotic treatment of hospitalized neonates, infants, children, and adolescents in Schwabing neonatal, pediatric, or pediatric surgery departments of MMHG and TUM in Munich.

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7 List of Figures

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9 List of Abbreviations

AAP ..... *American Academy of Pediatrics*
ABS ..... *antibiotic stewardship*
ARX ..... *aristaless-related homebox*
ATC ..... *anatomical therapeutic chemical*
AWMF ..... *Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften*
BLI ..... *beta-lactamase inhibitor*
CAP ..... *community acquired pneumonia*
CDC ..... *Centers for Disease Control and Prevention*
CFU ..... *colony forming unit*
CRP ..... *C-reactive protein*
CYP *Cytochrom-P450*
DDD ..... *defined daily dose*
DGHM ..... *German Society for Hygiene and Microbiology*
DGPI ..... *Deutsche Gesellschaft für Pädiatrische Infektiologie*
DoT ..... *days of therapy*
E. coli ..... *Escherichia coli*
EAU ..... *European Association of Urology*
ESIN ..... *elastic stable intramedullary nailing*
EU ..... *European Union*
GBS ..... *group B streptococci*
gp ..... *general pediatrics*
IDSA ..... *Infectious Disease Society of America*
Il-6 ..... *interleukin-6*
IQR ..... *interquartile range*
JAMA ..... *Journal of the American Medical Association*
KRINKO ..... *Kommission für Krankenhaushygiene und Infektionsprävention*
KS ..... *Klinikum Schwabing*
LMU ..... *Ludwig-Maximilians University*
LoT ..... *length of therapy*
max ..... *maximum*
MidP ..... *Medikamente in der Pädiatrie*
min ..... *minimum*
MMHG ..... *Munich Municipal Hospital Group*
MRGN ..... *multi-resistant gram-negative*
MRI ..... *Klinikum rechts der Isar*
MRSA ..... *methicillin-resistant Staphylococcus aureus*
MueK ..... *Muenchen Klinik*
NCHS ..... *National Center for Health Statistics*
neo ..... *neonatology*
NICE ..... *National Institute for Health and Clinical Excellence*
PAP ..... *perioperative antibiotic prophylaxis*
PD ..... *patient-days*
PIDS ..... *Pediatric Infecitous Disease Society*
ps ..... *pediatric surgery*
RKI ..... *Robert-Koch-Institute*
S. pneumoniae ..... *Streptococcus pneumoniae*
SSI ..... *surgical site infection*

StKM ..... *Staedtisches Klinikum München*
TUM ..... *Technische Universitaet Muenchen*
UK ..... *United Kingdom*
USA..... *United States of America*
UTI ..... *urinary tract infection*
VRE..... *vancomycin-resistant enterococci*
VUR ..... *versicoureteral reflux*
WHO ..... *World Health Organization*

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Anhang I

Eidesstattliche Erklärung

Ich erkläre an Eides statt, dass ich die bei der promotionsführenden Einrichtung
Klinik für Kinder- und Jugendmedizin des Klinikums rechts der Isar

der TUM zur Promotionsprüfung vorgelegte Arbeit mit dem Titel:
Analysis of Antibiotic Usage in the Children's Hospital Munich Schwabing: Identifying Interventions for an Optimized Antibiotic Therapy

in München

unter der Anleitung und Betreuung durch: Prof. Dr. med. Uta Behrends ohne sonstige Hilfe erstellt und bei der Abfassung nur die gemäß § 6 Ab. 6 und 7 Satz 2 angebotenen Hilfsmittel benutzt habe.

☒ Ich habe keine Organisation eingeschaltet, die gegen Entgelt Betreuerinnen und Betreuer für die Anfertigung von Dissertationen sucht, oder die mir obliegenden Pflichten hinsichtlich der Prüfungsleistungen für mich ganz oder teilweise erledigt.

☒ Ich habe die Dissertation in dieser oder ähnlicher Form in keinem anderen Prüfungsverfahren als Prüfungsleistung vorgelegt.

☐ Die vollständige Dissertation wurde in _____ veröffentlicht. Die promotionsführende Einrichtung
(große Teile der Arbeit wurden englischsprachig wie ausgewiesen und mit Einverständnis der Einrichtung in internationalen zugänglichen medizinischen Journalen veröffentlicht)

hat der Veröffentlichung zugestimmt.

☒ Ich habe den angestrebten Doktorgrad noch nicht erworben und bin nicht in einem früheren Promotionsverfahren für den angestrebten Doktorgrad endgültig gescheitert.

☐ Ich habe bereits am _____ bei der Fakultät für __der Hochschule _____unter Vorlage einer Dissertation mit dem Thema _____ die Zulassung zur Promotion beantragt mit dem Ergebnis:

Die öffentlich zugängliche Promotionsordnung der TUM ist mir bekannt, insbesondere habe ich die Bedeutung von § 28 (Nichtigkeit der Promotion) und § 29 (Entzug des Doktorgrades) zur Kenntnis genommen. Ich bin mir der Konsequenzen einer falschen Eidesstattlichen Erklärung bewusst.

Mit der Aufnahme meiner personenbezogenen Daten in die Alumni-Datei bei der TUM bin ich

☒ einverstanden, ☐ nicht einverstanden.

München, 24.07.2019 M. Bugger

Ort, Datum, Unterschrift