

Pediatric antibiotic stewardship: successful interventions to reduce broad-spectrum antibiotic use on general pediatric wards

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Abstract

Purpose Antibiotic stewardship programs (ASP) optimize antibiotic usage and combat antibiotic resistance of bacteria. The objective of this study was to assess the impact of specific ASP interventions on antibiotic consumption in general pediatric wards.

Methods We conducted a prospective study to compare a pre-intervention (Sept.–Dec. 2014) and post-intervention (Sept.–Dec. 2015) period. An ASP bundle was established including (1) infectious diseases (ID) ward rounds

(prospective-audit-with-feedback), (2) ID consultation service, (3) internal guidelines on empiric antibiotic therapy. Medical records on four general pediatric wards were reviewed daily to analyze: (1) antibiotic consumption, (2) antibiotic dosage ranges according to local guidelines, and (3) guideline adherence for community-acquired pneumonia (CAP).

Results Antibiotic prescribing for 273 patients (pre-intervention) was compared to 263 patients (post-intervention). Antibiotic prescription rate did not change (30.6 vs. 30.5%). However, overall days-of-therapy and length-of-therapy decreased by 10.5 and 7.7%, respectively. Use of cephalosporins and fluoroquinolones decreased by 35.5 and 59.9%, whereas the use of penicillins increased by 15.0%. An increase in dosage accuracy was noted (78.8 vs. 97.6%) and guideline adherence for CAP improved from 39.5 to 93.5%. Between the two study periods, no adverse effects regarding length of hospital stay and in-hospital mortality were observed.

Conclusions Our data demonstrate that implementation of an ASP was associated with a profound improvement of rational antibiotic use and, therefore, patient safety. Considering the relatively short observation period, the long-term effects of our ASP bundle need to be further investigated.

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Keywords Pediatric antibiotic stewardship · Quality of care, days of therapy (DoT) · Antimicrobial stewardship program (ASP) · Dosing accuracy · Patient safety

Abbreviations

ASP	Antibiotic stewardship program
ATC	Anatomical therapeutic chemical
CAP	Community-acquired pneumonia
CDI	<i>Clostridium difficile</i> -infection
CMI	Case mix index
CPOE	Computerized physician order entry

DDD	Defined daily dose
DGI	German Society of Infectious Diseases
DoT	Days of antibiotic therapy
ESBL	Extended spectrum β -lactamase producing Gram-negative bacteria
FQ	Fluoroquinolone
ID	Infectious diseases
IDSA	Infectious Diseases Society of America
i.v.	Intravenous
LMU	Ludwig-Maximilians-University
LoT	Length of antibiotic therapy
ME	Medication errors
MRGN	Multi-resistant Gram-negative bacteria
MRSA	Methicillin-resistant <i>Staphylococcus aureus</i>
PD	Patient-days
p.o.	Oral
RDD	Recommended daily dose
VRE	Vancomycin-resistant <i>Enterococcus</i>
WHO	World Health Organization

Introduction

The prevalence of drug-resistant pathogens is rising dramatically [1]. Regarding the lack of new antimicrobial drug classes, antibiotic resistance has become a major public health threat. Antibiotics are among the most commonly prescribed drugs in hospitalized children [2]. In pediatric patients, between 3.4 and 35% of antibiotic prescriptions were considered to be inappropriate [3, 4]. In light of a well-documented causal relationship between antibiotic overuse or misuse and emergence of resistant bacteria, action plans endorsed by different organisations like the World Health Organization (WHO), the Infectious Diseases Society of America (IDSA), and the German Society of Infectious Diseases (DGI) emphasize the importance of antibiotic stewardship programs (ASP) for monitoring and promoting the optimization of antimicrobial use to preserve our antibiotic armamentarium [5–7]. In adult patients, several studies have firmly established the positive impact of ASP on antibiotic density, expenditures, antimicrobial resistance, as well as antibiotic-related toxicity and complications such as *Clostridium difficile*-infections (CDI) [8, 9]. The main strategies of ASP include correct selection of the antimicrobial agent, dosing, and adequate lengths of antibiotic therapy. However, studies assessing the effects of ASP efforts in pediatrics are scarce [10–17]. Detailed analysis of antibiotic consumption beyond point prevalence studies from European pediatric hospitals [18, 19] is lacking.

In 2012, we established an ASP pilot program assessing the impact of ASP strategies [20]. This program resulted in estimated cost savings of more than 330,000 € per year

and was still ongoing during the pre-intervention period. The main goal of the present study was to enhance previous achievements (i.e., decreased use of broad-spectrum antibiotics) and to extend the program by defining areas for further improvement. We carefully evaluated the effectiveness of our interventions in improving guideline adherence, antibiotic selection, dosing accuracy, and reduction of overall and specifically targeted antibiotics such as cephalosporins and fluoroquinolones (FQs).

Methods

Setting and study design

The study was conducted at the Dr. von Hauner Children's Hospital, an academic tertiary care center at the Ludwig-Maximilians-University (LMU) Munich, Germany. Four general pediatric wards for all age-groups were included, with a total of 61 beds and approximately 3800 admissions per year. Pediatric surgery patients were not included.

Our goal was to assess the impact of an ASP using two 4-month periods of data collection: Sept 1, 2014–Dec 31, 2014 (pre-intervention period) and Sept 1, 2015–Dec 31, 2015 (post-intervention period). Drugs, including all antibiotics, are dispensed to each ward by the central pharmacy. No computerized physician order entry (CPOE) system, electronic medication record or unit-dose-system was available.

Antibiotic stewardship program (ASP)

As an extension to a previously reported pilot Antibiotic stewardship project [20], a more comprehensive ASP was implemented between January and August 2015. Core members of the ASP team were two pediatric infectious diseases (ID) specialists and two dedicated clinical pharmacists, trained in antibiotic stewardship and ID. The implemented interventions are described in detail below. Several main goals for the planned ASP were identified: (1) increased utilization of penicillins, (2) decreased use of second- and third-generation cephalosporins and FQs, (3) early de-escalation of broad empiric regimens guided by microbiological results, (4) dosing accuracy, (5) empiric antibiotic choice according to local guidelines, and (6) improving patient safety by optimizing antibiotic treatment and avoiding dosing errors.

Interventions

Core ASP strategies included activities earlier described in international and national guidelines: prospective-audit-with-feedback and bed-side academic detailing regarding

every antibiotic regimen during weekly pediatric ID ward rounds by the ASP team. Chart reviews were conducted daily by the clinical pharmacist. In brief, indications and laboratory data were reviewed, and antibiotic choice, dosing, route of administration, additional diagnostic procedures, and length of therapy were discussed. Feedback was provided to the physician staff as well as to the nursing personnel on respective wards. A pre-existing ID consultation service was intensified, now operating on a 24/7 on-call basis with formal (written) ID consults documentation. Recommendations were given during pediatric ID ward rounds and written ID consults were documented in electronic patient charts. In general, there were five types of recommendations: (1) modification of antibiotic treatment, (2) additional diagnostics, (3) dose adjustment, (4) conversion from intravenous (i.v.) to oral (p.o.) formulations and (5) use of topical antiseptics instead of systemic antibiotic treatment. The implementation rate of provided recommendations was evaluated within the following 24 h.

Furthermore, we revised and implemented guidelines for the most frequent pediatric infectious diseases, including detailed recommendations regarding correct choice and precise dosing of antibiotics (see electronic Supplementary material Tables S1, S2). Dosing recommendations were consented by an internal multidisciplinary expert panel in accordance with national and international dosing guidelines. Internal guidelines were consented by all clinical divisions and were made internally available between June and Aug 2015 in written and electronic formats. A pocket-sized index card was given to all prescribers. The list of specific antibiotics requiring prior authorization by a senior ID physician remained unchanged throughout the study period (see electronic Supplementary material Table S3).

Data acquisition

Medical records of all patients were reviewed by a clinical pharmacist on a daily basis. A dataset from all patients receiving antibiotic therapy was established. This dataset included demographic parameters (age, weight, height, sex), antibiotic agent (single dose per administration, number of doses per day, route of administration, duration of antibiotic therapy), indication(s) for antibiotic therapy, laboratory parameters (leukocyte count, C-reactive protein, creatinine, liver function tests), and microbiological results as well as radiographic findings. Included was every antimicrobial substance with either i.v. or p.o. route of administration. Topical drugs, systemic antifungal or antiviral agents were excluded. Antibiotics were classified according to the internationally standardized WHO Anatomical Therapeutic Chemical (ATC) classification system (ATC group J01).

The study was conducted according to the ethical standards at LMU Munich. Formal ethical approval was obtained from the research ethics committee of the LMU Munich (ID 404-14). Data on daily admissions, case mix index (CMI), and in-hospital mortality during the study period were obtained from the hospital administration.

Analysis of antibiotic consumption data

The impact of the ASP on antibiotic consumption was analyzed on antibiotic class and substance level. We assessed the (a) proportion of patients treated with antibiotics at any day during their hospital stay, (b) antibiotic density as days of antibiotic therapy per 1000 patient-days (DoT/1000 PD), (c) length of antibiotic therapy per 1000 patient-days (LoT/1000 PD), and d) doses administered per 1000 PD as described previously [11, 21]. DoT for a patient accounts for all antibiotics that this particular patient receives over a specific time. Thus, in case of prescription of three antibiotics for 4 days, each antibiotic contributes with individual DoT, in this example resulting in a total of 12 DoT. LoT calculates the actual length of the antibiotic treatment period for a patient, irrespective of how many antibiotics were prescribed per day. Thus, for a patient receiving three antibiotics for 4 days, the LoT is 4 [11]. LoT is always less than or equal to DoT. Our ASP did not focus on patients with chronic diseases; therefore, data of specific patient populations (i.e., cystic fibrosis, hematological diseases, pneumocystis prophylaxis, tuberculosis, and sickle cell anemia) were excluded from the study (Fig. 1). The denominator “patient-days” includes all hospital days for all patients admitted during the study period; hospital days of excluded patient groups were subtracted.

Analysis of antibiotic dosing

Prescribed dosages were compared to standard dosing as defined by a multidisciplinary expert panel in our hospital (see electronic Supplementary material Table S2) and categorized arbitrarily as follows: lower (i.e., <70% of standard dosing), higher (i.e., >130% of standard dosing) or within a range of $\pm 30\%$ of the recommended standard dose. Patients with dose adjustments due to special conditions (e.g., renal dysfunction, cystic fibrosis, or prophylactic therapies) were excluded from this analysis (Fig. 1).

Adherence to treatment guidelines for community-acquired pneumonia (CAP)

As a specific clinical question, guideline adherence was evaluated regarding empiric treatment of community-acquired pneumonia (CAP). All patients hospitalized for a suspected diagnosis of pneumonia and older than

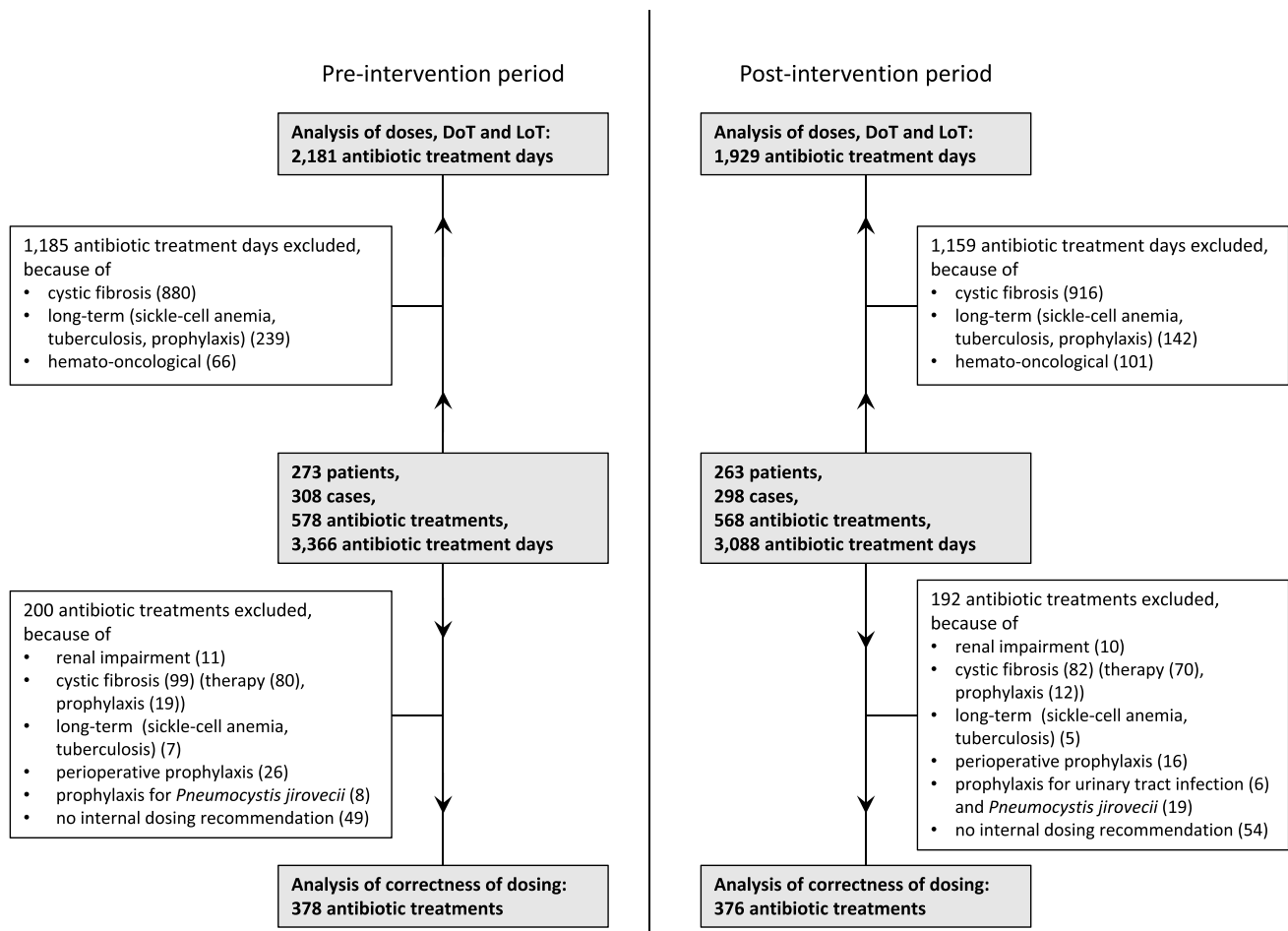


Fig. 1 Patient groups for pre-intervention and post-intervention analysis

six months of age were eligible for this analysis. Exclusion criteria were chronic respiratory disorders (e.g., asthma bronchiale or cystic fibrosis), immunosuppression, severe central nervous system comorbidities with risk of aspiration, respiratory failure requiring intubation, or previous admission to our hospital within the last 4 weeks. Pneumonia was diagnosed by the attending physician based on current guidelines and definitions of CAP [22]. This information was retrieved from medical records.

Statistical methods

For comparison of patient's characteristics during the two study periods, Chi square test was used for categorical variables, Fisher's exact test for in-hospital mortality, and Mann–Whitney *U* test for continuous variables. Antibiotic use density in the two periods was compared assuming Poisson distribution. Analysis and figures were performed using Microsoft Excel® 2010 and IBM SPSS Statistics® 23.

Results

Study population and descriptive data

In the pre-intervention period, a total of 273 patients receiving antibiotic therapy were enrolled. During the post-intervention period, 263 patients received antibiotics during their stay on general pediatric wards. Overall, no statistically significant differences were observed between the two patient populations (Table 1). The 273 and 263 patients resulted in 308 and 298 hospital admissions, respectively, as some patients were admitted more than once during the study period (Fig. 1).

Interventions

The ASP team gave 167 recommendations during regular ID ward rounds during the four-month post-intervention period. Modifications of antibiotic choice (81/167, 48.5%) were the most common interventions, followed by advice of additional diagnostics (49/167, 29.3%), dose adjustment

Table 1 Comparison of patient groups in pre-intervention and post-intervention period

	Patients pre-intervention group <i>n</i> = 273	Patients post-intervention group <i>n</i> = 263	Test for difference (<i>p</i> value [#])
Female /male (%)	130 (47.6)/143 (52.4)	112 (42.7)/151 (57.3)	0.242
Length of stay in days, median (range)	7.0 (1–93)	6.0 (2–123)	0.864
Body weight in kg, median (range)	15.0 (2.1–84.7)	15.5 (2.7–120)	0.637
Body height in cm, median (range)	101.0 (41–190) [§]	100.0 (36.5–193) [‡]	0.175
Age in years, median (range)	3.7 (1 day–29.7)	3.6 (1 day–30.5)	0.963
In-hospital deaths (%)	1 (0.37)	1 (0.38)	1000

Data missing for [§]14 and [‡]27 patients, respectively

Chi square, Fisher's exact test or Mann–Whitney *U* test

(20/167, 12.0%), use of topical antiseptics instead of systemic antibiotic treatment (10/167, 6.0%) and i.v.-to-p.o.-conversion (7/167, 4.2%). Among the modifications of antibiotic treatment, discontinuation represented the majority of recommendations (37/81, 45.7%), followed by de-escalation (12/81, 14.8%) and recommendations of alternative antibiotic therapy (12/81, 14.8%). The remaining modifications were: Escalation, prolongation and starting of antibiotic therapy (in total 20/81, 24.7%). Overall, compliance with recommendations was 95.8%.

Antibiotic usage, days of therapy (DoT), length of therapy (LoT)

During the pre-intervention period, 30.6% (308 of 1007) of hospitalized children received at least one antibiotic. After implementation of our ASP bundle approach, this percentage did not change significantly (298 of 976, 30.5%, $p = 1$).

However, overall antibiotic doses administered per 1000 PD decreased by 4.9% from 1233 to 1172 (see electronic Supplementary material Table S4). Antibiotic treatment days decreased by 10.5% ($p < 0.001$) from 483.6 (pre-intervention) to 432.9 (post-intervention) days of therapy per 1000 patient-days (DoT/1000 PD) with a significant effect regarding cephalosporin consumption (−35.5%, $p < 0.001$) (Table 2). The use of second-generation cephalosporins decreased by 36.3% ($p < 0.001$), while the use of third-generation cephalosporins decreased by 22.3% ($p < 0.05$). Use of FQ was reduced from 32 to 13 DoT/1000 PD (−59.9%, $p < 0.001$) and metronidazole use showed a similar result, declining from 27 to 13 DoT/1000 PD (−51.1%, $p < 0.001$). As intended, narrow-spectrum penicillins (phenoxymethylpenicillin and benzylpenicillin) and aminopenicillins (ampicillin and amoxicillin) were

more frequently prescribed during the post-intervention period [+22.5% ($p = 0.54$) and +20.8% ($p = 0.08$), respectively]. However, this effect needs to be classified as a “trend” as it did not reach statistical significance. The use of aminopenicillins with beta-lactamase inhibitors (ampicillin/sulbactam and amoxicillin/clavulanic acid) increased by 78.8% ($p < 0.001$). There was no impact on broad-spectrum antibiotic piperacillin/tazobactam use (−0.5%, $p = 0.95$). The overall consumption of carbapenems was low. However, there was an increase during the post-intervention period (16.6 to 30.1 DoT/1000 PD, +80.8%, $p < 0.001$). Specific substances for treatment of infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA) (i.e., vancomycin, teicoplanin, and linezolid) increased by 12% from 23.5 to 26.7 DoT/1000 PD. Prescriptions of antibiotics with activity against *Pseudomonas aeruginosa* (piperacillin/tazobactam, carbapenems, aminoglycosides, ceftazidime, and FQ) decreased by 8.8% from 164.5 to 151.3 DoT/1000 PD. On a substance level, the consumption data indicate that cefuroxime, piperacillin/tazobactam, and metronidazole were among the most commonly used antibiotics in the pre-intervention period. The ASP interventions in particular reduced cefuroxime (108 to 68 DoT/1000 PD, −37.0%), cefotaxime (24 to 19 DoT/1000 PD, −20.8%) and ciprofloxacin (20 to 10 DoT/1000 PD, −50.0%). In contrast, ampicillin (25 to 35 DoT/1000 PD, +36.7%), amoxicillin/clavulanic acid (10 to 18 DoT/1000 PD, +72.3%), and ampicillin/sulbactam (7 to 13 DoT/1000 PD, +88.9%) were more frequently prescribed in post-intervention period (Table 2; Fig. 2).

Assessing LoT instead of DoT, similar results were observed: Overall LoT decreased significantly by 7.7% (377.4 to 348.3 LoT/1000 PD, 95% CI 1.1–13.9%, $p = 0.02$).

Table 2 Comparison of average antibiotic use density expressed as days of therapy (DoT) per 1000 patient-days (PD) during pre-intervention and post-intervention period

Substance	Pre-intervention period			Post-intervention period			Difference		
	PD	4510	%	PD	4456	%	<i>p</i> value	DoT/1000 PD	%
	DoT total	DoT/1000 PD		DoT total	DoT/1000 PD				
J01C penicillins	736	163.2	33.7	836	187.6	43.3	<0.01	24.4	15.0
J01CR05 piperacillin + BLI	476	105.5	21.8	468	105.0	24.3	0.95	-0.5	-0.5
J01CR01-2 other penicillins + BLI	77	17.1	3.5	136	30.5	7.1	<0.001	13.4	78.8
J01CF beta-lactamase resistant penicillins	4	0.9	0.2	18	4.0	0.9	<0.01	3.2	355.5
J01CA penicillins with extended spectrum	160	35.5	7.3	191	42.9	9.9	0.08	7.4	20.8
J01CE beta-lactamase sensitive penicillins	19	4.2	0.9	23	5.2	1.2	0.54	0.9	22.5
J01D cephalosporins	726	161.0	33.3	463	103.9	24.0	<0.001	-57.1	-35.5
J01DB 1st-generation cephalosporins	37	8.2	1.7	2	0.4	0.1	<0.001	-7.8	-94.5
J01DC 2nd-generation cephalosporins	491	108.9	22.5	309	69.3	16.0	<0.001	-39.5	-36.3
J01DD 3rd-generation cephalosporins	198	43.9	9.1	152	34.1	7.9	<0.05	-9.8	-22.3
J01M fluoroquinolones	144	31.9	6.6	57	12.8	3.0	<0.001	-19.1	-59.9
Ciprofloxacin	90	20.0	4.1	44	9.9	2.3	<0.001	-10.1	-50.5
Levofloxacin	0	0	0	6	1.3	0.3	<0.05	-	-
Moxifloxacin	54	12.0	2.5	7	1.6	0.4	<0.001	-10.4	-86.9
J01XB nitroimidazoles (metronidazol)	122	27.1	5.6	59	13.2	3.1	<0.001	-13.8	-51.1
J01FA macrolides	112	24.8	5.1	133	29.8	6.9	0.16	5.0	20.2
J01XA glycopeptides	106	23.5	4.9	117	26.3	6.1	0.42	2.8	1.2
Vancomycin	92	20.4	4.2	117	26.3	6.1	0.07	5.9	28.7
Teicoplanin	14	3.1	0.6	0	0	0	<0.001	-	-
J01DH carbapenems	75	16.6	3.4	134	30.1	6.9	<0.001	13.4	80.8
J01FF lincosamides (clindamycin)	73	16.2	3.3	77	17.3	4.0	0.74	1.1	6.8
Others	55	12.2	2.5	48	10.8	2.5	0.56	-1.4	-11.7
J01G aminoglycosides	21	4.7	1.0	5	1.1	0.3	<0.01	-3.5	-75.9
J01XB polymyxine (colistin)	11	2.4	0.5	0	0	0	<0.001	-	-
Total	2181	483.6	100.0	1929	432.9	100.0	<0.001	-50.7	-10.5

Dosing accuracy

In the pre-intervention period, out of 378 antibiotic treatment courses, only 78.8% were within $\pm 30\%$ of our pre-defined target dosage, while 97.6% out of 376 antibiotic treatment courses were in this range during the post-intervention period ($p < 0.0001$) (Fig. 3). Regarding all published dosage ranges, in the pre-intervention period, 14 courses (3.7%) were not justified by any recommendation in the literature. 13 courses were below all available dose recommendations: Cefuroxime (6), ceftazidime (3), cefpodoxime (1), meropenem (1), clarithromycin (1), and ampicillin/sulbactam (1). In one case of metronidazole use, the dose was above all available recommended dose ranges. In the post-intervention period, only one therapy of metronidazole was below all available dose recommendations.

Adherence to treatment guidelines for community acquired pneumonia (CAP)

During the pre-intervention period, 38 patients were hospitalized for uncomplicated CAP. Nineteen (50.0%) of these patients were empirically treated with cephalosporins [second-generation cephalosporins (16), third-generation cephalosporins (3)] and 4 patients (10.5%) were treated with piperacillin/tazobactam. Aminopenicillins were prescribed for 15 (39.5%) patients: Ampicillin (14), amoxicillin (1). In total, six patients (15.8%) received an antibiotic combination therapy with additional macrolides. In the post-intervention period, out of 32 patients with CAP, 30 (93.8%) were treated with aminopenicillins (23 ampicillin, 7 amoxicillin) and two patients (6.2%) received second-generation cephalosporins. A combination with macrolides was prescribed for one patient (Fig. 4). During the pre-intervention

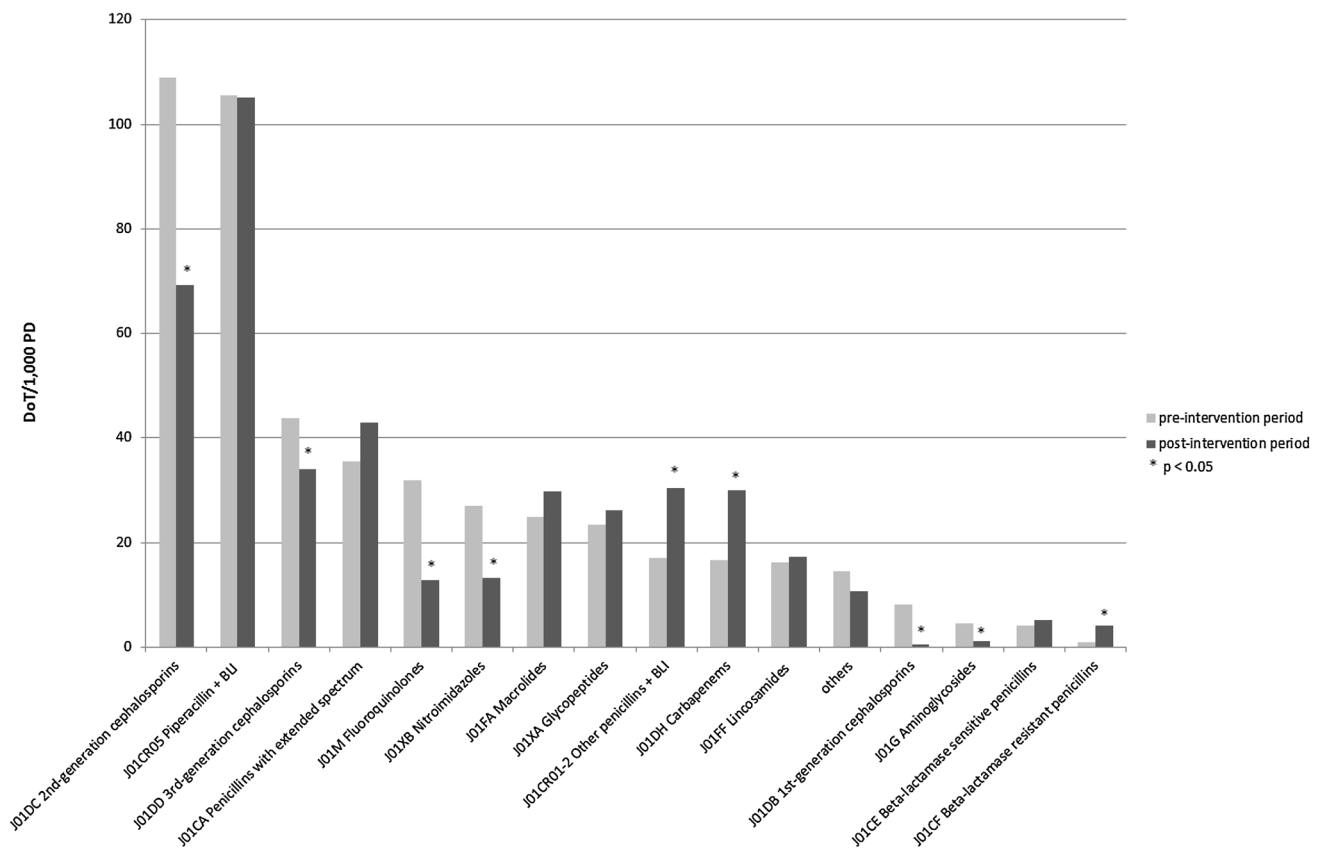


Fig. 2 Comparison of average antibiotic use density expressed as DoT per 1000 PD during pre-intervention and post-intervention period

period, 23/38 (60.5%) patients were treated with a maximum of 7 days, while in the post-intervention period, 30/32 (93.8%) received antibiotics for 7 days or less.

Length of stay, in-hospital mortality and case mix index (CMI)

The average length of stay remained stable: median 7.0 days in the pre-intervention period (range 1–93 days), and media 6.0 days in the post-intervention period (range 2–123 days), (Table 1). There was no significant difference with regard to in-hospital mortality during pre- and post-intervention period (1 death out of 273 patients and 1 death out of 263 patients, respectively (0.37% vs. 0.38%, $p = 1$)). The CMI increased slightly during the post-intervention period, but the difference was not statistically significant (data not shown).

Discussion

Despite global efforts to reduce antimicrobial prescribing, antibiotic consumption continues to increase in pediatric

and adult hospitals [23]. ASPs offer evidence-based tools to control antibiotic prescribing in different hospital settings. However, only few studies have carefully analyzed antibiotic use in pediatric hospitals [10–19, 24].

We performed a thorough analysis of all systemic antibiotics used in general pediatric wards of a large university children's hospital before and after the implementation of an ASP bundle. Our ASP interventions included different core ASP strategies described earlier [6, 25, 26] all of these being exceptionally well accepted with a compliance rate of more than 95%. To be able to compare our results with other studies, we assessed and calculated all process measures (compliance rates with ASP recommendations, antibiotic use, DoT/1000 PD, LoT/1000 PD, Doses/1000 PD, and antimicrobial appropriateness, i.e., guideline adherence), as well as outcome measures (length of stay and in-hospital mortality) as reported previously [27].

To better account for real antibiotic consumption in pediatrics, the antibiotic density is calculated as days of antibiotic therapy per 1000 patient-days (DoT/1000 PD). This parameter corresponds to the defined daily dose (DDD) or recommended daily dose (RDD) per 1000 PD used in adults ASP programs. Total antibiotic density was

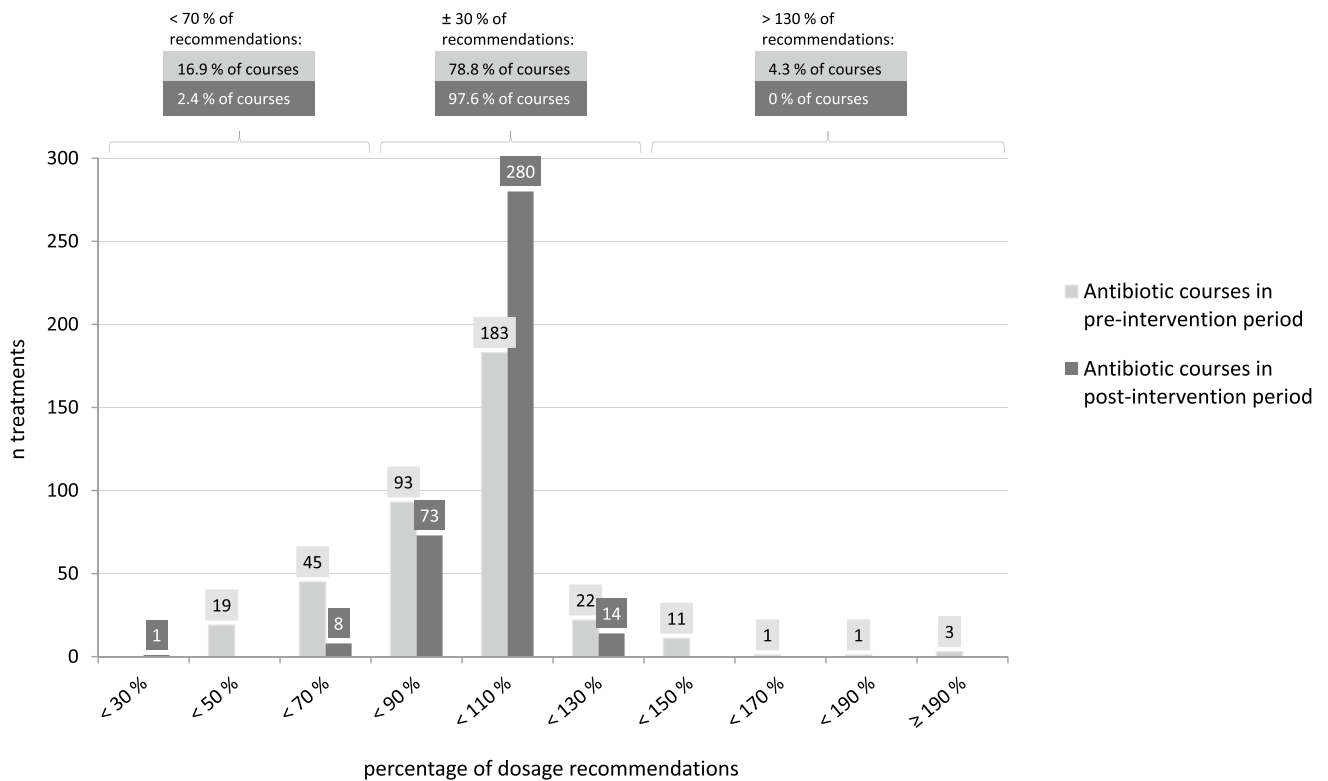


Fig. 3 Accuracy of antibiotic dosing, comparing pre-intervention and post-intervention data

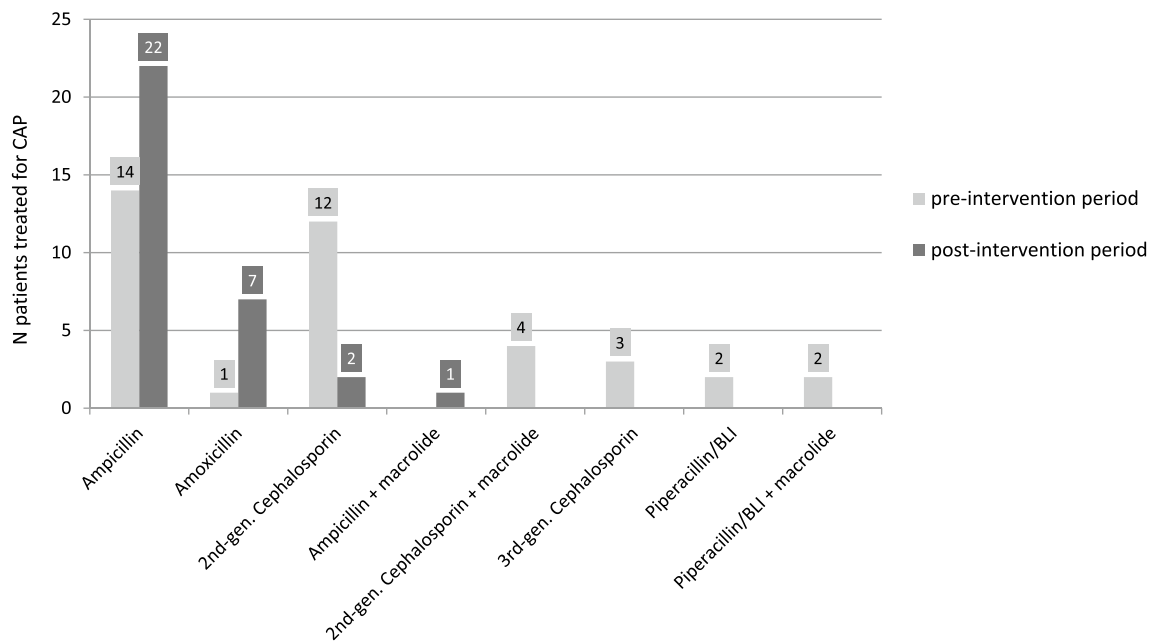


Fig. 4 Empiric antibiotic choice for community-acquired pneumonia, comparing pre-intervention and post-intervention data

low, 483.6 (pre-intervention) and 432.9 DoT/1000 PD (post-intervention), compared to Newland et al. (883 and 787 DoT/1000 PD) [11]. The difference in baseline antibiotic density is probably partly explained by the fact that Newland et al. assessed an entire tertiary care children's hospital, including hemato-oncological as well as neonatal and pediatric intensive care units, while we focused on general pediatric wards. We also previously established an antibiotic stewardship pilot program picking the "low-hanging fruits" [28] and reduced the overall antibiotic costs by about 50% [20].

Recently, a large point prevalence study showed that 39.5% of all children in one German Children's Hospital received antibiotics on a given day [19]. In our setting, the percentage of hospitalized children receiving at least one antibiotic was slightly lower and remained stable during the study periods (30.6 and 30.5%, respectively). These findings are in concordance with previously published data, where rates of patients treated with antibiotics remained unchanged with/without ASP strategies [15]. In this particular study, rates were higher (44 and 43%, respectively), probably because patients from intensive care units were included.

The proportion of children receiving at least one antibiotic remained stable in our study, while the overall antibiotic DoT/1000 PD decreased by 10.5% after introduction of the ASP. These results are in line with Newland et al. who analyzed the effect of prospective-audit-with-feedback using time series analysis. There was a decline in overall antibiotic DoT/1000 PD by 10.9% reported [11]. Comparable effects were shown by Agwu et al. (−14% DoT/1000 PD) after the implementation of an internet-based ASP in a pediatric tertiary care center [24]. Di Pentima et al. demonstrated that prospective-audit-with-feedback and reinforcement of prior authorization led to a decrease of targeted antibiotic doses of as much as 21%. However, this study did not provide DoT and evaluated only individual doses [15].

LoT as a metric for antibiotic usage was first introduced in an adult study by Polk et al. in 2011 to provide additional information complementing DoT evaluations [21]. A combination therapy with two antibiotics doubles the DoT. However, a broad-spectrum antibiotic may combine the activity of two narrow-spectrum antibiotics and prescription of this drug would reduce DoT by 50% as only one substance is used instead of two. Therefore, it is important to report also the absolute length of antibiotic therapy. In our study, the overall antibiotic usage expressed as LoT (377.4 pre- and 348.3 LoT/1000 PD post-intervention) is significantly lower than published data from Newland et al. (567 pre- and 523 LoT/1000 PD post-intervention) and Agwu et al. (485.4 pre- and 417.6 LoT/1000 PD post-intervention) [11, 24]. However, as

mentioned above, both studies measured antibiotic usage in tertiary care children's hospital, including intensive care units and hemato-oncology wards. Even though our reduction in LoT was significant (−7.7%) and similar to the impact described by Newland et al. (−7.8%), it was not as large as reported by Agwu et al. (−13.9%). This might be related to our lower LoT baseline, which might be influenced by our focus on general pediatric wards. By demonstrating a significant decrease of both metrics, DoT and LoT, we have achieved a reduction of the absolute number of antibiotics, as well as the actual lengths of antibiotic therapies.

Cefuroxime and ceftriaxone are among the most prescribed antibiotics in German adult hospitals [1]. In line with these epidemiological data, cefuroxime was the most used antibiotic in the pre-intervention period, while ceftriaxone with its wider antimicrobial spectrum was prescribed less often in our general pediatric wards. It is well known that cephalosporins, in particular third-generation cephalosporins and FQs, are associated with a significant increase in the incidence of CDI and are key selection drivers for hospital- and community-acquired MRSA, vancomycin-resistant *Enterococcus* (VRE), and extended-spectrum β -lactamase producing gram-negative bacteria (ESBL) [9, 29, 30]. Therefore, we specifically targeted third-generation cephalosporins and FQs. We were able to reduce the consumption of these substances by 22.3 and 59.9%, respectively (in total −38.1%). As intended they were mostly replaced by narrow- and intermediate-spectrum penicillins (+38.4% DoT/1000 PD). Di Pentima achieved a comparable decrease of targeted third-generation cephalosporin and FQ use, as well as a reduction of overall antibiotic consumption in a pediatric setting [15]. In adults, Borde et al. showed a similar impact on cephalosporins (−33% RDD/1000 PD) and FQs (−31% RDD/1000 PD) [31].

Meropenem prescription rates in our center (3.4 in pre- and 6.9% in post-intervention period of total antibiotic DoT) were not different from the data reported for Western European patients (4.2%) [18]. However, we observed an—albeit small (i.e., +13.4 DoT/1000 PD)—increase in meropenem use in the post-intervention period. This might potentially be caused by a rise in the number of patients colonized with multi-resistant Gram-negative bacteria (MRGN), as a higher number of refugees were treated in our hospital during the post-intervention period. In addition, the increase of meropenem use might be linked to our recommendation to use meropenem empirically in suspected septic shock. While this serious condition has a low incidence, inexperienced physicians may have used meropenem more broadly than intended (e.g., for sepsis without shock). Therefore, addressing the issue of inappropriate use of carbapenems will be a focus of future ID interventions in our setting, including educational measures towards more

accurate clinical identification of patients with severe sepsis or septic shock.

In published literature, the use of CPOE and the presence of ward-based pharmacists have been most successful in reducing the rate of medication errors (ME) in hospitalized patients [16, 32]. Published data demonstrate that the rate of dosage-related errors is much more substantial in children than in adults with underdosing being the most common ME in pediatrics [16, 33, 34]. Ekins-Daukes et al. confirmed that a high percentage (19.2%) of antibiotics prescribed in primary care setting showed lower doses than recommended in the Summary of Product Characteristic by the manufacturer [35]. These low doses may have caused the significant increase in the total number of antibiotic courses prescribed due to incomplete resolution of infection. Besides the risk of ineffective drug levels and treatment failure, low doses increase the risk for selection of resistant bacteria [36, 37]. Similar to previously published results, underdosing was common (16.9%) and overdosing was observed in only 4.3% of treatment courses during our pre-intervention period. However, the rate of correct dosing significantly increased from 78.8 to 97.6% after implementation of guidelines with precise dosing recommendations and a particular focus on dosing accuracy during regular ID ward rounds. Aseeri et al. achieved similar effects after disseminating standardized dosing tables resulting in a reduction of dosing errors from 34.3 to 5.1% [38]. Our dosing recommendations were based on the published literature and represent a consensus of an internal multidisciplinary expert panel. Accurate dosing was somewhat arbitrarily defined as $\pm 30\%$ of our internal recommendations. Therefore, we analyzed all under- or overdosed antibiotic treatment courses and compared dosing with the recommendations in the literature. We found that 3.7% antibiotic courses in the pre-intervention period and only one antibiotic course (0.27%) in the post-intervention period were not within the published dosing ranges. However, none of these antibiotic treatment courses resulted in significant toxicity for the patient.

For children over six months of age admitted with uncomplicated CAP, national and international guidelines recommend empiric therapy with aminopenicillins (i.e., amoxicillin or ampicillin) [22]. Our ASP strategies led to a remarkable and significant increase in guideline adherence. These findings are in accordance with published data where an increase of ampicillin use of 34% and a reduction of cephalosporin use of 72% were found after implementation of CAP guidelines [12]. Ambroggio et al. increased appropriate first-line antibiotic prescribing for children with CAP from 30 to 100% in hospital resident teams through implementing internal guidelines and education on CAP treatment [39]. Smith et al. analyzed the impact of an ASP team and CAP guideline and demonstrated an improvement of

their initially low rate of ampicillin prescribing 2–44% and a decrease of ceftriaxone usage (59–28%) [40].

Our approach has some limitations: The exclusion of patients with chronic diseases comprises a potential patient bias. However, this seems to be unlikely as the numbers of patients that were excluded were similar between the pre- and post-intervention periods (Fig. 1). In addition, this is a single-center study, investigating the effect of ASP strategies only on general pediatric wards. As patient characteristics vary widely between different subspecialties, we decided to focus on general pediatric wards since these are more homogenous and represent the majority of inpatients. Similar studies are currently ongoing in our hospital on high-prescribing units like hemato-oncology, neonatology, pediatric surgery, and intensive care. The endpoints assessed were limited to previously recommended outcome measures [27], as well as crude estimators of safety outcomes (length of stay and in-hospital mortality). Our study did not address changes in reinfection rate, changes in bacterial resistance rates, or the incidence of CDI in children. A recent Cochrane review showed that the effect of ASP interventions on microbiological endpoints is usually delayed [41]. Considering the relatively short four-month observation period, the risk of losing the observed positive impact cannot be excluded, as previously shown for adults (Standiford et al. [42]). The long-term effects of our ASP bundle need to be further investigated. However, this study demonstrates that an ASP bundle approach can successfully reduce the overall antibiotic use and the use of broad-spectrum antibiotics. In addition, our ASP interventions increased antibiotic dosing accuracy and guideline adherence for the treatment of CAP, which both are a major issue of patient safety.

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Compliance with ethical standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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