Opportunities for Antibiotic Stewardship Interventions in a Pediatric Hospital

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Abstract

Objective This study's objective was to assess an antibiotic stewardship intervention, compare pediatric antibiotic usage in a non-university hospital (Children's Hospital Traunstein [TS]) with a university hospital (Dr. von Hauner Children's Hospital, Ludwig Maximilians University Munich [MUC]), and assess adherence to national guidelines.

Methods Antibiotic usage pre- and post-antibiotic stewardship (ABS) intervention was compared, and antibiotic prescriptions over 4 months were prospectively recorded. ABS intervention consisted of weekly teaching sessions, antibiotic pocket cards, and rounds with pediatric infectious disease staff. Medical records were reviewed to describe antibiotic consumption, antibiotic dosages and length of use, and adherence to national guidelines. Pediatric antibiotic usage was compared between hospitals and patient groups.

Results After the ABS intervention, the use of second-generation cephalosporins decreased, while penicillin with β-lactamase inhibitors (BLI) increased. Survey of antibiotic prescriptions over the 4 months study period in the non-university hospital showed a high administration rate of second-generation cephalosporins and extended-spectrum penicillins in the non-intensive care units (ICU) wards (48.53 and 38.93 days of therapy [DoT]/1,000 patient days [PD], respectively) and a high rate of third-generation cephalosporins in the ICU ward (110.33 DoT/1,000PD). A high prescriptions rate was seen in the neonatal intensive care unit (NICU) wards (DoT/ length of therapy [LoT] ratio of 2.185). Reserve group antibiotics were only given in the ICU. Adherence to national guidelines was highest in the NICU and pediatric ICU wards. Striking was the relatively high rate of incorrect usage of second-generation cephalosporins. Comparing the pediatric wards of the non-university hospital (TS) and the university hospital (MUC), the prescription ratio was 11.1% (TS) versus 30.6% (MUC), and DoT/1,000PD 198.9 (TS) versus 483.6 (MUC), $p = 0.02$. ABS intervention changed the choice of described antibiotics, but not the overall frequency.

Keywords

- antibiotic prescription
- days of therapy per 1000 patient days
- defined daily dose per 100 patient days
- antibiotic stewardship

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Conclusion Adherence to national guidelines was highest in fields with standardized therapy recommendations, like in the NICU. In MUC, antibiotics, in particular restricted ones, were prescribed more frequently, probably due to higher severity of illness. These data indicate that the usage of antibiotics and adherence to national guidelines show a wide variety, but ABS interventions were effective in changing prescription behavior.

Introduction

As children are frequently admitted to the hospital with infections or for a rule-out of a bacterial infection, antibiotics are commonly administered in the pediatric population. An American multicenter retrospective cohort study of over 500,000 pediatric inpatient discharges showed that, overall, 60% of the children received at least one antibiotic agent and more than 90% of children who underwent surgery, central venous catheterization, or prolonged ventilation received antibiotics.[1] It is estimated that 30 to 50% of prescribed antibiotics are inappropriate.[2] Overuse of antimicrobials in children may elicit new antimicrobial resistance, be harmful to the intestinal microbiome, and unnecessarily prolong the time in hospital.

Antibiotic stewardship involves proper indication of antibiotics, the correct choice of the molecules, correct dosing, and appropriate length of therapy (LoT). Antibiotic choice is determined by the prescriber's preferences, the severity of the patient's illness, and other factors.[3] Antibiotic stewardship programs were shown to be effective in reducing inappropriate antibiotic usage. A pediatric antibiotic stewardship (ABS) program at the general pediatric wards of a German university hospital showed a significant reduction of broad-spectrum antibiotics. However, in general, the overall prescription rate of antibiotics did not alter significantly.[4] Implementation of ABS at a pediatric intensive care unit (ICU) in a German university hospital led to a reduction in antibiotic usage, LoT, and an approximately 50% reduction of meropenem and vancomycin.[5]

An ABS intervention at a German non-university tertiary care hospital was implemented and assessed, and antibiotic usage was compared with a German university tertiary care pediatric hospital.

Materials and Methods

Antibiotic prescribing was compared pre- and post-ABS intervention using the hospital's pharmacy data from 2014, 2015 (pre-), and 2016 (post-intervention). Twelve months of post-intervention were compared with 24 months of pre-intervention. Post-intervention was defined as a time period after which ABS measurements were set up. Antibiotic usage was expressed as a defined daily dose (DDD) per 100 patient days (DDD/100PD).[6] ABS intervention consisted of weekly teachings or journal clubs, antibiotic pocket cards, and pediatric infectious disease staff rounds. Pediatric and adult infectious disease specialists with ABS training provided all materials and teaching sessions. Weekly team teachings and journal clubs covered different subjects such as pediatric infectious diseases, antibiotic usage, and ABS programs. Antibiotic pocket cards were made according to ABS guidelines and input from pediatric infectious disease staff and other specialties (e.g., pediatric surgery). Pocket cards showed first-line therapy recommendations for common pediatric infectious diseases as well as dosage recommendations for antibiotic substances. An infectious disease staff made special rounds upon request. Subsequently, over 4 consecutive months (February–June 2017), a total of 175 case prescriptions (335 substance prescriptions) were assessed in a non-university tertiary children's hospital (Children's Hospital Traunstein [TS]). This hospital has a capacity for 60 inpatients in three pediatric wards, including a level-1 neonatal intensive care unit (NICU), representing the highest level of NICU care in Germany. Medical records were reviewed while respecting the patient's anonymity. The prescription rate was defined as the percentage of children receiving antibiotics relative to all in-ward admissions during the 4 months. To compare antibiotic usage between wards and hospitals, the LoT was calculated per 1,000 patient days (LoT/1,000PD), where multiple prescribed molecules count as one per day. Combined antibiotic prescriptions were measured in days of therapy per 1,000 patient days (DoT/1,000PD). To compare the combined usage of different antibiotics, the DoT/LoT ratio was calculated. Multisubstance therapy was considered likely when this ratio was higher than 1. Overall, a grouping of the different antibiotic substance classes was made according to the World Health Organization's AWaRe classification database in "access," "watch," "reserve," and "not recommended" antibiotics.[7] Antibiotics from the "not recommended" group of antibiotics were not administered. Restricted antibiotics are defined as follows: fourth-generation cephalosporins, glycopeptides, carbapenems, and all substances from the "reserve" group (mainly oxazolidinones).

The case mix index (CMI) is defined as the average relative diagnosis-related group weight of all inpatient discharges. Data were compared between the three wards of this non-university tertiary children's hospital, consisting of two general pediatric wards and one pediatric ICU ward. The differentiation between the two general pediatric wards was based on the German health care system, where children not older than 6 years are supposed to be admitted with one parent at a non-ICU ward, whereas children older than 6 years are admitted without a parent. As the ICU of this children's hospital is a mixed NICU and pediatric ICU, we also differentiated neonatal patients, defined as younger than 6 months. To assess adherence to guidelines indication, LoT and dosing of first and second-line therapies were compared with the German Society of Pediatric Infectious Diseases recommendations.[8] The indication was confirmed as adherent to guidelines if the right choice of the antibiotic substance was made (recommended first-line therapy for diagnosis or second line in case of allergy or drug interaction). The dosage was confirmed as appropriate if $\pm$ 10% of the recommended dose. The off-label use was confirmed if the dosage or indication was not recommended due to low patient age or if there was no recommendation to be found in the national guidelines, but other literature suggested a correct use (e.g., antibiotic prophylaxis in case of a postsurgical therapy with medical leeches). Results were compared with a previously published dataset on the antibiotic usage of the university children's hospital of LMU University (Dr. von Hauner Children's Hospital, Ludwig Maximilians University Munich).[4] The comparison was made between pre-intervention data of the university hospital and post-intervention data of the non-university hospital, the interventions at the university hospital being of a much wider range.[4] Interventions, such as total restriction of antibiotics or limitation of use to the ICU only, as well as regular and daily available rounds with ABS specialists, had not yet been implemented at the non-university children's hospital in contrast to the university children's hospital.[4]

The study timeline is visualized in ►**Fig. 1**.

Statistical analysis was performed using GraphPad Prism (GraphPad Software Inc., San Diego, CA, United States). The chi-square test was used for all comparisons. In the case of antibiotic usage development (DDD/100PD), a change in using a particular antibiotic as part of all used antibiotics was described rather than a change over time. Similar, chi-square test was used to compare prescription rates (in DoT/1,000PD or LoT/1,000PD), as antibiotic prescriptions were described as a part of all prescriptions at each hospital. Percentages (compliance to guidelines, DoT, LoT) were independently calculated from raw data. The level of significance was defined as $p \leq 0.05$.

Results

To show the linear development of annual antibiotic substance use at the non-university pediatric hospital, DDD/100PD was compared pre- and post-ABS intervention. Penicillins + β-lactamase inhibitors (BLI) (other than piperacillin) were used significantly more frequently post-ABS intervention (4.58 DDD/100PD) compared with pre-intervention (2.59 DDD/100PD)($p < 0.0001$). The use of second-generation cephalosporins (cefuroxime) post-intervention was significantly reduced, resulting in 8.77 (post-ABS intervention) compared with 12.46 (pre-ABS intervention) DDD/100PD ($p < 0.0001$). There was no significant difference in the use of third-generation cephalosporins ($p = 0.67$), though a declining trend was observed resulting in 3.02 DDD/100PD (post-ABS intervention) compared with 3.41 DDD/100PD (pre-ABS intervention). Fluoroquinolones were used only rarely pre- and post-ABS intervention (0.14 and 0.32 DDD/100PD, respectively).

During the 4-month study period for the assessment of antibiotic prescriptions, the general pediatric wards at the non-university hospital had an antibiotic prescription ratio of 11% and a case mix index (CMI) of 0.65. The ICU (pediatric and neonatal intensive care) had an antibiotic prescription ratio of 30% and a CMI of 4.108.

At all wards of the non-university pediatric hospital, access group antibiotics were used in 54.0%, compared with substances from the watch group in 46.0% (►**Fig. 2**). The most frequently prescribed antibiotics were second-generation cephalosporins in 24.4% of all prescribed antibiotic substances, followed by penicillins with extended spectrum in 19.6%, penicillins + BLI (other than piperacillin) in

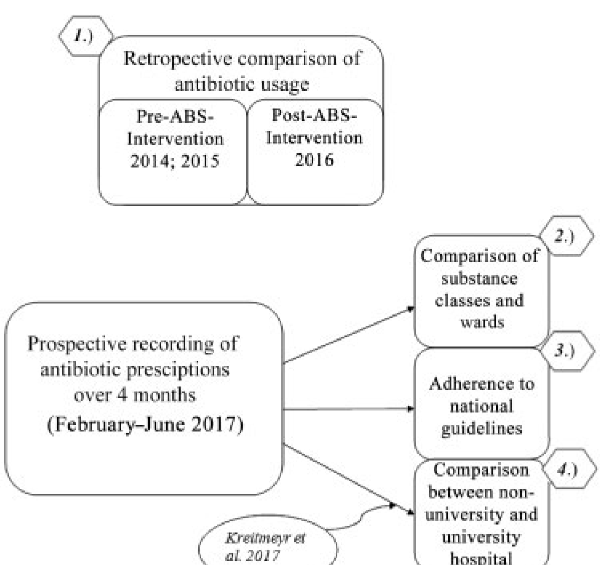

Fig. 1 Flowchart of study methods.

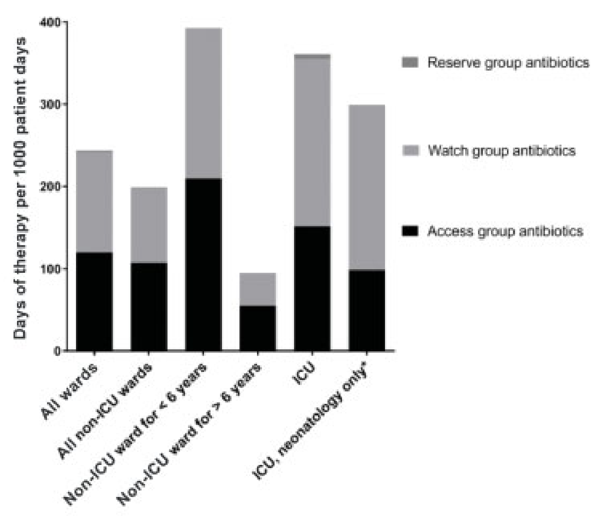

Fig. 2 Comparison of the prescription frequency of the antibiotic substance groups according to the World Health Organization AWaRe classification[6] at the wards of the non-university children's hospital, expressed as DoT/1,000PD (days-of-therapy per 1,000 patient days). The AWaRe group "not recommended antibiotics" is not shown, as no such substances were used.

Table 1 Comparison of prescribed antibiotic substances between university and non-university children's hospital in DoT/1,000PD and in percentage of all prescribed antibiotics

Substance group	Number of prescriptions at the non-university children's hospital	Non-university children's hospital non-ICU wards		University children's hospital non-ICU, non-oncologic, and non-CF wards		*p*-Value of comparison (Chi^2-test)
		DoT/1,000PD	%	DoT/1,000PD	%	
Piperacillin + BLI	4	3.2	1.2	105.5	21.8	<0.0001
Other penicillins + BLI	54	31.5	11.1	17.1	3.5	0.0001
Beta-lactamase-resistant penicillins	1	0	0.2	0.9	0.2	0.1894
Penicillins with extended spectrum	77	38.9	22.5	35.5	7.3	0.7097
Beta-lactamase sensitive penicillins	4	1.9	0.6	4.2	0.9	0.1660
First-generation cephalosporins	1	2.4	0.7	8.2	1.7	0.0020
Second-generation cephalosporins	56	48.5	16.8	108.9	22.5	<0.0001
Third-generation cephalosporins	73	25.9	20.3	43.9	9.1	0.0001
Fluoroquinolones	4	4.5	1.8	31.9	6.6	<0.0001
Nitroimidazoles	12	8.8	4.9	27.1	5.6	<0.0001
Macrolides	9	4.3	1.8	24.8	5.1	<0.0001
Glycopeptides	5	1.3	2.3	23.5	4.9	<0.0001
Carbapenems	9	2.4	5.1	16.6	3.4	<0.0001
Lincosamides	14	18.7	6.3	16.2	3.3	0.6906
Others	7	5.3	3.1	12.2	2.5	0.0047
Aminoglycosides	5	1.3	1.3	4.7	1	0.0272
Polymyxines	0	0	0	2.4	0.5	0.0103

Abbreviations: BLI, β-lactamase inhibitors; CF, cystic fibrosis; DoT/1,000PD, days of therapy per 1,000 patient days; ICU, intensive care unit.

15.8%, and third-generation cephalosporins in 13.0%. All other molecules were given in less than 10% of all antibiotic prescriptions; however, lincosamides (clindamycin) still showed a high percentage with 9.4% (►**Table 1**). At the parent–children ward (including children under 6 years of age), antibiotics from the access and watch group were prescribed in 53.4 and 46.6%, respectively (►**Fig. 2**). Those patients received penicillins with extended spectrum as the most frequently used antibiotic in 28.5%, followed by second-generation cephalosporins in 18.6%, third-generation cephalosporins in 16.7%, and penicillins + BLI (other than piperacillin) in 15.8%. Reserve group substances were only given in the ICU, representing 1.4% of the antibiotic prescriptions. Access group substances were prescribed in 42.1%, and watch group substances in 56.5% (►**Fig. 2**). In the third-generation ICU, cephalosporins were prescribed most frequently, resulting in 31.0% of all antibiotic substances. Penicillins with extended spectrum were prescribed in 26.9% and carbapenems in 10.9%. Vancomycin was prescribed in 4.7% and other restricted substances even less frequently. Second-generation cephalosporins, aminoglycosides, and vancomycin were used in less than 5%.

Most antibiotic substances were prescribed in the general pediatric ward for children under 6 years (parent-children ward) with 392.54 DoT/1,000PD, compared with the pediatric ICU with the second most prescriptions (355.59 DoT/1,000PD). No substances from the reserve group and only few other restricted antibiotics were given at the non-ICU pediatric wards, e.g., vancomycin 0.00 DoT/1,000PD, teicoplanin 1.33 DoT/1,000PD, and carbapenems 2.40 DoT/1,000PD, compared with 16.87 DoT/1,000PD (vancomycin), 0.00 DoT/1,000PD (teicoplanin), and 38.65 DoT/1,000PD (carbapenems), respectively, at the pediatric ICU ($p = 0.2526$) (►**Fig. 2**, ►**Table 1**).

The LoT per 1,000 patient days (LoT/1,000PD) was similar to DoT/1,000PD. The DoT/LoT ratio (1,004) in the general pediatric wards of the non-university children's hospital showed a low likelihood of combination therapy. However, the likelihood for combination therapy for ICU patients and especially for NICU patients was considerably high with a DoT/LoT ratio of 1.576 and 2.185, respectively, suggesting that almost every neonatal patient received combined antibiotic therapy.

Compliance with guidelines was measured, and off-label indications and dosages were also marked (►**Fig. 3**). Notably, penicillins + BLI were prescribed in 54 cases, of which 61% had a correct indication and 70% were dosed correctly, 9% of the prescriptions were off-label. Penicillins with extended-spectrum were used in 77 cases, of which 79% were prescribed with the correct indication and in 95% with the

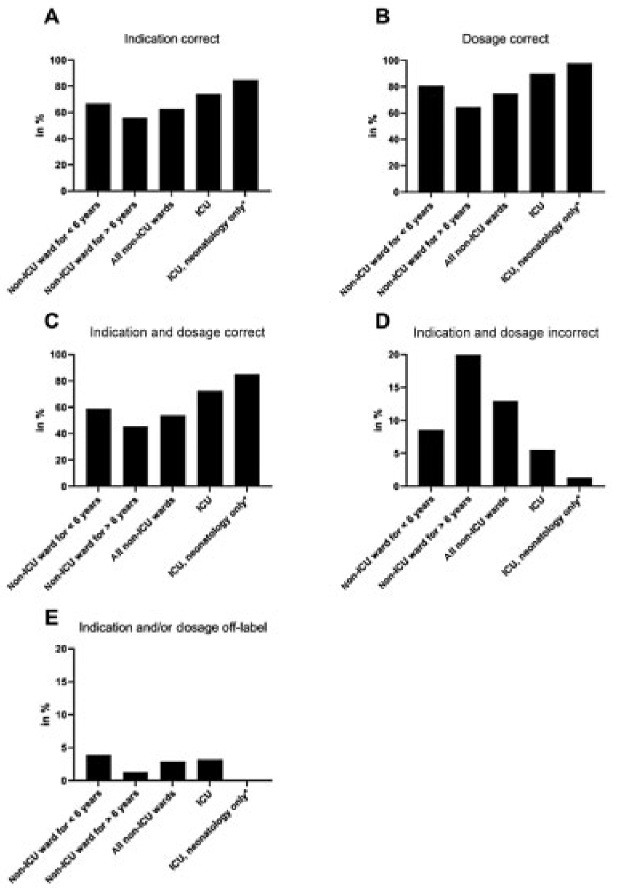

Fig. 3 Adherence to national guidelines for prescribing pediatric antibiotic therapy for all antibiotic substance groups in each ward in percent.

correct dosage, 3% of the cases were used off-label. Second-generation cephalosporins were prescribed in 56 cases; however, only 32% were prescribed correctly and 46% with the correct dosage, 5% were off-label, and 33% of the incorrect indications were either unnecessarily prolonged (>24 hours) or as surgical prophylaxis that was either not indicated or not the first-line therapy (e.g., cefuroxime instead of cefazolin). Third-generation cephalosporins were prescribed in 73 cases, 80% correctly prescribed, and 95% correctly dosed. Restricted substances were prescribed in 14 cases, and 86% with correct indication or dosage. Both indication and dosage were correct in 71% of the cases.

Both indications and dosages were correct in 85% of the NICU, 72% of the pediatric ICU patients, 59% at the non-ICU ward for children under 6 years, and 46% at the non-ICU ward for children older than 6 years (►**Fig. 3C**).

At all non-ICU pediatric wards of the university pediatric hospital, the most frequently prescribed antibiotics were second-generation cephalosporins in 22.5% of all antibiotics, followed by piperacillin + BLI in 21.8%. All other substances were used less than 10% (►**Table 1**).

At all non-ICU wards of the non-university pediatric hospital, overall penicillins with extended-spectrum were prescribed most frequently in 22.5% of all antibiotic substances prescribed, followed by third-generation cephalosporins in 20.3%, second-generation cephalosporins in 16.8%, and penicillins + BLI in 11.1% (►**Table 1**).

Comparing different substance classes, piperacillin with a BLI was prescribed more frequently at the university hospital compared with the non-university hospital (105.5 DoT/1,000PD vs. 3.2 DoT/1,000PD, $p < 0.0001$). Second generation cephalosporins were prescribed more frequently in the university hospital compared with the non-university hospital (108.90 DoT/1,000PD vs. 48.53 DoT/1,000PD, $p < 0.0001$).More third-generation cephalosporins were prescribed at the university hospital compared with the non-university hospital (43.9 DoT/1,000PD vs. 25.9 DoT/1,000PD, $p = 0.0001$). Restricted antibiotics were prescribed significantly more frequently at the university pediatric hospital (16.6 DoT/1,000PD vs. 2.4 DoT/1,000PD, $p < 0.0001$). There were no differences for penicillins with extended spectrum (mainly aminopenicillins) (DoT/1,000PD: 38.9 vs. 35.5, $p = 0.7097$) or lincosamides (DoT/1,000PD 16.2 vs. 18.7, $p = 0.6906$), (►**Fig. 4A**). In the non-ICU pediatric wards, DoT/1,000PD was significantly lower in the non-university hospital (198.9) compared with the university hospital (483.6), ($p = 0.02$) (►**Fig. 4B**).

Discussion

ABS training was implemented in a non-university pediatric tertiary pediatric hospital to achieve similar evidence-based standards in dosing, indication, and choice of antibiotics as in a university hospital. ABS training consisted of formal courses, antibiotic pocket cards, joint rounds with pediatric infectious disease specialists, and consultations via telephone. Antibiotic use pre- and post-ABS intervention and prescription rates between the two hospitals were compared.

After ABS intervention, there was a decrease in second-generation cephalosporins and an increase in penicillins with BLI. As a similar ABS program was implemented in the described pediatric university hospital a few years prior, Kreitmeyr described a reduction of cephalosporins and fluoroquinolones and an increase in the use of penicillins and aminopenicillins, similar to the effect observed in this study. In addition, dose accuracy increased, and adherence to treatment guidelines for community-acquired pneumonia improved.[4] A similar decrease in cephalosporins and fluoroquinolones was described in an adult university setting through ABS measures.[9] It was also shown in a 200-bed community hospital that the implementation of an ABS bundle is feasible; it decreased mortality from *Staphylococcus aureus* bloodstream infections and decreased the use of antibiotics, and lowered costs in an endoprosthetic center.[10,11]

In the non-university hospital, children under 6 years at the non-ICU ward had the highest rate of DoT/1,000 PD, even higher than neonates and children in the combined intensive care unit of the same hospital, probably secondary to the fact that many children of this age group are admitted to the hospital for evidence of bacterial infection or to rule out bacterial infection. Similar to recent studies, the average age of children receiving antibiotics in the hospital was between

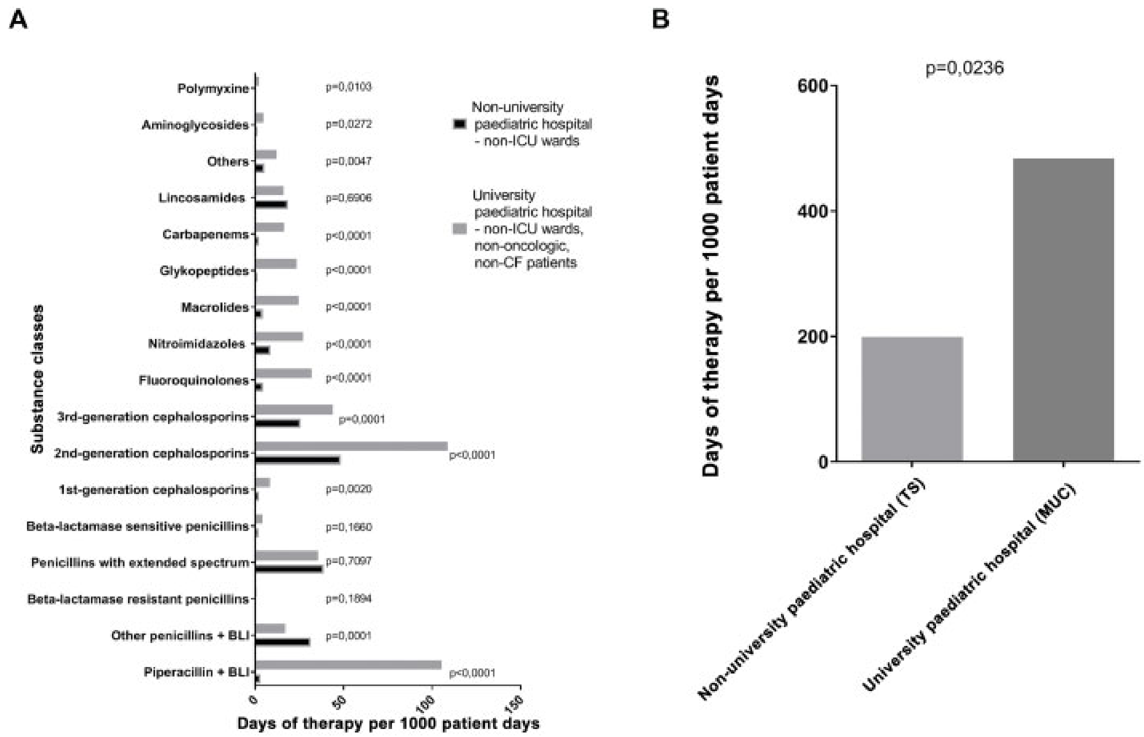

Fig. 4 Comparison of prescribed antibiotic substances between university and non-university children's hospital in days of therapy per 1,000 patient days (DoT/1,000PD).

3 and 4 years, highlighting that toddlers receive antibiotics most frequently in the inpatient pediatric setting and hence are most vulnerable to inappropriate prescribing of antibiotics.[2,4]

The prescription of lincosamides was relatively high with almost 10% in the present study and 16% in the Kreitmeyr study, probably due to two reasons: there is the general, not evidence-based perception that clindamycin penetrates tissue better than other antibiotics, especially in bone- and soft tissue infections, and that there is better staphylococcal activity including methicillin-resistant *Staphylococcus aureus* (MRSA) coverage, mainly in community-acquired MRSA infections.[8] However, a recent study found one-quarter of clindamycin in children suboptimal.[2] Further, no benefit of clindamycin was shown over aminopenicillin + BLI combinations in cases of osteomyelitis.[12]

In the NICU, almost every patient received two antibiotics, as evidenced by a DoT/LoT ratio higher than 2. This is likely due to guideline therapy recommendations for neonatal sepsis, which in most cases include the use of aminopenicillins with either an aminoglycoside or a third-generation cephalosporin.[8]

Prescribing substances of the reserve group of antibiotics only at the ICU may be interpreted as successful ABS regulation though still a significant proportion of antibiotics from the watch group was given at non-ICU wards.

Comparing antibiotic prescription in the non-ICU pediatric wards between the non-university hospital and the university hospital, DoT per 1,000 patient days was much higher in the university hospital, as was the use of restricted antibiotics such as vancomycin or meropenem. As the university hospital is in a large metropolitan area (Munich), a higher rate of MRSA and extended-spectrum beta-lactamases-producing gram-negative pathogens could account for that, as well as a higher rate of immunocompromised children. Especially, the more frequent prescribing of second-generation cephalosporins at the university hospital might be due to the higher rate of pediatric surgical procedures and the associated surgical prophylaxis.

It has been recently estimated that one in three hospitalized children are receiving antibiotics at any given time, a quarter of those children are receiving suboptimal therapy, and one-half of those children's antibiotics are not covered by current practice guidelines.[2] Similar, in the present study, only one-quarter of the second generation cephalosporins to three-quarters of the penicillin/extended-spectrum dosings were correct, highlighting the further need for rigorous antibiotic training, surveillance, and feedback on the use of antibiotic substances in the pediatric population. In addition, one-third of the incorrect indications of second-generation cephalosporins were due to prolonged or not recommended surgical prophylaxis, a finding that was also described by Tribble et al.[2]

This study has several limitations. First, there was a longer pre- than a post-intervention period (24 vs. 12 months). The post-intervention period still included ongoing ABS interventions; however, the results can still reflect an overall positive ABS development. As only hospital pharmacy data were used for data collection, there might be some missing data on medications used in the pre- and post-intervention period, as antibiotics given directly from the ward supply may not show; however, the amount of such antibiotics in 3 years should be small. During the 4-month prospective period, no data regarding prescribed in-ward antibiotics were lost; however, sufficient data on oral step-down therapies continued after discharge were not collected. The total amount of antimicrobial therapy prescriptions within 4 months is rather small, which may be attributed to the non-university pediatric hospital setting. Comparing the antibiotic use of the non-university with the university hospital, there was a time gap of 3 years (2017 vs. 2014). The 4-month period at the university children's hospital was from September to December, whereas at the non-university hospital from February to June, both periods include winter months. Further, no comparison of antibiotic prescription rates between the ICUs was possible as no data from the university hospital has been published by Kreitmeyr et al.[4] Also, the data from the university hospital were pre-ABS intervention compared with post-ABS intervention from the non-university hospital; however, the situation pre-ABS intervention at the university was comparable to the situation post-ABS intervention at the non-university.

ABS intervention was feasible to implement, and it effectively changed prescription behavior at a non-university children's hospital. Standardized therapy recommendations resulted in higher adherence to national guidelines. The highest adherence to national guidelines was seen in the NICU, compared with the lowest at the general pediatric ward for children older than 6 years. Children under 6 years of age at the general pediatric ward received antibiotics most frequently, even more frequently than in the pediatric ICU. In the university hospital, antibiotics, particularly restricted antibiotics, were prescribed more frequently, probably due to the higher severity of illness. Future antibiotic stewardship measures could be enhanced by the use of telemedicine, the use of an app, and virtual rounds with infectious disease specialists.

Ethical Approval

Only completely anonymized raw data were used for the study, and the ethics commission of the Ludwig-Maximilians-University Munich was informed about the planned study prior to the start of the study and the need for informed consent and ethics approval was waived.

Availability of Data and Materials

The datasets analyzed during the current study are available from G.G.-K., M.D., on reasonable request.

Authors' Contributions

G. G.-K. performed data analysis; G. G.-K., J. H., A. P., and G. W. all contributed to writing the manuscript; external statistical consultation was obtained by G. G.-K.; the manuscript was discussed on a regular basis between all authors; and all authors read the final version of the manuscript and approved submission to the journal.

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None.

Conflict of Interest

None declared.

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