Benefits of a Pediatric Antimicrobial Stewardship Program in Antimicrobial Use and Quality of Prescriptions in a Referral Children's Hospital

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Objectives To evaluate the results of the first 24 months of a postprescription review with feedback-based antimicrobial stewardship program in a European referral children's hospital.

Study design We performed a pre-post study comparing antimicrobial use between the control (2015-2016) and the intervention periods (2017-2018) expressed in days of therapy/100 days present. Quality of prescriptions was evaluated by quarterly cross-sectional point-prevalence surveys. Length of stay, readmission rates, in-hospital mortality rates, cost of systemic antimicrobial agents, and antimicrobial resistance rates were included as complementary outcomes.

Results Total antimicrobial use and antibacterial use significantly decreased during the intervention period ($P = .002$ and $P = .001$ respectively), and total antifungal use remained stable. A significant decline in parenteral antimicrobial use was also observed ($P < .001$). In 8 quarterly point-prevalence surveys (938 prescriptions evaluated), the mean prevalence of use of any antimicrobial among inpatients was 39%. An increasing trend in the rate of optimal prescriptions was observed after the first point-prevalence survey ($P = .0898$). Nonoptimal prescriptions were more common in surgical than in medical departments, in antibacterial prescriptions with prophylactic intention, and in empirical more than in targeted treatments. No significant differences were observed in terms of mortality or readmission rates. Only minor changes in antimicrobial resistance rates were noted.

Conclusions Our antimicrobial stewardship program safely decreased antimicrobial use and expenditure, and a trend toward improvement in quality of prescription was also observed. *(J Pediatr 2020;225:222-30)*.

The misuse of antimicrobial agents increase the rates of adverse effects related to their use, including the emergence and spread of antimicrobial resistance and results in higher morbidity and mortality.[1-6] Countries and organizations are responding with the development of coordinated action plans to fight antimicrobial resistance development, including the implementation of antimicrobial stewardship programs at the healthcare institution level.[5,7-11]

Antimicrobial stewardship programs are multifaceted, interdisciplinary approaches to optimizing anti-infective therapy that have proved their effectiveness in reducing antimicrobial use in children, although the evidence concerning the impact of antimicrobial stewardship program on antimicrobial resistance rates is limited.[3,5,10,12-16] Data on the most effective interventions for the pediatric population remain limited.[3-5] As per adult studies,[17] postprescription review with feedback (PPRF) may have a greater impact on decreasing antimicrobial use compared with preprescription authorization. A more restrictive approach may lead to conflicts, which are preventable with an educational-persuasive approach.[3,18]

Measuring the impact of antimicrobial stewardship program in pediatrics also remains unsolved; currently, there are no standardized, validated clinical end points.[5,10,15,17] Antimicrobial measures of consumption are the most

DOT	Days of therapy
LOS	Length of stay
PICU	Pediatric intensive care unit
PPS	Point-prevalence survey
PROA-SJD	Programa de Optimización del Uso de Antimicrobianos-Sant Joan de Déu
PPRF	Postprescription review with feedback

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commonly used metrics in hospital settings. Days of therapy (DOT), defined as the aggregate sum of days of exposure to an antimicrobial, based on the drugs administered rather than those prescribed, dispensed or purchased, is the preferred measure.[3,10,11,13,19,20] When DOT are aggregated, an antimicrobial use rate is calculated over a denominator of person time at risk (patient-days or days present).[21] Evaluating the appropriateness of antimicrobial use (considering whether the right agent, with the appropriate antimicrobial activity is being provided at the right dose, route, and schedule, for the right duration, taking into account patient allergies, drug interactions, and potential toxicities) is labor intensive and has no widely applicable standards of reference of best practices.[3,10,22] Point prevalence methodology makes monitoring quality of prescriptions feasible.[6,23] The potential impact on antimicrobial resistance is usually estimated by prevalence rates of infections owing to selected organisms and their evolution over time. Other metrics such as length of stay (LOS) must be interpreted with caution, because they can be affected by many other factors. Mortality is used as a balancing measure, ensuring that antimicrobial stewardship program interventions do not lead to increased harm. Finally, hospital expenditures have also been used as a complementary marker of the impact of antimicrobial stewardship program in healthcare centers.[11,18,24]

We aimed to describe and evaluate the results of the initial 24 months of a PPRF-based antimicrobial stewardship program in a European referral children's hospital, in terms of quality of prescription and antimicrobial use.

Methods

The study intervention was conducted in the inpatient area of Hospital Sant Joan de Déu (Barcelona, Spain), a 268-bed pediatric referral children's hospital for patients less than 18 years of age, with a full range of pediatric medical and surgical subspecialties, a 24-bed pediatric intensive care unit (PICU) (8.2%), and a 38-bed NICU (14.2%). The yearly number of hospital discharges is around 15 000.

Intervention

The hospital antimicrobial stewardship program (*Programa de Optimización del uso de Antimicrobianos Sant Joan de Déu* [PROA-SJD]) was first implemented in January 2017. The PROA-SJD core team was composed of a full-time pediatric infectious diseases specialist, and other part-time physicians including a pediatric intensive care specialist, clinical pharmacists, a microbiologist, a hospital epidemiology and infection control physician, and a nurse. Support was received from the computer, statistics, and hospital management teams.

The main antimicrobial stewardship program strategy was PPRF. All systemic antimicrobial agents (intravenous, intramuscular, or oral route) were included in antimicrobial stewardship program evaluation. An electronic form (**Appendix 1**; available at www.jpeds.com) was included in the patients' electronic clinical chart to inform the prescribers as to whether the antimicrobial prescription was considered "optimal" or "nonoptimal." For a prescription to be considered optimal, all the following criteria had to be met: (1) the administration of the antimicrobial was appropriate considering the diagnosis, the antimicrobial spectrum, our own reference guidelines, adapted to local epidemiology, and also accounting for patient allergies and comorbidities; (2) the drug was given via the right route, and at the right dose and with the right schedule; and (3) the expected and/or actual duration of the antimicrobial treatment were appropriate. Otherwise, prescriptions were categorized as nonoptimal and recommendations to discontinue or to modify therapy were provided not only in the antimicrobial stewardship program electronic form, but also face to face during clinical rounds or by phone in specific cases. Surgical teams received electronic and face-to-face recommendations every working day, and the rest of the departments received antimicrobial stewardship program recommendations weekly or twice a week. Acceptance of antimicrobial stewardship program recommendations was at the prescribers' discretion.

No preprescription authorization was implemented, but prescription filters for selected antimicrobial agents (meropenem, linezolid, teicoplanin, colistin, liposomal amphotericin B, itraconazole, voriconazole, posaconazole, micafungin, ganciclovir, cidofovir, valganciclovir, and foscarnet) were incorporated in the e-prescription system, making it necessary for the prescriber to specify the indication.

In parallel with the PPRF, an antimicrobial resistance awareness campaign based on posters and informative capsules was conducted, and a pocket hospital guide on antimicrobial prescription was distributed. To simplify the prescription process and to ensure the right dosing and duration, some preset protocols with automatic calculation of dosing according to patient weight for the most common procedures or diagnoses were included in the e-prescription program (**Appendix 2**; available at www.jpeds.com).

In addition, the antimicrobial stewardship program team organized monthly meetings to discuss protocols and specific aspects of antimicrobial use with the different medical and surgical teams and to share antimicrobial quality of prescription data.

Study Design

Two studies were conducted simultaneously from January 2017 onward.

Study 1. A pre-post study comparing antimicrobial use between the control period (2015-2016) and the intervention period (2017-2018). Owing to software limitations, data on antimicrobial use in the PICU and operating rooms were not available for this particular analysis. Antivirals and other pharmacy-compounded antimicrobial agents were not included. Systemic antibacterial and antifungal administration data were extracted from the e-prescription program and were expressed as DOT/100 days present. DOT was totaled for each month and then standardized to 100 days present using total days present for all admissions in a given

month, irrespective of antimicrobial administration. Person-time was calculated by subtracting hour and date-time of room exit from hour and date-time of room entry. Duplicated room entries were excluded. An individual patient counted 1 day present on each calendar day; between-unit transfers did not result in double counting.

Study 2. In 2017 and 2018, the quality of prescription of systemic antibacterials, antifungal agents, and antivirals was evaluated by means of 8 quarterly cross-sectional point-prevalence surveys (PPS). These PPS were conducted during the last week of the quarter in all admitted patients in all units, including PICU, with any active systemic antimicrobial prescription at 8:00 a.m. on the day of the survey. Prescribers were not aware of the PPS. The percentages of optimal and nonoptimal prescriptions were assessed and compared based on the department in charge, the intention of the prescription (empirical treatment, targeted treatment, or prophylaxis), the reason for treatment (community-acquired infections, nosocomial infections, and suspicion of infection in immunosuppressed patients), and the previously described reasons for nonoptimal prescription.

Complementary and Balancing Measures

Total hospital LOS, complexity-adjusted readmission rates, and complexity-adjusted in-hospital mortality rates according to national reference systems, cost of systemic antimicrobial agents based on the hospital expenditure data, and antimicrobial resistance rates were included as complementary outcomes of the PROA-SJD antimicrobial stewardship program. Antimicrobial resistance rates were obtained from the annual report of the local microbiology department, and included data on extended-spectrum β-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae*, quinolone-resistant urinary *E coli*, amoxicillin-clavulanate-resistant *E coli*, third-generation cephalosporin-resistant *Enterobacter*, carbapenemase-producing Enterobacteriaceae, meropenem-resistant *Pseudomonas aeruginosa*, extensively drug resistant *P aeruginosa*, multidrug resistant *Acinetobacter baumannii*, vancomycin-resistant *Enterococcus*, and methicillin-resistant *Staphylococcus aureus* isolation rates.[24]

Statistical Analyses

Statistical analysis was carried out using SPSS version 25.0 software (IBM Corp., Armonk, New York) and "R" software (R Development Core Team 2013. R: A language and environment for statistical computing, R Foundation for Statistical Computing, Vienna, Austria). Categorical variables are reported as proportions with 95% CIs, and continuous variables as means with SD or as medians with IQRs. Antimicrobial use before (2015-2016) and after (2017-2018) antimicrobial stewardship program implementation were compared with the Welch t test, and the change in antibacterial and antifungal use trend was assessed using interrupted time-series (step change model) analysis (Study 1). A χ^2 test and Fisher exact test were used to compare the quality of prescription in PPS (Study 2). Statistical significance was defined as a P value of less than .05.

This study was approved by Sant Joan de Déu Research Foundation Ethics Committee (ref. 32-20), which granted a waiver of the individual's informed consent. The research was conducted in accordance with the Declaration of Helsinki and national and institutional standards.

Results

During the 2017-2018 period, 5626 prescriptions corresponding with 50 different antimicrobial agents and with 3210 admissions of 2887 patients underwent PPRF in the antimicrobial stewardship program electronic form after a median time of 2.4 days (IQR, 1.5-3.6 days) from the first administration (Table I).

Study 1

In an interrupted time series analysis, total antimicrobial use and antibacterial use significantly decreased during the intervention period (2017-2018) as compared with 2015-2016 (Figure 1, A and B), and total antifungal use remained stable (Figure 1, C). The use of the parenteral route also declined after antimicrobial stewardship program implementation ($P < .001$). Antibacterial use also decreased in absolute values (median, 65.62 DOT/100 [95% CI, 63.56-67.68 DOT/100] in 2017-2018 vs 68.37 DOT/100

Table I. Characteristics of the 5626 prescriptions that underwent PPRF in patients' electronic clinical charts by the PROA-SJD antimicrobial stewardship program during 2017-2018

Characteristics	No. (%)
Department of the prescriber	
Surgical	1843 (32.7)
Hemato-oncology	1035 (18.4)
PICU	797 (14.2)
Neonatology	371 (6.6)
Other medical departments	1580 (28.1)
Type of antimicrobial	
Antibacterial	5135 (91.3)
Antifungal	335 (5.9)
Antiviral	156 (2.8)
Route of administration	
Parenteral (intravenous or intramuscular)	4607 (81.9)
Oral	1019 (18.1)
Intention of prescription	
Prophylactic	1580 (28.1)
Surgical	1058 (67.0)
Medical	522 (33.0)
Therapeutic	3945 (70.1)
Empirical	3276 (83.0)
Targeted	669 (17.0)
Not recorded/unknown	91 (1.6)
Other	10 (0.2)
Reason for therapeutic prescription (n = 3945)	
Community-acquired infection	2472 (62.7)
Nosocomial infection	969 (24.5)
Suspicion of infection in immunosuppressed patient	504 (12.8)
Classification of prescription	
Optimal	4435 (79.3)
Nonoptimal*	1039 (18.7)
Unclassified	152 (2.0)

*Reasons to classify a prescription as nonoptimal were distributed as follows (>1 reason applies for a single prescription): inadequate treatment duration, n = 479 (46.1%); not local guidelines first-choice antimicrobial, n = 252 (24.2%); inadequate spectrum, n = 227 (21.8%); dosing issues, n = 226 (21.7%); and lack of antimicrobial indication, n = 171 (16.5%).

[95% CI, 66.79-69.95 DOT/100] days present in 2015-2016; $P = .044$). Antimicrobial use in DOT/100 days present for all analyzed agents is summarized in **Table II**. Significant decreases in antimicrobial use were observed for amikacin, piperacillin-tazobactam, and meropenem; vancomycin and teicoplanin; cefazolin, the antibacterial of choice for surgical prophylaxis in most cases; and most antibacterials used in the treatment of community-acquired infections. Conversely, cefoxitin and ceftriaxone use increased after their inclusion as first-choice antibacterial for noncomplicated and complicated intra-abdominal infections, respectively, the latter in combination with metronidazole. Ciprofloxacin and cotrimoxazole prophylactic use also increased, mainly in children with immunosuppressive conditions, a growing group of patients in our institution. Global antifungal use rose (4.94 DOT/100 [95% CI, 4.24-5.64 DOT/100] vs 6.62 DOT/100 [95% CI, 6.04-7.21 DOT/100] days present; $P < .001$),

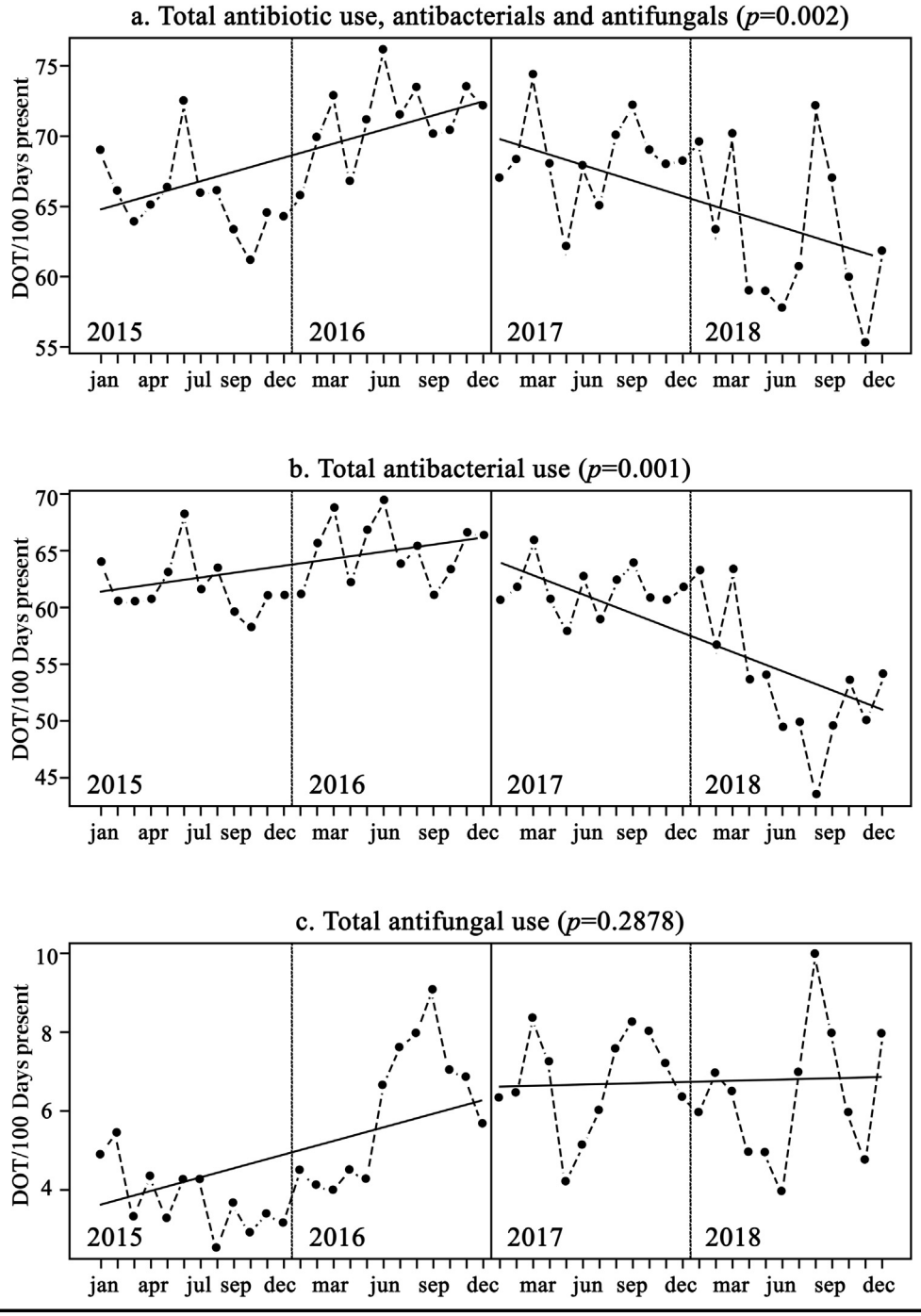

Figure 1. Antimicrobial use in DOT/100 days present over time. Continuous lines represent the tendency in antimicrobial use over time.

Table II. Antimicrobial use in DOT per 100 days present (DOT/100 days present)*

Drugs	Period	Median	95% CI	*P* value	Increase/decrease in use
Antibacterials and antifungals (all)	2015-2016	68.37	66.79-69.95	**.044**	Decrease
	2017-2018	65.62	63.56-67.68		
Parenteral route	2015-2016	50.52	47.85-53.21	**<.001**	Decrease
	2017-2018	44.18	41.83-47.91		
Antibacterials (all)	2015-2016	63.43	62.20-64.67	**<.001**	Decrease
	2017-2018	57.47	55.11-59.83		
Amikacin	2015-2016	0.95	0.81-1.08	**.044**	Decrease
	2017-2018	0.73	0.58-0.88		
Amoxicillin	2015-2016	3.44	2.49-4.40	.921	
	2017-2018	3.51	2.77-4.24		
Amoxicillin-clavulanate	2015-2016	13.49	12.91-14.08	**.002**	Decrease
	2017-2018	11.84	11.04-12.64		
Ampicillin	2015-2016	3.67	3.36-3.99	**.002**	Decrease
	2017-2018	3.04	2.82-3.25		
Azithromycin	2015-2016	1.42	1.11-1.73	**.026**	Decrease
	2017-2018	1.93	1.63-2.22		
Cefazoline	2015-2016	2.90	2.66-3.14	**<.001**	Decrease
	2017-2018	1.75	1.58-1.93		
Cefotaxime	2015-2016	2.44	2.21-2.69	**.001**	Decrease
	2017-2018	1.89	1.69-2.10		
Cefoxitin	2015-2016	1.02	0.68-1.35	**.011**	Increase
	2017-2018	1.55	1.36-1.73		
Ceftazidime	2015-2016	0.80	0.59-1.02	.748	
	2017-2018	0.84	0.69-1.01		
Ceftriaxone	2015-2016	3.67	3.37-3.97	**.027**	Increase
	2017-2018	4.16	3.86-4.45		
Ciprofloxacin	2015-2016	1.11	0.89-1.32	**.016**	Increase
	2017-2018	1.57	1.28-1.86		
Clarithromycin	2015-2016	1.01	0.81-1.21	**<.001**	Decrease
	2017-2018	0.31	0.20-0.43		
Clindamycin	2015-2016	1.08	0.88-1.26	**.007**	Decrease
	2017-2018	0.75	0.63-0.87		
Cloxacillin	2015-2016	1.03	0.87-1.19	.886	
	2017-2018	1.05	0.92-1.17		
Cotrimoxazole	2015-2016	3.98	3.68-4.28	**<.001**	Increase
	2017-2018	4.80	4.53-5.08		
Gentamycin	2015-2016	2.34	2.11-2.57	**<.001**	Decrease
	2017-2018	1.62	1.42-1.82		
Linezolid	2015-2016	0.40	0.29-0.52	.122	
	2017-2018	0.29	0.22-0.36		
Meropenem	2015-2016	6.38	5.94-6.81	**.019**	Decrease
	2017-2018	5.68	5.32-6.03		
Metronidazole	2015-2016	1.71	1.51-1.92	.799	
	2017-2018	1.66	1.35-1.97		
Piperacillin-tazobactam	2015-2016	3.02	2.64-3.40	**<.001**	Decrease
	2017-2018	1.68	1.29-2.07		
Teicoplanin	2015-2016	0.60	0.48-0.72	**<.001**	Decrease
	2017-2018	0.33	0.26-0.41		
Vancomycin	2015-2016	4.97	4.60-5.34	**.006**	Decrease
	2017-2018	4.23	3.89-4.57		
Antifungals (all)	2015-2016	4.94	4.24-5.64	**<.001**	Increase
	2017-2018	6.62	6.04-7.21		
Amphotericin-B lipid complex	2015-2016	0.97	0.71-1.23	.089	
	2017-2018	0.69	0.52-0.86		
Fluconazole	2015-2016	1.09	0.81-1.38	**<.001**	Increase
	2017-2018	2.76	2.41-3.16		
Itraconazole	2015-2016	0.12	0.03-0.22	**<.001**	Increase
	2017-2018	0.63	0.42-0.84		
Mycafungin	2015-2016	1.00	0.50-1.49	.777	
	2017-2018	0.91	0.65-1.18		
Posaconazole	2015-2016	0.24	0.09-0.40	**<.001**	Increase
	2017-2018	0.63	0.50-0.76		
Voriconazole	2015-2016	1.49	0.21-1.76	**<.001**	Decrease
	2017-2018	0.82	0.59-1.04		

*Antimicrobial drugs with a use of <0.4 DOT/100 days present in both periods are not shown.
Significant changes in antimicrobial use are presented in bold.

owing to increases in the use of fluconazole, itraconazole, and posaconazole related to protocol changes and a local outbreak of *Aspergillus flavus* invasive infection (Table II).

Study 2

Overall, 938 prescriptions (corresponding with 623 patients) were evaluated in the 8 quarterly PPS conducted during 2017

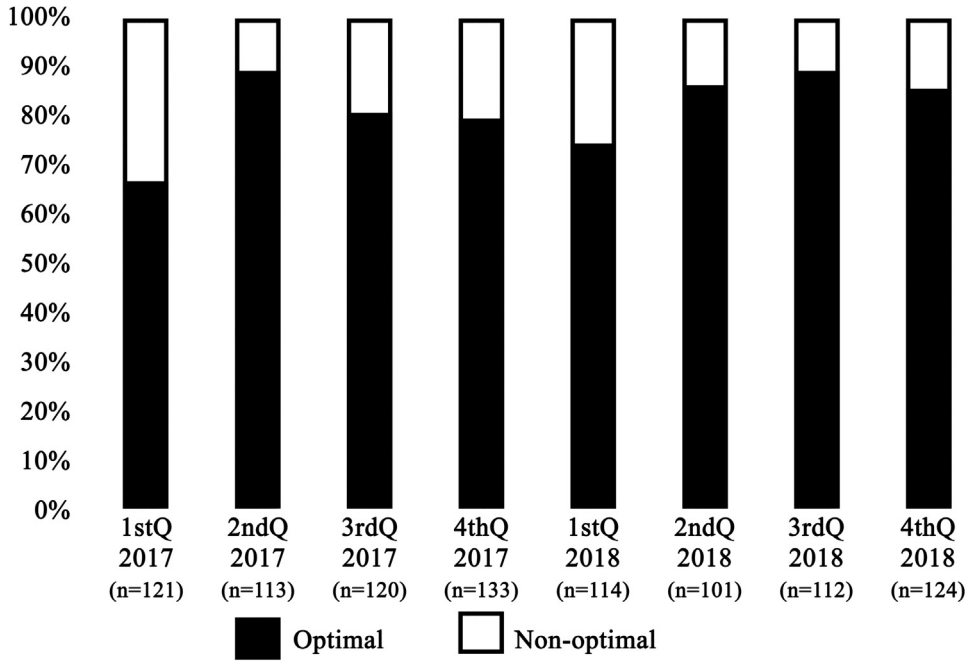

Figure 2. Distribution of optimal and nonoptimal antimicrobial prescriptions in the 8 quarterly PPS conducted during 2017 and 2018.

and 2018. The mean prevalence of use of any antimicrobial among inpatients was 39.0% ± 5.0%; 88.3%, 6.7%, and 5.0% of the evaluated prescriptions corresponded to systemic antibacterials, antifungal agents, and antivirals, and they were administered by parenteral or enteral route in 69.5% and 30.5% of cases, respectively. An increasing albeit nonsignificant trend in the rate of optimal prescriptions was observed after the first PPS ($P = .0898$; **Figure 2**).

Nonoptimal prescriptions (n = 132 [14.4%]) were more common in surgical departments (37.4% vs 8.5% in medical departments; $P < .001$), in antibacterial prescriptions with prophylactic intention (24.2% vs 11.3% in therapeutic regimens; $P < .001$), and in empirical treatment (13.0% vs 6.3% in targeted treatment; $P = .002$). No differences were observed according to the reason for treatment.

The highest rate of nonoptimal prescriptions (47.6%) was observed owing to the use of antibacterial prophylaxis in surgical patients during the postoperative period. The most frequent reasons for prescriptions being considered nonoptimal were excessive treatment duration (39.4%), lack of antimicrobial indication (22.7%), dosing issues (21.2%), not a first-choice antimicrobial according to local guidelines (21.2%), and inadequate spectrum (18.2%).

Complementary and Balancing Measures

No significant changes were observed in hospital mean LOS (4.5, 4.6, 4.5, and 4.5 days in 2015, 2016, 2017, and 2018, respectively), readmission rates (0.8, 0.8, 0.8, and 0.7), or in-hospital mortality rates (0.6, 0.5, 0.4, and 0.5) between the 2 study periods. Global hospital expenditure in antibacterials and antifungal agents decreased by a total of 64 406 Euros in 2017 and 137 574 Euros in 2018 as compared with the 2015-2016 mean expenditure (463 322 Euros), for an absolute savings of 201 980 Euros.

The rates of selected community- or nosocomial-acquired antimicrobial-resistant organisms that were isolated remained stable after PROA-SJD antimicrobial stewardship program implementation (**Table III**; available at www.jpeds.com). Only a decrease in multidrug resistant *P aeruginosa* isolates and increases in amoxicillin-clavulanate resistant *E coli* and fluoroquinolone-resistant urinary *E coli* isolates were observed.

Discussion

Reports on antimicrobial stewardship program performance in pediatric inpatients in the European healthcare setting remain scarce compared with the US healthcare setting.[16,25] In contrast with most previous pediatric reports, our antimicrobial stewardship program implemented 2 core strategies simultaneously, namely, interaction and feedback between an infectious disease physician and the prescriber and preauthorization requirements for specific agents. We were able to provide antimicrobial use data over time, but also healthcare costs, safety, and antimicrobial resistance outcomes. Our results confirm that antimicrobial stewardship programs successfully decrease antimicrobial use in pediatric inpatients.[3,5,12-14,16] Variations in the metrics used to evaluate their impact preclude direct comparisons between studies.[5,10,15,19]

Aiming to obtain accurate antimicrobial use data, we calculated DOT based on administered doses and patient exposure in days present.[3,10,13] E-prescription systems in healthcare centers should be able to provide such information, rather than mere dispensation and purchasing data that do not exactly reflect the amount of the drug the patient has actually received. The critical role of support from computer, statistics, and hospital management teams should

not be overlooked when planning antimicrobial stewardship program implementation.[4,13]

During the intervention period, we observed a decrease in global antimicrobial use owing to the decrease in antibacterial use, but not in antifungal use. The former was not associated with changes in LOS, a surrogate marker of the complexity and severity of admitted patients, or readmission or mortality rates.[3,11] Variations in antimicrobial use can be influenced by multiple factors (ie, infection outbreaks, protocol changes, drug shortages) that are often difficult to control, as happened in our case with antifungal use. The use of most broad-spectrum antipseudomonal agents significantly decreased without a significant rebound in the use of other drugs. The use of postoperative antibacterials in surgical wards also diminished, as shown by the decrease in cefazolin DOT, the antimicrobial prophylaxis of choice for most of the routine surgical procedures in our center, although the duration of postoperative antimicrobial prophylaxis still exceeded the recommended duration in current surgical guidelines.[26-28]

The optimal endpoint to assess the efficacy of ASPs, ideally a clinical one, remains to be determined.[11,19,22,29-31] Currently available evidence about antimicrobial stewardship program quality indicators' applicability and use in pediatrics remains scarce.[32,33] Objective, standardized, and easy-to-obtain quality indicators that focus on clinical outcomes of the most common clinical scenarios in which antibiotics are used in children are needed.

The mean antimicrobial prescription rates for hospitalized children remained stable at 39% during the study period, similar to other pediatric centers, and to the GLOBAL-PPS study (40.7%) that included data from 335 hospitals in 53 countries.[34-39] Few reports have described the optimal rates of antibiotic prescription in pediatric hospitals, with adherence to local guidelines being the most commonly used indicator.[34,38] We observed an improvement in quality of prescription after the first PPS of borderline significance. The high quality of prescription rate at antimicrobial stewardship program implementation (76%) and the short follow-up time may partially explain the lack of statistical significance. Unnecessarily prolonged antibiotic prophylaxis, and medical and surgical antimicrobial prescriptions had already been previously identified as being among the potential antimicrobial stewardship program targets to benefit most from this program.[23,25]

One of the ultimate goals of antimicrobial stewardship program is to decrease antimicrobial resistance rates. A decrease in infections caused by multidrug resistant bacteria upon antimicrobial stewardship program implementation has been reported in children in adult studies, a secondary decrease in mortality has also been observed.[40-42] The impact of antimicrobial stewardship program on antimicrobial resistance is often not seen in the short term, so long-term monitoring of antimicrobial resistance is critical.[42] We did not observe major changes in antimicrobial resistance rates after antimicrobial stewardship program implementation. Both the low prevalence of resistant pathogens at baseline in our hospital and the short follow-up period may explain these findings. Nevertheless, some of the minor changes in antimicrobial resistance rates we observed deserve further comment. A small increase in the use of ciprofloxacin was observed during the intervention period, from 1.11 to 1.57 DOT/100 days present, in parallel with increasing rates of fluoroquinolone-resistant urinary *E coli* isolates. It is likely that these findings are related, because the consumption of quinolones has been associated with the development of different mechanisms of quinolone resistance in gram-negative bacteria.[43] This finding emphasizes the importance of multifaceted and continuous antimicrobial stewardship program activities and discourages the exclusion of drugs from the scope of monitoring based exclusively in quantitative use criteria.

Financial savings are also a known consequence of antimicrobial stewardship program, directly owing to the reduction in antimicrobial expenditure, but also indirectly to the avoidance of infections by resistant microorganisms, the shortening of LOS, and the decrease in nursing time needed to administer intravenous antimicrobial agents.[11,14] Institutional support needs to be translated into human and technical resources to set up an antimicrobial stewardship program.[11,19,24]

Our study has several limitations. Complementary antimicrobial use metrics were not performed, so the possibility of having favored the use of less antimicrobial agents (even of broader spectrum) or the underestimation of antimicrobial exposure inherent to DOT in patients with renal impairment should be borne in mind when interpreting our results.[15,20,44] Also, by using days present, the denominator could be up to one-third higher than patient-days, causing antimicrobial use estimates to be lower with days present as compared with patient-days.[21] A longer follow-up is necessary to adequately evaluate the changes we observed and to clarify whether they are also part of periodic variations in antimicrobial use and prescription patterns. Other factors potentially affecting antimicrobial use and quality of prescription, such as protocol changes within a particular unit or variations in medical staff, were not considered. Owing to limitations of the prescription systems in the PICU and in operating rooms during the study period, antimicrobial use data from these areas could not be analyzed. Therefore, total antimicrobial use data are probably underestimated because preincisional antibiotic prophylaxis is indicated in about 60% of pediatric interventions and antibiotics are massively used in the ICUs.[45,46] Finally, professional satisfaction after antimicrobial stewardship program implementation was not quantified. The acceptance of prescribers is essential to achieving better results.[18]

A PPRF-based antimicrobial stewardship program safely decreased antimicrobial use during the initial 2 years of implementation in a referral children's hospital. A trend toward improvement in quality of prescription was also observed. To allow comparisons between studies and benchmarking, the most adequate metrics and end points to evaluate the impact of antimicrobial stewardship program interventions in pediatrics need to be identified. ■

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50 Years Ago in *The Journal of Pediatrics*

Neonatal Seizures: 50 Years of Progress

Freeman JM. Neonatal seizures–diagnosis and management. J Pediatr 1970;77:701-8.

One-half century ago, John Freeman presented in *The Journal* a review of neonatal seizures, listing the major causes, presentations, diagnostic approaches, and treatments of the different etiologies. A high initial mortality of about 40% after neonatal seizures in 2 unselected and 25% in 1 selected series was found. Intracranial hemorrhage accounted for approximately 50% of deaths, both in children born at term and preterm at the time, and accounted for 60%-80% of postmortem identified causes of seizure-related deaths. In a series of deaths excluding preterm infants, 20% were due to birth trauma and anoxia. In the current literature, mortality has decreased to approximately 20%.[1] The list of etiologies for neonatal seizures still encompasses the same causes as it did 50 years ago. Hypoxic-ischemic encephalopathy is now the most common reason in the term, and intraventricular hemorrhage in the preterm neonate. However, routine cranial ultrasound examination was not introduced in the neonatal intensive care unit until around 1980, and the latter would therefore likely have been diagnosed post mortem 50 years ago. There is a greater chance of both identifying and treating infants with hypoxic-ischemic encephalopathy today. There is a much better understanding of the metabolic causes of seizures today, and the field of genetics has identified several genetic epilepsy syndromes accounting for approximately 15% of all seizures in the neonatal population, with specific presentations and treatment options.[2] The higher rate of diagnosed seizures today is, to a large extent, due to the introduction of the amplitude integrated electroencephalogram, and the more widespread use of a full electroencephalogram with simultaneous video recordings. Reading Freeman's review reminds us of the immense progress that has been made in the field of neonatal seizures in the last 50 years, and also the fact that we still have neither the optimal diagnostic tools nor the optimal treatment options for this group of patients.

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Table III. Rates of selected community- and nosocomial-acquired antimicrobial-resistant organisms that were isolated during the study period

	2015-2016	2017-2018	*P* value
ESBL producing *E coli*	6.0 (14/233)	8.9 (21/236)	.233
ESBL producing *K pneumoniae*	15.5 (16/103)	14.7 (15/102)	.869
FQR *E coli* (urinary)	21.7 (20/92)	35.2 (32/91)	**.044**
AMCR *E coli*	16.3 (38/233)	23.7 (56/236)	**.045**
C3GR *Enterobacter spp* (AmpC gene)	27.9 (38/136)	24.3 (25/103)	.523
Carbapenemase producing Enterobacteriaceae	0.4 (2/545)	0.7 (0/610)	.499
Meropenem resistant *Pseudomonas aeruginosa*	10.5 (14/181)	7.9 (12/151)	.943
MDR *Pseudomonas aeruginosa*	11.1 (20/181)	4.6 (7/151)	**.033**
XDR *Pseudomonas aeruginosa*	0 (0/181)	0.7 (1/151)	.891
Meropenem resistant *Acinetobacter baumannii*	0 (0/12)	0 (0/8)	.803
VRE	1.2 (1/85)	0 (0/90)	.962
MRSA	15.7 (46/293)	18.7 (59/316)	.332

AMCR, amoxicillin/clavulanate resistant; *C3GR*, third-generation cephalosporin resistant; *ESBL*, extended-spectrum β-lactamase; *FQR*, fluoroquinolone resistant; *MDR*, multidrug resistant; *MRSA*, methicillin-resistant *Staphylococcus aureus*; *VRE*, vancomycin resistant *Enterococcus faecium*; *XDR*, extensively drug resistant.
Data are shown as % (resistant strains/total strain isolations).