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Antimicrobial Stewardship in Pediatric Intensive Care Unit

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ABSTRACT

Background

In hospitalized critically ill children both antimicrobial consumption and prevalence of multidrug resistant bacteria is higher than other pediatric inpatients, increasing the need for development and implementation of Antibiotic Stewardship Programs (ASPs). In this study, we aimed to identify studies implementing ASPs in Pediatric Intensive Care Units (PICUs) and analyze their strategy, structure, implementation and outcome metrics.

Methods

PUBMED was searched for studies reporting interventions for judicious use of antimicrobials in a PICU setting and published after 2006. Only studies that reported at least one outcome on antimicrobial use were included. Studies that applied ASPs throughout the hospital were included only if they reported separate results for PICUs. A checklist tool was created to assess the strategy of intervention, the structure of ASP team, the implementation and outcomes in all eligible studies.

Results

From 854 records found, 21 full text articles were reviewed and 11 of them were finally included in the analysis: 9 that applied ASP in PICUs and 2 that applied ASP at the hospital level, but with separate results for PICU. All PICU-dedicated ASPs applied a multi-modal intervention combining two or more strategies simultaneously; audit with feedback (6/9 studies) and facility-specific clinical practice guidelines (6/9 studies) were the most common strategies. A multidisciplinary team was formulated in all ASPs except for two that implemented biomarker-based interventions. Six out of 9 studies included techniques to enhance behavior change and 1 ASP implemented a behavior-based intervention. Antibiotic consumption was evaluated in all ASPs, cost in 3/9, antibiotic resistance in 1/9, length of hospitalization in 6/9 and mortality in 7/9. All hospital-wide ASPs used audit with feedback from a multidisciplinary team as a core strategy in addition to the implementation of facility-specific clinical practice guidelines and assessed antimicrobial consumption, expenditures, length of stay and mortality.

Conclusion

The prevalence of ASPs in pediatric settings is limited and few of the existing programs follow all Infectious Diseases Society of America recommendations. This overview of pediatric ASPs provides a benchmark to measure the implementation of new programs in the future.

Keywords: Antibiotic stewardship program, Pediatric intensive care unit, Pediatrics, Antimicrobials, Checklist tool, Intervention, antibiotic consumption, Compliance.

INTRODUCTION

Antimicrobial agents are the most commonly prescribed medicines in the pediatric population, with one third of hospitalized children receiving at least one antimicrobial. In hospitalized critically ill

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children both the total antimicrobial consumption and the proportion of antimicrobials with broad spectrum (61.3%) are much higher than in other pediatric inpatients [1,2]. In hospitalized pediatric patients, up to 10% of antibiotic prescriptions have been assessed as inappropriate and 5% as given without any obvious reason when evaluated by a pediatric infectious disease specialist [3].

Inappropriate and excessive antibiotic use has been clearly associated with emergence of antimicrobial resistance, a major global public threat. Antimicrobial resistance has also been spread in pediatric health care settings causing prolonged hospitalizations, treatment failures, significantly increased morbidity, mortality and healthcare cost [4-7]. Children in intensive care facilities are at higher risk for having infections caused by antimicrobial resistant bacteria [8,9].

Development of Antibiotic Stewardship Programs (ASPs) is one of the strategies for prevention and management of emergence of antimicrobial-resistant organisms [10,11]. Current reviews on pediatric ASPs give a great insight for both inpatient and outpatient settings [12-14]. However, critically ill children significantly differ from other inpatients in terms of disease severity, prevalence of multidrug resistant bacteria and pharmacokinetic/pharmacodynamic characteristics. To our knowledge, there is no review focusing on antimicrobial stewardship for critically ill children and Pediatric Intensive Care Units (PICUs). The aim of the present study is to review current literature on antimicrobial stewardship interventions in PICUs and analyze the strategies, structure, implementation and outcomes of the ASPs.

MATERIALS AND METHODS

We searched for studies published from January 1 2007 to May 31 2020 in PUBMED database using the search terms "antimicrobial stewardship AND pediatrics" and "antimicrobial stewardship AND pediatric intensive care units". We searched for studies published after 2006, because the guidelines for the organization of ASPs were first described that year by Infectious Diseases Society of America (IDSA) [10].

In this review, studies were included if they described an intervention for judicious use of antimicrobials in a PICU setting. Studies that did not specialize in PICU were excluded. Studies that included interventions implemented both in PICUs and other settings were included only if they reported separate results for intervention in the PICU. Studies were included only if they reported at least one outcome on antimicrobial use.

A checklist dedicated for PICUs was developed in order to assess the strategy of intervention, the structure of the team that worked on it, the implementation and the outcome (Figure 1).

Study	Intervention: ASP core strategy & activities: Audit and feedback	Pre-authorization	Didactic Education	Facility specific Clinical Practice Guidelines	Target specific infectious disease syndromes	Prescriber-led Review of appropriateness	CDS= Computerized Clinical Decision Support systems	Diagnostics: Stratified Antibiogram	Selective or cascade reporting of antimicrobials	Rapid Viral diagnostics for respiratory pathogens	Rapid diagnostics on blood	Procalcitonin	Optimization: Pharmacokinetic adjustment programm	Iv to Oral	Allergy assessment	Shortest Effective Duration	Other: Restriction of specific antimicrobial agents
Aizawa et al., 2018	✓	✓[2]							✓[3]	✓	✓		✓				
Jones et al., 2019	✓[1]			✓		✓											✓[5]
Downes et al., 2018			✓	✓	✓		✓				✓	✓[4]				✓	
Lee et al., 2016	✓[1]		✓	✓	✓												
Bobillo-Perez et al., 2019											✓	✓				✓	
Haque et al., 2018	✓					✓										✓	
Ding et al., 2007		✓[2]	✓	✓												✓	
Murni et al., 2015	✓[6]		✓	✓	✓												
Stocker et al., 2012	✓[7]			✓		✓										✓	

Study	Structure/ASP core personnel	Workflow/FTE	Implementation/Strategy
Aizawa et al., 2018	PID physician, pharmacists, microbiologists, clerks	ASP team was available any time of the day No FTE reported	
Jones et al., 2019	PICU consultant, microbiologist, antimicrobial pharmacist, medical and nursing staff, project management personnel	Daily meetings between PICU consultants and ASP team No FTE reported	Positive feedback delivered to HCP via an electronic system, appreciative HCP interviews, driver diagram, weekly meetings of the ASP team
Downes et al., 2018	Biomarker-based intervention, ASP team[8]	No FTE reported	Reminder emails, screensavers with the algorithm
Lee et al., 2016	ASP pharmacist, PID physician	1 FTE ASP pharmacist and 0.5 FTE ASP physician	Informational emails, posters with guidelines
Bobillo-Perez et al., 2019	Biomarker-based intervention without dedicated ASP team	No FTE reported	
Haque et al., 2018	Paediatric intensivist, critical care pharmacist specially trained in ASP,PID physician	Discussion during morning rounds No FTE reported	
Ding et al., 2007	No dedicated ASP team	No FTE reported	
Murni et al., 2015	Doctors, nurses, allied workers at the PICU ward	No FTE reported	Reminder emails, providing educational materials
Stocker et al., 2012	PICU physicians, pharmacists, nurses	No FTE reported	Checklists

Study	Outcome: Antimicrobial use/ consumption: DOT	Doses per Picu day	Antimicrobial prescription rate	Antimicrobial treatment Days	Antibiotic free days	Rate of de-escalation	Antimicrobial courses	LOT	Appropriateness	Expenditures: Antimicrobial cost	Healthcare cost	Resistance: Antimicrobial Resistance	Patient Safety: Mortality	Days of Hospitalization	PICU readmissions	Infection relapse rate	Length of stay	Infection rate
Aizawa et al., 2018	↓[9]												<->[10]		<->		<->	
Jones et al., 2019		↓[11]							↑[12]				<->				<->	<->
Downes et al., 2018	↓[13]							<->[13]									<->	
Lee et al., 2016	↓[14]								↑	↓[15]			<->				<->	
Bobillo-Perez et al., 2019			↓	↓	↑	↑[16]							<->			<->	<->	<->
Haque et al., 2018	↓[17]								↑[18]	↓			<->					
Ding et al., 2007			↓[19]					<->	↑[20]	↓		↓					<->	
Murni et al., 2015			<->						↑[21]				↓					↓
Stocker et al., 2012							<->		↑[22]				<->[23]	<->		<->		

Figure 1: PICU-dedicated ASPs.

Both IDSA guidelines for implementing antimicrobial stewardship programs and the Driving reinvestment in research and development and responsible antibiotic use (DRIVE-AB) were used for identifying key indicators, customized for PICUs [10,14]. Studies were further classified as a) ASP dedicated to PICUs (designed, implemented for PICUs) and b) hospital-wide ASP including PICU-specific implementations and outcomes.

RESULTS

A total of 854 records were found using our research methodology. Twenty-six full text articles were reviewed by two independent researchers (VK and EC) and 11 of them were finally included in the analysis (Figure 2).

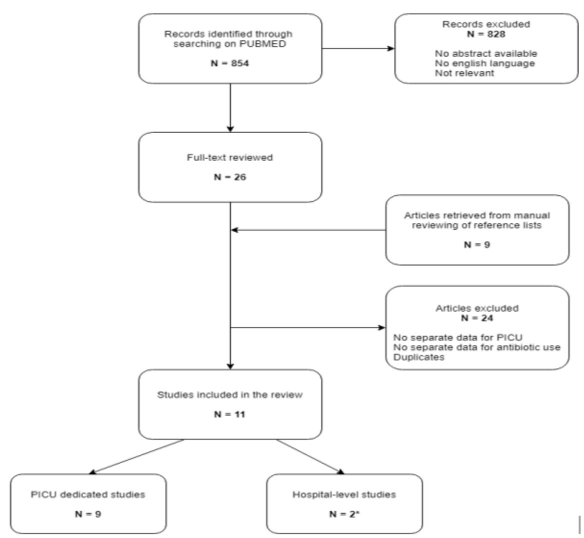

Figure 2: Flowchart of the study selection process.

Nine studies implemented dedicated ASPs for PICU. One of them was conducted in both pediatric, neonatal and cardiac ICU's, but both the intervention and the outcomes were assessed separately in each ICU and thus we decided to describe it with the ASPs dedicated to PICUs. Two studies included ASP implemented at hospital level and presented separate results for the antimicrobial consumption in the PICU setting. These studies were classified as hospital-wide ASPs and were analyzed separately. One of these ASPs was described in three different papers, thus all of them were included.

All studies were single centered, 3 of them conducted in Europe, 4 in the United States and 4 in Asia. Eight antimicrobial stewardship interventions were implemented in high-income countries, two in upper middle-income countries and one in a lower middle-income country as defined by the World Bank in July 2020 [15,16]. In terms of study design, five studies used a before-and-after design, five studies used an interrupted time series methodology and one used control charts to evaluate the weekly impact of the ASP (Figure 3)

Study	Intervention: ASP core strategy & activities							Diagnostics					Optimization				Other
	Audit and feedback	Pre-authorization	Didactic Education	Facility specific Clinical Practice Guidelines	Target specific infectious disease syndromes	Prescriber-led Review of appropriateness	CDS=Computerized Clinical Decision Support systems	Stratified Antibiogram	Selective or cascade reporting of antimicrobials	Rapid Viral diagnostics for respiratory pathogens	Rapid diagnostics on blood	Procalcitonin	Pharmacokinetic adjustment programm	Iv to Oral	Allergy assessment	Shortest Effective Duration	Restriction of specific antimicrobial agents
Aizawa et al., 2018	✓	✓[2]							✓[3]	✓	✓		✓				
Jones et al., 2019	✓[1]			✓		✓											✓[5]
Downes et al., 2018			✓	✓	✓		✓				✓	✓[4]				✓	
Lee et al., 2016	✓[1]		✓	✓	✓												
Bobillo-Perez et al., 2019											✓	✓				✓	
Haque et al., 2018	✓					✓										✓	
Ding et al., 2007		✓[2]	✓	✓												✓	
Murni et al., 2015	✓[6]		✓	✓	✓												
Stocker et al., 2012	✓[7]			✓		✓										✓	

Study	Structure/ASP core personnel	Workflow/FTE	Implementation/Strategy
Aizawa et al., 2018	PID physician, pharmacists, microbiologists, clerks	ASP team was available any time of the day No FTE reported	
Jones et al., 2019	PICU consultant, microbiologist, antimicrobial pharmacist, medical and nursing staff, project management personnel	Daily meetings between PICU consultants and ASP team No FTE reported	Positive feedback delivered to HCP via an electronic system, appreciative HCP interviews, driver diagram, weekly meetings of the ASP team
Downes et al., 2018	Biomarker-based intervention, ASP team[8]	No FTE reported	Reminder emails, screensavers with the algorithm
Lee et al., 2016	ASP pharmacist, PID physician	1 FTE ASP pharmacist and 0.5 FTE ASP physician	Informational emails, posters with guidelines
Bobillo-Perez et al., 2019	Biomarker-based intervention without dedicated ASP team	No FTE reported	
Haque et al., 2018	Paediatric intensivist, critical care pharmacist specially trained in ASP, PID physician	Discussion during morning rounds No FTE reported	
Ding et al., 2007	No dedicated ASP team	No FTE reported	
Murni et al., 2015	Doctors, nurses, allied workers at the PICU ward	No FTE reported	Reminder emails, providing educational materials
Stocker et al., 2012	PICU physicians, pharmacists, nurses	No FTE reported	Checklists

Study	Outcome: Antimicrobial use/ consumption									Expenditures		Resistance	Patient Safety					
	DOT	Doses per Picu day	Antimicrobial prescription rate	Antimicrobial treatment Days	Antibiotic free days	Rate of de-escalation	Antimicrobial courses	LOT	Appropriateness	Antimicrobial cost	Healthcare cost	Antimicrobial Resistance	Mortality	Days of Hospitalization	PICU readmissions	Infection relapse rate	Length of stay	Infection rate
Aizawa et al., 2018	↓[9]												<->[10]		<->		<->	
Jones et al., 2019		↓[11]							↑[12]				<->				<->	<->
Downes et al., 2018	↓[13]							<->[13]									<->	
Lee et al., 2016	↓[14]								↑	↓[15]			<->				<->	
Bobillo-Perez et al., 2019			↓	↓	↑	↑[16]							<->			<->	<->	<->
Haque et al., 2018	↓[17]								↑[18]	↓			<->					
Ding et al., 2007			↓[19]					<->	↑[20]	↓		↓					<->	
Murni et al., 2015			<->						↑[21]				↓					↓
Stocker et al., 2012							<->		↑[22]				<->[23]	<->		<->		

Figure 3: PICU-dedicated ASPs.

PICU-dedicated ASPs

In all studies, a multi-modal/multifaceted intervention was applied combining two or more strategies simultaneously. Audit with feedback was the most common strategy and was used in 6 out of 9 studies. Audit was based either on institutional [17,18] or on international guidelines [19-21]. Pre-authorization of specific antibiotic categories such as carbapenems, quinolones, aminoglycosides *via* order forms was conducted in one study, while both ASP core strategies that is audit with feedback and pre-authorization were used by another study [16].

Facility-specific clinical practice guidelines were designed and implemented in 6 out of 9 studies [17-20] and 3 of them were focused on specific infectious disease syndromes (sepsis and community or hospital-acquired infections), three studies reported a prescriber-led review of antimicrobial prescribing appropriateness and three studies aimed to shorten the duration of antibiotic use

Education of the healthcare personnel was included in four ASPs [18,20] and in 3 of them [18,20] educational material was displayed on posters and screensavers in the setting or sent *via* reminder emails to personnel. Lee et al. implemented a computerized clinical decision support system (CDS) for authorization of antibiotic prescriptions >48 hours [18].

Diagnostic stewardship activities were used in 3 studies, combined with other core or supplemental ASP strategies in 2 of them. Rapid diagnostics on blood were performed in 3 studies with procalcitonin being the most common biomarker measured. Similarly, Aizawa et al. used a selective reporting of susceptibility to meropenem, amikacin and levofloxacin combined with the need for pre-authorization of these antibiotics by an Infectious Disease (ID) physician [16].

In most of the studies the ASP team included a PICU consultant [17,20,21], a pharmacist, a Pediatric Infectious Diseases (PID) physician [16,19], a microbiologist and a nurse staff [17,20,21]. Bobillo-Perez et al. mentioned that there was no dedicated ASP team in their study as long as the ASP was based on a biomarker-based algorithm. In three studies, ASP team was available even off working hours but only Lee et al. reported on full time equivalence (FTE) for pharmacist and PID physicians.

In terms of implementation strategies, a behavior-based intervention, which provided positive feedback, was included in only one ASP program [17]. An electronic staff peer-reporting system followed by staff interviews in selected cases was used to provide feedback of good clinical practice to prescribers. In three other studies [18,20] techniques to enhance behavior change were included; reminder emails after educational meetings, screensavers and posters with guidelines were used to increase compliance to interventions.

The majority of studies used antimicrobial consumption in order to evaluate the impact of ASPs in PICUs. The most commonly used metric for antibiotic consumption was Days of Therapy/1000 patient-days (DOTs) [16,18,19] followed by antibiotic prescription rate [20] and Length of Therapy/1000 patient-days (LOTs). Measurement of antibiotic-free days and rate of de-escalation was performed only in one study. In the majority of studies, a significant decrease in antimicrobial use was observed after interventions [16]. In addition, prescribing appropriateness was increased in most of the studies. Rate of appropriate selection of new antimicrobials, number of empiric or targeted antibiotic courses, number of empiric antibiotic courses of <3 days, documentation for continuing antibiotic therapy, were measured to assess the quality of antibiotic prescribing after the implemented ASPs [17,21].

Cost-effectiveness of ASP in PICUs was assessed in three studies

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[18-20]. All these studies reported a significant decrease in antibiotic expenditures measured as overall and broad-spectrum antibiotics cost [18], cost of drug unit [19] or antibiotic usage cost per patient-day, whereas none of the studies recorded the impact of ASPs on healthcare costs (Figure 4).

Intervention	ASP core strategy & activities							Diagnostics					Optimization				Other
Study	Audit and feedback	Pre-authorizattion	Didactic Education	Facility specific Clinical Practice Guidelines	Target specific infectious disease syndromes	Prescriber-led Review of appropriateness	CDS=Computerized Clinical Decision Support systems	Stratified Antibiogram	Selective or cascade reporting of antimicrobials	Rapid Viral diagnostics for respiratory pathogens	Rapid diagnostics on blood	Procalcitonin	Pharmacokinetic adjustment programm	Iv to Oral	Allergy assessment	Shortest Effective Duration	Restriction of specific antimicrobial agents
Aizawa et al., 2018	✓	✓[2]							✓[3]	✓	✓		✓				
Jones et al., 2019	✓[1]			✓		✓											✓[5]
Downes et al., 2018			✓	✓	✓		✓				✓	✓[4]				✓	
Lee et al., 2016	✓[1]		✓	✓	✓												
Bobillo-Perez et al., 2019											✓	✓				✓	
Haque et al., 2018	✓					✓										✓	
Ding et al., 2007		✓[2]	✓	✓												✓	
Murni et al., 2015	✓[6]		✓	✓	✓												
Stocker et al., 2012	✓[7]			✓		✓										✓	

Study	Structure/ASP core personnel	Workflow/FTE	Implementation/Strategy
Aizawa et al., 2018	PID physician, pharmacists, microbiologists, clerks	ASP team was available any time of the day No FTE reported	
Jones et al., 2019	PICU consultant, microbiologist, antimicrobial pharmacist, medical and nursing staff, project management personnel	Daily meetings between PICU consultants and ASP team No FTE reported	Positive feedback delivered to HCP via an electronic system, appreciative HCP interviews, driver diagram, weekly meetings of the ASP team
Downes et al., 2018	Biomarker-based intervention, ASP team[8]	No FTE reported	Reminder emails, screensavers with the algorithm
Lee et al., 2016	ASP pharmacist, PID physician	1 FTE ASP pharmacist and 0.5 FTE ASP physician	Informational emails, posters with guidelines
Bobillo-Perez et al., 2019	Biomarker-based intervention without dedicated ASP team	No FTE reported	
Haque et al., 2018	Paediatric intensivist, critical care pharmacist specially trained in ASP,PID physician	Discussion during morning rounds No FTE reported	
Ding et al., 2007	No dedicated ASP team	No FTE reported	
Murni et al., 2015	Doctors, nurses, allied workers at the PICU ward	No FTE reported	Reminder emails, providing educational materials
Stocker et al., 2012	PICU physicians, pharmacists, nurses	No FTE reported	Checklists

Outcome	Antimicrobial use/ consumption									Expenditures		Resistance	Patient Safety					
Study	DOT	Doses per Picu day	Antimicrobial prescription rate	Antimicrobial treatment Days	Antibiotic free days	Rate of de-escalation	Antimicrobial courses	LOT	Appropriateness	Antimicrobial cost	Healthcare cost	Antimicrobial Resistance	Mortality	Days of Hospitalization	PICU readmissions	Infection relapse rate	Length of stay	Infection rate
Aizawa et al., 2018	↓[9]												<->[10]		<->		<->	
Jones et al., 2019		↓[11]							↑[12]				<->				<->	<->
Downes et al., 2018	↓[13]							<->[13]									<->	
Lee et al., 2016	↓[14]								↑	↓[15]			<->				<->	
Bobillo-Perez et al., 2019			↓	↓	↑	↑[16]							<->			<->	<->	<->
Haque et al., 2018	↓[17]								↑[18]	↓			<->					
Ding et al., 2007			↓[19]					<->	↑[20]	↓		↓					<->	
Murni et al., 2015			<->						↑[21]				↓					↓
Stocker et al., 2012							<->		↑[22]				<->[23]	<->		<->		

Figure 4: PICU-dedicated ASPs.

The incidences of isolates of *Pseudomonas aeruginosa* resistant to imipenem, cefepime and ceftazidime, as well as of cefepime-resistant *Escherichia coli* and *Klebsiella pneumoniae* before and after the intervention were only recorded by Ding et al.

Mortality was assessed in 7 out of 9 studies and length of stay was measured in 6 out of 9 studies; for both no increase or in some cases a reduction was shown after the intervention. Additional patient outcome measures reported were health care acquired infection rate [17,20] infection relapse rate [21], PICU readmissions rate within 48 hours per 1000 patient-days [16] and hospitalization days.

Hospital-wide ASPs and impact on PICUs

Both hospital-wide ASP studies used audit and feedback as a core strategy in addition to the implementation of facility-specific clinical practice guidelines aimed to shorten the duration of antibiotic use (Figure 5).

Intervention	ASP core strategy & activities							Diagnostics					Optimization				Other
Study	Audit and feedback	Pre-authorizattion	Didactic Education	Facility specific Clinical Practice Guidelines	Target specific infectious disease syndromes	Prescriber-led Review of appropriateness	CDS=Computerized Clinical Decision Support systems	Stratified Antibiogram	Selective or cascade reporting of antimicrobials	Rapid Viral diagnostics for respiratory pathogens	Rapid diagnostics on blood	Procalcitonin	Pharmacokinetic adjustment programm	Iv to Oral	Allergy assessment	Shortest Effective Duration	Restriction of specific antimicrobial agents
Turner al., 2016	✓			✓	✓											✓	
Hurst et al., 2016, Messacar et al., 2017, MacBrayne et al., 2019	✓		✓	✓							✓					✓	

Study	Structure/ASP core personnel	Workflow/FTE	Implementation/Strategy
Turner al., 2016	PID physicians, pharmacist	ASP team was available any time of the day No FTE reported	
Hurst et al., 2016, Messacar et al., 2017, MacBrayne et al., 2019	PID physician, PID pharmacist, data analyst	FTE support increased from 0.2 to 1.75 after implementation	

Outcome	Antimicrobial use/ consumption									Expenditures		Resistance	Patient Safety					
Study	DOT	Doses per Picu day	Antiicrobial prescription rate	Antimicrobial treatment Days	Antibiotic free days	Rate of de-escalation	Antimicrobial courses	LOT	Appropriateness	Antimicrobial cost	Healthcare cost	Antimicrobial Resistance	Mortality	Days of Hospitalization	Readmissions	Infection relapse rate	Length of stay	Infection rate
Turner al., 2016	↓[1]									↓			<->				<->	
Hurst et al., 2016, Messacar et al., 2017, MacBrayne et al., 2019	↓[2]									↓			<->		<->		<->	

Figure 5: Hospital-wide ASPs and impact on PICUs.

One of them had a specific, in person approach ("handshaking") strategy for audit and feedback and incorporated education and rapid testing on blood cultures in their ASP. The ASP by Turner et al. was targeted to specific infectious disease syndromes [21].

In both studies a dedicated ASP team was formed including PID physicians and pharmacists with or without a data analyst. Full time equivalence was reported in one of these studies for the PID pharmacist, physicians and data analyst. Both studies resulted in a significant decrease in antimicrobial consumption measured by DOTs/1000 patient-days. Antibiotic expenditures and outcomes for patient safety such as mortality, length of stay, readmissions rate was assessed at hospital level.

DISCUSSION AND CONCLUSION

The beneficial effects of ASPs in optimization of antimicrobial use, patient safety, reduction of healthcare cost and antibiotic resistance has well been established in adults. In this review, audit with feedback and implementation of facility-specific clinical practice guidelines in PICU settings resulted in reduction of antimicrobial consumption and cost and increased judicious use of antimicrobials without affecting morbidity or mortality in critically ill children.

Although studies implementing ASPs in pediatric settings are on the rise, most of them fail to use an optimal methodology to evaluate the implementation of the programs. A lot of studies use a "before and after" methodology to evaluate an ASP intervention, but this approach is susceptible to many biases such as the regression to the mean, the Hawthorne effect, history biases etc. The use of strategies to overcome these biases mainly includes the use of interrupted time series. In our review, only half studies were designed as interrupted time series analyses.

Most of the studies used audit and feedback as a core component of their ASPs. Although IDSA encourages the use of two core strategies when there is availability of resources, only one study

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incorporated both audit with feedback and preauthorization. A new approach, called "Handshaking stewardship" with review of all prescriptions by a pharmacist-physician team and in-person feedback was effective and sustainable in a US children's hospital including the PICU as well. Although direct communication of the ASP team with physicians can be more time-consuming, it seems to have a higher impact on reducing antibiotic use while helping in education of the medical team and engaging collaboration between the two teams. Education was included in four studies; although interventions. based solely on education are not considered enough, use of education is considered an essential supplementary strategy and should be part of every ASP. In a recent study about challenges in antimicrobial stewardship in pediatrics, the need for physicians' continuous education on antimicrobial prescribing was more than highlighted.

Antimicrobial stewardship in critical care settings is particularly challenging due to disease severity and high prevalence of healthcare-associated infections and antimicrobial resistance, therefore physicians are more often led to prescribe broad-spectrum antimicrobials especially as an initial treatment regimen. The use of diagnostic tools such as newer molecular syndromic diagnostic platforms as well as biomarkers could help in rapid pathogen identification or exclusion of bacterial infections and thus result in less days of treatment as well as more options for de-escalation. Rapid viral and blood diagnostic tests and procalcitonin were used in 3 out of 9 studies of our review. Rapid diagnostics and biomarkers could also be useful for early diagnosis of ventilator-associated pneumonia, which represents one of the most common reasons for prescribing antimicrobials in PICU. The implementation of such diagnostics activities could have a higher impact on optimization of antibiotic prescribing in PICU settings in comparison with other ASP strategies.

and traditional antimicrobial dosing may result in suboptimal therapeutic outcomes. In addition, data on optimal antimicrobial dosing in critically ill children are very limited. Although the individualization of dosing approach is required in PICU settings, we found that therapeutic drug monitoring strategy was included in only one ASP. Shortening treatment duration can be a feasible ASP approach in a PICU setting as intervening in the initial treatment regimen is more difficult to achieve. Audit of antibiotic prescriptions on 24 h or 72 h for example and feedback to PICU physicians along with diagnostic tools could help in de-escalation or early end of treatment. However, prescribers continue to have difficulty in discontinuing administration of antibiotics. Implementation of

Thirdly, we did not evaluate the quality of the studies included.

facility specific clinical practice guidelines including guidelines for duration of treatment can facilitate physicians' decision for shorter antibiotic duration.

Most studies reported the organization of multidisciplinary antimicrobial stewardship team except two that implemented interventions based on biomarker driven algorithms. The structure of ASP team proposed by IDSA guidelines is followed in most cases with PICU staff along with external qualified persons such as clinical pharmacist, ID physician or clinical microbiologist being part of the ASP team. In the majority of studies, details about the work of the ASP team were described, however the FTEs were only reported in two studies.

Many ASPs used techniques to improve implementation of the program (reminder emails, posters/screensavers with guidelines, checklists), whereas only Jones et al. incorporated a behavioral change intervention based on positive feedback of physicians' performance. Although ASPs require physicians to change their antimicrobial prescribing behavior, most programs do not integrate a behavioral perspective. Focus on improving the implementation of the interventions using knowledge from behavioral sciences should be a priority for ASP in every setting.

In most cases, the impact of ASP was assessed with monitoring of antibiotic consumption along with measurement of mortality and length of hospitalization as balancing measures in order to assure patient safety. DOTs, which are currently recommended by WHO, were used in the majority of the studies, although there is still no consensus on how to measure antimicrobial consumption in pediatric populations.

ASP may usually be self-funded and reporting of cost savings from ASPs is very important in attracting or maintaining administrative support from healthcare institutions. Most studies only measured the effect of intervention on antibiotic expenditure, although many other factors should be measured in order to estimate the actual effect of an ASP in cost savings including shorter length of hospitalization and less rate of readmission. However, the cost of the ASPs should also be measured but is reported in none of these studies.

A limitation of our study is that we searched only PubMed and there may be other studies with ASPs implemented in PICUs that we did not identify. A second limitation is that we excluded studies that had implemented stewardship in entire hospital settings including PICUs but without presenting dedicated PICU data. However, as previously noted, the characteristics of critically ill children are unique and ASPs in PICUs should be organized targeted to these.

However, the number of the studies in this field is very limited and

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any attempt to evaluate their quality would possibly negatively impact the number of the studies analyzed.

In conclusion, the prevalence of ASPs in pediatric settings is limited and few of the existing programs follow all IDSA recommendations. To our knowledge, this is the first review of pediatric ASPs, and therefore it provides a benchmark to measure the implementation of new programs in the future.

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