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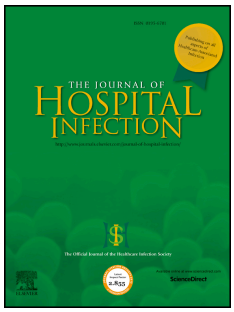

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PII: S0195-6701(17)30447-4

DOI: 10.1016/j.jhin.2017.08.003

Reference: YJHIN 5192

To appear in: *Journal of Hospital Infection*

Received Date: 14 June 2017

Revised Date: 0195-6701 0195-6701

Accepted Date: 4 August 2017

Please cite this article as: Araujo da Silva AR, Albernaz de Almeida Dias DC, Marques AF, Biscaia di Biase C, Murni IK, Dramowski A, Sharland M, Huebner J, Zingg W, The role of antimicrobial stewardship programmes in children: a systematic review, *Journal of Hospital Infection* (2017), doi: 10.1016/j.jhin.2017.08.003.

The role of antimicrobial stewardship programmes in children: a systematic review.

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Abstract:

The United Nations and the World Health Organization have designated antimicrobial resistance (AMR) as a major health priority and developed action plans to reduce AMR in all healthcare settings. Establishment of institutional antimicrobial stewardship programmes (ASPs) is advocated as a key intervention to reduce antibiotic consumption in hospitals and address high rates of multi-drug resistant (MDR) bacteria. We searched PUBMED and the Cochrane database of systematic reviews (1/2007-3/2017) to identify studies reporting about the effectiveness of ASPs in general paediatric wards and paediatric intensive care units (PICU), on reducing antibiotic consumption, on using broad spectrum/restricted antibiotics, and on antibiotic resistance and healthcare-associated infections (HAIs). Neonatal units and antifungal agents were excluded. Of 2509 titles and abstracts, nine articles were eligible to be included in the final analysis. All studies reported on the reduction of broad spectrum/restricted antibiotics or antibiotic consumption. One study reported on the reduction of HAI in a PICU, and another evaluated bacterial resistance, showing no effect following ASP implementation. Prospective audit on antibiotic use was the most common ASP core component (eight of nine studies). Antibiotic pre-authorisation was described in two articles. Other described interventions were providing guidelines or written information (five of nine articles), and training of healthcare professionals (one article). There is limited evidence about reducing antibiotic consumption and broad-spectrum/restricted agents following ASP implementation, specifically in PICU. Data evaluating the impact of ASPs on HAI and AMR in PICU is lacking. In addition, there is limited information on effective components of a successful ASPs in PICUs.

Key words: antimicrobial stewardship programme, PICU, multi-drug resistant bacteria, MDRO, children.

Introduction

Infectious diseases remain the most common indication for hospitalisation in paediatric wards and paediatric intensive care units (PICUs) worldwide. [1] Antibiotic use in paediatric inpatient settings was reported at 37% in a recent global point prevalence survey, with the highest antimicrobial use (61%) seen in PICU. [2] Although viral pathogens are a frequent cause of infection in paediatric populations, antibiotics are frequently inappropriately administered, owing to parental demand or physician uncertainty of the causative pathogen. [3]

Large-scale misuse of antibiotics in healthcare settings worldwide, both for community-acquired and healthcare-associated infections (HAIs) has contributed to the emergence of multi-drug resistant (MDR) bacteria, with increasingly limited therapeutic options. [4] The problem of antimicrobial resistance (AMR) was recognized by the World Health Organization (WHO) and the United Nations (UN) at the General Assembly of 2016. [5,6] Five key strategies to tackle AMR were defined including: understanding of AMR through effective communication, education and training, development of new drugs and diagnostic tools, and development of the economic case for sustainable investment that takes account of the needs of all countries. [6]

One strategy used to combat AMR is the development of country-level and institutional antimicrobial stewardship programmes (ASPs). The aim of this strategy is to analyse patterns of antibiotic use and identify local interventions to rationalize antibiotic therapy. The Infectious Disease Society of America (IDSA), defines ASP as "a set of coordinated interventions, designed to improve and measure the appropriate use of antimicrobials by promoting the selection of the optimal antimicrobial drug regimen (including the appropriate agent, dose, route of administration, and duration of therapy)". [7]

In critical care units such as PICU, where broad-spectrum antibiotic use is common, as well the presence of MDR bacteria and HAI; adequate monitoring of antibiotic use and improvement of rational antibiotic use are necessary. The introduction of institutional ASPs could contribute to patient safety in this population. Prospective audits with immediate feedback, formulary restriction, and pre-authorisation (also referred to as prior approval) influenced antibiotic use in a recent pilot study.[8] Based on the findings, the authors concluded that cost savings can be estimated at more than 330,000 € per year, and reduction would include broad-spectrum antibiotics and antifungals. [8]

The aim of this systematic review was to identify studies reporting on the effectiveness of ASPs in reducing antibiotic consumption/use of (broad-spectrum) antibiotics, reducing antibiotic resistance, and preventing HAI in children, including PICU settings. In addition, components of ASPs were to be described.

Materials and methods:

This systematic review was conducted according to the PRISMA guidelines. [9]

Search strategy:

We searched for publications in PUBMED and the Cochrane database of systematic reviews (from 1 January 2007 to 31 March 2017) using the search term "antimicrobial stewardship", limiting age (children from birth to less than 18 years), but without language restrictions.

Eligibility criteria

Inclusion criteria

Setting: Studies were eligible for full text review if they were conducted in children hospitalized in an acute care setting, including PICUs. Eligible study designs included quantitative studies, such as randomised controlled trials, controlled and non-controlled before-and-after studies, controlled and non-controlled interrupted time series, and cohort studies.

Exclusion criteria

Review articles, case series, letters, notes, conference abstracts, and opinion articles were excluded. Interventions in outpatient care, neonatal units, emergency departments, long-term care facilities, or a combination of such settings were also excluded, as well as quantitative or qualitative studies addressing ASPs in both adults and children (where extraction of paediatric data was not possible). Studies focusing on antifungal agents were also excluded.

Study selection:

Title and abstract sift as well as full text assessment was conducted independently by three investigators (ARAS, AFM and CBB); any differences in opinion regarding inclusion criteria were resolved by group discussion. Three rounds of article assessment were conducted before selecting the final list for data abstraction:

a) First-round: Exclusion of duplicate articles.

b) Second-round: Title and abstract sift.

c) Third round: Full text assessment.

After the third round, relevant papers cited as references of full text articles were included for analysis, if they fulfilled the eligibility criteria.

Data collection

Data were extracted using a standardized data-extraction form, which summarized the study details including authors, year of publication, country or countries where the study was performed, time frame of the study, and patient population (infant or early childhood, children, or adolescents).

Quality of articles and risk of bias

Quality of articles was assessed using the integrated quality criteria for systematic review of multiple study designs (ICROMS) tool. [10] In summary the tool consists of two parts: the first is a list of quality criteria specific for each study design, as well as criteria applicable across all study designs by using a scoring system, and the second is a 'decision matrix', which specifies the robustness of the study by identifying minimum requirements according to the study type and the relevance of the study to the review question. Only studies meeting the minimum score and the mandatory criteria, according the ICROMS methodology, were included for the final analysis and data abstraction. (Annex 1)

Analysis of antibiotic stewardship components (interventions) of identified articles

ASP was defined according to the IDSA and the Society for Healthcare Epidemiology of America (SHEA) with the following core components: prospective audit and feedback, formulary restriction, and pre-authorisation. [7] We also assessed the following components: use of guidelines or written information, and training of paediatric staff.

Results:

Of 2509 titles and abstracts, nine articles were eligible to be included in the final analysis (Figure 1). Six of the nine publications originated from the USA, one from Germany, one from Singapore, and one from Indonesia.

Three studies used a non-controlled before-and-after design, two were controlled interrupted series studies, two were non-controlled interrupted series, one was a cohort study, and one was a controlled before-and-after study. All studies included in final analysis met both mandatory criteria and the minimum score according the ICRMOS methodology. Study design, setting, number of subjects, country, study period, aims, interventions, and summary of key findings of the final articles are summarised in table 1.

Eight of the nine studies applied a multi-modal or multifaceted intervention, combining two or more components simultaneously. Five studies reported on the reduction of antibiotic consumption [11-15], seven reported on the reduction of broad spectrum/restricted antibiotic use [11,12,15-19], one reported on HAI reduction , [13] and one reported on reduction of bacterial resistance.[18] Two studies evaluated ASPs costs. [14,16] Eight of the nine studies reported statistically significant antibiotic reduction (either for all and/or for restricted antibiotics). [11-15, 17-19]

Prospective audit was one of the core components in eight studies. [11, 13-19] Antibiotic pre-authorisation was one of the core components in two studies.[16,18] Other core components included use of guidelines or written information (five studies), [11, 13, 14,17,19] and training of healthcare professionals (one study).[13]

Discussion:

One strategy to improve and rationalize the use of antibiotics is the adoption of an ASP. These programmes usually combine several measures to encourage rational antibiotic use both for inpatient and outpatient settings, and for all patient groups (adults, children, infants, neonates). ASP may have an important contribution to rationalizing antibiotic use in critically-ill children in PICUs, where the combination of AMR and high rates of invasive device use put patients at risk for HAI due to MDR pathogens.[20] In addition to tackle inappropriate antibiotic use, there is an urgency to conduct research on new antibiotics/antibiotic classes for critical MDR pathogens such as carbapenem-resistant *Acinetobacter baumannii*, carbapenem-resistant *Pseudomonas aeruginosa*, carbapenem-resistant Enterobacteriaceae, and extended spectrum beta-lactamase (ESBL)-producing enterobacteriaceae. [21,22]

It is plausible to assume that reducing antibiotic use would also reduce AMR in paediatric hospitals. A recent systematic review reported about the benefits of ASPs in reducing the incidence of infections and colonization with antibiotic-resistant bacteria and *Clostridium difficile* infections in adults. [23] However, other factors such as environmental control, outbreak management, isolation precaution measures, and hand hygiene contribute to the control of emerging resistance as well.

The most important difference between ASPs for children and ASPs for adults is outcome measurement: antibiotic dosage in children is based on body weight or body surface, and thus, defined daily dose (DDD) as the preferred measurement of antibiotic consumption is not applicable. [24] One alternative to measure antimicrobial use is days of therapy (as per 1000 patient-days).[11,14,15] Unfortunately, such data cannot be compared to DDDs from adults.

Eight articles of our systematic review came from high-income countries (six from the same country). Only one study was done in a low-middle-income country. [25] No articles from low-income countries were identified. This is very concerning because emerging resistance, particularly for Gram-negative microorganisms, appears to be alarming in countries with limited resources, and knowledge about how to introduce effective ASP in these setting is urgently required.[26, 27]

Although ASPs were effective in reducing antibiotic consumption for both all antibiotic use and selected antibiotic use in (general) paediatric wards, no effect was found in PICUs. No study was sufficiently powered to demonstrate any impact on AMR or HAI.

An important aspect of ASPs for hospitalised children, is training of healthcare professionals. We found this component only in one study. [13] From our point of view, continuous education and training of healthcare professionals on appropriate antibiotic use is essential. Local antibiotic resistance and case-mix must be taken into account to help clinicians making rational choices on antibiotic use.

This review highlights the difficulties in implementing and sustaining ASPs in PICUs, where critically-ill children frequently receive broad-spectrum antibiotic therapy to empirically cover MDR pathogens encountered particularly in HAI. Disease severity in PICUs may not allow to use narrow spectrum antibiotics empirically, but important aspects of ASPs in critical care include rapid identification of bacterial infections (if possible with rapid testing) to narrow treatment as soon as possible, and shortening the duration of antibiotic therapy by using ancillary tests. [28] These strategies allow the reduction of antibiotic exposure overall and avoiding the inappropriate use of broad-spectrum antibiotics while providing optimal care.

Our systematic review has some limitations. First, only two databases were searched and some potentially eligible studies might have been missed. Second, we only included reports from the past 10 years (from 1/2007 to 3/2017). Although inappropriate use of antibiotics in hospitals is not a recent problem, ASP as a strategy was rarely addressed before the introduction of the IDSA guideline on ASP in 2007.[7] Bias of articles included in final analysis were minimized by using ICRMOS methodology, which identified papers with mandatory requests and minimum criteria for inclusion.

This review provides a model for the implementation of ASPs in PICU and broader strategies to reduce antibiotic resistance. Implementation research on how to most effectively introduce ASPs in paediatric hospitals is needed, particularly from low- and middle-income countries where options for therapy of MDR infection are extremely limited.

Acknowledgements

We would like to thank C.H. Teixeira and L.S. Werneck.

Conflict of interest statement

None declared.

Funding sources

None.

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Table 1 - Quality criteria for application per study design- Integrated quality criteria for review of multiple study designs (ICROMS)

Quality criteria			Study design [b]						
Dimension		Specific criteria [a]	RCT	CBA	CITS	NCITS	NCBA	CS	QUAL
1.	Clear aims and justification	a. Clear statement of the aims of research?	++	++	++	++	++	++	++
		b. Rationale for number of pre-and post-intervention points or adequate baseline measurement	x	x	+	++	++	x	x
		c. Explanation for lack of control group	x	x	x	+	+	x	x
		d. Appropriateness of qualitative methodology	x	x	x	x	x	x	+
		e. Appropriate study design	x	x	x	x	x	x	++
2.	Managing bias in sampling or between groups	a. Sequence generation	++	x	x	x	x	x	x
		b. Allocation concealment	++	x	x	x	x	x	x
		c. Justification for sample choice	x	x	x	++	++	x	x
		d. Intervention and control group selection designed to protect against systematic difference/selection bias	x	++	x	x	x	x	x
		e. Comparability of groups	x	x	x	x	x	++	x
		f. Sampling and recruitment	x	x	x	x	x	x	++
3.	Managing bias in outcome measurements and blinding	a. Blinding	++	x	x	x	x	x	x
		b. Baseline measurement- protection against selection bias	x	++	x	x	x	x	x
		c. Protection against contamination	x	++	x	x	x	x	x
		d. Protection against secular changes	x	x	++	x	x	x	x
		e. Protection against detection bias: blinded assessment of primary outcome measures	+	+	+	+	+	+	x
		f. Reliable primary outcome measures	+	+	+	+	+	+	+
		g. Comparability of outcomes	x	x	x	x	x	++	x
4.	Managing bias in follow-up	a. Follow-up of subjects (protection against exclusion bias)	+	x	x	x	x	x	x
		b. Follow-up of patients of episodes of care	+	x	x	x	x	x	x
		c. Incomplete outcome data addressed	+	+	+	+	+	++	+
5.	Managing bias in other study aspects	a. Protection against detection bias: intervention unlikely to affect data collection	+	+	+	+	+	x	x
		b. Protection against information bias	x	x	x	x	x	+	x
		c. Data collection appropriate to address research aims	x	x	x	x	x	x	+
		d. Attempts to mitigate effects of no control	x	x	x	++	++	x	x
6.	Analytical rigour	a. Sufficient data points to enable reliable statistical inference	x	x	++	x	x	x	x
		b. Shaping of intervention effect specified	x	x	+	x	x	x	x
		c. Analysis sufficiently rigorous/free from bias	+	+	+	+	+	+	+
7.	Managing bias in reporting/ethical considerations	a. Free of selective outcome reporting	+	+	+	+	+	+	+
		b. Limitations addressed	+	+	+	+	+	+	+
		c. Conclusions clear and justified	+	+	+	+	+	+	+
		d. Free of other bias	+	+	+	+	+	+	+
		e. Ethics issues addressed	+	+	+	+	+	+	+

[a] Applicability of quality criteria to each study design: + Criteria to be included in quality assessment for study design; ++ Mandatory criteria to be met quality assessment; x Criteria not to be applied in quality assessment for study design.

[b] Study designs: RCT =randomised controlled trial; CBA =controlled before-after; CITS ¼ controlled interrupted time series; CS = cohort study; NCITS =non-controlled interrupted time series; NCBA =non-controlled before-after; QUAL = qualitative.

Table 2 -Decision matrix e mandatory criteria and minimum score for study type to be included in review.

Study Design [a]	Mandatory criteria [b]	Minimum score
RCT, cRCT	1A, 2A, 2B, and 3A	22
CBA	1A, 2D, 3B and 3C	18
CITS	1A, 3D and 6A	18
NCITS	1A, 1B, 2C and 5D	22
NCBA	1A, 1B, 2C and 5D	22
Cohort	1A, 2E, 3G and 4C	18
Qualitative	1A, 1E and 2F	16

[a] Study Designs: RCT = randomised controlled trial; CBA =controlled before-after; CITS = controlled interrupted time series; cRCT =cluster-randomized controlled trial; NCITS = noncontrolled interrupted time series; NCBA =non-controlled before-after.

[b] Scores applicable to each criteria: Yes (criterion met) =2 points; Unclear (unclear whether or not the criterion is met) =1 point; No (criterion not met) = 0 points.

Adapted from Zingg W et al. Innovative tools for quality assessment: integrated quality criteria for review of multiple study designs (ICROMS). Public Health 2016;133:19-37.

Table 1- Antimicrobial stewardship program in children, including PICU and outcomes (2007-2017).

Study author and reference	Study design	Setting, number of subjects	Country, study period	Aim (s)	Interventions	Summary of key findings
Kreitmeyr et al (11)	Non-controlled before-and-after study	273 patients (pre-intervention) and 263 patients (post-intervention) Four paediatric wards. Single centre	Germany, 2014-2015	a) to assess the impact of specific ASP interventions on antibiotic consumption in general paediatric wards. b) to evaluate the effectiveness of interventions in improving guideline adherence, antibiotic selection, dosing accuracy, and reduction of overall and specifically targeted antibiotics (cephalosporins and fluoroquinolones).	Guidelines, antibiotic restriction policy, audit and feedback	• Guideline adherence for community-acquired pneumonia improved from 39.5% to 93.5% • Dose accuracy improved from 78.8% to 97.6% • Decrease of cephalosporins and fluoroquinolones by 35.5% and 59.9% (p<0.001), respectively • Decrease of days-of-therapy and length-of-therapy by 10.5% (p<0.001) and 7.7% (p=0.02), respectively.
Hersh et al (12)	Controlled interrupted time series	31 freestanding children's hospitals affiliated with the Children's Hospital Association. General wards and PICUs.	USA, 2004-2012	a) to compare antibiotic prescribing rates in a group of paediatric hospitals with formalized ASPs (ASP+) (9 hospitals) to a group of concurrent control hospitals without formalized stewardship programs (ASP -) (22 hospitals).	ASP: elements of prospective audit and feedback, formulary restriction, and use of clinical guidelines. Intervention not fully described	• Average monthly decline in days of therapy/1000 patient-days of 5.7% (in 8 of 9 of ASP + hospitals) • Average monthly decline of 8.2% for selected antibiotics (vancomycin, carbapenems and linezolid) •Decrease of all antibiotic use in ASP + compared with ASP – (p=0.04)
Murni et al (13)	Controlled before-and-after study	2646 children aged 1 month to less than 18 years. General wards and PICU. Single centre	Indonesia, 2010-2013	a) to implement a multi-faceted infection control and antibiotic stewardship programme and evaluate its effectiveness on healthcare-associated infections, antibiotic use, and hand hygiene compliance.	Guidelines, training of human resources, audit and feedback, hand hygiene compliance	• Decrease of HAI in PICU from 45.1 % to 17.1% [RR = 0.37 (0.28-0.51)] • Decrease of patients exposed to inappropriate or incorrect antibiotics from 55.6% to 33% [RR = 0.64 (0.52-0.79)] • Increase of hand hygiene compliance from 11.7% to 62.4 %, (p<0.001)
Seah et al (14)	Non-controlled interrupted time series	830-bed tertiary care hospital. Paediatric and obstetric wards. Single centre.	Singapore, 2009-2013	a) to evaluate the impact of implementing a prospective audit and feedback ASP on appropriate utilization of carbapenems.	Guidelines, audit and feedback	• Decrease in DDDs per 100 patient-days by 55.6% from 0.9 to 0.4 (p=0.013) • Decrease of DOTs per 100 patient-days by 46.7% from 1.5 to 0.8 (p=0.06) • No changes in prescription rates • Paediatric carbapenems utilization cost

						decrease to a mean of $149 post-ASP (p=0.01)
Newland et al (15)	Controlled interrupted time series	317-bed tertiary care children's hospital. PICU, NICU and general wards. Single centre.	USA, 2004-2010	a) to demonstrate the impact of a prospective audit and feedback ASP on antimicrobial use.	Audit and feedback	• Compliance of 92% with ASP recommendations • Monthly decline in DOT and LOT for all antibiotics by 7% (p=0.045) and 8% (p=0.045), respectively • Monthly decline DOT and LOT for selected antibiotics by 17% (p<0.001) and 18% (p<0.001)
Sick et al (16)	Cohort study	188 bed paediatric hospital. General wards. PICU excluded Single centre.	USA, 2005–2011	a) to evaluate an internet-based pre-approval ASP for sustained reduction in antimicrobial prescribing and resulting cost savings.	Pre-authorisation, antibiotic restriction policy.	• Decrease of numbers of unrestricted doses but no decrease of numbers of restricted doses • Preapproval of ASP saved $103,787 (95% CI, $98,583–$109,172) per year, or $14,156 (95% CI, $13,446–$14,890) per 1,000 patient-days. • Average annual approval rate of 91.5% for restricted antibiotics
Newman et al (17)	Non-controlled before-and-after study	Paediatric wards. 530 children pre-intervention and 503 children post-intervention. Single centre.	USA, 2007-2009	a) to describe the impact of a clinical practice gguideline (CPG) on antibiotic management of children with community-acquired pneumonia.	Guidelines, audit and feedback	• Increase of ampicillin use by 34% after guideline implementation • Most commonly antibiotic prescribed for CAP (Pre-CPG): Ceftriaxone(72%); Most commonly antibiotic prescribed for CAP (Post-CPG): - Ampicillin(63%) • Change in antibiotic prescription at discharge: increase of amoxicillin (p<0.001); decrease of cefdinir and co-amoxiclav (p<0.001) • Overall treatment failure was infrequent (1.5% vs. 1%)
Di Pentima et al (18)	Non-controlled interrupted time series	180-bed tertiary care academic paediatric hospital. PICU, NICU and general wards included. Single centre.	USA, 2003-2007	a) to prospectively evaluate the effect of a comprehensive ASP on antimicrobial use, physician interventions, patient outcomes, and rates of antimicrobial resistance.	Antibiotic restriction policy, pre-authorisation, audit and feedback	• Decline of targeted antibiotics from 1250 to 988 doses administered per 1000 patient-days per year (p<0.001) • No changes of resistance to *Pseudomonas aeruginosa, Enterobacter cloacae*, *E.coli* and *Klebsiella pneumoniae* during the study
Di Pentima	Non-controlled before-	180-bed tertiary care academic paediatric hospital.	USA, 2004-2007	a) to evaluate the impact of implementing an ASP on vancomycin use	Guidelines, antibiotic	• Decrease of vancomycin use from 378 doses administered/1000 patient-days to 255 doses administered/1000 patient-days (p<0.001)

et al (19)	and-after study	PICU, NICU and general wards included. Single centre.			restriction policy, audit and feedback	• No increased use of other antibiotics with similar antimicrobial activity of vancomycin

Figure 1- Study selection- Systematic review on the role of antimicrobial stewardship programmes in children (2007-2017)