Original Research Article

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The outcome of implementing antimicrobial stewardship program for hospitalized children

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ABSTRACT

Background: An effective approach to improve antimicrobial use for hospitalized patients is an antimicrobial stewardship program (ASP). The present study aimed to implement ASP for inpatient children based on prospectiveaudit-with-feedback intervention in order to evaluate the impact on patient's outcome, antimicrobial use, and the hospital cost.

Methods: The study was conducted throughout 6 months over 275 children admitted with different infections at Main Children's hospital in Alexandria included; group I (with ASP) and group II (standard antimicrobials as controls).

Results: The study revealed that on patient's admission, single antibiotic use was higher among the ASP group while double antimicrobial therapy was higher among the non-ASP with significant difference (p=0.001). Less percentage of patients who consumed vancomycin, meropenem amoxicillin-clavulanic and metronidazole was observed among ASP group with a significant difference of the last two drugs when compared to controls (p=<0.001, 0.011, respectively). The study reported the higher percent of improved ASP patient's after 72 hours of admission with a significant difference to controls (73.2% versus 62.5%, p=0.038). Complications occurred more likely for the non-ASP group (odds ratio 7.374 with 95% CI 1.68-32.33). In general, there was a clear reduction of the patient antibiotic cost/day and overall cost per patient, however, it was not significant among the studied patients.

Conclusions: Our local ASP model provided a high quality of care for hospitalized children and effectively reduced the antimicrobial consumption.

Keywords: Antimicrobial resistance, Antibiotic misuse, Patient's outcome, Stewardship program

INTRODUCTION

The misuse of antimicrobial agents and the abuse of antibiotics has contributed to a growing problem of antimicrobial resistance, which has become one of the most serious and major threats to public health.^{1,2} In addition to increased healthcare costs, a great number of antibiotic prescriptions for children are unnecessary or inappropriate. Many children receive prescriptions with incorrect total daily dosage or for long period of time.³ Moreover, the incidence of drug-related adverse events is significantly increased in instances of improper drug use which raise the risk of children morbidity and mortality.^{2,4} Antimicrobial stewardship program (ASP) is designed to optimize the clinical use of antimicrobial medications. It is multidisciplinary team which promotes the appropriate use of antimicrobial through optimal selection of drug, dosage, duration and route of administration.⁵

The current interest in ASPs for paediatric settings is reflected in many publications most of them conducted over inpatients.⁶ The American Academy of Paediatrics at 2015 highlighted the importance of ASP in paediatrics;

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and recommended implementation of these programs in health care organizations that provide inpatients and outpatients care. However, development of local successful ASP program needs certain fundamentals as leadership, expert team from different fields and management guidelines. This motivated us to conduct the present study which aimed to implement ASP for hospitalized children at Alexandria University Children's hospital and to assess the impact of ASP system on patient's health, antimicrobial consumption and on hospital cost. The implementation of ASP and the research in this field are lacking in Egypt.

METHODS

Ethical considerations

Ethical approval was obtained from the Ethical Review Committee, Alexandria University. Ethical Review Committee of Faculty of Medicine, Alexandria University (approval no: 0103717).

Study settings and design

The current study was an interventional study conducted at Alexandria University Children's Hospital (El-Shatby) comparing the effect and value of intervention against control over a group of hospitalized children for 6 months' duration from 2013 to 2014. El-Shatby Hospital is a tertiary care teaching hospital formed of 252 beds.

Sample size calculation

The sample size was calculated using software of Epicalc 2000 version 1.02. Based on assumption of a reduction of 25% of antibiotic use after implementing of antimicrobial stewardship program 1% alpha error and 90% power, the sample was 218 (109 in each group). 9,10

Study population

The study included all admitted cases receiving antibiotics to two units of general pediatrics wards. Patients admitted to the first unit were the intervention ASP group, while the second unit represented the control group. Each unit has specific days per week for outpatient cases admission.

Group I (Intervention -ASP)

It included all patients admitted to the first unit (31 beds) and received antimicrobials based on the implemented ASP. The ASP team consisted of pediatric assistant lecturers, residents, nursing staff, microbiologists and was supervised by two professors of pediatric department. Training was done to the health- care personnel through lectures and interactive discussions one month before implementation of the study. However, regular meetings were conducted every two weeks during the study time for assessing the feedback.

Group II (control/Non- ASP)

It included all patients admitted to the second unit (25 beds), where the routine and standard antimicrobial medications were prescribed. The team included residents, assistant lecturers, nurses and professors of paediatrics department.

Exclusion criteria from the study

Patients with hospital stay less than three days and those referred to surgery department or received antibiotics for prophylaxis as illustrated in Figure 1.

Stewardship program

The used ASP for the current study at 2014 was prospective audit with feedback intervention every two weeks. It was adopted from pediatric intensive care unit (PICU) of the same hospital which was implemented since 2007 based on the several antibiograms and medical hospital records for several years. Printed booklets including antimicrobial guidelines were available for the ASP team to be applied for the ASP group during the study time.

Questionnaire

Questionnaire was done (appendix 1) and data were collected about all patients. It included demographic data about patients and some measurable outcomes, as length of hospital stay, response to therapy weather by stewardship program or traditional method, fate of patients, developing complications during hospital stay and cost of antibiotic use and cost /patient/day. Results of both groups were compared together.

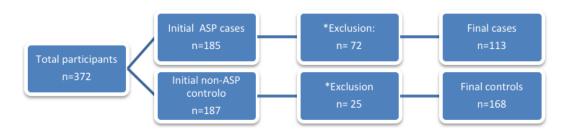


Figure 1: Flow chart of the full and the adjusted comparisons of studied groups.

Statistical analysis

The raw data were coded and transformed into coding sheets. The results were checked. Then, the data were entered into SPSS system files (SPSS package version including 18). Descriptive statistics frequency, distribution, mean, and standard deviation were used to describe different characteristics. Kolmogorov-Smirnov test was used to examine the normality of data distribution. Univar ate analyses including: t-test, Mann Whitney test, was used to test the significance of results of quantitative variables. Chi-Square test, Monte Carlo test and Fisher's Exact test were used to test the significance of results of qualitative variables. The significance of the results was at the 5% level of significance.

Exclusion criteria

Hospital stay <3 days, referral to surgery and or prescribing antibiotics as prophylaxis. (ASP: Antimicrobial stewardship program.)

RESULTS

The current study included 275 children, divided into two groups, ASP group (n=113) and control group (non-ASP) (n=162) with no significant difference in the mean age of both groups (25.12±23.62 month versus 29.82±21.35

month). Respiratory infections were the predominant among the studied groups without significant difference however, cardiac diseases and septicaemia were the least common but their percentage were higher among ASP groups when compared to the control group with significant difference (p<0.001, p=0.014, respectively) (Table 1).

Although the percentage of cases with positive CRP on admission was higher among the non-ASP group, the percentage of cases with very high values of CRP (>100) was higher among ASP group than controls with significant difference (p=0.008) (Table 2).

Concerning the drug prescriptions on admission, the percentage of children received single antibiotic initially was higher among the ASP group when compared to non-ASP group while the percent of children received double therapy was higher among non-ASP with significant difference to ASP (p=0.001). Less percent of cases changed antibiotics after 72 hours of initial therapy within the ASP group rather than non-ASP cases but without significant difference. The rationale of change of antimicrobial was based on either non improved cases or culture based for most of cases of ASP group. Meanwhile, higher percent of cases among non-ASP group changed antibiotics based on rational of developing complications with significant difference to study group (MC p=0.004) (Table 3).

Table 1: Distribution of demographic, clinical and laboratory data of the studied groups.

	ASP* group		Non-ASP grou	Non-ASP group	
Item	(n=113)		(n=162)	(n=162)	
Item	No	%	No	%	significance
Male	68	60.2	92	58.2	n=0.575
Female	45	39.8	70	43.2	p=0.575
Age (months)	25.12±23.62	•	29.82±21.35		tp=0.199
Weight (kg)	9.41±6.37		10.57±8.39	10.57±8.39	
(LOS) in (days)	9.29±6.49		8.91±8.13		tp=0.695
Urinary tract infections	11	8	15	8.9	p=0.895
CNS infections	15	11	25	14.8	p=0.618
Respiratory infections	46	33.8	80	47.6	p=0.155
Gastrointestinal infections	17	12.5	15	8.9	p=0.141
Cardiac infections	17	12.5	5	3.1	p <0.001**
Sepsis	15	11	8	4.7	p=0.014**
6>CRP<100	53	46.9	102	62.9	p=0.080**
CRP >100	60	53.1	60	37.0	p=0.080
WBC count on admission	13.72±8.37				tp=0.663
WBC shift to left	10	8.8	12	7.4	p=0.664
WBC (no shift)	103	91.2	150	92.2	p=0.004
(WBC) toxic granules	13	11.5	22	13.6	n=0.611
(WBC): no toxic granules	100	88.5	140	86.4	p=0.611
Sterile cultures	107	94.7	159	98.1	FEp=0.167
Positive cultures	6	5.3	3	1.9	

tp: p value of Student t test, P:p value of Chi- square test, MCp: p value for Monte Carlo test FEp: p value for Fisher exact test *ASP: Antimicrobial Stewardship program**: Statistically significant at p<0.05.

Table 2: Comparison of the strategy of antibiotic prescription among studied groups.

	ASP* group		Non-ASP	group	Test of				
Item	(n=113)	(n=113)			significance				
Tem	N	%	N	%	Significance				
Number of used antimicrobia	Number of used antimicrobials on admission								
Single	74	65.5	76	49.9					
Double	38	33.6	72	44.4	p=0.001**				
More than one	1	0.9	14	8.6					
The rational of choosing anti	microbial								
Physician experience	10	8.8	161	99.4					
Documented by culture	2	1.8	1	0.6	MCp<0.001**				
Protocol directed	101	89.4	0	0					
Cases changed antibiotics after 72 hours									
Yes	24	21.2	42	26.4	p=0.367				
No***	89	78.8	117	73.6	p=0.307				
Rationale of change of antimicrobial									
No Improvement	18	75	21	50					
New culture results	4	16.7	2	4.8	MCp=0.004**				
Developing complications	2	8.3	19	45.2	MCp=0.004				
Use of antimicrobial combination after changing the treatment									
Yes (double)	13	54.1	14	33.3	m_0 000				
No (single)	11	45.8	28	66.7	p=0.098				

P: p value for Chi-square test FEp: p value for Fisher Exact test MCp: p value for Monte Carlo test; *ASP: Antimicrobial Stewardship program. **Statistically significant at p<0.05- *** dropped cases.

Table 3: Comparison of the patient's outcome of studied groups.

	ASP gro	oup Non ASP group		_	Odds ratio	
	n=113	%	n=162	%		(95% CI UL-LL)
Effect of drugs >72 h						
Improved	83	73.4	102	62.9		
Stationary	29	25.6	50	30.8	p=0.038**	
Worse	1	0.9	10	6.1		
Complications***						-
Yes	2	1.8	19	11.7	0 002**	7.3 (1.6-32.3)
No	111	98.2	143	88.3	p=0.002**	7.3 (1.0-32.3)
Fate	•		•			
Discharged cases	111	97.3	151	93.3	p=0.085 FE-0.080	4.1 (0.89-19)
Deceased cases	2	1.7	11	6.7		

FEp: p value for Fisher Exact test; *ASP: Antimicrobial Stewardship program; **: Statistically significant at p<0.05;

Table 3 summarized data about patient's outcome. It showed that the percent of improved cases after 72 hours was higher in ASP group when compared to controls with significantly difference (p=0.038). The percent of complicated cases were reduced among the study group with significant difference to controls (1.8% versus 11.7%, p=0.002). Complications among non-ASP group were 7.374 times more likely than ASP group (95% CI 1.68-32.33). Discharged cases among ASP group were 4.1 times more likely than non-ASP group (95% CI 0.89-19). The number of deceased cases among study group were less than controls but without significant difference. Meanwhile, Table 4 presented the main demographic and outcome data of ASP subgroups whether deceased and

discharged cases. A significant difference between both subgroups as regards the percent of cases changed antibiotics after 72 hours (FEp=0.045) was being higher among deceased cases when compared to discharged group (100% versus 20%).

Concerning the drug consumption, the current study revealed less percentage of cases using same antimicrobials among ASP group in contrast to non-ASP cases (Table 5). The percentages of patients were on use of amoxicillin-clavulanic and metronidazole were less among ASP with significant difference when compared to non-ASP group (p≤0.001, 0.011). However, percentage of patients used ampicillin- sulbactam was higher among

^{***:} pneumothorax, empyema, septic shock.

ASP groups with significant difference in (p=0.004) to controls The mean duration of the used antibiotics in days

did not show statistical difference among the studied groups.

Table 4: Comparison of ASP* subgroups according to patient outcome.

Itam	Deceased (n=2)		Discharged (n=111)		T4 - C
Item	No	%	No	%	Test of significance
Male	1	50	67	60.4	FEp=1.000
Female	1	50	43	39.6	rep=1.000
Age (month)	3.0 ± 2.83		21.44±27.76		tp=0.352
Weight (kg)	3.75±0.35		9.51±6.38		tp=0.206
6 >CRP<100	0	0	58	52.3	FEp=0.497
CRP >100	2	100	53	47.7	гер=0.497
WBC shift to left	1	50	9	8.1	FEp=0.170
(WBC) toxic granules	1	50	12	10.8	FEp=0.218
The rational of choosing antim	icrobial				
Physician experience	1	50	9	8.1	
Documented by culture	0	0	3	2.7	EE=-0.214
Protocol directed	1	50	99	89.2	FEp=0.214
Effect of antimicrobial therapy	after 72 hou	rs			
Improved	0	0	82	74.5	
worse	0	0	1	0.9	MCn=0.092
stationary	2	100	27	24.5	- MCp=0.082
Cases that changed antimicrobial after 72 hours	2	100	22	20	FEp=0.045**
Rationale of change of antimic	robial				
No improvement	2	100	15	68.2	
New culture results	0	0	4	18.2	FEp=1.000
Developing complications	0	0	3	13.6	_
Use of antimicrobials combination on change	1	50	12	10.8	FEp=0.043**
Complication	0	0	2	1.8	FEp=1.000

P: p value for Chi-square test FEp: p value for Fisher Exact test MCp: p value for Monte Carlo test; *ASP: Antimicrobial Stewardship program; **: Statistically significant at p<0.05.

Table 5: distribution of patients using different antibiotics, antifungal and antiviral drugs during hospitalization.

	ASP		Non ASP	•	
Name of used antimicrobial	(n=113)		(n=162)		Test of significance
	N	%	N	%	
Cefoperazone/sulbactm	14	12.3	15	9.3	p=0.406
Ceftriaxone	57	50.44	70	43.2	p=0.237
Acyclovir	10	8.9	7	3.4	p=0.125
Cefotaxime	42	37.2	65	40.1	p=0.621
Sulfame thoxazole	2	1.8	1	0.6	Fep=0.57
Amoxicillin-clavulenic	5	4.4	66	38.9	p <0.001**
Ampicillin-sulbactam	10	8.9	2	1.2	Fep=0.004**
Fluconazole	1	0.9	5	3.1	Fep=0.406
Metronidazole	2	1.8	15	9.3	Fep=0.011**
Vancomycin	29	25.7	47	29.9	p=0.541
Clarithromycin	1	0.9	0	0	Fep=0.411
Meropenem	13	11.5	23	14.2	p=0.515
Amikacin	6	5.3	3	1.9	Fep=0.167
Azithromycin	2	1.8	5	3.1	Fep=0.704
Ceftazedime	4	3.5	4	2.5	Fep=0.721
Maxipime	6	5.3	-	-	-

P: p value for Chi-square test FEp: p value for Fisher Exact test; *ASP: Antimicrobial Stewardship program; **: Statistically significant at p < 0.05.

Table 6: Comparison between the studied groups according to cost of antimicrobial in US dollars.

Cost	ASP group (n=113)	Non-ASP group (n=162)	P value
Cost/patient/day			
Min–Max.	3.75-346.23	3.60-634.75	
Mean±SD	58.52±67.28	67.86±94.99	0.436
Median	33.70	36.25	
Overall cost/patient	•		
Min–Max.	10.80-6016.92	17.0–7673.75	
Mean±SD	499.20±836.46	544.28±981.54	0.657
Median	215.0	213.90	

P value for Mann Whitney test; Test of significance <0.05.

On the other side regarding the cost, The study showed a reduction in overall patient cost for ASP group in comparison to traditional antimicrobial group (499.20±836.46 versus 544.28±981.54) by US dollars without significant difference(P=0.657). The daily patient cost for ASP group ranged 3.75–346.23 with mean of 58.52±67.28, in comparison to range of 3.60–634.75 with for non- ASP with mean of 67.86±94.99 without significant difference (p=0.436) as shown in (Table 6).

DISCUSSION

The need for formal ASP in paediatrics was officially recognized recently, considering the widespread use of antibiotics in children and different antimicrobial resistance patterns. In 2014, an Egyptian study Talaat et al was conducted over 18 hospitals for adults and paediatrics patients identified that about 59% of inpatients were receiving one or more antibiotic agents and that was higher than the prevalence of antibiotic use reported in similar studies in Europe 29% and most of patients were below twelve years. 11,12 Egypt lack published studies about ASP for paediatric patients.

In Alexandria University Children's hospital most of patients received antibiotics and all of them had history of receiving previous antibiotic medication prior to hospital admission. An important goal for implementing ASP is 4 Ds of Joseph and Rodvold of optimal antimicrobial therapy: right drug, right dose, deescalation to pathogen directed therapy and right duration of therapy.¹³ The current study aimed to implement local ASP in paediatrics words and assessing the impact on children health status, antimicrobial use and hospital cost.

In the present study, we found respiratory tract infections were the most prevalent diagnosis among all patients with no significant difference between studied groups similarly to the study of McCulloh et al. ¹⁴ Despite the spectrum of patient's infections ranged from urinary tract infections, central nervous system, cardiac to septicaemia, trivial number of the positive cultures were reported because all patients received antibiotic therapy on outpatient before hospital admission. Therefore, no relevant antimicrobial resistance study was performed.

The impact of ASP on patient outcomes is important to many practitioners but is rarely used as metrics. Most of previous studies had included mortality, length of stay (LOS) and readmission rates as parameters of patient's outcome. ¹⁵ Meanwhile, the novel parameter in the present study was early evaluation of clinical conditions whether improved or not after 72 hours of the start of medications.

The current study revealed significant improvement of ASP cases after 72 hours of admission in contrast to non-ASP cases (73.2% versus 62.5%). Also, cases that became clinically worse were statistically less in ASP group when compared to control (0.9% versus 6.2%). Moreover, the percent of cases that changed antibiotic therapy based on developing complications were significantly lower among the ASP group in comparison to the control group (8.3% versus 45.2%, p=0.004). However, changing the antibiotic depending on culture results was only 16.7% of cases in ASP group because the ASP was applied from the start "on admission".

In spite that the study documented significant less morbidity (complications) for the intervention group, the impact of ASP on patient's mortality showed a clinical difference (2 for ASP group versus 11 for controls) but without significance. This may be explained by small total number of patients in the study and the short duration study (4 months). Similar to the present results, two studies from Singapore General Hospital showed that ASP intervention did alter mortality rate. 16,17 This was shown in a Swedish study that concluded no significant difference in mortality rates between ASP and non-ASP group with less morbidity. 18 We tried to elucidate the difference inside the ASP subjected subgroups to compare discharged from deceased and it was found that the less the need to change antibiotics at 72 hours from admission, and the less use of antibiotic combination on changing the treatment after 72 hours, the less was the mortality.

Strangely enough, length of hospital stay in our study was some times longer for study group rather than the controls and this was consistent with results found by Teo et al and Mc Culloh et al. ^{14,17} But it was contradictory to

others who reported short hospital stay under ASP protocol. 16,19

Concerning the use of antimicrobial agents, the current study provides an insight into the potential benefit of using a prospective-audit-with-feedback over other strategies to control the inappropriate antimicrobial use as they were reviewed 48-72 hours after starting therapy.¹³ The study revealed statistical significant reduction of amoxicillin-clavulanic acid and metronidazole use between the studied groups (4.4% versus 38.9% and 1.8% versus 9.3, respectively) which may explain why there was no significant difference in the length of hospital stay (LOS) (9.3 versus 8.9 days) as a direct reflection of clinical cure. Clear reduction in consumption percent of some antimicrobials was observed as vancomycin, meropenem and fluconazole even it was insignificant which matched Hersh et al who stated a decline in average antibiotic use in hospitals from 11% to 8%.20 The guidelines of the IDSA and SHEA revealed about 22% decrease in use of parenteral antibiotics. 14,16 On the other side, Di Pentima et al reported the same but he expressed results as the number of doses per 1000 patients targeted-antimicrobial use as recommended by WHO.²¹ In the present study, the reduced consumption of drugs was explained by significant less use of antibiotic combinations on admission by ASP group because of the use of protocol of antibiotics on admission and significantly they relied on single drug prescription. The most common selected drugs were ceftriaxone, cefotaxime and vancomycin which were consistent with Newland et al.²² Ampicillin-sulbactam use was significantly higher among ASP group may be because of protocol directed strategy for treatment of UTI cases.

As regards the cost, in general there was a decrease of about one fourth of the daily cost of antibiotic /patient (23.92%) in the ASP group and 8.29% decrease of the overall cost per patient however it was not significant as compared to non- ASP group. This may be attributed to more or less similar length of hospital stay for both studied groups. Different studies showed a reduction or savings in cost. Philemon and Agwa et al, showed reduction of antimicrobial cost per patient day by 22%-31%. 23,24 The cost-effectiveness of ASP which is the relation between reducing the price of antimicrobials and the team cost. In the present study for 2 subunits in the paediatric hospital with 275 patients admitted for 4 months the saving could be 12.375 US dollars. For a year, over 6 unites it could be 111.378 US dollars. It could be a significant amount of saving in a limited resource country. Similar to an Irish study resulted in a reduction of 293.000 US dollars with a cost of 43.000 US dollars for the team yearly.¹⁵ Bantar study and Principe studies concluded that more saving specially in treating cases suffering from bacterial resistance. 25,26

CONCLUSION

Implementing a local ASP model with prospective-audit-with-feedback strategy is considered an inter-professional effort providing good quality of health care for hospitalized children with limiting morbidity and mortalities. It is an effective strategy for optimizing antibiotic use which reduce the antimicrobial resistance. It worth to be supported by local health authorities and recommended to be applied for all paediatric hospitals.

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