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Implementation and Evaluation of Antimicrobial Stewardship Program in Medical ICU in Cairo University Specialized Pediatric Hospital

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Abstract

BACKGROUND: High antibiotics use in pediatric intensive care units (PICUs) results in antibiotic resistance, the unfavorable clinical outcome of patients, increase the length of hospital stay, and drug expenditure.

AIM: This study aimed at setting clinical guidelines customized according to local diseases epidemiology and local cumulative antimicrobial susceptibility, implementing, and evaluating the Antimicrobial Stewardship Program (ASP) effect in; optimizing antibiotics use, decreasing antibiotics expenditure, decreasing the length of therapy and stay in hospitals, and improving patients' clinical outcomes.

METHODS: A prospective study was conducted at a PICU of the Specialized Pediatric Hospital, Cairo University. Facility-specific guidelines were set, and the ASP was implemented and evaluated through the following indicators; adherence of physicians to the guidelines, ASP recommendations and acceptance of them, the rate of mortality, length of stay, drug costs, antibiotics days of therapy, and length of therapy.

RESULTS: The adherence to the ASP guidelines was positively correlated to the patient's clinical outcome ($p = 0.018$). In post ASP period, the average length of stay and the length of therapy significantly decreased ($p = 0.047$, $p = 0.001$, respectively), the rate of adherence to the ASP guidelines was (91.9%), the days of therapy of ceftazidime, ceftriaxone, and amikacin decreased significantly ($p = 0.041$, $p = 0.026$, $p = 0.004$, respectively). The most common ASP recommendation was drug schedule/frequency change (26.1%) followed by drug discontinuation (17.8%) and the most common antibiotic required intervention was ampicillin-sulbactam (21.6%).

CONCLUSION: The antimicrobial stewardship is very effective in optimizing antibiotics use and leads to favorable outcomes in terms of decreased length of therapy, hospital stay, and mortality rate of the patients.

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Introduction

Antibiotics abuse in the pediatric intensive care unit (PICU) is very high [1]. About one-third of prescribed antibiotics are inappropriate resulting in antibiotic resistance, especially with lacking new antibiotics. Hence, the importance of antimicrobial stewardship arises which means judicious and optimized use of antibiotics and reducing the adverse effect of antibiotics [2].

General practitioners in primary care settings are common causes of antibiotic over-prescription, which has been shown to increase the risk of reattendance and medicalization of self-limiting infectious diseases [3].

The utilization of antibiotics is not restricted only in health care settings. Agriculture, aquaculture, and farming consume a lot of antibiotics. The higher the antibiotic use, the higher the rate of resistance [4].

In 2014, the Centre for Disease Control and Prevention developed the core elements of a successful hospital Antimicrobial Stewardship Program (ASP) [5].

World Health Organization has reported that infections caused by resistant organisms are not only detected in developing countries but throughout the world [6].

Aim of the work

The aim of the study was to set clinical practice guidelines customized according to local epidemiology of diseases and local cumulative antimicrobial susceptibility and assess ASP implementation in the PICU.

Materials and Methods

This prospective study was conducted at the (PICU) in Specialized Pediatric Hospital, Cairo University (CUSPH), from April 1, 2016, to June 30, 2017; pre-implementation phase from April 1, 2016, to

September 30, 2016, intervention phase from October 1, 2016, to December 31, 2016, and post-implementation phase from January 1, 2017, to June 30, 2017.

The study was performed in the clinical microbiology department in collaboration with the departments of pediatrics and pharmacy at the specialized pediatric hospital, Cairo University (CUSPH).

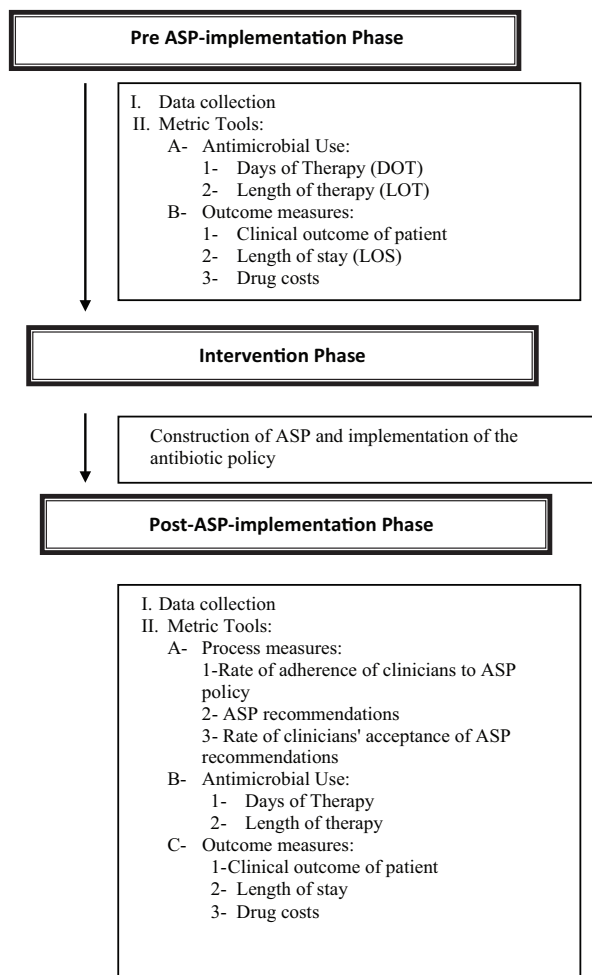
Ethical approval

The study was ethically approved by the research ethics committee of the Faculty of Medicine, Cairo University.

Settings

This prospective study was conducted at PICU with 12 beds capacity (6 beds per room) and 350 admissions per year in CUSPH which is a tertiary care teaching hospital. Staff of the unit working in 1:1 care (1 nurse/1 patient) in unstable patients and 1:2 care (1 nurse/2 patients) in stable non-ventilated patients. All admissions during the period of each phase were included within the corresponding phase.

Flow of work



Data collection included name, age, sex, weight, date of admission and discharge, pediatric risk of mortality score (PRISM III score), clinical diagnosis and outcome of the patient, and indication and proof of infection at the start of antibiotic therapy, 48 h and 5 days reviews.

Construction of ASP

- Multidisciplinary team members and their job description
 - Team leader: Organized and communicated all team members with the management to obtain adequate authority and was responsible for the expected outcomes of the ASP
 - Physician: Mainstay of stewardship program implementation
 - Clinical pharmacists: Responsible for pharmacy-driven interventions
 - Clinical microbiologists: Provide clinical advice about microbiological investigations and construction of local cumulative annual antibiograms
 - Infection control personnel: Monitored the healthcare-associated infections, antimicrobial resistance, and measures to prevent them
 - Nurses: Implemented all elements of the ASP.
- Before program implementation, the antimicrobial stewardship strategic plans were presented and approved by the ASP team members and the head of the studied PICU, to ensure their acceptance. The support and collaboration of hospital administration were essential for the success of the program
- The ASP team members regularly met twice/month to set policies that were applied in all situations for an optimal antibiotic prescription through:
 - Documentation of dose, duration, and indication for all courses of antibiotics to be easily identifiable and accessible
 - Development and implementation of facility-specific treatment policy based on national guidelines and local antimicrobial susceptibilities
 - Reassessment of continuous need and choice of empiric antibiotics after 48 h of initiating antibiotics when more diagnostic information was available (antibiotic time outs)
 - Regular education and training of staff groups on antibiotics use in the form of presentations in formal and informal settings and electronic communication
- PICU-specific antibiogram was constructed annually by microbiology laboratory staff members.

After approval of the new guidelines by the ASP team, they were distributed to all PICU staff members to be ready for implementation.

The program was officially launched in April 1, 2016 as the first ASP at PICU of CUSPH.

ASP implementation

Prior antimicrobial authorization

The clinician requested the ASP team for each targeted antimicrobial agent using prior authorization form. The ASP team reviewed cultures and sensitivities and the regimen of treatment. The ASP pre-approved certain indications for selected targeted antimicrobial agents. Approval for empiric use of certain antimicrobial agents was usually given for 48 h until the availability of the results of the cultures.

The antimicrobial prescription was classified into three groups according to the need of culture and prior approval as shown in Table 1:

Table 1: Antimicrobial prescription classification

Antimicrobials not requiring culture or prior approval	Antimicrobials requiring prior approval without culture	Antimicrobials requiring cultures and prior approval
Amoxicillin/flucloxacillin	Acyclovir	Maxipime
Amoxicillin/clavulanic acid	Azithromycin	Meropenem
Ampicillin/sulbactam	Cefobid	Imipenem
Amikacin	Ceftazidime	Ertapenem
Gentamicin	Ceftriaxone	Ciprofloxacin
	Cefotaxime	Levofloxacin
	Cefoperazone/sulbactam	Tigecycline
	Piperacillin/tazobactam	Colistin
	Amphotericin B	Vancomycin
	Fluconazole	Teicoplanin
		Linezolid
		Caspofungin
		N.B.: Vancomycin, meropenem, and imipenem only dispensed empirically in case of sepsis

Metric tools

Antimicrobial use measures

DOT

Was measured by calculating any amount of a specific antimicrobial agent administered on a calendar day to a particular patient, as documented in the medication administration record. The day of admission, discharge, and transfer to and from locations was included in the day's present count [7].

LOT

Was measured by calculating the number of days that a patient received systemic antimicrobials irrespective of their number and the total LOT of patients present during each phase was summed up [8].

Process measures

1. Rate of adherence of clinicians to ASP policy: Was measured by calculating the percent of

patients treated according to the ASP policy to all patients admitted

2. ASP recommendations: Was measured by calculating the percent of each ASP recommendation given to all ASP recommendations
ASP recommendations: Dose increase, decrease; drug change; drug formulation change; schedule/frequency change; discontinuation; add medication; other changes to therapy; education/counseling session; change diluents; change final solution concentration; change infusion rate; laboratory monitoring; request other investigation; request cultures; or no recommendation [9].
3. Rate of clinicians' acceptance to ASP recommendations: Was measured by calculating the percent of clinicians' acceptance to implement the ASP recommendation to all ASP given recommendations.

Outcome measures

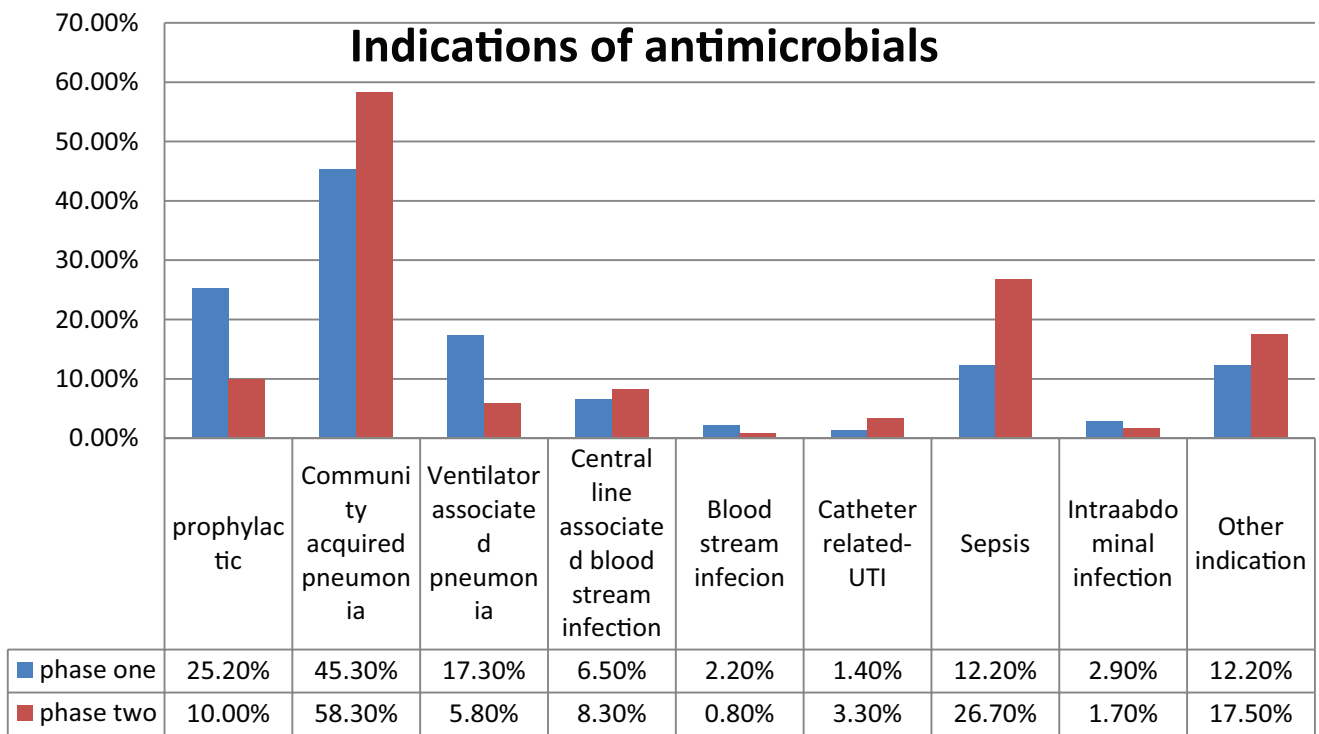
1. Clinical outcome of patients received ASP recommendations: Was measured by calculating the percent of discharge and deaths among patients received treatment according to the ASP recommendations
2. LOS was measured by dividing the total number of occupied hospital bed-days by the total number of admissions or discharges [10]
3. Drug costs were measured based on summing up the monthly dispensed amount of each antimicrobial during the study period [8].

Results

One hundred fifty-one patients were admitted to the PICU in the pre-implementation phase; 55.3% of them were males with a mean age of 32.12 ± 17.5 months old. Moreover, in the post-implementation phase, 161 patients were admitted, 54.7% were males with a mean age of 24.53 ± 12 months old. The most common indication for antimicrobials in both phases was community-acquired pneumonia (45.3% and 58.3%, respectively). The percent of patients who received prophylactic antimicrobials significantly decreased from 25.2% pre-implementation to 10% post-implementation ($p = 0.002$).

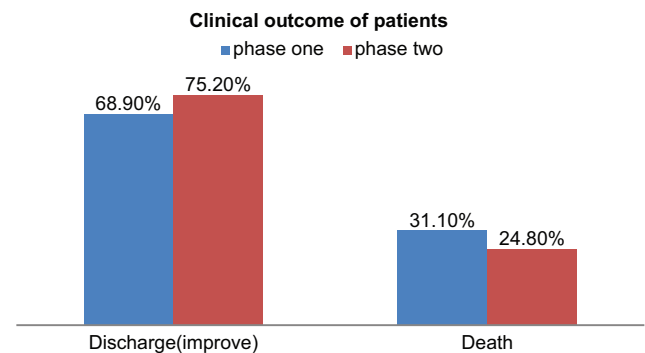
Process measures results

1. The rate of adherence of clinicians to ASP policy was 91.9%
2. ASP recommendations
In the post-implementation phase, the most frequent antimicrobials required interventions were ampicillin-sulbactam (21.6%) followed



by imipenem (8.1%) and vancomycin (6.4%). The most frequent drug-related problem was dose calculation error (15.8%) followed by prescribing an unnecessary drug with no medical indication (13.5%). Moreover, the most frequent recommendation was drug schedule/frequency change (26.1%) followed by drug discontinuation (17.8%).

- The rate of acceptance to ASP recommendations among patients in the post-implementation phase was 93.7%.



Antibiotic use measures

DOT

DOT of antibacterial drugs as shown in table 2 and DOT of all antimicrobials (antibacterial, antiviral, and antifungal) as shown in Table 3.

LOT

Significantly decreased from total 1502 days with mean 9.82 days pre-implementation to total 1318 days with mean 7.75 days post-implementation ($p = 0.001$).

Outcome measures results

Clinical outcome of patients

The percent of discharged patients was 68.9% pre-implementation and increased to 75.2% post-implementation. While the percent of deaths was 31.1% pre-implementation and decreased to 24.8% post-implementation ($p = 0.203$).

LOS

The mean \pm SD LOS was 10.66 ± 6.00 days pre-implementation and significantly decreased to 9.16 ± 5.00 days post-implementation ($p = 0.047$).

Drug costs

Drug costs significantly decreased by 19.66% from (68164.94 L.E.) pre-implementation to (54764.96 L.E.) post-implementation ($p = 0.01$).

Discussion

ASP implementation in hospitals is mandatory, especially with steadily developing global antimicrobial resistance. The current study showed that the clinical

services most commonly interacting with the ASP post-implementation were pediatric respiratory service (40.4%) followed by neurological service (18.6%), while the clinical service most commonly interacting with the ASP in a study of Newland *et al.*, 2012 was general pediatric/resident service (20%) followed by hematology/oncology (17%) and hospitalist (17%) [11].

The most common indication of antimicrobial intake was CAP (58.3%) followed by sepsis (26.7%) post-implementation. Newland *et al.*, 2012 reported that the primary indications for antimicrobials included suspected sepsis (28%), fever, neutropenia (12%), and intra-abdominal infections (9%) [11].

The percent of prophylactic antimicrobial courses in our study decreased significantly post-implementation from 25.2% to 10% ($p < 0.05$), and this was the aim of the study to optimize antibiotics use to decrease antibiotics expenditure. This result agreed with the study of Stocker *et al.*, 2012 who reported that the percent of prophylactic antimicrobial courses decreased significantly post-implementation from 66.5% to 55.5% ($p = 0.02$) [12].

Unlike our results, ASP implementation at PICU in Agha Khan University Hospital showed that the rate of antimicrobial courses taken for prophylaxis did not change in the pre-implementation phase 43% versus the post-implementation phase 43.2% [1].

The most common ASP recommendation in this study was drug schedule/frequency change (26.1%) followed by drug discontinuation (17.8%) which are consistent with those reported by Di Pentima *et al.*, 2011 as the dose adjustment formed 40.2% of total recommendations (672 of 1673) while the modification of antimicrobial therapy formed 34.8% (583 of 1673) [13]. Other authors showed different recommendations; the most common was the modification of antimicrobial therapy which accounted for 48.5% in the study of Kreitmeyr *et al.*, 2017, while in McCulloh *et al.* 2015 study, it was the discontinuation of antibiotic (28.6%) and the most common antibiotic required recommendation was ceftriaxone (44%) [2], [14].

The most frequent antimicrobial required interventions in our study were ampicillin-sulbactam (21.6%) followed by imipenem (8.1%) and vancomycin (6.4%). Other studies, in the USA, showed different results, in Di Pentima *et al.*, 2011 study the most frequent antimicrobial required interventions were vancomycin (16%) (268 of 1673), piperacillin-tazobactam (11%) (184 of 1673), ceftriaxone (6.3%) (105 of 1673), and fluconazole (5%) (82 of 1673) [13]. Newland *et al.*, 2012 reported that the most common antimicrobials reviewed by the ASP included ceftriaxone/cefotaxime (43%), vancomycin (18%), and ceftazidime (17%) of total 2378 recommendations [11].

The rate of acceptance of ASP recommendations in our study was 93.7% among 349 recommendations indicating the raised awareness of clinicians toward the

rationalized antibiotics use in this tertiary hospital with the high flow of patients and that was slightly higher than that reported by Di Pentima *et al.*, 2011 and McCulloh *et al.*, 2015 which was 86.9% in both studies (total recommendations were 1637, 350 respectively), [13], [14] and it was 80% of total recommendations 2378 in a study of Newland *et al.*, 2012 [11].

The rate of acceptance of ASP recommendations in Kreitmeyr *et al.*, 2017 study in German hospitals was slightly higher than in our study (95.8%) of total recommendations 167 [2].

The percent of patients received antimicrobials was 92.7% pre-implementation (151 patients) compared to 74.5% post-implementation (161 patients) ($p < 0.001$) indicating the beneficial effect of ASP in optimizing antibiotic use. Unlike our results, the impact of ASP in Kreitmeyr *et al.*, 2017 study which revealed a minimal change in the percent of hospitalized children who received antimicrobials pre-implementation (30.6%) (1007 patients) versus post-implementation (30.5%) (967 patients) [2].

Our study showed the positive effect of the ASP in optimizing antibiotic use as all antibiotics; DOT decreased by 13.5%, with significant effect regarding ceftazidime, ceftriaxone, and amikacin. Other antibiotics DOT, including cephalosporins, aminopenicillins with beta-lactamase (ampicillin-sulbactam and amoxicillin-clavulanic acid) piperacillin-tazobactam, meropenem, ciprofloxacin, all aminoglycosides, trimethoprim-sulfamethoxazole, vancomycin, and metronidazole also showed reduction post-implementation (Table 2). Kreitmeyr *et al.* 2017 study showed a similar reduction in all antibiotic use by 10.5% post-implementation, this reduction was significant in 3rd generation cephalosporins (22.3%), fluoroquinolones (59.9%) (from 32 to 13 DoT/1000 PD), and metronidazole (51.1%) (from 27 to 13 DoT/1000 PD). However, they differ from our study in the consumption of combined aminopenicillins with beta-lactamase inhibitors as ampicillin-sulbactam and amoxicillin-clavulanic acid in which DOT significantly increased by 78.8% (from 17.1 DoT/1000 PD to 30.5 DoT/1000 PD) [2].

Other studies reported similar effective ASP in a significant reduction of all antibiotics DOT/1000 PD in the ASP period includes Haque *et al.* study which reported reduction by 64% from 3477 DOT/1000 PD to 1323 DOT/1000 PD and Newland *et al.* study which reported reduction from 883 DOT/1000 PD to 787 DOT/1000 PD [1], [11].

This study showed significantly increased DOT in gentamicin by 75.4% (from 23.3 DOT/1000 PD to 94.7 DOT/1000 PD) ($p = 0.009$), unlike Di Pentima *et al.*, 2011 study which showed a significant reduction in the use of gentamicin (from 372 doses/1000 PD to 92 doses/1000 PD) ($p < 0.001$) [13].

Unlike our results where carbapenem DOT/1000 PD showed a mild insignificant increase by

Table 2: DOT antibacterial drugs

Antibiotic	Phase one – patient days=1804			Phase two – patient days=1648			Difference		
	DOT total	DOT/1000PD	%	DOT total	DOT/1000PD	%	p-value	DOT/1000PD	%
All (3 rd + 4 th) cephalosporins	271	150.2	9.7	153	92.8	6.9	0.093	-57.4	-38.2
3 rd cephalosporins	267	148	9.5	122	74	5.5	0.065	-74	-50
Ceftazidime	60	33.3	2.1	4	2.4	0.2	0.041	-30.9	-92.8
Ceftriaxone	161	89.2	5.7	51	31	2.3	0.026	-58.2	-65.2
Cefotaxime	46	25.5	1.6	67	40.7	3	0.937	15.2	37.3
4 th cephalosporins	4	2.2	0.1	31	18.8	1.4	0.310	16.6	88.3
All combinations	605	335.4	21.6	380	230.6	17.1	0.180	-104.8	-31.2
Amoxicillin/clavulanic acid + Ampicillin/sulbactam	424	235	15.1	292	177.2	13.2	0.394	-57.8	-24.6
Amoxicillin/clavulanic acid	29	16.1	1	0	0	0	0.065	-16.1	
Ampicillin/sulbactam	395	219	14.1	292	177.2	13.2	0.485	-41.8	-19.1
Cefoperazone/sulbactam	0	0	0	18	11	0.8	0.699	11	
Piperacillin/tazobactam	181	100.3	6.4	70	42.5	3.2	0.180	-57.8	-57.6
All carbapenems	407	225.6	14.5	427	259.1	19.2	0.485	33.5	1.4
Imipenem	87	48.2	3.1	154	93.4	6.9	0.394	45.2	48.4
Meropenem	320	177.4	11.4	239	145	10.8	0.485	-32.4	-18.3
Ertapenem	0	0	0	34	20.6	1.5	0.180	20.6	
All fluoroquinolones	262	145.2	9.3	306	185.7	13.8	0.065	40.5	21.8
Ciprofloxacin	229	127	8.2	187	113.5	8.4	0.818	-13.5	-10.6
Levofloxacin	33	18.3	1.2	119	72.2	5.4	0.026	53.9	74.7
All aminoglycosides	443	245.6	15.8	270	163.8	12.2	0.485	-81.8	-33.3
Amikacin	401	222.3	14.3	114	69.2	5.3	0.004	-153.1	-68.9
Gentamycin	42	23.3	1.5	156	94.7	7	0.009	71.4	75.4
Trimethoprim/sulfamethoxazole	116	64.3	4.1	31	18.8	1.4	0.240	-45.5	-70.8
Polymyxin B	99	54.9	3.5	121	73.4	5.5	0.589	18.5	25.2
Tigecycline	13	7.2	0.5	13	7.9	0.6	0.699	0.7	8.9
Neomycin	7	3.9	0.2	31	18.8	1.4	0.589	14.9	79.3
Metronidazole	122	67.6	4.3	70	42.5	3.2	0.485	-25.1	-37.1
Vancomycin	349	193.6	12.4	179	108.6	8.1	0.132	-85	-43.9
Teicoplanin	18	10	0.6	27	16.4	1.2	0.065	6.4	40.1
Erythromycin	86	47.7	3.1	119	72.2	5.4	0.394	24.5	33.9
Clindamycin	9	5	0.3	92	55.8	4.1	0.026	50.8	91
All antibiotics	2807	1556	100	2219	1346.4	100	0.394	-209.6	-13.5

Table 3: DOT – all antimicrobials (antibacterial, antiviral, and anti-fungal drugs)

Antimicrobial	Phase one – patient days=1804			Phase two – patient days=1648			Difference		
	DOT total	DOT/1000PD	%	DOT total	DOT/1000PD	%	p-value	DOT/1000PD	%
All antibiotics	2807	1556	88.1	2219	1346.4	90.1	0.394	-209.6	-13.5
Acyclovir	100	55.4	3.1	149	29.7	6	0.394	-25.7	-46.4
Tamiflu	8	4.4	0.3	9	5.5	0.4	0.818	1.1	20
Amphotericin B	64	35.5	2	18	11	0.7	0.485	-24.5	-69
Fluconazole	206	114.2	6.5	157	95.3	6.4	1.000	-18.9	-33.9
Mycamine	0	0	0	12	7.3	0.5	0.394	7.3	
All antimicrobials	3185	1765.5	100	2464	1495.1	100	0.180	-270.4	-15.3

1.4% (from 225.6 DOT/1000 PD to 259.1 DOT/1000 PD), Horikoshi *et al.*, 2017 Japan reported that carbapenem DOT/1000 PD significantly decreased by 59.3% (from 4.94 DOT/1000 PD to 2.01 DOT/1000 PD) [15].

Certain antimicrobials consumption improved post-implementation, as the DOT of amphotericin B declined by 69% (from 35.5 DOT/ 1000 PD to 11 DOT/ 1000 PD) ($p = 0.485$). Similarly, Di Pentima *et al.* 2011 reported that amphotericin B was peaked at 50 doses pre-implementation versus 4 doses per 1000 patient days post-implementation ($p < 0.0001$) [13].

A comparison in average antibiotic use was done in the USA (9 hospitals implemented ASP and 22 hospitals did not implement ASP). ASP+ hospital experienced a greater decline in all antibiotic use; (11%) versus (8%) in ASP- hospitals, ($p = 0.04$) [16].

The length of therapy in our study showed significant improvement which also denotes the positive effect of the ASP on antibiotic use (from 1502 days to 1318 days) ($p = 0.001$). Similarly, Kreitmeyr *et al.*, 2017 study demonstrated a significant decline in overall LOT by 7.7% (from 377.4 to 348.3 LOT/1000 PD) ($p = 0.02$) [2].

Similarly, the length of therapy decreased from 567 to 523 LOT per 1000 PD ($p < 0.001$) in Newland *et al.*, 2012 [11].

The overall mortality in the current study decreased insignificantly from 31.1% (among 151 patients) to 24.8% (among 161 patients). Similarly, Kreitmeyr *et al.*, 2017 reported an insignificant difference regarding in-hospital mortality during pre- and post-implementation periods (0.37% among 273 patients vs. 0.38% among 263 patients, respectively) [2]. However, Horikoshi *et al.* 2017 reported a significant decrease (from 0.087/1000 PD to 0.051/1000 PD) in infection-related mortality due to ASP's positive effect on the clinical outcome of the patient.

In this work, the mean length of hospital stays showed a significant decline from mean 10.66 days to 9.16 days post-implementation, giving this overcrowded tertiary hospital a better capacity to provide medical services for more patients. Comparable findings were reported by Horikoshi *et al.*, 2017 (from mean 20.6 to 18.6 days), [15] while Kreitmeyr *et al.* 2017 reported that the average length of stay remained stable with a median 7 days (range 1–93 days) versus 6 days (range 2–123 days) [2].

Antimicrobial costs significantly reduced by 19.66% ($p = 0.01$), which is consistent with the report of Haque *et al.*, 2018, where the drug costs were significantly decreased by 58% ($p < 0.0001$) [1].

Conclusion and Recommendations

The ASP is very important and very effective in optimizing and improving the antibiotic use to reach the best clinical outcome of the patients and to decrease hospital length of stay and drug costs.

Considering the relatively small population study and the short period of observation, lack of financial resources, lack of effective IT electronic system linking the multidisciplinary departments together, we recommend ASP implementation over a larger population and hospital settings with more comprehensive administration involvement that could afford financial resources and commit all departments to the ASP.

Ethical committee

The study was ethically approved by the research ethics committee of the faculty of medicine, Cairo University.

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