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Antibiotic regimens tailored by clinical pharmacist supported by intensivist enhance rational use of antibiotics

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ABSTRACT

Background: High antibiotics utility rates have been observed in surgical intensive care units (SICU). The present study was performed to evaluate the effect of engaging a clinical pharmacist in SICU on rational use of antibiotic treatment.

Methods: This retrospective quasi-experimental experiment involved 505 patients, over a period of one year, admitted to emergency department surgical/trauma ICU of a large tertiary care hospital. Before and during pharmacist participation periods of six months, 226 and 153 patients, respectively, are compared.

Results: Antibiotics consumption pattern changed with a decrease in total antibiotic consumption from 101.42 to 94.1 Defined Daily Dose/100 patients' days after the clinical pharmacist participation, in addition to, a statistically significant rise ($p = 0.001$) in percentage of appropriateness of the prescribed antibiotic therapy from 72.1% to 86.3%. Time to control infection (days) was not statistically different ($p = 0.825$) in both periods. The average ICU days of stay was statistically significant longer ($p = 0.046$) during pharmacist attendance (4.42 ± 5.61) in comparison with period without pharmacist attendance (3.31 ± 3.66). The difference in ICU mortality rate was not statistically significance ($p = 0.217$). Cost per stay increased by 65% during pharmacist intervention period.

Conclusions: Antibiotic management with pharmacist participation as a part of multidisciplinary team with intensivist can promote rate of the appropriateness of the prescribed antibiotic therapy, lower utility of antibiotic consumption, but with a longer ICU stay, no mortality reduction, and higher expenses per stay.

Trial Registry: ClinicalTrials.gov: NCT04931914.

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1. Background

In critical care units, polypharmacy is a quite common practice, and patients' care has developed into a multidiscipline [1]. Pharmacists offer a crucial role handling medication contained by the complexity of drug therapy, complexity of different routes of administration, severe and promptly changing pharmacokinetic and dynamic constraints, and extremes of critical illness physiology [2]. Clinical pharmacists are certified pharmacists with focused innovative education, who perform an important task in promoting the best possible application of antimicrobials and provide patients with broad drug supervision and associated concern in all medical fields. Interventions made by a clinical pharmacist committed to the postsurgical patient population, as a part of multidisciplinary team, allows for optimization of antimicrobial and other medications, improves outcomes for patients [3,4].

In surgical intensive care unit (SICU) patients' management of infections poses definite contests, diagnosis is often challenging and, with prompt processing of proper antibiotics as one of the most crucial aspects [5]. As in other infections, multidrug resistance is progressively reported in SICU, and changes in pharmacokinetics may necessitate special dosing plans [6]. The choice of antimicrobial prescriptions has to be a balance between the gains of an insistent empirical therapy and the threats of development of pathogens with antimicrobial resistance [7].

Analyses contemplating various facets of clinical pharmacist involvements in hospitalized patients came to be at the core of awareness and concern in the recent past. This study was directed to assess effects of the provision of antibiotic regimens tailored by clinical pharmacist supported by intensivist in critically ill patients in SICU of emergency department (ED)

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on the rational use of antibiotics. Antibiotics consumption was used to measure the effectiveness of the intervention as the primary outcome, and its impact on health and economy as the secondary outcomes.

2. Methods

The present study is a single-center, cohort, retrospective observational research using a pre-post quasi-experimental design of a single treatment cohort and a non-equivalent comparator cohort. Ethical approval was obtained from the Medical Ethics Committee of Alexandria Main University Hospitals (IRB # 00012098) on 18th February, 2021. The trial adhered to EQUATOR guidelines for observational studies and was registered in ClinicalTrials.gov (Clinical Trial ID: NCT04931914, date of registration: 6th August 2021). The study was performed in the SICU at the ED of the university-affiliated tertiary-care hospital in Alexandria, Egypt. Since data was abstracted from patient records when all patients were either discharged after recovery or died through admission, obtaining patients' approval consent was not possible.

The study sample included all patients who were admitted by transfer from ED operating rooms and then discharged/died all over the year 2020, with exception of patient had stayed less than 24 hours (comprising deaths and transfers), patients with renal failure, and pediatric patients weighted less than 50 kilograms. The study was divided into two phases; pre-intervention (from 1st January 2020, to 30th June 2020): antibiotic regimens were directed by intensivist alone, and post-intervention (from 1st July 2020, to 31st December 2020): antibiotic regimens were directed by a trained clinical pharmacist recommendation and supported by intensivist. During the intervention period, a trained pharmacist team who joined the SICU team shared in daily unit rounds with intensivists with an emphasis on optimization of anti-infectious pharmacotherapy.

Data including age, gender, comorbidity described as Charlson comorbidity score (CCS) [8], surgical procedure done, patients' temperature, white blood cells count, type of infections (e.g., intra abdominal infections, soft tissue infections, pneumonia, sepsis, intracranial infection), prescribed antibiotics regimen either they were used as surgical prophylaxis, empirical, or based on cultures, results of culture sensitivity tests, length of stay, and mortality were abstracted from the hospital patients' medical files. Review of medical records was done by personal who did not share in applying the intervention.

Antibiotic consumption was the primary outcome parameter and calculated as sum of defined daily doses (DDD), stated as DDD per one hundred patient-days. To calculate, ATC (Anatomical Therapeutic Chemical) codes and DDD for each antibiotic were obtained from WHO website. The following formula was used to calculate: DDD per 100 inhabitant per day (DID) = (total consumption in DDDs x 100)/(covered inhabitants x days in the period of data collection) [9]. Data for each and total antibiotic used was analyzed. The secondary outcome parameters were health outcomes including time (days) to control infection indicated by return of patient's temperature and white blood cells count to normal, appropriateness (Appropriate, or Inappropriate) of the prescribed antibiotic based on matching with culture sensitivity test results and/or the American Society of Infectious Diseases guidelines, average ICU length of stay (LOS) measured by dividing the entire number of days stayed by all admitted patients during a period by the number of admissions and ICU mortality rate estimated by dividing the number of deaths of admitted patients by the number of admissions, and economic outcome as antibiotic charges per patient.

Sample size was calculated by Power Analysis and Sample Size Software (PASS 2020) "NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/pass" based on previous study evaluating impact of the pharmacist on a multidisciplinary team [10]. A minimal total hypothesized sample size of two hundred eligible patients SICU in ED of the University hospital was needed to measure the effectiveness of using antibiotic regimens directed by clinical pharmacist recommendations on reducing antibiotics consumption; taking into consideration 95% confidence level and 90% power using Paired t-test. Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp). Categorical data were represented as numbers and percentages. Chi-square test was applied to compare between two phases. For continuous data, they were tested for normality by the Kolmogorov- Smirnov test. Quantitative data were expressed as range (minimum and maximum), mean, standard deviation and median. Student t-test was used to compare two phases for normally distributed quantitative variables while Mann–Whitney test was used to compare two phases for not normally distributed quantitative variables. Significance of the obtained results was judged at the 5% level.

3. Results

Figure 1 shows the study CONSORT flowchart. Four hundred and sixty-five patients' file were reviewed for eligibility to be included in the study, 270 of them were allocated in pre-intervention group while 193 were allocated in post-intervention group. After exclusions due to not meeting inclusions criteria or incomplete date, 226 and 153 patients in pre-intervention and post-intervention groups respectively were analyzed.

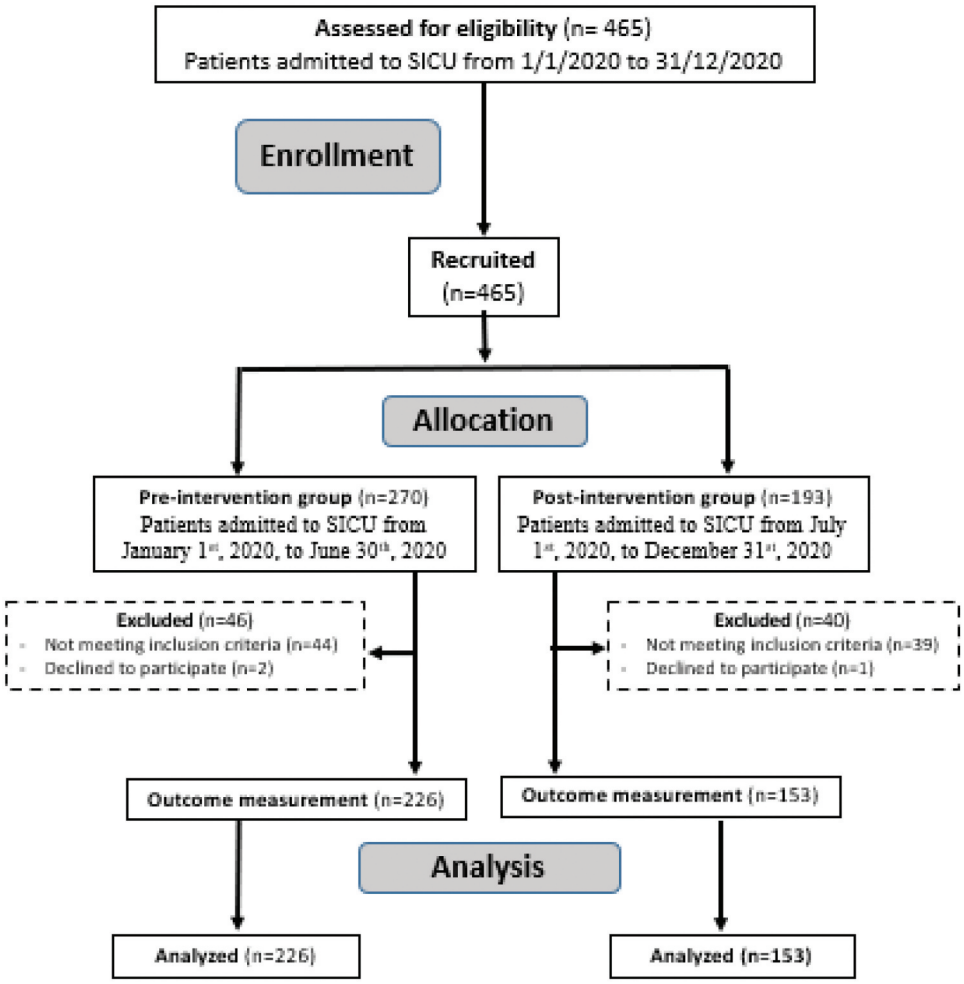

Figure 1. The study CONSORT flowchart.

4. Patient characteristics

The patients' basic characteristics prior to and afterwards pharmacist attendance showed no statistically significant differences (Table 1).

5. Antibiotics consumption

Antibiotics consumption presented as DDD/100 patients' days throughout the two phases are shown in Figure 2 and Table 2. During pre-intervention per-

Table 1. Patients' characteristics during the pre- and post-intervention periods.

Characteristics	Pre-intervention	Post-intervention
Admissions, n	226	153
Age, mean (SD)	49.73 (18.16)	47.08 (18.47)
Male, n (%)	162 (71.7)	100 (65.4)
Female, n (%)	64 (28.3)	53 (34.6)
Median Charlson Comorbidity Score (Min. – Max.)	2.0 (0.0–12.0)	2.0 (0.0–10.0)
Principal surgeries (top 5), n (%[a])		
Abdominal exploration	112 (49.6)	76 (49.7)
Craniectomy	52 (23.0)	33 (21.6)
Amputation	18 (8.0)	8 (5.2)
Neck abscess drainage	15 (6.6)	12 (7.8)
Thoracotomy	6 (2.7)	11 (7.2)
Principal infections (top 6), n (%[b])		
Intrabdominal infections	104 (46.0)	71 (46.4)
Soft tissue infections	44 (19.5)	29 (19.0)
Ventilator associated pneumonia	39 (17.3)	25 (16.3)
Sepsis	20 (8.8)	14 (9.2)
Intracranial infection	9 (4.0)	3 (2.0)
Community acquired pneumonia	2 (0.9)	6 (3.9)

Data are number (%) unless otherwise indicated. SD, standard deviation; [a]Mann–Whitney test; [b]Chi square test; *p*, *p* value for comparing between the studied phases, statistically significant at $p \leq 0.05$.

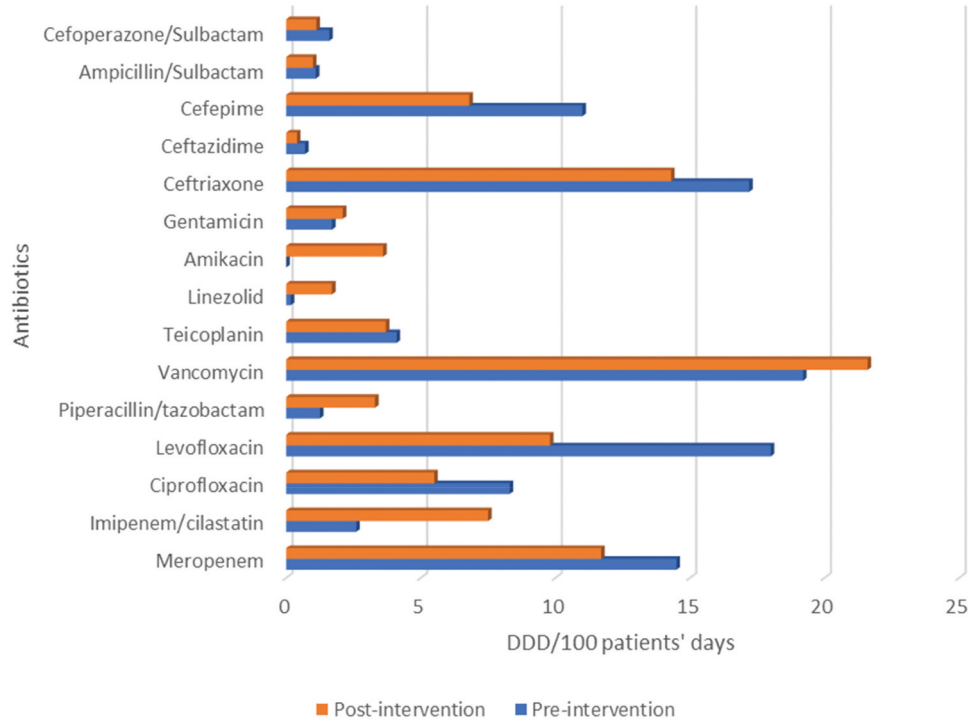

Figure 2. Antibiotic consumption (DDD/100 patients' days).

Table 2. Antibiotic consumption (DDD/100 patients' days).

Antibiotics	Pre-intervention	Post-intervention
Meropenem	14.5	11.7
Imipenem/cilastatin	2.6	7.5
Ciprofloxacin	8.3	5.5
Levofloxacin	18	9.8
Piperacillin/tazobactam	1.25	3.3
Vancomycin	19.2	21.6
Teicoplanin	4.1	3.7
Linezolid	0.17	1.7
Amikacin	0	3.6
Gentamicin	1.7	2.1
Ceftriaxone	17.2	14.3
Ceftazidime	0.7	0.4
Cefepime	11	6.8
Ampicillin/sulbactam	1.1	0.99
Cefoperazone/sulbactam	1.6	1.12
Total	101.42	94.1

Table 3. Clinical and economic outcomes during the pre- and post-intervention periods.

	Pre-intervention (n = 226)		Post-intervention (n = 153)		Test of sig.	p
Infections	**No.**	**%**	**No.**	**%**		
No infection	105	46.5	69	45.1	χ^2 = 0.068	0.966
Controlled infection	62	27.4	43	28.1		
Not controlled infection	59	26.1	41	26.8		
Time to control infection (days)						
Mean ± SD.	3.11 ± 2.23		3.26 ± 2.37		U = 1300.0	0.825
Median (Min. – Max.)	2.50 (1.0–11.0)		2.0 (1.0–11.0)			
Appropriateness	**No.**	**%**	**No.**	**%**		
No	63	27.9	21	13.7	χ^2 = 10.590*	0.001*
Yes	163	72.1	132	86.3		
Length of stay (days)						
Mean ± SD.	3.31 ± 3.66		4.42 ± 5.61		U = 15257.0*	0.046*
Median (Min. – Max.)	2.0 (1.0–34.0)		2.0 (1.0–30.0)			
Mortality	**No.**	**%**	**No.**	**%**		
Dead	69	30.5	56	36.6	χ^2 = 1.521	0.217
Discharged	157	69.5	97	63.4		
Average Cost (EGP)/patient	714.35		1179.04			

SD Standard deviation; U Mann–Whitney test; χ^2 Chi square test; p: p value for comparing between the studied phases; *: Statistically significant at $p \leq 0.05$.

iod, there was an increasing consumption of Meropenem, Ciprofloxacin, Levofloxacin, Ceftriaxone, Cefepime, Ceftazidime, Teicoplanin, Ampicillin/sulbactam, Cefoperazone/sulbactam, and of the total amount of antibiotics compared to post-intervention period, when a reduction in the consumption level of the previously mentioned antibiotics were noted, with concomitant increases in consumption of other antibiotics included Imipenem/cilastatin, Piperacillin/tazobactam, Vancomycin, Linezolid, Amikacin, and Gentamicin. Finally, there was a decrease in consumption in the overall amount of antibiotic during post-intervention period. The rate of antimicrobial utility in ICU declined from 101.42 to 94.1 DDD/100 patients' days after the clinical pharmacist participation.

6. Clinical and economic outcomes

As shown in Table 3 the percentage of the appropriateness of the prescribed antibiotic therapy was higher during the post-intervention period ($p = 0.001$), with an increase in percentage of patients with appropriate antibiotic prescription from 72.1% during pre-intervention period to 86.3% during post-intervention period which was a statistically significant difference, through a comparable percentage of infections that was controlled, analogous percentage of infections that was not controlled, and similar proportion of patients who received prophylactic antibiotics with no suspected infections in both groups. In studied patients who received antibiotics for a suspected infection, time to control infection (days) was not statistically different ($p = 0.825$) in both periods, with a mean ± SD of 3.11 ± 2.23 days in pre-intervention group and 3.26 ± 2.37 days in post-intervention group. The average ICU LOS was longer during post-intervention period in comparison with pre-intervention period and had a statistically significant difference. The statistical difference in mortality rate between both groups was not significant ($p = 0.217$). The average cost per stay changed during post-intervention period with 65% increase in expense.

7. Discussion

This article describes the incorporation of a clinical pharmacist into SICU of ED that have not received widespread attention, particularly in terms of antibiotics utility outcomes and appropriateness of antibiotics prescription. The results indicate that during pharmacist presence the rate of antibiotics agent utilizations changed but with increased percentage of the appropriate prescriptions beside a comparable average time to control infections, while length of ICU stay had failed to shorten, ICU mortality rate showed no statistically significant difference, and the average cost per patient was higher. In the current analysis, three indicators were applied to evaluate the usefulness of pharmacist involvements: antibiotics consumption, clinical indicators, and cost.

During pharmacist period there were a decrease in consumption of cephalosporins, penicillins, fluoroquinolones, meropenem from carbapenem group, and teicoplanin from glycopeptide group while in response to emergence of multidrug resistance strains which was proved by results of cultures and sensitivity, pharmacist intervention was accompanied with increased consumption of aminoglycosides, fourth generation penicillin, oxazolidinones, vancomycin from glycopeptide group, and imipenem from carbapenem group based on empirical antibiotic outlines that cover the possible pathogen(s) and augmented with local ecology information to govern the most suitable empirical antimicrobial treatment. Likewise, in the background of surgical infections, when chosen empirical and directed antimicrobial therapy, ICU team thought some constraints of the microbiology diagnostic procedures into account. First: infections are usually polymicrobial. Second: anaerobic microbes are difficult to isolate, and often overlooked; these should be covered by the antibiotic therapy [11].

Similar to current research, Carling et al. [12] with an interdisciplinary antibiotic handling plan throughout all the hospital to lessen the inappropriate usage of third generation cephalosporins, detected a 22% reduction in consumption of broad-spectrum antibiotics. Hisham et al. [1] study over a period of one year proved that the process of converting patients from a broad spectrum antibiotic, which covers several different types of disease-causing bacteria to a narrow spectrum antibiotic that targets a specific infecting organism, and dose optimization in the existence of a clinical pharmacist is advised in surgical/trauma ICU. In the study by Scaglione et al. [13], clinical pharmacist involvements were efficient in justifying use of antibiotics, especially in dose optimizing. Magedanz et al. [10] to support judicious application of antimicrobial drugs, multidisciplinary teams were developed with the presence of a pharmacist and reported a significant decline in utilization of ampicillin/sulbactam fluoroquinolones, and clindamycin and an increase in total cephalosporins use. These results also coincided with a retrospective chart review by Cappelletty and Jacobs [14] who detected that temporary lack of a pharmacist from the antimicrobial stewardship group was coupled with raised rates of inappropriate use of restricted antimicrobial drugs. In a tertiary care hospital, a cross-sectional study designed by Baral et al. [15] who observed that total DDD of parenteral antibiotics increased by 23%, DDD per 100 admissions increased by 10%. The antibiotic frequently consumed was ceftriaxone, with a growing

trend in the consumption of vancomycin and meropenem. The difference in the pattern of the change in antibiotics groups consumption with pharmacist intervention may be attributed to difference in type of patients and type of infections patient had been exposed in between all previous studies.

In the present study LOS was statistically significantly longer during pharmacist participation, which can be attributed to intra-abdominal infections that showed the highest incidence throughout both periods of the study. Abdominal infections more, are linked to a long ICU stay, more shock and acute kidney injury and above average mortality in contrast with other infections [16] and thus be worthy of appropriate awareness. In agreement, Saokaew et al. [17] reported 1 day increase in ICU LOS with the presence of a devoted ICU pharmacist in intervention group. Similarly, Klopotowska et al. [18] found a 0.6 day increase with presence of a resolute ICU pharmacist. In contrast to results of the current analysis, MacLaren et al. [19] reported that contrasted to ICUs with participation of clinical pharmacists in antibiotics management, LOS in ICUs that did not include clinical pharmacists were lengthy. Correspondingly, other analysis by Shen et al. [20] found that the ICU LOS was shorted after clinical pharmacist intervention. While Bedini et al. [21] revealed that the interference had no effect on the duration of stay, which may be associated to variances in the research design and analytical processes.

The current study did not demonstrate a reduction in mortality during pharmacist intervention which contradict the claims of Lee et al. [22] in a systematic review reported that intervention of critical care pharmacists was significantly correlated with the decreased probability of mortality compared with no intervention. Also, Bond et al. [23] indicated that clinical pharmacy interventions are associated with lower hospital mortality ratios, and MacLaren et al. [19] reported that contrasted to ICUs with clinical pharmacists, rates of mortality in ICUs that did not have clinical pharmacists were higher. This contradiction could be due to the nature of SICU and the type of patients as trauma and major surgeries particularly neurological trauma patients with its complications have its impact on mortality.

Contrary to the hypothesized association in this report increased average drug cost per patient during pharmacist intervention may be caused by factors such as rising medical expenses during that period which may be was related to exhaustion of medical supplies by pandemic of COVID-19 virus. Kucukarslan et al. [24] reviewed the influence of a pharmacist who is constantly assigned to the medical ICU and found no significant differences with clinical pharmacist participation on drug charges. Magedanz et al. [10] found that a significant reduction in consumption of some antibiotics use was concomitant with a significant reduction in hospital antibiotics expenses. In a similar retrospective analysis, multidisciplinary tertiary care hospital at a 500-bed in Oman at Sultan Qaboos University Hospital from January to December 2018, Salman et al. [25] found that pharmacists' interventions was translated into cost reductions. Lucca et al. [26] of a tertiary care Indian hospital investigated clinical pharmacist interventions to measure the pharmacoeconomic impact in intensive care settings and reported a considerable influence on the cost of drug therapy along with the patient outcomes.

The vitalities of the present study are that it is one of the few experiments in the region that examined the influence of clinical pharmacist interventions on antimicrobial therapy. In addition, these services were selected to high-risk areas such as the ED surgical ICU. Nevertheless, this study has limitations. First, it was planned short of relating a concurrent control group, consequently the outcomes may be predisposed by the period, notably the period of application of the intervention was associated with the timing of the lock down related to COVID-19 pandemic which might affect number of patients admitted to ED and was related to increased expenses of medical supplies and drugs and remained linked to inappropriate consumption of antibiotics by individuals in the community [27]. Second, this was a single-center study. Third, although mortality increased but not statistically significant for the period of the pharmacist actions, it may not only be assigned to the job of the pharmacist but could also be linked to the clinical supervision conducted during that time. Further research is required to establish the responsibility of the ICU clinical pharmacists in this type of intensive care units over a longer time than one year. These findings require to be reinforced with additional analyses and the specific actions related to the greatest value defined.

8. Conclusions

In developing countries, traditional obstacles to the application of Antibiotics Stewart Programs are complicated to overwhelm. A non-expensive program, with collaboration from the physician and pharmacist, may designate a more logical prescription of antimicrobials, and altering bacterial resistant patterns. In summary, in management of infections in critically ill surgical patients, this research revealed that the interventions offered by clinical pharmacist could improve the antibiotic therapy regimens and make antibiotics prescription more appropriate. Observing the results of this work we can say that the involvement of clinical pharmacist in consistent manner in SICU team provides improving in some clinical patients' outcomes and addressing more appropriate antibiotics consumption.

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Ethical approval

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Registry number

Clinical Trial Registry (NCT04931914) URL: https://clinicaltrials.gov/ct2/show/NCT04931914?term=NCT04931914&draw=2&rank=1

We wish to exclude this clinical trial registration from the similarity index.

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