original article

Antimicrobial stewardship program implementation in a medical intensive care unit at a tertiary care hospital in Saudi Arabia

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BACKGROUND AND OBJECTIVES: Antimicrobial stewardship programs (ASPs) have shown to prevent the emergence of antimicrobial resistance associated with an inappropriate antimicrobial use. The primary objective of this study was to compare the prescribing appropriateness rate of the empirical antibiotic therapy before and after the ASP implementation in a tertiary care hospital. Secondary objectives include the rate of Clostridium difficile–associated diarrhea (CDAD), physicians' acceptance rate, patient's intensive care unit (ICU) course, total utilization using defined daily dose, and total direct cost of antibiotics.

DESIGN AND SETTINGS: This is a comparative, historically controlled study. Adult medical ICU patients were enrolled in a prospective fashion under the active ASP arm and compared with historical patients who were admitted to the same unit before the ASP implementation. This study was approved by the institutional review board, and the need for informed consent was waived because the interventions and recommendations were evidence based and considered the standard of care. The study was conducted at KFSHRC, Riyadh.

METHODS: Adult medical ICU patients were enrolled under the active ASP arm if they were on any of the 5 targeted antibiotics (piperacillin/tazobactam, imipenem/cilastatin, meropenem, vancomycin, tigecycline), and had no official infectious disease consultation. The interventions were conducted via prospective audit and feedback.

RESULTS: A total of 73 subjects were recruited, 49 in historical control and 24 in the active arm. The appropriateness of empirical antibiotics was improved from 30.6% (15/49) in the historical control arm to 100% (24/24) in the proactive ASP arm (*P* value <.05). For the ASP group, initially 79.1% (19/24) of the antibiotic uses were inappropriate and diminished by ASPs to 0% on the recommendations implementation. A total of 27 interventions were made with an acceptance rate of 96.3%. The rate of CDAD did not differ between the groups. A reduction in antibiotics utilization and direct cost were also noticed in the ASP arm.

CONCLUSION: A proactive ASP is a vital approach in optimizing the appropriate empirical antibiotics utilization in an ICU setting in tertiary care hospitals. This study highlights the importance of such a program and may serve as a foundation for further ASP initiatives particularly in our region.

At the beginning of the mid-20th century, the development of new antibiotics led to remarkable improvements in the health outcomes. However, antibiotic-resistant microorganisms have become a clinical challenge in both inpatient and outpatient settings. Studies conducted over the years indicated that antibiotic use is unnecessary or inappropriate in 50% of cases in the United States.[1-6]

Numerous reports reviewed the relationship of the inappropriate use of antimicrobials in an acute care setting and increasing number of resistant pathogens resulting in a significant impact on patients' morbidity, mortality, and increasing health care costs.[1-6] Ibrahim et al[7] found that patients who received appropriate therapy, as compared with those who received inappropriate therapy, had significantly shorter durations of mechani-

cal ventilation (7 days versus 11 days, respectively) and shorter lengths of intensive care unit (ICU) stay (9 days versus 13.5 days, respectively). Carmeli et al[8] and Einarsson et al[9] reported a twofold increase in the hospital costs as a result of resistant Pseudomonas aeruginosa and penicillin-resistant Pneumococci. Therefore, the critical balance is to weigh the importance of the early appropriate empirical therapy, and the increase in mortality and antibiotic resistance when the initial therapy is delayed or inappropriate.[1-6]

Furthermore, Clostridium difficile is now recognized to be an important nosocomial ICU infection that is associated with considerable negative outcomes. A 2-year prospective observational study was conducted investigating the annual incidence of C *difficile* – associated diarrhea (CDAD) in Saudi Arabia. The incidence was estimated to be 1.2 and 0.9 per 1000 discharges, and 2.4 and 1.7 per 10 000 patient days in 2007 and 2008, respectively. The major risk factors for the CDAD acquisition were the use of broad-spectrum antimicrobials and increased duration of antibiotic therapy.[10,11]

A potential prevention and control approach to decrease the spread of resistance and extend the appropriate utility of antibiotics includes the implementation of an effective antimicrobial stewardship program (ASP), which is defined as the optimal selection, dosage, and duration of antimicrobial treatment that results in the best clinical outcome including cure or prevention of infection, decreased mortality and length of hospital stay, and minimal toxicity to patients.[1-6,12,13] The ASP utilizes a multidisciplinary initiative that overlaps with the membership of antimicrobial utilization & evaluation (AUE) subcommittee. Most ASPs include an infectious disease (ID) physician, supported by clinical pharmacists with ID training, in collaboration with microbiology, infection control, quality assurance, information system specialist, and a hospital epidemiologist.[14-20]

The Infectious Diseases Society of America (IDSA) and the Society for Healthcare Epidemiology of America (SHEA) published a landmark position paper in 2007 designed to guide the implementation of ASP at an acute care setting in line with the joint commission national patient safety goals of infection control measures.[14] The most effective approaches involved a comprehensive program that incorporated evidence based interventions.[6,12,21-24] The current ASP strategies adapted at King Faisal Specialist Hospital & Research Center (KFSHRC) are outlined in **Table 1**.

The ICU at KFSHRC represents a crucial setting where the ASP implementation is desperately needed for several reasons; high percentage of immune-compromised patients, and high incidence of antibiotic-resistant gram-negative rods including extended spectrum beta lacatmase, multidrug-resistant (MDR) Acinetobacter, and carbapenemase-producing Klebsiella.[12,13,21-28]

We hypothesized that implementing the ASP would enhance the appropriate use of empirical antimicrobial therapy in our ICU. Therefore, the main objective of our study was to assess the appropriateness of empirical antibiotic therapy before and after the implementation of "proactive" ASP in the medical ICU.

METHODS

Study design

This was a comparative, historically controlled study. Adult medical ICU patients were enrolled in a prospective fashion under the active ASP arm and compared with historical patients who were admitted to the same unit before the ASP implementation (**Figure 1**). This study was approved by the institutional review board, and the need for informed consent was waived because the interventions and recommendations were evidence based and considered the standard of care. The study was conducted at KFSHRC, Riyadh, which is an 894-bed tertiary care hospital with 20 adult beds at the medical ICU. Adult critically ill patients were defined for the ICU admission according to KFSHRC criteria as follows: those requiring mechanical ventilation (invasive or noninvasive); and/or those with a fraction of inspired oxygen (FiO_2) concentration ≥0.6; and/or those requiring intravenous infusion of inotropic or vasopressor medications. Patients ≥18 years were enrolled prospectively in the active arm if they were on 1 or more of 5 targeted antibiotics (piperacillin/tazobactam, imipenem/cilastatin, meropenem, vancomycin, tigecycline), and there was no official ID service consultation. Patients were excluded if they did not fit the previously mentioned inclusion criteria. The 5 targeted antibiotics were selected due to their broad spectrum of activity and represented 90% of the total antibiotics use in ICU.

The primary outcome of the study was to compare the appropriateness rate of empirical antibiotic therapy (initial and final) before and after the implementation of "proactive" ASP. The initial appropriateness was defined as the first intervention initiated by physicians in the ICU, while the final appropriateness was assessed following the ASP team interventions.

Secondary outcomes include the rate of CDAD, physicians' acceptance rate of the ASP recommendations, patient's ICU course, total antibiotics utilization, and direct cost of 5 targeted antibiotics. The

presence of CDAD was defined as the presence of loose bowel motions within 24 hours in a patient who recently (within 8 weeks) received or was receiving antibiotics and confirmed by 2 C *difficile* toxin assay from 2 separate bowel motions.[29] The consumption of antibiotics was converted into defined daily doses (DDDs) per 1000 patient-days according to the World Health Organization guidelines for anatomical therapeutic chemical classification and DDD assignment.[30] A patient-day was defined as the number of patients in the medical ICU per day and was calculated by multiplying the number of admissions by the average length of stay. The costs of medications were obtained from the hospital pharmacy warehouse and presented in US dollar ($).

The study was started by reviewing historical control data (when no ASP was implemented). The patients' microbiological results and medication profile were retrieved to determine the appropriateness of antibiotics that were used over 6 months.

In March 2011, the implementation of our ASP was initiated by the identification of team members (Intensivist/ID physician and ASP pharmacists), followed by defining the characteristics of ASP that would meet the hospital needs (prospective audit and feedback), and conducting educational in-services focused on study objectives, activities, and outcomes. The ASP pharmacists are ICU clinical pharmacy specialists and postgraduate year-1 residents. The designated ASP pharmacists used a standardized data collection tool to independently identify the patients who fit the inclusion criteria. The pharmacist then met with the Intensivist/ID physician to discuss each individual case, review the medical charts for pertinent subjective and objective information, monitor the patients' previous cultures, reduce adverse drug reactions by identifying individual patient factors that increase their risk of these reactions, and assess the appropriateness of empirical antibiotic therapy. The appropriateness was evaluated according to internally developed criteria including formulary restrictions and credible international guidelines to optimizing antibiotic regimen with regard to dose, frequency, route, and selecting the right antimicrobial agent for disease state and suspected causative pathogen. Stewardship interventions and recommendations were communicated to the primary ICU team verbally and through a form to determine the acceptability of the recommendation. Published reports supporting these recommendations were also sent to the primary ICU prescriber if requested. The complexity of cases was assessed with the acute physiology and chronic health evaluation (APACHE II) Score[31] obtained from the ICU information system database.

The commercial SPSS, version 19 (IBM company, copyright 1989, 2010 SPSS version 19, USA) was used for statistical analysis. Data were analyzed by using chi-square test for categorical data and student *t* test for continuous data. An a priori level of significance was ≤0.05.

RESULTS

A total of 139 patients were screened of which 73 were recruited: 49 in the historical control arm and 24 in the active arm (**Figure 2**). Baseline characteristics were similar between groups except for APACHE II score, which was higher in the active ASP group. Also there were no major differences detected in most common suspected infection types between groups (**Tables 2 and 3**).

The ASP implementation in the medical ICU improved appropriateness of empirical antibiotics utilization from 30.6% (15/49) in the historical control arm to 100% (24/24) in the proactive ASP arm (*P* value <.05). For the ASP group, initially 79.1% (19/24)

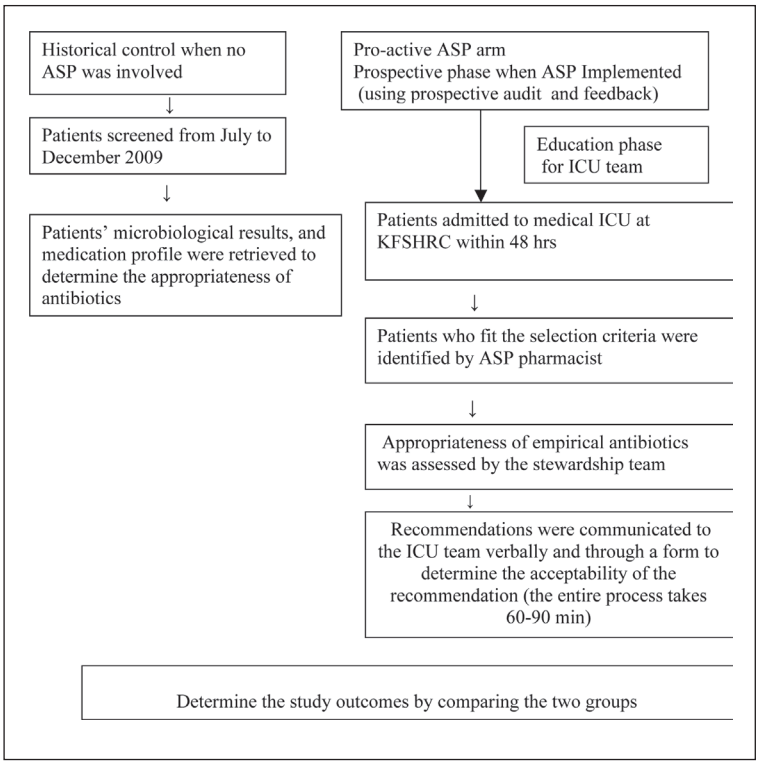

Figure 1. Study design showing historical control phase (in left side) and prospective phase of ASP (in right side). ASP: Antimicrobial Stewardship Program; ICU: Intensive Care Unit; KFSHRC: King Faisal Specialist Hospital & Research Center

Table 1. ASP strategies and current status at KFSHRC.

	Strategy	Advantages	Disadvantages	Current status at KFSHRC
Proactive Core Strategies	Formulary restriction and preapproval strategies (A-I /A-II)	Cost savings Encourage use of antibiotics in hospital formulary	Loss of autonomy	Active: restrict the use by certain prescribers, disease state, or units
	Prospective audit and feedback (A-I)	Direct interaction with prescriber Post hoc education and remediation Retains autonomy	Resource-intensive unless computerized feedback	Under consideration in this study
Supplemental Strategies	Education (A-III and B-II)	Informational, may increase knowledge Prescriber remains independent	Passive education not effective	Active: grand rounds, journal club, departmental conferences, e-mail alerts
	Guidelines (A-I)	Standardize practice and decreases variance	Loss of independence	Active: evidence-based guideline developed by AUE subcommittee based on local resistance patterns, national guidelines
	Antimicrobial order forms (B-II)	Use of information technology to display guidelines, make suggestions	Resource-intensive	Case-by-case basis using CPOE-based system and EMR
	Pharmacodynamic dose optimization (AII)	Optimal use of currently available antimicrobials based on organism, site of infection, and patient characteristics	Education of nursing staff might require for appropriate time to withdraw blood level	Active: on-call schedule is designed to contribute the clinical pharmacists and pharmacy residents competence in patient care
	Antimicrobial cycling (C-II)	Scheduled rotation of antimicrobials in specific sequenceà may reduce resistance by selective pressure	Loss of autonomy Theoretical concerns about effectiveness	Case-by-case basis

A-I: Good evidence with properly randomized controlled trials (RCT).

A-II: Good evidence from randomized controlled trials (RCT), cohort, or case-controlled.

A-III: Moderate evidence to support a recommendation for use from RCT.

B-II: Moderate evidence to support a recommendation from RCT, cohort, or case-controlled.

C-II: Poor evidence to support a recommendation based on clinical experience, descriptive studies, or reports of expert committees.

ASP: Antimicrobial stewardship program, AUE: antimicrobial utilization and evaluation, CPOE: computerized physician order entry, EMR: electronic medical record, KFSHRC: King Faisal Specialist Hospital & Research Center.

of the antibiotic uses were inappropriate and diminished by the stewardship team to 0% (**Table 4**). A total of 27 interventions were made, with an acceptance rate of 96.3%. The most common recommendations were regimen optimization with regard to dose, frequency, route of administration (89.5%) followed by discontinuation of unnecessary antimicrobial therapy (4%), change to broader spectrum antimicrobial for empirical coverage (4%), and modification of antibiotic selection to more effective and narrower spectrum (4%). Due to an overlap in interventions, each patient with inappropriate antibiotics had ≥1 interventions.

The rate of CDAD did not differ between the groups. The antibiotics utilization analysis showed that the ASP implementation resulted in 90.3 DDD total consumption of antibacterial agents compared with 1177.8 DDD in the historical control arm. These values correspond to 376.2 DDD/1000 patient-days in the active ASP arm compared with 2403.64 DDD/1000 patient-days in the historical control arm. The total cost of antibacterial agents during the study period was US$ 760.37 and 309.87 in the historical control arm and active ASP arm, respectively.

The patient's ICU course was also assessed; 16.7% deceased in the active ASP arm compared with 32.65% in the historical control arm (P=.150) and 83.3% patients were transferred to the regular floor in the active ASP arm within 4 to 5 days follow-up compared with 59.2% in the historical control arm (P=.091).

DISCUSSION

The Middle Eastern and Mediterranean hospitals have been identified as a region of high prevalence for MDR nosocomial pathogens. In Saudi Arabia, ciprofloxacin resistant Enterobacter cloacae have increased from 8.3% in 2000 to 17.4% in 2006.[32] Recently, a retrospective review at KFSHRC microbiology departments showed that tigecycline resistance rate increased from 10.4% in 2010 to 20.5% in 2011 among all clinical isolates of Acinetobacter. Colistin resistance increased over the same period from 2.6% to 4.7%.[33] Additional studies documented inappropriate antibiotic prescriptions in Saudi Arabian hospitals, ranging from 24% in community maternity hospital to over 80% in a provincial community hospital.[32] Although these studies were not exclusive to the ICU, our study is consistence with these data with an inappropriateness rate of 70% to 80% in the ICU, which highlights the need for ASP initiative to reduce this threat.

In 2006, a questionnaire was conducted to examine the ASP practice in 45 Middle Eastern hospitals (ARMed project) and showed that the ASPs were mostly limited in scope; 33.3% reported having antibiotic prescribing guidelines and 53.3% of hospitals fed back resistance rates to prescribers. Auditing of antibiotic consumption was carried out in 37.8% of responding hospitals. In addition, more than a quarter of the hospitals admitted donations of antibiotics from pharmaceutical industry, which reflects a potential conflict of interest and impact on prescribing decisions.[34] As of May 2013, this study represents the first, well-structured application of ASP in an ICU setting at a large tertiary care hospital in the Saudi Arabia and Middle East region. Due to the proactive nature of its implementation besides institutional restriction and antimicrobial guidelines established earlier at KFSHRC, the ASP achieved outstanding results.

The results of our study are in line with systematic review[35] that studied the impact of ASP in critical care and showed that ASP interventions were associated with shorter duration of antibiotic therapy, less inappropriate antimicrobial use, fewer antibiotic adverse events and neutral effect in nosocomial infection rates, and length of ICU stay or mortality. A reduction in antimicrobial utilization by 11% to 38% DDD/1000 patient-days and lower total antimicrobial costs (US$ 5-10/patient-day) were also reported similar to our study. However, indirect costs attributed to antibiotic resistance, increased length of ICU stay, hospital re-admission, and nosocomial superinfection should be taken into consideration for the successful application of this program.

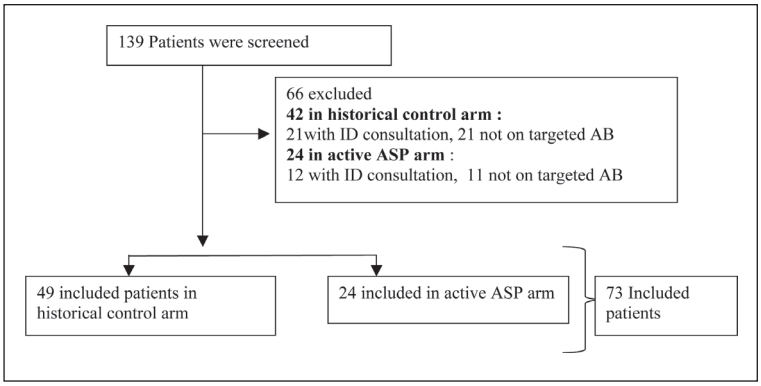

Figure 2. Study Population screening and recruitment. AB: Antibiotics; ASP: Antimicrobial Stewardship Program; ID: Infectious Disease.

Table 2. Baseline characteristics and demographics.

	Control N=49	Active ASP N=24	*P* value
Gender			
Male	31 (63%)	15 (63%)	.949
Female	18 (37 %)	9 (38%)	
Age mean	52.37	59.75	.087
APACHE II score[a] (mean)	10.51	19.38	<.0001
Comorbid conditions			
MRSA risk factors[b]	10 (20.4%)	10 (41.7%)	.056
P aeurginosa risk factors[c]	36 (73.5%)	21 (87.5%)	.173
MDR risk factors[d]	43 (87.7%)	18 (75%)	.191
Mechanical ventilation	38 (77.5 %)	11 (45.8%)	.007
Cardiovascular failure requiring vasopressors/ inotropic support	26 (53%)	9 (37.5 %)	.211
Solid organ transplant with immunosuppressant	9 (18.36%)	4 (17%)	.858
Other immunologic deficit	17 (34.7%)	8 (33.3%)	.908

[a]APACHE II score was calculated within 24 hours of ICU admission.

[b]Recent broad spectrum antibiotics treatment, patients known to be colonized, history of recent hospitalization in a geographic area of high prevalence, diabetes mellitus, head trauma, previous intensive care unit admission, structural lung disease, cavitary infiltrates, end-stage renal disease, prior influenza, and injection drug use.

[c]Structural lung disease (cystic fibrosis, bronchiectasis), steroid use (>10 mg prednisone daily for >2 weeks), broad spectrum antibiotics >7 days in last month, AIDS (CD4 < 50), neutropenia (ANC < 500), and severe COPD and alcoholism.

[d]Antimicrobial therapy in preceding 90 days, current hospitalization of 5 days or more, high frequency of antibiotic resistance in the community or the specific hospital unit, presence of risk factors for HCAP, hospitalization for 2 days or more in the preceding 90 days, residence in a nursing home or a long-term care facility, home infusion therapy (including antibiotics), chronic dialysis within 30 days, home wound care, and family member with multidrug-resistant pathogen.

APACHE II: Acute physiology and chronic health evaluation II, ASP: antimicrobial stewardship program, MDR: multidrug resistant organisms, MRSA: methicillin-resistant *Staphylococcus aureus*.

Table 3. Baseline characteristics with regard to diagnosis and types of infection.

	Control N=49	Active ASP N=24	*P* value
HCAP-simple (early or no MDR risk)	5 (10.2%)	2 (8.3%)	1.000
HCAP-complicated (late or MDR risk)	19 (38.8 %)	1 (4.1%)	.002
CAP-ICU with no Psuedomonas risk	0	1 (4.1%)	.329
CAP-ICU w/Pseudomonas risk	2 (4.1%)	5 (20.8%)	.035
Mild to moderate abdominal infection	0	1 (4.1%)	.329
High risk or severe abdominal infection	2 (4.1%)	1 (4.1%)	1.000
Primary bacteremia	6 (12.2%)	2 (8.3%)	.615
Catheter-associated bacteremia	9 (18.3%)	1 (4.1%)	.097
COPD exacerbation	0	5 (20.8%)	.003
SSTI simple (cellulitis)	1 (2%)	0	1.000
SSTI complicated (requiring surgery/amputation)	3 (6.1%)	2 (8.3%)	1.000
Osteomyelitis	2 (4.1%)	0	1.000
UTI community-acquired complex/systemic	0	5 (20.8%)	.003
UTI health care-acquired simple/localized	1 (2%)	0	1.000
UTI health care-acquired complex/systemic	11 (22.4%)	0	.012
Perforated bowel abdominal infection	0	1 (4.1%)	.329

ASP:Antimicrobial stewardship program, CAP: community-acquired pneumonia, COPD: chronic obstructive pulmonary disease, HCAP: health care-associated pneumonia, MDR: multidrug resistant organisms, MRSA: methicillin-resistant Staphylococcus aureus, SSTI: skin and soft-tissue infections, UTI: urinary tract infection.

Table 4. Results: Empirical antibiotics therapy appropriateness.

	Control (N=49)	Active ASP (N=24)	*P* value
Initial appropriateness			
Appropriate, no. (%)- change	15 (30.6%)	5 (20.8%)	.379
Final appropriateness			
Appropriate, no. (%)-change	15 (30.6%)	24 (100%)	.0001
Reasons for initial antibiotics inappropriateness[a]			
No current treatment for positive culture	9	0	.02
No indication (e.g., colonization) for current treatment	5	0	.15
Inadequate empiric coverage for indication	14	10	.37
Excessive empiric coverage for indication	2	2	.6
Resistant to current antibiotic	12	1	.02
Regimen excessive (failure to de-escalate)	8	0	.04
Regimen inadequate (wrong dose or frequency)	6	10	.006
Total	56	23	

ASP: Antimicrobial stewardship program.

[a]Each patient with initial inappropriate AB ≥ 1 reason for inappropriateness.

Despite the aforementioned findings, our study has certain limitations including lack of randomization, small sample sizes, short follow-up duration, and single institution's experience. Moreover, the staff in the ICU were aware of the intervention and the outcomes being measured, which might influence the validity of the comparative results. Ideally, future studies in this field may randomize allocation of the stewardship intervention to different ICUs. When randomization is not possible, bias can be minimized through inclusion of control units and the use of time series analysis with multiple measurements in the intervention and non-intervention time periods. With the overwhelming data supporting the ASP, concurrent randomization may carry an ethical concern.

As recommended by IDSA/SHEA guidelines,14 an ideal ASP team is multidisciplinary. This study included an Intensivist/ID consultant and clinical pharmacists. We believe that the involvement of microbiology and infection control personnel will have a valuable contribution in the ASP success. In addition, the ASP team spent 60 to 90 minutes per day (approximately 18 hours per month) of the individual effort to complete the program application. This would suggest the importance of the hospital's higher administration support to provide dedicated personnel and adequate budget that ensure a well-managed and fully functioning program.

Therefore, our long-term plan included reporting the ASP activities to AUE subcommittee, expanding the ASP tutorials and educational in-services, and instituting an electronic infectious diseases clinical decision support system (e.g., TheraDoc)[36] in collaboration with pharmacy informatics team. In our institution, this study served as a foundation for a larger study to expand the benefit of ASP to more patient care areas with the high levels of antimicrobial use and/or resistance and including de-escalation of empirical antimicrobial therapy.

In conclusion, the ASP is important in many health care settings; the ICU represents one setting where it is highly needed. Utilizing such data will greatly improve the appropriate use of antimicrobial therapy, prescribers' acceptance rate, thus reducing direct cost and antibiotic consumption. A peer-to-peer communication strategy is an essential element in building a sustainable ASP program and contributes to a higher acceptance rate of recommendations. More studies are needed to assess the long-term clinical benefits for patients (mortality and length of hospital stay), and the presence of resources is crucial to support the expansion of such programs, particularly in our region.

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