Educational ICU Antimicrobial Stewardship model: the daily activities of the AMS team over a 10-month period

Stefano Cappanera[1], Beatrice Tiri[1], Giulia Priante[1], Emanuela Sensi[2], Marialaura Scarcella[2], Lorenzina Bolli[2], Monya Costantini[3], Paolo Andreani[4], Susanna Sodo[5], Lucia Assunta Martella[1], Daniela Francisci[1]

[1]Infectious Diseases Clinic, Department of Medicine, "S. Maria" Hospital, Terni, University of Perugia, Italy;
[2]Department of Critical Care Medicine and Anesthesiology, "S. Maria" Hospital, Terni, Italy;
[3]Pharmacy Unit, "S. Maria" Hospital, Terni, Italy;
[4]Hematology and Microbiology Laboratory, "S. Maria" Hospital, Terni, Italy;
[5]General Health Care Management, "S. Maria" Hospital, Terni, Italy

SUMMARY

The emergence of antibiotic resistance as a consequence of inappropriate use results in higher mortality rates and has become a major public health challenge worldwide. Antimicrobial stewardship programs (ASPs) aim to ensure proper use of antimicrobials and reduce health care costs. We assessed the impact of using a behavioral approach during a persuasive ASP on antibiotic appropriateness, consumption and costs. We conducted a prospective interventional cohort before-and-after study in the intensive care unit (ICU) of a 554-bed, university teaching hospital in Terni, Italy, 14 of which are located in the ICU. We describe a 10-month persuasive ASP intervention model used in a referral ICU with daily rounds. The aim of the study was to improve medication appropriateness through educational action and reduce the consumption of carbapenems and echinocandins by conducting post-prescription reviews, prescribing reviews and holding daily discussions with the ICU team. We analyzed the prescribing appropriateness of the ICU team in accordance with the decisions made by the Antimicrobial Stewardship (AMS) team to improve the quality of antibiotic prescribing during the first five months and the last five months of the surveillance period. The results were expressed as the defined daily dose (DDD) per 100 occupied bed-days and costs. The data were compared with those previously obtained during the pre-educational period (the year before ASP implementation). Comparisons were made between the decisions taken to improve antimicrobial treatments administered during the first half of the surveillance period (March-July) and those administered during the second half (August-December). In all, 116 decisions were made from March to July while only 65 were made from August to December (p-value 0.00001). A significant reduction was observed in the consumption of carbapenems and echinocandins (11.15% and 25.62%, respectively). Total antibiotic cost savings amounted to 57,541.16 euros. The persuasive ASP strategy positively influenced the prescribing behavior of physicians, thus improving the appropriateness of antibiotic therapy and reducing antimicrobial consumption.

Keywords: Antimicrobial Stewardship Program, Intensive Care Unit, de-escalation, antimicrobial consumption, appropriateness in prescription, behavior.

INTRODUCTION

Antimicrobial stewardship programs have been defined by the IDSA (Infectious Diseases Society of America) as "coordinated interventions designed to improve and measure the appropriate use of antimicrobial agents by promoting the

Corresponding author
Cappanera Stefano
E-mail: s.cappanera@aospterni.it

selection of the optimal drug regimen including dosing, duration of therapy, and route of administration" [1].
Many antimicrobial stewardship programs (ASPs) focus on intensive care units (ICU) due to high antimicrobial utilization [2-4]. Several studies reported in literature indicate that 30% to 60% of the antibiotics prescribed in ICUs are unnecessary, inappropriate and suboptimal [5-8].
Inappropriate antibiotic use defined as wrong indication, spectrum, route, dose or duration of therapy [9, 10]. Antimicrobial resistance caused by antibiotic overuse and misuse leads to poor clinical outcomes and increased health care costs [11, 12]. Most European countries have developed national action plans to limit the inappropriate use of antimicrobials but as yet no European or Italian ASP guidelines have been established that indicate how to implement effective interventions that ensure appropriate antimicrobial prescribing in ICU setting [13-15].
We describe an organizational model of a persuasive ASP carried out during daily-ICU rounds in an Italian ICU that led to the integration of an AMS team in health care delivery. Our ASP core strategy was to change antimicrobial prescribing behavior by focusing on prescriber autonomy and participation in order to improve medication appropriateness through daily educational actions.
The aim of the study was to improve prescribing competency using an educational approach, to reduce carbapenem usage by implementing "carbapenem sparing" policies and to limit the prescription of echinocandins by carrying out daily prescribing assessments and holding daily discussions with the ICU team [16, 17].
In addition, the ASP effects on-cost reduction was evaluated.

MATERIALS AND METHODS

The proposed ASP was carried out in the ICU at "Santa Maria" hospital for 10 months from 1st March to 31st December 2016. Santa Maria hospital is a teaching hospital in Terni, Umbria (central Italy), with 554 beds, 14 of which are located in the ICU. The ICU cares for a population of post-surgical patients and patients suffering from life-threatening respiratory and cardiovascular conditions and trauma etc. Patients may also be admitted from surgical wards or emergency departments or from the sepsis clinic, since sepsis is considered an apparent life-threatening event, or any patients with conditions that warrant intensive care. The AMS core team was composed of one Senior Infectious Diseases physician and two Junior Infectious Diseases (ID) doctors. Daily ICU-AMS rounds were conducted from Monday to Saturday and patient data was collected daily and stored in a dedicated database. Patient data includes: hospitalization days, personal data, provenance (residential healthcare facility, home, ward, other), outcomes, antimicrobial therapies, rectal swab cultures for detecting Carbapenem-Resistent Enterobacteriaceae, access devices and microbiological isolations.
During the daily ICU rounds, the AMS team collaborated with the ICU team who provided additional information for each ICU patient with the aim of reviewing culture results and discussing antimicrobial therapy in order to ensure the appropriateness of the treatment plan.
The evaluation of patient medication and the improvement of the therapeutic regimens were based on pharmacodynamics, pharmacokinetics, source of infection, drug dose, duration of therapy. Together with the ICU team, the AMS team developed guidelines and algorithms for the clinical diagnosis and empirical therapy of intra-abdominal infections, urinary tract infections, low respiratory tract infections, skin and soft tissue infections and candidiasis. The AMS team made recommendations on antimicrobial use that were only noted in the medical chart if requested by the ICU team. Thus, the ICU team maintained prescribing autonomy, in accordance with the Dutch Method [18].
Antimicrobial appropriateness was measured by the decisions made by the AMS team for improving antibiotic therapy which were recorded and defined as de-escalation, escalation, start therapy, change drug and stop therapy. *De-escalation* or *streamlining* was defined as a process in which clinicians who begin broad-spectrum empirical antimicrobial treatment commit to narrowing the spectrum or antimicrobial therapy according to culture results or to discontinue antimicrobial therapy based on clinical criteria and negative culture results [19]. In accordance with literature, we defined *Escalation* as the prescription of new antibiotics with a broader spectrum of antimicrobial coverage; initiating empirical antimicrobial

therapy after obtaining blood cultures, taking into account the probable site of infection, local microbiology and susceptibility patterns; *changing medication* by substituting one type of antibiotic with another in the same class or with similar broad spectrum antimicrobial coverage; *stopping antibiotic therapy* if there is no evidence of infection [20-22].

All data analyses were carried out using Microsoft Excel 2010.

The decisions to improve antibiotic therapy made by the AMS team were analyzed as the decisions made during the first half (March-July) and the second half (August-December) of the surveillance period and were compared and analyzed using the Chi-square anaylsis.

Antibiotic consumption was expressed as Defined Daily Dose DDD per 100 occupied bed-days (BDU). The DDD for adults was obtained from the anatomical therapeutic chemical (ATC) classification system developed by the World Health Organization (WHO), with the DDD expressed in grams.

The DDD was calculated for carbapenems, piperacillin/tazobactam and echinocandins and compared using the chi-square statistic with the DDD/100 BDU during the same period in 2015 prior to ASP implementation.

The cost of the antibiotics (carbapenems, piperacillin/tazobactam and echinocandins) was calculated in Euros and compared with the cost of the same antibiotics in 2015 prior to ASP implementation.

Data on antibiotic consumption and costs collected over the study period were provided by the hospital's pharmacy department.

RESULTS

During the 10-month surveillance period, from 1st March to 31th December 2016, 18,7 monthly and 4,6 weekly ICU-AMS rounds were conducted. The AMS team made 1815 records and carried out 392 individual consultations with patients. The type of patients is reported in Table 1.

181 decisions were made to improve antimicrobial therapy for 92 individual patients (median 5 for patient, range 1-9), while the same treatments were confirmed for the remaining patients; a summary of the antimicrobial treatment decisions made during the ICU-AMS rounds are reported in Table 2.

Table 1 - Patients' typology underlying treatment modification.

Origin of patients	*Number of consultations No*	*%*	*Patients for whom decision were made No*	*%*
Neurosurgery	154	39	29	31
Abdominal surgery	78	20	18	20
Trauma Center	54	14	12	13
Cardiology	39	10	9	10
Pneumology	38	10	18	20
Others	29	7	6	6

Table 2 - Summary of antimicrobial decisions made during the ICU-AMS rounds.

	No. (%)
De-escalation	62 (34)
Escalation	53 (29)
Start therapy	40 (22)
Change drug	23(13
Stop therapy	3 (2)
Total	181

The decisions on the antimicrobial treatments made during the first half (March-July) and second half (August-December) of the surveillance period were compared. 116 decisions were made from March to July while 65 were made from August to December showing a significant downward trend (p-value 0.00001). The decisions made during the two periods are shown in Figure 1.

During the first ICU surveillance period from March to December 2016, data were collected on the consumption of carbapenems, piperacillin/tazobactam and echinocandins in DDD/100 Bed-Days-Use (BDU) and the DDD/100 BDU were compared during the same period in 2015 prior to ASP implementation. The data are shown in Figure 2.

The statistical analysis revealed a downward trend for carbapenems (p=0.76) and echinocandins (p=0.64) and an upward trend for piperacillin/tazobactam (p-value=0.69) both without significant p-values.

The direct cost savings for the antibiotics (Carbap-

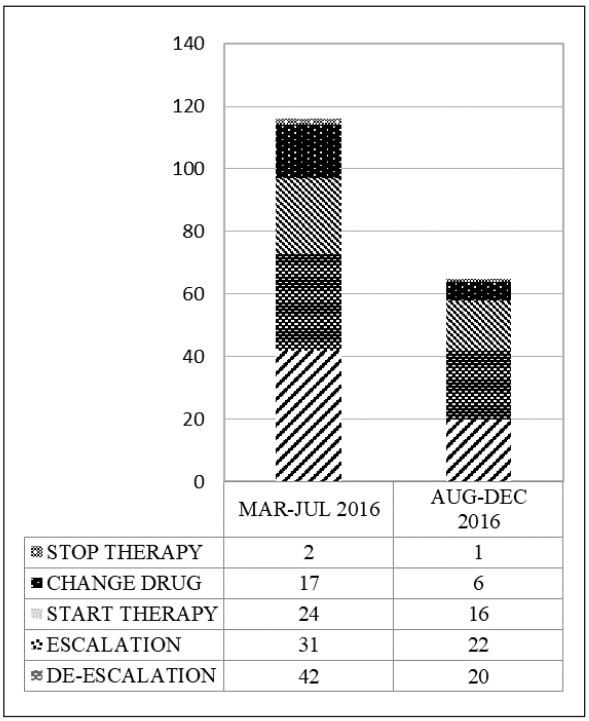


Figure 1 - Antimicrobial decisions made by the AMS team to improve antimicrobial therapy in the first half (March-July) and in the second half (August-December) of the ICU surveillance period.

enems; piperacillin/tazobactam; echinocandins) used in the ICU during the ASP (March-December 2016) were compared with the same data relative to March-Dec 2015, the results of which can be seen in Figure 3.

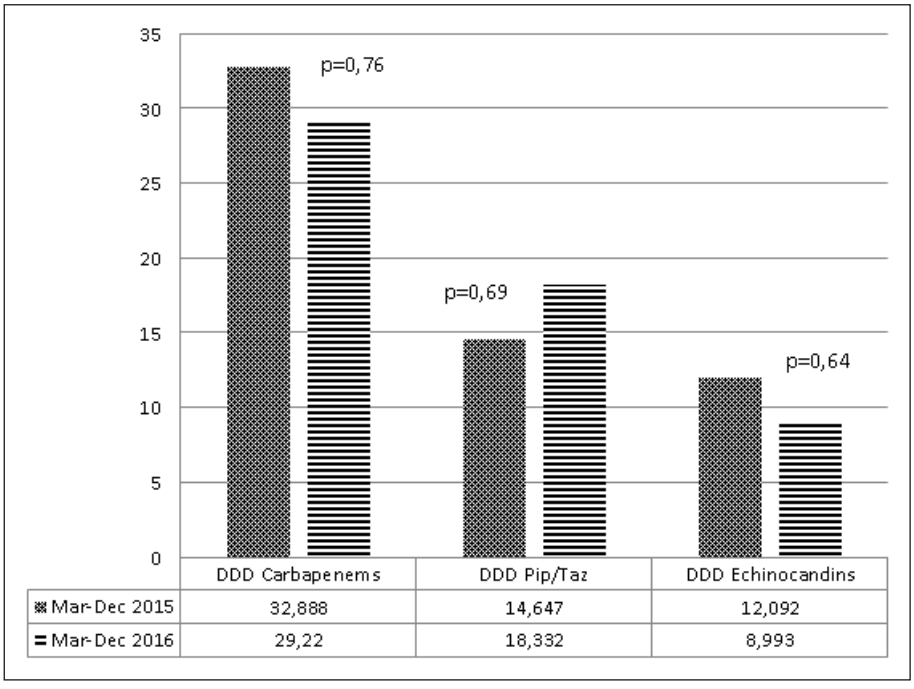
DISCUSSION

In this study the ASP was implemented using a persuasive strategy approach based on the behavior theory and was focused on preserving prescriber autonomy [23, 24].

We therefore shared the "right dose, right duration, right route, de-escalation" ASP guidelines concerning antibiotics with the ICU team, which emphasize the importance of involving prescribers in the assessment of prescribing appropriateness through monthly individualised audit and feedback with the aim of improving prescribing competency. The AMS was integrated into clinical care and has frequently been used as a resource by the ICU-team when information on antimicrobial therapy was required [25-27].

De-escalation was the most common decision taken (34%-62 out of 181) which is in line with the widespread acceptance of the concept that antibiotic de-escalation is a powerful strategy for re-

Figure 2 - Comparison of the DDD/100 BDU of carbapenems, piperacillin/tazobactam and echinocandins used in the ICU during the second half (March-December 2016) of the surveillance period with their consumption from March to December 2015.



ducing antibiotic resistance and optimizing the treatment of infectious diseases. Moreover, ASP interventions are essential for the implementation of antibiotic de-escalation.

De-escalation, which was based on culture results and clinical criteria in accordance with the concept of "starting broad" in order to maximize the likelihood of curing the causative organisms and minimizing the likelihood of missing a diagnosis, must be coupled with a de-escalation strategy that aims to narrow the spectrum of therapy and minimize the patient's exposure to antimicrobials as soon as clinically possible. The ASP also eliminated unnecessary duplicative therapy or redundant combination therapy [28-30]. However antibiotic de-escalation is not yet a standard practice and the frequency with which antibiotic regimens are de-escalated or should be de-escalated in the hospital setting have not been well documented.

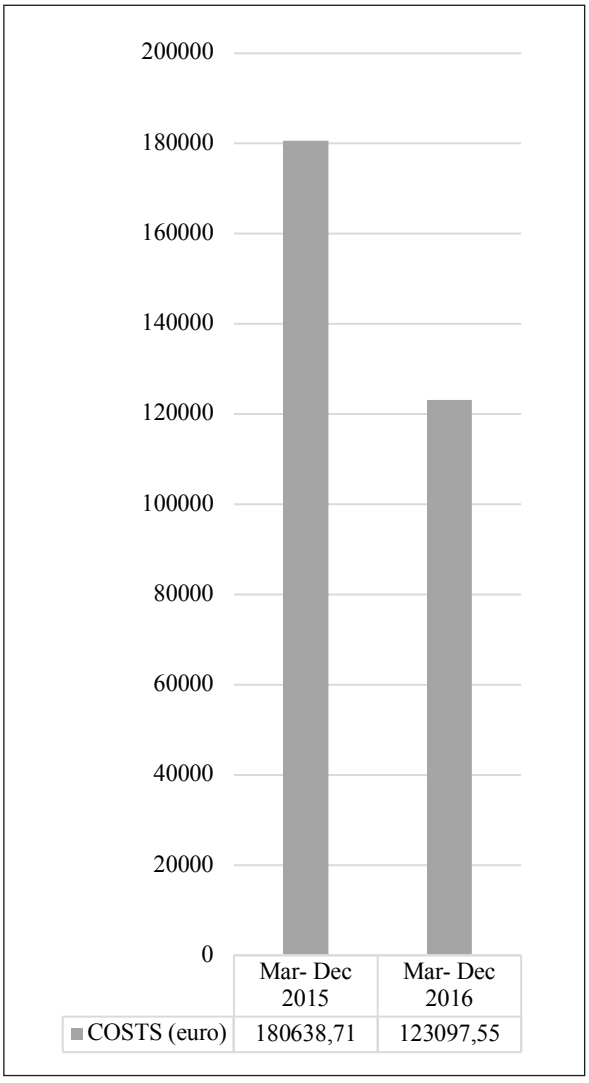


Figure 3 - The direct costs of all antibiotics (carbapenems; piperacillin/tazobactam; echinocandins) administered in the ICU during the ASP (March-December 2016) compared with the same data collected in the period March-December 2015.

27.9% of the decisions related to escalation and 22% of the decisions on starting therapy were made for patients suffering from complicated infections in order to improve patient safety.

22% of drug substitution were made to optimize the class of antibiotic paying particular attention to the pharmacodynamic and pharmacokinetic principles.

The fact that the decisions taken to stop treatment only amounted to 2% of decision volume was due to the enhanced vulnerability of the population to infection (reduced host defenses, deregulation of the immune responses) and the high risk of infection due to multiple procedures and the use of invasive devices. Moreover, when culture data were negative, clinicians were uncertain about the safety of stopping therapy as signs and symptoms of infection due to non-infectious causes are common. For this reason, physicians were reluctant to stop administering antibiotics to critically ill patients [31, 32].

There was a significant reduction of 43.9% ($p<0.0001$) in the total number of decisions made by the AMS team to improve antimicrobial appropriateness from the first half of the surveillance period (March-July) to the second half (August-December), which indicated that antimicrobial appropriateness gradually increased with enhanced ICU-team prescribing. In our opinion these results demonstrate that the effectiveness of the behavioral approach for preserving prescriber autonomy led to an increase in antimicrobial appropriateness. The intervention detected and corrected bad prescribing habits, thus reducing antibiotic consumption considerably and improving appropriate prescribing. Education is considered to be an essential element of any intervention and is graded as A III evidence in IDSA guidelines modifying prescribing behavior, which is demonstrated by the significant reduction in de-escalation actions and change drug actions [1]. We consider this to be a true antimicrobial stewardship

as it encouraged collaboration between the AMS team and prescribing clinicians with the aim of selecting an appropriate antimicrobial therapy. Our experience demonstrated that clinicians often regarded the AMS team as an advantageous resource to assist them in their choice of treatment, dose and duration.

The 11.15% DDD/100 BDU decrease in carbapenem consumption shows a downward trend suggesting that our "carbapenem sparing" policy is partially effective, which is a strategy that requires beta-lactam/beta-lactamase inhibitors mainly piperacillin/tazobactam. In fact, a 20% DDD/100BDU increase was observed in piperacillin/tazobactam even without a significant p-value.

It was furthermore observed that ASP implementation reduced echinocandins use by 25.5 % without a statistically significant result.

The average total cost of antimicrobials used in the ICU decreased from Euros 180,638.71 prior to intervention, to Euros 123,097.55 (31.85%) after intervention. The direct cost savings of the antimicrobials used amounted to Euros 57,541.16.

In our opinion the persuasive intervention led to a significant decrease in inappropriate antibiotic prescribing but it did not statistically and significantly reduce antibiotic consumption probably because persuasive interventions have a significantly greater impact on 12-24 month consumption patterns, while we analyzed 10-month data [32].

However there are some limitations to our study. Firstly, our patient characteristics do not include scores describing the patients' chronic underlying conditions, or acute physiology scores indicating the severity of illness. Secondly, therapeutic drug monitoring for changing drug or dosage is not available at our hospital.

In our opinion our model has several elements that should be included in ASPs carried out in the hospital settings described in the ECDC technical report and that daily interdisciplinary ICU rounds are essential for effectuating behavioral changes in difficult settings like ICUs.

Our study confirmed the effectiveness of persuasive intervention for modifying prescribing behavior, which resulted in more appropriate antimicrobial prescribing and reduced antibiotic consumption. Our results demonstrate the efficacy of ASP in reducing the associated costs. In conclusion, the implementation of ASPs is a cost effective strategy for improving the practice of prescribing antibiotics, as a preventive measure against MDR (Multi Drug Resistance).

Conflicts of interest

None.

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