ORIGINAL ARTICLE

A Coordinated and Multidisciplinary Strategy can Reduce the Time for Antibiotics in Septic Patients at a University Hospital

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Abstract

Objectives: We carried out this work with the aim of assessing the effectiveness of a set of interventions over time for the administration of antibiotics.

Design: Prospective observational study.

Setting: Patients admitted to the emergency room and ICU of the hospital where the study was conducted are evaluated daily for some sociodemographic and clinical variables. Among them are some quality indicators, such as the time between the diagnosis of sepsis or septic shock until the start of the infusion of antibiotics. This indicator reflects several aspects related to a set of assistance measures (adequacy of antibiotic dispensation, rapid response team (RRT), sepsis care quality improvement program, antimicrobial management program, improvements in emergency department assistance).

Patients or participants: Patients with sepsis or septic shock were admitted to the ICU of a university and public hospital in southern Brazil.

Main variables of interest: The time between the diagnosis of sepsis or septic shock and the beginning of the infusion of antibiotics.

Results: Between 2013 and 2018, 1676 patients were evaluated. The mean time for antibiotic infusion decreased from 6.1 ± 8.6 hours to 1.7 ± 2.9 hours ($p < 0.001$). The percentage of patients who received antibiotics in the first hour increased from 20.7 to 59.0% ($p < 0.001$).

Conclusion: In this study, we demonstrated that a set of actions adopted in a large tertiary hospital was associated with decreased time to start antibiotic therapy in septic patients.

Keywords: Antibiotic, Quality improvement, Sepsis, Septic shock.

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Highlights

Adequacy of dispensing antibiotics by the pharmacy, Implementation of a rapid response team (RRT), creation of an intrahospital program to combat sepsis (IPCS), antimicrobial stewardship program (ASP) by physicians and pharmacists and assistance improvements in the emergency department were the strategies used to reduce the time from 6.1 to 1.7 hours.

Introduction

Sepsis is described by organ dysfunction that occurs through a response to infection, being one of the main causes of death in the world. Afterwards, an inflammatory response in the host is triggered, releasing meters that can be used as biomarkers for diagnosing sepsis.[1,2] Sepsis is an important public health problem, given the increased incidence, high mortality and costs associated with its treatment. The management of sepsis patients is based on the adequacy of interventions and includes (1) early recognition, (2) early and adequate empirical administration of antibiotics, (3) control of the infectious focus, and (4) volume resuscitation with intravenous fluids and use vasoactive drugs when needed.[3] Observational studies have shown that delaying the administration of antibiotic therapy appears to significantly increase mortality for each hour of delay.[4,5] Among all recommended interventions, studies suggest that the initiation of antibiotic therapy appears to have the greatest impact on sepsis mortality.[6,7] Although there is controversy about how early the administration should be performed, it is difficult to argue against starting antibiotics as early as possible after the diagnosis of sepsis.[7,8] Thus, the guidelines of the Survival Sepsis Campaign establish as a strong recommendation for the infusion of intravenous antibiotics in the first hour after diagnosis of sepsis.[3] In countries with low- and middle-income or health systems lacking resources and organization, interventions that must be carried out to implement early antibiotic therapy and its effects are poorly studied.[9] In Brazil,

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public hospitals, when compared with private hospitals, are an independent risk factor for sepsis-related mortality.[10] Delays in antimicrobial administration are common and represent a marker in the overall quality of care. However, despite the early administration of antibiotics being a strong recommendation, the effort to reduce the time of initiation of antibiotics is challenging.[11] The improvement of the processes that lead to more agile, and early administration is the result of a multidisciplinary effort and involves nurses, doctors, and pharmacists.[12] Our study prospectively evaluated the effect of a set of interventions adopted in a public university hospital to decrease the time to initiate antibiotic therapy in septic patients.

Methods

Prospective cohort study conducted at a university hospital. This study was conducted as recommended by the Declaration of Helsinki and approved by the Research Ethics Committee of Hospital de Clínicas de Porto Alegre (HCPA, number: 2016-0317). As this is an observational study, it was not considered necessary to apply an informed consent form.

Patients diagnosed with sepsis (infection with organ dysfunction) and septic shock (sepsis with hypotension refractory to fluid replacement) were included according to the SEPSIS-2 consensus[13] and hospitalized in the ICU diagnosed with sepsis in the wards, emergency department (ED) or in the ICU between March 2013 and December 2018. Patients under 18 years old, with readmission in the same period of the study, or with an indication of therapeutic limitation were excluded.

Epidemiological data, APACHE II, SAPS 3, the time of onset of antimicrobials after the diagnosis of sepsis, and mortality rate were collected. Time-related data for the diagnosis of sepsis and antimicrobial treatment were obtained from the electronic medical records. Antibiotic initiation time was calculated as the time difference in hours elapsed between registering in the medical record of sepsis or septic shock and the start of the infusion of the first dose of antibiotics intravenously, as registered by the nurse.

Patients who were previously using antibiotics and those who had switched its antimicrobial regimen due to a new episode of sepsis were excluded. And HCPA is a public, tertiary, and university hospital. Approximately, 95% of consultations are performed by the public health system, being a regional reference center for highly complex consultations. The adult ICU consists of 45 beds with the hospital having approximately 600 beds for adults. Since 2013, HCPA has instituted several measures to reduce the time for an infusion of the first dose of antibiotics in septic patients. The measures implemented are as follows:

- Adequacy of dispensing antibiotics by the pharmacy. The Hospital de Clínicas de Porto Alegre has several surgical, clinical, and psychiatric wards for adult patients, an ED on the ground floor, and an adult ICU on the 13th floor. Until 2013, to obtain the prescribed medications, a nursing technician had to travel to the central pharmacy on the 9th floor. The emergency room satellite pharmacy started its activities in 2013. The ICU has had a satellite pharmacy since 2009. In addition, an automated medication supply system was implemented between 2013 and 2018 (Pyxis®) in all wards. An automated medication supply system allows the storage and organization of medication dispensing accessed by authorized employees with a barcode reader. The set of these interventions ended with the displacement of the nursing technician to the central pharmacy.
- Implementation of an RRT. The creation of the RRT was a decision by the institution's medical administration to improve emergency care in adult wards.[14,15] The RRT is composed of intensive care physicians, working 24 hours a day, 7 days a week, being triggered by the nurse responsible for each ward through pre-established clinical triggers. The RRT defines the suspicion of sepsis as a trigger and is responsible for the application of the initial sepsis management protocol that includes the prescription of empirical antibiotics and the definition of ICU admission.
- Creation of the IPCS. The IPCS is composed of five doctors (three intensivists, an emergency physician, and a doctor from the RRT), three nurses, and a nursing student. The program collects patient data and recommends assistance policies and conduct to the hospital's medical management. The program does not act directly on patient care, which is carried out by the RRT, emergency responders, intensivists, and other professionals at the institution. The IPCS monitors variables related to the quality of care (e.g., time for antibiotic therapy), adapts processes, and identifies barriers to the care of septic patients. Also, the program institutes and updates sepsis protocol, and operates in continuing education through face-to-face classes and distance learning, targeting all employees who work with septic patients, such as doctors, nurses, nursing technicians, pharmacists, nutritionists, physiotherapists, and technicians who collect blood for laboratory tests. During the study period, structured and repeated training was conducted annually with a focus on the nursing team, highlighting the importance of nurses at the bedside for the early identification of septic patients through triggers defined in institutional sepsis protocol, as well as the importance of administration of the immediate antibiotic.
- Antimicrobial Stewardship Program. The ASP is composed of infectiologists, intensivists, pediatricians, nurses, and pharmacists. It works by monitoring the bacterial resistance profile of the hospital, generating annual reports on them, making and updating protocols for the use of antimicrobials, and providing advice to an infectiologist to decide on the use of antibiotics on a full-time basis. During the study period, Hospital Infection Control Committee (HICC) started to audit all antimicrobials prescribed in the hospital within a maximum of 24 hours to assess the adequacy of the prescription. Over these years, there has been a gradual increase in the rate of the adequacy of antimicrobial prescriptions, and is currently 85%.
- Assistance improvements in the ED. In the ED, several logistical interventions were adopted, such as the adoption of time to start antibiotic therapy as a marker of care quality, the adoption of the PDSA methodology (Plan, Do, Study, Act),[16] and signaling septic patients in electronic medical records.

Statistical Analysis

Statistical analysis was performed using the SPSS 16 program. Descriptive analysis was performed, and the data are presented as means and standard deviations or as medians and interquartile ranges for continuous variables and absolute and relative frequencies for categorical variables. To identify the differences between the variables, the Chi-square or Fisher's exact tests were performed for categorical variables, and the Mann–Whitney test for continuous variables. The level of significance was 0.05.

Table 1: Patient characteristics

	Sepsis (n = 805)	*Septic shock (n = 871)*
Age (mean ± SD)	58.8 ± 17.2	60.4 ± 16.7
Sex (% male)	54.4	53.8
APACHE II (mean ± SD)	21.5 ± 7.1	26.9 ± 8.9
SOFA (mean ± SD)	4.6 ± 3	8.6 ± 3
SAPS 3 (mean ± SD)	65.8 ± 14.1	71.4 ± 13.5
MV (%)	43.8	83.4
Infectious focus		
Lung (%)	52.6	53.9
Abdomen (%)	17.05	21.4
Urinary tract (%)	11.1	6.3
Catheter (%)	1	2.1
Others (%)	17.8	16.3
Treated outside the ICU (%)*	48.9	13.6
Coming from ED (%)	49.7	47.1

APACHE II, acute physiology and chronic health evaluation II; ED, emergency department; MV, mechanical ventilation; SAPS 3 score, simplified acute physiology score; SOFA score, the sequential organ failure assessment score; *Patients whose treatment took place outside the ICU (ED or ward) in the first 24 hours after diagnosis of sepsis or septic shock

Box: Measures used to improve the time to start antibiotic therapy

Rapid response team

Pharmacy interventions
- Satellite Pharmacies (ICU and Emergency)
- Pyxis® (Automatic medication dispensers)

Interventions of the Sepsis Care Quality Improvement Program
- Sepsis protocol
- Face-to-face classes, distance learning
- Continuous monitoring of results and management of protocols

Interventions of the Antimicrobial Stewardship Program
- Monitoring of the hospital's microbiological profile
- Protocols for the use of antimicrobials
- Full-time antimicrobial decision-making advice

Emergency department interventions
- Adoption of time for antibiotic therapy as a care indicator
- Adoption of the PDSA methodology (Plan, Do, Study, Act)
- Signaling in the electronic system of septic patients

Results

Between March 2013 and December 2018, 2513 patients with sepsis or septic shock were admitted to the ICU were identified. Of these, 837 patients received antibiotics before meeting the criteria for sepsis or septic shock, while 1,676 patients received antibiotics after meeting these criteria. The profile of patients who received antibiotics after the diagnosis of sepsis or septic shock is given in Table 1. The interventions used to achieve a reduction in the time of antibiotic onset are described in Box. The mean time to start of the antibiotic infusion decreased from 6.13 ± 8.6 hours to 1.7 ± 2.9 hours between 2013 and 2018 ($p < 0.001$) (Fig. 1). The percentage of patients who received antibiotics in the first hour after the diagnosis of sepsis increased from 20.7 to 59.0% ($p < 0.001$) (Fig. 2). No decrease in lethality was observed during the study period (52% *vs* 54%).

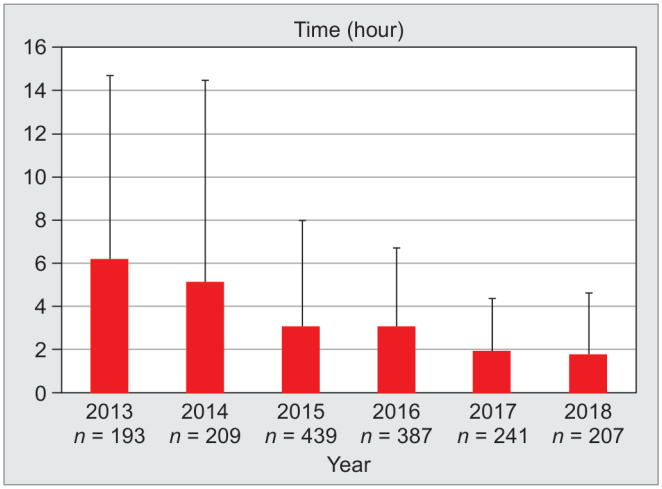

Fig. 1: Time to start antibiotic therapy in septic patients

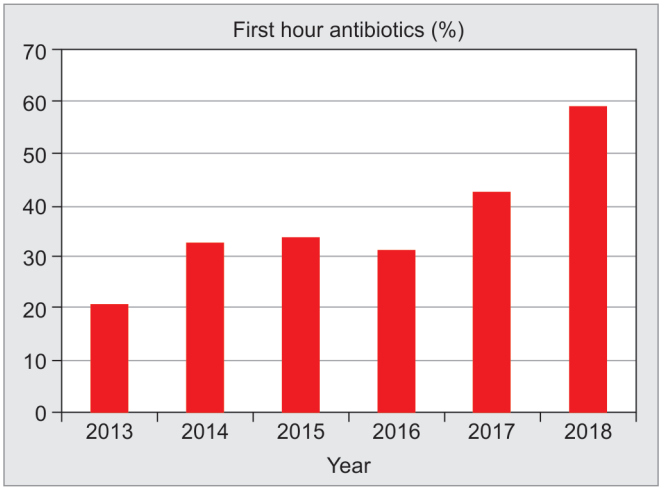

Fig. 2: The percentage of patients who received antibiotics in the first hour increased over time

Discussion

In this cohort, the adoption of a set of measures was associated with a significant decrease in the time to start antibiotic therapy in septic patients and an increase in the percentage of adequacy to the recommendation to start antibiotic administration in 1 hour. These measures demand integrated actions from different services, involving the Sepsis Care Quality Improvement Program, RRT, ASP, Pharmacy and Emergency Department, as well as the multidisciplinary involvement of doctors, nurses, and pharmacists. Our results are similar to a previous study, whose mean time for an infusion of antibiotics decreased from 6 hours to 1.4 hours.[17] Our study was not designed to indicate which measures individually are capable of speeding up the time for the infusion of antibiotics. Some studies emphasize the importance of prompt availability of the drug in the unit where the patient is hospitalized,[18,19] what was addressed in our intervention with the availability of satellite pharmacies and the use of an automated medication supply system (Pyxis®). Other studies emphasize the importance of optimizing the electronic prescription and continuing education system.[20,21] The association between early antibiotic use and decreased mortality observed in several studies supports the SSC recommendation[3]

for patients with sepsis or septic shock.[5,22,23] Despite this evidence, there is concern that the early use of antimicrobials is associated with unnecessary use, especially in patients with low-severity infections, and with the induction of microbial resistance.[24] Some authors are concerned that the obsession with starting antibiotics within 1 hour is a "septic hysteria."[25] Concerns about the unnecessary use of antibiotics seem to be relevant in places where the prevalence of septic patients of low severity and low mortality and who have effective health systems, is the most common scenario in developed countries. However, our data show a different scenario, typical of a developing country. In low- and middle-income countries, where most cases of sepsis and septic shock are found, the diagnosis of sepsis and recommended initial interventions are delayed, which appears to be a consequence of the low capacity of precarious health systems to effectively care for these patients.[11] However, regardless of the controversy about the need to administer antibiotics as early as possible, time to start antibiotic therapy is an indicator of quality, and the reduction in this time seems to reflect the ability to improve care for septic patients.[4,6] Our study supports the principle of health care improvement and the coordination of several measures was associated with reduced time to administer antibiotics. Although studies demonstrate the benefits of optimizing antibiotic prescriptions quickly, there is a lack of studies describing how to achieve this goal.[26] The early start of antimicrobials seems to be a simple intervention, but several processes need to be aligned from the prescription to the infusion of the antibiotic so that this occurs in the shortest possible time. The implementation of the RRT optimizes the communication between the prescribing physician and the nursing team responsible for the infusion of the antibiotic.[27] Structural and logistical measures, such as the implementation of satellite pharmacies and automated medication supply system, streamline the delivery of antibiotics to the location and to the patient who should receive the medication, corroborating the reduction and optimization of the workload of the pharmacy and nursing staff.[28] The adoption of protocols and consultancy carried out by ASP makes it possible to standardize prescriptions, optimize the availability of the drug and make the quickest decision on the best antibiotic therapy to be employed.[29] In the ED, the implementation of assistance improvements made it possible to prioritize the identification and treatment of septic patients, increasing the visibility of the problem and the engagement of professionals in the care of these patients. Education is relevant so that all professionals working in the process are aware of the importance of administering antibiotics as quickly as possible, feeling engaged in the patient care process, avoiding delaying the time of the antibiotic infusion, or postponing its use delaying the patient's transfer to the ICU.[26] Continuing education was offered to all professionals at the institution who participate in the care of septic patients, but there was particular attention in ensuring the training of nurses and nursing technicians. These professionals are fundamental in the evaluation and therapeutic implementation of septic patients. Nursing professionals are those who are in the longest contact with the patient, thus being able to recognize signs of sepsis earlier. They are also the professionals responsible for the initial application of care, such as the infusion of antibiotics. Protocols centered on the nurse's performance in the treatment of sepsis have been associated in several studies with improved patient care, among these improvements and the reduction of antibiotic administration time.[30–32]

Our study has limitations. As this is an observational study, it is not possible to state that there is a causal relationship between the interventions implemented during the study period and the decreased time for infusion of antibiotic therapy, and it is possible to infer an association between the interventions and the outcome. In addition, other interventions not measured, but adopted during the study period, as well as the evolution of patient care, may also be associated with the results. The interventions adopted at the institution were implemented simultaneously and gradually, making it impossible to measure the individual effect of each intervention. Unlike studies that demonstrate an association between decreased mortality and early prescription, we did not observe this in our study.[5,6] We speculate that although we have shortened the time to use antibiotics, a significant percentage of patients do not receive antibiotics in the first hour. In addition, all patients studied were admitted to the ICU and the severity was very high. Finally, our data indicate that we are still flawed in early diagnosis, which is the biggest trigger that leads to early interventions.[33]

Conclusion

The adoption of a package of measures involving various services and professionals was associated with a significant decrease in the time to start the first dose of antibiotics and increased the percentage of patients with sepsis or septic shock who received antibiotics within 1 hour at a university hospital in a developing country.

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