Early empirical antimicrobial therapy does not prevent sepsis development in critically ill surgical patients with suspected nosocomial infection: a retrospective analysis

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Abstract

Background: Early administration of antibiotics to septic shock patients decreases in-hospital mortality, but there is a lack of studies evaluating the role of early empirical antibiotics in surgical patients with suspected nosocomial infection without sepsis.

Methods: Retrospective cohort of adult patients admitted to a surgical Intensive Care Unit in a tertiary hospital. We defined early empirical antibiotic group by the initiation of antibiotic therapy within 24h after infection's suspicion, and conservative group by antibiotic therapy initiation 24 hours after infection's suspicion or not prescribed within 14 days. The primary outcome was a composite of death, septic shock or sepsis within 14 days from the clinical suspicion of infection. Regression models were used to identify associations between factors and the primary outcome.

Results: From 2007 patients admitted to intensive care unit, 341 surgical patients (71% trauma patients) with suspected nosocomial infection without sepsis and with no obvious source of infection were included in the cohort. Age, gender, traumatic brain injury, admission type (trauma vs. non-trauma), SAPS 3, SOFA, vasopressor use or rate of mechanical ventilation did not differ between early empirical antibiotic and conservative groups. In the conservative group, 57% of patients received antibiotics within 14 days. The composite primary outcome occurred in 41% of patients in the conservative group and 56% in the early empirical antimicrobial group, (p=0.007). The 14-day incidence of septic shock or mortality was similar in both groups. Multivariate analysis showed early antimicrobial therapy (OR 1.83 [95% CI 1.16-2.88] , p = 0.008), non-trauma admission (OR 2.32 [1.40-3.90], p = 0.001) and mechanical ventilation (OR 2.09 [1.31-3.35], p = 0.002) were associated with the primary outcome. Exploratory analysis including only patients with positive cultures also did not find any benefit of early empiric antibiotic therapy (OR 1.39 [0.78-2.49], p = 0.26)

Conclusions: Early empiric antibiotic therapy does not decrease the incidence of sepsis, septic shock or death within 14 days in critically ill stable surgical patients with suspected infection but with no obvious source.

Background

The Surviving Sepsis Campaign Guidelines advocate empirical antimicrobial therapy "as soon as possible after recognition of infection and within one hour for both sepsis and septic shock" [1]. A recent study including 49331 septic patients demonstrated the association of delays in antibiotic administration and an increase in in-hospital mortality. However, a subgroup analysis of 32610 patients without septic shock failed to show any benefit in early antibiotic administration [2]. In a before-and-after observational cohort including 201 critically ill surgical patients with suspected ICU-acquired infections without septic shock, early empirical administration of antimicrobial therapy was associated with higher all-cause mortality [3].

Inappropriate antibiotic use can directly harm individual patients due to systemic collateral effects and increased rate of colonization and infection by multi-drug resistant bacteria [3–5]. Furthermore, data suggest that excessive use of antimicrobial therapy leads to environmental damage by the selection of multi-resistant organisms [6]. Despite this, 65% of the therapeutic use of antibiotics in hospitalized patients are not guided based on microbiology data from a relevant clinical specimen [7].

This aggressive therapeutic approach, in the absence of a clear infectious source, is driven by the belief that antibiotics could prevent stable patients with suspected infections from deteriorating to sepsis or septic shock or even by fear of litigation [8]. Our study aimed to evaluate if early empirical antibiotic therapy prevents the development of sepsis, septic shock or death in critically ill surgical patients with suspected infections, compared to a conservative strategy.

Methods

Study design and population

We retrospectively evaluated a cohort of adult patients admitted to an emergency surgical intensive care unit in a tertiary university hospital in São Paulo, Brazil, between march 2012 and april 2016 that presented with new suspected nosocomial infection without sepsis during ICU stay. The analysis plan, study design and definition of Groups and Outcomes were defined before data extraction and mining from the electronic medical records (EMR) database. The study was approved by the institutional research ethics board (CAPPesq) under the number CAAE 44661615.7.0000.0068. Due to the retrospective and observational nature of the study, informed consent was waived by the ethics board.

We defined suspected nosocomial infection when microbiological cultures were drawn after 48 hours of hospital admission by the attending physician due to a hypothesis of nosocomial infection without an obvious source as documented in electronic medical records. Surveillance cultures (rectal, nasal, and axillary swabs) were excluded.

Exclusion criteria were: a) diagnosis of sepsis or septic shock according to the Sepsis 3.0 definitions[9] within 24 hours after cultures were drawn; b) an obvious infection source; c) hemodynamic deterioration in the first 24 hours of infection suspicion defined as an increase > 0.1 mcg/kg/min in norepinephrine dosage; c) ICU length of stay less than 48 hours; d) death within 48 hours of inclusion in the study; e) missing data on the primary outcome and f) patients under palliative care. Vasopressor use was not an exclusion criteria per se, as long as the patient did not meet sepsis, septic shock or hemodynamic deterioration definitions.

Data collection and patient management

We divided in two groups: 1) Early Empirical Antibiotic Group, in which patients received antibiotic therapy within 24 hours from the clinical suspicion of infection and; 2) Conservative Group, in which

patients received antibiotics after 24 hours or later from the clinical suspicion of infection or did not receive antibiotics within 14 days from the initial clinical suspicion.

The Simplified Acute Physiology Score (SAPS) 3 was obtained at ICU admission, while the Sequential Organ Failure Assessment (SOFA) score was retrospectively calculated based on EMR data from the day of inclusion up to 14 days, death or unit discharge, whichever occurred first.

Physiological and laboratory data within 24 hours of inclusion were obtained: maximum heart rate, highest and lowest body temperature, lactate, white blood cell count and C-reactive protein levels. Respiratory rate was not available in all patients, not being used in this study. Sepsis and septic shock were defined using the Sepsis 3.0 definition [9].

Electronic medical records of all patients included in the study underwent a thorough review by a member of the research team. Microbiologic data were obtained from the hospital's microbiological laboratory database. Blood cultures were drawn in any suspicion of infection. Respiratory, urinary or cerebral spine fluid samples were collected if there was clinical suspicion of infection in these sites. Confirmed infection was defined by isolation of a pathogenic microorganism in microbiological culture during the study period. Positive microbiological data were only considered true infection when it was used to guide antibiotic treatment, otherwise it was considered colonization. Whenever an antibiotic treatment was indicated, the timing of initiation and choice of the specific drug regimen were defined at the discretion of the attending physician, according to the institution infection treatment guidelines.

Outcomes

The primary outcome was defined a priori as a composite outcome including death, septic shock or sepsis 14 within days after inclusion. Secondary outcomes were ICU and hospital length of stay and in-hospital mortality. Time to adequate antibiotic treatment was defined as the time from the inclusion in the study up to the day when the first adequate antibiotic against the isolated microorganism was administered.

Statistical analysis

Continuous variables were expressed as mean and standard deviation (SD) or median and interquartile range (IQR), according to data distribution. Discrete variables were reported as counts and percentages. Differences between groups were compared using Student's t-test, Mann–Whitney U, chi-square or Fisher's exact test, when appropriated. Univariate logistic regression was used to access the variables potentially associated with the primary outcome. Variables with a p-value of less than 0.2 and other clinically relevant variables were included in a stepwise backward logistic regression model with the primary outcome as the dependent variable. Associations were expressed using the odds ratio (OR) with 95% confidence intervals (CIs). Matched analysis for patients with and without confirmed infection were performed. A p value < 0.05 was considered significant. Statistical analyses were performed using the R free source software [10].

Results

Of the 2007 ICU admissions, 751 patients had suspected nosocomial infection and were screened. As show in the flowchart presented in Fig. 1, 341 patients were included in the cohort. The most common reasons for exclusion were sepsis (214 patients), septic shock (74 patients) or an obvious infection source (49 patients) at the study entry.

The groups had similar mean age (44 years). Male gender predominated in both groups, composing 79% of the Conservative Group and 70% of the Early Empirical Antibiotic Group. Seventy one percent of the ICU admissions were trauma in both groups, being traumatic brain injury present in more than half of the patients included in the study. Severity of disease was similar in both groups, as assessed by hemodynamic and respiratory variables. No differences were observed in admission median Simplified Acute Physiology Score 3 (54 for both groups), median Sequential Organ Failure Assessment score at day of inclusion (5 in Conservative vs. 4 in Early Empirical Antibiotic Therapy Group), rate of mechanical ventilation (54% vs. 59%, respectively) or vasopressor use (19.8% vs. 18.4%, respectively), as shown in Table 1.

Table1: Baseline characteristics at inclusion.

	Conservative group	Early empirical antibiotic group	*p* value
Number %	210 (62)	131 (38)	
Age in years, mean (SD)	44.3 (18.3)	44 (17.7)	0.890
Male, *n* (%)	168 (79.3)	91 (70)	0.053
Admission type			0.951
Trauma, *n* (%)	151 (71.2)	93 (71.6)	
Non-trauma, *n* (%)	61 (28.8)	37 (28.4)	
Traumatic brain injury, *n* (%)	102 (50)	73 (56.2)	0.269
Admission SAPS 3median, (IQR)	54 (46-63)	54 (48-65)	0.498
SOFA median, (IQR)	5 (3-7)	4 (4-7)	0.210
Vasopressors, *n* (%)	42 (19.8)	24 (18.5)	0.759
Lactate, mmol/L (IQR)	2.0 (1.6-2.6)	2.2 (1.7-3.1)	0.042
Mechanical ventilation, *n* (%)	65 (54)	77 (59)	0.324
ICU LOS before inclusion, median(IQR)	5 (3-10)	6 (3-10)	0.502
Heart Rate, Highest, bpm(SD)	107 (22)	109 (30)	0.286
Highest Temperature, ºC (SD)	37.5 (0.76)	37.5 (0.74)	0.923
Lowest Temperature, ºC (SD)	35.8 (0.80)	35.8 (0.96)	0.605
WBC count, per µL (IQR)	12680 (9140-15155)	14283 (9748-17908)	0.022
CRP mg/L, mean (SD)	15.4 (9.2)	18.6 (10.8)	0.005

SAPS 3: Simplified acute physiology score 3; SOFA Sequential organ failure assessment score; LOS: Length of stay; WBC: White Blood Cell; CRP: C-reactive protein. Values within 24 hours at the day of inclusion.

ICU = Intensive Care Unit. Data are presented as mean (standard deviation), median (interquartile range), or *n*(%) as appropriate

In this cohort, the main reason for vasopressor use at inclusion was to keep adequate cerebral perfusion pressure in brain injured patients. Lowest MAP in patients using vasopressors was 74 ± 11 mmHg in Conservative Group vs. 74 ± 9 mmHg in Early Empirical Antibiotic Therapy Group. Within 24 hours of inclusion, 14% of the patients on vasopressors in the Conservative Group and 16% in the Early Empirical Antibiotic Therapy Group had a lowest MAP lower than 65 mmHg.

Clinical parameters suggested a similar inflammatory state in both groups: heart rate 107 ± 22 beats/min vs. 109 ± 30 beats/min, highest body temperature 37.5 ± 0.7 ºC vs. 37.5 ± 0.7 ºC, lowest body temperature 35.8 ± 0.8 ºC vs. 35.8 ± 0.9 ºC in Conservative and Early Empirical Antibiotic Therapy Group, respectively. As shown in Table 1, laboratory markers of inflammation (White Blood Cell Count and C-Reactive Protein) were slightly, but significantly higher in Early Empiric Antibiotic as compared to Conservative Group.

The median ICU length of stay before study inclusion was 5 days in the Conservative Group and 6 days in the Early Empirical Antibiotic Therapy Group ($p = 0.5$).

After 14 days of observation, only 57% of patients in the Conservative Group had received antibiotics (Table 2). Patients in the early empirical antibiotic group had more suspected lung infections (50.77% vs. 24.06%, $p < 0.001$), abdominal infections (9.23% vs. 2.83%, $p = 0.01$), and 10% received antibiotic without any suspected infection site. In the Early Empirical Antibiotic Group, more patients had microbiological confirmed infections (69.23% vs. 44.81%, $p < 0.001$). The median time to adequate antibiotic treatment, defined as the first day of effective antibiotic treatment based on microbiological data, was 4 days (IQR 2–5 days) in the Conservative Group vs. 1 day (IQR 0–3 days) in the Early empirical Antibiotic Group ($p < 0.001$) (Table 2).

Table 2 Infections and treatment characteristics.

	Conservative group	Early empirical antibiotic group	*p* value
Received antibiotics[1] *n*(%)	121 (57)	131 (100)	<0.001
Suspected infection site[2]			
Lung, *n*(%)	51 (24.1)	66 (50.8)	<0.001
Urinary, *n*(%)	16 (7.6)	8 (6.2)	0.624
Bloodstream, *n*(%)	19 (9)	10 (7.7)	0.682
Abdominal, *n*(%)	6 (2.83)	12 (9.2)	0.01
Central nervous sistem, *n*(%)	11 (5.2)	9 (6.9)	0.507
Other, *n*(%)	9 (4.3)	11 (8.5)	0.105
Unknown, *n*(%)	22 (47)	14 (10.8)	<0.001
Confirmed infection[3], *n*(%)	95 (44.8)	90 (69.2)	<0.001
Days until adequate antibiotic, median (IQR)	4 (2-5)	1 (0-3)	<0.001

1. Received antibiotics for nosocomial infection within 14 days.
2. Suspected infection site according to Electronic Medical Records within 14 days.
3. Confirmed infection with positive cultures at suspected infection site.

Data are presented as median (interquartile range) or n(%) as appropriate

The composite primary outcome of death, sepsis or septic shock within 14 days after inclusion occurred in 41% of patients in the Conservative Group and in 56.1% in the Early Empirical Antimicrobial Group, p = 0.007 (Table 3). There was no difference in the incidence of 14-day death or septic shock between groups. Patients in the Conservative Group had shorter ICU length of stay [18 days (IQR 13–29 days) vs. 23 days (IQR 24–37 days), p = 0.025]. However, there were no differences between groups in hospital length of stay [36 days (IQR 21–75 days) vs. 43 days (IQR 23–68 days), p = 0.54], discharge to a long-term facility (18.4% vs. 16.15%, p = 0.597) and in-hospital mortality (33% vs. 41%, p = 0.164) (Table 3).

Table 3 Outcomes.

	Conservative group	Early empirical antibiotic group	*p* value
Primary outcome, *n*(%)	87 (41)	73 (56.2)	0.007
Mortality in 14 days, *n*(%)	25 (12)	18 (14)	0.449
Septic shock in 14 days, *n*(%)	29 (13.7)	20 (15.4)	0.662
Sepsis in 14 days, *n*(%)	76 (36)	64(49)	0.009
ICU length of stay, median (IQR)	18 (13-29)	23 (24-37)	0.025
Hospital length of stay, median (IQR)	36 (21-75)	43 (23-68)	0.54
Discharge to long term facility, *n*(%)	39 (18.4)	21 (16.2)	0.597
In-hospital mortality, *n*(%)	70 (33)	53 (41)	0.164

The Primary Outcome, Mortality in 14 days, Septic Shock in 14 days, Sepsis in 14 days, Discharge to long term facility and In-hospital mortality were evaluated with chi-square or Fisher's exact test, as appropriate. ICU length of stay and Hospital length of stay were evaluated with Mann–Whitney test.

Data are presented as median (interquartile range) or *n*(%) as appropriate.

As shown in Table 4, the univariate logistic regression showed a possible association between group allocation, confirmed infection, mechanical ventilation, age, type of admission, white blood cell count, C-Reactive protein, highest body temperature, highest heart rate and serum lactate with the primary outcome. However, only allocation in the Early Empirical Antibiotic Group (OR 1.794, 95% CI 1.137–2.829; p = 0.012), non-trauma admission (OR 1.81, 95% CI 1.039–3.176; p = 0.036) and mechanical ventilation (OR 2.13, 95% CI 1.33–3.42; p = 0.002) were independently associated with the primary outcome in the multivariate regression model (Table 5).

Table 4 Variables evaluated for association with the primary outcome. Univariate analysis.

	Odds ratio	95% CI	*p* value
Empiric antibiotic group	1.85	1.19-2.86	0.006
Confirmed Infection	1.80	1.17-2.79	0.007
Mechanical Ventilation	1.74	1.13-2.70	0.001
Age	1.01	0.99-1.02	0.135
Non-trauma admission	1.85	1.15-2.99	0.011
WBC count > 12000 cells/mm^3	1.73	1.12-2.66	0.013
CRP> 10mg/dL	1.39	0.85-2.29	0.189
Highest Temperature > 38ºC	0.69	0.40-1.15	0.159
Highest Heart Rate> 90 bpm	0.60	0.35-1.03	0.064
Lactate (mmol/L)	1.03	1.00-1.05	0.044
SOFA	1.03	0.96-1.10	0.358
SAPS3	1.01	0.99-1.03	0.221
WBC count < 4000 cells/mm^3	0.58	0.08-3.00	0.530
Lowest Temperature < 36ºC	0.85	0.54-1.35	0.495
Vasopressors at inclusion	1.25	0.73-2.13	0.420

SAPS 3: Simplified acute physiology score 3; SOFA Sequential organ failure assessment score; SIRS: Systemic inflammatory response syndrome; WBC: White Blood Cell; CRP: C-Reactive Protein.

Variables with p<0.2 were included in Multivariate analysis (Table 5).

Table 5
Multivariate analysis.

All patients (n = 341)	Odds ratio	95% CI	p value
Empirical antibiotic group	1.83	1.16–2.88	0.008
Non-trauma admission	2.32	1.40–3.90	0.001
Mechanical ventilation	2.09	1.31–3.35	0.002
Patients with confirmed infection (n = 185)			
Non-trauma admission	2.43	1.27–4.77	0.008
Variables in Univariate Analysis (Table 4) with a p-value of less than 0.2 in the were included in a stepwise backward logistic regression model with the primary outcome as the dependent variable. Final models included only variables with a $p < 0.05$.			

A sensitivity analysis including only patients with confirmed infection was performed to control imbalances between groups regarding confirmed infection. In patients with confirmed infection, sources were not statistically different: Lung (21% vs. 28%), Urinary Tract Infection (15 vs 7%), Bloodstream (10 vs 5%), Abdominal (5 vs 6%), Central Nervous System (5 vs 5%) and Others (10 vs 11%) in Conservative vs Early Empirical Antibiotic Groups, respectively (p = 0.13). Furthermore, in this analysis, early empiric antibiotic therapy did not show any protective effect on sepsis development. In patients with subsequent confirmed infection (n = 185), early empirical antibiotic use did not prevent the primary outcome (OR 1.39 95% CI 0.78–2.49, p = 0.264). In patients without confirmed infection (n = 156), the univariate analysis showed an OR 2.18 (95% CI 1.05–4.57, p = 0.036) to the primary outcome, but group allocation was also not associated with the primary outcome on the in the multivariate regression model (OR 1.73 95% 0.63–4.86, p = 0.287).

Discussion

In this study, we observed that administration of early empiric antibiotic therapy to stable patients with suspected nosocomial infection was independently associated with an increase in the odds of the development of the composite primary outcome composed by sepsis, septic shock and/or death. When matched analysis for confirmed infection (by positive cultures) was performed, Early Empiric Antibiotic Therapy had no association with the primary outcome.

In critically-ill patients, common signs indicating the presence of an infection like fever and leukocytosis are non-specific and may occur in many non-infectious conditions, particularly in trauma patients [11, 12]. Moreover, the diagnostic criteria for sepsis are under scrutiny, with data showing the use of Systemic Inflammatory Response Syndrome criteria (Sepsis 2.0) has great sensitivity but low specificity while Sequential Organ Failure Assessment (Sepsis 3.0) is more accurate and specific [13]. Therefore, the

decision to initiate antibiotic therapy to critically ill patients is strongly dependent on clinical suspicion and/or the presence of new organic failures attributed to an infection and must take into account the balance between the benefits and harms of the therapy.

Some observational studies have investigated whether early antibiotic administration may reduce mortality in patients with suspected infections. This relationship appears to hold true for septic and septic shock patients admitted to emergency services. Among 49,331 patients at 149 hospitals in New York, Seymour et al. observed that a longer period before the administration of antibiotics was associated with higher risk-adjusted in-hospital mortality [2]. In another large multicenter cohort of patients presenting with suspected infection in the emergency department, Liu et al. observed that hourly delays in antibiotic administration were associated with a marginally significant increase in the odds of hospital mortality even in the absence of organ dysfunction or shock [14].

On the other hand, evidence to the contrary was published in critically ill patients by Hranjec et al. showing that early empiric antibiotic treatment was associated with a lower chance of receiving initially appropriated treatment, a prolonged duration of antimicrobial treatment, and a significantly lower survival rate in ICU patients with suspected nosocomial infections without shock [3]. Furthermore, Seymour et al. observed that the time to the administration of antibiotics were not significantly associated with greater in-hospital mortality in a subgroup analysis that included 32610 septic patients without vasopressors [2]. Recently, Abe et al also did not find any association between earlier antibiotic administration and reduction in in-hospital mortality in 1124 patients with severe sepsis (Sepsis 2.0 criteria) admitted to ICU [15].

In our sample, early empirical antimicrobial therapy administered to critically ill surgical stable patients without an obvious source of infection was independently associated with an increase in the incidence of sepsis, septic shock or death within 14 days from the initial suspicion of infection with an OR of 1.83 (1.13–2.82). The other factors independently associated with the incidence of the primary outcome were non-trauma admission (OR 2.32 95% CI: 1.4–3.9) and mechanical ventilation (OR 2.09–95% CI: 1.31–3.35).

The groups were well balanced regarding the cause of admission, age, SAPS 3 and SOFA at inclusion, ICU length of stay before inclusion, and clinical markers of inflammation (heart rate and body temperature). However, laboratory markers of inflammation (White Blood Cell Count and C-Reactive Protein) were higher in Early Empiric Antibiotic Group, as well as confirmed infection (69% vs. 45% in the Conservative Group).

When we performed a sensitivity analysis, adjusting by confirmed infection, early empiric antibiotic therapy had no association with the primary outcome neither in patients with confirmed infection (OR 1.39–95% CI: 0.77–2.48), nor in patients without confirmed infection (OR 1.73 95% 0.63–4.86, p = 0.287). Although these sensitivity analyses were underpowered and showed no significant statistical association between early empiric antibiotic therapy and the development of the primary outcome, neither of them indicates any trend in favor of better outcomes if early empiric antibiotic therapies were administered. Our results are in line with those published by Hranjec et al evaluating a similar cohort of patients [3]. The

reasons why early empiric antibiotics in non-septic critically ill patients with suspected but not yet confirmed infection might be detrimental, as shown in our study and others, are a question worth speculating.

Firstly, it is important to highlight that robust evidences for the benefit of an early empiric antibiotic therapy, often disseminated as “the sooner, the better” by guidelines might be true only for sepsis and septic shock [1, 2]. In other clinical scenarios, this potential benefit is not supported by hard evidence. In a multicentric, open label, randomized trial, Alam et al. did not observed any beneficial effect on survival of early antimicrobial therapy improved survival rate in pre-hospital patients with infection suspicion [16].

Secondly, when infection is not evident, overuse of antimicrobial agents may delay the determination of the correct etiology of the inflammatory process and lead to misdiagnosis. In our study, 31% of patients in the early antibiotic treatment group did not show any positive cultures supporting the diagnosis of nosocomial infection. According to Tamma et al., at least 20% of patients exposed to antibiotics are expected to experience significant systemic adverse side effects [17]. Consequently, we can speculate that these adverse effects were not counterbalanced by the overall benefits of these drugs in some patients. The odds ratio for colonization with carbapenem-resistant Enterobacteriaceae in patients exposed to antibiotics is five times higher than in non-exposed individuals[18]. Colonization by multidrug-resistant bacteria can last for months [19], and infection caused by these strains carries a mortality rate as high as 44%[20]. Data also suggest that the use of broad-spectrum antibiotics is associated with more severe microbiome disruption increasing the risk of subsequent sepsis within 90 days of discharge[21]. Hence, patients in the aggressive group are more prone to new sepsis, and these infections have higher chances to be caused by multidrug-resistant strains. Indeed, Guidry et al. followed 190 patients for four years from the initial cohort published in 2012 [3, 22]. Adjusted analysis showed higher long-term mortality for patients in the aggressive antimicrobial therapy at both one and four years, when compared with a conservative approach.

Thirdly, inflammatory markers are not specific for infection, particularly in the critically ill trauma patient. In this population the incidence of Systemic Inflammatory Response Syndrome may reach 91% in the first week post injury [23]. Furthermore, 94% of multiple-trauma patients may present an increase in the systemic inflammation marker C-reactive protein that may persist for more than 7 days [24]. In our study, 43% of patients in the conservative group did not receive any antibiotic therapy within 14 days after suspected infection. Hence, a more conservative led to a more thorough diagnostic investigation and detection of the condition causing hyperthermia, tachycardia and elevated laboratory inflammatory markers.

Even when infection is indeed present, early administration of antibiotics may not the main factor associated with better outcomes in the critically ill non-septic patient [25]. Delay on the diagnosis of the correct source of infection is associated with significant increase in mortality (> 10% increase in in-hospital mortality) [26]. Therefore, efforts should be made to establish a diagnosis as soon as possible,

since treatment will probably fail if this premise is wrong [27]. In the meantime, early empiric antimicrobial therapy should be prescribed for septic or deteriorating patients.

Our study has weaknesses and limitations. It was a single center observational trial, and confounders such as selection and information biases might have influenced the results. Also, there was no standardization in the criteria for initiation of antibiotic therapy, with the attending physician being responsible for the decision. This might explain the higher number of culture-confirmed infection in the early empirical antibiotic group. Although there was no difference between groups when using Sequential Organ Failure Assessment, Simplified Acute Physiology Score 3 scores or others markers of disease severity (vasopressor or mechanical ventilation use), we cannot underestimate the clinical impression of the treating physician, which takes into account numerous known and intangible factors in the process of decision making and might have been the explanation for the early initiation of antibiotic treatment. Even though, early empiric antibiotic treatment was also not associated with better outcomes in matched analysis of patients with confirmed infection by positive cultures. This subgroup analysis, however, is probably underpowered. Lastly, our results are valid only for a strict number of critically ill patients in a specific situation.

Conclusions

Early empirical antibiotic therapy does not decrease the incidence of sepsis, septic shock or death within 14 days in stable non-septic critically ill surgical patients with suspected nosocomial infection but with no obvious source. A conservative approach can decrease antibiotic use might be associated with short-term better outcomes.

Abbreviations

ICU
Intensive care unit
EMR
electronic medical records
SAPS3
Simplified Acute Physiology Score 3
SOFA
Sequential Organ Failure Assessment
SD
Standard deviation
IQR
interquartile range
MAP
Mean Arterial Pressure

Declarations

Availability of data and materials

The datasets analyzed during the current study are available with the corresponding author on reasonable request.

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None.

Ethics approval and consent to participate

The study protocol was reviewed and approved by the institutional research ethics board (CAPPesq) under the number CAAE 44661615.7.0000.0068. Due to the retrospective and observational nature of the study, informed consent was waived by the ethics board.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

EB, TG, FFCN, EMU and LMSM conceived and designed the study.

EB, BVC, AROS and SROS collected and analyzed the data.

EB, BMT, PP, LMSM did the statistical analysis and interpreted the data.

EB, BMT, TG, FFCS, EMU, PP, LMSM wrote the manuscript.

All authors revised the manuscript for important intellectual content and approved the final version.

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Figures

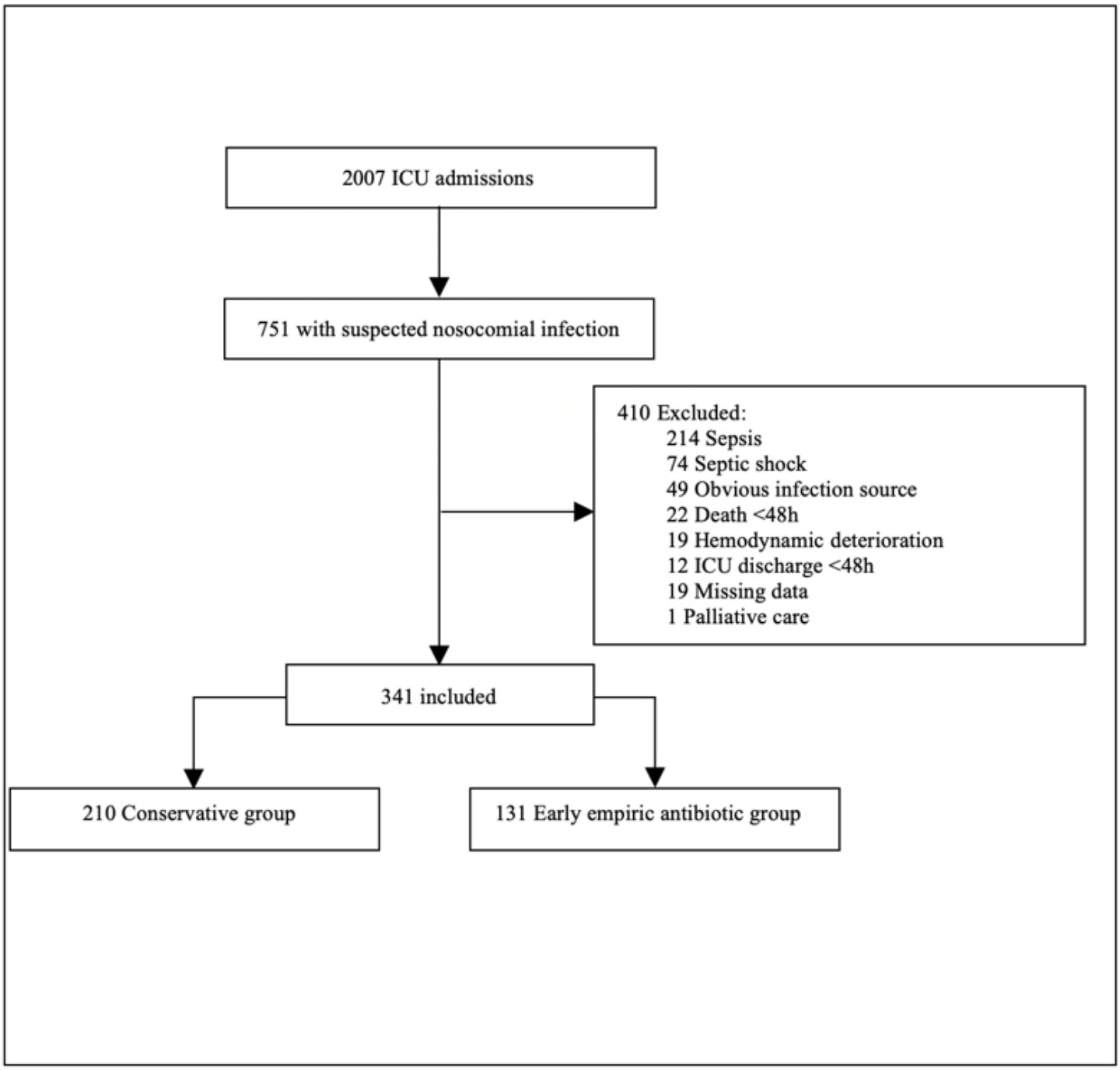

Figure 1

Flowchart. Sepsis 3.0 definition was used for sepsis and septic shock [6]. Hemodynamic deterioration: defined as an increase > 0.1 mcg/kg/min in norepinephrine dosage in the first 24h after inclusion. Conservative group: antibiotics were either initiated only after 24 hours of suspected nosocomial infection or not prescribed within 14 days from the clinical suspicion. Early empiric antibiotic group: antibiotics were initiated within 24 hours from the clinical suspicion