Sociedade Brasileira de Anestesiologia

Brazilian Journal of ANESTHESIOLOGY

ORIGINAL INVESTIGATION

Impact of withholding early antibiotic therapy in nonseptic surgical patients with suspected nosocomial infection: a retrospective cohort analysis

Estevão Bassi [a,b,*], Bruno Martins Tomazini [a,c], Bárbara Vieira Carneiro [a], Amanda Rodrigues de Oliveira Siqueira [d], Sara Rodrigues de Oliveira Siqueira [d], Thais Guimarães [e], Fernando da Costa Ferreira Novo [a], Edivaldo Massazo Utiyama [a], Paolo Pelosi [f,g], Luiz Marcelo Sá Malbouisson [h]

[a] *Universidade de São Paulo, Faculdade de Medicina, Hospital das Clínicas (HCFMUSP), Departamento de Cirurgia, Disciplina de Cirurgia Geral e Traumatologia, São Paulo, SP, Brazil*
[b] *Hospital Alemão Oswaldo Cruz, Unidade de Tratamento Intensivo, São Paulo, SP, Brazil*
[c] *Hospital Sírio-Libanês, Instituto de Ensino e Pesquisa, São Paulo, SP, Brazil*
[d] *Irmandade da Santa Casa de Misericórdia, Departamento de Medicina Interna e Cardiologia, São Paulo, SP, Brazil*
[e] *Universidade de São Paulo, Faculdade de Medicina, Hospital das Clínicas (HCFMUSP), Departamento de Controle de Infecção, São Paulo, SP, Brazil*
[f] *University of Genoa, Department of Surgical Sciences and Integrated Diagnostics, Genoa, Italy*
[g] *San Martino Policlinico Hospital, IRCCS for Oncology and Neurosciences, Anaesthesia and Intensive Care, Genoa, Italy*
[h] *Universidade de São Paulo, Faculdade de Medicina, Hospital das Clínicas (HCFMUSP), Divisão de Anestesiologia, São Paulo, SP, Brazil*

Received 20 August 2022; accepted 14 March 2023
Available online 23 March 2023

KEYWORDS
Antimicrobial stewardship;
Critical care;
Prescription drug overuse;
Sepsis;
Septic shock

Abstract

Background: Systemic inflammatory responses mimicking infectious complications are often present in surgical patients.

Methods: The objective was to assess the association between withholding early antimicrobial therapy while investigating alternative diagnoses and worse outcomes in nonseptic patients with suspected nosocomial infection in a retrospective cohort of critically ill surgical patients. The initiation of antibiotic therapy within 24 h of the suspicion of infection was defined as the Early Empirical Antibiotic strategy (EEA) group and the initiation after 24 h of suspicion or not prescribed was defined as the Conservative Antibiotic strategy (CA) group. Primary outcome was composite: death, sepsis, or septic shock within 14 days. Main exclusion criteria were sepsis or an evident source of infection at inclusion.

Abbreviations: 95% CI, 95% Confidence Interval; CA, Conservative Group; DAG, Direct Acyclic Graphic; EEA, Early Empirical Antibiotic Group; EMR, Electronic Medical Records; ICU, Intensive Care Unit; IQR, Interquartile Range; SAPS-3, Simplified Acute Physiology Score; SOFA, Sequential Organ Failure Assessment; VIF, Variance Inflation Factor; WBC, White Blood Cell.

* Corresponding author.
E-mail: estevao.b@hc.fm.usp.br (E. Bassi).

https://doi.org/10.1016/j.bjane.2023.03.003

Results: Three hundred and forty patients were eligible for inclusion (74% trauma patients). Age, sex, reason for hospital admission, SAPS3 score, SOFA score, and use of vasopressors or mechanical ventilation were not different between the groups. Within 14 days of inclusion, 100% (130/130) of EEA patients received antibiotics compared to 57% (120/210) of CA patients. After adjusting for confounding variables, there was no association between primary outcome and the groups. In a post hoc subgroup analysis including only patients with *a posteriori* confirmed infection (by microbiological cultures), delay in initiation of adequate antimicrobial therapy was independently associated with the primary outcome (Odds Ratio = 1.19 per day of delay; 95% CI 1.05—1.37).
Conclusions: Withholding early empiric antibiotic therapy was not associated with progression of organ dysfunction within 14 days in nonseptic surgical patients with suspected nosocomial infection without an obvious source.

Introduction

Early antimicrobial drugs are the cornerstone of treatment of bacterial infections.[1] In patients with sepsis or septic shock, delays in antibiotic therapy are strongly associated with worse outcomes.[2-5] The Surviving Sepsis Campaign Guidelines advocate "immediate" empirical antimicrobial therapy, ideally within 1h of recognition, in patients with a high likelihood of sepsis or septic shock.[6]

On the other hand, the evidence for early empirical antimicrobial therapy is not strong in stable surgical patients with suspected infections.[7] The causal inference for this strict time-dependent benefit in this situation lacks robust causal association.[8] Early empiric antibiotic treatment is often prescribed to these patients, even in the absence of a clear infectious source, driven by the belief that antibiotics could prevent stable patients from deteriorating or by fear of litigation.[9] Antibiotic overuse is associated with an increase in the rate of systemic adverse effects,[10] and colonization and infection by multidrug resistant microorganisms.[11-14] Millions of deaths are estimated to be caused by or associated with multidrug-resistant bacteria.[12] Critically ill surgical patients admitted to the Intensive Care Unit (ICU) commonly have a persistent inflammatory response that mimics nosocomial infection,[15,16] which influences clinical reasoning and may contribute to the excessive use of antibiotics.

Our study aimed to evaluate the impact of withholding early empirical antibiotics during diagnostic workup on clinical outcomes in nonseptic surgical patients with suspected nosocomial infections.

Methods

We retrospectively evaluated a cohort of adult patients admitted to an emergency surgical Intensive cCare Unit (ICU) in a tertiary university hospital in São Paulo, Brazil between 2012 and 2016. The analysis plan, study design, and definition of the groups and outcomes were defined before data extraction and mining from the Electronic Medical Record (EMR) database. The study was approved by the institutional research ethics board (CAPPesq — CAAE 44661615.7.0000.0068). Due to the retrospective nature of the study, the requirement for informed consent was waived by the ethics board. This article was written based on the Reporting of Observational Studies in Epidemiology (STROBE) statement to assess the reporting of cohort studies (Supplemental Fig. 1).[17]

The inclusion criteria were as follows: stable postsurgical or trauma (irrespective of the mechanism or site or surgery) patients who were admitted to the ICU, who were older than 14 years, and who had a suspected nosocomial infection during ICU stay. Suspected nosocomial infection was defined when microbiological cultures were drawn after 48 hours of hospital admission due to a suspicion of infection, as documented in the EMRs. Stable patients were those with no significant increase in their Sequential Organ Failure Assessment (SOFA) score (< 2 points) within the previous 24 hours.[18] Surveillance cultures (rectal, nasal, and axillary swabs) were excluded. The exclusion criteria were as follows: a) Rapid progression of organ dysfunctions with an increase in the SOFA score that is > 1 (sepsis) or hyperlactatemia, hypotension and vasopressor use (septic shock) according to the Sepsis 3.0 definitions[19] within 24 hours of inclusion; b) Hemodynamic deterioration within the first 24 hours of the suspected infection defined as an increase > 0.1 mcg.kg^{-1}.min^{-1} in the norepinephrine dosage; c) An obvious infectious source identified in the EMR (e.g., antibiotics initiated for pneumonia, urinary tract infection, meningitis); d) An ICU length of stay less than 48 hours after inclusion; e) Missing data on the primary outcome; f) Patients in palliative care; and g) Predicted death within 48 hours of inclusion. Vasopressor use was not an exclusion criterion *per se* if the patient did not meet the sepsis, septic shock, or hemodynamic deterioration definitions. All patients who fulfilled the inclusion criteria without any of the exclusion criteria during the period were included in the analysis. Time zero was defined as the moment in which the first microbiological cultures were drawn led to suspicion for the presence of a nosocomial infection.

Data collection and patient management

We divided the study population into two groups: 1) The Early Empirical Antibiotic strategy (EEA) group, in which the patients received antibiotic therapy within 24 hours of the clinical suspicion of infection, and 2) The Conservative Antibiotic strategy (CA) group, in which the patients received antibiotics 24 hours or later after the clinical suspicion of infection or did not receive antibiotics within 14 days of

inclusion. The physiological and laboratory variables up to 24 hours after inclusion were considered the baseline values and included the following variables: the use of mechanical ventilation or vasopressors, highest and lowest heart rate, highest and lowest body temperature, serum lactate, white blood cell count, and C-reactive protein levels. When more than one measure of these variables were available, the most abnormal value within this time window was chosen. Respiratory rate was not available in all patients and was not used in this study. Sustained tachycardia was defined when the lowest heart rate in the first 24 h of inclusion was ≥ 90 bpm. Blood cultures were drawn if there was any suspicion of infection. Respiratory, urinary, or cerebral spine fluid samples were collected when infection was suspected. Presumed infection was defined when a specific source of infection (e.g., lung, abdomen, central nervous system, etc.) was diagnosed more than 24 hours after inclusion and within 14 days according to the EMR. Confirmed infection was defined by the isolation of a pathogenic microorganism from the presumed source during the study period. Infection was defined when positive microbiological data were used to guide antibiotic treatment; otherwise, it was considered colonization. Whether antibiotic treatment was indicated, the timing of the initiation of antibiotics and the choice of the specific drug were defined at the discretion of the attending physician. Time to adequate antibiotic treatment was defined as the time from inclusion in the study up to the first day when an active antibiotic against the isolated microorganism was administered, according to the susceptibility on the antibiogram.

Outcomes

The primary outcome was defined *a priori* as a composite outcome including death, hypotension, hyperlactatemia and vasopressor use (septic shock) or worsening of organ dysfunction (an increase > 1 in the SOFA score — sepsis) within 14 days of inclusion, according to the Sepsis 3.0 definitions.[19] The secondary outcomes were ICU and hospital length of stay, and in-hospital mortality. Follow-up was performed until the end of hospitalization.

The timeline with the time points of the study is presented in Supplemental Figure 2.

Statistical analysis

All patients admitted to the ICU during the period were evaluated for inclusion in the study. Continuous variables were expressed as the mean and Standard Deviation (SD) or the median and Interquartile Range (IQR), according to data distribution. Discrete variables were reported as counts and percentages. Differences between the groups were compared using Welch's *t*-test, irrespective of the distribution of the numeric data,[20] or chi-square when appropriate. Confounding variables were evaluated using a Direct Acyclic Graphic (DAG), as shown in Figure 1.[21-23]

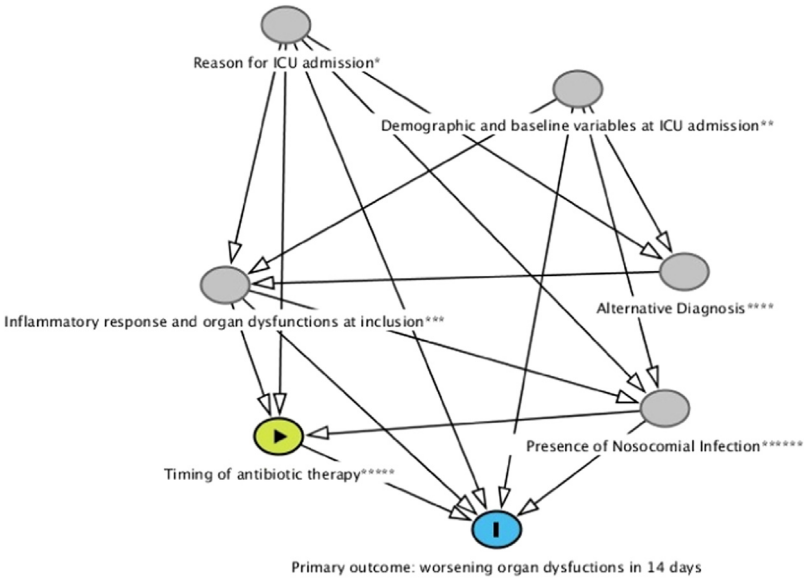

Figure 1 Direct acyclic graph for causal inference. The direction of the arrows indicates potential causality. The inference tested was between variables "Timing of antibiotic therapy" (independent variable) and "Primary outcome: worsening organ dysfunctions in 14 days" (dependent variable). Variables included in the model were the following: *Reason for Intensive Care Unit admission: trauma or surgery. ** Sex, age, comorbidities, Simplified acute physiology score-3. *** Inflammatory Response: dysregulation of body temperature (hypothermia or hyperthermia), white blood cell count alteration (leucocytosis or leukopenia) and sustained tachycardia (heart rate above 90 bpm in 24 h); Organ Dysfunctions: defined as the SOFA (Sequential Organ Failure Assessment) score. **** Alternative Diagnostics to nosocomial infection: such as inflammatory response to trauma or surgery, intracranial hypertension, thromboembolic events, heart failure etc. ***** Timing of Antibiotic: defined as the group (CA or EEA). ****** Nosocomial Infection: presumed or confirmed infection, according to different analyses that were performed. Data were imputed at http://www.dagitty.net/dags.html.[20-22]. Minimal adjustment sets for estimating the total effect of "Timing of antibiotic therapy" on "Primary Outcome" were: Reason for Intensive Care Unit admission*, Inflammatory response and organ dysfunctions at inclusion***, Presence of Nosocomial Infection******

Following the guidance of the DAG, a multivariate analysis was performed. The potential confounding variables in the association between time point of starting antibiotics and the primary outcome were dysregulation of body temperature (hypothermia or hyperthermia), white blood cell count alteration (leukocytosis or leukopenia), sustained tachycardia (heart rate above 90 bpm in 24 h), baseline SOFA score and diagnosis of a presumed nosocomial infection within the 14 days after inclusion. A sensitivity analysis was performed using univariate logistic regression to assess the variables potentially associated with the primary outcome. Clinically relevant variables with a *p*-value of less than 0.2 were included in a stepwise backward logistic regression model. A post hoc subgroup analysis including only the patients with confirmed infection was also performed. In this case, the variable "Timing to antibiotic therapy" had two components: group (CA or EEA) and time to adequate antibiotic treatment, as described above. Multicollinearity was evaluated through the variance inflation factor. VIF > 5 was considered to have significant multicollinearity.[24] Associations were expressed using the Odds Ratio (OR) with 95% Confidence Intervals (CIs). A *p*-value < 0.05 was considered significant. Statistical analyses were performed using R free source software.[25]

Results

Of the 2007 ICU admissions, 751 patients had suspected nosocomial infections and were screened. As shown in Figure 2, 340 patients were included in the cohort. The most common reasons for exclusion were sepsis (221 patients), septic shock (81 patients) or an obvious infectious source (51 patients) at inclusion. The group allocation was as follows: 210 patients to the CA group and 130 to the EEA group. The median ICU length of stay before study inclusion was 5 days in the CA group and 6 days in the EEA group ($p = 0.8$).

In Table 1, patients' characteristics at ICU admission and time of infection suspicion (inclusion) are shown. The groups had a similar mean age (44±18 years in both). Male sex was predominant in both groups. Seventy-four percent of the ICU admissions were due to trauma, and most of the trauma patients had a traumatic brain injury. The mean SAPS 3 score (55±14 vs. 56±12), median SOFA (5, IQR 3–7 vs. 5, IQ 4–7), rate of mechanical ventilation (119/210, 57% vs. 82/130, 63%) and vasopressor use (43/210, 21% vs. 28/130, 22%) were similar in the CA and EEA groups, respectively. Body temperature was also similar in both groups: the highest body temperature was 37.8 ± 0.7°C vs. 37.8 ± 0.8°C, and the lowest body temperature was 35.6 ± 0.8°C vs. 35.6 ±

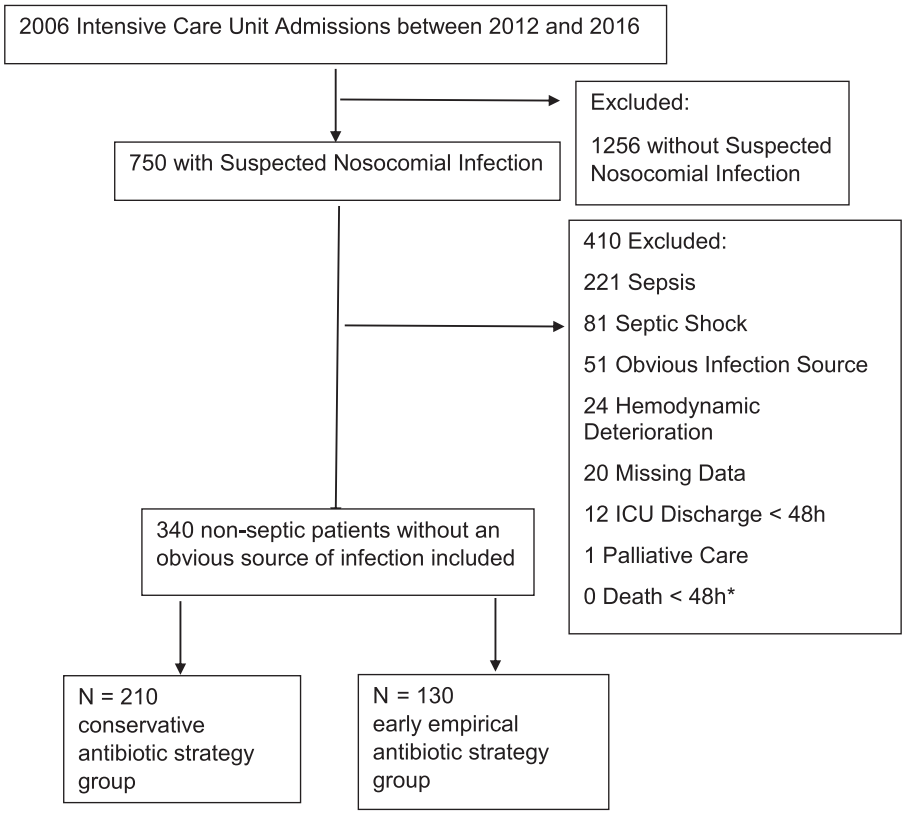

Figure 2 Flowchart. Flow diagram for the study population and number of patients analysed for suspected nosocomial infection, according to the STROBE statement.[25] Patients were selected to constitute the study population based on suspected infection after 48h of Intensive Care Unit admission. STROBE, Strengthening for Reporting of Observational Studies in Epidemiology. Conservative antibiotic strategy group: patients received antibiotics after 24 hours or later from the initial clinical suspicion of infection or did not receive antibiotics within 14 days from the inclusion. early empirical antibiotic strategy group: patients received antibiotic therapy within 24 hours from the initial clinical suspicion of infection. *Without other exclusion criteria.

Table 1 Baseline patients' characteristics at Intensive Care Unit admission and at infection suspicion (study inclusion).

	CA group	EAA group	*p*-value
N (% of total)	210 (62%)	130 (38%)	
Age (years)	44±18	44±18	0.81
Male, n (%)	166 (79%)	91 (70%)	0.08
Reason for Hospital Admission, n (%)			
Trauma	155 (74%)	97 (75%)	0.94
Brain Trauma Injury	109 (52%)	75 (58%)	0.35
Surgery[a]	55 (26%)	32 (26%)	0.38
Neurosurgery	31 (57%)	15 (47%)	
Abdominal	15 (27%)	15 (47%)	
Vascular	6 (11%)	1 (3%)	
Other	3 (6%)	1 (3%)	
Number of Comorbidities, n (%)	0 (0–1)	0 (0–0)	0.45
Arterial Hypertension	49 (23%)	24 (19%)	
Alcohol Abuse	28 (13%)	16 (12%)	
Diabetes Mellitus	19 (9%)	10 (8%)	
SAPS-3	55±14	56±12	0.48
Baseline at infection suspicion			
Previous Length of Stay at ICU (days)	5 (3–10)	6 (3–10)	0.80
SOFA score	5 (3–7)	5 (4–7)	0.18
On antibiotics, n (%):	108 (51%)	61 (47%)	0.49
Ceftriaxone ou Cefuroxime, n (%)	68 (32%)	43 (33%)	0.99
Clindamycin, n (%)	43 (21%)	30 (23%)	0.67
Other antibiotics, n (%)	41 (20%)	19 (15%)	0.31
On vasopressors, n (%)	43 (21%)	28 (22%)	0.92
Lactate (mmoL.L^{-1})	1.8-2.8 (2.2)	1.8-3.2 (2.4)	**<0.01**
On Mechanical Ventilation, n (%)	119 (57%)	82 (63%)	0.29
Highest Heart Rate (bpm)	113±20	119±21	**<0.01**
Highest Body Temperature (°C)	37.8±0.7°C	37.8±0.8°C	0.80
Lowest Body Temperature (°C)	35.6±0.8°C	35.6±0.9°C	0.62
White Blood Cell count (per μL)	12625 (10095–16282)	15870 (10960–20140)	**<0.01**
C-Reactive Protein (mg.L^{-1})	16 (10–24)	22 (11–30)	**<0.01**

Data are presented as mean ± standard deviation, median (interquartile range), or N of group (%) as appropriate.
CA, Conservative Antibiotic sStrategy group – patients received antibiotics after 24 hours or later from the clinical suspicion of infection or did not receive antibiotics within 14 days from the inclusion; EEA, Early Empirical Antibiotic strategy group – patients received antibiotic therapy within 24 hours from the initial clinical suspicion of infection. ICU, Intensive Care Unit; LOS, Length Of Stay; SAPS-3, Simplified Acute Physiology Score-3; SOFA, Sequential Organ Failure Assessment score.
Values within 24 hours on the day of infection suspicion.
[a] Value of p for differences in types of surgery in the groups.
** Hypertension, diabetes, alcohol abuse, coronary artery disease, heart failure, chronic pulmonary obstructive disease, chronic kidney disease, HIV, or cancer.

0.9°C in the CA and EEA groups, respectively. Other markers of inflammation, such as heart rate, white blood cell count, and C-reactive protein, were slightly but significantly higher in the EEA group than in the CA group (Table 1).

In both groups, patients with neurologic and respiratory organ dysfunction were prevalent at baseline (Supplemental Fig. 3).

The composite primary outcome of death, sepsis or septic shock within 14 days after inclusion occurred in 40% of the patients in the CA group and 56% of the patients in the EEA group, $p < 0.01$. There was no difference in the incidence of 14 day death or septic shock between the groups. Length of stay in the ICU or hospital and hospital mortality were not significantly different between the groups (Table 2). The main organs that had worsening dysfunction within the first 14 days after study inclusion were cardiovascular and renal (Supplemental Fig. 3).

During the 14 days of observation, 57% of the patients in the CA group had received antibiotics (vs. 100% of the patients in the EEA group). The patients in the EEA group had more suspected lung (50% vs. 24%) and abdominal infections (9% vs. 3). The EEA group had a higher *a posteriori* proportion of patients with presumed (88% vs. 53%) and microbiologically confirmed infections (70% vs. 45%) ($p < 0.01$). The median time to adequate antibiotic treatment was 3 days (IQR 2−5 days) in the CA group vs. 1 day (IQR 0−3 days) in the EEA group ($p < 0.01$) (Supplemental Table 1).

The multivariate analysis, which was adjusting with confounding variables according to the DAG model, showed that EEA was no longer associated with the primary outcome (OR = 1.27; 95% CI 0.77−2.08) (Table 3). A sensitivity analysis was performed using stepwise backward logistic regression based on the univariate analysis (Supplemental Table 2) and yielded similar results (Supplemental Table 3).

Table 2 Primary and secondary outcomes.

	CA group	EAA group	Odds Ratio (95% CI)	*p*-value
Primary Outcome[a]	85 (40%)	73 (56%)	1.88 (1.21–2.93)	**<0.01**
Sepsis[a]	76 (36%)	67 (52%)	1.88 (1.20–2.92)	**<0.01**
Septic Shock[a]	28 (13%)	21 (16%)	1.25 (0.68–2.31)	0.58
Mortality[a]	24 (11%)	20 (15%)	1.41 (0.74–2.67)	0.37
Cause of death[b]				0.56
Infection associated	9 (4%)	11 (8%)		
Intracranial Hypertension/Brain death	9 (4%)	6 (5%)		
Other causes	6 (3%)	3 (2%)		
Length of ICU stay (days)	18 (13–29)	24 (14–37)	–	0.27
Length of hospital stay (days)	36 (21–76)	44 (24–68)	–	0.40
In-hospital mortality	68 (32%)	54 (42%)	1.48 (0.94–2.33)	0.11

Data are presented as median (interquartile range) or n (%) as appropriate.
CA, Conservative Antibiotic strategy group – patients received antibiotics after 24 hours or later from the clinical suspicion of infection or did not receive antibiotics within 14 days from the inclusion; EEA Early Empirical Antibiotic strategy group – patients received antibiotic therapy within 24 hours from the initial clinical suspicion of infection; ICU, Intensive Care Unit.
The Primary Outcome, Mortality in 14 days, Septic Shock in 14 days, Sepsis in 14 days, and In-hospital mortality were evaluated with Chi-Square.
ICU length of stay and hospital length of stay were evaluated with Welch's *t*-test.
[a] In the timeframe of 14 days, as defined in the primary outcome.
[b] According to Electronic Medical Record analysis.

A subgroup analysis including only patients with confirmed infection (by cultures) also did not detect an association between the groups (CA or EEA) and the primary outcome. However, delays in initiating appropriate antibiotic therapy in these patients were associated with worse outcomes, irrespective of the group (Table 4), with an Odds Ratio of 1.19 per day of delay with 95% CI 1.05—1.37 (p-value < 0.01).

Discussion

In this study, withholding early empirical antibiotics during diagnostic workup in nonseptic surgical patients with suspected nosocomial infections was not associated with death, worsening of organ dysfunction, or shock. In critically ill patients, signs indicating the presence of infection are nonspecific and may occur in many noninfectious conditions, particularly in trauma and surgical patients,[16,26] making a definitive diagnosis harder to achieve. In this setting, antibiotics are often prescribed, even to nonseptic patients who do not have an identifiable infectious source.

However, the adverse effects of antimicrobials are significant[10,27] and, in noninfected patients, may not be counterbalanced by the benefits. The present findings suggest that widespread administration of early empiric antimicrobials to a heterogeneous group of nonseptic surgical patients with and without a true infection (diagnosed posteriorly) does not translate into an overall clinical benefit. Efforts should be made to establish a diagnosis as soon as possible. In the meantime, antimicrobial therapy should be promptly administered to septic or deteriorating patients. Additionally, stable patients with a high likelihood of infection with a probable source who have been diagnosed based

Table 3 Multivariate Analysis Association of early empiric antibiotic strategy and primary outcome.[a]

	Odds ratio	95% CI	*p*-value
Presumed infection[b]	2.57	1.48–4.56	**<0.01**
Sustained tachycardia[c]	1.74	1.02–2.98	**0.04**
Reason for admission: surgical (non-trauma)	1.69	1.00–2.88	0.05
Abnormal WBC count[d]	1.39	0.82–2.37	0.22
SOFA at inclusion (per point)	1.04	0.97–1.12	0.29
Early Empirical Antibiotic strategy (EEA) group	1.27	0.77–2.08	0.35
Hyperthermia or Hypothermia[e]	1.01	0.62–1.65	0.96

OFA, Sequential Organ Failure Assessment; WBC, White Blood Cell; EEA, Early Empirical Antibiotic strategy group: patients received antibiotic therapy within 24 hours from the initial clinical suspicion of infection.
Variance Inflation Factor varied between 1.03 and 1.25 for all variables, indicating no significant multicollinearity.
[a] Variables were selected from the Direct Acyclic Graphic depicted in Figure 1.
[b] Probable infection site diagnosed according to Electronic Medical Records within 14 days (as opposed to a source of infection none or unknown), confirmed or not by cultures
[c] Lowest Heart Rate > 90 bpm within 24 hours of inclusion.
[d] WBC count > 12000 cells.mm^{-2} or WBC count < 4000 cells.mm^{-2}.
[e] Body Temperature > 38°C and/or < 36°C.

Table 4 Multivariate Analysis Association of timing of antibiotic therapy and primary outcome[a]. Post-hoc subgroup analysis in patients with confirmed infection by microbiological cultures.

	Odds ratio	95% CI	*p*-value
Time until adequate antibiotic therapy (per day)[b]	1.19	1.05–1.37	**<0.01**
Reason for admission: Surgical (non-trauma)	2.11	1.01–4.53	0.05
Sustained Tachycardia[c]	2.07	0.95–4.70	0.07
Early Empirical Antibiotic strategy (EEA) group	1.82	0.91–3.71	0.09
Abnormal WBC count[d]	1.67	0.82–3.47	0.16
Hyperthermia or Hypothermia[e]	0.73	0.37–1.43	0.36
SOFA at inclusion (per point)	1.02	0.92–1.13	0.74

Post-hoc analyses including only patients with confirmed infection (by cultures).
WBC, White Blood Cell; EEA, Early Empirical Antibiotic strategy group: patients received antibiotic therapy within 24 hours from the initial clinical suspicion of infection.
Variance Inflation Factor varied between 1.04 and 1.28 for all variables, indicating no significant multicollinearity.
[a] Variables were selected from the Direct Acyclic Graphic depicted in Figure 1.
[b] As defined in Methods.
[c] Lowest Heart Rate > 90 bpm within 24 hours of inclusion.
[d] WBC count > 12000 cells.mm^{-2} or WBC count < 4000 cells.mm^{-2}.
[e] Body Temperature > 38°C and/or < 36°C.

on clinical, radiologic and laboratory criteria should not have therapy withheld, since nonseptic patients who have a confirmed infection *a posteriori* also have a time-dependent benefit from therapy according to our data and others.[3,28]

Similar to our findings, in a multicentric, open-label, randomized trial, Alam et al did not find better outcomes of early antimicrobial therapy in 2672 prehospital patients with suspicion of infection and with various degrees of severity.[29] A before and after observational cohort study in critically ill surgical patients also did not observe an association of better outcomes when using a strategy of early antibiotic therapy in patients with suspected nosocomial infections without septic shock before the results of the microbiologic exams were available.[7] However, even when an infection is present, early administration of antibiotics may not be the main factor associated with better outcomes in critically ill nonseptic patients.[11,30-32]

An apparent paradox merits further discussion in our study. Delays in initiating appropriate therapy were associated with worse outcomes in the subgroup of patients with confirmed infections. The patients in the early empiric antibiotic group were prescribed adequate therapy faster in cases of confirmed infection (median 1 day vs. 4 days in CA, Table 1 Supplement); however, this was not sufficient to translate into better outcomes for the group. Two possible explanations are provided below.

First, despite our best efforts to adjust for confounding factors in the multivariate analysis, the patients included in the EEA group may have been more severely ill than the patients in the CA group as perceived by the attending physician but were not captured by the registered standard clinical data. In addition to the multivariate analysis, a paired analysis of the SOFA score and the associated subcomponents, as shown in Supplemental Figure 3, functioned as an additional way to adjust for the baseline organ dysfunction severity. This analysis also did not detect a benefit for early antibiotic therapy regarding any organ dysfunction or total SOFA.

Second, the uncertainty of the diagnosis of infection in stable patients is very common in nosocomial settings.[33] Large observational studies showed an association between the timing of antibiotic therapy administration and worse outcomes in septic patients in a time-dependent fashion.[2-4] Nevertheless, nonseptic surgical patients and patients with suspected infections (not confirmed posteriorly) are often excluded from most of the studies. The benefit of earlier appropriate therapy obtained in some patients may not be valid for a heterogeneous group including infected and non-infected patients, simulating real-life situation scenarios when a confirmed infection is only granted *a posteriori*.

We opted to perform a multivariate analysis based on a direct acyclic graphic model to control for the confounders as the primary analysis. This kind of analysis takes into account clinically relevant variables that can be inappropriately removed from the model due to insufficient power related to a small sample size and avoids the impact of collider variables.[21-23] Furthermore, direct acyclic graphic models bring transparency to the proposed causal inference. We also performed a sensitivity multivariate analysis based on a more traditional stepwise backward regression model with data derived from the univariate analysis. The variables included in the sensitivity analysis were different from those used in the primary analysis, but both these analyses yielded similar results. Therefore, we can hypothesize that our results are consistent and have internal validity.

Our study has limitations. It was a single-center observational trial, and confounders such as selection and information biases might have influenced the results. There was no standardization in the criteria for the initiation of antibiotic therapy, with the attending physician being responsible for the decision. This might explain the higher number of culture-confirmed infections in the EEA group. Although there was no difference between the groups in the markers of severity of disease, we cannot underestimate the importance of the clinical impression of the treating physician, who takes into account numerous known and intangible factors in the process of decision-making. Finally, since 74% of our cohort was trauma patients and the mean age was 44 years, our results are valid only for a strict number of critically ill patients.

Conclusions

In critically ill nonseptic surgical patients with a suspected nosocomial infection without an obvious source, withholding early empiric antibiotic therapy was not associated with the progression of organ dysfunction in 14 days. In the subanalysis including only confirmed infection patients, delays in the administration of active therapy against the isolated pathogens were associated with worse outcomes. Our results only apply to a strict number of critically ill surgical patients.

Conflicts of interest

The authors declare no have conflicts of interest.

No specific funding has been received for this work. Data were generated as part of the routine work of the Trauma Intensive Care Unit in HCFMUSP.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.bjane.2023.03.003.

References

1. Hutchings M, Truman A, Wilkinson B. Antibiotics: past, present and future. Curr Opin Microbiol. 2019;51:72–80.
2. Kumar A, Roberts D, Wood KE, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med. 2006;34:1589–96.
3. Liu VX, Fielding-Singh V, Greene JD, et al. The timing of early antibiotics and hospital mortality in sepsis. Am J Respir Crit Care Med. 2017;196:856–63.
4. Seymour CW, Gesten F, Prescott HC, et al. Time to treatment and mortality during mandated emergency care for sepsis. N Engl J Med. 2017;376:2235–44.
5. Whiles BB, Deis AS, Simpson SQ. Increased time to initial antimicrobial administration is associated with progression to septic shock in severe sepsis patients. Crit Care Med. 2017;45:623–9.
6. Evans L, Rhodes A, Alhazzani W, et al. Executive summary: surviving sepsis campaign: International Guidelines for the Management of Sepsis and Septic Shock 2021. Crit Care Med. 2021;49:1974–82.
7. Hranjec T, Rosenberger LH, Swenson B, et al. Aggressive versus conservative initiation of antimicrobial treatment in critically ill surgical patients with suspected intensive-care-unit-acquired infection: A quasi-experimental, before and after observational cohort study. Lancet Infect Dis. 2012;12:774–80.
8. Rothman K, Greenland S, Poole C, Lash T. Causalidade e inferência causal. In: Rothman K, Greenland S, Lash T, eds. Epidemiologia Moderna, 3rd ed., Porto Alegre: Artmed; 2011:15–45.
9. Rhee C, Gohil S, Klompas M. Regulatory mandates for sepsis care - Reasons for caution. N Engl J Med. 2014;370:1673–6.
10. Arulkumaran N, Routledge M, Schlebusch S, Lipman J, Conway Morris A. Antimicrobial-associated harm in critical care: a narrative review. Intensive Care Med. 2020;46:225–35.
11. Hranjec T, Sawyer RG. Conservative initiation of antimicrobial treatment in ICU patients with suspected ICU-Acquired infection: More haste less speed. Curr Opin Crit Care. 2013;19:461–4.
12. Murray CJ, Ikuta KS, Sharara F, Swetschinski L, Robles Aguilar G, Gray A, et al. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. Lancet. 2022;399:629–55.
13. Almagor J, Temkin E, Benenson I, Fallach N, Carmeli Y. The impact of antibiotic use on transmission of resistant bacteria in hospitals: Insights from an agent-based model. PLoS One. 2018;13:e0197111.
14. Aslam B, Wang W, Arshad MI, et al. Antibiotic resistance: a rundown of a global crisis. Infect Drug Resist. 2018;11:1645–58.
15. Hoover L, Bochicchio GV, Napolitano LM, et al. Systemic inflammatory response syndrome and nosocomial infection in trauma. J Trauma. 2006;61:310–6.
16. Talmor M, Hydo L, Barie PS. Relationship of systemic inflammatory response syndrome to organ dysfunction, length of stay, and mortality in critical surgical illness: Effect of intensive care unit resuscitation. Arch Surg. 1999;134:81–7.
17. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet. 2007;370:1453–7.
18. Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. Intensive Care Med. 1996;22:707–10.
19. Singer M, Deutschman CS, Seymour C, et al. The third international consensus definitions for sepsis and septic shock (sepsis-3). JAMA. 2016;315:801–10.
20. Rasch D, Kubinger KD, Moder K. The two-sample t test: Pre-testing its assumptions does not pay off. Stat Pap. 2011;52:219–31.
21. Textor J, van der Zander B, Gilthorpe MS, Liśkiewicz M, Ellison GT. Robust causal inference using directed acyclic graphs: The R package "dagitty. Int J Epidemiol. 2016;45:1887–94.
22. Lederer DJ, Bell SC, Branson RD, et al. Control of confounding and reporting of results in causal inference studies, 16. Ann Am Thorac Soc; 2019. p. 22–8.
23. Brumback BA. Causal Directed Acyclic Graphs. Fundam Causal Inference with R. 2021;327:81–98.
24. P. Vatcheva K, Lee M. Multicollinearity in Regression Analyses Conducted in Epidemiologic Studies. Epidemiol Open Access. 2016;06:1–20.
25. Core R Team. A Language and Environment for Statistical Computing [Internet]. Vol. 2, R Foundation for Statistical Computing. 2019. p. https://www.R–project.org. Available from: http://www.r-project.org.
26. Miller PR, Munn DD, Meredith JW, Chang MC. Systemic inflammatory response syndrome in the trauma intensive care unit: Who is infected? J Trauma. 1999;47:1004–8.
27. Tamma PD, Avdic E, Li DX, Dzintars K, Cosgrove SE. Association of adverse events with antibiotic use in hospitalized patients. JAMA Intern Med. 2017;177:1308–15.
28. Zasowski EJ, Bassetti M, Blasi F, et al. A Systematic Review of the effect of delayed appropriate antibiotic treatment on the outcomes of patients with severe bacterial infections. Chest. 2020;158:929–38.
29. Alam N, Oskam E, Stassen PM, et al. Prehospital antibiotics in the ambulance for sepsis: a multicentre, open label, randomised trial. Lancet Respir Med. 2018;6:40–50.
30. Abe T, Kushimoto S, Tokuda Y, et al. Implementation of earlier antibiotic administration in patients with severe sepsis and septic shock in Japan: A descriptive analysis of a prospective observational study. Crit Care. 2019;23:360.
31. Singer M. Antibiotics for sepsis: Does each hour really count, or is it incestuous amplification? Am J Respir Crit Care Med. 2017;196:800–2.
32. Abe T, Tokuda Y, Shiraishi A, et al. In-hospital mortality associated with the misdiagnosis or unidentified site of infection at admission. Crit Care. 2019;23:202.
33. Klein Klouwenberg PMC, Cremer OL, van Vught LA, et al. Likelihood of infection in patients with presumed sepsis at the time of intensive care unit admission: A cohort study. Crit Care. 2015;19:319.