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Bacteraemia in ICU Patients and Antibiotic Adequacy

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To my father…

Bacteraemia in ICU patients and antibiotic adequacy

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Abstract

Background: Infection and sepsis represent major problems for Intensive Care Units (ICU) patients**.** It is important to identify factors that may give early clues as to the adequateness of empiric antibiotic therapy in septic patients so that an “early rescue” strategy can be implemented. We tried to correlate the timing of administration of appropriate antibiotics with the evolution of early organ dysfunction and daily C-reactive protein (CRP) measurements.

Methods: A retrospective review of 58 adult ICU patients with bacteraemia was performed. Bacteraemia was defined according to Centers for Disease Control and Prevention criteria.

The primary combined outcome was ICU/hospital mortality and secondary outcomes were infection resolution, SOFA evolution (day0-day3) and the pattern of CRP response.

Results: ICU mortality in patients with inappropriate initial ATB was more than double of patients with appropriate ATB ($p = 0.044$). At 48h of antibiotic effect, patients with appropriate therapy had 10.0% mean decrease in CRP, while it continued to rise in those with inappropriate therapy ($p<0.001$).

Results were similar for patients with adequate therapy having a smaller increase in CRP value in the first 24h under antimicrobial treatment (p=0.218), but a significant bigger decrease by the second day (p=0.025).

Conclusions: We found a strong relationship between ATB appropriateness and ICU mortality (p=0.044). Differences in CRP variation between groups become evident early in the course of events and may be helpful when deciding on the need to change antibiotics.

Key Words: Sepsis, Bacteraemia, ICU, Anti-Infective Agents, Timing

Introduction

Infection and sepsis represent major problems for patients admitted to intensive care units (ICU).

Whether as the cause for ICU admission [1] or as an ICU-acquired [2,3] event, it is associated with a significant risk of death and prolonged hospital stay. Patients who develop acute organ dysfunction in this setting (severe sepsis) are at particular risk [4] mainly those with severe hemodynamic failure (septic shock). In these latter patients, mortality is reported to be greater than 50% [3,5-8].

Optimal therapy for these patients is based on three fundamental principles, namely appropriate antibiotic therapy (ATB) (i.e., agents active against the causative microorganism), source control and support of failing organs [9]. Of these, the appropriateness of antibiotic therapy is likely to be the intervention with the most impact on prognosis, particularly in more severe patients [8,10] if adequate organ support is supplied.

Also, there is evidence that failure to promptly initiate appropriate therapy has as much adverse consequences on outcome as a wrong choice of the antibiotic [11]. Several studies have shown a link between late administration of appropriate antibiotics and poor outcomes in many different settings [12,13].

This gave rise to the concept of antibiotic adequateness which widens the one of appropriateness by taking in consideration the timing of administration, use of adequate doses and dosing regimens and utilisation of agents with adequate penetration into the focus of infection [9].

As such it is important to identify factors that may give early clues as to the adequateness of empiric antibiotic therapy in septic patients so that an “early rescue” strategy can be implemented. This would entail clinical reevaluation, looking for unsuspected foci or collections amenable to source control measures, and eventually early escalation of the antibiotic spectrum, for example in the case of worsening organ failure.

One of the variables to consider in this setting is the evolution of organ dysfunction/failure. Several tools are available that allow quantification of organ failure (OF) [14-16] and the variation of OF with time has been shown to correlate well with prognosis in ICU patients [16,17].

Patterns of C - reactive protein (CRP) evolution have also been shown to be of use in predicting response to antibiotics [18,19].

We tried to correlate the timing of administration of appropriate antibiotics with the evolution of early organ

dysfunction and daily CRP measurements in patients with bacteraemia.

Materials and Methods

A retrospective cohort analysis of adult ICU patients between 1st January and 30th June 2010 was performed in two general ICUs, at Hospital de São João, a teaching hospital in Oporto, Portugal.

Patients were included if they were ≥18 years old and had primary or secondary acquired bloodstream infection (BSI) according to the Centers for Disease Control and Prevention criteria (CDC) [20]. An exception to this was catheter related BSI where a less stringent criterion was used. In these cases the source was considered to be the central line if CDC criteria for diagnosis were met or if there was no other apparent foci of infection and the opinion of the attending physicians, based on review of the clinical records, was that the catheter was the likely source of infection. It must be noted that formal microbiological documentation (i.e., CVC and peripheral cultures plus catheter tip) was lacking in most of these cases. If a patient had more than one episode of BSI during a hospitalization, only the first episode was considered.

The following data were obtained by trained medical abstractors from each patient's medical records: age, gender, comorbidities, ICU and hospital length of stay, reason for ICU admission, presence or absence of infection upon admission to the ICU, place of infection acquisition (community, nosocomial or ICU) and primary focus of infection. Simplified Acute Physiology Score (SAPS II) severity score at ICU admission and Sepsis-related Organ Failure Assessment score (SOFA) at days 0, 1 and 3 were also calculated. Central Nervous System (CNS) SOFA was not valorized because of great number of sedated patients.

Also the following comorbid conditions were recorded: diabetes, chronic heart failure (≥ II class of New York Heart Association), cerebral vascular disease, other significant neurological diseases (ex: lateral sclerosis, epilepsy), chronic renal disease (requiring dialysis or glomerular filtration rate:GFR<60ml/min/1.73m2), chronic lung disease (requiring home oxygen therapy or ventilation), chronic hepatic disease (cirrhosis histological confirmation or clinical diagnosis of portal hypertension), immunosuppression (including prednisolone treatment >30mg/day for more than 3 months/cancer chemotherapy or immunomodulating agents in the last 30 days) and active neoplasms.

Both ICUs have standing protocols regarding adequate drawing and handling of blood and tip cultures. Specifically catheter tips are only cultured if there is a clinical suspicion of catheter associated infection. Routine drawing of blood cultures is not local ICU practice. We thus regarded all positive blood cultures obtained as indicative of suspected infection. In accord to CDC guidelines, we did not include cultures of coagulase-negative staphylococci or other common commensal skin organisms unless two cultures separately isolated the same species of microorganism. Data from intravascular device tip culture wasn't always available, so most of the catheter related BSIs (CRBSI) were only clinically defined and rarely documented according the accepted CDC criteria for CRBSI.

Hospital microbiology records of positive blood cultures were gathered. Date, time and susceptibility profiles for all positive blood cultures were obtained.

All antimicrobials administered were noted, including the date, time, dose, route, and duration. Antibiotic appropriateness was determined according to microbiological susceptibility and adequacy was defined as appropriateness plus timely (< 3 hours) antibiotic administration.

For the purpose of calculating time (in minutes) elapsed until administration of antibiotics, zero time (t0) was considered the time of registration of the blood cultures in the central laboratory and day zero (day0) was the day of first positive bloodstream. Time of antibiotic administration was abstracted from nursing charts. Whenever registration of blood cultures was latter than the hour of the administration of antibiotics we considered therapy to have been given immediately after the drawing of blood cultures.

The primary combined outcome was ICU/hospital mortality and secondary outcomes were infection resolution (as documented in the clinical records), organ dysfunction improvement (defined by a decrease in global SOFA score ≥ 2 from day zero to day one/day zero to day three or a positive variation in delta SOFA day1-3 on “per organ” SOFA) and the pattern of CRP response to antibiotherapy, defined as the CRP rate of decline from day1 to day2, day3 and day5.

Data were screened in detail for missing information, implausible and outlying values.

Continuous variables were expressed as means and standard deviations (SD) or median and interquartile range (IQR) if the distribution was clearly asymmetric.

Comparisons between groups were performed with two-tailed unpaired Student's *t* test or Mann-Whitney U test for continuous variables according to data distribution. Fisher's exact test and Chi-square test was used to carry out comparisons between categorical variables as appropriate. All statistics were two-tailed and significance level was set at 0.05. Data were analyzed using PASW v.18.0 for PC (SPSS, Chicago, IL).

Since this observational study did not require any deviation from routine medical practice, the Health Ethics Committee of the Hospital São João approved the study design and waived the need of informed consent.

Results

We analyzed a total of 58 patients with a first episode of bacteraemia.

Mean age was 62 years. 62% were male (see Table 1). Median ICU and in-hospital length of stay was 16 days and 38 days, respectively. During the same period global ICU length of stay was 13 days.

Most of the patients (91.2%) had severe sepsis, half of them (53.4%) with septic shock, on day0.

70.7% of the bloodstream infections were hospital acquired (Table2), 51.7% in the ICU.

Clinically documented resolution of infection occurred in 64% of patients (37/54 patients).

ICU and hospital mortality were 37.9% and 53.4%, respectively.

Half of the bloodstream infections (49.8%) were due to Gram negative bacilli (GNB). Gram positives accounted for 37.9 % and *Candida spp* was recovered in 12% of patients. Most of the bloodstream infections were catheter related (22.4%), with intra-abdominal (19%) and respiratory (15.5%) foci being the second and third most common. 10% of infections had an unknown focus.

When relating microorganisms (MO) and focus of infection (Table 3), GNB bacteraemias were more commonly associated with respiratory and intra-abdominal foci, while gram positives were predominantly related with catheter infections. Fungaemia was mainly seen in Intra-abdominal infection.

With regard to antibiotic *appropriateness* (i.e., using an antibiotic active against the causative microorganism) we found no differences in the mean age of patients, gender, and severity (severe sepsis or septic shock), or place of acquisition, of infection.

ICU mortality in patients with inappropriate initial ATB was more than double that of patients with appropriate

ATB, differences that were statistically significant (p = 0.044), see Table 1. When analyzing hospital death, patients with inappropriate ATB had a higher mortality than patients with initially appropriate ATB (76.9% vs 42.5%) although not statistically significant (p = 0.054). Most (80.6%) of patients with appropriate ATB had infection resolution against 38.5% in the inappropriate group (p=0.01).

Regarding the CRP variation with antibiotic appropriateness, patients with appropriate antibiotics had a significantly greater decrease comparing with the inappropriate group. In the first 24h under the antibiotic effect (day one to day two), those with appropriate therapy had a median smaller increase (2.4%) in the CRP comparing with those with inappropriate therapy (39.9%; p=0.03). At 48h post-antibiotic, patients with appropriate therapy had 10.0% mean decrease in CRP, while it continued to rise in those with inappropriate therapy (26.7%; p<0,001). At the fourth day of antimicrobial therapy, the CRP value decreased almost to half in the appropriate group (48.1%) and only 8.5% in the inappropriate group (p=0.002) (see Figure 1).

Antibiotic adequacy. When comparing the characteristics of the two groups (adequate/inadequate), there were

significant differences (p = 0.001) with respect to the origin of the bacteraemia. Most cases of bacteraemia in patients with adequate (i.e., appropriate and early) ATB came from the community (68.8%), while infections in patients with inadequate therapy were mostly nosocomial (82.4%). There were no significant differences between groups regarding mean age, gender, comorbidities and severity of infection on admission (SAPS II, presence / absence of septic shock). Although, patients with adequate ATB had a mean SAPS II score higher than those with inadequate (p=0.09)

The proportion of patients with septic shock was 68.6% in the group of adequate therapy and 44.1% in patients receiving inadequate antimicrobials.

Both ICU (43.8% vs 35.3%) and hospital (56.3% vs 52.9%) mortality was higher in patients with adequate ATB than on those with inadequate ATB, although these differences were not significant (p = 0.75 and p = 1.0 respectively). The same happened when looking at the resolution of the infection. Patients with adequate ATB achieved a higher rate of infection resolution (66.7% vs 65.6%), again not statistically significant (p = 1.0).

Regarding the relationship of antibiotic adequacy and CRP evolution the results were as follows: patients with adequate therapy had a non-significant smaller increase

in CRP value in the first 24h under antimicrobial treatment (2.3% vs 7.7%; p=0.218), but a significant larger decrease by the second (19% decrease vs 1.1% increase; p=0.025) and fourth day (53% decrease vs 38% decrease; p=0.04) of therapy.

Evolution of organ failure. Global Organ dysfunction worsened in 70% of patients with a median increase in SOFA score of 2 points between days 0 and 3. We found no significant differences in total SOFA score variation when looking at both appropriateness and adequacy.

The evolution of “per organ” SOFA on days 0, 1 and 3 in relation with appropriateness is presented on Table 4.

Patients with adequate antimicrobials had a significant higher median lactate level at day zero (2.1 vs 1.5 mmol/L; p=0.01). Differences in median lactate levels between appropriate and inappropriate groups from day zero to day three were non-significant.

Timing of ATB. With regard to the timing of antibiotic administration we found that patients with nosocomial infection were significantly more likely to receive delayed antibiotic therapy when compared with patients with community acquired sepsis (78.1% vs 25%; p=0,001). We also found that the presence of septic shock was

associated with earlier administration of antibiotics (56% of patients under 3 hrs vs 21.7% in no shock; p=0.02).

Discussion

The diagnosis of infection in ICU patients can be challenging. Therefore, we decided to limit this analysis to patients with bacteraemia in order to include only patients with an undisputed diagnosis of infection.

Bacteraemia in ICU patients is a frequent event and is associated with elevated mortality (during the study period global ICU mortality in both participating units was 28.6%) and longer ICU stays.

The main finding of this study is the striking relationship between antibiotic inappropriateness and mortality. Even with a small sample size it was possible to demonstrate a significant increase in ICU mortality (61.5%) in patients who received initially inappropriate antibiotics against 27.5% in the appropriate ATB group (p=0.044). This clearly underscores the need to thoroughly access the patient with severe infection upon admission in order to make the best possible decision regarding empiric antibiotics. In fact a number of previous studies have described this association in different settings [8,10,11].

The results found when combining appropriateness and timing (i.e., adequacy) were confounding. The higher

mortality (56.3% vs 52.9%; p=1.0) in the group that received early (<3h), appropriate antibiotics, although statistically insignificant is, nevertheless, bewildering. It must be noted that the proportion of patients in this group who developed septic shock was greater than in the rest of the study sample and that this may have biased this result as the expected mortality resulting from septic shock is extremely high [3,6,7].

With regard to delays in antibiotic administration we found that patients with hospital acquired infection are at a greater risk of receiving delayed therapy when compared with those admitted through the Emergency Department (ED). Our hospital has an ED based rapid response system for sepsis instituted since 2008 and this may account for some of this difference. These kind of systems have been associated with improved process of care (including diminished time to antibiotic administration) in a number of different settings [21,22], and a recent meta-analysis confirmed this finding [23].

Another issue that may be relevant is the difficulty associated with identifying sepsis. This has been recognized as a major barrier to implementation of bundled care in American EDs [24] and one must admit that it may be an even larger problem in ward acquired infection.

The analysis of SOFA score variation showed that, although global SOFA seems to be of little use in the earlier stages of disease some of its components may have some value when trying to decide, on the basis of limited data, whether therapy was appropriate - namely CV and respiratory SOFA may be reasonable indicators of improvement. Probably due to the small sample size, we were unable to find any statistically significant differences.

As for CRP variation we found significant differences that become evident as soon as 24h after administration of appropriate antibiotics (assuming that most of patients were already doing antibiotics), suggesting this may be a good indicator for “early rescue” strategies. The early variation of CRP has been also associated with antibiotic adequacy [25] and outcomes [18]

Our study has several important limitations. The first is its retrospective design that impairs adequate data gathering and limits the strenght of our conclusions. Second is the small sample size, again limiting the statystical power of the study.

In conclusion, we found a strong relationship between ATB appropriateness and mortality in concordance with findings previously reported by other groups. Patients

with hospital-acquired infection may be at greater risk of receiving delayed therapy.

The lack of association between antibiotic adequacy and outcomes was unexpected but may be related to the small sample size and to the greater proportion of patients with septic shock in this group.

Differences in CRP variation between groups become evident early in the course of events and may be helpful when deciding on the need to change antibiotics.

Learning Points

-Bacteraemia in ICU patients is frequently associated with poor outcomes

-Inappropriate therapy is significantly related to increased mortality

-Patients with hospital-acquired infection may be at increased risk of delayed therapy

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References:

[1] Cardoso T, Carneiro AH, Ribeiro O, Teixeira-Pinto A, Costa-Pereira A. Reducing mortality in severe sepsis with the implementation of a core 6-hour bundle: results from the Portuguese community-acquired sepsis study (SACiUCI study). Crit Care, 2010;14:R83.

[2] Vincent JL, Rello J, Marshall J, Silva E, Anzueto A, Martin CD, et al. International study of the prevalence and outcomes of infection in intensive care units. JAMA : the journal of the American Medical Association, 2009;302:2323-9.

[3] Vincent JL, Sakr Y, Sprung CL, Ranieri VM, Reinhart K, Gerlach H, et al. Sepsis in European intensive care units: results of the SOAP study. Critical care medicine, 2006;34:344-53.

[4] Rangel-Frausto MS, Pittet D, Costigan M, Hwang T, Davis CS, Wenzel RP. The natural history of the systemic inflammatory response syndrome (SIRS). A prospective study. JAMA : the journal of the American Medical Association, 1995;273:117-23.

[5] Annane D, Aegerter P, Jars-Guincestre MC, Guidet B. Current epidemiology of septic shock: the CUB-Rea Network. American journal of respiratory and critical care medicine, 2003;168:165-72.

[6] Engel C, Brunkhorst FM, Bone HG, Brunkhorst R, Gerlach H, Grond S, et al. Epidemiology of sepsis in Germany: results from a national prospective multicenter study. Intensive care medicine, 2007;33:606-18.

[7] Povoa PR, Carneiro AH, Ribeiro OS, Pereira AC. Influence of vasopressor agent in septic shock mortality. Results from the Portuguese Community-Acquired Sepsis Study (SACiUCI study). Critical care medicine, 2009;37:410-6.

[8] Kumar A, Ellis P, Arabi Y, Roberts D, Light B, Parrillo JE, et al. Initiation of inappropriate antimicrobial therapy results in a fivefold reduction of survival in human septic shock. Chest, 2009;136:1237-48.

[9] Dellinger RP, Levy MM, Carlet JM, Bion J, Parker MM, Jaeschke R, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. Critical care medicine, 2008;36:296-327.

[10] Valles J, Rello J, Ochagavia A, Garnacho J, Alcala MA. Community-acquired bloodstream infection in critically ill adult patients: impact of shock and inappropriate antibiotic therapy on survival. Chest, 2003;123:1615-24.

[11] Ibrahim EH, Sherman G, Ward S, Fraser VJ, Kollef MH. The influence of inadequate antimicrobial treatment

of bloodstream infections on patient outcomes in the ICU setting. Chest, 2000;118:146-55.

[12] Kumar A, Roberts D, Wood KE, Light B, Parrillo JE, Sharma S, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Critical care medicine, 2006;34:1589-96.

[13] Proulx N, Frechette D, Toye B, Chan J, Kravcik S. Delays in the administration of antibiotics are associated with mortality from adult acute bacterial meningitis. QJM : monthly journal of the Association of Physicians, 2005;98:291-8.

[14] Vincent JL, Moreno R, Takala J, Willatts S, De Mendonca A, Bruining H, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intensive care medicine, 1996;22:707-10.

[15] Marshall JC, Cook DJ, Christou NV, Bernard GR, Sprung CL, Sibbald WJ. Multiple organ dysfunction score: a reliable descriptor of a complex clinical outcome. Critical care medicine, 1995;23:1638-52.

[16] Jones AE, Trzeciak S, Kline JA. The Sequential Organ Failure Assessment score for predicting outcome

in patients with severe sepsis and evidence of hypoperfusion at the time of emergency department presentation. Critical care medicine, 2009;37:1649-54.

[17] Routsi C, Pratikaki M, Sotiropoulou C, Platsouka E, Markaki V, Paniara O, et al. Application of the sequential organ failure assessment (SOFA) score to bacteremic ICU patients. Infection, 2007;35:240-4.

[18] Povoa P, Teixeira-Pinto AM, Carneiro AH. C-reactive protein, an early marker of community-acquired sepsis resolution: a multi-center prospective observational study. Crit Care, 2011;15:R169.

[19] Coelho LM, Salluh JI, Soares M, Bozza F, Verdeal JC, Castro-Faria-Neto HC, et al. Patterns of C-reactive protein ratio response in severe community-acquired pneumonia: a cohort study. Crit Care, 2012;16:R53.

[20] Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. American journal of infection control, 2008;36:309-32.

[21] Jones AE, Focht A, Horton JM, Kline JA. Prospective external validation of the clinical effectiveness of an emergency department-based early goal-directed therapy protocol for severe sepsis and septic shock. Chest, 2007;132:425-32.

[22] Sebat F, Musthafa AA, Johnson D, Kramer AA, Shoffner D, Eliason M, et al. Effect of a rapid response system for patients in shock on time to treatment and mortality during 5 years. Critical care medicine, 2007;35:2568-75.

[23] Barochia AV, Cui X, Vitberg D, Suffredini AF, O'Grady NP, Banks SM, et al. Bundled care for septic shock: an analysis of clinical trials. Critical care medicine, 2010;38:668-78.

[24] Carlbom DJ, Rubenfeld GD. Barriers to implementing protocol-based sepsis resuscitation in the emergency department--results of a national survey. Critical care medicine, 2007;35:2525-32.

[25] Schmit X, Vincent JL. The time course of blood C-reactive protein concentrations in relation to the response to initial antimicrobial therapy in patients with sepsis. Infection, 2008;36:213-9.

Table 1 – Demographics characteristics of population

	n = 58	Appropriate ATB (n=45)	Inappropriate ATB (n=13)	*p*
Age (mean)	62.05	60.10	66.08	0.347
Gender				0.345
Male	36 (62.1%)	25 (62.5%)	6 (46.2%)	
Female	22 (37.9%)	25 (37.5%)	7 (53.8%)	
Co-morbidities				
Diabetes	10 (17.2%)	8 (20.0%)	2 (16.7%)	1.00
Heart Failure	8 (13.8%)	5 (12.5%)	1 (8.3%)	1.00
Renal disease	10 (17.2%)	7 (17.5%)	3 (25.0%)	0.679
Chronic lung disease	11 (19.0**%)**	5 (12.5%)	4 (33.3%)	0.185
Chronic liver failure	4 (6.9%)	3 (7.5%)	0 (0%)	1.00
Cerebro-vascular disease	7 (12.1%)	4 (10.0%)	3 (25%)	0.33
Other neurological disease	5 (8.6%)	4 (10.0%)	1 (8.3%)	1.00
Immune Deficiency	9 (15.5%)	5 (12.5%)	3 (25.0%)	0.366
Neoplasia	8 (10.3%)	3 (7.5%)	3 (23.1%)	0.156
Reason for ICUa admission				
Medical non coronary	39 (67.2%)	28 (70.0%)	8 (61.5%)	-
Coronary	2 (3.4%)	0 (0%)	1 (7.7%)	-
Emergency surgery NT	6 (10.3%)	3 (7.5%)	3 (23.1%)	-
Emergency surgery trauma	4 (6.9%)	3 (7.5%)	1 (7.7%)	-
Trauma non-surgicaL	7 (12.1%)	6(15.0%)	0 (0%)	-
Severe Sepsis	(91.2%)	36 (92.3%)	13 (100%)	0.564
Septic Shock	(53.4%)	20 (50.0%)	8 (61.5%)	0.536
SAPS II (mean)	51.53(StdDev. 16.66)	49.85	52.69	0.475
ICU LOS (median)	16 (IQR 7-28)	16.00	17.00	0.641
Hospital LOS (median)	38(IQR 16-67)	36.5	46.00	0.542

ICU Mortality	37.9 (%)	11 (27.5%)	8 (61.5%)	0.044[a]
Hospital Mortality	53.4 (%)	17 (42.5%)	10 (76.9%)	0.054
Resolution of infection	37 (63.8%)	29 (80.6%)	5 (38.5%)	0.011 [a]

ICU: intensive care unit, SAPS: Simplified Acute Physiology Score, ATB: antibiotics, LOS: length of stay, Emergency surgery NT: emergency surgery non-trauma. [a] Statistical significant

5

Table 2 – Bloodstream infection provenance

	n = 58	Appropriate ATB (*n*=40)	Innapropriate ATB (*n* =13)	*p*
Place of acquisition				
Community	17 (29,4%)	13 (32.5%)	3 (23.1%)	0.731
Nosocomial	41 (70.7%)	27 (67.5%)	10 (76.9%)	0.731

ATB: antibiotic

Table 3 – Microbiology and Focus of infection

	Central Line	Abdominal	Respiratory	Urinary	Skin/soft tissue	CNS	Other	Total
Gram positives								
Count	8	0	1	2	1	2	5	19
% within MO	42.1%	0%	5.3%	10.5%	5.3%	10.5%	26.3%	100%
% within focus of infection	65.5%	0%	11.1%	25.0%	33.3%	100%	83.3%	36.5%
Fungi								
Count	1	3	0	0	0	0	0	4
% within MO	25.0%	75%	0%	0%	0%	0%	0%	100%
% within focus of infection	7.7%	27.3%	0%	0%	0%	0%	0%	7.7%
Gram negatives								
Count	4	8	8	6	2	0	1	29
% within MO	13.8%	27.6%	27.6%	20.7%	6.9%	0%	3.4%	100%
% within focus of infection	30.8%	72.7%	88.9%	75%	66.7%	0%	16.7%	55.8%
Total[a]								
Count	13	11	9	8	3	2	6	52
% within MO	25.0%	21.2%	17.3%	15.4%	5.8%	3.8%	11.5%	100%
% within focus of infection	100%	100%	100%	100%	100%	100%	100%	100%

[a]n=52; MO: microorganism; CNS: Central Nervous System

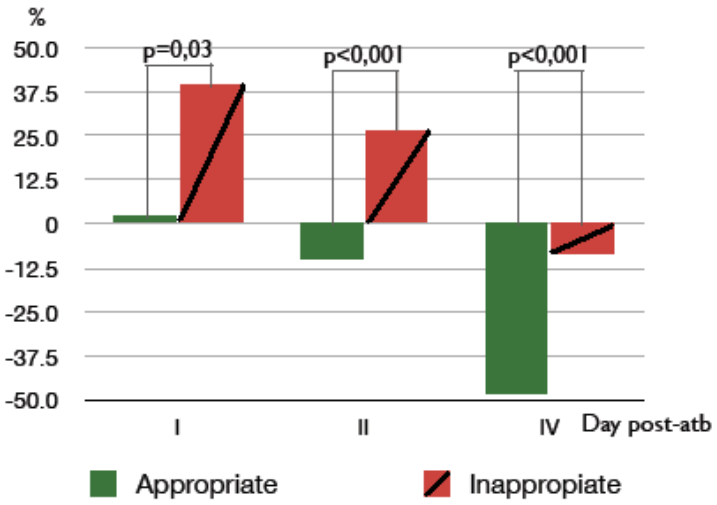
Table 4 – SOFA score variation between day 0, 1 and 3

	Appropriate ATB[a]	Innapropriate ATB[b]	*p*
	Improved / Not improved	Improved / Not improved	
Cardiovascular SOFA			
Day 0 – 1	7 (18.4%) vs 31 (81.6%)	1 (7.7%) vs 12 (92.3%)	0.662
Day 0 – 3	8 (22.2%) vs 28 (77.8%)	1 (8.3%) vs 11 (91.7%)	0.416
Respiratory SOFA			
Day 0 – 1	6 (17.6%) vs 28 (82.4%)	0 (0.0%) vs 13 (100.0%)	0.167
Day 0 – 3	10 (32.3%) vs 21 (67.7%)	1(8.3%) vs 11 (91.7%)	0.139
Renal SOFA			
Day 0 – 1	3 (8.6%) vs 32(91.4%)	1 (8.3%) vs 11 (91.7%)	1.00
Day 0 – 3	2 (5.9%) vs 32 (94.1%)	3 (27.3%) vs 8 (72.7%)	0.085
Hepatic SOFA			
Day 0 – 1	5 (15.6%) vs 27 (84.4%)	0 (0%) vs 12 (100%)	0.301
Day 0 – 3	4 (14.8%) vs 23 (85.2%)	1 (10.0%) vs 9 (90.0%)	1.00
Hematologic SOFA			
Day 0 – 1	2 (5.3%) vs 36 (94.7%)	2 (15.4%) vs 11 (84.6%)	0.266
Day 0 – 3	6 (16.2%) vs 31 (83.8%)	1 (8.3%) vs 11 (91.7%)	0.665

SOFA: Sepsis-related Organ Failure Assessment. [a]n=40,[b]n=13

Figure 1

CRP variations in appropriate vs inappropriate therapy groups



CRP: C-reactive protein, atb: antibiotics

Attachments

Guide for Authors

European Journal of Internal Medicine

Guide for Authors

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