Averroes European Medical Journal
Open Access Publisher
ISSN: 0772-9200

March 2017 • Volume 2 • Number 3

Characteristics of and reasons of or antibiotic changes in an Intensive Care Unit

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Background: Healthcare associated infections, commonly observed in the intensive care unit (ICU), are strongly correlated with increased mortality, morbidity and medical costs. To address this, the contribution of both prophylactic and therapeutic antibiotics is incontestable. However, in ICU, the empirical choice of antibiotics is in 50% cases inappropriate and its use has often an arbitrary duration. This engenders not only undesirable effects that can prove to be fatal; but eventually favors the emergence of multi-resistant bacteria, and even Pan-resistant bacteria. Therefore, the efficient use of antibiotics in terms of their initiation, duration and regimen re-evaluation must be correctly managed. In this study, we look at antibiotic therapy data, especially the motivating factors of changing antibiotic therapies in the peri-ICU stay period. **Material and Methods:** Retrospective this study included patients aged ≥ 16 years, who had an ICU stay ≥ 72 hours and had received antibiotics. Clinical data were collected and the following scores calculated: logistic organ dysfunction (LOD), sequential organ failure assessment (SOFA), McCabe, and acute physiology and chronic health evaluation II (APACHE II). **Results**: Out of 291 eligible patients, 250 were enrolled with a mean age (± standard deviation, SD) of 60.23 years (± 14.49), and gender ratio of 1.72:1, male: female. On admission to the ICU, 72.8% had been transferred from the emergency room (ER), 20.8% from other hospital departments and 6.4% from other hospitals. The percentage of patients taking antibiotics prior to ICU admission was 64.8% (n = 162). Antibiotic therapies were modified for 35.6% (n = 89) of patients upon ICU admission and for 49.2% (n = 123) of patients during their ICU stay. The sequential organ failure assessment (SOFA) score on the day of antibiotic change was higher than the SOFA score on ICU admission (P = 0.002). **Conclusions:** Antibiotic therapies are very common in the ICU pre-admission period, as are antibiotic regimen changes post-admission. The SOFA score is a potentially reliable tool for assessing the need to alter antibiotic therapy.

Keywords: Critically ill, severity scores, infection, antibiotic, intensive care unit

Introduction

Intensive care unit (ICU)-acquired infections are a real public health problem. They are associated with a significant increase in mortality, morbidity and medical costs.[1-4] However, in the ICU, the empirical choice of antibiotics in 50% cases is inappropriate and their duration of use is often arbitrary. According to several studies, the most common risk factors for causing infections in ICU patients are: comorbidities present, severe acute physiological troubles, relative immune-suppression and invasive procedures.[5,6] In addition, the antibiotic therapy type and the risk factors mentioned above are intrinsically linked to the emergence of resistant bacterial strains and even multi- or pan-drug resistant bacteria.[7,8] A real therapeutic impasse is reached, as bacterial resistance also directly increases mortality, morbidity and medical costs.[9,10] Taking into consideration these elements, the relevance of the implemented antibiotic therapy strategies is crucial, both before and during the ICU stay. Hence, in this study, we document the frequency of antibiotic use during the ICU pre-admission period, the frequency of antibiotic changes during the ICU stay and the factors relating to changing the current antibiotic therapy -

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Methods

For this retrospective study, data acquired from the ICU of the CHUM, region Provence Cote d'Azur (PACA), were analyzed. The data were collected from 01 January 2011 to 30 June 2012.

Out of 565 hospitalized patients, there were 291 eligible patients (aged ≥ 16 years, with an ICU stay ≥ 3 days, and benefited from antibiotic therapy in pre- or post-ICU admission period).

Of the 291 eligible patients, 41 were excluded because of missing data.

Data were collected using a standard form. Age, sex, ICU admission and discharge date, length of stay in ICU, length of stay in hospital, clinical settings (comorbidities), patient's origin, pathology type, infection type and the causative pathogen(s) were recorded.

Also recorded were the following invasive procedures: intubation, tracheotomy, urinary sampling, central venous and arterial catheterization, as well as sedation, duration and pattern(s) of antibiotic therapy before and after ICU admission, C-reactive protein (CRP) and procalcitonin (PCT) values at admission and on the day of antibiotic therapy change.

For each patient, the following was retrospectively calculated: the logistic organ dysfunction (LOD) score, the sequential organ failure assessment (SOFA) score, the McCabe score and the acute physiology and chronic health evaluation II (APACHE II) score.

All the reported pejorative values from the last 24 hours were used for calculating LOD and SOFA scores.

The values used to calculate McCabe and APACHE II scores were those on the ICU admissions day.

All statistical analyses were performed using the SPSS software at the significance level $P \leq 0.05$. The descriptive statistical method was used for demographic data. The Wilcoxon test was used for the analysis of ordered variables. The Pearson correlation test was used to evaluate the correlation between the numerical variables. The results are presented as mean ± standard deviation or median (minimum-maximum).

SOFA and LOD scores were divided into two groups according to the median values of each score.

Results

Table 1. Descriptive and demographic data of patients

Characteristics	**Number of patients**
Age mean ± SD	60.23 ± 14.49
Gender ratio	1.72 (63.2% male and 36.8% female)
Patient type	12.8% surgical 87.2% medical
McCabe score 1 McCabe score 2 McCabe score 3	169 (67.6%) 72 (28.8%) 9 (3.6%)
APACHE II mean ± SD	20.48 ± 7.94
SOFA mean ± SD	5.78 ± 2.51
SOFA ≤ 4	74 (29.6%)
SOFA > 4	176 (70.4%)
LOD mean ± SD	5.95 ± 2.99
LOD ≤ 5	108 (43.2%)
LOD > 5	142 (56.8%)
Place before ICU admission n (%)	
ER	182 (72.8%)
Inpatient department	52 (20.8%)
Other hospital	16 (6.4%)
Reason for ICU admission n (%)★	
Acute respiratory failure	91 (36.4%)
Sepsis	41 (16.4%)
Neurologic Failure	72 (28.8%)
Diabetes	44 (17.6%)
CRA	23 (9.2%)
Comorbidities n (%)★★	
Sepsis	44 (17.6%)
Hematology disorders	6 (2.4%)
Hypertension	19 (7.6%)
Chronic pulmonary disease	27 (10.8%)
Congestive heart failure	31 (12.4%)
Cancer	30 (12.0%)
Diabetes mellitus	44 (17.6%)
Renal disease	8 (3.2%)
Transplant	7 (2.8%)

★ Total is not equal 100%, since some patients had more than one reason for ICU admission
★ ★Total is not equal 100%, since some patients had more than one comorbidity.
ICU: intensive care unit
SD: standard deviation

Table 2. Data regarding antibiotic use, isolated microorganisms and culture sites

	Number of patients (%)
Reason for antibiotic initiation before intensive care	
Pneumonia	93 (37.2)
COPD exacerbation	26 (10.4)
Sepsis	21 (8.4)
Other	22 (8.8)
Taking cultures prior to antibiotic treatment	173 (69.2)
Antibiotic change at admission to ICU	89 (35.6)
Frequency of antibiotic change during ICU stay	123 (49.2)
1	81
2	22
>3	20
Frequency of positive cultures during ICU stay	152 (60.8)
Isolated microorganisms	
Acinetobacter baumannii	89
Klebsiella pneumonia	31
Escherichia coli	36
Enterococcus spp.	26
Pseudomonas aeruginosa	21
Staphylococcus aureus	11
Mycobacterium tuberculosis	12
Polymicrobial microorganisms	49
Other microorganisms	52
Culture sites ★	
Quantitative deep tracheal aspirate	79
Blood	58
Intravascular catheter	38
Urine	41
Others	33
Multiple sites	51

★ Total is not equal to 100% since some patients were infected with more than one type of microorganism from different sites.
COPD: Chronic obstructive pulmonary disease

Table 3. SOFA score and infection biomarkers at ICU admission day and at antibiotic change day

	ICU admission day	Antibiotic change day	P
SOFA	5.78 (± 2.51)	6.5 (±6.7)	0.002
PCT	7.3 (± 27.6)	11.2 (± 35.9)	0.609
CRP	12.5 (± 10.6)	12.2 (±9.6)	0.703

Table 4. Correlation of infection biomarkers and SOFA score on antibiotic change day

	r	P
PCT and CRP (n=114)	0.483	<0.001
PCT and SOFA (n=96)	0.493	<0.001
CRP and SOFA (n=87)	0.216	0.003

Out of 565 hospitalized patients, there were 291 eligible patients (aged ≥ 16 years, with an ICU stay ≥ 3 days and benefited from antibiotic therapy in pre- or post-ICU admission period). Of the 291 eligible patients, 41 were excluded because of missing data. All patients' demographic data are shown in Table 1.

The median lengths of ICU stays and hospital stays were 7.3 days (range: 1-86) and 19 days (range: 5-184), respectively. The overall mortality in the study population was 23.20%. Antibiotics were started prior to ICU admission in 162 patients (64.8%). The median duration of antibiotic use before ICU admission was 2 days (range: 0-64). The median total duration of antibiotic use was 21.3 days (range: 1-121).

The most common reason for antibiotic initiation before ICU admission was pneumonia (93 patients, 37.2%). Cultures were taken from at least one site in 173 patients (69.2%) prior to antibiotic treatment (Table 2). It should be noted that a resistant profile is mentioned in 23.91% of the bacteria.

Antibiotic regimen changes during the ICU stay occurred in 49.2% of patients (Table 2). There was a statistically significant difference between the SOFA score on ICU admission and that on the day the antibiotic was changed (P = 0.002, Table 3). The relationship between SOFA, CRP and PCT values on the ICU admission day and on the antibiotic change day are shown in Table 4. A weak yet significant correlation was found between SOFA-CRP, SOFA-PCT and CRP-PCT values (Table 4).

Discussion

We investigated the use of antibiotics in an ICU. We found large numbers of patients both who received an antibiotic therapy prior to admission to the ICU and for whom the antibiotic was changed during their stay in the ICU. However, SOFA scores were significantly elevated on the day of antibiotic change.

According to a previous study, the use of antibiotics during pre-admission to the ICU is one of the main causes of increasing bacterial resistance.[11] In our study, the proportion of patients having received antibiotic therapy before their ICU admission was greater than that reported in the literature. We found 64.8% of patients were on antibiotics before they were admitted to the ICU, which corresponds to 2.3 times more than the proportion reported in the study by Montravers *et al.*[12]

Importantly, we found that the percentage of patients in which a microbiological culture was taken prior to antibiotic therapy was 69.2%. This result reveals the proportion of antibiotics used in an empirical sense and which may not be the correct type. This is often dictated by the need for urgent treatment; nevertheless, it is an important factor in the emergence of antibiotic-resistant bacteria.

Looking at the sites of infection identified in our study, lung compartment infections were the most common (59% of sites/infections) followed by urinary tract infections (19% of sites/infections). These results are consistent with those described in the study 'Extended Prevalence of Infection and Epidemiology in Critically-ill' (EPIC),[13,14] in which the incidence of pulmonary infections was slightly higher (64%) than in our study.[13]

The most common isolated microorganism was *Acinetobacter baumannii*, with a frequency of 27.2%. These results are in contrast with those described in the literature, particularly compared with the average prevalence rate of 9% reported in the EPIC II study.[13] However, in this earlier study, there was a geographical variance in *Acinetobacter* infection rates (3.7% in North America, 20% in Asia).

In the ICU, the severity of the patient's condition is one of the major factors that determines whether the current antibiotic therapy is maintained. This is commonly

measured by gravity scores at admission and during the ICU stay. The predictive capabilities and diagnosis of gravity scores have been documented in several works. Studies have shown[14,15] a potential further use for the SOFA score to be an objective factor to evaluate the infectious risk during the ICU stay, beyond its predictive ability of death risk.[16,19,20]

In this study, we found a statistically significant difference between the SOFA score on the ICU admission day and that on the day when the antibiotic therapy was changed (P=0.002, Table 3). Considering this result and those reported previously,[15,16] an increase in the SOFA score appears to represent a potential warning sign or "an alarm signal" that a new infection has been acquired or a new microorganism with a different antibiotic susceptibility profile is present. SOFA scores could thus be used as a guide to initiate or amend the current antibiotic therapy.

Concerning the diagnostic capacity of biological inflammation markers to discriminate between infectious versus non-infectious processes, the debate remains open.

Indeed, the results of several studies suggest that, in a context of systemic inflammatory response syndrome (SIRS), PCT has greater diagnostic accuracy than CRP, interleukin(IL)-6 and IL-8 to distinguish between bacterial sepsis and non-infectious etiologies.[21-23] However, according to other studies, CRP has shown a greater diagnostic accuracy than PCT.[26,27]

In addition to these studies (whose results are contradictory), the randomized controlled study carried out by Stolz *et al* investigated PCT values.[26] 101 patients with (PAVM) were studied and PCT measured throughout the patient's hospital stay. The antibiotic initiation was based on the PCT measurement, and the authors found a significant overall decrease in the number of days of antibiotic therapy, from 15 to 10 days. The advantage of this biological parameter in the same context as that described above has been reported elsewhere.[28]

In their study [28] performed in seven ICUs on non-surgical patients with a suspected bacterial infection (including 73% with a respiratory infection), Boudma *et al* reported that PCT-guided treatment initiation and discontinuation gave 23% more antibiotic free days compared with the control group.[28]

However, according to the results of another study conducted in two Brazilian ICUs, a CRP-based algorithm was found to have similar success to a PCT-based algorithm in patients with severe sepsis and septic shock.[29]

In our study, the obtained results do not allow the establishment of a CRP vs PCT hierarchy. Indeed, we found a moderate correlation between both PCT vs SOFA and CRP vs SOFA on the antibiotic change day. These results could be explained by the fact that PCT and CRP had not been performed on all patients.

Antibiotic treatment duration is an important factor in the emergence of resistant bacterial strains. In light of this fact, antibiotic treatment duration has been progressively reduced for severe infectious syndromes.[31] According to current recommendations, derived from the guidelines, duration of antibiotic treatment for community-acquired pneumonia is about 7 days,[32] for ventilator-associated pneumonia (VAP) 8 days,[33] and for pyelonephritis 5-7 days.[33]

The length of antibiotic treatment in the present study is estimated to be 2 days (range: 0-64) before ICU admission and 21.3 days (range: 1-121) during the ICU stay.

There are several reasons for the long antibiotic therapy periods observed in this study. The first is the ICU context, where therapies are often dictated by urgency (and are therefore probabilistic and empirical), by the complexity of the pathologies and by the concomitant comorbidities. Secondly, the increasing notion that antibiotic therapy in the ICU pre-admission period often induces resistance phenomenon in turn complicates the strategy of care in the ICU

post-admission period. Finally, the absence of an efficient therapeutic decision tool which would help practitioners optimize treatment by choosing the appropriate antibiotic regimen. Some limitations in the present study have been identified, namely its monocentric and retrospective nature. In addition, PCT and CRP measurements were not performed on the antibiotic changing day for all patients and data was absent relating to exact reasons for antibiotic changes in some patients.

Conclusion

ICU infection and mortality have multiple and complex risk factors. However, antibiotic use among ICU patients should be better managed to help prevent the emergence of resistant bacteria. On the day of antibiotic change, the SOFA score was higher than on the day of ICU admission (P=0.002). The SOFA score has the potential to be used to influence the decision to alter antibiotic therapy.

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