Control of Multi-Resistant Bacteria and Ventilator-Associated Pneumonia: Is It Possible with Changes in Antibiotics?

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Potent antimicrobial agents have been developed as a response to the development of antibiotic-resistant bacteria, which especially affect patients with prolonged hospitalization in Intensive Care Units (ICU) and who had been previously treated with antimicrobials, especially third-generation cephalosporins. This study was to determine how changes in the empirical treatment of infections in ICU patients affect the incidence of Gram-negative bacteria species and their susceptibility to antimicrobials, and examine the impact of these changes on nosocomial infections. A prospective interventional study was performed in a university hospital during two periods: 1) First period (September 1999 to February 2000); and 2) Second period (August 2000 to December 2000); empirical treatment was changed from ceftriaxone and/or ceftazidime in the first period to piperacillin/tazobactam in the second. ICU epidemiological and infection control rates, as well as bacterial isolates from upper airways were analyzed. Ceftazidime consumption dropped from 34.83 to 0.85 DDD/1000 patients per day (p=0.004). Piperacillin/tazobactam was originally not available; its consumption reached 157.07 DDD/1000 patients per day in the second period (p=0.0002). Eighty-seven patients and 66 patients were evaluated for upper airway colonization in the first and second periods, respectively. There was a significant decrease in the incidence of *K. pneumoniae* (p=0.004) and *P. mirabilis* (p=0.036), restoration of *K. pneumoniae* susceptibility to cephalosporins (p<0.0001) and reduction of ventilator-associated pneumonia rates (p<0.0001). However, there was an increase in *P. aeruginosa* incidence (p=0.005) and increases in ceftazidime (p=0.003) and meropenem (p<0.0001) susceptibilities. Changing antimicrobial selective pressure on multi-resistant Gram-negative bacteria helps control ventilator-associated pneumonia and decreases antimicrobial resistance.
Key-Words: Ventilator associated pneumonia, multi-resistant bacteria, infection control.

Since the introduction of penicillin, bacteria have been shown to have the capacity of developing resistance when exposed to antibiotics. There is considerable evidence that previous exposure to antibiotics plays an important role in the development of resistance [1].

Nowadays, the problem of resistance is of great concern in the hospital setting due to multi-resistant *S. aureus*, *Enterococcus* spp., *Acinetobacter* spp., and *Pseudomonas* spp., giving birth to the so-called post-antibiotic era [2].

There is some evidence that increased use of third-generation cephalosporins leads to resistance in Gram-negative bacilli, especially *Citrobacter, Enterobacter, Serratia* and *Providencia* species, and also to emergence of extended-spectrum beta-lactamase (ESBL)-producing bacteria [3,4]. Once this happens, the use of carbapenems, which can induce resistance in *P. aeruginosa* and *Acinetobacter* spp. [5], becomes mandatory.

Hospital São Paulo, a large university hospital in Brazil, experienced an increase in ESBL-producing *Klebsiella pneumoniae* in 1995, when 39% of the isolates were found to be resistant to cephalosporins. These bacteria were not clonal; their spread was thought to be due to the use of third-generation cephalosporins [6]. This led to increased use of carbapenems, favoring an increase in the incidence of

Acinetobacter baumannii [7], seen in 1998; more recently, *Pseudomonas aeruginosa* became one of the most common pathogens, mainly in the ICU setting. These latter organisms posed a substantial therapeutic dilemma, as they also became resistant to carbapenems, therefore making polymixin the only therapeutic choice for them.

In an attempt to reverse the trend of increasing antibiotic resistance, we conducted a prospective interventional study in patients who developed any infection defined as an ICU infection.

The main goal of our study was to determine whether or not substitution of third-generation cephalosporins by piperacillin/tazobactam can decrease the prevalence of *Klebsiella* spp. and *Enterobacter* spp. resistance to cephalosporins, so that carbapenems would be less frequently prescribed, in order to diminish their selective pressure on *P. aeruginosa* and *Acinetobacter* spp.

Materials and Methods

Hospital São Paulo is a tertiary university hospital in São Paulo, Brazil, with 624 beds, of which 40 are used for the adult Intensive-Care Unit (ICU). Our study was conducted in a 16-bed general ICU that provides treatment for acutely-ill patients. All patients admitted to that ICU from September 1999 to December 2000 and who were under mechanical ventilation for more than 48 hours were included in the study. Patients who did not stay in the ICU for 48 hours were excluded from the study. All patients who were in the ICU during the study period received the proposed antibiotic for every infection believed to be due to Gram-negative bacilli in any site.

The following data were recorded at admission: age, sex, pre-existing diseases and APACHE II score. Subsequently, the numbers of days in the ICU and mortality rates were monitored.

Due to the need for intervention, the study had a "before-after" design, as follows:

1. First period (from September, 1999, to February, 2000): ceftazidime was used as the antibiotic of choice for empirical treatment of suspected Gram-negative bacilli infections.
2. Second period (from August 2000, to December 2000): piperacillin/tazobactam was used for the same indication, replacing ceftazidime.

One of the investigators made daily rounds with the ICU team to ensure understanding and compliance to the study protocol. Antibiotic consumption, nosocomial infection, and microbiologic colonization were analyzed in both periods, as described below.

Some antibiotics were selected for analysis: ceftriaxone, ceftazidime, cefepime, imipenem, amikacin, ciprofloxacin and piperacillin/tazobactam. Consumption of these antibiotics was measured by using the defined daily dose (DDD), as proposed by the WHO [8]. The DDD per 1000 patient-days (DDD_N) was obtained according to:

$$DDD = \frac{Antibiotic\ consumption\ in\ grams}{"Defined\ Daily\ Dose"}$$

and

$$DDD_N = \frac{DDD}{No.Patients-Day} \times 1000$$

Data on nosocomial infection and on ventilator-associated pneumonia (VAP) were obtained according to NNIS methodology, defined by the Centers for Disease Control and Prevention [9]. A diagnosis of ventilator-associated pneumonia was considered by the infectious diseases team whenever a new or progressive roentgenographic infiltrate developed in conjunction with two or more of the following clinical criteria: fever, leukocytosis and purulent tracheal aspirate.

One of us (EMJ) was responsible for collecting lower tracheal aspirates, under sterile conditions, of all patients on the second day of mechanical ventilation; this was repeated every week that patients were maintained on mechanical ventilation. The material was stored for posterior culture using classic methods of identification; susceptibility tests were performed by using National Committee for Clinical Laboratory Standards (NCCLS) disc diffusion standards [10]. Discs with ceftazidime and amoxicillin/clavulanate were used to check for ESBL in suspected isolates.

Computer-based antibiogram records were used to determine the prevalence of resistance to amikacin, ceftriaxone, ceftazidime, cefepime, ciprofloxacin, imipenem and piperacillin/tazobactam.

Statistical Analysis

The student's t test was used to compare antibiotic consumption and hospital-infection rates between the two periods. Survival analysis of patient outcomes (discharge from ICU or death) was performed by using a Cox-rank test for the two periods. A Chi-square test was used to compare periods in terms of prevalence of pathogens and susceptibility profile of the isolated microorganisms. The statistical significance level adopted was 5%. Analyses were performed using STATISTICA for Windows 4.5™. The study was submitted to the Ethics Committee of São Paulo Hospital and it was approved.

Results

Patient Characteristics

Eighty-seven and 66 patients met the criteria for analysis in the first and second periods, respectively. There were no significant differences in the clinical and epidemiological characteristics of the patients between the periods (Table 1). The survival analyses showed no significant difference in the length of stay in ICU between the periods (p=0.19, Figure 1). In addition, the probability of death did not differ between periods (58.6 and 59.0%, respectively (p=0.91).

Changes in Antibiotic Use

There was no significant variation in the consumption of most of the antibiotics (Table 2). However, there was a significant reduction in the use of third-generation cephalosporins and a significant increase in piperacillin/tazobactam use.

Hospital Infection Surveillance

The nosocomial infection rate decreased from an average of 31.75/1000 patient-days in the first period to 18.99/1,000 patient-days in the second period. This was mainly due to the decrease in ventilator-associated pneumonia (VAP) rates, decreasing from 19.93 VAP/1000 patient-days to 5.13 VAP/1,000 patient-days (p < 0.0001, Figure 2).

Microbiological Surveillance

Microorganisms obtained from tracheal secretions were analyzed. These organisms were collected from 153 patients who met the criteria for sampling. There were decreases in the prevalence of *K. pneumoniae* and *P. mirabilis* and an increase in the prevalence of *Pseudomonas aeruginosa* (Table 3).

The rate of resistance of *K. pneumoniae* to ceftriaxone and ceftazidime decreased from the first to the second period (0.78 *versus* 0.07 and 0.97 *versus* 0.21, p<0.0001, respectively). When these bacteria were tested for production of ESBL enzymes, 87.9% were positive in the first period and 22.2% in the second period (*p*=0.0003). Piperacillin/tazobactam was not available in the first period, but its use in the second period did not increase the resistance of *K. pneumoniae* to it (0.31 x 0.14, p=0.2).

Table 1. Baseline and clinical characteristics of the cohort of patients in the intensive care unit

Characteristics	First period (N = 87)	Second period (N = 66)	p value
Age, years*	52.44	54.29	0.75
Sex			
Male n (%)	47 (54)	40 (60)	
Female n (%)	40 (46)	26 (40)	0.41
Length of stay in intensive care (days)	19.46	26.06	0.08
Underlying diseases			
Congestive heart failure n (%)	22 (25.28)	15 (22.73)	0.86
Chronic pulmonary disease n (%)	5 (5.74)	4 (6.06)	0.79
Malignancy n (%)	16 (18.40)	18 (27.27)	0.26
Stroke n (%)	8 (9.20)	2 (3.03)	0.21
Traumatism n (%)	8 (9.20)	9 (13.64)	0.54
Metabolic diseases n (%)	8 (9.20)	2 (3.03)	0.23
No underline diseases n (%)	15 (17.24)	13 (19.70)	0.85
Hepatic disorder	5 (5.74)	3 (4.54)	0.73
Admission diagnoses			
Post-operative neurosurgery	22 (25.28)	9 (13.64)	0.11
Post-operative cardiac surgery	4 (4.60)	1 (1.51)	0.54
Post-operative pulmonary surgery	5 (5.74)	2 (3.03)	0.68
Post-operative abdominal surgery	20 (23.00)	23 (34.85)	0.15
Other surgeries	4 (4.60)	7 (10.61)	0.26
Cardiac	17 (19.54)	5 (7.57)	0.06
Respiratory	9 (10.34)	13 (19.70)	0.16
Neurological	4 (4.60)	2 3.03)	0.94
Other clinical disorders	2 (2.30)	4 (6.06)	0.44
APACHE II Score[§]	19.37	17.31	0.10

* Student T test or c-square test, with Yates correction when indicated. [§]Values are means.

Table 2. Antibiotic consumption, in DDD_N, in the first and second periods

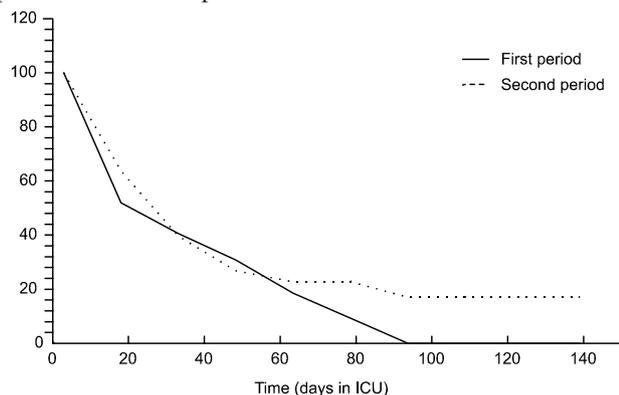| Antibiotic	First period	Second period	p*
Amikacin	35.25	7.36	0.095
Ceftriaxone	73.50	15.80	0.001
Ceftazidime	34.83	0.85	0.004
Cefepime	11.17	6.60	0.39
Ciprofloxacin	50.95	24.70	0.561
Imipenem-cilastatine	58.91	64.00	0.832
Piperacillin-tazobactam	-	157.07	0.0002

* Student T test.

Table 3. Frequency of tracheal isolate results in the first and second periods

Microorganism	First period (%)	Second period (%)	p*
Sterile	13 (5)	9 (4)	0.76
S. aureus	24 (9)	16 (8)	0.67
K. pneumoniae	43 (16)	14 (7)	0.004
A. baumannii	45 (17)	34 (17)	0.94
P. aeruginosa	89 (33)	94 (46)	0.005
Enterobacter spp.	13 (5)	8 (4)	0.7
Serratia spp.	10 (4)	3 (1)	0.13
P. mirabilis	13 (5)	2 (1)	0.036
Other bacteria	16 (6)	19 (9)	0.23
Candida spp.	3 (1)	5 (2)	0.16
Total	269	204	

*χ-square test, with Yates correction when indicated.

Figure 1. Survival analysis during intensive care unit stay of patients in the two periods.

Figure 2. Rates of ventilator-associated pneumonia (VAP) in the first and second periods, considering all cases.

* p<0.001.

There were increases in *P. aeruginosa* resistance to piperacillin/tazobactam (0.60 *versus* 0.76, p=0.02), meropenem (0.33 *versus* 0.45, p<0.0001) and ciprofloxacin (0.69 *versus* 0.78, p<0.0001) from the first to the second periods. Increased resistance was also observed to ceftazidime (0.67 *versus* 0.86, p=0.003).

Resistance to other Gram-negative bacilli (including *A. baumannii* and *Enterobacter* spp.) and to other antimicrobials did not differ from the first to the second period.

Discussion

The increasing dilemma posed by the treatment of multi-resistant Gram-negative bacteria emphasizes the importance of interventional measures directed towards minimizing this problem.

We tested the hypothesis that an intervention designed to reduce the incidence of ESBL and chromosome-induced beta-lactamase (class 1 or AmpC)-producing bacteria would make the use of carbapenems less necessary, and therefore would allow better control of the emergence of multi-resistant *A. baumannii* and *P. aeruginosa* strains, which are frequently seen in infections related to health care in ICU settings [5]. To address this issue, we proposed a prospective-interventional study to evaluate the impact of changing empirical antibiotic treatment of nosocomial VAP from third-generation cephalosporins to piperacillin/tazobactam, evaluated not only with hospital microbiology, but also by examining clinical and epidemiological aspects.

The intervention took place in the general ICU of Hospital São Paulo, because antimicrobial resistance is especially important in that unit. Recorded data on bacteremia isolates showed a high rate of *P. aeruginosa* resistance to ceftazidime (37.5%), ciprofloxacin (71.5%) and imipenem (75%). *Acinetobacter* spp. was also resistant to ceftazidime in 93.2% of isolates [11] These findings were expected because several risk factors for antimicrobial resistance had been previously described in ICU patients [2,12,13], including acutely and severely-ill patients, widespread use of empirical polyvalent antimicrobial therapy and frequent need for invasive devices and procedures.
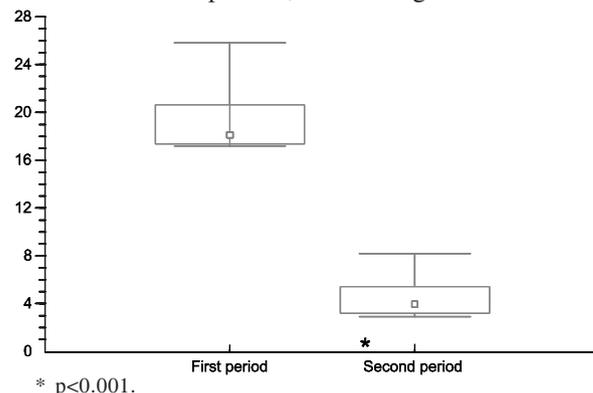
The demographic and epidemiological profiles of the patients attended in the ICU did not change during the study and the survival analysis showed no difference in the length of stay in the ICU between the periods. In addition, there was no difference in mortality from all causes. These findings allow us to conclude that bias in the intended analysis was minimized. Apparently, the study intervention caused no measurable harm to the patients attended in that ICU.

There was good adherence to the proposed intervention, as we found a significant decrease in ceftazidime and ceftriaxone usage, while piperacillin/tazobactam use rapidly increased to an average of 157.07 DDD_N/month.

As expected, a significant reduction in *K. pneumoniae* isolates resistant to ceftazidime was observed from one period to the other, as well as a reduction in the overall incidence of *K. pneumoniae*. These phenomena had been described earlier [9-11] in reports of outbreaks of resistant *K. pneumoniae* controlled by restriction of the use of third-generation cephalosporins.

Control of chromosome-induced (class 1 or AmpC) beta-lactamase production was also expected, since Gram-negative bacteria develop resistance to cephalosporins when exposed to third-generation cephalosporins. However, we were not able to prove this. We found a significant decrease in the incident of *P. mirabilis*, but no change in its susceptibility profile, as we also found for other Gram-negative bacteria. There is some evidence [4] that the resistance of *Enterobacter* spp. is reversible by restricting the use of third-generation cephalosporins. As our interventional period was only five months, it may have been too short to reverse a resistance that was not very frequent in the first period.

There was no increase in the use of carbapenems, as opposed to the findings of Rahal et al. [13], who found a significant increase in the use of this class of antibiotic after the substitution of ceftazidime in their institution. Patterson et al. [11] also evaluated the use of imipenem after the substitution of ceftazidime with piperacillin/tazobactam, demonstrating no difference after the changing of antibiotics. However, the rate of use of imipenem in our ICU was very

high when compared to that reported from other institutions. In one report [15] from the ICARE surveillance project, for instance, the rate of imipenem use was only 10 DDD per 1,000 patient-days, six times less than what we found. This may justify the increased frequency of *P. aeruginosa*, along with the increase in its resistance to imipenem. Troillet et al. [18] analyzed the risk factors associated with the development of imipenem-resistant *P. aeruginosa* and concluded that the most important one was previous use of this antibiotic (OR 15.4; 95% CI 4.0-58.9). This is consistent with what we found in our study, as there was an increasing incidence of imipenem-resistant *Pseudomonas* strains associated with the extremely high rate of use of this antibiotic, which might have resulted in high selective pressure on those microorganisms. Reducing carbapenem use was not the focus of our study. Additional restriction in carbapenem use would probably be necessary in order to reduce the frequency of resistant *P. aeruginosa*.

Even with the increased incidence of resistant *P. aeruginosa*, we observed an important reduction in overall infection rates, resulting basically from a decrease in the ventilator-associated pneumonia rates. Other researchers [16,17] also suggested that antibiotic changes are effective measures in VAP control.

In conclusion, although this was not a randomized study, the change in empirical antibiotic treatment from third-generation cephalosporins to piperacillin/tazobactam was effective in reducing *K. pneumoniae* and *P. mirabilis* incidence and in reducing ventilator-associated pneumonia rates, since no other intervention to reduce the occurrence of this event was used during our study. In addition, it also promoted a significant reduction in the frequency of ceftazidime-resistant *K. pneumoniae* isolates.

Acknowledgements

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