

Ceftriaxone and ciprofloxacin restriction in an intensive care unit: less incidence of *Acinetobacter* spp. and improved susceptibility of *Pseudomonas aeruginosa*

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ABSTRACT

Objective. To determine whether restricting the use of ceftriaxone and ciprofloxacin could significantly reduce colonization and infection with resistant Gram-negative bacilli (r-GNB).

Methods. A two-phase prospective study (before/after design) was conducted in an intensive care unit in two time periods (2004–2006). During phase 1, there was no antibiotic restriction. During phase 2, use of ceftriaxone or ciprofloxacin was restricted.

Results. A total of 200 patients were prospectively evaluated. In phase 2, the use of ceftriaxone was reduced by 93.6% ($P = 0.0001$) and that of ciprofloxacin by 65.1% ($P = 0.041$), accompanied by a 113.8% increase in use of ampicillin-sulbactam ($P = 0.002$). During phase 1, 48 GNB were isolated [37 r-GNB (77.1%) and 11 non-r-GNB (22.9%)], compared with a total of 64 during phase 2 [27 r-GNB (42.2%) and 37 non-r-GNB (57.8%)] ($P = 0.0002$). *Acinetobacter* spp. was isolated 13 times during phase 1 and 3 times in phase 2 ($P = 0.0018$). The susceptibility of *Pseudomonas aeruginosa* to ciprofloxacin increased from 40.0% in phase 1 to 100.0% in phase 2 ($P = 0.0108$).

Conclusions. Restriction of ceftriaxone and ciprofloxacin reduced colonization by *Acinetobacter* spp. and improved the susceptibility profile of *P. aeruginosa*.

Key words

Drug resistance, multiple; *Acinetobacter baumannii*; *Pseudomonas aeruginosa*; antibacterial agents; Uruguay.

Infections by resistant Gram-negative bacilli (r-GNB) in the nosocomial environment have been highlighted as particularly problematic for clinical practice (1, 2). This problem has been described for *Acinetobacter baumannii* (3), *Pseudomonas aeruginosa* (4), *Klebsiella pneumoniae*

(5), and *Enterobacter cloacae* (6, 7). Epidemic and endemic situations due to r-GNB are increasingly recognized in Latin American countries (8–10).

The resistant strains are generally isolated after wide spectrum cephalosporin treatment because they generate strain selection pressure (11–13). This problem is particularly important in intensive care units. Vignoli et al. (14) documented that the administration of oxyimino-cephalosporins was associated with the selection of resistant strains of Entero-

bactereaceae in the fecal flora. Previous use of ceftriaxone and ciprofloxacin was recently identified as a significant independent predictor for the development of ventilator-associated pneumonia with *Acinetobacter* spp. (15).

The importance of patients infected and colonized by r-GNB is reflected in the recommendation to isolate them as an effective means to decrease cross-colonization (16, 17). However, this measure is not enough to limit the increased incidence of r-GNB. Other strategies,

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such as antimicrobial rotation (18–20) and restriction (21) policies, have been developed for this purpose. These strategies have not been evaluated in great detail in the South America region. The increased isolation of r-GNB, particularly *Acinetobacter* spp. (15) and *Pseudomonas aeruginosa* in the intensive care unit at Hospital Policial, Montevideo, Uruguay, motivated this study in order to determine whether restricting the use of ceftriaxone and ciprofloxacin could result in a significant reduction in the incidence of r-GNB colonization and infection in critically ill patients. The secondary objective was to test whether such a change in strategy would improve the susceptibility pattern of any microorganism.

MATERIALS AND METHODS

Study design

A two-phase prospective study (before/after design) was conducted in the intensive care unit of Hospital Policial, Montevideo, Uruguay, within two periods of time (2004–2006). All patients admitted to the intensive care unit for 48 hours or more were successively included. During phase 1, clinicians could freely prescribe antibiotics like ceftriaxone and ciprofloxacin when they suspected either community or early nosocomial infection. During phase 2, both antibiotics were restricted. To achieve a successful restriction, staff were educated for 2 months before the beginning of the second phase; in addition, researchers (J.C.M.P. and J.G.) constantly monitored antibiotic indications. When a patient had a suspected community or early nosocomial infection, the clinician used ampicillin-sulbactam instead of ceftriaxone and aminoglycoside alone or associated with another antibiotic instead of ciprofloxacin. The staff were in charge of the prescription and duration of the antibiotic therapy. However, approval by an investigator (J.C.M.P. or J.G.) was required before empirical or definitive use of ceftriaxone and ciprofloxacin, with the exception of the use of ceftriaxone for acute bacterial meningitis.

Cefepime, antipseudomonal penicillin, and piperacillin-tazobactam were not available for use in the intensive care unit.

Study location

The study was conducted at a university-affiliated tertiary-care public hospi-

tal: Hospital Policial (241 beds) in Montevideo, Uruguay. The intensive care unit is an eight-bed general intensive care unit, with air-conditioned closed units without negative pressure.

Patients

All patients admitted to the intensive care unit from 1 May 2004 to 28 February 2005 were eligible for phase 1 of the study; phase 2 included patients admitted from 1 May 2005 to 28 February 2006. Standard care for management of infections was maintained in both periods. Data are presented so that individual patients cannot be identified.

Data collection

Patients were followed up daily until discharge from the intensive care unit. The recorded variables were: gender, age, severity of underlying illness (22), previous medical condition (23), diagnosis at admission, length of stay in the intensive care unit, mortality, invasive procedures, infection and colonization focuses, type of pathogens, and antibiotic resistance profile. The number of hours of nursing was recorded in each phase and is expressed as hours of nursing per 1 000 patient-days. Antibiotic use was reviewed for each patient and was recorded as total grams of the drug and was then converted to defined daily doses per 1 000 patient-days, in accordance with the World Health Organization recommendation. Only the expenditure for drugs that were administered intravenously was analyzed (24, 25).

Microbiology

Cultures were obtained according to clinical indications. One isolate was recorded per body site per patient. All isolates were identified by standard microbiological methods, and susceptibility testing was performed according to international guidelines (26).

The susceptibility of GNB to ceftriaxone, ceftazidime, ciprofloxacin, imipenem, meropenem, gentamicin, amikacin, and ampicillin-sulbactam was evaluated.

Definitions

Colonization or infection was determined by criteria of the Centers for Disease Control and Prevention (Atlanta,

Georgia, United States of America) (27). An infection acquired in the intensive care unit was defined as an infection that was not present at admission and that developed after a stay of 48 hours.

The diagnosis of ventilator-associated pneumonia was determined according to previously established definitions (15, 28–30).

r-GNB were defined as any GNB resistant to one or more of the following: all aminoglycosides, all third-generation cephalosporins, and all carbapenems (18).

Statistical analysis

Continuous variables were compared by using Student's *t*-test and a chi-square test or Fisher's exact test to compare categorical variables. All comparisons were unpaired and all tests of significance were two-tailed. A *P* value < 0.05 was considered statistically significant. In order to evaluate the day of resistant GNB colonization, a Kaplan-Maier curve was prepared.

RESULTS

Patients

A total of 200 patients were prospectively evaluated (*n* = 100 in each phase). A comparison of clinical and demographic characteristics, mortality, and stay in the intensive care unit during both periods showed no significant differences other than the diagnosis at admission of non-traumatic acute brain injury at 33.0% in phase 1 versus 18.0% in phase 2 (*P* = 0.02) (Table 1). No significant differences were registered between phases in relation to invasive procedures and days of device usage (Table 2).

Changes in antibiotic use

During phase 2, the use of ceftriaxone declined by 93.6% (*P* = 0.0001), the final consumption of ciprofloxacin decreased by 65.0% (*P* = 0.041), and the use of ampicillin-sulbactam increased by 113.8% (*P* = 0.002). Although an increase in the use of carbapenems by 12.7% and aminoglycoside by 30.7% was also seen, the findings were not statistically significant (Table 3).

Incidence of infection and colonization

Nosocomial infection device-related rates, like ventilator-associated pneumo-

TABLE 1. Demographic and clinical characteristics of patients without and with restriction of antimicrobials, intensive care unit, Hospital Policial, Montevideo, Uruguay, 2004–2006

| Characteristic | Phase 1 ^a | Phase 2 ^b | P value |
|----------------------------------|----------------------|----------------------|---------|
| Male, % | 50.0 | 46.0 | 0.67 |
| Female, % | 50.0 | 54.0 | |
| Years of age | | | |
| Mean ± SD | 62.8 ± 13.7 | 56.6 ± 19.8 | 0.07 |
| Median (interquartile range) | 64 (55.7–73) | 61 (42.2–72) | |
| APACHE II score | | | |
| Mean ± SD | 21.6 ± 7.7 | 21.3 ± 6.6 | 0.79 |
| Median (interquartile range) | 21 (17–25.7) | 21 (17–26) | |
| McCabe and Jackson (23) criteria | | | |
| Rapidly fatal disease, % | 0.0 | 1.0 | 0.487 |
| Ultimately fatal disease, % | 23.0 | 19.0 | |
| Nonfatal disease, % | 77.0 | 80.0 | |
| Preexisting comorbidity | | | |
| Chronic alcoholism, % | 13.0 | 20.0 | 0.25 |
| Received corticosteroids, % | 5.0 | 8.0 | 0.56 |
| Hospitalized 3 months before, % | 20.0 | 19.0 | 1.0 |
| Diabetes, % | 22.0 | 23.0 | 1.0 |
| Cardiovascular disease, % | 10.0 | 21.0 | 0.49 |
| Liver disease, % | 2.0 | 5.0 | 0.44 |
| Diagnosis at admission | | | |
| Nontraumatic ABI, % | 33.0 | 18.0 | 0.02 |
| Severe CAP, % | 8.0 | 12.0 | 0.48 |
| COPD exacerbation, % | 1.0 | 2.0 | 1.0 |
| Severe trauma, % | 6.0 | 14.0 | 0.09 |
| Severe sepsis, % | 15.0 | 7.0 | 0.11 |
| Cardiovascular disease, % | 11.0 | 14.0 | 0.66 |
| Cardiac arrest, % | 3.0 | 1.0 | 0.62 |
| Thoraco-abdominal surgery, % | 10.0 | 14.0 | 0.51 |
| Miscellaneous, % | 13.0 | 18.0 | 0.14 |
| All-cause death, % | 38.0 | 35.0 | 0.76 |
| Days in ICU, mean ± SD | 11.2 ± 10.1 | 10.0 ± 9.2 | 0.41 |

Note: SD: standard deviation, APACHE II: Acute Physiology and Chronic Health Evaluation II, ABI: acute brain injury, CAP: community acquired pneumonia, COPD: chronic obstructive pulmonary disease, ICU: intensive care unit.

^a Without restriction, 1 May 2004 to 28 February 2005 ($n = 100$).

^b With restriction, 1 May 2005 to 28 February 2006 ($n = 100$).

TABLE 2. Invasive procedures performed on patients without and with restriction of antimicrobials, intensive care unit, Hospital Policial, Montevideo, Uruguay, 2004–2006

| Variable | Phase 1 ^a | Phase 2 ^b | P value |
|--|----------------------|----------------------|---------|
| Invasive mechanical ventilation, % | 80.0 | 84.0 | 0.46 |
| Days of invasive mechanical ventilation, mean ± SD | 9.3 ± 9.8 | 9.1 ± 9.9 | 0.89 |
| Reintubation, % | 12.0 | 10.0 | 0.65 |
| Tracheotomy, % | 18.0 | 11.0 | 0.16 |
| Urinary tract catheterization, % | 91.0 | 97.0 | 0.07 |
| Days of urinary tract catheterization, mean ± SD | 10.5 ± 9.8 | 10.0 ± 9.3 | 0.72 |
| Central vein catheterization, % | 89.0 | 96.0 | 0.06 |
| Days of central vein catheterization, mean ± SD | 8.4 ± 6.2 | 7.1 ± 5.4 | 0.058 |

Note: SD: standard deviation.

^a Without restriction, 1 May 2004 to 28 February 2005.

^b With restriction, 1 May 2005 to 28 February 2006.

nia, catheter-related urinary tract infection, and central venous catheter-related bloodstream infections, were 19.2, 10.4, and 1.9 episodes per 1 000 device days for phase 1 and 23.2, 10.1, and 2.5 for phase 2, respectively. The rate of other

infections acquired in the intensive care unit was 5.3 per 1 000 patients/day in phase 1 as opposed to 12.9 per 1 000 patients/day in phase 2.

During the first half of phase 1, 8 of 26 patients acquired at least one nosocomial

infection, while 21 of 36 acquired at least one infection ($P = 0.04$) in the first half of phase 2. Average nursing hours per 1 000 patients/day were $2\,187 \pm 178$ and $1\,986 \pm 44$ in the first half of phase 1 and 2, respectively ($P = 0.02$).

The day-by-day probability of remaining free of r-GNB was calculated for both phases with the Kaplan–Meier estimate. There was a nonsignificant tendency for patients in phase 2 to be colonized by r-GNB at a later period (log rank 0.7698) (Figure 1).

Changes in GNB antibiotic susceptibility

In phase 1, 48 GNB were isolated [37 r-GNB (77.1%) and 11 non-r-GNB (22.9%)], whereas 64 GNB were isolated in phase 2 [27 r-GNB (42.2%) and 37 non-r-GNB (57.8%)] ($P = 0.0002$).

During phase 1, *Acinetobacter* spp. was isolated 13 times from a total of 48 GNB, but only 3 *Acinetobacter* spp. from a total of 64 GNB ($P = 0.0018$) were isolated in phase 2. An increase in *Klebsiella* spp. and other GNB was observed in phase 2 ($P = 0.0149$ and $P = 0.0415$, respectively) (Table 4).

Table 4 shows the total GNB distribution and its resistance profile. Table 5 shows the distribution of r-GNB isolated from colonizations and infections. With regard to the resistance profile of *P. aeruginosa* during phase 1, 60.0% were resistant to ciprofloxacin; in phase 2, none of the isolated *P. aeruginosa* was resistant to this antimicrobial ($P = 0.0108$).

A total of 22 Enterobacteriaceae (*Enterobacter* spp., *Escherichia coli*, *Proteus* spp., *Klebsiella* spp.) were isolated in phase 1, and 39 were isolated in phase 2. *Enterobacter* went from representing 36.3% of the Enterobacteriaceae in phase 1 to representing 12.8% in phase 2 ($P = 0.049$), while *Proteus* spp. plus *Klebsiella* spp. increased from 22.7% in phase 1 to 61.5% in phase 2 ($P = 0.0069$).

There was no significant variability in the resistance of GNB to ceftazidime, carbapenemes, aminoglycosides, and ampicillin-sulbactam.

DISCUSSION

The most important finding of this study is that the restriction of ceftriaxone and ciprofloxacin positively affected the ecology of the intensive care unit. r-GNB isolations declined significantly

TABLE 3. Change in antibiotic use without and with restriction of antimicrobials, intensive care unit, Hospital Policial, Montevideo, Uruguay, 2004–2006

| Antibiotic | Defined daily doses per 1 000 patient-days | | Change, % | P value |
|-------------------------------------|---|----------------------|-----------|---------|
| | Phase 1 ^a | Phase 2 ^b | | |
| All third-generation cephalosporins | 166.3 | 66.5 | -60.2 | 0.02 |
| Ceftriaxone | 111.1 | 6.9 | -93.6 | 0.0001 |
| Cefotaxime | 8.0 | 6.9 | -12.5 | 0.48 |
| Ceftazidime | 47.3 | 52.6 | +10.6 | 0.29 |
| Ciprofloxacin | 149.9 | 52.4 | -65.1 | 0.041 |
| Carbapenem | 126.2 | 142.8 | +12.7 | 0.065 |
| Ampicillin-sulbactam | 382.2 | 817.5 | +113.8 | 0.002 |
| Aminoglycosides | 117.0 | 153.3 | +30.7 | 0.055 |
| Total | 1 108.1 | 1298.8 | +17.1 | 0.08 |

^a Without restriction, 1 May 2004 to 28 February 2005.

^b With restriction, 1 May 2005 to 28 February 2006.

from 77.1% in phase 1 to 42.2% in phase 2. However, a more detailed analysis shows that the greatest impact in the reduction of r-GNB was in colonizations. It is known that colonized patients are an important source of r-GNB for later dissemination and possible infection in the intensive care unit, which is why it has been recommended that patients colonized with r-GNB be isolated as an effective means to control patient-to-patient transmission (16, 17). A clinical and molecular typification study (31) showed that 64.0% of the strains of mul-

ti-resistant *P. aeruginosa* were transmitted by cross-colonization.

Murthy showed that an infection by r-GNB doubles the probability of a long-term stay in the intensive care unit and the risk of dying due to the infection (32). Raymond et al. showed that r-GNB are independent predictors of mortality and that they can be associated with a prolonged hospital stay (33).

Most studies of restriction of certain antimicrobial molecules fail to show a change in bacterial ecology or an impact on the susceptibility profiles of the mi-

croorganism. This study achieved both a decreased incidence in a particular pathogen and a change in the susceptibility profile of another r-GNB.

Acinetobacter spp. was significantly reduced in phase 2, leading to the notion that it is directly related to the restriction of ceftriaxone and ciprofloxacin. A prospective study has already demonstrated that previous use of these antimicrobials is independently associated with the development of ventilator-associated pneumonia caused by *Acinetobacter* spp. (15). In the case of ceftriaxone, the explanation could be that it is mainly excreted through the bile (34, 35), causing a rapid colonization of the digestive tract by *Acinetobacter* spp. (36). Gruson et al. achieved reduction of a particular microorganism, like *Burkholderia cepacia*, by restricting ceftazidime and ciprofloxacin (19).

An impact on the susceptibility profile was seen in *P. aeruginosa* in relation to ciprofloxacin, in which susceptibility increased from 40.0% in phase 1 to 100.0% in phase 2. Aubert et al. documented a decrease in resistant strains from 71.3% in the prerestriction period to 52.4% in the postrestriction period (37). Neuhauser et al. (38) and Friedland et al. (39) documented the increasing incidence of ciprofloxacin resistance among GNB associated with increased use of fluoroquinolones. The benefit of recovering susceptibility lies in the possibility of other therapeutic options for *P. aeruginosa*. It has been shown that adequate empirical treatments are associated with less morbidity and mortality (40), so if one must empirically cover GNB with a less restricted susceptibility profile, the possibility of performing an adequate empirical therapy is greater (41).

As far as Enterobacteriaceae are concerned, there has been an increase in phase 2 that can be attributed to a smaller nursing staff during this phase (42, 43), considering that other variables like demographical data, severity, and invasive procedures were similar. There was a significant decrease in *Enterobacter* spp. and a significant increase in *Klebsiella* spp. and *Proteus* spp. The explanation for this phenomenon could be related to two events that occurred during this research. The decrease in *Enterobacter* spp. could be directly related to the reduced use of oxyiminocephalosporins. Vignoli and others (14,

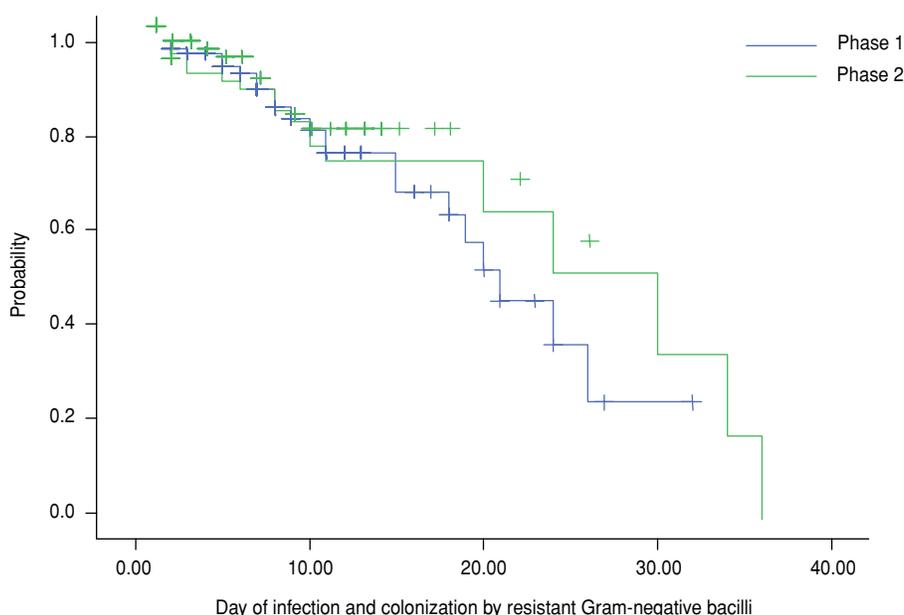
FIGURE 1. Day-by-day probability of remaining free of infections and colonization with resistant Gram-negative bacilli in patients without (phase 1) and with (phase 2) restriction of antimicrobials, intensive care unit, Hospital Policial, Montevideo, Uruguay, 2004–2006 (log rank 0.7698)

TABLE 4. Resistance of isolated Gram-negative bacilli without and with restriction of antimicrobials, intensive care unit, Hospital Policial, Montevideo, Uruguay, 2004–2006

| Bacillus | No. of strains | Percent resistance to: | | | | | | | |
|-------------------------------------|-----------------|------------------------|-------|-------------------|------|------|------|------------------|-------|
| | | CRO | CAZ | CIP | IMP | MER | GEN | AK | AM/SB |
| <i>Pseudomonas aeruginosa</i> | | | | | | | | | |
| Phase 1 ^a | 10 | ... | 0.0 | 60.0 | 0.0 | 0.0 | 70.0 | 0.0 | ... |
| Phase 2 ^b | 9 | ... | 25.0 | 0.0 ^a | 11.1 | 11.1 | 44.4 | 0.0 | ... |
| <i>Acinetobacter</i> species | | | | | | | | | |
| Phase 1 ^a | 13 | 100.0 | 100.0 | 100.0 | 0.0 | 33.3 | 50.0 | 91.7 | 91.7 |
| Phase 2 ^b | 3 ^c | 100.0 | 100.0 | 100.0 | 0.0 | 0.0 | 33.3 | 100.0 | 100.0 |
| <i>Enterobacter</i> species | | | | | | | | | |
| Phase 1 ^a | 8 | 0.0 | 100.0 | 100.0 | 0.0 | 0.0 | 71.4 | 85.7 | 100.0 |
| Phase 2 ^b | 5 | 50.0 | 75.0 | 75.0 | 0.0 | 0.0 | 71.4 | 0.0 ^a | 75.0 |
| <i>Escherichia coli</i> | | | | | | | | | |
| Phase 1 ^a | 9 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 11.1 | 0.0 | 88.9 |
| Phase 2 ^b | 10 | 20.0 | 20.0 | 10.0 | 0.0 | 0.0 | 10.0 | 0.0 | 50.0 |
| <i>Klebsiella</i> species | | | | | | | | | |
| Phase 1 ^a | 4 | 66.7 | 33.3 | 50.0 | 0.0 | 0.0 | 50.0 | 0.0 | 75.0 |
| Phase 2 ^b | 18 ^d | 44.4 | 44.4 | 27.8 | 0.0 | 0.0 | 44.4 | 11.1 | 50.0 |
| <i>Proteus</i> species | | | | | | | | | |
| Phase 1 ^a | 1 | 100.0 | 100.0 | ... | 0.0 | 0.0 | ... | 0.0 | 100.0 |
| Phase 2 ^b | 6 | 50.0 | 16.7 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 33.3 |
| <i>Stenotrophomonas maltophilia</i> | | | | | | | | | |
| Phase 1 ^a | 2 | ... | ... | 0.0 | ... | ... | ... | ... | ... |
| Phase 2 ^b | 4 | ... | ... | 0.0 | ... | ... | ... | ... | ... |
| <i>Citrobacter</i> | | | | | | | | | |
| Phase 1 ^a | 1 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| Phase 2 ^b | 2 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| <i>Flavobacterium</i> | | | | | | | | | |
| Phase 1 ^a | 0 | | | | | | | | |
| Phase 2 ^b | 1 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 100.0 |
| <i>Haemophilus influenzae</i> | | | | | | | | | |
| Phase 1 ^a | 0 | | | | | | | | |
| Phase 2 ^b | 3 | 0.0 | ... | ... | ... | ... | ... | ... | 0.0 |
| <i>Serratia marcescens</i> | | | | | | | | | |
| Phase 1 ^a | 0 | | | | | | | | |
| Phase 2 ^b | 3 | 33.3 | 33.3 | 33.3 | 0.0 | 0.0 | 33.3 | 0.0 | 33.3 |
| Total | | | | | | | | | |
| Phase 1 ^a | 48 | 68.8 | 45.8 | 62.5 ^e | 4.2 | 8.3 | 45.8 | 25.0 | 87.5 |
| Phase 2 ^b | 64 | 39.1 | 37.5 | 20.3 | 9.4 | 9.4 | 29.7 | 7.8 | 54.7 |

Note: CRO: ceftriaxone, CAZ: ceftazidime, CIP: ciprofloxacin, IMP: imipenem, MER: meropenem, GEN: gentamicin, AK: amikacin, AM/SB: ampicillin-sulbactam, ...: not applicable.

^a Without restriction, 1 May 2004 to 28 February 2005.

^b With restriction, 1 May 2005 to 28 February 2006.

^c $P < 0.01$, phase 2 versus phase 1.

^d $P < 0.05$, phase 2 versus phase 1.

^e $P = 0.0557$, phase 2 versus phase 1.

44) demonstrated that, in the absence of cross-colonization, the use of oxyimino-cephalosporins fundamentally selected enterobacteria with class C β -lactamases on their chromosomes. In this sense, reduction in the use of ceftriaxone decreases selection pressure in *Enterobacter* spp. mutants that constitutionally express these enzymes. On the other hand, the increase in isolation of *Klebsiella* spp. and *Proteus* spp. could be related to increased cross-colonization.

The Kaplan–Maier method fails to significantly document that the day-by-day

colonization or infection by r-GNB occurs at a later point in time in phase 2. The Kaplan–Maier curve validates that, on day 10 of admission to the intensive care unit in both phases, 80.0% of the patients were free of r-GNB colonization or infection. This percentage holds up to day 20 in phase 2, while on the same day in phase 1 it drops to 52.5%.

The importance of this work lies in the fact that the impact is achieved with the use of a simple ceftriaxone and ciprofloxacin restriction policy, substituting them with similar spectrum mol-

ecules such as ampicillin-sulbactam or aminoglycosides. Most research, after restricting ceftriaxone or ciprofloxacin, tends to replace them with cefepime, antipseudomonal penicillins, piperacillin-tazobactam, or even a carbapenem group (20–21, 45). However, the use of these types of molecules can have a negative impact on the change in susceptibility profile, as described by Rahal et al. (45), who achieved restricted use of ceftazidime through greater use of a carbapenem group, which in turn determined an increased resistance of *P. aeruginosa* to imipenem. The advantage of using ampicillin-sulbactam lies in its wide availability in different intensive care units, its cost-effectiveness, and the fact that its spectrum is similar to that of ceftriaxone but it has less impact on the bacterial ecology and a narrower spectrum than the alternatives used by other authors. Physicians, for example, when diagnosing a severe community-acquired pneumonia during phase 2, indicated ampicillin-sulbactam rather than ceftriaxone, which is supported by a Latin American consensus (46). Ampicillin-sulbactam was also used instead of ceftriaxone when treating other infections in which participation of non-multiresistant GNB was suspected. This treatment did not expose patients to a higher risk, as evidenced by the similar length of hospital stays and mortality in both phases.

Unlike Du et al. (21), an impact on mortality during the postrestriction period was not achieved. This result can be explained in various ways. First, the sample is smaller. Second, the patient population is more severely ill, as shown by an Acute Physiology and Chronic Health Evaluation II (APACHE II) score of 21 versus 12.5 and a greater need for mechanical ventilation (80.0% versus 53.4%).

Some limitations of this study must be acknowledged. The sample size was small, according to the type of intensive care unit observed, but the statistical analysis was performed with specific tests for small samples. Another limitation is that colonizations were analyzed without having previously adopted a universal culture policy, which means the colonizations came from cultures of patients suspected of having an infection. Nevertheless, it should be emphasized that there was no intervention

TABLE 5. Infections and colonizations with resistant Gram-negative bacilli in patients without and with restriction of antimicrobials, intensive care unit, Hospital Policial, Montevideo, Uruguay, 2004–2006

| | Phase 1 ^a | | Phase 2 ^b | | P value |
|---|----------------------|------|----------------------|------|----------|
| | No. | % | No. | % | |
| Patients with r-GNB colonizations | 14 | ... | 4 | ... | 0.0006 |
| Colonizations with r-GNB | 19 | ... | 4 | ... | < 0.0001 |
| r-GNB isolates of colonizations | 22 | ... | 5 | ... | 0.0001 |
| <i>Pseudomonas aeruginosa</i> | 5 | 22.7 | 1 | 20.0 | 0.22 |
| <i>Acinetobacter baumannii</i> | 11 | 50.0 | 1 | 20.0 | 0.0066 |
| <i>Stenotrophomonas maltophilia</i> | 1 | 4.5 | 0 | ... | 1.00 |
| Enterobacteriaceae | 5 | 22.7 | 3 | 60.0 | 1.00 |
| Patients with r-GNB nosocomial infections | 12 | ... | 16 | ... | 0.54 |
| Infections with r-GNB | 12 | ... | 20 | ... | 0.65 |
| r-GNB, number of isolates of infections | 14 | ... | 22 | ... | 0.61 |
| <i>Pseudomonas aeruginosa</i> | 3 | 21.4 | 3 | 13.6 | 0.41 |
| <i>Acinetobacter baumannii</i> | 2 | 14.3 | 2 | 9.1 | 0.60 |
| <i>Stenotrophomonas maltophilia</i> | 1 | 7.1 | 4 | 18.2 | 0.65 |
| Enterobacteriaceae | 8 | 57.1 | 13 | 59.1 | 0.78 |

Note: r-GNB: resistant Gram-negative bacilli, ...: not applicable.

^a Without restriction, 1 May 2004 to 28 February 2005.

^b With restriction, 1 May 2005 to 28 2006.

during phase 2 from which to obtain further samples.

Conclusions

The restriction of ceftriaxone and ciprofloxacin reduces *Acinetobacter* spp. colonization and improves the susceptibility profile of *P. aeruginosa* by means of a simple protocol that uses low-cost antibiotics such as ampicillin-sulbactam that are widely available in intensive care units.

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RESUMEN

Restricción del uso de ceftriaxona y ciprofloxacino en una unidad de cuidados intensivos: menor incidencia de *Acinetobacter* spp. y mayor sensibilidad de *Pseudomonas aeruginosa*

Objetivo. Determinar si la restricción del uso de ceftriaxona y ciprofloxacino reduce significativamente la colonización y la infección por bacilos gramnegativos resistentes.

Métodos. Se efectuó un estudio prospectivo de dos fases (diseño antes/después de la intervención) en una unidad de cuidados intensivos en dos períodos sucesivos entre los años 2004 y 2006. Durante la fase 1, no hubo ninguna restricción de antibióticos. Durante la fase 2, se restringió el uso de ceftriaxona y ciprofloxacino.

Resultados. Se evaluó prospectivamente a 200 pacientes en total. En la fase 2, el uso de ceftriaxona se redujo en 93,6% ($P = 0,0001$) y el de ciprofloxacino en 65,1% ($P = 0,041$), lo que se acompañó de un aumento de 113,8% en el uso de ampicilina/sulbactam ($P = 0,002$). Durante la fase 1, se aislaron 48 bacilos gramnegativos (37 resistentes [77,1%] y 11 no resistentes [22,9%]), en comparación con un total de 64 durante la fase 2 (27 resistentes [42,2%] y 37 no resistentes [57,8%]) ($P = 0,0002$). Se aisló *Acinetobacter* spp. 13 veces durante la fase 1 y 3 veces en la fase 2 ($P = 0,0018$). La sensibilidad de *Pseudomonas aeruginosa* al ciprofloxacino aumentó de 40,0% en la fase 1 a 100,0% en la fase 2 ($P = 0,0108$).

Conclusiones. La restricción del uso de ceftriaxona y ciprofloxacino redujo la colonización por *Acinetobacter* spp. y mejoró el perfil de sensibilidad de *P. aeruginosa*.

Palabras clave

Resistencia a múltiples medicamentos; *Acinetobacter baumannii*; *Pseudomonas aeruginosa*; agentes antibacterianos; Uruguay.