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Original Article

Analysis of antimicrobial consumption and healthcare-associated infections after an antimicrobial stewardship program implantation in a neonatal intensive care in Rio de Janeiro

Análise do consumo de antimicrobianos e infecções relacionadas à assistência à saúde após implantação de um programa de gestão de antimicrobianos em unidade de tratamento intensivo neonatal do Rio de Janeiro

ABSTRACT

Background and objectives: The Antimicrobial stewardship programs (ASPs) could contribute to optimize antimicrobial use within neonatal intensive care units (NICUs). The aim of this study was to measure the antimicrobial consumption, including carbapenems and healthcare-associated infections (HAI), specifically infections caused by carbapenem-resistant Gram-negative bacteria (CR-GNB) in neonates, after the implementation of an ASP. **Methods:** A prospective descriptive study of antimicrobial and carbapenem consumption; and healthcare-associated rate in an NICU, during a one-year follow-up. The consumption was measured in days of therapy/1000 patients-days (DOT/1000PD). **Results:** In September 2017, the ASP was implemented, with the following core components: antibiotic audit and feedback, restriction of target antimicrobials, measure of antimicrobial consumption and improvement of results from microbiologic laboratory. Between September 2017 and September 2018, we admitted 308 patients, totalizing 2223 patient-days. The median of total antimicrobial consumption was 1580 DOT/1000PD (range from 1180.7 to 2336.6/month) and carbapenems was 12 DOT/1000PD (range from 0 to 162.3/month). The carbapenem consumption was reduced between April and September of 2018 (p value=0.07) when we compared the first six months of the study. Eight HAI were detected, corresponding to the density of incidence of 3.6/1000 patient-days. No HAI due to CR-GNB was reported. **Conclusion:** The total antimicrobial consumption did not increase during all the year after the ASP implantation. Moreover, there was a significant reduction of carbapenem consumption. Carbapenem-resistant bacteria were not found in NICU, causing HAI.

Key-words: Cross infection, antimicrobial stewardship, newborn, newborn intensive care units (NICU)

INTRODUCTION

Healthcare-associated infections (HAI) caused by multi-drug resistant bacteria are important causes of increased morbidity and mortality in neonates admitted to neonatal intensive care units (NICU). The main risk factors commonly described in the literature for the acquisition of HAI in neonates include: prolonged hospitalization period, low birth weight, use of antibiotics, use of mechanical ventilation, previous surgeries and colonization by multiresistant microorganisms, use of central venous catheters and other invasive procedures. Effective

infection control programs are able to considerably reduce rates of HAI in neonates, including those caused by multi-resistant microorganisms.¹⁻⁴

Carbapenem-resistant Gram-negative bacteria (CR-GNB) are considered by the World Health Organization (WHO) to be critical in relation to the need to control the spread and research of new effective antimicrobials. The main measures described for prevention and control of these bacteria include: hand hygiene, contact precaution, patient isolation, environmental cleanliness, crop surveillance and monitoring, auditing and feedback of infection prevention and control interventions.^{5,6}

In addition to measures to prevent and control colonization and infection by these agents, antimicrobial management programs (AMPs) have contributed to improve the measurement of consumption of broad-spectrum antibiotics such as carbapenems, and evaluation of the correct indication, avoiding indiscriminate use in hospitals.^{7,8}

CR-GNB has been reported in NICUs causing outbreaks, colonization and infections. A 5-year retrospective study conducted in an NICU found that after an average of seven days of detection of colonization of patients by carbapenem-resistant *Klebsiella pneumoniae*, 18.1% developed infections by this bacterium. *Acinetobacter baumannii* was reported as the second most frequent infectious agent causing late neonatal sepsis in a teaching NICU. *Bacterial resistance* to meropenem and imipenem was 73% and 100%, respectively.⁹⁻¹²

Due to the scarcity of data on the results of an AMP in neonates, mainly in relation to the consumption of antimicrobials and the emerging importance of CR-GNB causing severe and potentially fatal infections in this population, the authors conducted a prospective study with the objective of measuring the consumption of antimicrobials, including carbapenems, in neonates after the implantation of an AMP and the rates of HAI, specifically those caused by CR-GNB in a NICU.

METHODS

Type of study and scenario:

The authors performed a prospective descriptive study of HAI occurred in a NICU during 1 year of follow-up. The study was performed at Hospital Prontobaby, an exclusively pediatric, private unit located in the city of Rio de Janeiro, Brazil. The NICU had 10 beds at the time of the study and received patients coming from the hospital emergency room or referred

from other services, with clinical or surgical diseases. The hospital did not have its own associated maternity clinic.

Inclusion and exclusion criteria:

All neonates (up to 28 days) admitted to the NICU and who remained in the unit for more than 24 hours between September 2017 and September 2018 were included. Neonates admitted for more than 24 hours, but who were transferred to other units where the follow-up was not possible, were excluded.

Definition of infection related to health care/surveillance:

The authors used the diagnostic criteria for HAI in neonatology established by the National Health Surveillance Agency (ANVISA – *Agência Nacional de Vigilância Sanitária*) in 2017. Patient surveillance was performed daily from Monday to Friday by a doctor and nurse from the hospital infection control committee (HICC). With "*in loco*" verification of all patients and daily discussion with the assistant doctors in the sector.¹³

Infection control measures and antimicrobial management program:

HICC has been operating uninterruptedly in the hospital since 2005 and systematically carries out the following measures for HAI prevention and control: periodic audits of hand hygiene adherence; admission surveillance for critical unit patients with research through nasal and rectal swabs of methicillin-resistant *S. aureus*, extended spectrum beta-lactamase producing enterobacteria, vancomycin-resistant enterococcus and carbapenem-resistant *Acinetobacter spp*; monthly measurement of consumption of soap and alcoholic preparations in hospital; formal and in-service training for health professionals; adoption of contact precautions for patients identified as having multi-resistant microorganisms until discharge; cohort of patients when an outbreak of colonization/infection by the same multi-resistant microorganism is identified; periodic reports of the unit's resistance profile; monthly meetings with the HICC consulting members; updating of treatment guides for major infectious syndromes every two years; and formal antimicrobial guidance for treatment of HAI, according to the site of infection.

Antimicrobial Management Program:

The AMP was initially implemented in September 2017 for all wards of the hospital, including the intensive care units, and was effective in January 2018. The following

components of the AMP were established: antibiotic audit and feedback, target antimicrobial restriction, monthly antimicrobial consumption assessments by measuring antimicrobial use density, days of therapy/1000 patients-day (DOT/1000PD), and faster dissemination of culture results by introducing a semi-automated method by the microbiology laboratory. Furthermore, discussions on clinical cases of patients using antimicrobials were intensified, focusing mainly on the antimicrobial dose, duration, and possibility of de-escalation. Thirteen antimicrobials were listed as restricted use, released only after formal request in a standardized electronic form and evaluated by the HICC infectologist. All carbapenems available for use in the unit were considered restricted (ertapenem, imipenem and meropenem).

Antimicrobial consumption measure:

The individual consumption of each systemic antimicrobial (antibiotics, antivirals and antifungals), administered orally or intravenously, was measured monthly at the NICU through the use density of antimicrobials.

The measure density of use of antimicrobials (DOT/1000 PD) consists of dividing the number of days a patient received a given antimicrobial by the number of patient-days in the sector in which the patient was hospitalized. The individual sum (in DOT/1000PD) of each antimicrobial consumed generated in turn the measurement of the total consumption of antimicrobials.

Analysis variables:

The following variables were analyzed: weight at admission, use of invasive devices (central venous catheters, invasive ventilation and bladder catheter), HAI site, infectious agent identified causing HAI, resistance of infectious agent causing HAI, HAI rate (measured in percentage and incidence density per 1000PD), consumption of all antimicrobials in the sector and carbapenems (in DOT/1000PD).

Data Analysis:

The data were collected in the patient's records and from the HICC surveillance records. A descriptive analysis of the data was performed using the Excel program. The authors used the nonparametric Mann-Whitney test to compare continuous variables using medians. Data analysis was performed using the Stata 13.0 program (Stata Corp LP). A p value of <0.05 was considered statistically significant.

Ethical aspects:

The project was submitted to and approved by the Fluminense Federal University's ethics committee through opinion 2,279,190 of September 15, 2017 and registered on the Brazil platform under number CAAE: 69902317.3.0000.5243

RESULTS

Between September 2017 and September 2018, 308 patients were admitted, totaling 2223 PD. The quantitative of patients, patient-days and invasive devices-days according to the weight intervals at admission are shown in Table 1.

Table 1- Total of patients and patient-days admitted on NICU, according to the weigh (Prontobaby, September 2017 to September 2018)

Indicators	<750 g	751-1000g	1001-1500g	1501-2500g	>2500g	Total
Nº of patients	0	2	3	43	260	308
Pacients-days	0	4	20	440	1,759	2,223
Central venous catheter-days	0	0	11	131	533	675
Mechanical ventilator-days	0	0	0	120	120	240
Urinary cateter-days	0	0	0	68	134	202

Eight HAI were diagnosed, corresponding to a rate of 2.6% of HAI and an incidence density (ID) of 3.6 per 1000 PD. HAI were not verified in the weight intervals of patients <750g, 751-1000g and 1001-1500g. The overall incidence density of HAI was 4.5 per 1000 PD in patients with weight intervals of 1500-2500g and 3.4 per 1000 PD in patients greater than 2500g.

The sites of infection described were: two primary laboratory confirmed bloodstream infections, two clinical sepsis, a bladder catheter-associated urinary infection, one peritonitis, one conjunctivitis, and a non-bladder catheter-associated urinary infection.

Infections associated with invasive devices, according to weight ranges, are shown in Table 2.

Table 2- Density of incidence of HAI related to invasive devices in patients admitted in the NICU (Prontobaby, September 2017 to September 2018)

Weight	CVC	MV	UC
	N° of infections/device-days (DI*)	N° of infections/device-days (DI)	N° of infections/device-days (DI)
<750g	0/0	0/0	0/0
751-1000g	0/0	0/0	0/0
1000-1500g	0/11	0/0	0/0
1501-2500g	1/131 (7.6)	0/120 (0)	0/68 (0)
>2500g	1/533 (1.9)	0/120 (0)	1/134 (7.5)
Total	2/675 (3.0)	0/240 (0)	1/120 (5.0)

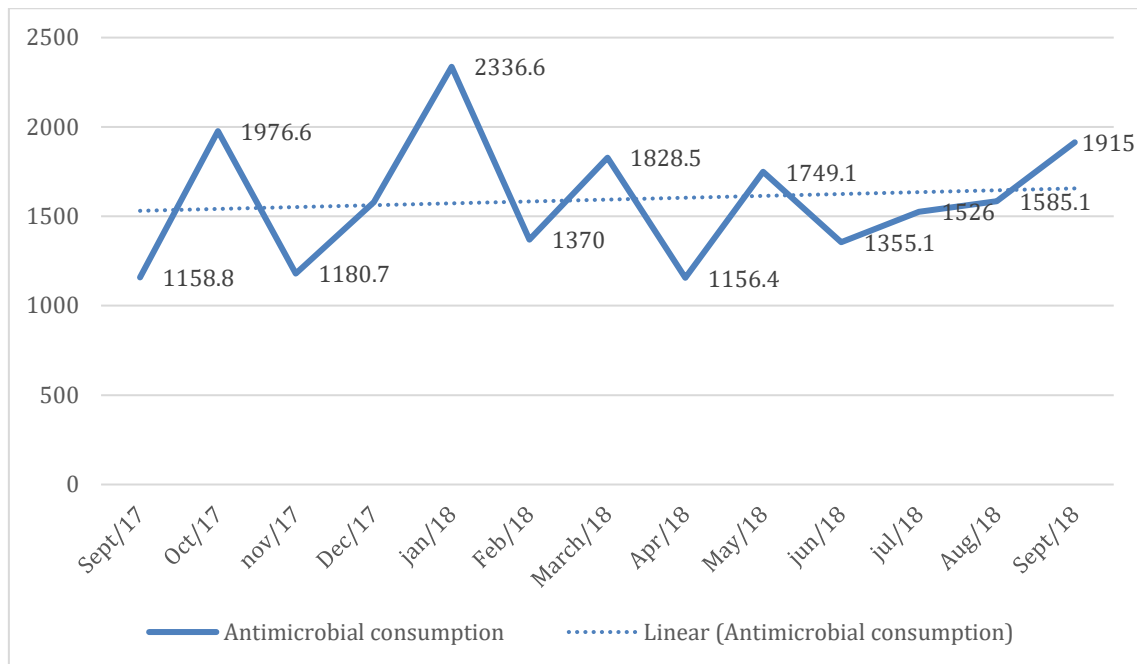
CVC- Central venous catheter, MV- Mechanical ventilator, UC- Urinary cateter DI*- Density of incidence per 1000 patient-days

Infectious agents were isolated in five of the eight infections (62.5%), of which three (60%) were GNB (all *K. pneumoniae*, of which two were producers of extended spectrum beta-lactamase and one multi-sensitive) and two fungal infections by *Candida sp.* CR-GNB infections were not recorded in the period.

The median of the DOT/1000 PD was 1580 (range 1180.7 to 2336.6/month) and the carbapenems of 12 (range 0 to 163.2/month). This group of antibiotics represented 3% of the total consumption of all antimicrobials. The median consumption of carbapenems (in DOT/1000PD) between September 2017 and March 2018 was 19 and 0 between April and September 2018 (p value = 0.07).

Graphs 1 and 2 present the consumption of antimicrobials and carbapenems, respectively, during the period of the study in the NICU.

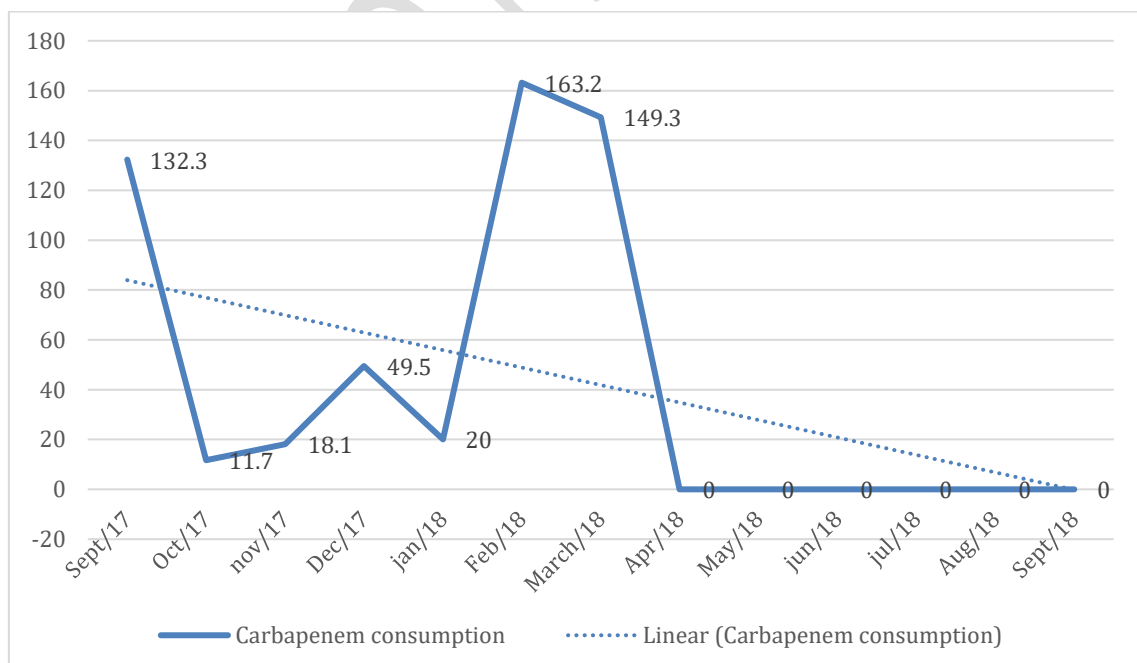
Graph 1- Antimicrobial consumption in NICU (Prontobaby-September 2017 to September 2018)



* values expressed in DOT/1000 patients days

Dotted blue line- Antimicrobial consumption trend, Continuous line- Antimicrobial consumption

Graph 2- Total carbapenem consumption in NICU (Prontobaby-September 2017 to September 2018)



* values expressed in DOT/1000 patients days

Dotted blue line- Antimicrobial consumption trend, Continuous line- Antimicrobial consumption

DISCUSSION

Avoiding HAI, decreasing the consumption of global antimicrobials and broad spectrum antibiotics is a difficult but achievable goal even in settings such as neonatal ICUs, where treatment of severe infections often requires prolonged antibiotic courses and long hospitalizations¹⁴. For example, a study conducted at an NICU in Turkey reported an HAI rate of 8.3% and incidence density of 7.69/1000 PD. Much higher values were reported in a study in Egypt, with an infection rate of 21.4% and an incidence density of 13.8/1000 PD. Incidence densities/1000 invasive device-days of primary bloodstream infections and pneumonias found (3.0 and 0, respectively) were lower when compared to those reported in a long historical series of HAI in a Brazilian ICU (17.3 and 3.2, respectively). Some factors may explain the low rates found in this study, such as: small number of newborns admitted with low birth weight, absence of maternity associated with the unit and long performance in the unit of the same infection control team.¹⁵⁻¹⁷

Analysis of the infection profile at the unit demonstrated the absence of CR-GNB causing HAI, which we can attribute to a sustained and uninterrupted infection control policy adopted by the institution, surveillance at the entrance of patients colonized by multi-resistant microorganisms and the local epidemiological profile itself. The small number of infectious agents causing HAI did not allow inference of effects of AMP on the non-occurrence of infections attributed to CR-GNB during the analysis period. Despite our positive results, several institutions in different countries report significant rates of CR-GNB causing colonization/infection or outbreaks in neonates. *A. baumannii* resistant to multiple drugs and *K. pneumoniae* producers of carbapenemases were found in 20 out of 68 cases of laboratory confirmed sepsis in a Jordanian NICU and were statistically associated with high mortality when compared to other non-resistant bacteria.^{10,18-20}

The control of antimicrobial consumption, through the implementation of AMP, is a necessary measure to be used in NICU in order to preserve the sensitivity of state-of-the-art antibiotics, refine indications when strictly necessary and reduce long periods of treatment. In the authors' analysis they verified stability in the total consumption of all antimicrobials, with no tendency to increase along the follow-up. When the carbapenem group was specifically analyzed, there was a trend of statistically significant reduction in consumption throughout the year of follow-up, demonstrating the possibility of a reduction in consumption, even in an ICU. Previous studies conducted in neonatal ICUs demonstrated the feasibility of reducing both total consumption and consumption of broad spectrum antibiotics. Additionally, restrictive antibiotic use policies have not impacted on increased patient mortality, as this issue is a pertinent concern of care teams, especially for critically ill newborns who often require broad spectrum treatment regimens.^{8,14,21-23}

The study has some limitations, the first of which was carried out in a single center. However, the authors believe that similar positive results can be achieved in institutions with similar patient profiles and with effective and continuous infection control actions. Secondly, because the unit basically treats newborns larger than 1500g, few extremely underweight neonates were included in the analysis, which may have impacted the low number of infections found, since this subcategory is known to be a risk factor for acquisition of HAI and late neonatal sepsis. Because AMPs are still a new approach in national healthcare institutions, the study evaluated a relatively short period of time and, in this work, it was not possible to measure the long-term results of AMP on the sustained reduction in antimicrobial consumption and impact on bacterial resistance.^{24,25}

The authors concluded that the total consumption of antimicrobials at the NICU did not increase during the first year of implementation of an AMP. However, there was a significant reduction in carbapenem consumption in the last six months of the study. No HAI by CR-GNB were verified in the study period.

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Contributions:

ARAS: Planning, revision and final approval of the article;

ATA, IVA, JVMO, LTS: Conception, data collecting, revision and final approval of the article;

All the authors approved the final version to be published and are responsible for all aspects , including assurance about precision and integrity.

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