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ORIGINAL ARTICLE

Patterns of antimicrobial consumption in neonatal and pediatric intensive care units in Germany and Brazil

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Abstract

Antibiotic consumption (AC) is a key component of antimicrobial stewardship programs to recognize local patterns of antibiotic use. Our aim was to measure AC in neonatal units, including neonatal (NICU)/paediatric (PICU) intensive care units in different countries. We conducted a multicenter, retrospective, cohort study in three NICUs, one neonatal ward, and three PICUs with a total of 84 beds. Global and individual AC in days of therapy (DOT) and DOT per 1000 patient-days were assessed. During the study period, 2567 patients were admitted, corresponding to 4961 patient-days in neonatal units and 9243 patient-days in PICUs. Multidrug-resistant Gram-negative bacteria and methicillin-resistant *Staphylococcus aureus* were more frequent in Brazil than in Germany. Average AC was 386.5 and 1335.5 DOT/1000PD in German and Brazilian neonatal units, respectively. Aminopenicillins plus 3rd generation cephalosporins were the most commonly prescribed antibiotics in German neonatal units, while aminopenicillins plus aminoglycosides were the class most commonly used in Brazilian NICU. Average AC was 888.1 and 1440.7 DOT/1000PD in German and Brazilian PICUs, respectively. Antipseudomonal penicillins were most commonly used in the German PICU, and glycopeptides were the most frequently prescribed in Brazilian PICUs. Carbapenems represented 2.3–14% of total DOTs in German neonatal units and 4% in the Brazilian NICU and 13.0% in the German PICU and 6–12.2% in Brazilian PICUs. We concluded that different patterns of most commonly prescribed antibiotics were observed in neonatal units and PICUs in these two countries, probably related to different local patterns of antibiotic resistance, with a higher antibiotic consumption in Brazilian study units.

Keywords Antimicrobial consumption · Paediatric intensive care unit · Neonatal intensive care unit

Introduction

One of the most important components of antimicrobial stewardship programs (ASP) in children is monitoring of antimicrobial use in all units of healthcare institutions, including neonatal (NICU) and pediatric (PICU) intensive care units [1–3]. Knowledge about antimicrobial consumption in healthcare institutions helps to identify patterns of overutilization or misuse and contributes to define priorities of antimicrobial restriction according to local resistance patterns [1–4].

Days of therapy (DOT) and length of therapy (LOT) are two measures most common reported for evaluate antimicrobial consumption in paediatrics [2, 3, 5–10]. The first parameter is a direct measure of the number of days of therapy of any antimicrobial, regardless of dose or frequency. Each individual antibiotic received per day represents 1 DOT. For example, if a patient receives three antimicrobials for 3 days, the

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DOT would be reported as 9 [3, 5]. LOT represents total days of antimicrobial use, irrespective of the number of individual antimicrobials prescribed [4].

Considering that antimicrobial resistance is a global health problem caused primarily by antibiotic overuse, neonatal, and pediatric intensive care units represent settings where broad-spectrum antibiotic consumption is higher than on general wards; efforts to promote rational use of antibiotics are urgently needed, and accurate knowledge about antibiotic consumption in these respective units is necessary [11]. Few articles described patterns of antibiotic consumption in paediatrics as a component of local ASP, with positive results about antibiotic consumption reduction, even in critical care units [1, 9, 12].

To better understand the antimicrobial use in critical care units, the aim of this study was to measure antibiotic consumption in neonatal units, including NICUs and PICUs of two different countries (Germany and Brazil) using DOT and DOT/1000 patient-days (DOT/1000PD).

Methods

Study design and setting

We conducted a multicenter, retrospective, cohort study in three academic hospitals in Germany and in Brazil.

Institutions and intensive care units classification:

1. The Dr. von Hauner Children's Hospital (Munich, Germany) is a 119-bed pediatric tertiary care center, with 3 ICUs and one neonatal ward, at the city campus: 2 NICUs, being one classified as level IV (named in the paper as NICU 1) and other one classified as level III (named as NICU 2); and one neonatal ward. NICU 2 patients are admitted from delivery suites and NICU 1 admitted clinical and surgical patients referred from other obstetrics and perinatology services. NICU 1 capacity is 13 beds; NICU 2, 10 beds and neonatal ward, 8 beds. The PICU (named in the paper as PICU 1) has 14 beds and is a reference service for the Munich metropolitan area, receiving patients with clinical and surgical pathologies from its own wards and referred from other services.
2. Prontobaby Hospital da Criança (Rio de Janeiro, Brazil) is a 135-bed private hospital including one level IV NICU (10-bed capacity, named as NICU 3) and one PICU (15-bed capacity, named as PICU 2). Both units receive clinical and surgical patients referred from its own wards and from other services. This hospital hosts medical students from Universidade Federal Fluminense for practical classes.
3. Centro Pediátrico da Lagoa (Rio de Janeiro, Brazil) is a 39-bed private hospital including a 15-bed PICU (named as PICU 3), with the same profile as Prontobaby PICU patients.

The study was conducted from January 1, 2018, to December 31, 2018, in Brazil and between May 1 and August 31, 2016, in Germany. These different periods of analysis represented the period after full implementation of antimicrobial stewardship programs in these units.

The inclusion criteria were neonatal ward, NICU or PICU admission, and antimicrobial use for more than 24 h. Children that used topic and inhaled antibiotics were excluded.

Definition of metrics

We calculated DOT for each antibiotic used (oral or intravenous) and DOT/1000 PD in the intensive care units during the stay of children in each unit, using the definition by Polk et al. [5].

Antibiotic resistance data

Data from hospitals regarding antibiotic resistance for whole samples isolated during the period of study were assessed for the following bacteria: *Escherichia coli*, *Klebsiella pneumoniae*, *and other* Enterobacteriacea (resistance to 3rd generation cephalosporins and carbapenems), *Pseudomonas aeruginosa* and *Acinetobacter baumannii* (resistance to carbapenems), *Staphylococcus aureus* and coagulase-negative staphylococcus (resistance to methicillin). Data about resistance samples were obtained from the respective microbiology laboratory of the participant institutions using Siegel and Magiorakos criteria for definition of resistance [13, 14].

Antimicrobial stewardship programs

Both institutions adopted an antimicrobial stewardship program before collection of antibiotic consumption data in their critical care units. Details of the ASP program components in Dr. von Hauner Children's hospital have been previously published [9, 15]. ASP components of Brazilian hospitals included in the study were written guidelines for antimicrobial use, rounds and discussion of cases, antibiotic restriction policy, de-escalation of antibiotic, support of microbiology laboratory, and training of staff.

Antibiotic policy restriction

The following antimicrobials were included in an antimicrobial restriction policy, requiring pre-approval by a pediatric infectious disease specialist:

a) Dr. von Hauner Children's Hospital—aztreonam, ceftaroline, ceftobiprole, ceftolozane/tazobactam,

Table 1 Demographic data of patients that received antibiotics in neonatal and paediatric intensive care units (LMU-Germany, Prontobaby and Centro Pediátrico da Lagoa-Brazil)

Data	Germany units	Brazilian units	P value
Female (%)			
PICUs	40.2	55.6	0.01
Neonatal units	49.3	49.8	ns*
Age-median (range)			
PICUs (in years)	4.4 (0.16–17.2)	1.6 (0.12–18.0)	< 0.001
Neonatal units (in days)	2.0 (0–270)	21.5 (0–120)	< 0.001
Body weight in kg-median (range)			
PICUs	16.7 (2.9–82.0)	14 (3.0–58.0)	< 0.001
Neonatal units	2.8 (0.7–8.3)	3.15 (0.9–6.0)	0.001
Neonatal units patients weight classes (%)			
<750 g	2.2	0	0.12
751–1000 g	2.9	0.8	0.2248
1001–1500 g	5.1	0.8	0.0496
1501–2500 g	36.2	15.7	< 0.001
> 2500 g	53.6	82.7	< 0.001

*_ns_ not significant

ceftazidime/avibactam, chloramphenicol, dalbavancin, fidaxomicin, telavancin, tedizolid.

b) Prontobaby and Centro Pediátrico da Lagoa—amphotericin B lipid formulations, caspofungin, ceftobiprole, colistin (inhaled), daptomycin, ertapenem, imipenem, linezolid, meropenem, micafungin, polymyxin B, teicoplanin, tigecycline, voriconazole.

Data source and statistical analysis

The antibiotics were analysed separately according to classes as described elsewhere [9]. A descriptive analysis was performed using Microsoft Excel. When appropriate, we used chi-square test for categorical variables and Mann–Whitney *U* test for continuous variables.

Results

During the study period, 1805 patients were admitted to Brazilian intensive care units, 762 patients were admitted to LMU care units, corresponding to 1613 and 3348 patient-days admitted in neonatal units and 7956 and 1287 patients-days admitted in PICUs from the units from Brazil and Germany, respectively. Two hundred twenty-five patients (29.5%) received antibiotics in LMU units, being 138 in neonatal units and 87 in PICU and 479 patients (26.2%) received antibiotic in Brazilian units, being 118 in NICU and 361 in PICUs.

Demographic data of patients receiving antibiotics are summarized in Table 1. Bacterial resistance profiles of all samples collected in hospitals during the study period are shown in Table 2.

Demographics of all patient characteristics showed statistically significant differences between both countries, with exception of gender in neonatal units. Relative frequency of patients > 1500 g admitted in NICU where higher in Brazil than in German neonatal units.

Table 2 Resistance profile of hospitals units during the study period (LMU/Germany, Prontobaby, and Centro Pediátrico da Lagoa/Brazil)

Agents	LMU/ Germany	Prontobaby/ Brazil	CPL/ Brazil
Gram-negative bacteria resistance (resistant samples/total samples (%)			
A. baumanni resistant to carbapenem	1/100 (1)	7/7 (100)	5/6 (83.3)
E. coli 3rd generation cephalosporin resistant	245/641 38.2)	27/99 (27.3)	15/27 (55.5)
E. coli carbapenem-intermediate or resistant	0/641 (0)	0/99 (0)	0/29 (0)
K. pneumoniae 3rd generation cephalosporin resistant	108/314 (34.4)	38/89 (42.7)	26/39 (66.7)
K. pneumoniae carbapenem-intermediate or resistant	17/314 (5.4)	7/89 (7.9)	2/39 (5.1)
Other Enterobacteriaceae 3rd generation cephalosporin resistant	100/644 (15.5)	18/47 (38.3)	5/26 (19.2)
Other Enterobacteriaceae-intermediate or resistant to carbapenems	4/644 (0.9)	1/47 (2.1)	6/26 (23.1)
P. aeruginosa carbapenem-resistant	394/962 (41)	4/66 (6.1)	0/9 (0)
Gram-positive bacteria resistance (resistant samples/total samples (%)			
MRSA	171/1117 (15.3)	15/36 (41.2)	4/5 (80)
CoNS oxacillin resistant	147/211 69.7)	41/51 (80.4)	11/17 (64.7)

The largest differences between resistant pathogens were found in *A. baumannii* resistant to carbapenems, *K. pneumoniae* 3rd generation cephalosporin resistant, and MRSA. The resistance was always higher in Brazil compared with the German hospital. On the other hand, carbapenem-resistant *P. aeruginosa* showed high levels of resistance in Germany compared with the Brazilian hospitals.

In Tables 3 and 4, antibiotic consumption in neonatal units and PICUs study units is shown, categorized according to the class of antimicrobial. Average antibiotic consumption was 386.5 and 1335.5 DOT/1000PD in German and Brazilian neonatal units. Antibiotic classes most commonly used in Brazil NICU were a combination of aminopenicillins and aminoglycosides while in two of three neonatal units from Germany the most common combination was aminopenicillins and 3rd generation cephalosporins. In NICU 1 from Germany, the most common classes consumed were antipseudomonal penicillins followed by carbapenems.

Carbapenems represented 14% of total DOT in NICU 1/LMU, 4.2% in NICU 2/LMU, 2.3% in neonatal ward/LMU, and 4% in NICU 3/Brazil.

Average antibiotic consumption was 888.1 and 1440.7 DOT/1000PD in German and Brazilian PICUs, respectively. In both Brazilian PICUs, glycopeptides represented the most commonly consumed antibiotics while antipseudomonal penicillins were the most commonly consumed antibiotics in the German PICU. Carbapenems were among the most commonly used antibiotic classes in all units and represented 13.0% of total DOT in the German PICU, 6% in PICU 2/Brazil, and 12.2% in PICU 3/Brazil.

Discussion

The present study focuses on the description of patterns of antibiotic consumption in neonatal and pediatric intensive care units, using DOT and DOT/1000 PD as unit of measurement. In our casuistic, demographic data of patients and resistance profiles of hospitals were different in neonatal units and in PICUs studied, so, demands of antibiotics were different and comparisons of antimicrobial consumption in both countries should be interpreted with care to avoid misinterpretations. Since there is a lack of data for antibiotic consumption in neonatal and pediatric intensive care units, we here provide data for units with similar profile to ours.

Table 3 Antibiotic consumption in NICUs, according to the class

Antibiotics (examples)	NICU 1/Germany PD = 1062		NICU 2/Germany PD = 1220		Neonatal ward/Germany PD = 1066		NICU 3/Brazil PD = 1613	
	DoT	DoT/1000PD	DoT	DoT/1000PD	DoT	DoT/1000PD	DoT	DoT/1000PD
Aminoglycosides (amikacin, gentamicin)	0	0	0	0	0	0	770	477.3
Carbapenems (meropenem, imipenem)	68	64.0	19	15.6	8	7.5	86	53.3
Cephalosporins								
1st generation (cefalotin, cefazolin, cephalexin)	0	0	0	0	0	0	16	9.9
2nd generation (cefuroxime, cefoxitin)	23	21.7	0	0	0	0	0	0
3rd generation (ceftriaxone, cefotaxime, ceftazidime)	64	60.3	205	168.0	181	169.8	4	2.5
4th generation (cefepime)	0	0	0	0	0	0	40	24.7
Glycopeptides (vancomycin, dalbavancin)	27	25.4	1	0.82	0	0	122	75.6
Macrolides (erythromycin, clarithromycin)	0	0	13	10.7	0	0	224	138.9
Nitroimidazoles (metronidazole)	20	18.8	0	0	0	0	32	19.8
Oxalidinones (linezolid)	0	0	0	0	0	0	5	3.1
Penicillins								
Natural	0	0	0	0	0	0	13	8.1
Beta lactamase resistant (methicillin, oxacillin, dicloxacillin, flucloxacillin)	56	52.7	0	0	0	0	85	52.7
Aminopenicillins (ampicillin, amoxicillin)	48	45.2	199	163.1	165	154.8	639	396.1
Antipseudomonal (piperacillin/tazobactam)	78	73.4	17	13.9	0	0	17	10.5
Other penicillin combinations (amoxicillin/clavulanate, ampicillin/sulbactam)	65	61.2	0	0	0	0	42	26.0
Polymyxins (colistin, polymyxin B)	0	0	0	0	0	0	10	6.2
Quinolones (ciprofloxacin, moxifloxacin, levofloxacin)	37	34.8	0	0	0	0	46	28.5
Total	486	457.6	454	372.1	354	332.1	2151	1335.5

PD Patient-days

As expected, patterns of antimicrobial resistance were different between the two countries. In particular multiresistant Gram-negative (MRGN) bacteria (with exception of carbapenem-resistant *P. aeruginosa*) and methicillin-resistant *S. aureus* were significantly more frequently encountered in Brazilian than in German units. The Dr. von Hauner Children's hospital is a reference centre for patients with cystic fibrosis and probably that is the reason for high levels of carbapenem-resistant *P. aeruginosa* founded in this hospital. Since local bacterial resistance data should be taken into account when choosing empiric antibiotic regimens, the differences described between the units may in part be an explanation for the different amounts and the different spectrum of antibiotics prescribed.

Demographic characteristics of hospitals could explain some differences about patterns of antibiotic prescription in neonatal ward and NICUs. For example, presence of more preterm babies in Germany units, usually with a prolonged length of stay and necessity of second and third-line antibiotic treatment, certainly contributed for these differences. But, the main reason about most consumed antibiotic scheme is attributed to Dr. von Hauner Children's hospital policy for neonatal units which tries to avoid aminoglycosides because of their toxicity, preferring cephalosporins and thus explaining the

Table 4 Antibiotic consumption (in DoT) according to the class in PICUs

Antibiotic class	PICU 1/Germany PD = 1287		PICU 2/Brazil PD = 3612		PICU 3/Brazil PD = 4344	
	DoT	DoT/ 1000PD	DoT	DoT/ 1000PD	DoT	DoT/ 1000PD
Aminoglycosides (amikacin, gentamicin, tobramycin)	17	13.2	392	108.5	622	143.2
Ansamycins (rifampicin)	0	0	11	3	0	0
Carbapenems (meropenem, imipenem)	149	115.8	287	79.5	815	187.6
Cephalosporins						
1st generation (cefalotin, cefazolin, cephalexin)	0	0	114	31.6	50	11.5
2nd generation (cefuroxime, cefoxitin)	143	111.1	30	8.3	100	23
3rdgeneration (ceftriaxone, cefotaxime, ceftazidime)	118	91.7	203	56.2	137	31.5
4th generation (cefepime)	0	0	292	80.8	306	70.4
Dihydrofolate reductase inhibitors and combinations, sulfonamides (sulfamethoxazole, trimethoprim)	96	74.6	34	9.4	174	40.1
Glycopeptides (vancomycin, dalbavancin)-	116	90.1	646	178.8	1143	263.1
Glycylcyclines (tigecycline)	7	5.4	0	0	0	0
Lincosamides (clindamycin)	0	0	180	49.8	228	52.5
Macrolides (erythromycin, clarithromycin, azithromycin)	45	35.0	537	148.6	775	178.4
Nitrofurantoins (nitrofurantoin)	3	2.3	2	0.6	8	1.8
Nitroimidazoles (metronidazole)	49	38.1	67	18.5	97	22.3
Oxalidinones (linezolid)	11	8.5	95	26.3	207	47.7
Penicillins						
Natural	3	2.3	0	0	0	0
Beta lactamase resistant (methicillin, oxacillin, dicloxacillin)	0	0	173	47.9	110	25.3
Aminopenicillins (ampicillin, amoxicillin)	32	24.9	365	101	132	30.4
Antipseudomonal (piperacillin/tazobactam)	176	136.8	526	145.6	497	114.4
Other penicillin combinations (amoxicillin/clavulanate, ampicillin/sulbactam)	56	43.5	565	156.4	516	118.8
Polymixins (colistin, polymyxin B)	24	18.6	12	3.3	203	46.7
Quinolones (ciprofloxacin, moxifloxacin, levofloxacin)	88	68.4	228	63.1	583	134.2
Tetracycline (doxycycline)	10	7.8	0	0	0	0
Total	1143	888.1	4759	1317.6	6703	1543

PD Patient-days

relatively high consumption of this antibiotic class, while a combination of aminopenicillins and aminoglycosides was the first option in Brazilian NICU, following recommendation of local guideline.

Antibiotic consumption in Brazilian NICU (1335.5 DOT/1000 PD) was similar to reports from two NICUs in Saint Petersburg (1425.8 DOT/1000PD), Russia, but in both countries the rate was almost 3 times higher than in the German neonatal units (range 332.1 to 457.6 DOT/1000PD) [16]. Similar patterns of consumption as in German neonatal units were observed by Cantey and colleagues in NICUs in the USA, describing a decline in antibiotic consumption from 343.2 DOT/1000PD to 252.2 DOT/1000PD after implementation of an antimicrobial stewardship intervention [17].

Antibiotic consumption data from PICUs showed also different patterns between Brazil and Germany. The most consumed antibiotic class in the German PICU were antipseudomonal penicillins, while glycopeptides were the antibiotic class most commonly used in Brazilian PICUs. The higher consumption of glycopeptides in Brazilian PICUs could reflect the high rate of MRSA (40.7%) found in bloodstream infections reported to the Brazilian surveillance system and also found in local resistance reports [18]. Previous data from German intensive care units suggested a resistant rate of 9.1% in invasive *S. aureus* isolates, as reported by the European Center for Disease Control and Prevention surveillance system [19]; and combined with local MRSA resistant rate of 15.8%, support the relatively low consumption of glycopeptides.

Again, with regards to PICUs antibiotic consumptions, different patterns were observed in Germany and Brazil. Koopmans and colleagues evaluated antibiotic consumption in a single PICU in South Africa between May and November of 2015 and found a rate of 1323 DOT/1000 PD, similar to Brazilian PICUs but also much higher than the German PICUs. In their study, 3rd generation cephalosporins were the most commonly used antibiotic class [10]. Ding et al. described the use of antibiotics and the effectiveness of an intervention in a PICU at a single center in Beijing, China and reported a change in the most commonly prescribed antibiotic class in the post-intervention period (2nd generation cephalosporins) compared with the pre-intervention period (3rd generation cephalosporins) [20].

This study has a few obvious limitations. First, we used retrospective data from different years in two countries, though both of them represented periods after full ASP implementation. Although important differences were found regarding antibiotic consumption between the institutions, other aspects (such as financial and human resources, antibiotics available and quality of antibiotic prescriptions) were not assessed in this study. Aspects mentioned above as well as the severity of illness at admission are essential to better understand when broad-spectrum antibiotics are really necessary to save lives and when unnecessary treatment courses are prescribed, increasing costs, and ultimately leading to antibiotic resistance.

We conclude that different patterns with regards to most frequently used antibiotics were observed in NICUs: aminopenicillins plus 3rd generation cephalosporins in German units versus aminopenicillins plus aminoglycosides in Brazil. In PICUs, antipseudomonal penicillins showed a predominant pattern in Germany whereas glycopeptides were most frequently prescribed in Brazil.

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Compliance with ethical standards

Conflict of interest The authors declared that they have no conflict of interest.

Ethical approval Formal ethical approval was obtained from the research ethics committee of the LMU Munich (ID 404-14) and national Brazilian Committee (CAEE 69902317.3.0000.5243, 15/09/2017)

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