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Original Article

Colonization by multidrug-resistant microorganisms of hospitalized newborns and their mothers in the neonatal unit context

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Abstract

Introduction: The mother plays a fundamental role in the constitution and regulation of her child's healthy microbiota, however, preterm newborns are separated from their mothers soon after birth and transferred to Neonatal Intensive Care Units, being exposed the constant risk for the development of multidrug-resistant microorganisms' infections. The aim of this study was to explore the multidrug-resistant microorganism colonization of hospitalized babies and their mothers in the neonatal unit context.

Methodology: A prospective case study conducted with hospitalized babies and their mothers in the Neonatal Unit at a university hospital. The sample was composed of 433 binomials (mother-child). Colonization culture samples were taken at the moment of the baby's discharge, via two swabs in the oral, nasal, axillary, inguinal, and rectal regions.

Results: The colonization incidence among the binomials, 30 (6.9%) were both colonized by multi-resistant microorganisms. Mothers of colonized babies (24.4%) demonstrated a higher chance of colonization in comparison to mothers of non-colonized babies (11.9%) ($p = 0.002$). Relationships were drawn between baby colonization and prematurity, extremely low birth weight, and non-exclusive maternal breastfeeding ($p<0.05$). ESBL-producing Gram-negative microorganisms were more frequent in the cultures of the binomials, with 35.9% of the babies colonized with *Klebsiella* spp. ESBL and 42.0% of the mothers with *Escherichia coli* ESBL. Furthermore, 50% of the binomials were colonized with *E. coli* ESBL.

Conclusion: The prematurity, extremely low birth weight, and non-exclusive breastfeeding at hospital discharge were associated with baby colonization by multidrug-resistant microorganism. Furthermore, mothers of colonized children presented higher chances of colonization.

Key words: Premature; neonatal intensive care; mother-child relations; multiple antibacterial drug resistance.

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Introduction

The affective bond between mother-child, created from gestation, contributes to the physical, emotional and psychological development of the baby [1]. Therefore, the mother plays a fundamental role in the constitution and regulation of her child's healthy microbiota, considering that the first microorganisms are acquired intrauterine, and later through the vaginal canal and maternal skin [2-6].

In contrast, preterm newborns are separated from their mothers soon after birth and transferred to Neonatal Intensive Care Units (NICU) [7,8]. In the NICU, the extensive use of antimicrobials contributes to the selection of multidrug-resistant (MDR) [9]. These microorganisms in turn infect and colonize babies, in addition to contaminating the environment [7,10].

MDR threaten human health due to the limitation of antimicrobials available for the treatment of infections, which can therefore become incurable and fatal [11].

In the other hand, studies show that skin-to-skin contact between the mother and baby presents innumerable benefits, such as reduction in infections and length of hospitalization, as well as contributing to the weight gain of very low birth weight babies and a reduction in mortality [12].

Considering this scenario, there are many gaps in the knowledge related to the role of the mother in the transmission chain of MDR, thus, present study aims to explore the process of colonization by MDR of babies hospitalized and of their mothers in the context of a neonatal unit.

Methodology

A prospective case study with a quantitative approach was carried out with babies admitted to the neonatal unit of a university hospital and their respective mothers, between January 2014 and February 2018.

The study population were 1395 babies, of which 665 were excluded because they did not stay in the neonatal unit for more than 72 hours, because they were transferred, died, or their mothers did not agree to participate in the study, 433 binomials was eligible for the study sample. Mothers were included in the study according to the inclusion or exclusion criteria of their respective baby, and in the case of multiple births, the mothers were counted more than once according to the number of babies (Figure 1).

The study hospital is reference in high complexity cases and its maternity unit provides care for high risk pregnancies. It is composed of a NICU with 10 beds and a Neonatal Intermediate Care Unit with 20 beds. In both units, mothers can remain full-time and are encouraged to perform skin-to-skin contact and assist in the basic care of their baby when this one is in a stable state of health.

The neonatal variables were: gender, prematurity, birth weight, invasive procedures, antimicrobial therapy, type of breastfeeding (exclusive breast milk, use of infant or mixed formula), and hospitalization period. The maternal variables were age and type of delivery.

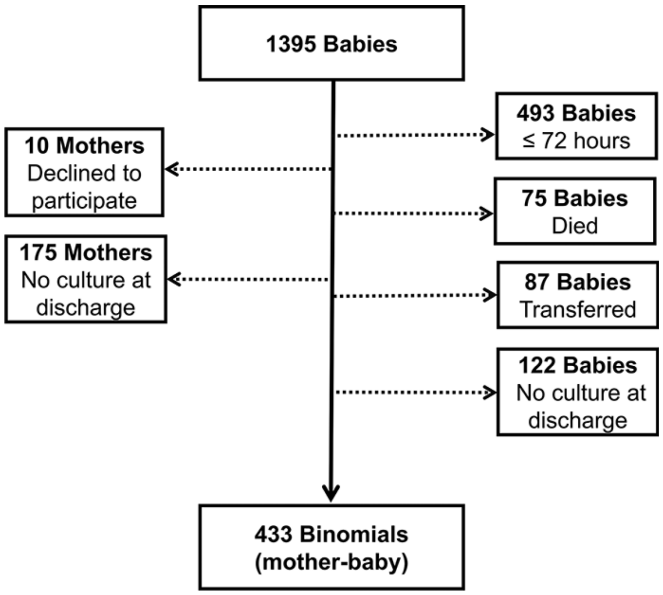
The colonization cultures of the baby and its mother were collected at baby's discharge from hospital, after the mother had signed the informed consent form. The binomial was denominated colonized when mother and baby was colonized. Cultures were collected through two swabs [using the COPAN Transystem Stuart collection device (COPAN Diagnostic, Italy)], one of the oral, nasal, axillary, and inguinal regions, and the other in the rectal region. The swabs were sent to the microbiology laboratory and processed within 72 hours.

The susceptibility profile of the bacteria to the antimicrobial agents was analyzed by the disc-diffusion technique as recommended by the Clinical and Laboratory Standard Institute [13-17] using antimicrobial discs recommended for each identified bacterial species.

Is defined as MDR the bacteria non-susceptibility to at least one agent in three or more antimicrobial categories, considered: *Enterobacteria, Acinetobacter baumannii*, and *Pseudomonas aeruginosa* resistant to 3rd or 4th generation cephalosporin or monobactam (Extended Spectrum β-lactamase – ESBL) and the carbapenems (carbapenem resistant) – CR); methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin resistant Enterococci (VRE) [18]. After performing the antimicrobial susceptibility test, the bacteria were stored in 30% TSB-glycerol at -20°C.

The data were tabulated in Microsoft Office Excel 97 - 2013® and analyzed in the statistical program Statistical Package for the Social Sciences (SPSS) version 20.0. The results of the continuous variables are described as mean, standard deviation (SD) or median. Categorical variables were analyzed using the Pearson chi-square test. To investigate the magnitude of association between the variables, a binary logistic regression was performed to obtain the odds ratio (OR) and 95% confidence interval (95% CI). The variables that presented p-value <0.200 were submitted to

Figure 1. Flowchart of the study sample design. Paraná, Brazil, 2014 - 2018.



multivariate logistic regression analysis, adjusted for confounding variables related to gestational factors, such as gestational age and birth weight. The level of significance adopted was 5%.

This study was approved by the Ethics Committee on Research involving Human Subjects of Universidade Estadual de Londrina (15415413.4.0000.5231).

Results

The study sample consisted of 433 mother-child binomials. The incidence of colonization of the babies was 28.4% and of the mothers 15.5% (Figure 2).

Figure 2. Diagram of the study sample and incidence of colonization at hospital discharge of babies and their mothers. Paraná, Brazil, 2014 - 2018.

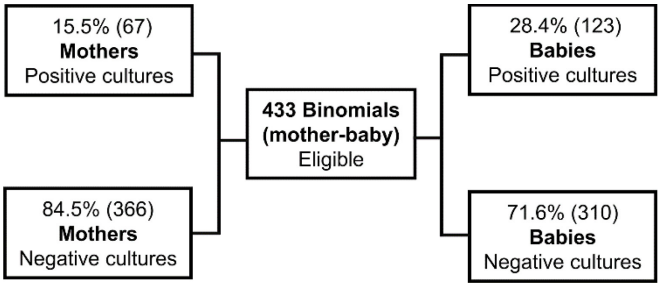


Table 1. Association of perinatal and clinical variables of babies (n = 433) with colonization by multidrug-resistant microorganisms at discharge from the neonatal unit. Paraná, Brazil, 2014 – 2018.

Neonatal variables	Babies		OR	CI 95%		p-value
	Colonized 123 (28.4%) n (%)	Non-colonized 310 (71.6%) n (%)				
Type of birth						
Normal	30 (24.4)	86 (27.7)	1.00			
Cesarean	93 (75.6)	224 (72.3)	1.19	0.74	1.93	0.478
Gestational age						
< 30 weeks	45 (36.6)	70 (22.6)	2.06	1.09	3.90	0.026
31-34 weeks	51 (41.5)	134 (43.2)	1.22	0.67	2.24	0.518
35-36 weeks	8 (6.5)	45 (14.5)	0.57	0.23	1.42	0.228
≥ 37 weeks *	19 (15.4)	61 (19.7)	1.00			
Corrected age at discharge						
34 to 37 weeks	62 (50.4)	155 (50.0)	1.02	0.67	1.54	0.939
> 37 weeks	61 (49.6)	155 (50.0)	1.00			
Birth weight						
< 1000g	25 (20.3)	26 (8.4)	2.85	1.41	5.77	0.004
1000-1499g	25 (20.3)	62 (20.0)	1.19	0.63	2.27	0.588
1500-1999g	34 (27.6)	98 (31.6)	1.03	0.57	1.85	0.928
2000-2499g	13 (10.6)	47 (15.2)	0.82	0.38	1.75	0.606
> 2500g*	26 (21.1)	77 (24.8)	1.00			
Discharge weight						
≥ 2,500g	38 (30.9)	88 (28.4)	0.83	0.51	1.37	0.472
2,000-2,499g	27 (22.0)	110 (35.5)	0.47	0.28	0.80	0.005
< 2,000g	58 (47.2)	112 (36.1)	1.00			
Maternal breastfeeding at discharge						
Exclusive	67 (54.5)	203 (65.5)	1.00			
Not exclusive	56 (45.5)	107 (34.5)	1.58	1.04	2.43	0.034
Hospitalization period						
≤ 10 days	18 (14.3)	86 (27.7)	1.00			
> 10 days	105 (85.4)	224 (72.3)	2.24	1.28	3.92	0.005
Invasive procedures						
Yes	83 (67.5)	183 (59.0)	1.44	0.93	2.23	0.104
No	40 (32.5)	127 (41.0)	1.00			
Number of procedures						
None	40 (32.5)	127 (41.0)	1.00			
1	26 (21.1)	79 (25.5)	1.05	0.59	1.84	0.879
2 or more	57 (46.3)	104 (33.5)	1.74	1.08	2.81	0.024

OR: odds ratio; CI: confidence interval.

The sample characterization showed that most of the babies were male (53.3%), premature (81.5%), born by cesarean (73.2%), had low birth weight (76.2%), underwent an invasive procedure (61.4%), used antimicrobials (85.0%) during the hospitalization period (median 21 days) and at discharge were exclusively breastfeeding (62.3%). Regarding the mothers, the mean age was 27 years (14 ± 43), 16.2% were adolescent mothers (14-19 years), 67.4% were young adults (20 to 34 years) and 16.4% were mothers with an advanced age for gestation (≥ 35 years).

Whereas the infant's perinatal variables, their colonization by MDR was associated to prematurity, extremely low birth weight and not exclusively breastfeeding at hospital discharge (Table 1).

The variables that influenced the chances of colonization of the baby demonstrated no association with the colonization of the mothers, or the other perinatal variables and intrinsic factors of the babies (p<0,05), except for the corrected age, considering that the mothers of children classified as premature at discharge (19.4%) were more likely to be colonized by MDR when compared to mothers of full-term children at discharge (11.6%) (OR = 1.83 / CI = 1.07-3.13 / p = 0.027).

Regarding the clinical variables related to hospitalization, exposure to more than one invasive procedure was higher among the babies colonized by MDR (OR = 1.74 / CI = 1.08-2.81 / p = 0.024) and was not associated to colonization of the mother. Among the colonized babies, 57 were exposed to more than one invasive procedure, totaling 179, of which the most frequent was central venous catheter (41.3%), followed by mechanical pulmonary ventilation (33.0%), urinary catheter 20.7%) and surgery (5.0%).

In relation to the hospitalization period, remaining hospitalized for more than 10 days increased the odds of the baby being colonized by MDR (OR = 2.28 / CI = 1.12-4.96 / p = 0.024), independently of gestational factors (gestational age and birth weight), and did not influence maternal colonization (p<0,05).

Regarding the antimicrobial therapy of the baby, in the multivariate analysis, exposure to the drug ≥ 15 days (OR = 2.18 / CI = 1.35-3.53) was associated to the baby's colonization (Table 2).

Among the binomials studied, 6.9% (30/433) were both colonized by MDR, and of these, 36.7% (11/30) were colonized by the same microbial species exhibiting the same antimicrobial resistance profile. Most colonized babies, 75.6% (93/123), had non-colonized mothers, while more than half of the colonized mothers, 55.2% (37/67), had non-colonized children; 56.1% (243/433) baby or mother were not colonized (Figure 3).

Table 2. Association of neonatal antimicrobial therapy with colonization of the baby and their mother (n = 433) by multidrug-resistant microorganisms at discharge from the neonatal unit. Paraná, Brazil, 2014 – 2018.

Antimicrobial therapy	Babies					Mothers				
	Colonized 123 (28.4%)	Non-colonized 310 (71.6%)	OR (CI 95%)	p-value	p-value*	Colonized 123 (28.4%)	Non-colonized 310 (71.6%)	OR (CI 95%)	p-value	p-value*
Yes	111 (90.2)	257 (82.9)	1.91 (0.98-3.71)	0.057	0.177	63 (94.0)	305 (83.3)	3.15 (1.10-8.98)	0.032	0.070
No	12 (9.8)	53 (17.1)	1.00			4 (6.0)	61 (16.7)	1.00		
Number of classes										
Did not use antimicrobial	12 (9.8)	55 (17.7)	1.00			4 (6.0)	63 (17.2)	1.00		
1 class	02 (1.6)	09 (2.9)	1.02 (0.19-5.33)	0.983	0.876	3 (4.5)	8 (2.2)	5.91 (1.11-31.31)	0.037	0.050
2 classes	68 (55.3)	179 (57.7)	1.74 (0.88-3.45)	0.112	0.168	39 (58.2)	208 (56.8)	2.95 (1.02-8.58)		0.071
≥ 3 classes	41 (33.3)	67 (21.6)	2.81 (1.34-5.85)	0.006	0.051	21 (31.3)	87 (23.8)	3.80 (1.24 -11.62)		0.073
Period of use										
< 15 days	50 (40.7)	193 (62.3)				33 (49.3)	210 (57.4)	1,00		
≥ 15 days	73 (59.3)	117 (37.7)	2.41 (1.57-3.69)	< 0.001	0.001	34 (50.7)	156 (42.6)	1.39 (0.82-2.34)	0.219	
Pen, Gen*** and other classes**										
Did not use antimicrobial	12 (9.8)	55 (17.7)	1.00			0 (-)	67 (15.8)			
Used Pen** and Gen***	36 (29.3)	103 (33.2)	1.60 (0.77-3.33)	0.206	0.276	3 (37.5)	136 (32.0)			
Used Pen**, Gen*** and others	10 (8.1)	29 (9.4)	1.58 (0.61-4.09)	0.346	0.482	1 (12.5)	38 (8.9)			
Other classes	65 (52.8)	123 (39.7)	2.42 (1.21-4.84)	0.012	0.061	4 (50.0)	184 (43.3)			

OR: odds ratio; CI: confidence interval; *: Model adjusted for gestational age and birth weight (gestational factors); Pen**: penicillin; Gen***: gentamicin.

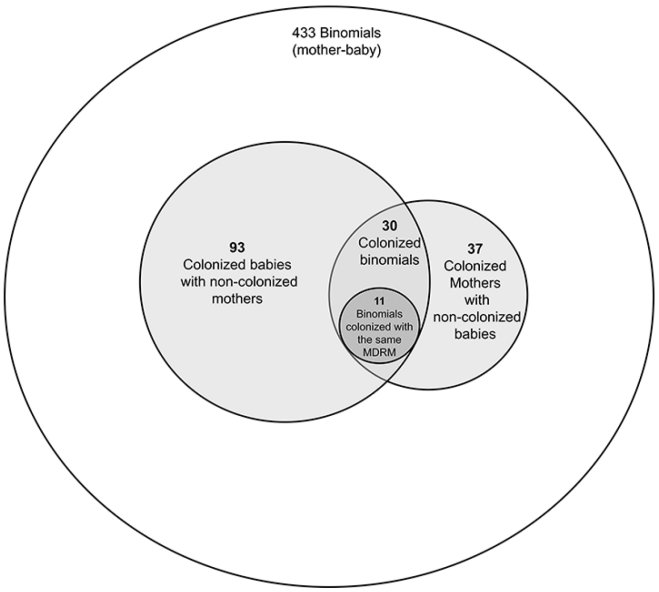
Mothers of babies colonized by MDR (24.4%) presented a greater chance of colonization when compared to mothers of non-colonized babies (OR = 2.38 / CI = 1.39-4.07 / p = 0.002).

A total of 841 microbiological cultures were performed of the binomials. Of these, 433 (51.5%) were of the babies and 408 (48.5%) of their mothers. The number of cultures of the mothers was lower than that of the babies due to the pairing of mothers of twins (23 mothers of 48 twin babies).

Regarding MDR present in microbiological cultures, colonization by more than one microbial species was observed in 16.3% (n = 20) of babies, of which up to three microbial species were isolated in 2.4% (n = 3); and 11.3% of the mothers were colonized with two MDR. *Klebsiella* spp. ESBL was more frequent among the babies and *Escherichia coli* ESBL among the mothers. Furthermore, 16.4% (n = 11) of the mothers presented the same MDR as their respective children, with *E. coli* ESBL being the most frequent microorganism among the binomials (Table 3).

Regarding the antimicrobial resistance phenotype, ESBL-producing Gram-negative bacilli were the most frequent in colonization of both mother and babies, as well as in the mother-baby binomial.

Figure 3. Venn diagram illustrating colonization by multidrug-resistant microorganisms between mother-baby binomials (n = 433) from a neonatal unit. Paraná, Brazil, 2014 – 2018.



Discussion

Few studies on the process of colonization by MDRs of babies hospitalized with their mothers in the context of a NICU have been described in the literature. In this sense, our study showed that being a mother of a MDR colonized baby increased the chances of maternal colonization by MDR. In previous study carried out in a hospital in Germany, identified higher incidence of colonization by MDR among children of mothers colonized by MDR in prenatal care [19]. Although the results are distinct between these two studies, both evidenced that there is a relationship of colonization by MDR between mother and baby binomials.

Table 3. Frequency of multidrug-resistant microorganisms isolated from colonization cultures at discharge of the baby, the mother, and the binomial in the context of a neonatal unit (*n*=226). Paraná, Brazil, 2014 – 2018.

Multidrug-resistant microorganisms	Baby (n = 123)	Mother (n = 62)	Binomial (n = 11)
	Nº (%)	Nº (%)	Nº (%)
Gram-negative			
Klebsiella spp. ESBL	52 (35.9)	4 (5.8)	2 (16.7)
Serratia marcescens ESBL	39 (26.9)	5 (7.2)	3 (25.0)
Escherichia coli ESBL	19 (13.1)	29 (42.0)	6 (50.0)
Enterobacter spp. ESBL	17 (11.7)	7 (10.1)	1 (8.3)
Citrobacter freundii ESBL	4 (2.8)	2 (2.9)	0 (0)
Acinetobacter spp. CR	1 (0.7)	6 (8.7)	0 (0)
Enterobacter spp. CR	1 (0.7)	0 (0)	0 (0)
Pseudomonas aeruginosa ESBL	1 (0.7)	0 (0)	0 (0)
Escherichia coli CR	0 (0)	2 (2.9)	0 (0)
Klebsiella spp. CR	0 (0)	2 (2.9)	0 (0)
Pseudomonas spp.CR	0 (0)	4 (5.8)	0 (0)
Gram-positive			
Staphylococcus aureus MRSA	10 (6.9)	6 (8.7)	0 (0)
Enterococcus spp. VRE	1 (0.7)	2 (2.9)	0 (0)
TOTAL	145 (100)	69 (100)	12 (100)

CR: Carbapenem resistant; ESBL: Extended Spectrum Beta-Lactamases; VRE: *Enterococcus* spp. vancomycin-resistant; MRSA: *Staphylococcus aureus* resistant to methicillin/oxacillin.

Prematurity and extreme low birth weight are frequent in the population of babies hospitalized in intensive care [20]. These variables were associated with infant colonization by MDR, as reported in a prospective cohort study conducted in NICU [21] and our study corroborated this relationship, and in addition it also showed that these variables are associated with the colonization of the mother-child binomial.

In contrast to the neonatal colonization by MDR, exclusive breastfeeding favors the formation of a healthy intestinal microbiota [22], and in this sense, the current study showed that non-exclusive breastfeeding was associated to colonization by MDR of the baby.

Another factor associated with colonization by MDR is the baby's exposure to the NICU environment [7]. In this context, studies in neonatal units evidenced that the hospitalization period was considered an risk factor for colonization of the baby by MDR [21,23]. Corroborating with this evidence, in the present study babies hospitalized for more than 10 days were more likely to be colonized by MDR, as well as the binomial, regardless of gestational factors (gestational age and birth weight). However, the NICU of this research was not investigated for environmental contamination and its relationship to the colonization by MDR, which should be a topic to future research.

In addition, in the intensive care setting, the use of invasive procedures is frequent considering the severity of the patients and is related to neonatal hospital infections [20,24]. In addition to infections, a randomized study conducted with babies in an NICU reported that colonization by MDR was also related to the use of a central venous catheter (CVC) [25]. CVC was the most frequent procedure among babies in the current study, which showed an increased chance of colonization by MDR among babies exposed to these procedures, as well as colonization of babies undergoing more than two invasive procedures.

Antimicrobial agents are the most prescribed therapeutic group in Neonatal Intensive Care Units [26] and their overuse can contribute to microbial resistance selection [27]. Corroborating these findings, our study showed that antimicrobial therapy was associated to increased chances of colonization by babies and the binomial when used for a period of more than 15 days.

Colonization by Gram-negative bacteria predominated in the binomial sample. In the neonatal epidemiological scenario, the incidence of enterobacteria has been increasing, especially *K. pneumoniae* ESBL and *E. coli* ESBL [21]. This trend was also endorsed by the present study, as most frequent MDR among the babies was *Klebsiella* spp. ESBL.

The pattern of bacterial colonization with this profile of antimicrobial resistance extended to the mothers, as well as to the mother-child binomial, which showed a predominance of *E. coli* ESBL in the current study. In this study, it was not possible to identify the route of MDR transmission, since the time of collection of the colonization culture of both, mother and child, occurred concomitantly at hospital discharge, which is a limitation of this study.

Conclusion

Among the perinatal variables, prematurity, extremely low birth weight, and non-exclusive breastfeeding at hospital discharge were associated with baby colonization by MDR. Furthermore, mothers of colonized children presented higher chances of colonization by MDR. *Klebsiella* spp. ESBL was more frequent among the babies and *E. coli* ESBL among the mothers.

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