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EARLY SKIN-TO-SKIN CONTACT: PROTECTION AGAINST COLONIZATION BY MULTIDRUG-RESISTANT BACTERIA IN PRETERM NEWBORNS?

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INTRODUCTION

Preterm Newborns (PTNB) constitute a unique population that is especially vulnerable to microorganisms (Valentine *et al.* , 2018) . These have peculiar characteristics that predispose them to healthcare-associated infections (HAIs), such as fragility of skin and mucosal barriers and a poor innate and adaptive immune *status* (Bokulich *et al.* , 2013) , with the need for long-term life support. period of hospitalization (Pereira *et al.* , 2016) , invasive procedures (Hartz *et al.* , 2015) , use of parenteral nutrition (Pereira *et al.* , 2016) and prolonged broad-spectrum antimicrobial therapy (Hartz *et al.* , 2015; Clock *et al.* , 2017; Valentine *et al.* , 2018) . Thus, when affected by infections, PTNBs tend to evolve more severely than older children or adults (Anvisa, 2017) .

Due to the extensive use of antimicrobials in neonatal intensive care, selective pressure in these sectors poses a greater risk for infections of multidrug-resistant etiology (Clock *et al.* , 2017) .

Microbial resistance challenges the treatment of infections and results in irreparable damage to human health worldwide, making the situation not only a public health problem but also a global security issue (Center for Disease Control and Prevention, 2019) .

Extended -*spectrum beta* - lactamase -producing Enterobacteriaceae *beta-lactamase - ESBL*) and the *Staphylococcus* methicillin resistant *aureus* (MRSA) stand out as the main hospital pathogens involved in neonatal colonization and infection (Oliveira *et al.* , 2019) . Among enterobacteria , there is a predominance of *Klebsiella pneumoniae* and ESBL positive *Escherichia coli* (Giuffre *et al.* , 2016; Clock *et al.* , 2017; Baier *et al.* , 2019; Oliveira *et al.* , 2019; Sakai *et al.* , 2020) . ESBL-producing bacteria show co-resistance to many classes of antimicrobials, which

increases severity, makes treatment difficult and predisposes to outbreaks in neonatal units (Folgori *et al.* , 2018) .

Contrary to the high investments in high technology and the development of new antimicrobial drugs, Kangaroo Care (CC) has been presented as a therapeutic intervention with an excellent cost-benefit ratio for reducing the morbidity and mortality of PTNB (Chan *et al.* , 2016; Conde-Agudelo and Diaz-Rossello, 2016; Brazil. Ministry of Health, 2017) .

The CC is formed by three pillars. The main component of the CC is the skin-to-skin contact between the mother/father and the newborn (NB), this should be started as soon as the NB presents clinical stability and should last as long as the mother and baby find pleasant and sufficient. , always under adequate care support (Conde-Agudelo and Diaz-Rossello, 2016; Brasil. Ministério Da Saúde, 2017) . The CC is also composed of the promotion of breastfeeding and early discharge with adequate follow-up (Chan *et al.* , 2016; Conde-Agudelo and Diaz-Rossello, 2016; Brasil. Ministério Da Saúde, 2017) .

Although there are numerous studies regarding the benefits of CC (Ludington-Hoe *et al.* , 2006; Lawn *et al.* , 2010; Mori *et al.* , 2010; Chidambaram *et al.* , 2014; Conde-Agudelo and Diaz-Rossello, 2016 ; Mekonnen *et al.* , 2019) , there are few studies on the association of skin-to-skin contact with PTNB colonization (Hendricks-Munoz *et al.* , 2015; Lamy Filho *et al.* , 2015) especially on the ideal start, frequency and duration of skin-to-skin contact needed to cause the desired effects (Casper *et al.* , 2018; Jones and Santamaria, 2018; Joshi *et al.* , 2018) .

Given the scarcity of follow-up studies to determine the timing and intensity of skin-to-skin contact necessary to bring about its benefits, this study aimed to verify the association of skin-to-skin contact with the colonization of the PTNB by multidrug-resistant (MR) bacteria and to investigate the factors associated with carrying out this care, by monitoring the microbiota of the PTNB mother binomial.

METHODS

STUDY DESIGN

This is a longitudinal, prospective study, carried out in the Neonatal Intensive Care Units (UTN) and Neonatal Intermediate Care Units (NICU) of a university hospital in southern Brazil, with a census sample over a period of thirteen months, starting in August 2018, which aimed to study all binomials, according to the inclusion criteria, hospitalized during the study period.

The maternity ward of the study hospital is a reference for high-risk pregnancies. It has a UTN with 10 beds and an ICU with 14 beds. This hospital is part of the Baby Friendly Hospital Initiative and is accredited in the Kangaroo Care strategy, therefore, it encourages all mothers to perform CC according to the baby's clinical stability.

INCLUSION AND EXCLUSION CRITERIA

PTNB with birth weight less than or equal to 2500 grams (LBW) hospitalized at the study institution and their respective mothers were included, upon acceptance of participation in the research and signature of the free and informed consent form by the same. PTNBs who were hospitalized for less than 7 days were excluded.

The study population consisted of 207 PTNB and their respective mothers (n=207). In the case of multiple pregnancies, the mother was considered more than once according to the number of her children (Figure 1).

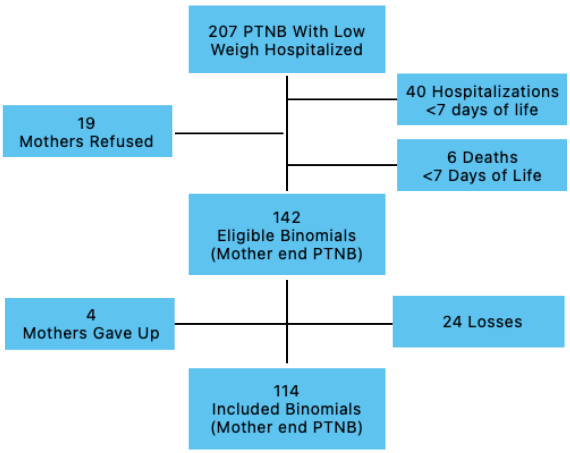

FIGURE 1. Flowchart of the study sample of preterm and low birth weight newborns admitted to neonatal units, Brazil, 2018-2019.

Caption: PTNB - Preterm newborns.

VARIABLES STUDIED

The neonatal variables studied were: date of birth, gestational age, birth weight, occurrence of infection, use and duration of antimicrobials, invasive procedures, skin-to-skin contact, age of onset and frequency of skin-to-skin contact, type of breastfeeding, period of hospitalization and outcome (discharge, transfer or death). The time of exposure to skin-to-skin contact between mother and newborn was recorded daily. The group that performed skin-to-skin contact was divided according to the baby's lifetime at the time of the first skin-to-skin contact, considered early onset, in the first 7 days of life, and late, after 7 days of life.

MICROBIOLOGICAL ANALYSIS

The investigation of the colonization of the PTNB mother binomial was carried out by microbiological monitoring through the collection of *swabs* in *Stuart medium* (COPAN Diagnostic, Italy). A *swab* from the nasal, oral, axillary and inguinal region and another from the inguinal and rectal region. The *swabs* were sent to the laboratory and processed within 24 hours. The first collection was performed within 48 hours of birth, followed by a new collection every seven days, until discharge, transfer or death.

Biological samples were inoculated in selective media for each MR bacteria. Isolation and identification of bacteria were performed according to standardized methodology (Jorgensen *et al.* , 2015) .

The sensitivity of bacteria to antimicrobial agents was analyzed using the disk-diffusion technique as recommended by CLSI (Clinical and Laboratory Standards Institute, 2018) .

MR bacteria were considered: Enterobacteria, *Acinetobacter baumannii* and *Pseudomonas aeruginosa* resistant to 3rd or 4th generation cephalosporins or monobactams (ESBL producers) and carbapenems (carbapenem resistant – CR); MRSA and *Enterococcus spp* resistant to vancomycin (VRE) (Magiorakos *et al.* , 2012) .

STATISTICAL ANALYSIS

Statistical analysis was performed using the *Statistical Package for the Social Sciences* (SPSS) program. In addition to the relative and absolute frequencies of the studied variables, Poisson logistic regression with robust variance was performed to obtain the prevalence ratio (PR) and 95% Confidence Interval (95%CI). Analyzes that showed $p < 0.05$ were considered statistically significant.

CONSIDERATIONS ETHICS

This study was approved by the Ethics Committee for Research involving Human Beings and responds to the Presentation Certificate for Ethical Appreciation (CAAE) number 69249617.7.0000.5231, with opinion number 2.197.608.

RESULTS

Among the 114 PTNB mother binomials studied, the incidence of colonization by MR bacteria in PTNBs was 44% (n=50) (Figure 2). The median time for colonization to occur was 14 days of life. The incidence of maternal colonization by MR bacteria was 34% (n=39).

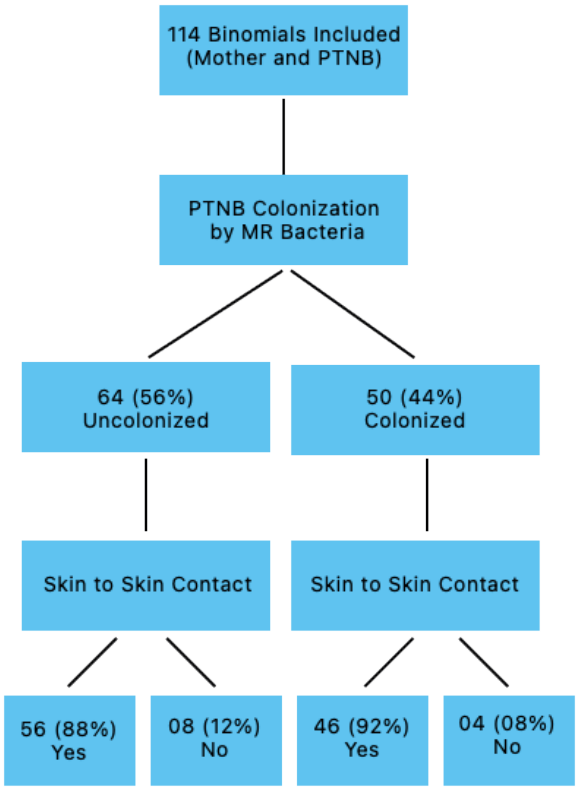

FIGURE 2. Flowchart of the incidence of colonization by multidrug-resistant bacteria and skin-to-skin contact in preterm and low birth weight newborns admitted to neonatal units, Brazil, 2018-2019.

Caption: PTNB - Preterm Newborns; MR – Multi Resistant.

In the sample of neonates, there was a predominance of children younger than 34 weeks of gestational age (71.1%) and birth weight from 1500 to 2499 grams (65.8%) (Table 1).

The predominant hospitalization time was more than 10 days (87.7%), with an average of 36 days of hospitalization. Most PTNBs used antimicrobials (83.3%) for a period of 10 days or more (74.7%) and an average of 31 days of use. More than half of the sample required invasive procedures (58.8%) and central venous catheter (CVC) (53.5%) and approximately one third required an orotracheal tube (OTC) (32.5%) (Table 1). almost all _ it received milk maternal (92.1%).

The group of PTNB colonized by MR bacteria showed a higher prevalence of gestational age less than 34 weeks, birth weight less than 1500 grams, hospitalization period greater than 10 days, higher frequency of infection episodes, use of CVC, late contact initiation skin-to-skin and maternal colonization by MR bacteria (Table 1).

Most PTNB underwent skin-to-skin contact (n=102, 89%), with an average of 10 days of life to initiate skin-to-skin contact (Figure 2). The mean total time of skin-to-skin contact was 14 hours and 12 minutes and the mean total frequency of skin-to-skin contact was 7 times, during the entire hospital stay.

Table 2 evaluates the association of neonatal variables and maternal colonization by MR bacteria with early skin-to-skin contact. We could observe that the three factors that presented the greatest differences in the prevalence ratios were having presented only one episode of infection compared to the group that had 2 or more episodes of infection, use of antimicrobials for a shorter period (less than 10 days) and not having been intubated (Table 2).

DISCUSSION

Little is known about the association of skin-to-skin contact with the colonization of the baby's microbiota, and knowledge about the ideal start period and frequency of skin-to-skin contact in order to bring about its benefits is even rarer. Difficulties in designing a cohort study justify the scarcity of studies on this subject. The only two studies found on skin-to-

Neonatal Variables and Maternal	Colonized (n 50)	Not colonized (n 64)	PR	IC	p -value
Gestational age (weeks)					
< 34	41 (50.6)	40 (49.4)	1.47	1.09-1.96	0.012
34 to 36	09 (27.3)	24 (72.7)	1.00		
Birth weight (grams)					
< 1500	26 (66.7)	13 (33.3)	2.04	1.28-3.27	0.003
1500 to 2499	24 (32.0)	51 (68.0)	1.00		
Hospitalization period (days)					
≤ 10	2 (14.3)	12 (85.7)	1.00		
> 10	48 (48.0)	52 (52.0)	1.65	1.24-2.19	0.001
Infection					
Yes	22 (51.2)	21 (48.8)	1.24	0.87-1.78	0.240
No	28 (39.4)	43 (60.6)	1.00		
Infection episodes					
1	7 (33.3)	14 (66.7)	1.00		
≥ 2	15 (68.2)	7 (31.8)	2.09	1.06-4.15	0.034
Use of antimicrobial					
Yes	42 (44.2)	53 (55.8)	1.04	0.68-1.58	0.864
No	8 (42.1)	11 (57.9)	1.00		
Duration of antimicrobial use (days)					
< 10	10 (41.7)	14 (58.3)	1.00		
≥ 10	32 (45.1)	39 (54.9)	1.06	0.71-1.58	0.767
invasive procedures					
Yes	34 (50.7)	33 (49.3)	1.34	0.97-1.84	0.072
No	16 (34.0)	31 (66.0)	1.00		
Number of invasive procedures					
1	14 (40.0)	21 (60.0)	1.00		
≥ 2	20 (62.5)	12 (37.5)	1.60	0.95-2.69	0.078
orotracheal tube					
Yes	20 (54.1)	17 (45.9)	1.33	0.89-1.97	0.156
No	30 (39.0)	47 (61.0)	1.00		
central venous catheter					
Yes	34 (55.7)	27 (44.3)	1.58	1.13-2.20	0.007
No	16 (30.2)	37 (69.8)	1.00		
skin to skin contact					
Yes	46 (45.1)	56 (54.9)	1.21	0.78-1.88	0.384
No	04 (33.3)	08 (66.7)	1.00		
Age of onset of skin-to-skin contact (days)					
≤ 7	17 (31.5)	37 (68.5)	1.00		
> 7	29 (60.4)	19 (39.6)	1.73	1.67-2.57	0.006
Frequency of skin-to-skin contact (times/week)					
< 2	39 (47.6)	43 (52.4)	1.24	0.85-1.82	0.271
≥ 2	7 (35.0)	13 (65.0)	1.00		
Maternal colonization by multidrug-resistant bacteria					
Yes	23 (59.0)	16 (41.0)	1.17	1.03-1.33	0.015
No	27 (36.0)	48 (64.0)	1.00		

TABLE 1. Prevalence ratio for colonization by multidrug-resistant bacteria in preterm and low birth weight neonates admitted to neonatal units, according to clinical and demographic characteristics of neonates, Brazil, 2018-2019.

PR = prevalece ratio.

CI = 95% confidence interval

Performed test - Poisson logistic regression with robust variance.

Neonatal and Maternal Variables	Home skin-to-skin contact ≤ 7 days (n 54)	Home skin-to-skin contact > 7 days (n 48)	PR	IC	p -value
Gestational age (weeks)					
< 34	36 (45.6)	43 (54.4)	1.0		
34 to 36	18 (78.3)	5 (21.7)	1.23	1.09-1.38	0.001
Birth weight (grams)					
< 1500	10 (25.6)	29 (74.4)	1.00		
1500 to 2499	44 (69.8)	19 (30.2)	1.35	1.19-1.54	< 0.001
Hospitalization period (days)					
≤ 10	11 (91.7)	1 (8.3)	1.29	1.17-1.44	< 0.001
> 10	43 (57.8)	47 (52.2)	1.00		
Infection					
Yes	10 (25.0)	30 (75.0)	1.00		
No	44 (71.0)	18 (29.0)	1.37	1.21-1.55	< 0.001
Infection episodes					
1	9 (47.4)	10 (52.6)	1.41	1.18-1.68	< 0.001
≥ 2	1 (4.8)	20 (95.2)	1.00		
Use of antimicrobial					
Yes	40 (47.1)	45 (52.9)	1.00		
No	14 (82.4)	3 (17.6)	1.24	1.09-1.40	0.001
Duration of antimicrobial use (days)					
< 10	14 (77.8)	4 (22.2)	1.40	1.09-1.79	0.007
≥ 10	26 (38.8)	41 (61.2)	1.00		
invasive procedures					
Yes	23 (36.5)	40 (63.5)	1.00		
No	31 (79.5)	8 (20.5)	1.32	1.18-1.47	< 0.001
Number of invasive procedures					
1	19 (55.9)	15 (44.1)	1.37	1.17-1.59	< 0.001
≥ 2	4 (13.8)	25 (86.2)	1.00		
orotracheal tube					
Yes	7 (20.6)	27 (79.4)	1.00		
No	47 (69.1)	21 (30.9)	1.40	1.23-1.59	< 0.001
central venous catheter					
Yes	20 (34.5)	38 (65.5)	1.00		
No	34 (77.3)	10 (22.7)	1.32	1.18-1.48	< 0.001
Frequency of skin-to-skin contact (times/week)					
< 2	38 (46.3)	44 (53.7)	1.00		
≥ 2	16 (80.0)	4 (20.0)	1.23	1.09-1.39	0.001
Maternal colonization by multidrug-resistant bacteria					
Yes	12 (34.3)	23 (65.7)	1.00		
No	42 (62.7)	25 (37.3)	1.21	1.06-1.39	0.006

TABLE 2. Prevalence ratio for initiation of skin-to-skin contact in preterm and low birth weight neonates admitted to neonatal units, according to clinical and demographic characteristics of neonates, Brazil, 2018-2019.

PR = prevalece ratio.

CI = 95% confidence interval

Performed test - Poisson logistic regression with robust variance.

skin contact as a dose-dependent intervention were carried out with small samples of 26 preterm infants with a gestational age of 24 to 29 incomplete weeks (Casper et al., 2018) and another one from *28* to 35 incomplete weeks (Jones and Santamaria, 2018) . Prospective longitudinal studies demand a long data collection time, high cost, specific population and adequate sampling. This cohort, which involved a multidisciplinary team, integrated clinical and laboratory practice in an attempt to fill in the gaps on this subject and, despite the losses, obtained a significant sample number, considering binomial follow-up (mother PTNB).

The incidence of 44% of PTNB colonized by MR bacteria found in this sample was high when compared to other studies (Giuffre *et al.* , 2016; Baier *et al.* , 2019; Oliveira *et al.* , 2019; Sakai *et al.* , 2020) . However, the sample consisted of low-weight preterm infants hospitalized in intensive care and intermediate care units, linked to a high-risk maternity, while the other authors investigated the neonatal and pediatric population. It is worth noting the occurrence of an outbreak by *Klebsiella* spp in this hospital during the study period.

Other authors have already investigated the association of maternal factors with the colonization of their children (Rautava, 2016; Danino *et al.* , 2018; Valentine *et al.* , 2018; Bulabula *et al.* , 2020; Sakai *et al.* , 2020) , this study corroborates the others and adds the identification of an increase in the prevalence ratio of 17% in neonatal colonization when there is maternal colonization.

More studies must be carried out to unravel the gaps that this study did not address, such as the transmissibility relationship in the colonization between mother and baby through genotypic analysis of the bacteria. The gift study did not set out to carry out this investigation.

Like other authors (Giuffre *et al.* , 2016; Pereira *et al.* , 2016) , it was found in this sample that gestational age and birth weight are associated with colonization by MR bacteria in PTNBs. Gestational age of less than 34 weeks and birth weight of less than 1500 grams increase, respectively, 47% and 104% of the prevalence ratio of colonization by MR bacteria in PTNB.

Studies similar to this one have shown that the length of hospital stay is an independent risk factor for colonization of the NB by MR microorganisms (Giuffre *et al.* , 2016; Sakai *et al.* , 2020) . This study showed that PTNBs colonized by MR bacteria were often hospitalized for longer periods (greater than 10 days). In contrast, previous research has shown that skin-to-skin contact is associated with shorter hospital stays (Hendricks-Munoz *et al.* , 2015) . In addition to the present study corroborating this evidence, as it is a follow-up study, it also allowed us to verify that there was a higher prevalence of shorter hospitalization period (up to 10 days) in PTNBs who started skin-to-skin contact early when compared to those who started skin-to-skin contact late skin.

The only study found on the interference of skin-to-skin contact in the development of the NB's oral microbiota found that skin-to-skin contact was associated with colonization by healthier oral microbiota in PTNBs when compared to the group that did not have skin-to-skin contact. skin and was colonized by oral bacteria that predispose to intestinal dysfunction (Hendricks-Munoz *et al.* , 2015) . Although the present study did not find an association with colonization by MR bacteria among PTNBs simply because they had skin-to-skin contact or not, in the bivariate analysis, late onset of skin-to-skin contact doubled the prevalence of colonization by bacteria RM in the PTNB when compared with the group that made skin-to-skin contact from the first

week of life. This finding was not confirmed in the multivariate analysis, probably due to the determining value of the other factors that aggravated the babies, plus the low frequency and intensity of duration of skin-to-skin contact.

To the best of our knowledge, this is the first study that investigated the median time for colonization, which was 14 days of hospitalization, an innovative result made possible by being a follow-up study with microbiological control.

Although prior colonization may contribute to the development of infection (Folgori *et al.* , 2018) , no significant association was found between colonization and infection in this sample, however, two or more episodes of infection were associated with colonization. A previous study demonstrated that early skin-to-skin contact may be associated with reduced infection (Casper *et al.* , 2018) . In the present study, the group that initiated early skin-to-skin contact had a higher prevalence ratio for non-occurrence of neonatal infection.

The use of antimicrobial therapy alters the NB microbiome through competition mechanisms and is an important risk factor for colonization (Pereira *et al.* , 2016; Clock *et al.* , 2017) . The duration of treatment is also crucial for the development of antimicrobial resistance. Although, a multicenter study with a surveillance rectal *swab* performed in a NICU demonstrated that antimicrobial treatment is associated with colonization by MR Gram-negative bacilli (Clock *et al.* , 2017) , the present study did not show an association between antimicrobial use and duration of antimicrobial therapy with colonization by MR bacteria. However, the group of PTNB who started skin-to-skin contact early showed a lower prevalence of use and duration of antimicrobial therapy (less than 10 days of antimicrobial use).

Another factor that interferes with the constitution of the NB microbiota is breast milk (Hartz *et al.* , 2015; Rautava, 2016; Valentine *et al.* , 2018) . A recent study proved the association of non-exclusive breastfeeding at the time of hospital discharge with colonization by MR microorganisms in the NB (Sakai *et al.* , 2020) . In the current research sample, the vast majority were fed human milk during hospitalization, as the study hospital has a Human Milk Bank, and therefore it was not possible to compare the effect with a group that did not receive human milk.

More than half of the PTNBs studied required some invasive procedure, with the CVC being the most used. Although the study did not find an association between the use of invasive procedures and multidrug-resistant colonization, the group of PTNB colonized by MR bacteria showed a higher prevalence of CVC use. However, the group that initiated early skin-to-skin contact had a lower prevalence of OTC and CVC use, as well as a lower prevalence of the need for invasive procedures, which, when necessary, occurred less frequently.

The study found that most PTNBs (89%) had skin-to-skin contact, however, the average duration and frequency were low, respectively 14 hours and 12 minutes and 7 times during the entire hospitalization period, which had an average duration of 36 days. Regarding the frequency, once a week *versus* twice or more a week, no association was found with the colonization of the PTNB. This result may indicate that the low frequency of skin-to-skin contact performed in the study may be a limiting factor, not only for the study, but also for verifying the benefits of the intensity of skin-to-skin contact. However, the study showed that the group that started skin-to-skin contact early had a higher prevalence of more frequent skin-to-skin contact (twice or more per week).

There are several difficulties in carrying out early, continuous and prolonged skin-to-skin contact, and its implementation together with the other CC components is still not at the desired pace for several reasons: the CC is incorrectly perceived as a practice for PTNB only in low-income countries; many health professionals do not know or do not believe in the benefits of CC, in addition to the lack of skills for its effective implementation; cultural and social norms and routines related to maternal and neonatal practices have made CC a challenge; O maternal role is neglected and CC is not on the agendas and policies of many institutions (Chan *et al.* , 2016; Brasil. Ministério Da Saúde, 2017) . A meta-analysis carried out in 2015 showed that the main barriers in performing the CC are associated with the inadequate environment for carrying out this practice, difficulties in the family's relationship with the health team or between the health team, little help in performing the CC or in other obligations and little knowledge about CC (Seidman *et al.* , 2015) . This study found a higher prevalence of gestational age above 34 weeks and birth weight above 1500 grams in the group that started early skin-to-skin contact, showing that gestational age and birth weight

Although the frequency and minimum duration of skin-to-skin contact are not well established for each specific benefit for the PTNB and their family, the present study proved a lower incidence of colonization by MR bacteria in the PTNB when skin-to-skin contact is initiated in the first week of life of the neonate. Such evidence helps to reinforce how early we should start the practice of this care with a valuable cost-benefit ratio, however, it requires a change in the conception of care with inclusion, involvement and active participation of the family from the beginning of hospitalization. Although the technology in question does not have a high financial cost, given its complexity, it can be recognized as a challenge to be consolidated in practice.

CONCLUSION

The incidence of colonization by MR bacteria in PTNBs and underweight in this study was 44% and the median time of colonization was 14 days of life. The incidence of maternal colonization by MR bacteria was 34%.

Despite the high incidence of colonization by MR bacteria in PTNB and low weight, the study identified that skin-to-skin contact is associated with colonization of PTNB by MR bacteria depending on the time at which it is initiated, with a tendency to also be dependent on the intensity of frequency as early initiation of skin-to-skin contact was associated with more frequent skin-to-skin contact. The PTNB that initiates skin-to-skin contact early has a lower prevalence of colonization by MR bacteria, as well as a lower prevalence of hospitalization period longer than 10 days, episodes of neonatal infection, use of CVC and maternal colonization by MR bacteria, factors that , associated with neonatal colonization by MR bacteria.

IMPLICATIONS FOR PRACTICE

Sensitize the team about the importance of practicing early skin-to-skin contact. Implement criteria for skin-to-skin contact in the first week of life, considering the stability of the newborn as a way to guarantee its safety during practice.

GRADES

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