J Pediatr (Rio J). 2015;91(2):168–174

Jornal de Pediatria
www.jped.com.br

ORIGINAL ARTICLE

Practices related to late-onset sepsis in very low-birth weight preterm infants☆

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Received 6 November 2013; accepted 2 July 2014
Available online 6 November 2014

KEYWORDS
Sepsis;
Newborn;
Premature;
Hand hygiene;
Prevention and control

Abstract
Objective: To understand the practices related to late-onset sepsis (LOS) in the centers of the Brazilian Neonatal Research Network, and to propose strategies to reduce the incidence of LOS.
Methods: This was a cross-sectional descriptive multicenter study approved by the Ethics Committee. Three questionnaires regarding hand hygiene, vascular catheters, and diagnosis/treatment of LOS were sent to the coordinator of each center. The center with the lowest incidence of LOS was compared with the others.
Results: All 16 centers answered the questionnaires. Regarding hand hygiene, 87% use chlorhexidine or 70% alcohol; alcohol gel is used in 100%; 80% use bedside dispensers (50% had one dispenser for every two beds); practical training occurs in 100% and theoretical training in 70% of the centers, and 37% train once a year. Catheters: 94% have a protocol, and 75% have a line insertion team. Diagnosis/treatment: complete blood count and blood culture are used in 100%, PCR in 87%, hematological scores in 75%; oxacillin and aminoglycosides is the empirical therapy in 50% of centers. Characteristics of the center with lowest incidence of LOS: stricter hand hygiene; catheter insertion and maintenance groups; use of blood culture, PCR, and hematological score for diagnosis; empirical therapy with oxacillin and aminoglycoside.
Conclusion: The knowledge of the practices of each center allowed for the identification of aspects to be improved as a strategy to reduce LOS, including: alcohol gel use, hand hygiene training, implementation of catheter teams, and wise use of antibiotic therapy.

☆ Please cite this article as: Bentlin MR, Rugolo LM, Ferrari LS, on behalf of the Brazilian Neonatal Research Network (Rede Brasileira de Pesquisas Neonatais). Practices related to late-onset sepsis in very low-birth weight preterm infants. J Pediatr (Rio J). 2015;91:168–74.

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http://dx.doi.org/10.1016/j.jped.2014.07.004

PALAVRAS-CHAVE
Sepse;
Recém-nascido;
Prematuro;
Higiene das mãos;
Prevenção & controle

Práticas relacionadas à sepse tardia em prematuros de muito baixo peso

Resumo
Objetivo: Conhecer as práticas relacionadas a sepse tardia (ST) nos centros da Rede Brasileira de Pesquisas Neonatais (RBPN) e propor estratégias para redução da ST.
Métodos: Estudo transversal, multicêntrico da RBPN, aprovado pelo CEP. Três questionários sobre higienização das mãos, cateteres vasculares e diagnóstico/tratamento da ST foram elaborados e enviados aos coordenadores de cada centro. O centro com a menor incidência de ST foi comparado aos demais.
Resultados: Todos os 16 centros responderam aos questionários. Quanto a higienização das mãos: 87% utilizam chlorhexidine ou álcool 70%; 100% álcool gel; almotolia/leito em 80% (50% dispõe de 1 dispensador para cada 2 leitos); Treinamento prático ocorre em 100%, teórico em 70% dos centros e 37% treinam 1 vez/ano. Cateteres: 94% tem protocolo para passagem, 75% grupo de inserção. Diagnóstico/tratamento: Hemograma e hemocultura são utilizados em 100% dos centros; PCR em 87%; 75% usam escores hematológicos; oxacilina e aminoglicosídeo são usados como terapia empírica em 50% dos centros. Características do centro com menor incidência de ST: rigorosa higienização das mãos; grupos de inserção e manutenção de cateteres; uso de hemocultura, PCR e escores hematológicos para diagnóstico da ST; tratamento empírico com oxacilina e aminoglicosídeo.
Conclusões: O conhecimento das práticas de cada centro permitiu identificar aspectos a serem otimizados como estratégia para a redução da ST incluindo: uso de álcool gel, treinamento em higienização das mãos, implantação de grupos de cateteres e uso racional de antibióticos.

Introduction

Late-onset sepsis (LOS) is a major cause of neonatal morbidity and mortality. The World Health Organization (WHO) estimates that of the four million neonatal deaths worldwide per year, more than one-third are caused by severe infections, and one-quarter are due to neonatal sepsis/pneumonia.[1,2] In Brazil, the neonatal mortality rate represents 60% of infant mortality, and sepsis is a major cause of neonatal deaths.[3]

Research networks worldwide are dedicated to the study of neonatal sepsis. The National Institute of Child Health and Human Development (NICHD Neonatal Research Network) documented a 21% incidence of LOS confirmed in preterm infants weighing < 1,500 g, ranging from 10-38% among centers.[4] In the Brazilian Neonatal Research Network (BNRN), consisting of 16 reference centers in the maternal-child health area, the LOS study group showed, in the years 2009-2010, 50% incidence of LOS (range 29-72% among centers) in preterm infants weighing < 1,500 g, with 27.5% confirmed LOS (unpublished data).

LOS is related to the postnatal environment, characteristics of the newborn, and care practices. Among these practices, the use of vascular catheters and parenteral nutrition are important risk factors for sepsis.[5,6] Hand hygiene is another practice that deserves attention, as the transmission of microorganisms through the caregivers' hands is a constant concern. The Centers for Disease Control and Prevention (CDC), the WHO, and the Brazilian National Health Surveillance Agency (ANVISA) periodically publish guides on hand sanitizing, but warn that the adherence of health professionals is low, even in campaign periods.[7–9]

The percentage of professionals' adherence to hand washing varies from 28% to 62%, and greater adherence to hand hygiene practices is associated with reduced rates of hospital infection.[10] Another relevant aspect is the difficulty in the diagnosis of sepsis, as clinical data and laboratory tests are nonspecific and blood culture, considered the gold standard, has low positivity.[11,12] The difficulty in diagnosis can lead to treatment delay or excessive use of antibiotics, allowing the selection of flora and development of bacterial resistance, another frequent problem in the neonatal intensive care unit (NICU).

The scarcity of national data regarding LOS, together with the fact that NICUs that are part of BNRN reference units, makes it crucial to analyze the current situation of the BNRN NICUs and disseminate data, to map the national scenario, and to advise on preventive measures to be instituted aiming to reduce the incidence of LOS in very low birth weight premature infants. These aspects motivated this study, which aimed to identify care practices related to late-onset sepsis in 16 BNRN centers, focusing on hand hygiene, use of vascular catheters, diagnosis, empiric treatment of sepsis, and identification of aspects that can be improved as a strategy to reduce LOS.

Method

This was a multicenter study involving 16 BNRN centers, which was approved by the research ethics committee of each center. All centers are a reference in the area of maternal-child health and meet the needs of women with high-risk pregnancies in the health care system. In the BNRN, the criterion for defining late-onset sepsis includes the

presence of clinical and hematological alterations after 72 hours of life, and LOS is considered confirmed when the blood culture is positive and clinical when the blood culture is negative.

In 2011, the LOS study group of the BNRN created and sent three questionnaires to the coordinators of each of the 16 centers, which included open and multiple choice questions regarding care practices used in their units. These questionnaires addressed issues about hand hygiene, use of vascular catheters, diagnosis, and empirical treatment of LOS.

The main issues addressed in the questionnaire were:

Questionnaire 1: Hand hygiene

Product used in hand hygiene, specific information about the use of alcohol gel and training of health staff that cares for newborns.

Questionnaire 2: Vascular catheters

Presence of groups of catheter insertion and maintenance, catheter insertion protocol, length of stay, sending the catheter tip for culture, and information on dressings and infusion system changes.

Questionnaire 3: Diagnosis and treatment of LOS

Tests used for the diagnosis of LOS: blood culture (peripheral and/or central method used for its implementation, interpretation of results taking into account time and growth curve), use of blood count, acute phase reactants, hematological scores, CSF collection indications and repeat lumbar puncture, and interpretation of growth of coagulase-negative staphylococci in blood culture (contamination or infection). Most commonly used antibiotics in antimicrobial therapy and duration of use.

Statistical Analysis

After receiving the responses, they were tabulated and analyzed using frequency and association tables, maintaining the confidentiality of the centers, which were identified only by letters. The practices of the BNRN center with the lowest incidence of ST, including clinical and confirmed sepsis (incidence of 29% - unpublished data) were compared with the others. Based on these data, suggestions were made for LOS reduction.

Results

The 16 participating BNRN centers answered the three questionnaires. No question was excluded and the percentage was calculated based on the number of answers obtained for each question.

Questionnaire 1: Hand hygiene (Table 1)

Most centers use chlorhexidine or and alcohol 70% for hand hygiene, and have alcohol gel bedside dispensers. However, regarding the use of dispensers, only seven centers have dispensers at the appropriate proportion ($\geq$ 0.5 per bed). The 16 centers carry out practical training for hand hygiene; however, only 25% conduct training more than twice a year.

Questionnaire 2: Vascular catheters (Table 2)

All centers, except one, use catheter insertion protocols, but only 12 centers have PICC (peripherally-inserted central catheter) insertion groups, consisting of nurses, and ten centers have catheter maintenance groups. In most centers, the umbilical venous catheter is maintained for a period $\geq$ five days, the arterial catheter for three to six days, and the PICC for up to 30 days. All centers use transparent dressings; 56% change the dressings only if they are soiled. Most centers request catheter tip culture if infection is suspected. All centers withdraw the catheter immediately in the presence of blood culture positive for fungi, 56% in the presence of Gram-negative bacteria or *S. aureus*, and 12.5% in the presence of coagulase-negative staphylococci.

Questionnaire 3: Diagnosis and empiric treatment of LOS (Table 3)

All centers collect blood culture samples before starting antibiotic therapy; 15 of them use the automated culture method and most collect peripheral blood only.

In 11 centers, coagulase-negative staphylococci are considered the etiological agent of infection if there is associated clinical and laboratory alteration; 12 centers (75%) take into account the time of bacterial growth for diagnosis of infection.

As for nonspecific tests, most centers use C-reactive protein (CRP) as the acute-phase reactant and consider this marker useful both for excluding the diagnosis of infection and for infection control. Hematologic scores are used in most centers, especially the Rodwell score. Five centers did not repeat the nonspecific tests for suspected infection if the initial test was normal. The vast majority performed CSF collection in suspected infection and repeated the test if the result of the first CSF was abnormal. Only half of the centers use oxacillin and aminoglycoside as initial empiric regimen in LOS and 50% of the services maintain the treatment until negative cultures are obtained.

Practices in the center with the lowest incidence of LOS

The center with the lowest incidence of LOS (29%) in the period 2009-2010 showed the following results:

- **Hand hygiene (**Table 1**):** uses chlorhexidine 2% and alcohol 70%; alcohol gel dispensers at the bedside and one dispenser for two beds; trains the entire health team twice a year through practical activities and leaflets.
- **Vascular catheters (**Table 2**):** has catheter insertion protocol and catheter insertion and maintenance group; keeps the umbilical venous catheter for up to five days, arterial catheter for up to seven days, and PICC for up to 15 days. Uses transparent dressings and changes the dressing

Table 1 Main questionnaire answers on hand hygiene in 16 Brazilian Neonatal Research Network centers and practices in the center with the lowest incidence of late-onset sepsis (LOS).

	No. of centers/No. of responding centers (%)	Center with the lowest LOS incidence
PRODUCT USED		
Chlorhexidine	12/15 (80)	Yes
Alcohol 70%	11/14 (79)	Yes
Iodine-based antiseptic	2/13 (15)	No
USE OF GEL ALCOHOL		
Dispenser/bed	13/16 (81)	Yes
Dispenser/professionals	3/16 (19)	No
Dispenser/bed $\leq$ 1:2	7/14 (50)	Yes
Dispenser/bed 1:3 to 1: 7	7/14 (50)	No
TRAINING		
Practical	16/16 (100)	Yes
Theoretical	11/16 (69)	No
Leaflets	10/16 (62)	Yes
Head of HICC	14/16 (87)	Yes
FREQUENCY OF TRAINING		
Once a year	6/16 (37.5)	No
Two times a year	5/16 (31)	Yes
$\geq$ 3 times a year	4/16 (25)	No

HICC, Hospital Infection Control Commission.

every seven days, collects catheter tip culture in suspected infection, uses the roll plate culture, and removes the catheter immediately if blood culture is positive for fungi.

- **Diagnosis and empiric treatment of LOS (**Table 3**):** collects peripheral blood culture, has automated method available, uses growth time to differentiate infection and contamination, considers coagulase-negative staphylococci as pathogen if there are clinical and laboratory alterations. Nonspecific tests include blood count and CRP, taking Rodwell score into account. Uses oxacillin and aminoglycoside as empiric therapy for LOS.

Table 2 Main questionnaire answers on vascular catheter use in the 16 Brazilian Network on Neonatal Research centers and practices in the center with the lowest incidence of late-onset sepsis (LOS).

	No. centers/No. of responding centers (%)	Center with the lowest LOS incidence
CATHETER GROUP		
PICC insertion	12/16 (75)	Yes
Catheter maintenance	10/16 (62.5)	Yes
TIME OF CATHETER PERMANENCE		
Umbilical venous		
$\leq$ 3 days	4/16 (25)	No
$\geq$ 5 days	11/16 (69)	Yes
Umbilical arterial		
$\leq$ 3 days	5/16 (31)	No
> 3 days	10/16 (62.5)	Yes
Do not use arterial	4/16 (25)	
PICC		
7 to 15 days	5/16 (31)	Yes
16 to 30 days	6/16 (37.5)	No
Undetermined	5/16 (31)	No
CATHETER TIP CULTURE		
At suspected infection	13/15 (87)	Yes
Always	2/15 (13)	No
roll plate culture technique	10/15 (67)	Yes

PICC, peripherally inserted central catheter.

Table 3 Main questionnaire answers on diagnosis and empirical treatment of late onset sepsis (LOS) in the 16 Brazilian Network on Neonatal Research centers and practices in the center with the lowest incidence of LOS.

	No. centers/No. of responding centers (%)	Center with the lowest LOS incidence
BLOOD CULTURE COLLECTION		
Only peripheral	10/16 (62.5)	Yes
Peripheral and central	6/16 (37.5)	No
Automated method	15/16 (93.7)	Yes
Time of growth	12/16 (75)	Yes
COAGULASE-NEGATIVE STAPHYLOCOCCUS		
Infection if there is clinical/laboratory alteration	11/16 (69)	Yes
UNSPECIFIC EXAMS		
Whole blood count	16/16 (100)	Yes
Rodwell score	8/12 (66)	Yes
CRP	14/16 (87.5)	Yes
CSF		
Suspected sepsis	12/16 (75)	Yes
EMPIRIC TREATMENT		
Oxacillin + aminoglycoside	8/16 (50)	Yes
Vancomycin	6/16 (37.5)	No
Cephalosporin + carbapenem	3/16 (18.7)	No

CRP, C-reactive protein; CSF, cerebrospinal fluid.

Discussion

Neonatal infection surveillance networks have been implemented in many countries, aiming to verify the national scenario, compare the results with other networks, and propose strategies to improve the quality of care provided to newborns. In the centers of the BNRN, all contribute to the maintenance of a database on very low birth weight premature infants, which allows monitoring of morbidity, care practices, and mortality rates. One of the priority-monitoring morbidities in the BNRN is LOS.[13]

LOS is common in premature infants, is associated with high morbidity and mortality, and may impair the neurodevelopment of survivors.[14] A BNRN study showed that 27% of very low birth weight premature infants developed confirmed LOS (range 14-51%) and 23% (range 7.5-41%) clinical LOS (unpublished data). The mortality in septic groups was higher when compared to the group without sepsis, even considering the variability between centers. The great variability in infection rates between centers is a common finding in research networks and differences in care practices have been identified in the literature as a contributing factor.[15–18] Knowing the care-related practices is critical in developing strategies to reduce LOS. Interventions to improve care practices can attenuate these differences.

Hand hygiene is a practice that arouses great concern and should always be monitored. The main products used for hand washing are alcohols (concentration of 70%, no residual effect) and chlorhexidine (concentrations of 2% and 4%, with a residual effect of 6 hours).[10,19] In the BNRN, most centers use chlorhexidine and alcohol 70%, have alcohol gel dispensers, and have hand hygiene training. This shows that the basic items are available; what probably makes the difference between the centers is the quality in practice, reinforcing the hypothesis that the most important factor is to invest in continuing education of health professionals to improve adherence to recommended procedures. One purpose of this study is to expand the use of alcohol gel, which is preferred by professionals due to being easy to use, taking less time to use and having comparable efficacy to other antiseptics, provided the hands are not soiled.[10,20]

Another risk factor monitored in this study was the use of vascular catheters. Central catheters are widely used in very low birth weight premature infants for parenteral nutrition infusion, medication, and antibiotic administration, and can be a source of infection: contamination during the insertion, excessive manipulation, interruption in the closed system maintenance for administration of drugs and blood products, use of contaminated solution, the hub itself, or contamination by skin pathogens.[5,21,22] Data from seven Brazilian NICUs showed that the incidence of bloodstream infection associated with vascular catheter varies by birth weight: 34.9/1,000 vascular catheter (VC) days in premature infants weighing < 1,000 g, 20.4/1,000 VC days in premature infants weighing between 1,001-1,500 g, 17.3/1,000 VC days in those weighing between 1,501-2,500 g and, 18.1/1,000 VC days in infants weighing > 2,500 g.[23]

These rates are much higher than those found in the National Healthcare Safety Network (NHSN), which shows rates of 4.4/1,000 VC days in those weighing < 1,000 g, 4.8/1,000 VC days between 1,001-1,500 g, 4.2/1,000 VC days between 1,501-2,500 g. and 3.1/1,000 VC days in those weighing > 2,500 g, and reinforce the importance of catheter-associated infection in this environment and the need for preventive measures against this condition of concern.[5,24,25]

In the questionnaire on vascular catheters, it was observed that only two-thirds of the centers have a PICC

insertion and maintenance team, with this representing an aspect to be improved, which can be crucial as a LOS prevention strategy. The other catheter care procedures were similar between centers.

In the third and last questionnaire on diagnosis and empirical treatment of sepsis, the answers were variable, showing great heterogeneity between centers. All centers use blood count, CRP, and blood culture, but do not follow a protocol. Premature newborns are immunocompromised and exposed to many infectious risk situations that favor the use of antibiotics. Another aspect that requires the frequent use of antibiotics is the difficulty in the diagnosis of sepsis, due to the low specificity of clinical assessment and laboratory tests, as well as the low positivity of blood cultures, which have been classically reported in literature.[14] Antibiotic therapy, in turn, alters the intestinal flora, which favors the emergence of resistant strains.[26–28] The proposed strategy was to optimize the interpretation of blood count, taking hematological scores into account, such as the Rodwell score, and associate the use of serial quantitative PCR for exclusion and infection control.

Empirical antibiotic therapy is among the items with greater variability between centers. In order to define protocols on the empirical use of antibiotics, it is necessary to know the prevalent agents in each unit, but it is known that the use of broad-spectrum antibiotics increases colonization and infection with multidrug-resistant organisms.[27] The presence of coagulase-negative staphylococci as one of the main LOS agents in the BNRN (60% of cases) may have favored the use of vancomycin in the empiric therapy. The use of antibiotics, as well as time of use, must be strictly monitored and reassessed, and empirical therapy with broad-spectrum antibiotics should be avoided.[27,28]

Once the diagnosis of infection is ruled out, these antibiotics should be discontinued immediately, and if the presence of the agent is confirmed in blood or other sterile fluids, gradual antimicrobial dosing decrease should always be performed.

The center with the lowest incidence of LOS showed no extraordinary or costly practices to justify its results. In general, the practices between centers were similar, which reinforces the hypothesis that the difference lies in the quality of adherence to practices and the commitment of the entire staff involved in the care of the newborns when applying them.

The differences found in the 16 BNRN centers reflect what occurs in a country of continental dimensions such as Brazil and depicts the current reality. The fact that these centers have come together with the goal of reducing LOS, making a diagnosis of the current situation, identifying the centers with the lowest incidences and best practices, and aiming to improve their performance justifies the work of the BNRN's study group on sepsis. Based on these data, a set of measures has been proposed aimed at reducing LOS:

- Institute the use of alcohol gel/glycerin dispensers at a rate of one for every bed in the NICU.
- When using alcohol gel wall dispensers, maintain a proportion of at least one dispenser for two beds.
- Perform theoretical and practical training for hand hygiene more than twice a year, for the entire health care team.
- Have standardized procedures for insertion and maintenance of PICCs.
- Have a team assigned to perform PICC insertion and maintenance.
- Carry out regular (monthly) meetings with the Infection Control Committee to monitor infection rates.
- Ensure the adequacy of human resources (physicians and nurses) proportion per bed according to current recommendations.
- Periodically assess the results attained at the unit in reducing sepsis and institute several means of disseminating this analysis: meetings, bulletin boards, and electronic messages.

Low-cost measures such as those proposed by the BNRN can have high impact and make a difference in sepsis prevention, decreasing the length of hospital stay, reducing the social and economic costs, and generating an expected improvement in the quality of care of very low birth weight premature infants in the BNRN centers.

One limitation of the study lies in the fact that the questionnaire was not sent to doctors and nurses that work shifts, but to the coordinators of the centers, which were responsible for the information. Despite the possibility of individualized behaviors, there was a commitment on the part of the coordinators to answer the questions according to the service protocols and after checking the information with their teams. Another limitation was the lack of data on the sensitivity patterns for sepsis agents in each unit, so that the evaluation of the empirical therapy could be detailed.

One must also consider that the aim of this study was to evaluate care practices related to sepsis and not investigate risk factors for LOS. Therefore, the characteristics of the population treated at each center were not analyzed, which limits data interpretation, but does not interfere with the study's proposal regarding LOS prevention measures, as the characteristics of the treated population are not preventable, whereas improving care practices can minimize the risk of LOS.

The major contribution of the study was to demonstrate the conduct of clinical practice in reference centers in Brazil and show that, even in these centers, practices and routine procedures can be improved.

In conclusion, the knowledge of the practices in each center allowed for the identification of aspects to be optimized as a strategy to reduce LOS including: use of alcohol gel, training in hand hygiene, implementation of catheter groups, and the rational use of antibiotics.

Conflicts of interest

The authors declare no conflicts of interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jped.2014.07.004.

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