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VANCOMYCIN AND CEPHALOSPORIN USE AS A FIRST CHOICE OF ANTIMICROBIAL THERAPY IN NEONATAL INTENSIVE CARE UNIT: IMPACT ON A LATE-ONSET SEPSIS

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ABSTRACT

Background: late-onset sepsis continues to be an important cause of morbidity and mortality and appropriate antibiotic treatment is one of the cornerstones of successful treatment. The aims of this study were: to evaluate the rate of late onset sepsis, risk factors for disease and pathogenic micro-organisms isolated in one neonatal intensive care unit were compared following a change in antibiotic policy. **Methods:** the comparison was performed between three time periods: A (Sept 2010 to Aug 2011), B (Dec 2011 to Nov 2012), C (May 2013 to Apr 2014). The periods were based on different antibiotic protocols during each one. **Results:** we analysed 632 newborns, the use PICC was 70%, and 64.5% were associated with sepsis. The infection rate was 34.5%, and sepsis was the infection with higher frequency and the occurrence of death was 11.9%. There was no statistically significant difference in the reduction of Gram-positive organisms. **Conclusion:** After two changes in the protocol of use for antibiotics, we concluded that there was no impact on the frequency of sepsis in changing empiric antibiotic therapy for LOS. The results highlight the importance of using antibiotics judiciously in NICU settings, which may minimize the collateral damage associated with antibiotic therapy and benefit neonatal outcomes.

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INTRODUCTION

Although advances in neonatal intensive care have led to the improved survival of very low birth weight (VLBW) infants, late-onset sepsis continues to be an important cause of morbidity and mortality (Tsai, 2014). The risk of late-onset sepsis increases with decreasing birth weight and gestational age (Geffers, 2013). Ongoing infectious disease surveillance is essential because immature neonates are increasingly surviving when being provided with intensive care, in spite of requiring prolonged hospitalisation (Tekin, 2013). Appropriate early antibiotic treatment is one of the cornerstones of successful treatment (Russell, 2012).

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However, the emergence of resistant bacteria may result in inadequate empirical antibiotic regimens and revision of protocols (Ergaz, 2013). A change in antibiotic usage policy may not only minimize the resistance problem but also leads to a change in the identity of organisms and the patterns of antimicrobial resistance (Bagla, 2013). In this study, the rate of late-onset sepsis, risk factors for infection and isolated pathogenic microorganisms in one neonatal intensive care unit have been compared aftera change in antibiotic policy.

METHODOLOGY

Setting and Protocols: The Medical Hospital of the Federal University of Uberlândia is a 533-bed public teaching general hospital and a tertiary care center. The Neonatal Intensive Care Unit (NICU) consists of 3 rooms with a capacity of 20

neonates and also serves as a referral center forseveral hospitals in the vicinity. This is a retrospective comparative study of data between the epidemiology of late-onset sepsis, risk factors and pathogenic microorganisms isolated in a NICU before and after changes in the policy of antimicrobial use. The comparison was performed between three time periods: period A – 216 neonates: (from Sept 2010 to Aug 2011), period B – 207 neonates: (Mar 2012 to Feb 2013) and period C – 209 neonates: (Sep 2013 to Aug 2014). Each of the three periods was based on different antibiotic protocols. During period A, the first line antibiotics were Oxacilin and Amikacin and second line drugs were Vancomycin and Cefotaxime. The antibiotic policy during period B consisted of Vancomycin and Cefotaxime and period C consisted of Vancomycin and Cefepime.

Data collection and Definitions: Infection data, gestational age, birth weight, Apgar value, SNAPPE value, use of central vascular catheter, use of parenteral nutrition, use of mechanical ventilation, length of stay, and use of antibiotics prior to infection were collected. Very low birth weight (VLBW) children are babies born weighing equal to or less than 1,500 grams. A late-onset infection was recognised if the neonate had one or more blood cultures positive obtained after 72 hours of life.

Blood cultures positive for microorganisms that generally are considered contaminants (e.g. diphtheroids, *Corynebacterium* spp., *Propionibacterium* spp., *Penicillium* spp.) were excluded from analysis. The CoNS were include if at least two blood cultures were positive.

Ethical Committee: The study was approved by the Ethical Committee for Human Research of the Federal University of Uberlândia.

Statistical Analysis: The qualitative variables were described through double table entries. The associations of the qualitative variables with the periods were evaluated by means of Likelihood Ratio test (Zar, 1999 and Agresti, 2007). following multiple comparison periods with Bonferroni correction. The risk factors for late sepsis and weighing less than 1,500 g were assessed by univariate logistic regression, as well as by multiple logistic regression followed by the selection of variables by the Stepwise method (Hosmer, 2004). A probability value (p value) less than 0.05 was considered statistically significant. All statistical calculations were done using the computer programs Microsoft Excel 2010 and SPSS version 21 for Microsoft Windows.

RESULTS

A characterisation of the population of the study, comparing the neonates admitted in the three study periods with different demographic and clinical variables is described in Table 1. There was no statistically significant difference, demonstrating

Table 1 Description of the study population

Neonates	Period A N=216		Period B N=207		Period C N=209	
Weight(g)	N	%	N	%	N	%
<750g	12	5.6	20	9.7	14	6.7
750-999g	21	9.7	22	10.6	17	8.1
1000-1499g	49	22.6	56	27.1	55	26.3
1500-2499g	75	34.8	58	28	74	35.4
≥2500g	59	27.3	51	24.6	49	23.4
GA (weeks)						
≤ 34	125	57.8	135	65.2	133	63.6
>34	91	42.2	72	34.8	76	36.4
Apgar5°min	207	100	203	100		
<7	28	13.5	27	13.3	24	12.0
≥7	179	86.5	176	86.7	176	88.0
Reason for Hospitalization						
Respiratory System	167	77.3	161	77.8	170	81.3
Cardiovascular System	13	6.0	7	3.4	8	3.8
Digestive System	13	6.0	21	10.1	16	7.7
Nervous System	10	4.6	9	4.4	9	4.3
Genitourinary System	4	1.8	0	0	1	0.5
Sepsis	6	2.8	6	2.9	0	0
Others	3	1.5	3	1.4	5	2.4
Use ofantimicrobials< 72hrs						
Yes	104	48.1	110	53.1	107	51.2
No	112	51.9	97	46.9	102	48.8
Use ofPN						
Yes	118	54.6	133	64.3	115	55
No	98	45.4	74	35.7	94	45
Time ofHospitalization NICU						
≤7 days	87	40.3	65	31.4	63	30.1
>7 days	129	59.7	142	68.6	146	69.9
Use CVC	257		249		242	
Umbilical Venous	86	33.4	99	39.8	89	36.8
PICC	150	58.4	139	55.8	139	57.5
VenousDissection	14	5.4	9	3.6	9	3.7
Intracath	7	2.8	2	0.8	5	2
TypeofInfection						
Sepsis	68	31.5	50	24.2	58	27.8
Conjunctivitis	11	5.1	8	3.9	10	4.8
Urinary	4	1.8	1	0.5	3	1.4
Others	1	0.5	3	1.4	0	0
Deaths	29	13.4	30	14.5	16	7.7

GA: gestational Age, PN: parenteral nutrition, CVC: central venous catheter, PICC: peripherally inserted central catheter

Table 2. Risk factors for late-onset sepsis in neonates hospitalized at the NICU

PeriodA (N=216)									
						Univariate Analysis		Multivariate Analysis	
		Without LOS		With LOS		p	OR	p	OR
	N	N	%	N	%				
GA ≤34	125	81	65.0	44	35.0	0.169	1.516	0.064	7.695
Weight<1,500g	82	44	53.7	38	46.3	0.000*	2.994	-	-
APGAR 5min	28	21	75.0	7	25.0	0.468	1.402	-	-
SNAPPE >24	80	44	55.0	36	45.0	0.001*	2.939	0.003*	7.079
PICC	150	93	62.0	57	38.0	0.003*	3.065	-	-
UVC	86	46	53.5	40	46.5	0.000*	3.168	-	-
PICC days						0.000*	1.067	0.061	1.048
UVC days						0.29	1.251	0.15	1.434
PN	118	64	54.2	54	45.8	0.000*	5.062	-	-
MV	113	62	54.9	51	45.1	0.000*	4.161	-	-
Hospitalization> 7 days	129	71	55.0	58	45.0	0.000*	6.290	-	-
ATB <72h	104	72	69.2	32	30.8	0.793	1.080	-	-
Period B (N=207)									
GA ≤34	135	100	74.0	35	26.0	0.416	1.330	-	-
Weight<1500	96	65	67.7	31	32.3	0.012*	2.309	-	-
APGAR 5min	27	21	78.0	6	22.0	0.755	1.167	-	-
SNAPPE >24	66	45	68.0	21	32.0	0.071	1.867	-	-
PICC	139	93	66.9	46	33.1	0.000*	7.914	-	-
UVC	99	72	72.7	27	27.3	0.222	1.500	-	-
PICC days						0.000*	1.099	0.000*	1.106
UVC days						0.089	1.163	-	-
PN	133	89	66.9	44	33.1	0.000*	6.625	-	-
MV	114	77	67.5	37	32.5	0.003*	2.957	-	-
Hospitalization> 7 days	142	93	65.5	49	34.5	0.001*	33.720	0.069	7.826
ATB <72h	110	80	72.7	30	27.3	0.266	1.444	-	-
Period C (N=209)									
GA ≤34	133	90	68.0	43	32.0	0.084	1.792	-	-
Weight<1500	86	50	58.1	36	41.9	0.000*	3.130	-	-
APGAR 5min	24	16	67.0	8	33.0	0.496	0.729	-	-
SNAPPE >24	58	33	57.0	25	43.0	0.013*	2.323	0.028*	2.485
PICC	139	90	64.7	49	35.3	0.002*	3.267	-	-
UVC	89	50	56.0	39	44.0	0.000*	3.900	-	-
PICC days						0.001*	1.060	0.001*	1.058
UVC days						0.176	1.129	-	-
PN	115	65	56.5	50	43.5	0.000*	7.265	0.016*	4.465
MV	116	70	63.0	46	39.7	0.000*	4.044	-	-
Hospitalization> 7 days	146	90	61.6	56	38.4	0.000*	12.444	-	-
ATB <72h	107	77	72.0	30	28.0	0.867	1.053	-	-

GA: gestational Age, PICC: peripherally inserted central catheter, UVC: umbilical venous catheter,
PN: parenteral nutrition, MV: mechanical ventilation, ATB <72h: antibiotic use less than 72 hours of life.
* p≤0.05

Table 3. Predictors of LOS in VLBW infants

Period A (N= 216)									
						Univariate Analysis		Multivariate Analysis	
		Without sepsis		With sepsis		p	OR	p	OR
	N	N	%	N	%				
GA ≤34	81	44	54.3	37	45.7	-	-	-	-
APGAR 5min	10	6	60.0	4	40.0	0.644	0.727	-	-
SNAPPE >24	49	20	40.8	29	59.2	0.005*	3.867	0.011*	0.195
PICC	70	35	50.0	35	50.0	0.121	3.000	-	-
UVC	68	34	50.0	34	50.0	0.152	2.500	-	-
PICC days						0.019*	1.058	0.042*	1.346
UVC days						0.052	1.269	-	-
PN	77	39	50.6	38	49.4	0.999	-	-	-
MV	52	21	40.4	31	59.6	0.002*	4.850	-	-
Hospitalization> 7 days	62	26	41.9	36	58.1	0.001*	12.462	-	-
ATB <72h	51	27	52.9	24	47.1	0.867	1.079	-	-
Period B (N=207)									
GA ≤34	94	63	67.0	31	33.0	-	-	-	-
APGAR 5min	17	13	76.5	4	23.5	0.381	0.581	-	-
SNAPPE >24	50	32	64.0	18	36.0	0.406	1.453	-	-
PICC	80	51	63.8	29	36.3	0.081	3.980	-	-
UVC	81	55	67.9	26	32.1	0.925	0.945		
PICC days						0.005*	1.088	0.033*	1.068
UVC days						0.111	1.155	-	-
PN	93	63	67.7	30	32.3	0.969	0.952	-	-
MV	67	44	65.7	23	34.3	0.517	1.372	-	-
Hospitalization> 7 days	80	50	62.5	30	37.5	0.038*	9.000	-	-
ATB <72h	59	40	67.8	19	32.2	0.981	0.990	-	-

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Period C (N=209)									
GA ≤34	84	48	57.1	36	42.9	-	-	-	-
APGAR 5min	15	9	60.0	6	40.0	0.919	0.943	-	-
SNAPPE >24	43	22	51.2	21	48.8	0.238	1.705	-	-
PICC	81	47	58.0	34	42.0	0.931	1.085	-	-
UVC	74	42	56.8	32	43.2	0.521	1.524	-	-
PICC days						0.019*	1.063	0.010*	1.099
UVC days						0.141	1.179	-	-
PN	80	46	57.5	34	42.5	0.622	1.478	-	-
MV	54	27	50.0	27	50.0	0.050*	2.556	-	-
Hospitalization> 7 days	81	46	56.8	35	43.2	0.329	3.043	-	-
ATB <72h	57	33	57.9	24	42.1	0.949	1.030	-	-

GA: gestational Age, PICC: peripherally inserted central catheter, UVC: umbilical venous catheter,
PN: parenteral nutrition, MV: mechanical ventilation, ATB <72h: antibiotic use less than 72 hours of life.
* =Significant univariate Analysis p≤0.05

Table 4. Late-onset sepsis occurrence, microorganisms and use of antimicrobials

Neonates	Period A N=216		Period B N=207		Period C N=209		Total 632	
	N	%	N	%	N	%	N	%
Late Sepsis	68	31.5	50	24.2	58	27.8	176	27,8
Clinical Sepsis	25	36.8	22	44.9	25	42.3	72	11,4
Sepsis with Laboratory Diagnosis	43	63.2	27	55.1	33	55.9	103	16,3
Microorganisms (blood culture +)	52	100	33	100	34	100	119	18,8
Gram positive	36	69.2	23	69.6	21	61.8	80	12,6
Gram negative	9	17.3	10	30.4	9	26.5	28	4,4
Fungi	7	13.5	0	0	4	11.7	11	1,7
Multi resistant Microorganisms	28	100	17	100	14	100	59	9,3
Coagulase negative staphylococci	27	96.4	14	82.3	13	92.8	54	8,5
MRSA	0	0	0	0	1	7.2	1	0,1
Gram negative	1	3.6	3	17.7	0	0	4	0,6
Use of antimicrobials								
Oxacilin	53	21.6	11	5.9	11	5	75	11,8
Amikacin / Gentamicin	35	14.3	12	6.5	15	6.8	62	9,8
Vancomycin / Teicoplanin	54	22.3	62	33.3	76	34.5	192	30,3
Cefotaxime	57	23.3	23	12.3	13	5.9	93	14,7
Cefepime	8	3.2	41	22	57	25.9	106	16,7
Meropenem	12	4.8	5	2.7	7	3.3	24	3,8
Metronidazole	5	2	3	1.6	3	1.4	11	1,7
Amphotericin B	4	1.6	0	0	0	0	4	0,6
Fluconazole	11	4.5	13	7	13	5.9	37	5,8
Others	6	2.4	16	8.7	25	11.3	47	7,4

Table 5. Frequency of isolated microorganisms of late-onset sepsis in the three periods of the study

Micro-organisms	Period A		Period B		Period C		Total	
	N	%	N	%	N	%	N	%
CoNS	31	59.6	15	45.5	14	41.1	60	50.4
Staphylococcus aureus	4	7.8	8	24.3	7	20.6	19	16.0
Enterococcus faecalis	1	1.9	2	6	1	2.9	4	3.3
Escherichia coli	4	7.8	5	15.2	2	5.9	11	9.2
Klebsiella pneumoniae	2	3.8	1	3.0	0	0	3	2.6
Pseudomonas aeruginosa	0	0	1	3.0	1	2.9	2	1.7
Serratiamarcescens	2	3.8	0	0	1	2.9	3	2.6
Stenotrophomonasmaltophilia	1	1.9	0	0	0	0	1	0.8
Acinetobacter baumannii	0	0	1	3.0	0	0	1	0.8
Enterobactercloacae	0	0	0	0	4	11.8	4	3.3
Candidaalbicans	6	11.5	0	0	3	9.0	9	7.6
Other Candida	1	1.9	0	0	1	2.9	2	1.7
Total of Blood Cultures	52	100	33	100	34	100	119	100

When the three study periods were evaluated separately regarding the occurrence of late-onsetsepsis, several statistically significant risk factors in univariate analysis were observed, with emphasis on weight of 1,500g, SNAPPE>24, use of peripherally inserted central catheter (PICC), use of umbilical venous catheter (UVC), time (days) of stay of the PICC, parenteral nutrition, mechanical ventilation and length of stay longer than seven days. When the multivariate analysis by multiple logistic regression was performed, independent factors for late sepsis ranged between periods A, B and C. SNAPPE >24, days of use of PICC and the use of mechanical ventilation were significant in the first period (A).

In period B only days of PICC were significant and in period C were SNAPPE >24, days of use PICC and use of parenteral nutrition (Table 2). Out of the 176 (80.7%) cases of sepsis, about 60% had alaboratory confirmation, with Gram-positive bacteria being the most common, accounting for 67.2%; amongmulti-drug resistant, CoNS was the most frequent (90.5%). There was no statistically significant difference in the reduction of Gram-positive microorganisms between periods, as well as in the reduction of multi-drugresistance. As established by the protocol of antimicrobial use in the unit, a significant increase in Vancomyc in use between periods A and C ($p<0.001$) was observed, as well as an increase of

cefepime between periods A and B ($p<0.001$) and A and C ($p<0.001$), likewise the significant reduction of amikacin and cefotaxime ($p<0.001$) (Table 3). All Gram-positive isolates during all three periods were susceptible to Vancomycin. Additionally, it is important to note that for comparative purposes regarding the occurrence of sepsis and microorganisms, the statistical analysis was performed in the three period sending in August 2014. However, the use of Vancomyc in andcefepime was extended until January 2016. Ananalysis of the events after August 2014, we highlight the occurrence of two outbreaks of *Acinetobacterbaumanni*; in the first outbreak (November 2014 to March 2015) ESBL positive, resistant to carbapenemics, with 7 cases and 2 deaths, and in the second outbreak (July 2015 to August 2015), 11 cases and 2 deaths being caused by *Acinetobacter baumannii*s ensitive to all antimicrobials. Then, an outbreak of necrotizing enterocolitis with out micro organism isolation (November to December 2015) occurred with 7 cases and 5 deaths. Andan outbreak of *Pseudomonas aeruginosa*, notmulti-drugresistant, was observed from August to October 2016 with 14 cases and 5 deaths.

DISCUSSION

Late-onset sepsis (LOS) remains an important and potentially lethal complication among VLBW infants[10]. These infections are particularly poignant for parents and physicians because this complication affects VLBW infants who have survived early causes of mortality but remain at ongoing risk of infection. With increasing survival of VLBW preterm infants, late-onset sepsis will continue to be a challenging complication that affects other morbidities, length of hospitalisation, cost of care, and mortality rates[11]. In this study, 40.0% of VLBW neonates who survived beyond 3 days of age had at least one episode of late-onset sepsis. The median age of onset for the first episode of sepsis was over 2 weeks of age and the risk factors for sepsis were: weight <1,500g, SNAPPE >24, PICC use, umbilical venous catheter, day use of PICC, parenteral nutrition, mechanical ventilation, hospitalisation more than seven days. Day use of PICC was an independent predictor of sepsis for VLBW when evaluated by a multivariate logistic regression model, in all three periods of study. Some studies have also shown that the risk of LOS, especially in VLBW, was directly related to duration of central catheters (Tsai, 2014; Geffers, 2010; Tekin, 2013 and 2014). The most prevalent microorganisms in neonatal LOS are CoNS, accounting for 35.5-77.9% (Hammoud, 2012 and Tröger, 2014). In terms of toxin production, CoNS are not asvirulent as Gram-negative bacteria and fungi, which partly explains the lower rate of short-term infectious complications as well as mortality associated with CoNS sepsis (Dong, 2015 and Cheng, 2016). In this study, the CoNS was the most frequently etiologic isolated agent, followed by *S. aureus*, Gram-negative bacteria and fungi. Most of the CoNS samples were identified as *S. epidermidis*, a reflection of the prevalence of this organism in skin microbiota and its potential to biofilm formation (Pinheiro, 2014). The high prevalence of these microorganisms in this unit has been described previously (Brito, 2009 and Urzedo, 2014). This predominance of bloodstream infections caused by Gram-positive bacteria followed by Gram-negative bacteria and fungi, reveals that the isolation profile of the NICU studied resembles that observed in countries like the United States (Boghossian, 2013), Taiwan (Tsai, 2014 and Hsu, 2010), and Israel (Ergaz, 2013) as well as in other Brazilian hospital NICUs (Rios, 2014). In this study, there were the implementation of a three different protocol for the use of antibiotics, particularly the insertion of Vancomycin as the initial therapy for sepsis (Periods B and C). This measure was influenced by the high frequency of resistant CoNS in our unit. Vancomycin is the antibiotic most commonly used for CoNS infection (Jacqz-Aigrain, 2013 and Linder, 2013). Almost all CoNS isolated carry the gene that confers resistance to Mec A methicillin, which has justified the initial therapy with Vancomycin (Rodriguez-Guerineau, 2013). The success rate of Vancomycin increases significantly with the removal of the catheter, due to the reduced glycopeptide antibiotic effect on microorganism in biofilms (Karlowicz, 2002), however in this study, despite CVChad not beenremoved, infection by CoNS was solved in all cases with Vancomycin in periods B and C. On the other hand, there was no impact of changing empirical antibiotic therapy for LOS from oxacillin and amikacin (Period A) to vancomycin and cefotaxime (Period B) on the frequency of sepsis.

Vancomycin is one of the most used antimicrobial, even though has been related to increase prevalence of multi-drug resistance. A decrease of vancomycin use has been encouraged by some researchersto treat late-onset sepsis because of its high nephrotoxicity, especially if it isa long-term therapy (Holzmann-Pazgal, 2015 and Sivanandan, 2011). Another serious problem is the emergence of vancomycin-resistant organisms, such as *Staphylococcus aureus* and *Enterococcus*, and also the fact that it enables the increase of *Candida* infections rates which would lead to severe infections increasing morbidity and mortality (Carmona, 2012). Many of Neonatal Intensive Care Unit have no guidelines to restrict use of this antibiotic, even with Centers for Disease Control and Prevention recommendation for its prudent use. In this series, shortly after the antibiotic protocol change period, three outbreaks of Gram negative bacteria were observed, one of them being multi-resistant Gram negative and one outbreak of necrotizing enterocolitis. The 2009 American Academy of Pediatrics Report of the Committee for infections Diseases attributes the increase of enterococcal infections and emergence of microorganism resistant to the increased use of vancomycin (Carmona, 2012). Additionally, third-generation cephalosporins used as first-line treatment for neonatal infections, causing increased of resistant isolates mainly among Gram-negative species.As it is possible to observe the ways to face the problems of infection and the control of the dissemination of multiresistant microorganisms, it is the rational use of antimicrobials. The protocol of antimicrobial agents should be dynamic, being re-discussed from time to time, since it takes into account the service rendering, the resistance profile of the microorganisms, such as the most frequent species, the severity of the patients, among other factors, so that they can minimize the risk of dissemination of drug resistant microorganisms, especially MDR (multi-drug resistant).

Conclusions

The profile of microorganisms responsible for the occurrence of late-onset sepsis in newborns admitted at the NICU studied had still remained the similar compared to previous studies at the same unit, with a predominance of CoNS. The most important risk factors for late-onset sepsis, common in all three period studied, was use of peripherally inserted central catheter and umbilical venous catheter, according to multivariate analysis. After two changes in the protocol of use

forantibiotics, we concluded that there was no impact on the frequency of sepsis in changing empiric antibiotic therapy for LOS. The results highlight the importance of using antibiotics judiciously in NICU settings, which may minimize the collateral damage associated with antibiotic therapy and benefit neonatal outcomes.

Conflict of interest: There are no conflicts of interest to declare.

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