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Avaliação do diagnóstico da sepse neonatal: uso de parâmetros laboratoriais e clínicos como fatores diagnósticos
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Evaluation of the neonatal sepsis diagnosis: use of clinical and laboratory parameters as diagnosis factors

AVALIAÇÃO DO DIAGNÓSTICO DA SEPSE NEONATAL: USO DE PARÂMETROS LABORATORIAIS E CLÍNICOS COMO FATORES DIAGNÓSTICOS

EVALUACIÓN DEL DIAGNÓSTICO DE SEPSIS NEONATAL: USO DE PARÁMETROS LABORATORIALES Y CLÍNICOS COMO FACTORES DIAGNÓSTICOS

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ABSTRACT

The purpose of this study was to describe and compare the clinical, laboratory and health care characteristics of newborns (NBs) with confirmed late onset sepsis and NBs with unconfirmed late sepsis, verify if there were any differences between the groups, and describe the germs prevalent in the studied neonatal unit. This is a descriptive study, involving 168 cases. It was observer that 33.3% had a confirmed diagnosis for late onset sepsis. The age at the time of sepsis onset, the length of stay, the total number of neutrophils, the number of immature neutrophils and the value of PC-r proved good parameters to differentiate between the two groups when analyzed separately. The most common isolated bacteria were: *Klebsiella pneumoniae, Staphylococcus coagulase* negative and *S. aureus*.

RESUMO

Objetivou-se descrever e comparar as características clínicas, laboratoriais e assistenciais de RN que apresentaram sepse comprovada tardia e de RN que apresentaram sepse não comprovada tardia. Em seguida, avaliar se houve diferença entre os grupos, além de descrever os germes prevalentes na unidade de neonatal estudada. Estudo descritivo, envolvendo 168 casos. Observou-se que 33,3% tiveram sepse tardia provada. A idade no momento da sepse, o tempo total de internação, a quantidade total de neutrófilos, a quantidade de neutrófilos imaturos e o valor da PC-r mostraram bons parâmetros na diferenciação entre os dois grupos quando analisados de forma isolada. A *Klebisiella pneumoniae*, o *Staphylococcus coagulase* negativo e o *S. aureus* foram as bactérias mais comumente isoladas.

RESUMEN

Se objetivó describir y comparar las características clínicas, laboratoriales y asistenciales de RN que presentaron sepsis comprobada tardía y de RN que presentaron sepsis no comprobada tardía para, entonces, evaluar si hubo diferencia entre los grupos, además de describir los gérmenes prevalentes en la unidad neonatal estudiada. Estudio descriptivo, involucrando 168 casos, 33,3% tuvieron sepsis tardía probada. La edad al momento de la sepsis, el tiempo total de internación, la cantidad total de neutrófilos, la cantidad de neutrófilos inmaduros y el valor de la PC-r mostraron buenos parámetros en la diferenciación entre los dos grupos cuando fueron analizados en forma aislada. La *Klebsiella pneumoniae*, el *Staphylococcus coagulase* negativo y el *S. aureus* fueron las bacterias aisladas con mayor prevalencia.

KEY WORDS

Sepsis.
Infant, newborn.
Diagnosis.
Neonatal nursing.

DESCRITORES

Sepse.
Recém-nascido.
Diagnóstico.
Enfermagem neonatal.

DESCRIPTORES

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INTRODUCTION

Late-onset sepsis is significantly associated with prolonged hospitalization and mortality in newborn infants (NI) hospitalized at the intensive care unit (ICU). The incidence of sepsis is higher in low-weight NI and can reach approximately 25%[1]. In developing countries, sepsis is responsible for 30 - 40% of neonatal deaths[2].

Sepsis should be adequately diagnosed at the start of the problem as, if not, actually affected NI can rapidly evolve to septic shock, disseminated intravascular coagulation and death[3].

As they spend more time with the NI, nurses and their team can detect clinical alterations compatible with the emergence of sepsis faster, provided that they know the parameters and factors that should be overseen, signalizing a rapid intervention when necessary.

At the neonatal ICU, empirical antibiotics therapy is commonly started for infants with suspected late-onset sepsis, although many of these NI are not developing sepsis, but a non-specific manifestation that can confound professionals. When antibiotics are administered but not actually necessary, the number of multi-resistant germs increases, as well as hospital cost and the chance of related adverse effects[4].

As they spend more time with the NI, nurses and their team can detect clinical alterations compatible with the emergence of sepsis faster, provided that they know the parameters and factors that should be overseen

Many studies try to correlate clinical and laboratory findings with the presence of proven sepsis. Until date, none of them has managed to define the most adequate parameters to diagnose neonatal sepsis with certainty[5]. In addition, there is the aggravating factor that no laboratory tests and clinical signs exist with sufficiently high sensitivity and negative predictive values for a diagnosis with certainty.

This study aims to describe and compare the clinical, laboratory and care characteristics of NI with late-onset primary bloodstream infection (proven sepsis) and NI with late-onset unproven sepsis (unproven sepsis), and then assess whether differences existed between both groups, besides describing the prevalent germs at the neonatal unit under analysis.

METHOD

A descriptive study was carried out between April 1st 2004 and December 31st 2008, based on prospective data collected by the Hospital Infection Control Commission (HICC).

The study started with data collection from the NI epidemiological surveillance forms that contained the diagnosis of late-onset hospital infection, based on an active search by the HICC at Hospital Universitário Antônio Pedro. Then, these NI's patient files were systematically analyzed for clinical alterations, care characteristics and laboratory results that supported the suspected diagnosis of late-onset neonatal sepsis.

The definition of sepsis published by the Brazilian National Health Surveillance Agency (ANVISA) was considered, in which it is defined as a systemic response, without any other recognized cause than infection, associated with at least two or more of the following signs and symptoms: thermal instability, bradycardia, apnea, food intolerance, worsening of respiratory discomfort, glucose intolerance, hemodynamic instability, hypoactivity and lethargy[6-7].

Infants diagnosed with proven or unproven hospital infection were included in the research, who were obligatorily hospitalized at the ICU for more than 72 hours of life, independently of their Gestational Age or weight range at birth.

The NI with late-onset sepsis, presence of two clinical signs and at least one altered laboratory result, associated with the obligatory use of antibiotics, were divided and studies in two different groups, which were:

Group 1: Unproven sepsis - NI with compatible clinical and laboratory situation, associated with negative blood culture (BC), obligatorily treated with antibiotics for at least seven days.

Group 2: Proven sepsis - RN with clinical and laboratory situation suggesting sepsis, associated with positive BC and who obligatorily received antimicrobial treatment for at least seven days.

The collected data were analyzed in Statistical Package for the Social Sciences (SPSS) software for Windows 16.0. Continuous variables were described using central tendency measures (mean, median, standard deviation and variance), while categorical variables were described through relative frequencies. Parametric tests were used for comparisons (t-test for variables with normal distribution), as well as non-parametric tests (when the variable showed no normal distribution), chi-square test and Fisher's exact test (when necessary), with significance set at 95%. Approval for this research was obtained from the Institutional Review Board at Hospital Universitário Antônio Pedro (HUAP).

RESULTS

During this period, 168 cases of late-onset neonatal sepsis occurred at HUAP, but no cases of meningitis and urinary tract infections, which are cases of proven sepsis.

The study cases were joined in two groups:

Group 1- Cases of unproven sepsis: with positive clinical signs and negative blood culture (66.7% - 112 cases).

Group 2- Cases of proven sepsis - PBSI: with positive clinical signs and positive blood culture (33.3% - 56 cases).

As for the clinical characteristics, the groups differed in terms of the NI's age at the moment the sepsis was diagnosed and the total hospitalization time, which were higher in the group of NI with PBSI. No significant differences were found for the other characteristics (Tables 1 and 2).

Table 1 - Comparison between clinical characteristics of infants under analysis - categorical variables - Niterói - 2008

		Sepsis			χ^2	p - value
		Proven	Unproven	Total		
Gender	Male	26	59	85		
	Female	30	53	83	0.583	0.445
	Total	56	112	168		
Delivery Type	Vaginal	23	31	54		
	C-section	33	81	114	3.07	0.08
	Total	56	112	168		
Birth Weight	≤ 1500g	31	63	94		
	>1500g	25	49	74	0.012	0.912
	Total	56	112	168		
Presence of asphyxia at birth	Yes	12	29	41		
	No	44	83	127	0.403	0.525
	Total	56	112	168		
Appropriateness birth weight/ gestational age*	SGA	20	46	66		
	AGA	36	64	100		
	LGA	0	2	2	1.593	0.451
	Total	56	112	168		

Obs.: *Weight for gestational age curve proposed by Alexander GR et al.. A United States national reference for fetal growth. Obstet Gynecol. 1996;87(2):163-8.

Table 2 - Comparison between clinical characteristics of infants under analysis (56 infants with proven sepsis and 112 with unproven sepsis) - continuous variables - Niterói - 2008

	Sepsis	Mean	SD	Median	Vm - VM	p - value
Birth weight (grams)	Proven	1612.86	821.31	1442.5	530-3505	
	Unproven	1614.73	851.06	1335.0	530-4430	0.989
Gestational age (weeks)	Proven	31.95	3.85	32.0	26-41	
	Unproven	32.24	4.27	32.0	24-42	0.664
Age of infant at sepsis (day)	Proven	30.93	41.10	13.5	3-213	
	Unproven	18.15	25.93	11.5	3-150	0.015
Age at the start of enteral diet (day)*	Proven	9.98	19.51	3.0	0-70	
	Unproven	5.95	10.32	3.0	0-70	0.921
Days to reach Total Oral Diet	Proven	14.09	10.61	11.0	0-42	
	Unproven	12.34	9.48	11.0	0-47	0.260
Hospitalization time (day)	Proven	62.70	60.90	37.5	6-225	
	Unproven	44.14	42.82	30.0	3-225	*0.023*

Obs.: PBSI: Primary bloodstream infection; N: quantity; SD: Standard deviation; Vm: minimum value; VM: maximum value; *Kruskal-Wallis non-parametric statistical comparison method - t-test for others; (+)/(-) Positive blood culture /Negative blood culture, respectively.

As for the presence and duration of invasive support, no significant differences between the groups appeared (Table 3). No difference was found either for usage time of peripherally inserted central catheter (PICC) (N=37 - mean 13.4 days vs. 18.8 days), of umbilical catheter (N=17 - mean 3.87 days vs. 3.20 days) and vesical catheter (N=3 - 2 RN with unproven sepsis and 1 RN with proven sepsis).

Table 3 - Comparison between usage time of invasive support in infants who used this support in the study groups - Niterói - 2008

	Sepsis	N	Mean	SD	Median	Vm - VM	p - Value
Days of O_2 use at sepsis	Proven	48	16.25	21.69	8	1-105	0.877
	Unproven	90	16.91	24.81	8	1-174	
Days of CPAP use	Proven	41	11.10	13.93	7	1-83	
	Unproven	77	12.83	15.48	7	1-83	0.550
Days of Oxi-HOOD use	Proven	37	4.27	5.45	2	1-31	
	Unproven	70	4.71	5.45	2	1-31	0.690
Days of O_2 catheter use	Proven	9	15.22	16.51	10	1-45	
	Unproven	18	9.72	13.37	4	1-45	0.360
Days of Mechanical Ventilation use	Proven	28	18.32	21.00	9	1-86	
	Unproven	76	16.57	19.30	10	1-86	0.689
Days of PN	Proven	38	16.84	15.12	12	1-85	
	Unproven	82	15.40	15.15	11	1-85	0.629

Obs.: PBSI: Primary bloodstream infection; N: quantity; SD: Standard deviation; Vm: minimum value; VM: maximum value; (+)/(-) Positive blood culture / Negative blood culture, respectively. PN: parenteral nutrition; O2: oxygen; CPAP: continuous positive airway pressure; Oxi- HOOD: oxygen therapy hood.

None of the clinical manifestations showed differences between the study groups, as shown in Table 4.

Table 4 - Comparison between presence of clinical alterations in study groups -Niterói - 2008

		Blood culture result			χ^2	p - value
		Positive	Negative	Total		
Respiratory Problems	Yes	28	49	77		
	No	28	63	91	0.587	0.443
	Total	56	112	168		
Intestinal Tract Manifestations	Yes	9	30	39		
	No	47	82	129	2.404	0.121
	Total	56	112	168		
Neurological Manifestations	Yes	24	65	89		
	No	32	47	79	3.453	0.063
	Total	56	112	168		
Temperature	Hypothermia	4	8	12		
	Normothermia	36	83	119		
	Hyperthermia	16	21	37	2.144	0.342
	Total	56	112	168		
Coagulation manifestations	Yes	1	5	6		
	No	55	107	162	0.778	0.378
	Total	56	112	168		
Cardio-Respiratory manifestations	Yes	15	32	47		
	No	41	80	121	0.059	0.808
	Total	56	112	168		
Metabolic Alterations	Yes	4	7	11		
	No	52	105	157	0.049	0.825
	Total	56	112	168		

As for the laboratory tests, differences were found in the total quantity of neutrophils and the quantity of immature neutrophils, collected within 24h after the start of clinical signs (Table 5).

Table 5 - Comparison between hematologic parameters in study groups - Niterói - 2008

	Sepsis	N	Mean	SD	Median	Vm - VM	p- value
White cells (cells/mm3)	Proven	56	13,814	9,069	11200.00	1,600-56,600	
	Unproven	112	13,580	9,446	11000.00	2,300-70,000	0.831
Total Neutrophils(%)	Proven	56	61	15	61	27-90	
	Unproven	112	54	15	52	16-92	0.004
Immature Neutrophils* (%)	Proven	56	12	11	10	0-55	
	Unproven	112	8	7	7	0-41	0.010
Ratio of Immature on Total Neutrophils	Proven	56	0.20	0.17	0.19	0-0.9	
	Unproven	112	0.15	0.13	0.13	0-0.63	0.350
Platelets (units/mm3)	Proven	56	192,898	153,647	148,000	1,000-590,000	
	Unproven	112	240,042	158,695	223,000	890-913,000	0.700
Serum value of C-reactive protein (mg%)**	Proven	23	5,50	4,89	3,7	0,04-17,01	
	Unproven	35	1,17	2,18	1,0	0,02-10,16	0.000

Obs: PBSI: Primary bloodstream infection; N: quantity; SD: Standard deviation; Vm: minimum value; VM: maximum value; *Kruskal-Wallis non-parametric statistical comparison method - t-test for others. ** Values related to 2007 and 2008.

A significant difference was found for C-reactive protein (PC-r) levels between the study groups. These data, however, only refer to NI hospitalized between 2007 and 2008 (N=65), when this test was routinely collected (Table 5).

The most commonly isolated bacteria were Klebsiella pneumoniae, Staphylococcus coagulase-negative and S. aureus. Out of the 50 germs isolated in the cultured blood samples, 14 bacteria were multi-resistant, nine of which were Klebsiella pneumoniae extended-spectrum beta-lactamases (ESLB) positive and five S. aureus methicillin-resistant (MRSA) (Table 6).

Table 6 - Frequency of isolated bacteria in blood cultures of infants with proven sepsis - Niterói - 2008

Isolated bacteria	Frequency	Percentage(%)
K. pneumoniae total	20	34,5
K. pneumoniae ESBL+*	9	45,0
S. coagulase negative	10	17,2
S. aureus total	8	13,8
MRSA*	5	62,5
Serratia marcensens	6	10,3
P. aeroginos	4	6,9
Enterobacter	3	5,2
E. coli	1	1,7
Acinetobacter	1	1,7
Streptococcus viridans	1	1,7
Enterococo	1	1,7
Candida spp	1	5,2
Total	**56**	**100**

* Multiresistant bacteria; ESBL:xxx ; MRSA:xxx

DISCUSSION

Clinical and laboratory findings have been analyzed in medical literature to define the diagnosis of proven sepsis in NI more precisely.

The clinical characteristics observed at the start of late-onset sepsis (24 hours before and after the start of the condition) in the NI under analysis did not show precision to distinguish between the two study groups, except for age at the moment of sepsis and total hospitalization time, which were both higher in infants with proven sepsis.

The NI's higher age at the moment they presented proven sepsis reflects greater exposure to risk factors and invasive procedures occurred during the hospitalization period, an important fact to increase the risk of proven sepsis. On the other hand, the fact of presenting nosocomial sepsis generates an often prolonged stay and, thus, increased hospitalization time. The duration of hospitalization is significantly longer in children who develop late-onset sepsis in comparison with those who do not develop sepsis[1]. The time of hospital stay and use of invasive devices make the NI more vulnerable to hospital sepsis[8]. In this study, it was verified that longer hospitalization is related with higher incidence of proven sepsis.

It is important to highlight that no difference occurred in the use of invasive devices between the two groups (PICC, vesical catheter and umbilical catheter). As reported in literature[9-10], the prolonged use of invasive support devices put the NI at risk of systemic and local infectious complications by potentially pathogenic germs like Staphylococcus coagulase negative spp, Enterococcus, Staphylococcus aureus, Enterobacter spp, Candida albicans, Pseudomonas areuginosa and Klebsiella pneumoniae.

The presence of certain clinical manifestations did not distinguish between the NI in both study groups. Clinical alterations are described as predictive signs with low diagnostic value for sepsis, needing other associated diagnostic proof to confirm the condition[11]. Even if the clinical alterations associated with neonatal sepsis are not specific, but can be attributed to another problems or diseases than neonatal sepsis, authors[12] report that, besides laboratory alterations, the patient's clinical situation should be valued,

as the risk of bacterial infections in asymptomatic infants is very low.

Negative blood culture results do not imply the inexistence of bacterial sepsis in NI, as the sensitivity of blood culture is low[13], which justifies the difficulty to isolate the germ even when present in the bloodstream. The number of positive blood culture results varies, ranging between 33 and 53% in neonatal sepsis cases[4]. In this study, it corresponded to 33.3% among cases treated as late-onset sepsis.

The total quantities of neutrophils and immature neutrophils were higher in the NI group with proven sepsis. A study[14] involving patients with late-onset sepsis showed that increased quantities of total neutrophils showed low sensitivity (65%) and low positive predictive value (18%) for the sepsis diagnosis, but an excellent negative predictive value (98%).

Thus, normal values could exclude the occurrence of sepsis and calculating the relation between the absolute number of total and immature leukocytes can help to diagnose neonatal sepsis, showing the best sensitivity among all hematological parameters[15].

This study did not intend to calculate sensitivity, specificity, positive and negative predictive values of the clinical, laboratory and care parameters under analysis, as no proven non-infected group was included for the sake of comparison.

In this study, the PC-r showed to be an excellent laboratory method to distinguish between the NI in both study groups (Table 5). Levels were higher for NI with proven sepsis, suggesting that this dosage can support the initial diagnosis of proven neonatal sepsis. Nowadays, in function of its high negative predictive value, PC-r dosage is used, when negative, to discard the sepsis diagnosis, and also guides the treatment time with antibiotics therapy[16].

Bacteria are the main responsible for infectious complications in neonates. The epidemiological profile of these germs apparently changes at each neonatal ICU. Today, a larger number of cases caused by gram-negative bacteria is observed in late-onset sepsis[8], but the proportion of late-onset sepsis cases associated with gram-positive bacteria has progressively increased over the last two decades and, today, S. aureus, S. coagulase negative and Enterococos are responsible for 30 to 50% of cases[8]. In this study, these bacteria represented 34% of all isolated germs.

As for the bacteria isolated in blood samples of NI with late-onset sepsis, the most important bacteria were K. pneumoniae, S. coagulase negativo, S. aureus, in line with current medical literature[5].

The main infectious agent of late-onset infections is Klebsiela[17]. In this study, these bacteria were responsible for 34.5% of sepsis cases. The K. pneumoniae that produce positive ESBL are increasingly common in hospital sepsis in neonates and are associated with increased morbidity due to the difficult and prolonged treatment[18]. In this research, 45% of isolated K. pneumoniae were ESBL positive.

Another germ constantly related with the severity of late-onset nosocomial infection and increased morbidity is methicillin-resistant S. aureus (MRSA)[8,1]. This germ represented 62.5% of S. aureus isolated in blood cultures in this research. In a study[19] of NI with proven late-onset sepsis caused by S. aureus, only 8% were due to MRSA.

CONCLUSION

Clinical manifestations were insufficient to distinguish between NI with proven sepsis and NI with unproven sepsis. Alertness to these manifestations can be very important though, which can often represent early signs of proven late-onset sepsis. Neonatology Nurses need to rapidly identify these suspicious signs, besides other factors, supporting a fast diagnosis.

Care characteristics have shown that age at the moment the sepsis is diagnosed and total hospitalization time can contribute to an early suspicion of sepsis, as they distinguished between both study groups.

In the laboratory tests, the PC-r serum level found was different in the two groups. Medical literature, however, only indicates its use to discard sepsis cases in case of negative results, due to its high negative predictive value.

Total and immature neutrophils efficiently distinguished the study groups and, hence, can help to diagnose sepsis. They should not be analyzed separately though, due to their low positive and negative predictive value.

The search for more efficient methods to identify proven sepsis should be a constant focus in research, as this disease is one of the main causes responsible for infant mortality at neonatal ICUs and, consequently, for high social and financial costs.

REFERENCES

1. Stoll BJ, Hansen N, Fanaroff AA, Wright L, Carlo WA, Ehrenkranz RA, et al. Late-onset sepsis in very low birth weight neonates: the experience of the NICHD Neonatal Research Network. Pediatrics. 2002;110(2 Pt 1):285-91.

2. World Health Organization (WHO). Young Infants Study Group. Bacterial etiology of serious infections in young infants in developing countries. Pediatr Infect Dis J. 1999;18(10 Suppl):S17-22.

3. Chiesa C, Panero A, Osborn JF, Simonetti AF, Pacifico L. Diagnosis of neonatal sepsis: a clinical and laboratory challenge. Clin Chem. 2004;50(2):279-87.

4. Hudome SM, Fisher MC. Nosocomial infections in the Neonatal Intensive Care Unit. Curr Opin Infect Dis. 2001;14(3):303-7.

5. Polin RA. The "ins and outs" of neonatal sepsis. J Pediatr. 2003;143(1):3-4.

6. Brasil. Ministério da Saúde. Agencia Nacional de Vigilância Sanitária. Neonatologia: Critérios Nacionais de Infecção Relacionadas à Assistência à Saúde. Brasília; 2008.

7. Bone RC. The patoghenesis of sepsis. Am Intern Med. 1991;115(6):457-69.

8. Sundaram V, Kumar P, Dutta S, Mukhopadhyay K, Ray P, Gautam V, et al. Blood culture confirmed bacterial sepsis in neonates in a North Indian tertiary care center: changes over the last decade. Jpn J Infect. Dis. 2009;62(1):46-50.

9. Perlman SE, Saiman L, Larson EL. Risk factors for late-onset health care-associated bloodstream infections in patients in neonatal intensive care units. Am J Infect Control. 2007;35(3):177-82.

10. Ottolini MC, Lundgren K, Mirkinson LJ, Cason S, Ottolini MG. Utility of complete blood count and blood culture screening to diagnose neonatal sepsis in the asymptomatic at risk newborn. Pediatr Infect Dis J. 2003;22(5):430-4.

11. Weber MW, Carlin JB, Gatchalian S, Lehmann D, Muhe L, Mulholland EK, et al. Predictors of neonatal sepsis in developing countries. Pediatr Infect Dis J. 2003;22(8):711-7.

12. Escobar GJ, Li DK, Armstrong MA, Gardner MN, Folck BF, Verdi JE, et al. Neonatal sepsis workups in infants >/=2000 grams at birth: a population-based study. Pediatrics. 2000;106(2 Pt 1):256-63.

13. Gerdes JS. Clinicopathologic approach to the diagnosis of neonatal sepsis. Clin Perinatol. 1991;18(2):361-81.

14. Berger C, Uehlinger J, Ghelfi D, Blau N, Fanconi S. Comparison of C-reactive protein and white blood cell count with differential in neonates at risk for septicaemia. Eur J Pediatr. 1995;154(2):138-44.

15. Manroe BL, Weinberg AG, Rosenfeld CR, Browne R. The neonatal blood count in health and disease. I. Reference values for neutrophilic cells. J Pediatr. 1979;95(1):89-98.

16. Rezende Junior DC, Moraes JMMF, Lucca MG, Orrico SRP, Spegiorin MA, Christiano Junior AC, et al. O rápido declínio da concentração sérica de proteína C-Reativa na fase inicial da sepse é preditivo de boa evolução. Rev Bras Terapia Intensiva. 2005;17(2):104-7.

17. Gaynes RP, Edwards JR, Jarvis WR, Culver DH, Tolson JS, Martone WJ. Nosocomial infections among neonates in high-risk nurseries in the United States. Pediatrics. 1996;98(3 Pt 1):357-61.

18. Sirot D. Extended-spectrum plasmid-mediated beta-lactamases. J Antimicrob Chemother. 1995;36 Suppl A:19-34.

19. Naimi TS, LeDell KH, Como-Sabetti K, Borchardt SM, Boxrud DJ, Etienne J, et al. Comparison of community-and health care-associated methicillin-resistant Staphylococcus aureus infection. JAMA. 2003;290(22):2976-84.

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