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Editor in Chief, Clinical Medicine Insights: Pediatrics

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Sat, Jul 10, 10:48 PM

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Sincerely,
Mr. Umair Shafique
Editor in Chief, Clinical Medicine Insights: Pediatrics

Clinical Medicine Insights:Pediatrics

Clinical manifestations and laboratory findings in late-onset neonatal sepsis: An observation at a pediatric center in Vietnam

Journal:	*Clinical Medicine Insights: Pediatrics*
Manuscript ID	PDI-21-0026
Manuscript Type:	Original Research Article
Keywords:	neonate, sepsis, culture, Blood
Abstract:	Background: Neonatal sepsis is one of the major causes of morbidity and mortality in newborns. Early diagnosis of neonatal sepsis is important for timely initiation of correct antimicrobial therapy. We aim to investigate clinical manifestations and laboratory findings of late-onset neonatal sepsis (LOS). Methods and Material: In a cross sectional study from May 2018 to September 2020, a total of 158 consecutive infants with clinical manifestations of sepsis were analyzed. Check list of infant's data, presenting symptoms or signs and laboratory data of all objectes were evaluated and recorded. Results: The mean age at the time of late-onset sepsis (LOS) presentation was 17.7±6.3 days. Gastroenteritis made the most contribution to LOS, with 32.9%, followed by proportions of pneumonia and omphalitis, 29.7% and 17.7% respectively. The figures for sepsis and bacterial meningitis were only 1.9% and 2,5%. Additionally, the percentages of skin infection and respiratory manifestations were 57.0% and 42.4% respectively. Neurologic symptoms approximately accounted for 31.0% and the figure for umbilical cord symptoms was 23.4%. The percentage of cardiocirculatory symptoms was only 9.5%. Fever made up around 58.9% of clinical manifestations, by contrast, there was no hypothermia symptom. Anemia, leukocytosis, leukocytopenia and C-reactive protein (CRP) positive results was detected in 41.1%, 8.4%, 4.3% and 18.4% neonates, respectively. Bacterial cultures were positive in 7 (4.4%) of neonates. Conclusions: The clinical signs and symptoms of late-onset neonatal sepsis are unspecific. The routine laboratory findings are varied, and bacterial cultures are positive in a small number of neonates.

Title of the article: Clinical manifestations and laboratory findings in late-onset neonatal sepsis: An observation at a pediatric center in Vietnam

Abstract:

Background: Neonatal sepsis is one of the major causes of morbidity and mortality in newborns. Early diagnosis of neonatal sepsis is important for timely initiation of correct antimicrobial therapy. We aim to investigate clinical manifestations and laboratory findings of late-onset neonatal sepsis (LOS).

Methods and Material: In a cross sectional study from May 2018 to September 2020, a total of 158 consecutive infants with clinical manifestations of sepsis were analyzed. Check list of infant's data, presenting symptoms or signs and laboratory data of all objectes were evaluated and recorded.

Results: The mean age at the time of late-onset sepsis (LOS) presentation was 17.7±6.3 days. Gastroenteritis made the most contribution to LOS, with 32.9%, followed by proportions of pneumonia and omphalitis, 29.7% and 17.7% respectively. The figures for sepsis and bacterial meningitis were only 1.9% and 2,5%. Additionally, the percentages of skin infection and respiratory manifestations were 57.0% and 42.4% respectively. Neurologic symptoms approximately accounted for 31.0% and the figure for umbilical cord symptoms was 23.4%. The percentage of cardiocirculatory symptoms was only 9.5%. Fever made up around 58.9% of clinical manifestations, by contrast, there was no hypothermia symptom. Anemia, leukocytosis, leukocytopenia and C-reactive protein (CRP) positive results was detected in 41.1%, 8.4%, 4.3% and 18.4% neonates, respectively. Bacterial cultures were positive in 7 (4.4%) of neonates.

Conclusions: The clinical signs and symptoms of late-onset neonatal sepsis are unspecific. The routine laboratory findings are varied, and bacterial cultures are positive in a small number of neonates.

Key-words: neonate, sepsis, culture, blood

Introduction:

According to World Health Organization (WHO) stastistics and The National Institute for Health and Clinical Excellence (NICE) 2014, sepsis is a significant cause of mortality among newborn infants.[1-3] In neonatal sepsis, apart from early-onset sepsis (EOS), late-onset sepsis (LOS), which the onset of symptoms ≥ 72 hours of life, is likely to make up the great proportion and present with a wide range of clinical manifestations including pneumonia, umbilical infection, meningitis and sepsis.[4-6] According to Shehab El – Din's surveillance in Egypt from 2011 to 2012, 45,9% among amitted neonates were diagnosed with suspected sepsis, in which 55,8% were classified as LOS and the mortality rate for this was 42,9%. Etiologic agents are commonly from enviromental sources or maternal flora including S.aureus, GBS, Listeria, negative gram bacteria and fungi.[7] Although currently many studies has described neonatal sepsis and early-onset sepsis in Vietnam, there are limited contemporary data on late-onset sepsis. Therefore, in this study, we aim to investigate clinical manifestations and laboratory findings of late-onset neonatal sepsis.

Subjects and Methods:

This prospective study was performed on 158 consecutive neonates with clinical symptoms of sepsis, who were admitted to Neonatal Intensive Care Unit of Hue

Central Hospital from May 2018 to September 2020. The study was approved by the Ethics Committee of Hue Central Hospital (reference number: 07-2018/NCKH-BVH). The study included all neonates aged more than 72 hours exhibiting clinical symptoms of sepsis such as lethargy, poor feeding, fever, reduced primitive reflexes,hypothermia, cyanosis, apnea, convulsion, emesis, respiratory distress, and abdominal distension.

All neonates underwent complete blood count (CBC) with white blood differential, C-reactive protein (CRP), blood/umbilical cord culture, serum glucose and electrolyte. Cultures were collected using the BACTEC 9120 blood culture system. Chest X-rays and abdominal ultrasound were performed in cases of respiratory or digestive symptoms, respectively.

LOS were considered based on exhibited clinical symptoms after 72 hours of age. Definitive sepsis was diagnosed based on the clinical symptoms of sepsis, and positive blood or CSF cultures. Cultures were immediately recollected in case of probable septic cultures.

Neonatal data were captured and analyzed using Statistical Package for Social Sciences (SPSS) version 22.0. Comparisons and statistical inference were made using the Chi square test to assess risk factors and the t test to assess the degree of statistical significance when comparing means. Statistical significance was accepted at a 5% probability level, that is, a p-value of less than 0.05.

Results:

Clinical manifestations

One hundred fifty-eight suspected late-onset neonatal sepsis cases were analyzed. The study was conducted on both positive and negative culture subjects. The baseline characteristics of the neonates are listed in Table 1. The number of male

and female was approximately equal. The rate of normal weight infants was 89.9% and in-term neonates accounted for 94.3%. The rate of neonates from rural area (64.6%) roughly doubled that from urban area (35.4%). There was no difference between the rate of Cesarean section and vaginal delivery. The mean age at the time of LOS presentation was 17.7±6.3 days.

Gastroenteritis made the most contribution to LOS, with 32.9%, followed by proportions of pneumonia and omphalitis, 29.7% and 17.7% respectively. The figures for sepsis and bacterial meningitis were only 1.9% and 2,5% (Table 2).

Table 3 shows the clinical symptoms of LOS. The proportion of gastrointestinal symptoms in LOS was the highest figure in all manifestations, with 73.4%. Additionally, the percentages of skin infection and respiratory manifestations were 57.0% and 42.4% respectively. Neurologic symptoms approximately accounted for 31.0% and the figure for umbilicus was 23.4%. The percentage of cardiocirculatory symptoms was only 9.5%. Fever made up around 58.9% of clinical manifestations, by contrast, there was no hypothermia symptom.

Neonates presented with tachycardia accounted for 7.6%. The figure for bradycardia and shock sign was only 1.3% and 0.6% respectively (Table 4). In all respiratory symptoms, the proportions of cough, use of accessory muscles and rales stood at the roughly same level, with 17.7%, 18.4% and 12% correspondingly. As for others, the percentages of apnea and grunting was the lowest figures, with 3.2% and 5.1% (Table 5). The percentages of abdominal distention and poor feeding stood at much higher figure, with 43.7% and 45.6%. Hepatomegaly and bloody stool accounted for only 1.9% and 4.4% (Table 6). Altered levels of consciousness accounted for approximately one third of neurological symptoms, in which the percentage of

confusion was 15.8%. The proportions of poor tone and seizure were inconsiderable (Table 7).

Laboratory findings

Table 8 shows the type and frequency of isolated pathogens. Out of 108 blood cultures, only 3 (2.8%) showed the growth of different bacteria, in which Streptococcus Agalactiae was found in 2 cases and Enterococcus Faecalis was isolated in 1 case. There was 6/21 cases with positive umbilical cord blood culture, in which Staphylococcus aureus was identified of all cases and half of the cases were positive for MRSA. A total of 2 pustule cultures were positive. Only 1 stool culture showed the growth of E.coli, which accounted for 14.3%. All 4 cerebrospinal fluid culture results were negative. Complete blood count results and CRP level are presented in Table 9 and Table 10, respectively. Anemia stood at much higher figure, with 41.1%. The figures for high WBC count and low WBC count were 8.4% and 4.3% respectively. The platelet count hardly changed in our study. In late-onset neonatal sepsis, elevated CRP levels made up one third of all cases, in which there was 18.4% moderate elevation of CRP levels. CRP median of the study was 12.4 mg/L. Blood glucose and electrolyte levels are listed in Table 11. Hyponatremia accounted for 19,3% of cases in late-onset neonatal sepsis. There was no change in both blood glucose levels and potassium levels in our research.

Discussion:

Clinical manifestations

Our results illustrated that the incidence of late-onset neonatal sepsis in male (53.8%) is higher than that in female (46.2%). According to Burstein's research, there was high rate of late onset neonatal sepsis in newborn infants with gestational age <32 weeks or birth weight <1500 gram.[8] The difference could be resulted from

exclusion criteria which we excluded preterm or low birth weight infants acquired hospital infection. As for delivery methods, there was no difference between vaginal delivery and cesarean section.

In our study, gastrointestinal infection and pneumonia stood at much higher figures with 32.9% and 29.7% respectively. This result was similar to other outcomes which indicated the high proportion of pneumonia in LOS. Moreover, gastrointestinal infection accounted for the highest percentage of LOS in the research. Therefore, in order to reduce the rate of gastrointestinal infection and boost the neonates' immune system, raising the public's awareness in personal hygiene, breast feeding during first six months of life play an important role.

We found that, the gastrointestinal symptoms occupied the highest proportion, with 73.4%, followed by skin and respiratory manifestations, 57.0% and 42.4% respectively. Moreover, cardiocirculatory symptoms made up the least figure, with 9.5%. Of all nenates, 58.9% presented with hyperthermia, while there was no one manifesting hypothermia. The presence of fever is related to the body immune's response to pathogens, so the fever in first month of life should be considered a symptom of infection.[9] However, our study's results indicated that fever seemed not to be a specific sign to diagnose neonatal sepsis. Therefore, the diagnosis of neonatal sepsis should be established by all clinical and subclinical symptoms.[10] Although, in many cases, hypothermia could be a symptom of neonatal sepsis, particularly in preterm infants; the majority of our research subjects were the full term infants (94.3%). As a result, there was no infant manifesting hypothermia in the study.

Cardiocirculatory symptoms only occupied the small percentage in our study, with 9.5%, in which the percentages of tachycardia, bradycardia and shock signs were

7.6%, 1.3% and 0.6% correspondingly. The changes of heart rate were the most important symptoms related to infection;[11] however, these symptoms are affected by many factors and the lack of patient monitoring devices. Therefore, repeated examinations to detect the changes in neonatal heart rate play an important role in timely diagnosis and treatment.

In present study, neonates presented with respiratory symptoms made up 67.0%, in which tachypnea was the most commonplace signs with 27.2%. As for the others, the figures for use of accessory muscles, cough and rales were 18.4%, 17.7% and 12.0% respectively. Meanwhile, grunting and apnea stood the lowest figures, with 5.1% and 3.2%. In neonates, pneumonia may be similar to that in children. However, the most outstanding features in this age were apnea and signs of diffuse infection. The infected infants may often be afebrile without cough and rales.[12]

It is remarkable that respiratory manifestations are the ubiquitous and essential signs of neonatal infection. Additionally, apnea and grunting are commonly presented on the preterm newborns because of the impairment of lung function caused by immature cartilages of infant's airway.[13] Moreover, preterm infants often have the narrow thorax, fragile ribs and immature intercostal muscles, so these features reduce the capability of their chest movement.[14] Beside that, the lacks of full lung surface area, blood flow, surfactant are also the considerable factors. However, the majority of our research subjects are full term infants; as a result, the proportions of apnea and other respiratory sympstoms are low.

In our study, gastrointestinal symptoms made up 73.4%, in which the percentages of poor feeding and abdominal distention were 43.7% and 45.6% correspondingly. Meanwhile those of vomiting and diarrhea were 27.2% and 24.7%. These statistic data showed that poor feeding, abdominal distention and vomiting are the ubiquitous

symptoms of neonatal sepsis. However, these symptoms may not be specific to sepsis because the signs could also be found in gastrointestinal infection, meningitis or pneumonia. Therefore, when an infant present with gastrointestinal manifestations, careful physical examination is the most important thing for probable management and prognosis.

Regarding to neurological symptoms, 31.0% neonates in our study presented with neurological symptoms, in which the changes of consciousness level occupied 29.8%. In addition, while confusion and irritability were the popular signs, with 15,8% and 10,8%, lethargy only made up the least figure. As for the others, the figures for poor tone and seizure were 0,6% and 1,9%. Although neurological manifestations are the crucial symptoms, they requires the physician's carefullness and the general physical examinations of patients. Neonates' cortex could be easily triggered or inhibited, so irritablity and lethargy are remarkably common. Bulging fontanelle is not the ubiquitous finding in meningitis in the neonates.[15]

Laboratory features.

In our study, the incidence of positive cultures of specimens was actually low, in which positive blood cultures occupied only 2.8%. As for the others, the percentage of positive umbilical cord blood cultures stood the highest figure of all, with 28.6%, while that of positive stool cultures was only 14.3%. One hundred percent of pustule cultures were positive, by contrast, all cerebrospinal fluid culture results were negative.

Thanks to the data, two thirds of the blood culture results were positive for GBS, which might be transmitted from colonized mothers or aqquired from the environment.

Overall, stool culture was positive for E.Coli in 1 case and up to 8 specimen cultures were positive for S.Aureus and MRSA. These pathogens are the main etiologic agents causing both hospital and community acquired infections. In addition, E.Coli is also the main cause of gastrointestinal infection in neonates, particularly in the developing countries.[16]

The positive umbilical cord blood cultures accounted for 28.6%. All these specimens tested positive for S.Aureus, in which half of the results were positive for MRSA. These also the typical predominant pathogens resulting in infants' umbilicus. Therefore, principles of cleaniness in umbilical cord cutting and taking care of umbilicus play an important role in reduction of infants' omphalitis after birth. S.Aureus, which was one of the most common causes of skin and soft tissue in infants, also was found in pustule cultures.

In our series, most of infected neonates had no change in the number of white blood cells. Only 12.7% of neonates showed the abnormal number of white blood cells and the percentage of low number of platelets was 3.2%. The incidence of anemia stood at much higher figure, with 41.1%. Additionally, anemia is also the feasible feature of neonatal sepsis, particularly in severe sepsis. However, anemia are also found in many diseases including preterm childbirth or hemolysis, so the deeper researches in sepsis related anemia would be necessary. 26.4% of infected neonates showed their elevated CRP levels, in which the proportion of the infants with moderate elevation of CRP was 18.4% and that with very high CRP levels was only 3.8%. It is clear that there is no strong association between elevation of CRP and neonatal sepsis; therefore, evaluation for late onset neontal sepsis includes a comprehensive physical examination, laboratory testings and repeated CRP level measurements. Moreover, the changes in CRP levels are also the important tool for follow-up and evaluation.

The percentage of neonates with very high CRP levels was 3.8% in our study might be caused by the low proportion of severe infection including severe sepsis or bacterial meningitis.

The false positive CRP reactions might be resulted from noninfectious causes, so the CRP elevation is not the compulsory criteria in indications for antibiotic therapy. However, CRP levels is an useful implements for follow-up and evaluation.

1.9% of neonates was the figure for neonates with both hypoglycemia and hyperglycemia. Acute stress hyperglycemia could do wonder for infants' body because the high glucose delivery to tissues or organs could meet the cells' energy demands in order to cope with stress. However, many researches has illustrated that hyperglycemic response , especially long-term hyperglycemia, tends to be harmful to serious illnesses. In our study, the proportion of neonates with glycemic instability was remarkable low because the majority of subjects was full term neonates and the low rate of the infants with severe sepsis or meningitis.

Our study illustrated that there were the small proportions of infants with glycemic instability or electrolyte disorders because of the high public awareness of taking care of their children and detection of neonatal warning signs such as vomiting or poor feeding.

Conclusion

The mainly clinical features of late-onset neonatal sepsis are gastrointestinal infection and pneumonia. Sepsis and meningitis accounted for the small figures. The clinical signs and symptoms of LOS are unspecific. The routine laboratory findings are varied and bacterial cultures cultures are positive in a small number of neonates. S.Aureus and E.coli are the common causes of LOS in our center.

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Declaration of conflicting interests:

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Author Contributions

All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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Table 1. Baseline characteristics of the neonates

Baseline characteristics		n	%
Gender	Male	85	53.8
	Female	73	46.2
Birth weight (gram)	< 2500	11	7.0
	2500 - < 4000	142	89.9
	≥ 4000	5	3.2
Gestational age (weeks)	Preterm	9	5.7
	Term	149	94.3
Geographical location	Urban region	56	35.4
	Rural region	102	64.6
Type of delivery	Vaginal delivery	86	54.4
	Cesarean section	72	45.6
Total		158	100%

Table 2. Clinical manifestations of late-onset neonatal sepsis

Clinical manifestation	**n**	**%**

Gastroenteritis	52	32.9
Pneumonia	47	29.7
Omphalitis	28	17.7
Skin infection	12	7.6
Bacterial meningitis	4	2.5
Sepsis	3	1.9
Others	12	7.6
Total	158	100

Table 3. Frequency of clinical symptoms

Clinical symptoms (n=158)		**n**	**%**
Temperature instability	Fever	93	58.9
	Hypothermia	0	0.0
Skin and soft tissue infection		90	57.0
Cardiocirculatory symptoms		15	9.5
Respiratory symptoms		67	42.4
Gastrointestinal symptoms		116	73.4
Neurologic symptoms		49	31.0
Umbilical cord symptoms	Omphalitis	20	12.7
	Severe	17	10.8

Table 4. Cardiocirculatory manifestations

Cardiocirculatory manifestations		n	%
Heart rate	Tachycardia (> 160)	12	7.6
	Bradycardia (<120)	2	1.3
	Normal (120 - 160)	144	91.1
Shock signs		1	0.6

Table 5. Respiratory symptoms

Respiratory symptoms **(n=158)**	**n**	**%**
Tachypnea	43	27.2
Use of accessory muscles	29	18.4
Cough	28	17.7
Rales	19	12.0
Grunting	8	5.1
Apnea	5	3.2

Table 6. Gastrointestinal symptoms

Gastrointestinal symptoms (n=158)	**n**	**%**
Abdominal distention	72	45.6
Poor feeding	69	43.7
Vomiting	43	27.2
Diarrhea	39	24.7

Bloody stool	7	4.4
Hepatomegaly	3	1.9

Table 7. Neurological symptoms

Neurological symptoms **(n=158)**		**n**	**%**
Consciousness level	Confusion	25	15.8
	Irritability	17	10.8
	Lethargy	5	3.2
Poor tone		3	1.9
Seizure		1	0.6

Table 8. Type and frequency of isolated pathogens

Culture		**n**	**%**	**Pathogens**
Blood culture (n = 108)	Positive	2	2.8	Streptococcus Agalactiae
		1		Enterococcus Faecalis
Umbilical cord blood culture (n = 21)	Positive	3	28.6	Staphylococcus Aureus
		3		MRSA
Stool culture (n = 7)	Positive	1	14.3	E.Coli
Pustule culture (n = 2)	Positive	1	100	Staphylococcus Aureus
		1		MRSA

Cerebrospinal fluid culture (n = 4)	Negative	4	100	

Table 9. Complete blood count results

Complete blood count		**n**	**%**	**Median ± SD**
Hemoglobin (g/dl)	Anemia	65	41.1	13.7 ± 2.1
	Normal	93	58.9	
White blood cells (K/ul)	High	15	8.4	12 ± 5.1
	Low	5	4.3	
	Normal	138	87.3	
Platelets (K/ul)	Low	5	3.2	365.1 ± 133.2
	Normal	153	96.8	

Table 10. CRP level

CRP value (mg/l)		n	%	Median ± SD
Normal		116	73.4	12.4 ± 27.7
Elevated	Moderate (10 - 40)	29	18.4	
	High (40 - 80)	7	4.4	
	Very high (> 80)	6	3.8	

Table 11. Blood glucose and electrolyte levels

Results			n	%
Blood glucose levels (n = 103)	Normal		99	96.1
	Hyperglycemia		2	1.9
	Hypoglycemia		2	1.9
Potassium levels (n = 88)	Normal		87	98.9
	Abnormal	Hyperkalemia	0	0.0
		Hypokalemia	1	1.1
Sodium levels (n = 88)	Normal		71	80.7
	Abnormal	Hypernatremia	0	0.0
		Hyponatremia	17	19.3