ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES
Knowledge to Innovation

Vol 18, Issue 7, 2025

Online - 2455-3891
Print - 0974-2441

Research Article

CURRENT TRENDS IN ANTIBIOGRAM WITH SPECIAL REFERENCE TO ANTIBIOTIC STEWARDSHIP FOR CASES OF NEONATAL SEPSIS AND CORRELATION WITH PROCALCITONIN AND INTERLEUKIN-6 AS DIAGNOSTIC MARKERS AT NEONATAL INTENSIVE CARE UNIT, MEDICAL COLLEGE, KOLKATA

SUBHRANIL MAL[1], BIYANKA SAU[2], DIBYENDU RAY CHAUDHURI[3], BIRUPAKSHA BISWAS[4], SUHENA SARKAR[5]*

[1]Department of Pharmacology, Medical College, Kolkata, West Bengal, India. [2]Department of Microbiology, Medical College, Kolkata. [3]Department of Paediatrics, Medical College, Kolkata. [4]Department of Pathology, Burdwan Medical College, Burdwan, [5]Department of Pharmacology, Medical College, Kolkata, West Bengal, India.
***Corresponding author: Suhena Sarkar; Email: suhena.m@gmail.com**

Received: 11 April 2025, Revised and Accepted: 04 June 2025

ABSTRACT

Objectives: The objectives of this study were to assess current trends in the microbiological profile and antibiotic resistance in neonatal sepsis, with emphasis on the diagnostic utility of procalcitonin (PCT) and interleukin-6 (IL-6) as early markers.

Methods: Blood samples were collected from neonates with suspected sepsis for microbial culture, antibiotic susceptibility testing, and quantitative estimation of PCT and IL-6. Clinical correlation was established to assess the utility of these biomarkers in early diagnosis and prognosis.

Results: The most frequently isolated pathogens included *Klebsiella pneumonia* (16%), *Acinetobacter baumannii* complex (15%) and coagulase-negative staphylococci (11%), with significant resistance to commonly used antibiotics. PCT and IL-6 levels were elevated in cases with clinical symptoms, suggested by their p-values. IL-6 showed strong associations with respiratory distress, bronchial breathing, and abnormal chest X-rays (**p<0.01), whereas PCT was significant for bronchial breathing and chest X-ray findings (*p<0.05). A positive correlation between elevated biomarker levels and radiological or clinical findings reinforced their diagnostic importance.

Conclusion: PCT and IL-6 serve as valuable adjuncts in the early diagnosis and monitoring of neonatal sepsis. The research asserts the need of combining biomarker-based diagnostics with antibiotic stewardship to combat antimicrobial resistance and improve clinical outcomes in neonates.

Keywords: Neonatal sepsis, Procalcitonin, Interleukin-6, Antibiotic resistance, Antibiotic stewardship, Biomarkers.

 DOI: http://dx.doi.org/10.22159/ajpcr.2025v18i7.54976. Journal homepage: https://innovareacademics.in/journals/index.php/ajpcr

INTRODUCTION

Sepsis is one of the most common causes of death among neonates, especially in developing countries. Defined as a systemic infection occurring in infants who are ≤28 days of age,neonatal sepsis is characterised by signs and symptoms of infection with or without bacteraemia, producing complications such as septicaemia, meningitis, pneumonia, arthritis, osteomyelitis, urinary tract infections and so forth. The incidence ranges from 1 to 20 per 1,000 live births, with a high mortality rate of about 11–19% - harbouring a particular inclination towards preterm and very low birth weight (VLBW) babies (those weighing<1.5 kg) [1].

The causative organisms may vary according to the geographical location and the time. Early institution of antimicrobial agents to counter the infection may not always be effective due to development of resistance to these agents in the causative organisms. Hence, early and accurate diagnosis using reliable biomarkers is essential to guide treatment in both early- and late-onset sepsis (EONS and LONS).

While there has been a constellation of promising pioneering work on different biomarkers specific to the aforesaid, clinicians and laboratory personnels still heavily rely on the clinical symptomatology for the diagnosis and treatment, due to the frequent inconclusiveness of blood culture reports [1]. This underscores the need for dependable diagnostic markers.

Procalcitonin (PCT) is a 116-amino acid precursor of the hormone calcitonin that is released from parafollicular cells of the thyroidin bacterial infections [2]. It rises within 2–4 h of infection onset, peaks around 18–20 h and stays elevated for 24–48 h. On the other hand, interleukin-6 (IL-6) is a cytokine involved in immune responses which stimulates the production of various antibodies and promotes helper T-cell proliferation. Notably, IL-6 levels increase even before the escalation of the heavily measured C-reactive protein (CRP) – making it a potentially valuable early marker for neonatal sepsis [3].

Our study, thus, focuses on the need to extract neonatal blood samples to identify the causative organisms and their corresponding resistance pattern, and to quantify the levels of PCT and IL-6 – for early diagnosis and timely institution of targeted therapy.

Objectives

(a) To find out the recent trends in the bacteriological profile associated with neonatal sepsis, and their antimicrobial sensitivity and resistance.
(b) To assess the levels of the biomarkers, PCT and IL-6, in the neonates under study and gauge the severity of the existing medical condition.

METHODS

Ethical approval for the study was obtained from the Institutional Ethics Committee (IEC) of Medical College, Kolkata (Memo Number: MC/KOL/IEC/NON-SPON/2554/07/2024). The study was conducted in Neonatal

Intensive Care Unit, Department of Microbiology and Central Clinical Laboratory, Medical College, Kolkata, for a period of 6 months. Blood samples of 100 septicaemic neonateswere collected and thereafter sent for investigating the trends in the bacteriological profile and antimicrobial susceptibility, as well as to measure the levels of PCT and IL-6.

Chemicals and reagents

The bacterial profile with resistance pattern was checked in VITEK and BD BACTEC. On the other hand, PCT and IL-6 levels were monitored using Cobas C 501 fully automated analyser and ADVIA Centaur XP, respectively.

Sample size and calculation technique

According to a study done by Adib *et al*., the mean±SD values of PCT levels among proved sepsis cases was 5.70±8.72 [4]. Hence, the sample size for this cross-sectional observational study has been determined by the formula:

$n = 4\sigma^2/d^2 = 4 \times (SD)^2/d^2$

Where, SD=standard deviation= 8.72 (according to similar study)
D = allowable error = 20% of SD

$n = 4 \times (8.72)^2/(20\% \text{ of } 8.72)^2 = 100.$

Statistical analysis

The study specific data were collected in respective case study forms (CSF). The data from the CSF were then transcribed onto an Excel database and statistical analysis was done in SPSS software version 20.

RESULTS

Microbiological profile and antibiotic resistance pattern

The microbiological profiles of neonatal sepsis in different studies reveal a diverse spectrum of pathogens, with both Gram-positive and Gram-negative organisms contributing to the disease burden. In the present study, a similar result was obtained, with *Klebsiella pneumoniae* being the most frequently isolated pathogen, accounting for 16% of all cases. This was closely followed by *Acinetobacter baumannii* complex (15%), *Coagulase-negative staphylococci* (CoNS) (11%), *Burkholderia cepacia* (8%), *Pseudomonas aeruginosa* (7%), *Escherichia coli* (5%) and *Staphylococcus aureus* (4%); while 34% of the cases turned out to be culture-negative. This is demonstrable in Figure 1 as shown.

The high prevalence of *Klebsiella* spp. was particularly alarming, as it is suggestive of improper sterilization practices and lack of antibiotic stewardship. They typically grow as opportunistic pathogens, affecting susceptible neonates, and usually resistant to a number of antibiotics – as is illustrated in various studies [5,6].

In our study, *Klebsiella* isolates exhibited complete resistance (100%) against a broad range of commonly used antibiotics, including third-generation cephalosporins (cefotaxime, ceftriaxone), beta-lactam/beta-lactamase inhibitor combinations (piperacillin–tazobactam, ampicillin–sulbactam), fluoroquinolones (ciprofloxacin), carbapenems (imipenem), and aminoglycosides (amikacin). High levels of resistance were also seen against cefepime (90%), tobramycin (90%), netilmicin (90%), ceftazidime (80%), gentamicin (80%), meropenem (80%), and several others illustrated in Figure 2. Though some sensitivity was retained – most notably to cotrimoxazole (100%) and doxycycline (70%) – manyagents showed only limited effectiveness, with sensitivity rates of 20–30% for commonly used antibiotics such as ceftazidime, gentamicin and amoxicillin-clavulanic acid. Intermediate sensitivity was observed in a subset of isolates to levofloxacin, doxycycline, meropenem, minocycline, colistin, and polymyxin B.

Relevance of PCT and IL-6 in early diagnosis of neonatal sepsis

As shown in Table 1, PCT and IL-6 levels were evaluated in relation to clinical symptoms of neonatal sepsis. IL-6 showed significant elevation

Table 1: Mean±SD and p-values of various parameters against PCT and IL-6 levels (n=100)

Condition	PCT (ng/mL)	IL-6 (pg/mL)
Difficulty in feeding or drinking (NO)	0.707±1.312	3.664±3.193
Difficulty in feeding or drinking (YES)	1.790±3.781	5.350±3.510
p-value	0.206	0.086
Lethargy (NO)	1.106±1.482	5.335±3.612
Lethargy (YES)	1.490±3.856	3.989±3.236
p-value	0.655	0.171
Respiratory Rate >60/min	0.908±3.120	3.577±2.689
Respiratory Rate 50-60/min	2.113±1.323	7.967±3.081
Respiratory Rate 40-50/min	4.170±1.317	9.875±3.221
p-value	0.087	0.000
Diminished Breath Sounds (NO)	0.671±1.242	3.164±2.291
Diminished Breath Sounds (YES)	1.495±3.306	5.015±3.627
p-value	0.424	0.116
Inspiratory Crepitations (NO)	0.388±0.889	3.411±2.184
Inspiratory Crepitations (YES)	1.880±3.634	5.342±3.882
p-value	0.086	0.053
Bronchial Breathing (NO)	1.065±2.966	4.150±3.091
Bronchial Breathing (YES)	4.170±1.317	9.875±3.221
p-value	0.045	0.001
Chest X-ray (ABSENT)	0.147±0.122	2.368±1.431
Chest X-ray (PRESENT)	2.230±3.766	6.368±3.558
p-value	0.013	0.000

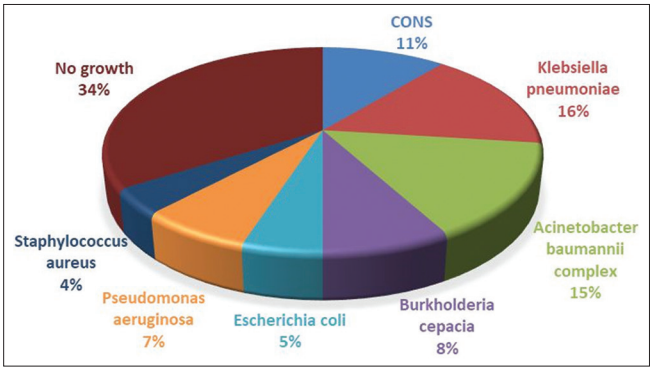

Fig. 1: Pie chart showing the percentages of individual organisms isolated from septicaemic neonates

with increasing respiratory distress (**p=0.000), bronchial breathing (**p=0.001), and abnormal chest X-rays (**p=0.000), indicating a strong association with respiratory involvement. PCT levels also escalated in these conditions but were significant only for bronchial breathing (*p=0.045) and chest X-ray abnormalities (*p=0.013). Other symptoms like feeding difficulty, lethargy, diminished breath sounds and inspiratory crepitations showed no statistically relevant correlations, despite the appreciation of certain trends. Overall, IL-6 demonstrated better sensitivity as an early diagnostic and prognostic marker, whereas PCT proved to be a valuable supportive indicator. Thus, acombined approach using both markers could improve early detection and evaluation of disease severity.

Correlation between biomarker levels with infecting organism

Table 2 instituted below attempts to find any correlation, if present, between the infecting organism and the respective PCT and IL-6 values in so affected neonates.

Gram-negative bacteria such as *Burkholderia cepacia*, *Escherichia coli* and *Klebsiella pneumoniae* tend to elicit higher biomarker levels. Highest mean PCT levels were depicted by *Burkholderia* spp., whereas highest IL-6 levels were exhibited in *E. coli* infections – suggesting the development of a robust defense mechanism against these organisms. On the contrary, *Staphylococcus* spp. and *Pseudomonas* spp. showed

relatively low PCT and IL-6 values. Therefore, these findings support the use of PCT and IL-6 as useful adjunctive tools in the early diagnosis and pathogen-specific management of neonatal sepsis.

DISCUSSION

Sepsis is recognized as part of the systemic inflammatory response syndrome (SIRS), which is defined by clinical signs such as hyperthermia or hypothermia (>38.5°C or <36°C respectively), rapid breathing (tachypnea), abnormal heart rate (tachycardia or bradycardia in infants <1 year), abnormal white blood cell counts, or >10% immature neutrophils in the blood. Neonatal sepsis can be further categorized into early-onset sepsis, occurring within the first 3 days of life, and late onset sepsis, which occurs thereafter.

Table 2: The correlation of PCT and IL-6 levels with infecting organism (n=100)

Blood culture	PCT (in ng/mL)	IL-6 (in pg/mL)
CoNS		
Mean	0.727	4.000
Standard deviation	1.514	3.237
Klebsiella pneumoniae		
Mean	1.472	5.819
Standard deviation	1.589	3.455
Acinetobacter baumannii complex		
Mean	1.298	4.273
Standard deviation	1.515	3.069
Burkholderiacepacia		
Mean	3.663	5.175
Standard deviation	3.064	3.397
Escherichia coli		
Mean	1.792	7.100
Standard deviation	1.426	3.445
Pseudomonas aeruginosa		
Mean	0.634	3.614
Standard deviation	1.543	3.226
Staphylococcus aureus		
Mean	0.119	3.650
Standard deviation	1.442	3.332
No growth		
Mean	1.284	3.950
Standard deviation	1.624	3.334

CoNS: Coagulase-negative staphylococci

Different researches conducted all-round the globe have reported various patterns of microbiological infectivity patterns and corresponding antimicrobial resistance and sensitivities. Saha *et al*. (2020) in a research article observed that among cases of suspected septicaemia, majority showed growth of organisms such as *Candida* spp., and bacteria such as *Klebsiella* spp., *Escherichia coli*, *Staphylococcus aureus*, *Enterococcus* spp., etc [7]. A more recent study conducted in Kolkata, 2023 by Chakraborty *et al*. showed that the most commonly isolated pathogens were Gram-negative Enterobacterales and non-fermenters. *Escherichia coli* from pediatric patients were found to be resistant to second generation cephalosporins, beta-lactams, fluoroquinolones and cotrimoxazole, whereas *Enterococcus* spp. from ICUs were especially resistant to ampicillin and fluoroquinolones [8].

These evolving resistance patterns pose a significant challenge to early and effective diagnosis of neonatal sepsis. This has led to growing interest in the use of blood biomarkers to aid in early detection, diagnosis, monitoring, and prognosis. Among the various biomarkers studied, PCT and IL-6 have shown significant promise.

PCT was first described as a potential sepsis marker by Assicot et al. in 1993 using monoclonal immunoradiometric techniques on patients with confirmed septicaemia [9]. Although early comparisons between PCT and CRP produced dubious results, further researches displayed the clinical authority of PCT over CRP– establishing it as a more reliable early marker [10]. Pontrelli *et al*. would further illuminate on the cutoff values to be approximately 2.5 ng/mL, especially for the late onset variant [11]. Fendler also documented the effectiveness of PCT in distinguishing sepsis from other impersonating conditions, like inborn errors of metabolism [12]. Al-Zahrani and others emphasized PCT's value as a prognosticator [13]. However, studies done by Ballot and Beaumont question the usage of PCT as a sole marker in septicaemia, due to revelation of uncertain results and a supposed predilection toward Gram-positive bacteria over Gram-negative ones [14,15].

To address this issue, combining PCT with IL-6 is suggested. IL-6, produced by mononuclear macrophages and the liver after activation of toll-like receptors, is an early inflammatory cytokine. IL-6 levels rise within the first 24 h of infection – earlier than CRP – and can be detected at levels of 40–80 pg/mL by the third day of life. Studies have shown high sensitivity and specificity for IL-6 as both a diagnostic and prognostic marker [16]. Importantly, it has been proposed that IL-6 levels drop after effective antibiotic therapy, which can help guide escalation or de-escalation of therapy – though IL-6 is thought to produce idiosyncrasy depending on the chronological age of the baby.

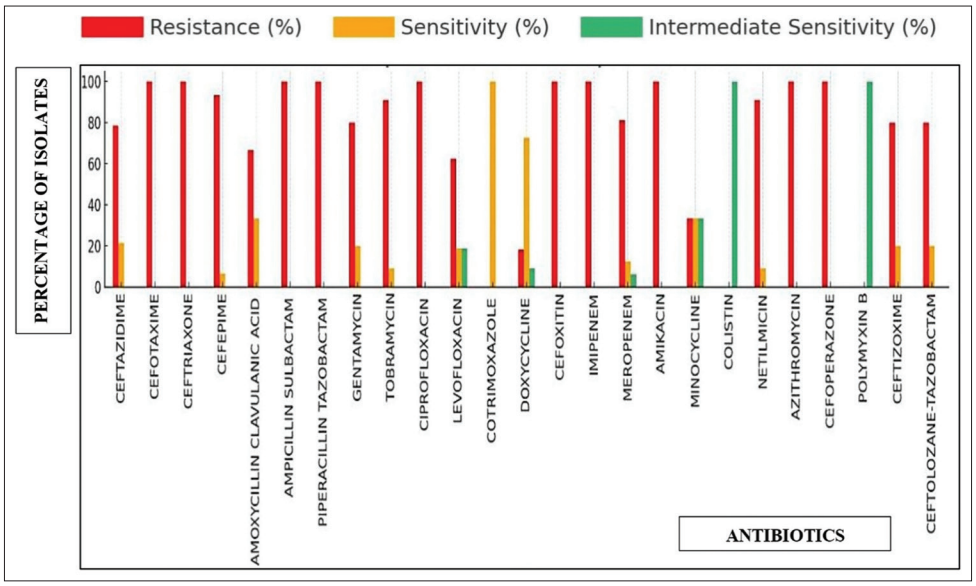

Fig. 2: Bar diagram showing the antimicrobial resistance profile of Klebsiella spp. Isolated

Studies would further certify that IL-6 would increase in the cord blood of the neonate, thereby providing early evidence of infection [17]. Liu *et al*. moves a step forward to state that the increase in IL-6 within a minimal 2 h duration and its drastic decrease after antibiotic therapy further elevates the significance of such a parameter with respect to the diagnosis and prognosis of the patients [18]. Given this background, our study aims to evaluate both PCT and IL-6 as combined markers for the rapid and accurate diagnosis of neonatal sepsis, while also emphasizing the need for further research to support these findings.

CONCLUSION AND FUTURE PERSPECTIVES

The current research emphasizes the pivotal position of early diagnosis and specific antibiotic treatment in disentangling the dilemma of neonatal sepsis and its proper management [19-21]. Antibiogram analysis unveils emerging patterns of resistance in microorganisms, underscoring the need for urgent antibiotic stewardship, while PCT and IL-6 evaluation as diagnostic biomarkers sheds light on their capability to enable early and precise detection of sepsis – especially in situations with indecisive blood cultures. Synthesis of biomarker testing with culture and sensitivity reporting can aid in appropriate treatment decisions, avoid unwarranted use of antibiotics, and enhance clinical outcome. The results highlight the necessity of sustained monitoring, validation of biomarkers, and individualized treatment planning in neonatal intensive care environments, particularly in areas with limited resources.

ACKNOWLEDGEMENTS

The authors would like to express their sincere gratitude to the Heads of the Departments of Pharmacology, Microbiology and Paediatrics of Medical College, Kolkata, for their valuable support and guidance during the course of this study. We also acknowledge the support of all medical and technical staff who contributed to sample collection and data acquisition. Finally, we extend our appreciation to the patients and their families for their cooperation, without whom this study would not have been possible.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR FUNDING

The authors received no financial support for the research, authorship, and/or publication of this article.

AUTHOR CONTRIBUTIONS

Subhranil Mal: Drafting of initial manuscript, review of literature, data collection. Dr. Biyanka Sau: Microbiological and biomarker assays, management of laboratory data, assistance in result interpretation. Dr. Dibyendu Ray Chaudhuri: Sample collection, data analysis. Dr. Birupaksha Biswas: Review of literature. Dr. Suhena Sarkar: Conceptualisation of research, supervision of research, result interpretation.

REFERENCES

1. Tuoni C, Ciantelli M, Morganti R, Violi M, Tamagnini S, Filippi L. Procalcitonin levels in preterm newborns: Reference ranges during the first three days of life. Front Pediatr. 2022;10:925788. doi: 10.3389/fped.2022.925788, PMID 36105855
2. Bartolovic D, Ignjatovic S, Stankovic S, Nada MS. Procalcitonin and other biomarkers of sepsis in newborns in the intensive care unit. EJIFCC. 2011;22(1):24-30. PMID 27683386
3. Küng E, Unterasinger L, Waldhör T, Berger A, Wisgrill L. Cut-off values of serum interleukin-6 for culture-confirmed sepsis in neonates. Pediatr Res. 2023;93(7):1969-74. doi: 10.1038/s41390-022-02329-9, PMID 36216867
4. Adib M, Bakhshiani Z, Navaei F, Saheb Fosoul FS, Fouladi S, Kazemzadeh H. Procalcitonin: A reliable marker for the diagnosis of neonatal sepsis. Iran J Basic Med Sci. 2012;15(2):777-82. PMID 23493845
5. Mukherjee S, Bhadury P, Mitra S, Naha S, Saha B, Dutta S, *et al*. Hypervirulent *Klebsiella pneumoniae* causing neonatal bloodstream infections: Emergence of NDM-1-producing hypervirulent ST11-K2 and ST15-K54 strains possessing pLVPK-associated markers. Microbiol Spectr. 2023;11(2):e0412122. doi: 10.1128/spectrum.04121-22, PMID 36752639
6. You T, Zhang H, Guo L, Ling KR, Hu XY, Li LQ. Differences in clinical characteristics of early and late-onset neonatal sepsis caused by *Klebsiella pneumoniae*. Int J Immunopathol Pharmacol 2020;34:1-10. doi: 10.1177/2058738420950586, PMID 32816593
7. Saha N, Sengupta M, Sarkar S, Sengupta M. Clinical and microbiological profile of neonatal septicemia in a tertiary care hospital in Kolkata. J Pure Appl Microbiol. 2020;14(2):1537-43. doi: 10.22207/JPAM.14.2.52
8. Chakraborty M, Sardar S, De R, Biswas M, Mascellino MT, Miele MC, *et al*. Current trends in antimicrobial resistance patterns in bacterial pathogens among adult and pediatric patients in the intensive care unit in a tertiary care hospital in Kolkata, India. Antibiotics (Basel). 2023;12(3):459. doi: 10.3390/antibiotics12030459, PMID 36978325
9. Assicot M, Gendrel D, Carsin H, Raymond J, Guilbaud J, Bohuon C. High serum procalcitonin concentrations in patients with sepsis and infection. Lancet. 1993;341(8844):515-8. doi: 10.1016/0140-6736(93)90277-n, PMID 8094770
10. Park IH, Lee SH, Yu ST, Oh YK. Serum procalcitonin as a diagnostic marker of neonatal sepsis. Korean J Pediatr. 2014;57(10):451-6. doi: 10.3345/kjp.2014.57.10.451, PMID 25379046
11. Pontrelli G, De Crescenzo F, Buzzetti R, Jenkner A, Balduzzi S, Calò Carducci F, *et al*. Accuracy of serum procalcitonin for the diagnosis of sepsis in neonates and children with systemic inflammatory syndrome: A meta-analysis. BMC Infect Dis. 2017;17(1):302. doi: 10.1186/s12879-017-2396-7, PMID 28438138
12. Fendler WM, Piotrowski AJ. Procalcitonin in the early diagnosis of nosocomial sepsis in preterm neonates. J Paediatr Child Health. 2008;44(3):114-8. doi: 10.1111/j.1440-1754.2007.01230.x, PMID 17927729
13. Javeed IB, Shaib MB, Zubair MT, Bashir AC. Role of procalcitonin in predicting newborn hospital-acquired sepsis: A case-control study. Gaz Egypt Paediatr Assoc. 2023;71(1):48. doi: 10.1186/s43054-023-00193-8
14. Ballot DE, Perovic O, Galpin J, Cooper PA. Serum procalcitonin as an early marker of neonatal sepsis. S Afr Med J. 2004;94(10):851-4. PMID 15532763
15. Beaumont R, Tang K, Gwee A. The sensitivity and specificity of procalcitonin in diagnosing bacterial sepsis in neonates. Hosp Pediatr. 2024;14(3):199-208. doi: 10.1542/hpeds.2023-007318, PMID 38415310
16. Al-Zahrani AK, Ghonaim MM, Hussein YM, Eed EM, Khalifa AS, Dorgham LS. Evaluation of recent methods versus conventional methods for diagnosis of early-onset neonatal sepsis. J Infect Dev Ctries. 2015;9(4):388-93. doi: 10.3855/jidc.5950, PMID 25881528
17. Shahkar L, Keshtkar A, Mirfazeli A, Ahani A, Roshandel G. The role of IL-6 for predicting neonatal sepsis: A systematic review and meta-analysis. Iran J Pediatr. 2011;21(4):411-7. PMID 23056824
18. Liu C, Fang C, He Q, Xie L. The value of interleukin-6 (IL-6) within 6 hours after birth in the prompt diagnosis of early-onset neonatal sepsis. Transl Pediatr. 2020;9(5):629-35. doi: 10.21037/tp-20-239, PMID 33209725
19. Wei TI, Ascobat P, Rohsiswatmo R, Instiaty I. Qualitative review of antibiotic use for neonatal sepsis. Int J App Pharm. 2018;10(1):364-6. doi: 10.22159/ijap.2018.v10s1.80
20. Kocabaş E, Sarikçioğlu A, Aksaray N, Seydaoğlu G, Seyhun Y, Yaman A. Role of procalcitonin, C-reactive protein, interleukin-6, interleukin-8 and tumor necrosis factor-alpha in the diagnosis of neonatal sepsis. Turk J Pediatr. 2007;49(1):7-20. PMID 17479639
21. Shinde AR, Mohite RV, Shinde RV. Pattern of antibiotics utilization in neonatal septicemia: A cross-sectional study from rural tertiary care hospital western Maharashtra, India. Int J Pharm Pharm Sci. 2017;9(3):60-3. doi: 10.22159/ijpps.2017v9i3.16210