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Research Article



# Interleukin-6 as an early marker for the diagnosis neonatal septicemia

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## Abstract

Sepsis is a leading cause of death and morbidity in newborns, especially those with very low birth weight and premature babies. The aim of our study diagnoses bacterial neonatal septicemia by direct techniques and some immunological biomarkers. The present study would include 75 neonates with clinically suspected neonatal sepsis and 50 healthy controls. Interleukin -6 levels of the blood were significantly higher in the suspected neonatal septicemia group compared with the control group. A significant increase in IL-6 levels in the blood can be used to make diagnose sepsis early.

**Keywords** Morbidity, Bacterial neonatal septicemia, Immunological biomarkers, IL-6 level

## Introduction

Neonatal sepsis still causes mortality and morbidity in newborns, particularly among those born prematurely or with a low birth weight (Stoll et al., 2003; Sherman et al., 2010). The extremely short time that can elapse between both the onset of acute infection and the development of bloodstream infection (BSI) and sepsis is the primary cause of newborn deaths (Cortese et al., 2016). Early onset sepsis (EOS) and late-onset sepsis are two types of sepsis (LOS). Early-onset sepsis can occur up to 72 hours after delivery and is usually caused by high-virulence etiological factors colonizing both the maternal vaginal and GI microbiota (*Escherichia coli* and other Gram-negative rods). Late-onset sepsis, on the other hand, is caused by immature immunity in the skin, respiratory, and gastrointestinal (GI) systems, as well as the need for invasive procedures, exposure to the environment, and a prolonged hospital stay. Positive blood cultures could be linked to catheter-associated infection, nosocomial transmission, and colonization factors, in this case, Monocytes from newborn infants produce Interleukin-6 is thought to be the most important inducer of hepatic protein synthesis (Wójkowska-Mach et al., 2014). It can interfere with the

production of C-reactive protein, allowing it to be detected earlier during bacterial infection than C-reactive protein (Rosenthal et al., 2012).

## Methods

### Patients

A record number of 75 cases of clinically suspected neonatal septicemia have been included in the study. Between September 2020 and April 2021, 51 cases of positive culture and 50 cases of control were admitted to Tikrit Hospital and Baghdad Hospital. For culture and sensitivity studies, blood samples (1.5-2 ml) were collected under aseptic conditions.

### Control groups

Fifty healthy neonates were randomly selected from the Pediatric Department's follow-up clinic while they were there for a routine checkup to serve as control groups and compare the levels of IL-6 and IL-8 in neonates. They were born to healthy mothers with no medical or obstetric history and were appropriate for gestational age were admitted during the study period and initially passed the screening criteria for not having

clinical sepsis, but were later found to have negative bacterial cultures.

### Culture Techniques

Blood cultures were processed as Gram's staining, colony characteristics, and biochemical properties have been used to examine standard and aerobic isolates in depth (Shim et al., 2011). The blood samples were inoculated into 30 ml of Brain Heart Infusion Broths, which were then incubated at 37°C for 7 days. After an overnight incubation on MacConkey agar with crystal violet, NaCl, 0.15 percent Bile salts, and a 5% sheep blood agar base, the broths were blindly sub-cultured by aseptically removing a few drops of well-mixed medium and spreading this inoculum onto the previous media. Examining the broth daily and performing a final subculture at the end of 7 days or when turbidity appeared was done on culture-negative bottles (Arnon et al., 2007).

### Biochemical and Other Identification Tests

Bacterial identification tests included the IMViC tests (Indole testy, Methyl red test, Voges Proskauer test, and Citrate utilization test), catalase test, oxidase test, coagulase test, and culture on Simmons citrate agar (India) differentiation of Enterobacteriaceae (Wayne et al., 2013).

### Identification of bacteria using VITEK® 2 system

- 1- Using the VITEK Densitometer colorimeter, the bacterial pellet was suspended in 0.45 percent saline to 0.5 McFarland units
- 2- Because Gram-positive cocci grow more slowly in blood culture bottles, 9 mL of culture fluid was used to obtain enough bacteria (Rosenthal et al., 2012). If no bacterial pellet was obtained after centrifugation, 1.5 ml 0.45% saline and 3 mL Brain-Heart Infusion (BHI) broth were added.
- 3- Incubated tube at 37°C with shaking. After 2 hours of incubation, bacteria were pelleted and resuspended in 0.45 percent saline to the required McFarland units. Approximately 2 mL was used with the VITEK 2 system and the 2.01 release software. This was an unintentional suspension. Loaded into the VITEK 2 IDGNB (Identification-Gram-negative bacilli) and AST (antimicrobial susceptibility testing)-GN04 cards (for Gram-negative bacilli) and VITEK 2 ID-GPC (Identification-Gram-positive cocci) and AST P526 cards (for Gram-positive cocci). Within 3 hours, the VITEK 2 ID and AST systems provided results (Etinkaya et al., 2009).
- 4- Standard method for bacterial identification and susceptibility testing: inoculated blood agar and chocolate agar plates with 0.1 mL of culture fluid from a blood culture bottle and incubated for 24 hours at 35°C in 5% CO<sub>2</sub>.

- 5- Bacteria were then suspended in 0.45% saline to a McFarland unit value of 0.5-0.63 and loaded into the correct spot VITEK identification and antimicrobial susceptibility testing cards, as previously described (Fan Yet al., 2012).

### Maglumi IL-6 (CLIA)

#### Principle of the test

For IgM, the MAGLUMI is a capture chemiluminescence immunoassay, while for IgG, it is an indirect chemiluminescence immunoassay. Two cassettes, one for the detection of IgG antibodies and the other for the detection of IgM antibodies from barcoded patient samples, are run separately. The system generates one report with results for both IgM and IgG detection after both cassettes have been run individually (Pierrakos et al., 2010).

#### For IgM detection, use the MAGLUMI IgM/IgG cassette

The sample (serum in standard sampling tubes or tubes containing separating gel (SST), buffer, and anti-human IgM monoclonal antibody-coated magnetic microbeads are thoroughly mixed and incubated to form immune complexes. The supernatant is decanted after precipitation in a magnetic field, and a wash cycle is run. The supernatant is decanted after precipitation in a magnetic field, and another wash cycle is run. The Starter Buffer is then added to start the chemiluminescent reaction. A photomultiplier measures the light signal in relative light units (RLUs), which are proportional to the amount of IgM in the sample. The test is run on a fully automated chemiluminescence immunoassay analyzer from the MAGLUMI 2000 series (Dark et al., 2012).

The sample (serum in standard sampling tubes or tubes containing separating buffer and magnetic microbeads coated with antigen) is precipitated in a magnetic field, the supernatant is decanted, and a wash cycle is performed with the MAGLUMI IgM/IgG-Cassette for IgG detection. The anti-human IgG antibody labeled with ABEI is then added, and the complexes are incubated. The supernatant is decanted after precipitation in a magnetic field, and another wash cycle is run. The Starter Buffer is then added to start the chemiluminescent reaction. A photomultiplier measures the light signal as relative light units (RLUs), which are proportional to the amount of IgG present in the sample. The test is run on a fully automated chemiluminescence immunoassay analyzer from the MAGLUMI 2000 series (Schuetz et al., 2008).

### Results and Discussion

#### Study population

In this case-control study, blood culture was obtained from neonatal cases admitted to Tikrit Hospital and Baghdad Hospital, during the period from September 2020 to April 2021. This was done on 75 suspected cases of neonatal sepsis,

51 (68%) of which were confirmed by bacterial isolation by culture technique with neonatal sepsis, and 24 (32%) of which showed no signs of growth. A control group of fifty healthy people was used. <sup>(16)</sup> A low blood culture isolation rate in this study could be dependent on several factors, including the administration of antibiotics to either the mother or the baby before blood collection, or the possibility of anaerobe infection, which was not ruled out. Additionally, negative blood cultures do not rule out sepsis. Cases of fatal illness and post-mortem evidence of infection have been reported in cases with negative blood cultures (Edwards et al., 2004).

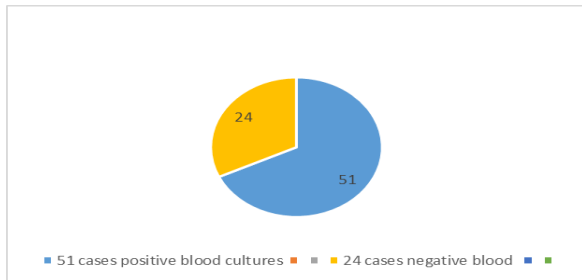


Fig. 1 Positive and negative blood cultures are used to identify neonatal septicemia

Identification of bacterial neonatal septicemia

The most common bacteria isolated in this study include Gram-positive bacteria constituted *Staphylococcus aureus* only, which appear as predominant pathogen 19(37.2 %), and Gram-negative bacteria constituted the major groups of isolates 32 (62.8%) from neonatal septicemia cases, among this group of Gram-negative bacteria which includes *Escherichia coli* 15 (29.4%), *Klebsiella Pneumonia* 14(27.4 %) which constituted as predominant pathogen and the least infection of Gram-negative bacteria appear as *Serratia marcescens*, *Citrobacter freundii* and *Burkholderia cepaca* as isolate for each one 1(2.0%) of cases.

Table 1. Types of bacteria isolated from neonatal septicemia cases

Isolated Organism	Number	Total isolates (%)
<i>Staphylococcus aureus</i>	19	37.2 %
<i>Escherichia coli</i>	15	29.4 %
<i>Klebsiella Pneumonia</i>	14	27.4 %
<i>Serratia marcescens</i>	1	2%
<i>Citrobacter freundii</i>	1	2%
<i>Burkholderia cepacai</i>	1	2%
<b>Total</b>	<b>51</b>	<b>100 %</b>

(Shah et al., 2014; Døllner et al., 2001) reported that high culture positivity rate in studies (57% and 65.3%) which agree with my study (68%) and disagree with (Døllner et al., 2001) (5.6%) which reported in studies. The findings of this study revealed that *Staphylococcus aureus* causes a Horizontal transmission of *S. aureus* from colonized visitors or health care workers to infants, poorly developed host defense mechanisms, the need for central venous catheters, endotracheal and upper gastrointestinal tract tube placement,

and procedures that disrupt skin integrity all contribute to a high incidence of neonatal septicemia. These findings correspond to (Maamouri et al., 2006) who reported a high incidence of neonatal septicemia caused by *S. aureus*, but not to which reported a low incidence of neonatal septicemia caused by *S. aureus* (Arani et al., 2013) the second-high incidence of neonatal septicemia occurred by *E. coli* due to Gram-negative organisms especially *E. coli* are dominant flora in pregnant females increasing the probability of these organisms (Silveira et al., 1999) catheterization, Hospital-acquired infections have increased as a result of immunosuppressive therapy, antibiotic therapy, and life support measures these result matching to (Verboon-Maciolek et al., 2006) which reported a high incidence of neonatal septicemia by *E. coli* and these result matching to (Sonawane et al., 2015) which reported low incidence of neonatal septicemia by *E. coli*. The third high incidence of neonatal septicemia occurred by *Klebsiella Pneumonia* due to early gestational age, prolonged membrane rupture, assisted ventilation, umbilical catheterization, and formula feeds are all factors to consider, *K. pneumoiae* showed multidrug resistance against most of the commercial drugs (Boskabadi et al., 2010). These results were agreeing with (Khassawneh et al., 2007) who reported a high incidence of neonatal septicemia by *K. Pneumonia*, and disagree with (Sonawane et al., 2015) who reported a low incidence of neonatal septicemia by *K. Pneumonia*. At least causes of neonatal septicemia *Serratia marcescens*, *Citrobacter freundii* and *Burkholderia cepaca* in my study 2% agree with (Khassawneh et al., 2007) disagree with (Bhargava et al., 1979). The low incidence of neonatal septicemia by these bacteria due to low antibiotic resistance compared with *S. auras*, *E. coli* and *K.pneumonia* in my study *Serratia marcescens*, *Citrobacter freundii* and *Burkholderiay cepaca* widely found in the environment, and manual transmission due to lack hospital hygiene, sources of contamination catheters, heparin solution, dialysis machine, liquid soap (Faridi et al.,1972) and all these bacteria are an opportunistic pathogen causing disease in patients with definite pre-disposing factors (Mir et al.,1987). These results were agreeing with (Shroufi et al., 2013) which reported neonatal septicemia by *B. cepaca*, *C.freundii* and *S. marcescens* disagree with (Waseem et al., 2005) who reported a low incidence of neonatal septicemia

Relationship between isolated organism from neonatal septicemia cases and type of onset

The result of this study showed the late onset with high incidence of neonatal septicemia especially with *S. aureus*12 (63%), *K. penmonia* (64%), *E. coli* (53%) and *C. freundii* (100%) and absent of *S. marcescens* (100%) and *B. cepacai* (100%), while in the early onset of neonatal septicemia the low rate of infection with *S. aureus*, *K. pneumonia*, *E. coli*, *S. marcescens* and *B. cepacai* and absent of *C. freundii* compared with late-onset.

**Table. 2 Relationship between Isolated Organism from neonatal septicemia cases and type of onset**

Isolated Organism	Type of onset		Total
	Early onset	Late-onset	
<i>Staphylococcus aureus</i>	7	12	19
<i>Escherichia coli</i>	7	8	15
<i>Klebsiella Pneumonia</i>	5	9	14
<i>Serratia marcescens</i>	1	0	1
<i>Citrobacter freundii</i>	0	1	1
<i>Burkholderia cepacai</i>	1	0	1
	Ns Chi-Square = 4.064 P-Value = 0.246		51

**Early-onset neonatal sepsis**

In most cases, organisms acquired intrapartum cause early-onset neonatal sepsis. The majority of infants develop symptoms within 6 hours or more than 6 days after delivery (Thilo et al., 1999; Manucha et al., 2002). Gram-positive and Gram-negative (Movahedian et al., 2006) maternal illnesses can predispose to neonatal sepsis when amniotic fluid is contaminated with meconium or vernix caseosa. The bacteriologic characteristics of early-onset neonatal sepsis, which reflect the flora of the maternal vaginal vault and multiple gestation, are prolonged rupture of membranes, foul-smelling amniotic fluid, the increased risk of infection in the twin closer to the birth canal, and the bacteriologic characteristics of early-onset neonatal sepsis, which reflect the flora of the maternal vaginal vault and multiple gestation (Rasu et al., 2007). Organisms usually reach the bloodstream by fetal aspiration or swallowing of contaminated amniotic fluid, leading to bacteremia (Silveira et al., 1999).

The result of my study agreed with (Waseem et al., 2005) who reported a low incidence of early neonatal septicemia causes by *S.auruas*, *E.coli*, *K.pneumonia*, *S. marcescens* and *B. cepaca*. While this agrees with (Dagnew et al., 2013) which reported the absent of *S. auruas*, *E.coli*, *K.pneumonia*, *S. marcescens* and *B. cepaca*.

**Late onset neonatal sepsis**

Late-onset neonatal sepsis develops after 72 hours of life, and organisms could be acquired from the environment (e.g. hospital or home) After the first 72 hours of life, late-onset neonatal sepsis develops, and the organisms can be acquired from the environment (e.g. hospital or home) <sup>(21)</sup> Infectious disease The organisms colonize superficial sites and the upper respiratory tract before spreading to cause widespread sepsis, pneumonia, or meningitis. Late-onset neonatal sepsis is commonly transmitted by care providers' hands (Santana et al., 2001). Gram-positive organisms (e.g., Staph. aureus) can enter the body through the skin or the environment (Døllner et al., 2001). Gram-negative enteric bacteria are usually derived from the patient's endogenous flora, which may have

been altered by antecedent antibiotic therapy or populated by contaminated equipment. As a result, situations that increase bacteria exposure (e.g., insufficient nurse staffing, inconsistent provider handwashing) lead to higher rates of hospital-acquired infection (Meem et al., 2019). Long-term use of invasive interventions like mechanical ventilation and intravenous catheterization, failure of early enteral feeding with breast milk, hospitalization, and underlying respiratory and cardiovascular diseases are all known LOS risk factors (Santana et al., 2001). It's important to note that genetic factors like polymorphisms in immunity-related genes could play a role in neonatal susceptibility to LOS (Meem et al., 2019). The result of my study agreed with (Hotoura et al., 2012) who reported that late neonatal septicemia is caused by *S. auruas*, *E. coli*, *K. pneumonia*, and *C. freundii* While this agree with (Berger et al.,1987) who reported that absent of *S. auruas*, *E. coli*, *K. pneumonia* and *C. freundii*.

**Comparison between cases and controls regarding the level of IL6**

This table showed the level of IL6 were significantly higher in cases with sepsis than in controls (P-value<0.001)

**Table. 3 Comparison between cases and controls regarding the level of IL6**

Type of interleukin Pg./ml	neonate septicemia cases	Control
IL-6	40.4 a	3.7 b

IL6 is created by monocytes, endothelial cells, fibroblasts, and lymphocytes T and B and are much more sensitive than CRP (Shah et al., 2006). IL-6 belongs to the family of cytokines. It is one of the mediators of inflammation that are released early in the course of septic shock and is crucial in initiating the immune response, as well as the activation of T lymphocytes and B lymphocytes and lymphocyte proliferation and differentiation (Shabuj et al., 2017). The level of IL-6 reaches the peak after 2 h of bacterial stimulus onset; thus, its level may be elevated before the start of the symptoms and before the rise of routinely used markers (Magudumana et al., 2000).

**Conclusion and Recommendations**

Gram Negative organisms are the most common causative pathogens in neonatal septicemia.

Serum IL-6 levels were significantly higher in infants confirmed with control.

Early detection of the cause of neonatal septicemia is essential.



The IL6 level in the blood is an inflammatory mediator that can be used to diagnose neonatal septicemia early.

## Conflict of Interest

The author hereby declares no conflict of interest.

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