ROLE OF MANNOSE-BINDING LECTIN (MBL) LEVELS IN DIAGNOSIS OF NEONATES WITH PNEUMONIA AND SEPSIS

Thesis

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@Mohammad Emam Mohammad Abdelgawad


وأنزل الله عليك
الكتاب والحكمة
وعلَّمَكَ مَا لَمْ تَكُن
تَعْلَمُ وكَانَ فَضْلُ
اللَّهِ عَلَيْكَ عَظِيماً
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List of Abbreviations

AAP ..... American Academy of Paediatrics
ARDS ..... Acute respiratory distress syndrome
CD ..... Crohn's disease
CMV ..... Cytomegalovirus
CONS ..... Coagulase negative staphylococci
CRD ..... Carbohydrate recognition domain
CRP ..... C-reactive protein
CS ..... Complement system
CSF ..... Cerebrospinal fluid
CSFs ..... Colony Stimulating Factors
EOS ..... Early-onset sepsis
ESR ..... Erythrocyte sedimentation rate
Fn ..... Fibronectin
GCSF ..... Granulocyte colony stimulating factor
G-CSF ..... Granulocyte colony-stimulating factor
GM-CSF ..... Granulocyte- macrophage colony-stimulating factor
HbS ..... Hemoglobin s
HIV ..... Human immunodeficiency virus
HMD ..... Hyaline membrane disease
hMPV ..... human metapneumovirus
HSV ..... Herpes simplex virus
HVS ..... Maternal high vaginal swab
IBD ..... Inflammatory bowel diseases
IFN ..... Interferon
Ig ..... Immunoglobulin
IL-1β Interleukin-1β
IVIG ..... Intravenous immunoglobulin
LBW ..... Low birth weight

List of Abbreviations (Cont…)

LOS ..... Late onset sepsis
MASPs ..... MBL-associated serine proteases
MBL2..... Mannose-binding lectin-2
MBP ..... Mannose-binding protein
MRSA ..... Methicilin Resistant Staphylococcus Aureus
NEC ..... Necrotizing enterocolitis
NICU ..... Neonatal intensive care unit
PCR ..... Polymerase chain reaction
PROM ..... Premature rupture of membranes
RA ..... Rheumatoid arthritis
RCT ..... Randomized controlled trial
RDS ..... Respiratory distress syndrome
RSA ..... Recurrent spontaneous abortion
RSV ..... Respiratory syncytial viruses
SCA ..... Sickle cell anaemia
SD ..... Standard deviation
SIADH ..... Syndrome of Inappropriate Antidiuretic Hormone
TB ..... Tuberculosis
TCC ..... Terminal complement complex
TNF ..... Tumor necrosis factor
UC ..... Ulcerative colitis
UTI ..... Urinary tract infection
VOC ..... Vaso-occlusive crisis
WHO ..... World Health Organization

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Introduction

Neonatal sepsis is a major problem across the world. Infections are a major contributor to neonatal deaths in developing countries. Majority of these deaths occur at home without coming to medical attention. The child survival cannot be achieved without substantial reductions in infection-specific neonatal mortality ***(Thaver and Zaidi, 2009)***.

Around 1 million deaths a year occurring in the neonatal period (0-28 days) are caused by infection, accounting for over 25% of global neonatal deaths and 10% of all mortality in infants under the age of 5 ***(Black et al., 2010).***

It is classified as 'early-onset' if it occurs within the first 7 days of life and as 'late-onset' if it occurs after this time. Typically, early-onset sepsis is considered maternally-acquired, usually from the maternal genital tract, and late-onset sepsis is generally regarded to originate from the care giving environment – either a health care or community setting. Consequently early- and late-onset sepses are also associated with different distributions of pathogens ***(Zaidi et al., 2005).***

The complement system helps or "complements" the ability of antibodies and phagocytic cells to clear pathogens from an organism. It is part of the immune system called the innate immune system ***(Janeway et al., 2001).*** That is not adaptable and does not change over the course of an individual's lifetime. However, it can be recruited and brought into action by the adaptive immune system.

The complement system consists of a number of small proteins found in the blood, generally synthesized by the liver, and normally circulating as inactive precursors (pro-proteins). When stimulated by one of several triggers, proteases in the system cleave specific proteins to release cytokines and initiate an amplifying cascade of further cleavages. The end-result of this activation cascade is massive amplification of the response and activation of the cell-killing membrane attack complex. Over 25 proteins and protein fragments make up the complement system, including serum proteins, serosal proteins, and cell membrane receptors. They account for about 5% of the globulin fraction of blood serum ***(Abbas et al., 2010).***

Three biochemical pathways activate the complement system: the classical complement pathway, the alternative complement pathway, and the lectin pathway ***(Abbas et al., 2010).***

The human collectin**,** mannose binding lectin (MBL) is one of the important components of the innate immunity ***(Bouwman et al., 2006)***. It provides first line of defence by its ability to bind sugar residues on the bacterial surface through its carbohydrate recognition domain and activates the complement pathway leading to lysis of bacteria independent of antibody ***(Dommett et al., 2006).***

Aim of the Work

To evaluate Role of serum mannose binding-lectin in diagnosis of neonatal pneumonia and sepsis.

Neonatal Sepsis

Definition:

Neonatal sepsis or septicaemia is a clinical syndrome characterized by systemic signs of circulatory compromise (e.g., poor peripheral perfusion, pallor, hypotonia, poor responsiveness) caused by invasion of the bloodstream by bacteria in the first month of life. In the pre-antibiotic era neonatal sepsis was usually fatal. Case fatality rates in antibiotic treated infants now range between 5% and 60% with the highest rates reported from the lowest- income countries ***(Thaver and Zaidi, 2009).***

The World Health Organization (WHO) estimates that 1 million deaths per year (10% of all under-five mortality) are due to neonatal sepsis and that 42% of these deaths occur in the first week of life ***(Healy and Baker, 2007).***

There are wide disparities in neonatal care between high- and low-income countries. In high-income countries the major concern is the increasing numbers of extremely premature infants with high nosocomial infection rates due to multi-resistant organisms in intensive care units. Health facility infections are also a major problem in low- income countries, but the more pressing issues are the high proportion of home deliveries in unclean environments predisposing to sepsis and ensuring that all neonates have access to effective interventions from health care providers in the first days of life. Indeed, new strategies that can prevent, diagnose, and treat neonates with sepsis are needed in both low- and high-income settings ***(Karen and Anita, 2010).***

Pathogenesis:

A-Risk factors:

1. Prematurity and low birth weight:

The most important neonatal factor predisposing to infection are prematurity and LBW. Preterm infants have 3- to 10-folds higher incidence of infection than full-term normal birth weight infants ***(Stoll, 2007)***.

2. Premature rupture of membrane (PROM) & chorioamnionitis:

Uncomplicated ROM lasting longer than 24 hours has been associated with a 1% incidence of neonatal sepsis above the baseline rate of 0.1% to 0.5% ***(Edwards, 2006)***. The bacteria that cause neonatal sepsis are acquired shortly before, during, and after delivery ***(Edmond and Zaidi, 2010).***

3. Maternal peripartum fever:

Fever $\geq 38^{o}C$ or infection, Chorioamnionitis, urinary tract infection (UTI), vaginal colonization with GBS, previous delivery of a neonate with GBS disease, perineal colonization with E. coli and other obstetric complications ***(Naglie, 2004)***.

4. Amniotic fluid problem.

Meconium-stained or foul-smelling, cloudy amniotic fluid ***(Naglie, 2004)***.

5. Resuscitation at birth.

Perinatal asphyxia, defined as a 5-minute Apgar score of less than 6, in the presence of prolonged ROM has been

associated with an increased incidence of sepsis ***(Edwards, 2006)***.

B. Causative agents:

In Egypt, a study done by ***Abdelhady and Zaki (2003)*** showed that causative organism of neonatal sepsis were as follow: Staphylococcus aureus (10.3%), Coagulase negative Staphylococci (6.9%), Methicilin Resistant Staphylococcus Aureus (MRSA) (6.9%), and Streptococcus fecalis (3.5%). Klebsiella pneumonia was the commonest gram-negative organism (41.3%) followed by Pseudomonas (13.8%), E coli (10.3%), Serratia marscense (3.5%) and Enterobacter (3.5%).

In addition, ***Ali et al (2006)*** found that Klebsiella pneumonia was the commonest causative organism in neonatal sepsis (88%). Other organisms causing neonatal sepsis were as follows: Pseudomonas aeruginosa (3.9%), Enterobacter (3.9%), Coagulase negative staphylococci (3.9%) and fungi (3.9%).

The pathogens most often implicated in neonatal sepsis in developing countries differ from those seen in developed countries. Overall, Gram negative organisms are more common and are mainly represented by Klebsiella, Escherichia coli, Pseudomonas, and Salmonella. Of the Gram positive organisms, Staphylococcus aureus, coagulase negative staphylococci (CONS), Streptococcus pneumoniae are the most commonly isolated ***(Vergnano et al., 2005).***

Neonatal meningitis in developing countries is a serious problem, with a mortality of 33–48% The pathogens involved are similar to those associated with sepsis, mainly Gram negative organisms such as Klebsiella, E coli, Serratia marscesens, Pseudomonas, and Salmonella, and among the

Gram positive organisms Staph aureus and coagulase negative staphylococci (CONS) ***(Vergnano et al., 2005).***

Classification:

In newborns, sepsis can be either "early-onset" or "late-onset." Early-onset sepsis (EOS) occurs in the first 3 to 7 days of life and is usually caused by microorganisms from the mother. Late onset sepsis (LOS) occurs after the first week of life, can be from the mother or the environment, and has a higher incidence of meningitis (though mortality is usually less than with early-onset infections **(**Table 1) ***(Rubarth, 2010).***

Table (1): Classification of neonatal sepsis:

	Early onset sepsis	**Late onset sepsis**
Incidence	1.5 %	25%
Time of presentation	Usually within first 12 h Usually the first 3-7d of life	Usually term infant older than 1 wk
Most common pathogens	Escherichia coli Group B streptococci	Coagulase-negative staphylococci
Onset	Fulminant	Subtle
Type of infection	Pneumonia and sepsis (multisystem)	Meningitis with sepsis (focal)
Most acquired from	Mother`s birth canal (OB complication)	Environmental (rarely OB complication)
Infant gestation	Majority term, but preterm unusually susceptible	Majority term
Mortality rate	15-20% or higher with preterms	10-20%
Morbidity	Less long term issues	Late neurodevelopmental sequale
OB indicates obstetric		

(Rubarth, 2010)