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Potential biomarkers for effective screening of neonatal sepsis infections: An overview

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ABSTRACT

Neonatal sepsis, a clinical disorder developed by bacterial blood stream infections (BSI) in neonates, is one of the serious global public health problems that must be addressed. More than one million of the estimated global newborn deaths per year are occurred due to severe infections. The genesis of the infection is divided into early-onset sepsis (EOS) and late-onset sepsis (LOS) of the disease. The clinical complications of neonatal sepsis may be associated with bronchopulmonary dysplasia, ductus arteriosus and necrotizing enterocolitis. The clinical diagnosis and treatment of neonatal sepsis is highly complicated. Over the past few years distinct biomarkers have been identified. Most widely used biomarkers are C-reactive protein, Procalcitonin (PCT) and Serum amyloid A (SAA). Until recently, many potential biomarkers including Cell Surface antigens and Bacterial surface antigens and genetic biomarkers are being investigated. Protein biomarkers, cytokines and chemokines are getting much interest for identification of neonatal sepsis infection.

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1. Introduction

Neonatal sepsis can be referred as the clinical syndrome, comprised of abnormalities in systemic circulation in neonates. The virulent bacteria reach into the blood stream, which results into the profuse microbial infection causing an ineffective host response [1]. In case of a term baby, these infections impart their effects during the first 28 days of life. However, in preterm baby, it extends up to 4 weeks from the expected date of delivery [2]. Neonatal sepsis is the global prime cause of morbidity and mortality amongst preterm and term neonates. Unfortunately, in a very low birth weight infants cases, the neonatal sepsis is the major infection causing more number of neonatal deaths [3]. Neonatal infections alone are responsible for approximately 23.4% of mortality in neonates, worldwide each year [4]. Neonatal sepsis diagnosis is intricated by other non-infectious conditions which exist in neonates resembling the symptoms of sepsis and therefore lacking in optimization of diagnostic tests. The administration of antibiotics to the neonates exhibit the high risk factors associated with sepsis. The extended treatment of antibiotics corresponds to associated risk factors enhancing the rate of antimicrobial resistance [5]. Caregivers have a low ability for the assessment and treatment for the disease in neonates, which results into delayed treatment and infant's immunosuppression. This later leads to the development of major serious sequela like mortality in neonates. Due to high rates of neonatal mortality, efforts are needed to be taken for eliminating the rate of sepsis in the preterm infants. Differentiating neonatal sepsis from other infections, the problem can be overcome by effectively diagnosing the disease in the early phases of infection. In order to diagnose the infections, many effective biomarkers are being identified and therefore, in recent years, systematic and meta-analysis suggested that molecular assays have significant sensitivity (>0.98) and specificity (>0.95) over microbial cultures [6]. The study of protein biomarkers will provide efficient benchmarks for the detection of neonatal sepsis. Study reveals that their levels become altered and serve as a direct measure for the identification demonstrating high specificity and sensitivity. These biomarkers include C-reactive protein, Procalcitonin (PCT), Serum amyloid A, Lipopolysaccharide-binding protein, α-1 antitrypsin lactoferrin, Haptoglobulin, Fibronectin and neopterin. Furthermore, it has been suggested that genetic biomarkers can also be utilized as effective measures detecting neonatal sepsis infections. Recently, genetic biomarkers are being established since they are highly specific and therefore confer high sensitivity for the effective diagnosis of infections caused by sepsis. These biomarkers include hlyA gene, cnf1 gene, sat1 gene, focG gene, cfb, rov S and neuA. However, the specificity and selectivity of these biomarkers and their implications in disease diagnosis have not been significantly evaluated. Our review will assess the potential biomarkers in neonatal sepsis since there is a high requirement for a rapid, highly sensitive, point of care and early detection platform identifying neonatal sepsis infections and its severity from neonatal blood samples.

1.1. Early onset sepsis

Based on the period of the infection, neonatal sepsis is classified into early-onset sepsis (EOS) and late-onset sepsis (LOS). This classification helps to guide antibiotic therapy as it implies differences in the presumed mode of transmission and predominantly associated organisms [1]. Early-onset sepsis (EOS) is referred as the onset appeared in the first week of the life. Few studies limit EOS to infections prevalent in the first 72 h due to maternal intrapartum transmission of invasive organisms [7]. Group B streptococcus (GBS), Gram positive encapsulated bacteria, is a prime pathogen for neonatal infections. *E. coli* is considered another potent pathogen for causing neonatal sepsis in both term and preterm infants [8]. The neonatal mortality in very-low-birth weight infants is mainly associated with infections caused by *Escherichia coli* (*E. coli*) [9]. However, almost 70% incidences of EOS are ascribed to the infections occurred by GBS and *E. coli* [10]. Few pathogens including *Listeria monocytogenes* are also associated with early onset sepsis in infants [10].

1.2. Late onset sepsis

Transmission of pathogens from the hospital, home or community may lead to the development of Late-onset sepsis (LOS) to the neonates [11,12]. The prevalence of LOS has raised along with the better survival rate of premature infants suffered from EOS, including the very low birth weight (VLBW) infants. This assumes that the life-sustaining medical devices and hospitalisation are associated with the development of LOS in infants [13,14]. More than 70% incidences of LOS are associated with Gram positive bacteria, among which 48% of the cases are predominantly associated with coagulase-negative Staphylococci [15], *Escherichia coli* (*E. coli*), *Pseudomonas aeruginosa*, *Serratia marcescens* and *Candida albicans*, which are responsible for the high prevalence of neonatal mortality [16]. GBS infection remains the prime cause of neonatal infection, regardless of intra-partum antibiotic prophylaxis. GBS is mainly responsible for meningitis in the infants with serious neurological impairment [17,18].

2. Clinical impediments associated with neonatal sepsis infections

As a result of neonatal sepsis infections, the clinical conditions including patent bronchopulmonary dysplasia, ductus arteriosus,