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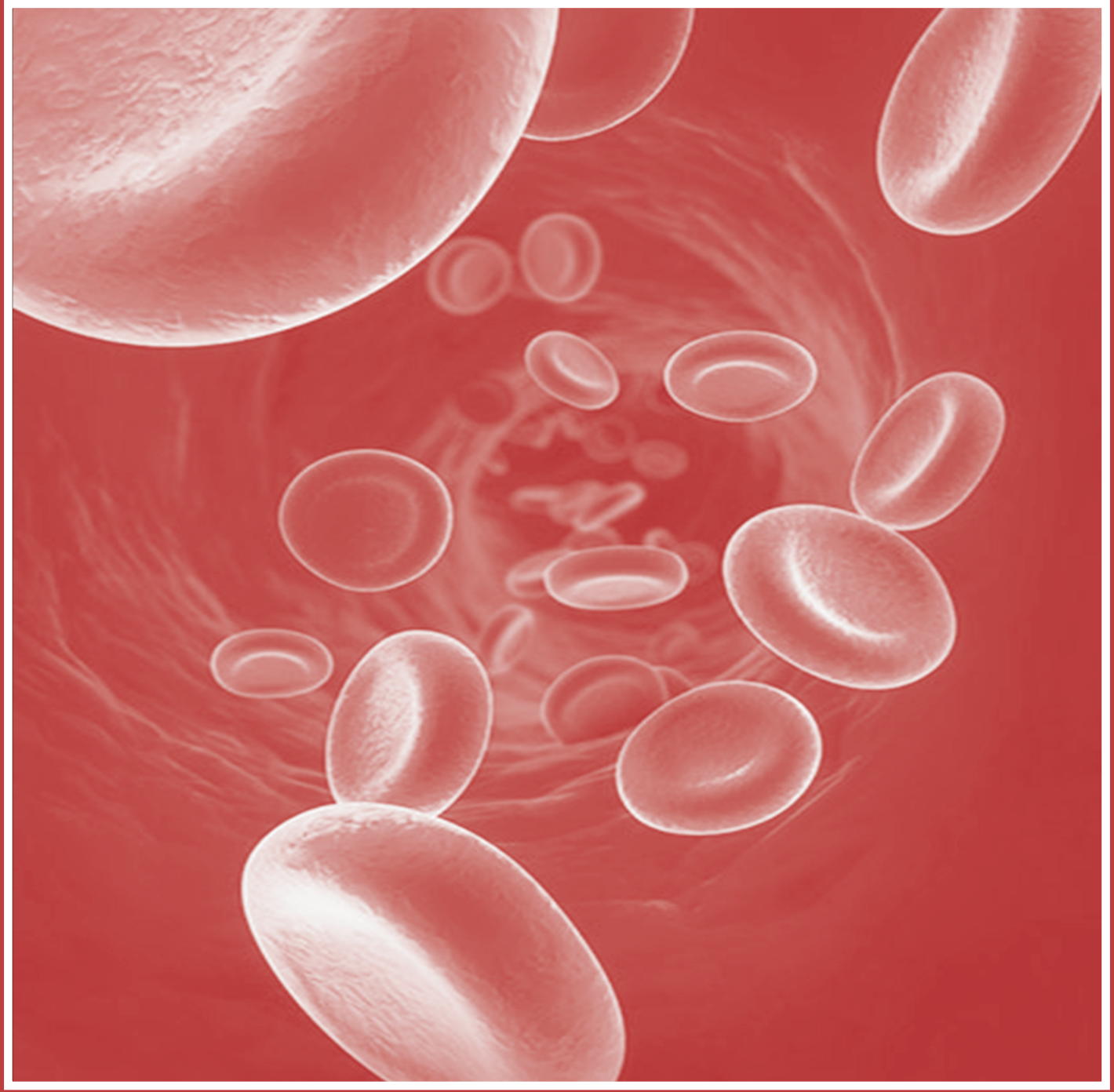

Pledge Ceremony during Sadbhavana Day


Sanitation Cleanliness Campaign
at KEM Hospital


Swachh Bharat Abhiyaan
at School and KEM Hospital

# Neonatal Sepsis: An Overview

**Snehal L Martin**

Sepsis is a polygenic and complex syndrome which is caused by infection and is characterized by a systemic inflammatory response. Invasive infection triggers both pro-inflammatory and anti-inflammatory host responses. The magnitude of the problem depends on multiple factors like pathogen virulence, site of infection, host genetics and comorbidities. Sepsis related morbidity and mortality concerns in all Neonatal Intensive Care Units (NICU) especially in very low birth weight infants (VLBW <1500gms) regardless of the improvements in quality of neonatal assistance. Neonatal sepsis is one of the major causes of neonatal death in developing countries. Preterm neonates show the clinical characteristics that make them prone to infections due to different microorganisms according to the age at onset. Although intraparturm antibiotic prophylaxis has decreased the incidence of infections, nevertheless, still it remains a major cause of neonatal sepsis. As the signs and symptoms of neonatal sepsis are nonspecific, early diagnosis and prompt treatment remains a challenge. Genetic polymorphisms in the immune response have also been shown to be associated with clinical outcomes. Functional and association studies involving genetic polymorphisms in crucial genes in the inflammatory response and coagulation pathways have provided important information on the mechanisms involved in the pathogenesis of sepsis.

**Introduction:**

Despite significant advances in neonatal healthcare, treatment and diagnosis, sepsis related morbidity and mortality is an increasing concern in all the NICUs worldwide. Neonatal sepsis is a clinical and a complex syndrome that is characterized by signs and symptoms of infection which may or may not be accompanied by bacteremia in the first 28 days of life. It encompasses various systemic responses to infections like meningitis, pneumonia, etc. Prematurity, low birth weight and prolonged hospitalization are the commonest predisposing factors for neonatal sepsis. Depending on the onset, sepsis in neonates has been classified as: early onset sepsis (EOS) occurs within 72hrs after birth and late onset sepsis (LOS) occurs >72hrs after birth. Studies suggest that host genetic factors significantly contribute to inter individual variations in susceptibility to infections. Over the years genetic association studies have suggested that one or more candidate genes have a role in the pathogenesis of sepsis (1). In particular, identification of genetic variations in the Toll-like receptors (TLRs) and pro inflammatory cytokines has provided valuable insights into the influence of genetic heterogeneity on the response to bacterial or fungal infection.

**Incidence and Mortality:**

The incidence of sepsis in the neonate is more than at any other period of life and varies from hospital to hospital. The overall incidence of neonatal sepsis in developed countries is 1-5 cases per 1000 live births while a higher incidence of 49-70 per 1000 live births is reported in the developing countries. The incidence of neonatal sepsis varies among the different geographic areas, the highest being in Africa and Asia (23-38/1,000 live births) and the lowest, in countries such as the U.S. and Australia (range, 1.5-3.5 /1,000 live births). In South America and the Caribbean, the incidence of neonatal sepsis ranges between 3.5 and 8.9/1,000 live births respectively, while in Mexico, the incidence rates varies between 4 and 15.4/1,000 live births (2). Sepsis arises from the host response to infection which leads to exuberant release of inflammatory mediators and

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biomarkers which is indirectly directed to kill the invading pathogens. However, these effector molecules fail to discriminate between the microbial and host target and hence may lead to tissue damage, which may further cause multiple organ failure and death may be the possible outcome. The most common sites of infection are the lungs, meninges, the urinary tract, the abdominal cavity and primary infections of the bloodstream.

Sepsis is estimated to affect 18 million people worldwide each year and to kill 1400 people each day. It is estimated that 20% of all neonates develop sepsis and approximately 1% die due to sepsis related causes (3). Neonatal sepsis remains a major and commonest cause of death in the newborns around the world. As per the WHO reports, around 1 million deaths occuring globally per year are due to neonatal sepsis and that 42% of these deaths are in the 1st week of life (4). Thus, neonatal sepsis is a relevant public health issue because it is consistently emerging as a major cause of neonatal morbidity and mortality.

**Etiology:**

The most frequent microorganisms involved in EOS are *Streptococcus agalactiae* (GBS), *Escherichia coli (E.coli)* and *Haemophilus influenzae* while in LOS, Coagulase-negative staphylococci (CoNS), *Enterobacteriaceae* including *Escherichia coli* and *Klebsiella pneumoniae,* and *Acinetobacter baumannii* are frequently observed (5). The most frequently isolated pathogens observed in patients with sepsis in developed countries include Coagulase-negative Staphylococcus (CoNS) and group B Streptococcus (GBS) while in developing countries like Pakistan, India, Nigeria, Bangladesh, are *E.coli, Klebsiella, Enterobacter etc.* (4). Depending on the age of onset different microorganisms are responsible for causing the disease. Stoll et al. (6) and Hornik et al. (7) reported that the most common etiologic agent in EOS was *E.coli* (33.4%) and the mortality rate was found to be 23.4% while in LOS, CoNS (28.3%) was mainly found to be responsible causative agent with a mortality rate of 9.7%. In another study, Li et al. (8) showed that *Staphylococcus epidermidis* was the leading pathogen in EOS and *Staphylococcus epidermidis* and *E.coli* are common causative pathogens of LOS.

**Risk factors:**

Host susceptibility, socioeconomic factors, obstetric and nursery practices, and health and nutrition of the mother are important in the pathogenesis of neonatal sepsis. Diversity of infectious exposures is relevant to the clinical differences between EOS and LOS. Organisms causing EOS are typically colonizers of the maternal genitourinary tract, leading to contamination of the amniotic fluid, placenta, cervix, or vaginal canal. Thus, the infant may acquire the pathogen either in utero or intrapartum. Table:1 summarizes the different neonatal and maternal risk factors observed in neonatal sepsis. Risk factors for EOS include both maternal and neonatal factors. Maternal risk factors during labor include prolonged rupture of membranes, fever, vaginal colonization with GBS, and GBS bacteriuria. In utero inhalation or swallowing of infected amniotic fluid by the fetus may lead to intrapartum sepsis, which may partially explain the high sepsis incidence in infants delivered of mothers with chorioamnionitis. Infant factors associated with EOS in addition to the maternal factors include prematurity, low birth weight, congenital anomalies, complicated or instrument-assisted delivery, and low APGAR scores. Immaturity of the premature neonatal immune system, including low immunoglobulin levels related to decreased transplacental transfer of maternal IgG, also increases the risk of sepsis in preterm infants. Poor or late prenatal care, low socioeconomic status of the mother, poor maternal nutrition, maternal substance abuse, male sex, and African American mother (higher rate of GBS colonization) are additional ethnic and social factors associated with neonatal sepsis (9).

Apart from immaturity, other well-recorded risk factors for LOS include the long term use of invasive interventions, such as mechanical ventilation and intravascular catheterization, the failure of early enteral feeding with breast milk, a prolonged duration of parenteral nutrition, hospitalization, surgery and underlying respiratory and cardiovascular diseases (10).

Table 1: Risk factors for Neonatal sepsis

| | | EOS | LOS |
|---|---|---|---|
| Risk Factors | Maternal | Premature Rupture of Membrane<br>Foul smelling Liquor<br>Multiple per vaginum examinations<br>Maternal fever<br>Difficult or prolonged labor<br>Vaginal colonization by bacteria | Lack of breastfeeding |
| | Neonatal | Prematurity<br>Low Birth weight<br>Perinatal asphyxia [APGAR <4(1min)] | Disruption of skin integrity by mechanical ventilation, indwelling catheter lines and other invasive procedures.<br>Aspiration of feeds<br>Superficial infections like pyoderma, umbical sepsis.<br>Prolonged parenteral nutrition and hospitalization. |
| Causative organisms | | Prevalent in the maternal genital tract or in the delivery area | Organisms thriving in the external environment |

**Clinical manifestations:**

Sepsis is a heterogeneous syndrome and hence its response may vary from mild to severe in a host, depending on the virulence and load of the invading pathogen, duration of infection, the degree of maturity of host defense mechanisms and also the host genetic makeup. The clinical signs and symptoms of neonatal septicemia are often nonspecific and therefore a high index of suspicion for prompt diagnosis is necessary. Feeding pattern, level of activity, muscle tone and peripheral perfusion are all affected. Signs of fetal distress could be the earliest indication of infection in neonates with sepsis either at the beginning or soon after delivery. Neonatal tachycardia, bradycardia, apnea, hypotension, gastrointestinal disturbances are some of the common signs of sepsis (11). A variety of skin lesions accompanying bacteremia, including abscesses, sclerema, petechia, etc. are also commonly observed. Septic neonates can also present with neurologic problems such as seizures and full fontanel even in the absence of meningitis.

**Diagnosis:**

The diagnosis of neonatal sepsis based on the clinical findings alone is difficult because the signs and symptoms are not always specific. Ideally, the mother should be evaluated and appropriate specimens should be obtained if she is suspected of having an infection. Over the years, blood culture still remains to be the gold standard for the diagnosis of sepsis (12, 13); however it takes 24 – 48 hours for the culture results. Therefore a rapid and sensitive diagnostic laboratory tests are essential for the effective and prompt treatment, however, there is no reliable single laboratory test with 100% sensitivity and specificity (12). The correct diagnosis of sepsis is based on a combination of clinical and laboratory findings. In order to improve the outcome associated with sepsis, hematological tests like total leukocyte count, absolute neutrophil count (ANC), immature to total neutrophil ratio (I/T) along with the biomarkers like levels of C-reactive protein (CRP), procalcitonin, etc. in the serum are found to be reliable indicators for infection when used in combination (11-13).

C-reactive protein is one of the most frequently used laboratory test for the detection of sepsis which holds promise to enable a fast and accurate diagnosis of neonatal sepsis. However, it is not useful as an early phase infection marker and it lacks specificity. Serial determination of CRP at 12 hour intervals after the onset of signs of sepsis increased the sensitivity of CRP in detecting sepsis. Procalcitonin (PCT) is a precursor peptide of the hormone

calcitonin and has proven to be superior to CRP in children but its value on the first day of life is limited by a marked physiological increase after birth (11).

Sepsis can also be misdiagnosed in those cases that are negative for blood culture but positive for sepsis screening and have signs and symptoms of sepsis. Conversely sometimes, isolation of bacteria in a blood culture may reflect asymptomatic bacteremia or contamination (13). Though several biomarkers are available for clinical use in the diagnosis of sepsis, their effectiveness in many instances is limited by the lack of sensitivity and specificity (14). Therefore, the quest to search for an ideal biomarker still remains on.

**Pathogenesis of the Immune system:**

Neonates are highly susceptible to infections because of their immature immune system and poorly developed skin barrier. The pathophysiology of sepsis involves highly complex interactions between the host immune system and the invading organism which triggers a myriad of immune reactions. These might further lead to multiple organ dysfunction of the brain, cardiovascular system, lungs, liver, kidney, skin and eventually may result in death (Fig.1). The inflammatory response is mediated by innate cells like the neutrophils, macrophages, dendritic cells, T lymphocytes, T regulatory cells (Treg cells), natural killer T cells (Nkt cells) which can initiate and suppress host inflammation by producing proinflammatory and antiinflammatory cytokines respectively (15). Innate immunity plays a key role in host defenses against microbial infection. The primary response to pathogens in the innate immune system is triggered by pattern recognition receptors (PRRs) that bind to pathogen associated molecular patterns (PAMPs) and subsequent initiation of number of signaling pathways. The PRRs are specific for PAMPs that are found exclusively on the surface of pathogens. Multiple classes of PRRs have been identified which serve as detectors of microbial products including cell wall and membrane components like lipopolysaccharide (LPS), peptidoglycan, lipopeptide, flagellum, nucleic acids and carbohydrates (16,17).

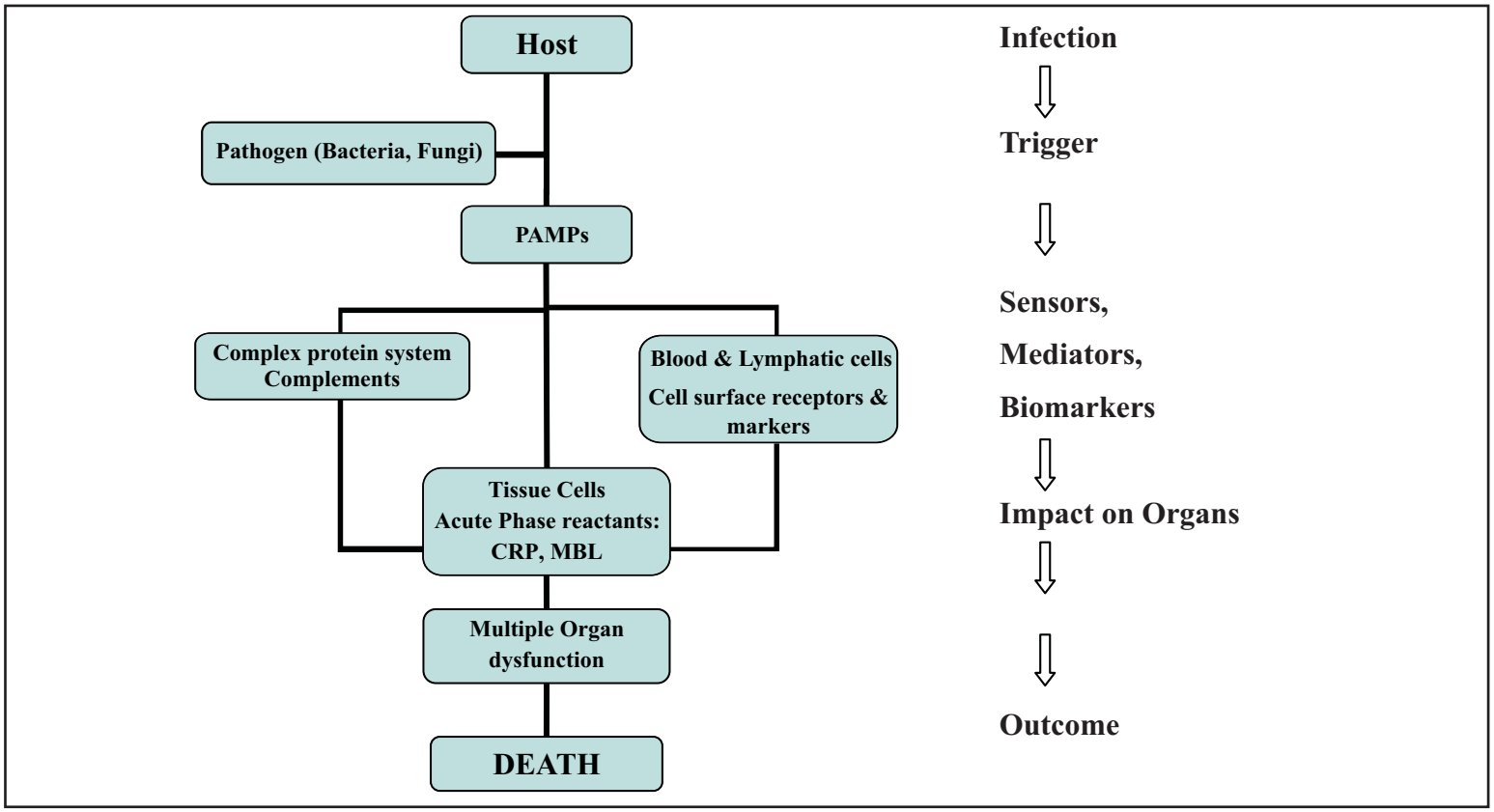


**Fig. 1: Pathogenesis in sepsis**

One of the most well studied PRR is a family of transmembrane proteins known as Toll like receptors (TLRs). Toll protein was first studied in Drosophila for its crucial role in protection against fungal infection (18). Currently, there are 13 different Toll homologues that recognize bacterial (lipopolysaccharide, peptidoglycan), parasitic or viral (Poly I:C) products and of these 10 are expressed in humans. TLR signaling takes place via a common pathway that further leads to expression of different inflammatory genes. Depending on their localization, TLRs are expressed intracellularly or on the cell surfaces of immune effector cells like the macrophages, neutrophils and dendritic cells. Each TLR elicits a specific cellular response to pathogens by using different intracellular adapter proteins (1). TLR2 plays an essential role in recognition of Gram positive bacterial cell wall components such as the peptidoglycan, lipoteichoic acid and lipoproteins and are well studied (19). TLR2 forms heterodimers along with TLR1 and TLR6 that recognize lipoproteins while the other TLRs are believed to be homodimers and are known to recognize different endogenous and exogenous ligands. Once the microbial recognization takes place, the TLRs dimerize further leading to a cascade of signaling pathways, which originate from the cytosolic TIR (Toll/IL-1 receptor) domain. TLR4 along with CD14 (cluster of differentiation 14) and MD2 (also known as Lymphocyte antigen 96) binds LPS abundantly which is present on the cell wall of Gram negative bacterium (20).TLR5 recognizes flagellin a component of the bacterial flagella. While other TLRs located in endosomes and endolysosomes mostly recognize nucleic acids from the pathogens.

CD14 is a multifunctional receptor constitutively expressed on the primary surfaces of monocytes, macrophages and neutrophils as membrane bound CD14 (mCD14) (21). It functions as an anchor protein and enhances TLR2 and TLR4 responses (19). CD14 acts as an opsonic receptor and is essential to mediate the LPS activation of monocytes (22). sCD14 is a soluble form of CD14 which is abundant in serum and apparently derived both from secretion and enzymatic cleavage of mCD14. Increased sCD14 levels have been shown to be associated with shock and greater mortality in patients with both Gram negative and Gram positive bacterial infections (19).

Another receptor, nucleotide oligomerization domain (NOD) a mammalian cytosolic PRR is known to recognize common fragments of bacterial peptidoglycan and LPS (16, 23), thereby activating the inflammation for host defense against infection. Inflammation is generally characterized by elevated levels of proinflammatory cytokines and acute phase response caused due to the production of acute phase proteins by the liver. The early inflammatory response is characterized by elevated levels of proinflammatory cytokines such as tumor necrosis factor- α (TNF-α), interleukin-1 (IL-1) and interleukin-6 (IL-6) followed by rapid release of anti-inflammatory cytokines like interleukin-10 (IL-10) and interleukin-1 receptor antagonist (IL1RA). Changes in the blood levels of cytokines occur rapidly in neonatal sepsis even before that of the acute phase reaction. Several of the acute phase proteins like the Mannose Binding Lectin (MBL), C-reactive protein (CRP), Procalcitonin (PCT) and complement factors have been widely studied in sepsis.

MBL is a circulating pattern recognition molecule that recognizes carbohydrate structures present on microbes, thereby providing first line of defense by enhancing phagocytosis and also by promoting the activation of complement system. MBL deficiency is associated with an opsonization defect and has been associated with recurrent infections especially in immunocompromised individuals (24). Newborns have an undeveloped immune system and hence are considered to be immunocompromised, therefore, they are prone to develop infections which could be life threatening, especially the premature babies admitted in the NICUs.

Bacterial permeability increasing protein (BPI) is found mainly in the azurophilic granules of neutrophils and plays a role in defense against Gram negative infections in resolution of endotoxin inflammatory reactions (1).

It is generally believed that the interaction between coagulation and inflammatory processes play a crucial role in the pathophysiology of sepsis and multiorgan dysfunction. Enhanced pro-coagulant processes may exacerbate inflammatory processes and vice versa, coagulation factor deficiencies result in bleeding abnormalities which may both predispose to multiple organ failure (22). Sepsis is known to be associated with

multiple alterations in procoagulant and anticoagulant mechanisms (16).

**Genetic polymorphisms and sepsis:**

The advancement of high-throughput single nucleotide polymorphism (SNP) genotyping provides valuable information on the interaction of multiple allelic variants and clinical outcome. SNPs are the most common but stable genetic variations in a population (frequency >1%). These variations usually do not significantly alter gene expression; however there are different ways that SNPs can lead to aberrant gene products. Likewise in the neonates, wherein the immune system is immature, small variations or changes in the innate genes might affect the network of immune responses, which would further impact susceptibility, severity as well as in the risk to sepsis due to specific pathogens.

More recently, the focus has evolved to the identification of genetic variations (Fig.2) in crucial genes involved in the host immune system, in particular Toll-like receptors (TLRs) and proinflammatory cytokines that have provided valuable insights into the influence of genetic heterogeneity on the response to bacterial infection. By definition, no single locus is thought to control susceptibility to neonatal sepsis, but a number of candidate genes have been studied because of their biological effects that have been demonstrated or predicted would be consistent with a plausible pathogenetic mechanism (25).

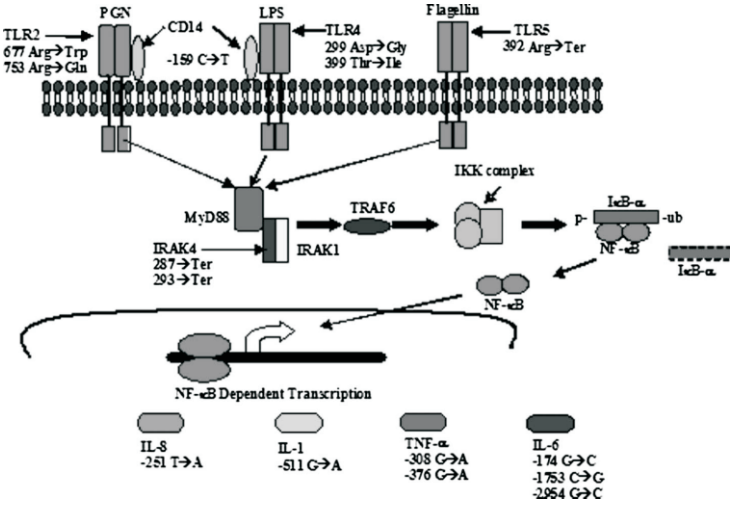


**Fig.2 Toll-related pathway and cytokine polymorphisms (Adapted from Arcaroli 2005)**

Although number of SNPs in the candidate genes involving innate immune receptors like CD14, TLR1, TLR2, TLR4, TLR5, IRAK4, related molecules like MBL, BPI and cytokines like, IL-6, TNF-α, IL-10, etc. have been studied, however, not all the SNPs are found to be associated with neonatal sepsis. The SNPs shown to be associated with sepsis are listed in Table 2. Studies have shown that a polymorphism in the CD14 gene within the promoter region at position 159 CT increases sCD14 and is associated with sepsis and mortality and prevalence of Gram negative infections (19). In a case-control study, Wurfel et al. (26) studied -7202G in the TLR1 gene and was found to be associated with sepsis-related acute lung injury with a higher prevalence of Gram-positive cultures. Variations in the TLR2 (Arg753Gln) and TLR4 (Asp299Gly) genes were found to be associated with Gram positive and Gram negative sepsis respectively, while variations in the TLR5 (Arg392Ter) gene showed susceptibility to flagellated organisms (1, 19). Variations in other receptor related genes like MD2, TIRAP, MyD88 were also shown to be associated with sepsis (32, 37). By reviewing several studies, Arcaroli et al (19) showed that SNPs in codon 52, 54 and 57 (D, B and C respectively) of exon 1 in the MBL gene were associated with low serum MBL concentration and also had an increased susceptibility to a wide range of bacterial infections. Genotypic variations in the NOD and BPI genes are also found to be associated with proven sepsis (22, 27). Genetic polymorphisms in different proinflammatory like TNF-α, IL-1, IL-6, IL-8 and anti-inflammatory cytokines like IL-10, IL1RA, have also been studied in association with sepsis. It has been observed that an increased sepsis related mortality in the patients carrying the mutant allele of the TNF-α 308 G/A polymorphism. (19,22). IL6 is a key pro-inflammatory cytokine, and the effect of the IL6-174 C gene variant has been shown to increase IL6 production which makes this a biologically plausible protective variant against sepsis. (25,28). Of the many SNPs studied in the coagulation gene pathway, only rs5985 (Val34leu) in the Factor XIII gene was found to be associated with increased risk of sepsis and prolonged hospital stay (25, 28)

**Table 2: Genes and SNPs associated with Sepsis:**

| Genes | SNPs | Location | | Association Studies | Ref. |
|---|---|---|---|---|---|
| CD14 | rs2569190 159 C>T | Promoter | i. | Alter the risk for multiple blood stream infections. | (22) |
| | | | ii. | Increased sCD14 levels in the serum | (21) |
| | | | iii. | Increased prevalence, septic shock and mortality rate in patients with Gram positive and Gram negative bacterial infections. | (19,27, 29, 30) |
| TLR1 | rs5743551 -7202 G/A | Promoter | | Associated with a higher likelihood of organ dysfunction and death in patients with gram positive sepsis and sepsis related acute lung injury | (26, 31) |
| TLR2 | rs4696480 T16933A | Intron | | Increased risk of sepsis with Gram positive infections in both adults and neonates | (1,30,32, 33) |
| TLR 4 | rs4986790 Asp299Gly 896G | Exon | i. | Associated with increased septic shock with Gram negative infection | (32,34, 35) |
| | | | ii. | Associated with meningococcal sepsis | |
| TLR5 | rs5744105 392Ter | Exon | i. | Associated with elevated WBC counts during infection | (34) |
| | | | ii. | Associated with sepsis, due to flagellated organisms | (1) |
| TIRAP | rs8177374 Ser180leu | Exon | | Associated with sepsis | (32) |
| NOD | rs2066847 3020insC | Exon | | Associated with blood culture proven sepsis | (23) |
| MBL | rs5030737 Arg52Cys | Exon | | Low serum MBL levels and increased susceptibility bacterial infections | (19) |
| | rs1800451 Gly57Glu | Exon | | | |
| | MBL haplotype group (O) | Promoter /Exon | | | |
| IRAK 4 | rs121908002 C877T 293TER | Exon | | Associated with both recurrent Gram positive and Gram negative bacterial infections | (19), (36) |
| | rs4358188 | | | Associated with significantly reduced risk of developing sepsis | (27) |

| | | | | | |
|---|---|---|---|---|---|
| MyD88 | rs137853064 Arg196Cys<br>rs137853065 Leu93Pro | Exon | | Associated with pyogenic bacterial infection in children | (37) |
| TNF-α | rs1800629 308 G/A | Promoter | | Increased sepsis related mortality | (22) |
| IL-6 | rs1800795 174G/C | Promoter | i. | Considered to be an early and sensitive marker of neonatal infection. | (13) |
| | | | ii. | Associated with sepsis and prevalence in VLBW infants. | (23) |
| IL-1RA | A2 (2repeats) | Intron | | Increased frequency and mortality in patients with sepsis | (19) |
| Factor XIII | rs5985 Val34leu | Exon | | Associated with higher rate of sepsis | (25) |

**Indian Scenario:**

The incidence of neonatal sepsis is 30 per 1000 live births as per the National Neonatal Perinatal Database (38) comprising of 18 tertiary care neonatal units across India. Sepsis was found to be one of the major causes of neonatal mortality contributing to 19% of all neonatal deaths. Septicemia is the commonest clinical category with an incidence of 23 per 1000 live births while the incidence of meningitis was reported to be 3 per 1000 live births. Reports from India showed that 50-60% of the septic neonates are premature and very low birth weight (39). Infections caused due to Gram negative organisms are most predominant than those caused by Gram positive organisms (3,40). *Klebsiella pneumoniae* is the most frequently isolated pathogen (38, 41-45), followed by *Staphylococcus aureus* (41). In India, sepsis accounts one fourth to nearly, half of neonatal deaths with a case mortality ranging from 24-69%. In a north Indian tertiary care center, Sundaram et al (47) studied the incidence of neonatal sepsis between the two time periods (epoch-1:1991-1996, and epoch-2: 2001-2006) and was found that that incidence of early onset sepsis did not change between the epochs but the incidence of late onset sepsis increased from 12-16.5 per 1000 live births in epoch 2. Verma et al (41) reported that neonatal sepsis is one of the major causes of morbidity and mortality in the newborns. Mortality in early onset septicemia was found to be more (27.77%) than the late onset septicemia (14.86%) and was higher in culture positive cases due to invasion of blood stream by large number of bacteria. The major risk factors were found to be low birth weight (68.0%), prematurity (46.0%), and poor hygiene/cord care (46.0%) with clinical presentations like lethargy or refusal to feed (77.0%), hypothermia (47.5%), and respiratory distress (44.0%) (44). The antibiotics which are routinely used like ampicillin and ceftriaxone showed poor activity against most of the organisms (41). In another study, Samayam et al (48) observed predominantly Gram negative organisms like *Klebsiella, Pseudomonas, E.coli* and CoNS in EOS and *Klebsiella, E.coli, S. aureus* and *Pseudomonas* in LOS among the neonates in a rural setting located in Bangalore, South India. Sometimes it is difficult to determine whether neonatal sepsis is due to inherited genetic defects or other causes. Little is known, about the genes that are responsible for fatal outcomes caused by systemic infectious diseases such as sepsis. So far, no comprehensive study has been done to explain the genetic basis of neonatal sepsis in our country.

**NIIH experience:**

Our study on neonatal sepsis suggests that 16.0% of the neonates who were admitted to the NICU for various complications are positive for sepsis screening and majority of them (43.0%) had higher CRP levels and abnormal WBC counts. Of these septic screening positive cases, 48.5% of the neonates were blood culture positive for a bacterial or fungal pathogen. Infections were mainly caused due to Gram negative organisms (65.00%) than Gram positive (22.00%) and fungal infections (11.00%). *Enterococcus,* Methicillin resistant coagulase negative *Staphylococcus aureus(MRCoNS), Klebshiella pneumoniae, Acinetobacter, Streptococcus* and *Enterobacter* are some of the organisms mainly found to be responsible for causing sepsis in these neonates. Respiratory distress, hypoglycemia, hyperglycemia, perinatal asphyxia, anemia, apnea are some of the common clinical signs and symptoms observed among the sepsis cases. In our cohort, an overall mortality rate due to sepsis was found to be 21.85%.

To look for polymorphic variation in the population, nine SNPs in the CD14, TLR2, TLR4, TLR5 and IRAK4 genes were studied in apparently healthy individuals and six were found to be polymorphic (MAF >1%). These six SNPs were further studied in sepsis cases and control neonates. A higher proportion of the neonates in the sepsis groups showed variation either in heterozygous or homozygous state of the mutant allele only for rs2569190 in the CD14 gene as compared to the control group. It was also observed that 91.17% of the neonates, who died due to sepsis had the mutant genotype (CT or TT) for the rs2569190 CT variant in the CD14 gene. Therefore genetic polymorphism in the CD14 gene could be genetic risk factor for neonatal sepsis.

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## Department of Pediatric Immunology and Leukocyte Biology

**Dr Manisha Madkaikar, Scientist F & Director-in-charge**

1. Invited to deliver a lecture on "Laboratory approach to diagnosis of Primary Immunodeficiency Disorders" during CME on Primary Immunodeficiency Disorders held at GIPMER, Pondicherry on 18th October 2015.
2. Organized Flow Cytometry Workshop on Diagnosis of Primary Immunodeficiency Disorders (PID) from 27th to 28th Octerber 2015 at National Institute of Immunohaematology, Parel, Mumbai as a part of the '16th Indo-US Cytometry Workshop'
3. Attended 58th Annual Conference on Hematology and Blood transfusion and CME held at Bangalore from 5th to 8th November 2015 and delivered following lectures:
   a. Application of lymphocyte subset analysis for diagnosis of PID: Case based discussion.
   b. Flow cytometric diagnosis of PNH.
   c. Clinical and Laboratory approach to PID.
4. Invited to deliver a lecture on "Diagnosis of Primary Immunodeficiency disorders" in the CME for pediatricians at Lilavati Hospital, Mumbai on 5th Dec 2015.

**Ms Aparna Dalvi, Technician**

Presented a poster entitled "Flow cytometric evaluation of IL 12-23/IFNγ pathway in patients with suspected Mendelian Susceptibility to Mycobacterial Diseases" in 8th annual meeting of The Cytometry Society, India held at Tata Memorial Hospital, Mumbai from 24th to 25th October 2015.

**Ms Swati Garg, SRF**

Received best paper award in clinical category for the year 2015, by The Cytometry Society, India for the paper entitled "Differential antigen expression and aberrant signaling via PI3/AKT, MAP/ERK, JAK/STAT and Wnt Beta catening in Lin-/CD38-/CD34+ cells in AML".

**Ms Jahnavi Aluri, SRF**

Received Best poster award for the paper entitled "Flow Cytometry for Diagnosis of Severe Combined Immunodeficiency- A guide to molecular diagnosis" in 8th annual meeting of The Cytometry Society, India held at Tata Memorial Hospital, Mumbai from 24th to 25th October 2015.

## Department of Hematogenetics

**Dr Malay Mukherjee, Scientist E**

1. Attended IITB Healthcare Consortium Advisory Committee Meeting held at IIT, Mumbai on 2nd September 2015.
2. Attended PRC meeting for the Task Force Project on Hemoglobinopathies held at ICMR, New Delhi on 22nd September 2015.
3. Attended Inaugural ceremony of the Hemoglobinopathies Satellite Centre at Chandrapur on 25th October 2015.

**Dr Anita Nadkarni, Scientist E**

1. Attended 1st Red cell meet at CMC Vellore on 26th September 2015 and delivered a lecture on " HPLC for identification of Hb variants "
2. Attended 3rd International Conference on Hematology and Blood disorders held at Atlanta USA from 2nd to 4th November 2015 and presented a paper entitled "Effect of group of genetic markers on induction of fetal Hemoglobin and disease severity in Hemoglobinopathies"

**Dr Prabhakar Kedar, Scientist D**

1. Attended workshop on "Bio-safety Waste - Risks

Management and Environmental Concerns" held at NIV, Pune from 21st to 22nd September 2015

2. Attended 6th International conference on "Promotion of Animal Research, Welfare and Harmonization of Laboratory Animal Science" organized by Laboratory Animal Scientists Association (LASA) in collaboration with ACTREC-TMC and CPCSEA held at ACTREC, Mumbai from 15th to 16th October 2015.

## Department of Transfusion Medicine

**Dr Ajit Gorakshakar, Scientist F**

Received Manorama Sapre Oration Award by the Indian Society of Hematology and Blood Transfusion during 56th Annual Conference of ISHBT held at Bengaluru from 6th to 8th November 2015.

**Dr Swati Kulkarni, Scientist C**

1. Invited to deliver a lecture on "Relevance of extended phenotyping - need of the hour?" at the 40th Annual National conference of Indian Society of Blood Transfusion and Immunohaematology held at New Delhi from 25th to 27th September 2015 and also presented the following papers:

   i. A simple PCR assay for identification of RhD variants.

   ii. Database of extensively phenotyped regular blood donors for transfusion support of thalassemic patients.

2. Participated in Second Granulocyte Immunobiology Practicum held at Bali, Indonesia from 12th to 13th November 2015.

3. Attended XXVIth Regional Conference of International Society of Blood Transfusion, held at Bali, Indonesia from 14th to 16th November 2015 and presented following posters:

   i Noninvasive fetal RhD genotyping by multiplex real time PCR.

   ii Extended red cell antigen typed regular blood donors for thalassemic patients.

4. Attended 4th Annual Conference of Indian Society of Transfusion Medicine-Transmedcon 2015 held at Kolkata from 4th to 6th December, 2015 and presented the following papers:

   i. Frequency of clinically significant blood group antigens in Ahir community from Valsad (South Gujarat) (Awarded first prize for the Best Poster).

   ii. Rh null: a rare blood group phenotype.

   iii. Phenotype frequencies of antigens of clinically significant blood group systems in blood donor population from Nagaland.

   iv. Significance of detecting Weak-D / Partial-D in Patients and Donors.

**Ms Disha Parchure, SRF**

Received PG Travel fellowship award for the 40th Annual National Conference of Indian Society of Blood Transfusion and Immunohaematology held at New Delhi, from 25th to 27th September 2015 and presented a paper entitled "Noninvasive fetal RhD genotyping using cell-free fetal DNA from maternal plasma".

**Ms Harita Gogri, SRF**

Participated in Second Granulocyte Immunobiology Practicum held at Bali, Indonesia from 12th to 13th November 2015.

Attended XXVIth Regional Conference of International Society of Blood Transfusion held at Bali, Indonesia from 14th to 16th November 2015 and presented a poster entitled "Frequency of human neutrophil antigen-2 among Indian blood donors".

## Department of Hemostasis

**Dr Shrimati Shetty, Scientist E**

1. Invited to deliver a lecture on "Inhibitor prevalence in India" at the Annual General Body Meeting of HFI held at YMCA, Mumbai on 13th September 2015.

2. Invited to deliver a Guest lecture on "Thromboelastography" in the Annual conference of Indian society of hematology and Blood Transfusion held at Bangalore from 6th to 8th November 2015.

3. Invited as an examiner for pre PhD examination under Rajeev Gandhi University of Health sciences at St. Johns Medical college, Bangalore on 14th December 2015.

**Dr Bipin Kulkarni, Scientist C**

1. Awarded the Best Paper Award for his presentation on "Second trimester prenatal diagnosis in Glanzmanns thrombasthenia" at the Quarterly Mumbai Hematology Meet held at Mumbai on 20th December 2015.

## Department of Cytogenetics

**Dr V. Babu Rao, Scientist E**

1. Attended as a member of the selection committee for the selection of Scientist D at National AIDS Research Institute, Pune on 8th September 2015.

2. Attended 27th Annual Fanconi Anemia Research Fund Scientific Symposium held at Toronto, Canada from 17th to 20th September 2015 and presented a paper entitled "Molecular study of FANCA complementation group in Indian population".

3. Delivered a guest lecture on "Chromosomes to microarrays: Diagnosis and prevention of Genetic disease" at SNDT Womens University, Mumbai on 8th October 2015.

4. Attended as a Chairman of the selection committee to select Research Associate in a project at NIRRH, Mumbai on 15th December 2015.

**Ms Avani Solanki, SRF**

Attended 27th Annual Fanconi Anemia Research Fund Scientific Symposium held at Toronto, Canada from 17th to 20th September 2015 and presented a paper entitled "Mitochondrial gene variations in pathogenesis of Fanconi anemia".

Scientific Advisory Committe Meeting of the Institute

Visit of Dr Soumya Swaminathan, Secretary DHR & DG ICMR

Fairwell to Dr Lily Kerketta, Scientist E

Indo-US Workshop on PID


Dr. Ajit Gorakshakar receiving Dr. Manorama Sapre Oration Award

Inauguration of Hemoglobinopathies Satellite centre at Chandrapur, Maharashtra


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