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A Study on Neonatal Sepsis and its Clinical Features, Diagnosis Management and Prevention

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Abstract – Neonatal sepsis is a bacterial clinical indication and symptom of systemic implication in the first month of existence and is characterized by this infection. Neonatal death is the most often reported source. It is not necessary to diagnose neonatal sepsis from clinical signs. While it has become the traditional gold-type diagnostic isolation of causative microorganisms using blood crops, the result is not ready until 24-72 hours after the sample is taken and the suspect babies must be treated with antibiotics on the basis of reporting during this time span. Several hematological indicators were used for sepsis, the majority of them were either not quite responsive or precise, and perinatal factors such as maternal hypertension, asphyxia, and hemolytic disease were generally affected.

Keywords – Sepsis, Neonatal sepsis, Clinical Features, Diagnosis Management, Prevention

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INTRODUCTION

Neonatal septic sepsis is a pediatric condition characterized in the first 4 weeks of its existence by signs and symptoms of infection. The most frequent condition in NICU is "Suspected sepsis" due to its ambiguous signs and symptoms. Although increased obstetric treatment, intra-partum monitoring and proof-based antibiotic usage are now performed every day, sepsis remains a major contributor to neonate mortality and morbidity.

About 40% of fatalities below the age of five were neonatal mortality. The global prevalence of septic neonatal deaths is only 15% but sepsis accounts for about 30 to 50% of neonatal mortality in developed countries such as ours. In the past two years, significant progress has been made towards the decline in post-neonatal mortality globally in the proportion of neonatal mortality to only five deaths.

Sepsis:

Sepsis is characterized as an invasion into the bloodstream by microorganisms or their toxins and the reaction of the host to the invasion. When SIRS happens in a patient whose infection has been established or assumed, sepsis is identified. In the US consensus framework, SIRS is considered sepsis.

Septicemia:

Septicemia, also known as blood poisoning, is an infection caused by bacteria in the blood (bacteremia). A high fever, chills, weakness, and excessive sweating precede the onset of septicemia, which is followed by a drop in blood pressure.

Neonatal infections:

This merits analysis because of the difference in maternal health, hygiene conditions during delivery and the medical facilities available between developed & developing countries. Besides this, asymptomatic colonization of multidrug-resistant (MDR) and/ or ESBL-producing organisms in the gut of neonates may serve as the source of subsequent infections. There is limited information on the colonization of ESBL-producing Enterobacteriaceae in neonates from around the globe and from India. Pneumoniae in the gut of neonates and the risk factor (if any) leading to colonization and infection with these two organisms in the same NICU. We thus investigated the production and variability of ESBLs in pathogens like K. pneumoniae and E. coli from blood and gut of hospitalized neonates in view of the cephalosporin resistance.

Neonatal sepsis:

Based on the onset of sepsis-related symptoms, neonatal sepsis can be divided into two categories.

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Sepsis with an early onset usually appears within the first 72 hours of life. The maternal genital tract is usually the source of infection. Neonatals usually have respiratory distress and pneumonia when they arrive at the hospital (1, 2).

Etiology of neonatal sepsis:

In emerging nations, pathogens more commonly involved in neonatal sepsis vary from in advanced countries. In general GNB is more prevalent and consists primarily of Klebsiella spp, Escherichia coli, Pseudomonas spp, Enterobacter spp, Acinetobacter spp and Salmonella spp. Staphylococcus aureus, CONS, Streptococcus pneumonia, and Streptococcus pyogenes are the most often isolated of the gram-positive species. In Asia GBS is also reported to be extremely rare. In South America GBS incidence is comparable to the West. In Asiatic countries GNB (£'. coli, Klebsiella spp., Pseudomonas spp., Acinetobacter spp.) are the important causes of sepsis. In developing countries in the first week of life, Klebsiella species (25%), E. coli (15%), and S. aureus (18%) were major pathogens. While there were geographical variations, GBS was reasonably unusual (7 percent) (3-5).

Major pathogens in neonatal septicaemia:

- **Klebsiella spp.**

Klebsiella belongs to the Klebsiellae tribe, which is part of the Enterobacteriaceae family. Klebsiellae are gram-negative bacteria that are nonmotile and have a prominent polysaccharide capsule.

- **Klebsiella pneumonia**

In neonatal intensive care units, septicaemia is a leading cause of neonatal mortality, and a significant proportion of newborns are infected with Klebsiella spp (NICUs). Several unrelated outbreaks of multidrug-resistant K. pneumoniae in NICUs in Italy, the United States, Madagascar, Brazil, Chaina, Tunisia, and elsewhere(56-60) are frequently caused by new strains known as ESBL producers.

- **Escherichia coli**

E. coli form part of the gastrointestinal microflora of many animals where they normally exist without causing disease. The host gastrointestinal microflora is an important part of the healthy gut and so can be described as a component of host innate defence.

- **Clinical categories of E. coli**

Recent Phylogenetic Reactions of the Polymerase Chain (PCR), indicating that E. coli strains are classified in four major phylogenetic classes (A, Bl, B2 and D). Extra virulence strains primarily belong to Group B2 and, to a lesser degree, to Group D.

- **Extraintestinal infections due to E. coli**

E. coli can cause bacteremia. If the microorganisms begin to multiply, the bacteremia progresses to septicaemia. Neonates, older people and those at risk for immunological sepsis are especially vulnerable. The ompT virulence gene was highly predictive of sepsis in E. coli Isolates. The evidence collected from Johnson et al., 2001 & 2002 and Sannes et al., 2004 show that the common ExPEC pathogens are strains of E. coli, which cause sepsis. There was reporting of a new kind of HI secretion mechanism involving septicaemic ExPEC virulence.

Epidemiology:

It is projected that the worldwide distribution of septic-based neonatal deaths is 1.6 million a year. In developed nations, about 40% of this mortality occurs. Neonatal septicemia was recorded to have an occurrence in Africa of about 42 per 1000 living births, in Latin America and Caribbean regions of 17 per 1000 live births10. The average prevalence of culture sepsis is 1-8/1,000 live births in developing countries.

In India, neonatal septic sepsis varies from 4.8 to 20.7 incidences per 1,000 live births while the prevalence of meningitis is 3 in 1000 live births. In India septic mortality is around 40%-65%, which is around 1/40% to almost half neonatal.

Early onset sepsis:

Even prior or after delivery, sepsis is obtained early onset. The presentation normally takes less than 72 hours. It is usually linked to parental, premature and multi-system manifestations. Neonates are more vulnerable to early sepsis with a relatively tiny birth weight (<1000 gm).

Late onset sepsis:

After 3 days of life in the late starting septic the appearance is normally between the 10th and 22nd day of life with peak incidences. This shows that LOS pathogenesis is implicated in hospitalization and life-support devices. Late septic sepsis leads to severe mortality caused by nosocomia infections. It contains infections that are not developed tran-placentally yet are admitted to the neonatal intensive care unit.

Verylate onset sepsis:

Here, after 1 month of birth signs and symptoms are obvious. It occurs in particularly babies who need long-term care in NICU, especially with very low birth weight babies (VLBWs).

One third of VLBW children with sepsis have a greater prevalence of meningitis, but they are

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negative for blood culture. This cultural discrepancy and the elevated clinical suspicion in these babies highlight the need for CSF culture in neonatal neptic sepsis suspected.

Bacteriological spectrum:

There are significant geographical variations in the bacteriological continuum of neonatal septicism. Any microorganism that colonizes the genitourinary or the gastrointestinal tract of the mother may lead to infections in both the intrapartum and postpartum.

In comparisons with the Gram positive species, gram negative organisms are most often blamed for neonates sepsis (65-85 percent). Common isolates present are Clebsiella, Citrobacter, Proteus and Group B. Streptococcus, E.coli, Pseudomonas, Staphylococcal aureus, Enterobacter.

Immunity of neonatal:

In neonates the immune system is separate from the adult system and its reaction. Termally and preterm neonates were also found and seen to have qualitative and quantitative deficiencies.

The successful killing of bacteria is based on neutrophils or polymorphonuclear cells. In new neonates these cells have decreased adherence, thereby decreasing the movement into the tissues of the lining of the vascular endothelium.

These polymorphs often display poor chimiotaxis (neutrophil migration) as selectins and molecules adhering to the cell membranes decreased expression of β-2 integrins. The polymorphic neonatal cells are less distorted than the adult cells. This reduces the phagocytic function of the cells and thus impairs the effective killing of bacteria in septicism. Easy loss of the reserve of neutrophils due to decreased reaction from the bone marrow allows the neonate more infectious.

In the supplementary method, the terminal cytotoxic components responsible for effective killing of Gram negative bacteria are inadequate in neonates. The mechanism supplementary to the E.coli system is primarily responsible for bactericidal action and acts as opsonins with the phagocytose antibody.

Pathophysiology:

The unparalleled pathophysiology leads to neonatal sepsis clinical syndrome. Because of their impaired immune status, neonates are less efficient to initiate an infection response than adults. The identification becomes a dynamic procedure and its symptoms differ in neonates. Conditions coexist with sepsis.

The pathogensis depending on either the duration of their exposure, the state and reaction of the host immune system, the quantity of the inoculum, the infectious microorganisms virulents o, or new neonate maturities, o comorbid conditions underlying comorbid conditions, o invasion-made operations, or hereditary predisposition o the occurrence of maternal transplacental anticuerpos.

After birth, neonates can acquire mothers and families infection, inanimate resuscitation sources, or direct interaction with health workers. The majority of cases of meningitis are caused by hematogenic diffusion and fewer by adjoining propagation.

Neonatal sepsis markers:

Numerous molecules, such as total leucocyte count, absolute neutrophil count, established & immature neutrophils ratio, creactive protein, and different cytokines such as IL-6 & 8 and TNF-α, were recommended as valuable markers for diagnosis of septic tissue. However, none of them is 100% resilient or specific. While blood culture is the traditional gold-based approach for diagnosis of septic septicism, fast methods of diagnosis may be an additional benefit.

Due to its low predictive ability, the number of platelet indicators has increased considerably less in prognosis. Almost 50 percent of them experience thrombocytopenia as a late occurrence in bacterial infections, rendering it a less accurate predictor. In some diseases other than sepsis, it is often elevated.

Interleukins:

Interleukins are leukocyte products which regulate the other cells. They are classified under cytokines that control inflammatory, immunological, and reparative reactions in the host cells. They are hormones that even in femtomolar levels are extremely potent and active.

Lymphocyte, macrophages, fibroblasts and platelets, for example, contain interleukins. It acts localized near the generating cell or directly on the cell that produces it (paracrine effect) (autocrine effect). They are generally pleotrophic, and the results caused by various cytokines are considerably overlapped.

Tumor necrosis factor α is an active pro-inflammatory cytokine with host defense pleotropic effects against predominantly monocyte, macro and lymphocyte pathogens. The future goal for its intervention would be both cells and tissues. There are two facets of TNF induced impacts. Firstly, there is growing proof that it participates in a variety of pathological mechanisms. In the other side, the development of anti-microbial immune response is assumed to be crucial for.

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C-reactive protein:

The cytokine induced reaction causes the most types of tissue damage, which dramatically increases the circulation amounts of the natural plasma protein, CRP. It is therefore called an acute reactor prototype that plays a key role in innate immunity. This plasma protein is synthesized through infection and inflammation in the hepatocytes.

CRP leads to the protection of the host within hours of tissue damage and inflammation in the context of an innate immune response, as can be seen by a fast serum elevation. The removal from the body of the microbial stimulation results in a fast decline in serum CRP levels since it takes around 19 hours to achieve its shorter half-life.

Procalcitonin:

The hormone calcitonin peptide precursor is constructed from 116 amino acids with 13 kDa molecular weight. It is encrypted in the chromosome CALC1 gene. CT-DNA is converted into mRNA and pre-procalcitonin is the first translation element.

Action of numerous cytokines and endotoxins produced during infection inhibits the transfer of pro-calcitonin to calcitonin. Therefore as Gram endotoxins raise the amount of negative bacteria, the level of procalcitonin gradually increases and is not linked to the increase of the level of calcitonin in parallel.

There are several cases where procalcitonin is high because of non-bacterial origin, though, like major stress conditions, and treating cytokine releases.

Clinical manifestations:

The unusual pathway to infection is recognised as the Systematics Inflammatory Syndrome (SIRS). SIRS is known as hypothermia, modified gas exchange, respiratory distress, hypoxemia, infusion abnormalities contributing to oliguria and metobolic acidosis in neonates. SIRS incidents as multisystem organ loss and death cause this escalating tissue harm untreated.

The presentation should be clinical:

a) Non- specific signs and symptoms

b) Specific features pertaining to the organ systems

Early diagnosis of the first signs and symptoms needs a strong degree of skepticism. Fevers, weaker screams, avoidance of eating, lethargy, long capillaire refill times, inadequate infusion, lack of neonatal reflexes, hypotony, tachy/bradycardial disease, apnea, gasping and respiratory distress, hypo/hyperglycaemia, metabolic acidosis, may be considered for this procedure (11).

Diagnosis:

A significant role in the diagnosis of septic disease is a maternal background that provides helpful details about antenatal susceptibility to immune status, infection, colonization & other obstetrical risks along with clinical features.

A laboratory diagnosis that supports signs of infections, such as separation from a usually clean site, may be carried out as a diagnosis of the biologic marker of sepsis, such as blood, brain spinal fluids, or tissue/fluid demonstration, molecular diagnostic testing and serology testing.

As blood cultivation is considered the gold standard of sepsis diagnosis, it should be performed before initiation of antibiotic therapy in all instances of clinical suspicion.

Antimicrobial resistance:

Drug aversion is a wellbeing problem for septic neonates since these people are limited to minor care choices. The world's most commonly used antibiotics are increasingly resistant. The emergence of resistance is characteristic of and is inevitable for bacterial evolution.

Most clinically important bacteria express and acquire tolerance to medicines. The characterization of an organism that involves testing to assess tolerance pattern shall be performed while the organism is is isolated in the laboratory.

Popular drug resistance mechanisms generally involve enzymatic elimination of the antibiotic, an altered action goal leading to lower affinity or decreased antibiotic binding, lower intracelular absorption, or enhanced drug efflux. Bacterial degradation of the β-lactam loop is the most popular mechanism of resistance among β-lactam antibiotics.

The first antibiotic β-lactam has been the alternative for several years since penicillin was discovered. However, via the synthesis of βlactamase enzyme, bacteria evolved pathways to avoid the action of this antibiotic. The first β-lactamase induced plasmid identified in the 1960s was TEM-1. Organisms removed from acute treatment units appear to be highly resistant to antibiotics.

In the last two decades, several modern antibiotics with β-lactam have been formulated specially intended to counteract β-lactamases hydrolytic actions. In the last few years, the emergence of drug resistance has increased considerably because of inadequate and widespread application of these emerging substances as well as the mutation of these β lactamases.

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The division of β-lactam contains four main antibiotic classes, including penicillins, cephalosporins, monobactam and carbapenems.

AccOf Karen Bush and George A. Jacoby (2010), while a structure classification is the more convenient and least controversial method to classify this diversity, it is possible to associate β lactasis with their clinical position through exercising selective resistance against various classes of β-lactam antibiotics (12).

Clinical features:

There are mild symptoms, from intermittent bacteremia to resplendent septic septic sepsis, leading to septic shock, DIC, high fatality, and lifestyles. Endocartitis (intrevascular) is synonymic for continuous bacteremia and other extravascular infections such as typhus (first week). During minor operations or coercion, transient bacteremia occur.

Intermittent bacteremia tend to be secondary to any local abscess. In almost all patients, fever is the most common indication of intermittent, continuous bacteremia. This health properties include higher respiratory rate, heart rate and lower blood pressure. Bryan pointed out that patients with stable blood cultures are twelve times more likely to die than negatively influenced blood cultures.

Laboratory diagnosis of blood stream infections:

In patients with conditions predisposing to BSI2, blood culture is an effective diagnostic method. Manual techniques and automatic methods can detect bacterial development. There are now several automated systems which produce quick results. The organism is removed and its immunity to various antimicrobials is tested (13).

Treatment:

Indications for initiating antimicrobial therapy in neonates include presence of ≥3 risk factors, foul smelling liquor, proven sepsis and high degree of suspicion.

The reluctance to promote them as first line drugs is attributed to their high susceptibility to the ESBLs and significant association with repressor mutations. Antibiotics like piperacillin/tazobactam or methicillin/vancomycin are preferred over them in a place with high prevalence of resistance due to ESBL producing strains.

Reserve antibiotics like monobactams and carbapenems should be used only where sensitivity of the bacterial isolate warrants its use. Treatment with granulocyte-monocyte colony stimulating factor is under experimental study at present.

The treatment regimen is undergoing constant re-evaluation to give the most effective outcome. Further there cannot be a single recommendation of the anti-biotic regime for all settings as the choice of antibiotic is influenced by the microbial flora in the given setting and its susceptibility pattern. At present good infection control and more research for the development of newer antibiotics are the two potential domains which determine the outcome of sepsis in future.

Neonatal mortality due to sepsis: global current scenario:

Each year 3.6 million neonates die during the first four weeks of life.

In neonatal fatalities (aged 0-27 days), 41% (3-575 million) of all fatalities occurred in children under five years old (Figure 1).

There is a significant variation in the distribution of deaths (Figure 2) around WHO areas and their causes. In the African area (4-199 million) and in the Southeast Asian (2-390 million) there was a high proportion of neonatal deaths (142). The patterns of death in both regions vary: less neonatal deaths in Africa (29%, 1–224 million vs. 54%) than in the area around South-East Asia; and more o1 deaths (16%, 0–677 million) in Africa; and AIDS (4%, 0–181 million) than in the South-eastern Asia, where there are about 1%, are known to occur in both areas. The large proportion of infant mortality in neonates happened in the Americas and Europe, Asia, varying in 48% (0-137 million/0-284 million) of premature birth complications and childhood smoking in America, up to 54% (1-295 million/2-390 million) of premature birth complications in South East Asia. Congenital factors have been proportionately more significant in countries with low neonatal mortality.

According to World Health Organization (WHO) Almost all deaths occur in developing countries; half of them in the African region In developed nations. The number of neonatal deaths caused by birtl's asphyxia (53 per cent, 0 to 443 million), sepsis (52 per cent, 0 to 271 million), prelude to childbirth (49 per cent) and defects of the congenital (43 per cent, 0 to 161 million), was large in countries like India, Nigeria, the Democratic Republic of the Congo and the Chinese. The key reasons o: premature birth problems in the neonatal stage mortality, birth asphyxia and sepsis and pneumonia have become ever more significant.

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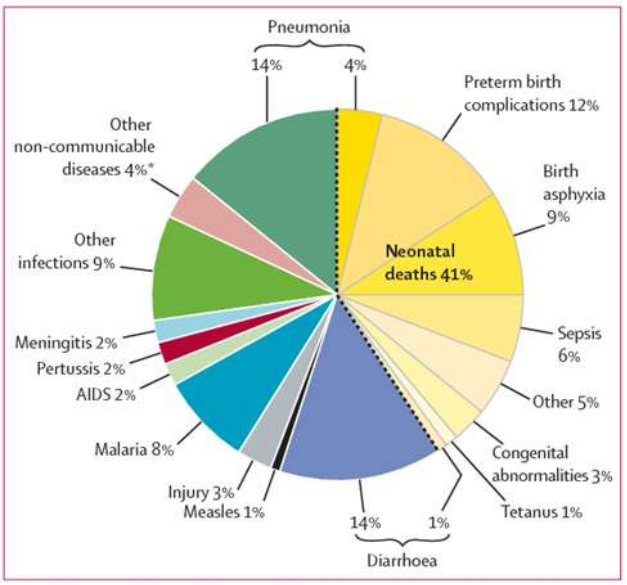

Figure 1: Causes of neonatal deaths around the world. Deaths of neonates aged 0-27 days and children aged 1-59 months are separated in the data. Causes that led to less than 1% of deaths are not presented. *Includes data for congenital abnormalities.

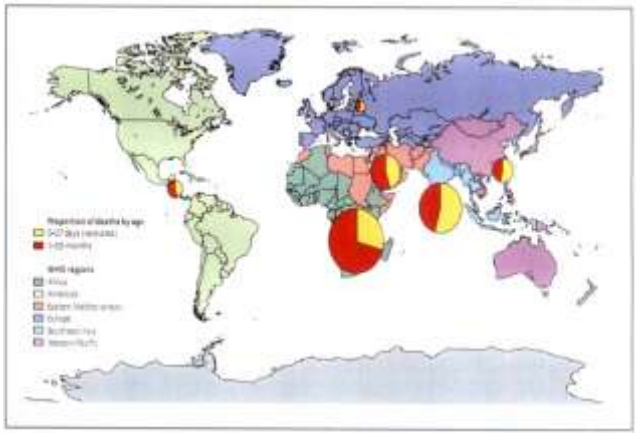

Figure 2: Global age wise distribution of neonatal deaths

CONCLUSION:

Gram negative bacteria are also the leading source of neonatal sepsis in most developed countries. In newborn babies, clinical diagnosis of sepsis is not straightforward, because symptoms and indications are unspecific. There is no 100% specificities and accuracy laboratory research and thus an accurate test has been carried forward. Blood culture was the gold standard for diagnostic evidence, but test findings are still available 48-72 hours afterwards. Neonates with "risk factors" are thus handled with wide range antibiotics for neonatal septicism which undergo extended treatments. The preference of antibiotics should be dependent on the antibiotic resistance trends and the causative species.

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