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NEONATAL SEPSIS: A BRIEF REVIEW ON THE TYPES, ETIOLOGY AND DIAGNOSIS

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ABSTRACT Neonatal sepsis is a major cause of neonatal mortality in developing as well as developed countries. It can be classified into early onset and late onset neonatal sepsis. The causative organisms of early onset and late onset sepsis varies in both developing and developed countries. In this review we discuss briefly about early and late onset neonatal sepsis, along with various tests to diagnose neonatal sepsis.

KEYWORDS : Neonatal sepsis, early-onset, late-onset, developing, developed, countries, diagnosis

Neonatal sepsis is a broad term used to define all infections of neonates i.e septicaemia, pneumonia, urinary tract infection, arthritis, meningitis, diarrhoea, neonatal tetanus, birth asphyxia and injuries (1,2). It remains an important cause of mortality and morbidity among term and preterm neonates in developing countries (3). Out of ten infants with sepsis, four of them die or experience significant disabilities one of them being permanent neurodevelopmental impairment in the developed countries (4).

It is difficult to diagnose neonatal sepsis with the laboratory tests used commonly. Yet neonatal sepsis remains the most common diagnosis in the Neonatal Intensive Care Unit (NICU), when the paediatricians encounter any neonate with the struggle to survive after birth (5). Neonates are immediately started on antimicrobials. The dilemma is that if they are not immediately started on antibiotics, then they would worsen and if they are started, the liberal use of antimicrobials would lead to the emergence of resistant microorganisms, along with unfortunate clinical outcomes (6,7,8,9,10).

Depending on the time the infection is acquired, neonatal sepsis has been classified into early onset sepsis (EOS) and late onset sepsis (LOS) (6). EOS is classically the onset within the first two days to six days and usually occurs as a result of vertical transmission of microbes from the mothers to infants at the time of delivery (11). LOS typically occurs after one week of life and it is due to the horizontal transmission of microbes acquired after delivery either from nosocomial or community sources. It is often more insidious in onset (6). Very low birth infants are particularly at risk because of the immature immune system, prolonged hospitalization, prolonged mechanical ventilation, presence of indwelling catheters, endotracheal tubes and so on (12).

The rate of deliveries at home is high in case of developing countries. Therefore it is difficult to establish exact numbers and causes of neonatal deaths in developing countries because a high number of babies who are delivered at home, die without ever being in contact with health care workers who are trained. Thus their numbers never ever reach the statistics (13). Furthermore in some of these countries babies, especially small for dates and preterm are not registered because of various factors like ignorance, operational difficulties and registration fees which leads to underreporting. Some countries follow a tradition where babies do not become a part of the family until they are a few days or weeks old, due to which early deaths do not get acknowledged (14).

Comparison between early onset and late onset neonatal sepsis

Neonatal sepsis	Early onset	Late onset
Cause	Maternally transmitted pathogens	Nososcomial infections
Risk factors	Chorioamnionitis Maternal intrapartum fever Prematurity Premature Rupture Of Membranes (PROM)	Very low birth weight (VLBW) babies Newborns with prolonged hospitalization Use of central lines, parenteral feeding and mechanical ventilation
Incidence in developed countries	0.9-1.5 per 1000 live births	3-3.7 per 1000 live births
Causative organisms in developed countries	Group B *Streptococcus* (in half of the cases) *Escherichia coli* (in one fourth of the episodes) *Staphylococcus aureus* Coagulase-negative *Staphylococci* (CONS) *Listeria monocytogenes* Other gram negative bacteria (In VLBW *Escherichia coli* is more common than GBS)	Coagulase-negative *Staphylococci* (in half of the episodes) Escherichia coli, Klebsiella species and Candida species all contribute to one third of the cases. Escherichia coli, Klebsiella species, Candida species} one third of the cases *Staphylococcus aureus* *Enterococcus* sp *Pseudomonas aeruginosa*
Causative organisms in developing countries	*Klebsiella* sp *Escherichia coli* *Staphylococcus aureus* GBS (2-8% of cases) S. *pneumonia* *Salmonella* spp	*Klebsiella* sp *Escherichia coli* *Staphylococcus aureus* Coagulase-negative *Staphylococci* (12% of cases) *Pseudomonas* spp *Enterobacter* spp *Candida* spp
Resistance to antibiotics	Less resistant	More resistant

References: (15, 16, 17, 18, 19)

Diagnosis of neonatal sepsis:

Diagnosis of neonatal sepsis is very challenging. Usually a combination of findings is necessary for the accurate diagnosis (20). The gold standard for diagnosis is blood culture. But the sensitivity of it gets affected by use of antibiotics prenatally, extent of sepsis, volume of blood inoculated and laboratory testing capacities (21). One major drawback of this is the 24-48 hour assay time required for diagnosis (22). Sensitivity and specificity of blood cultures can be improved by proper disinfection of skin before collection, culturing early in the episode of sepsis and collecting an appropriate volume of blood for culture (23).

Rapid diagnostic tests which can in the early neonatal period differentiate infected from non-infected infants are the need of the hour (22). The test should have high sensitivity, rather than high specificity (24). In patients with preterm labour and intact membranes, Amniotic fluid tumour necrosis factor α (TNF α) is a better predictor for early onset neonatal sepsis than amniotic fluid gram stain and/or culture or placental histology. The other good predictors are IL1β for vascular extension of chorioamnionitis and TNF α for the development of severe early onset sepsis (25,26).

Surface enhanced laser desorption ionisation (SELDI) technology was used for the amniotic fluid analysis in women with intrauterine inflammation and risk of preterm delivery (27). Leucocyte indices like

total leucocyte count, immature to total neutrophil count, platelet count and C-reactive protein are "late" markers and are not sensitive enough for the early diagnosis of neonatal sepsis . But a detection in the abnormalities of these markers soon after birth along with clinical signs of sepsis, together with the presence of obsteritic risk factors for sepsis are highly suggestive of early onset neonatal sepsis (28, 29). Another acute phase reactant is procalcitonin produced by hepatocytes and monocytes and which rises four hours after exposure to bacterial endotoxin, reaches a peak at six to eight hours and remains raised for atleast a day (30). Serum procalcitonin concentrations increases in necrotising enterocolitis, systemic bacterial infections and during both early and late onset neonatal sepsis. It is a useful marker in assessing the severity of infection, predicting outcomes and assessing the progress of treatment (31).

Two neutrophil markers CD11b and CD64 are highly sensitive and specific markers for the diagnosis of early and late onset sepsis (32,33,34). Another mediator produced by the bone marrow, the granulocyte colony stimulating factor, has been suggested to be a reliable marker of infection for the early diagnosis of neonatal sepsis (35). Another sensitive marker for diagnosing early onset neonatal sepsis has been umbilical cord blood IL6 (35). Increase in IL8 has also been considered to be an accurate marker with a high sensitivity and specificity (35). Inter alpha inhibitor protein is a protease inhibitor secreted by the liver, which has shown to be decreased in neonates with severe sepsis, it may be a promising protein for the early detection of neonates with sepsis (36).

Real time PCR allows DNA isolation in as early as twenty minutes (36). If bacterial infection is excluded at an early period it can avoid antibiotic overuse. DNA Microarray technology combined with Real time PCR allows for the identification of the antimicrobial sensitivity pattern of the organism along with its identification (37).

Conclusion:

Neonatal sepsis is a condition which requires immediate diagnosis and treatment. The challenge lies always in its diagnosis, because the signs and symptoms are not specific. Further research is needed in identification of diagnostic tests, with high sensitivity and accuracy. A biomarker with high diagnostic accuracy and reliability is the need of the hour which would guide paediatricians to assess the risk of infection and the need for treatment with antibiotics.

References:

1. Rawat, S., Neeraj, K., Preeti, K., & Prashant, M. (2013). A review on type, etiological factors, definition, clinical features, diagnosis, management and prevention of neonatal sepsis. JSIR, 2 (4), 802-813.
2. Costello, A., Francis, V., Byrne, A., & Puddephatt, C. (2001). The state of the world's newborns. Save the children fund. Washington, DC: Kinetik Communications; 2001.
3. Bang, A.T., Reddy, H.M., Deshmukh, M.D,, Baitule, S.B., & Bang, R.A. (2003). Neonatal and infant mortality in the ten years (1993 to 2003) of the Gadchiroli field trial: Effect of home-based neonatal care. J Perinatol, 25, 92-107.
4. Brocklehurst, P., Farrel,l B., King, A., Juszczak, E., Darlow, B., Haque, K.,..... Tarnow-Mordi W. (2011). Treatment of neonatal sepsis with intravenous immune globulin. N Engl J Med, 365(13), 1201-1211. DOI: 10.1056/NEJMoa1100441.
5. Clark, R.H., Bloom, B.T., Spitzer, A.R., & Gerstmann, D.R. (2006). Reported medications use in the neonatal intensive care unit: Data from a large national data set. Pediatrics,117(6), 1979-1987.
6. Bizzarro, M.J., Dembry, L.M., Baltimore, R.S., & Gallagher, P.G. (2008). Changing patterns in neonatal Escherichia coli sepsis and ampicillin resistance in the era of intrapartum antibiotic prophylaxis. Pediatrics, 121(4), 689-696.
7. Hill, D.A., Hoffmann, C., Abt, M.C., Du, Y., Kobuley, D., Kirn, T.J.,.....Artis, D. (2010). Metagenomic analyses reveal antibiotic-induced temporal and spatial changes in intestinal microbiota with associated alterations in immune cell homeostasis. Mucosal Immunol, 3(2), 142-158. DOI: 10.1038/mi.2009.132.
8. Jernberg, C., Loffmark, S., Edlund, C., & Jansson, J.K. (2010). Long-term impacts of antibiotic exposure on the human intestinal microbiota. Microbiology, 156(Pt 11), 3216-3223. DOI: 10.1099/mic.0.040618-0.
9. Cotten, C.M., Taylor, S., Stoll, B., Goldberg, R.N., Hansen, N.I., Sánchez, P.J.,..... Benjamin, D.K.Jr. (2009). Prolonged duration of initial empirical antibiotic treatment is associated with increased rates of necrotizing enterocolitis and death for extremely low birth weight infants. Pediatrics, 123(1), 58-66. DOI: 10.1542/peds.2007-3423.
10. Sjogren, Y.M., Tomicic, S., Lundberg, A., Bottcher, M.F, Bjorksten, B., Sverremark-Ekstrom, E., & Jenmalm, M.C. (2009). Influence of early gut microbiota on the maturation of childhood mucosal and systemic immune responses. Clin Exp Allergy, 39(12), 1842-1851. DOI: 10.1111/j.1365-2222.2009.
11. Baker, C.J., & Barrett, F.F. (1974). Group B streptococcal infections in infants. The importance of the various serotypes. JAMA, 230,1158–1160. doi: 10.1001/jama.1974.03240080040025.
12. Stoll, B.J., Hansen, N., Fanaroff, A.A., Wright, L.L., Carlo, W.A., Ehrenkranz, R.A.,..... Poole, W.K. (2002). Late-onset sepsis in very low birth weight neonates: the experience of the NICHD Neonatal Research Network. Pediatrics, 110, 285–291. doi: 10.1542/peds.110.2.285.
13. Vergnano, S., Sharland, M., Kazembe, P., Mwansambo, C., & Heath, P.T. (2005). Neonatal sepsis: an international perspective. Arch Dis Child Fetal Neonatal Ed, 90(3), 220-224. doi: 10.1136/adc.2002.022863.
14. Bang, A.T., Bang, R.A., Baitule, S., Deshmukh, M., & Reddy, M.H. (2001). Burden of morbidities and the unmet need for health care in rural neonates--a prospective observational study in Gadchiroli, India. Indian Pediatr, 38(9), 952-65. PMID: 11568371.
15. Puopolo, K.M., Draper,D., Wi, S., Newman, T.B., Zupancic, J., Lieberman, E.,..... Escobar, G.J. (2011). Estimating the probability of neonatal early-onset infection on the basis of maternal risk factors. Pediatrics,128,e1155–1163.
16. Stoll, B.J., Hansen, N., Fanaroff, A.A., Wright, L.L., Carlo, W.A., Ehrenkranz, R.A,..... Poole WK. (2002). Late-onset sepsis in very low birth weight neonates: the experience of the NICHD Neonatal Research Network. Pediatrics, 110, 285–291.
17. Vergnano, S., Menson, E., Kennea, N., Embleton, N., Russell, A.B., Watts, T.,..... Heath PT. (2011). Neonatal infections in England: the NeonIN surveillance network. Arch Dis Child Fetal Neonatal Ed,96, F9–14.
18. Stoll, B.J., Hansen, N.I., Sa´nchez, P.J., Faix, R.G., Poindexter, B. B., Meurs, K.V.P.,.....Higgins, R.D. (2011). Early onset neonatal sepsis: the burden of group B Streptococcal and E. coli disease continues. Pediatrics, 127, 817–826.
19. Muller-Pebody, B., Johnson, A.P., Heath, P.T., Gilbert, R.E., Henderson, K.L., & Sharland, M. (2011) Empirical treatment of neonatal sepsis: are the current guidelines adequate? Arch Dis Child Fetal Neonatal Ed, 96, F4–8.
20. Zea-Vera, A., & Ochoa, T. J. (2015). Challenges in the diagnosis and management of neonatal sepsis. Journal of Tropical Pediatrics, 61(1), 1–13. http://doi.org/10.1093/tropej/fmu079.
21. Camacho-Gonzalez, A., Spearman, P.W., & Stoll, B. J. (2013). Neonatal infectious diseases: evaluation of neonatal sepsis. Pediatr Clin North Am, 60, 367–389.
22. Mishra, U. K., Jacobs, S. E., Doyle, L. W., & Garland, S. M. (2006). Newer approaches to the diagnosis of early onset neonatal sepsis. Arch Dis Child Fetal Neonatal Ed, 91(3), F208–F212. http://doi.org/10.1136/adc.2004.064188.
23. Buttery, J.P. (2002). Blood cultures in newborns and children: optimising an everyday test. Arch Dis Child Fetal Neonatal Ed, 87, F25–8.
24. Mehr, S., & Doyle, L.W. (2000). Cytokines as markers of bacterial sepsis in newborn infants: a review. Pediatr Infect Dis J, 19, 879–887.
25. Park, K.H., Yoon, B.H., Shim, S.S., Jun, J.K. &, Syn, H.C. (2004). Amniotic fluid tumor necrosis factor-alpha is a marker for the prediction of early-onset neonatal sepsis in preterm labor. Gynecol Obstet Invest, 58, 84–90.
26. Baud, O., Emilie, D., Pelletier, E., Lacaze-Masmonteil, T., Zupan, V., Fernandez, H.,..... Ville, Y. (1999). Amniotic fluid concentrations of interleukin- 1beta, interleukin-6 and TNF-alpha in chorioamnionitis before 32 weeks of gestation: histological associations and neonatal outcome. Br J Obstet Gynaecol,106,72–77.
27. Buhimschi, I.A., Christner, R., & Buhimschi, C.S. (2005). Proteomics biomarker analysis of amniotic fluid for identification of intra-amniotic inflammation. Br J Obstet Gynaecol,112,173–181.
28. Fowlie, P.W., & Schmidt, B. (1998). Diagnostic tests for bacterial infection from birth to 90 days: a systematic review. Arch Dis Child Fetal Neonatal Ed,78,F92–98.
29. Ng PC, Cheng SH, Chui KM, Fok TF, Wong MY, Wong W. (1997). Diagnosis of late onset neonatal sepsis with cytokines, adhesion molecule, and C-reactive protein in preterm very low birthweight infants. Arch Dis Child Fetal Neonatal Ed, 77, F221–227.
30. Dandona, P., Nix, D., Wilson, M.F., Aljada, A., Love, J., Assicot, M., & Bohuon, C. (1994). Procalcitonin increase after endotoxin injection in normal subjects. J Clin Endocrinol Metab,79,1605–1608.
31. Guibourdenche, J., Bedu, A., Petzold, L., Marchand, M., Mariani-Kurdjian, P., Hurtaud-Roux, M.F.,..... Porquet, D. (2002). Biochemical markers of neonatal sepsis: value of procalcitonin in the emergency setting. Ann Clin Biochem,39,130–135.
32. Fjaertoft, G., Hakansson, L., Ewald, U., Foucard, T., & Venge, P. (1999). Neutrophils from term and preterm newborn infants express the high affinity Fcgamma-receptor I (CD64) during bacterial infections. Pediatr Res,45, 871–876.
33. Weirich, E., Rabin, R.L., Maldonado, Y., Benitz, W., Modler, S., Herzenberg, L. (1998). Neutrophil CD11b expression as a diagnostic marker for early-onset neonatal infection. J Pediatr, 132, 445–451.
34. Ng, P.C., Li, G., Chui, K.M., Chu, W.C., Li, K., Wong, R.P.,..... Fok, T.F. (2004). Neutrophil CD64 is a sensitive diagnostic marker for early-onset neonatal infection. Pediatr Res, 56, 796–803.
35. Mehr, S., & Doyle, L.W. (2000). Cytokines as markers of bacterial sepsis in newborn infants: a review. Pediatr Infect Dis J,19,879–887.
36. Fries, E., & Blom, A.M. (2000). Bikunin-not just a plasma protienase inhibitor. Int J Biochem Cell Biol, 32, 125-137.
37. Jaffe, R.I., Lane, J.D., Albury, S.V., & Niemeyer, D.M. (2000). Rapid extraction from and direct identification in clinical samples of methicillin-resistant staphylococci using the PCR. J Clin Microbiol, 38, 3407–3412.
38. Mishra, U. K., Jacobs, S. E., Doyle, L. W., & Garland, S. M. (2006). Newer approaches to the diagnosis of early onset neonatal sepsis. Archives of Disease in Childhood. Fetal and Neonatal Edition, 91(3), F208–F212. http://doi.org/10.1136/adc.2004.064188.