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PATHOPHYSIOLOGY OF NEONATAL SEPSIS: A REVIEW

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ABSTRACT

Neonatal sepsis is not describes as a single entity but a part of continuum from Systemic Inflammatory Response Syndrome (SIRS) to septic shock. Sepsis contributes to a substantial proportion of neonatal death both in developing and developed world. Understanding the pathophysiology of neonatal sepsis forms the key process in determining the management and subsequently the prognosis of infants. A delicate balance between pro-inflammatory and anti-inflammatory cytokines is needed to contain the infection and inhibit the propagation of SIRS leading to multi-organ dysfunction syndrome.

KEYWORDS : neonate; sepsis; systemic inflammatory response syndrome; cytokines

Introduction

It is estimated that over 1 million newborns die globally every year due to sepsis. The incidence of sepsis and the mortality due to sepsis show wide variation depending on gestation age, birth weight and time of onset of sepsis. Neonatal sepsis is a continuum of disease spectrum, from systemic inflammatory response syndrome (SIRS) to septic shock. SIRS in the presence of or as a result of suspected or proven infection is described as sepsis (1). Pathophysiology of neonatal sepsis is briefly described here.

Initial event: pro-inflammatory cytokines

Pathogen associated molecular pattern (PAMP) is expressed by invading microbial organism over its cell surface. It includes lipopolysaccharides (LPS) for gram negative bacteria, Lipoteichoic acid (LTA) for gram positive bacteria and viral RNA and DNA for pathogenic virus. Similarly, pattern recognition receptors (PRR) are expressed by initial sentinel cells including monocyte-macrophage system(2,3). Toll-like receptors (TLR), Nod-like receptors (NLR) and Rig-like receptors (RLR) are PRRs expressed by immune cells. Mechanism of TLR interaction is extensively studies in neonates but literature is limited regarding NLR and RLR interaction and subsequent inflammatory action. TLR-4 ligands with gram negative LPS, TLR3 with viral DNA/RNA and TLR2 with gram positive lipoteichoic acid (LTA)(4,5).

Damage associated molecular pattern (DAMP) are another group of protein which ligand with pattern recognition receptors. Heat Shock Protein (HSP), urokinase and High Mobility Group Box 1 (HMGB1) are some DAMP described(6).

The end product of interaction of PAMP and PRR is gene expression, transcription and translation of pro-inflammatory cytokines. Pro-inflammatory cytokines include Interleukin 1 beta (IL-1 beta), IL-6, IL-8, IL-12, IL-18, Interferon gamma (INF gamma) and Tumor Necrosis factor alpha (TNF alpha)(7).

Pro-inflammatory- anti-inflammatory balance

Escalation of unchecked expression of pro-inflammatory cytokine is detrimental and hence maintaining a delicate balance of pro-inflammatory and anti-inflammatory mediators of inflammation is of paramount importance. Anti-inflammatory cytokines include IL-4, IL-10, IL-11, IL-13 and TGF beta. This anti-inflammatory mediator counteracts action of unchecked inflammation leading to containment of inflammation and thus preventing systemic inflammatory response and multi-organ damage(4).

Cellular activation

Following release of pro-inflammatory cytokines, the vascular endothelial cell will express cell adhesion molecule (CAM). Main CAM expressed by endothelial cell includes intercellular adhesion molecule (ICAM), vascular cell adhesion molecule (VCAM) and E-Selectin. CAM mediates recruitment, rolling and adhesion of PMNs to endothelial surface and finally transmigration to local inflammatory site. The movement of PMNs is along a chemotactic gradient created by chemokines secreted by endothelial cells and macrophages. Activated endothelial cell also produces leukotriene (LTE), prostaglandin, nitric oxide and endothelin(5,8).

Complement activation

Complement system is an important part of innate immune system up-regulated by pro-inflammatory cytokines. Complement system gets activated by three pathways in the body- classical, alternate and lectin pathway. It has got direct cell lysis activity by forming membrane attack complex (MAC), mediates inflammatory activity and opsonization of microbes leading to phagocytosis by monocyte-macrophage system. Unchecked complement activation also leads to escalated systemic inflammatory response in the body(9).

Coagulation cascade

Up-regulation of coagulation pathway is by both extrinsic and intrinsic pathway leading to formation of thrombin. Thrombin converts fibrinogen to fibrin which gets stabilized with help of factor XIII. Fibrinolysis occurs when plasminogen activator activates and forms plasmin which lyses the fibrin clots to fibrin degradation products (FDPs). Inhibition of fibrinolysis process and decreased expression of anti-thrombin III, protein C and protein S is also described in sepsis leading to propagation micro-vascular clots. Unchecked activation of coagulation cascade leads to disseminated intravascular coagulation (DIC) in SIRS(10).

Multi-organ dysfunction and death

SIRS and systemic capillary endothelial damage cause capillary leak, microvascular occlusion and overproduction of vasoactive substances. This leads to hypoxia, acidosis and hypotension. The resultant tissue damage will lead to organ dysfunction. Pulmonary failure, cardiovascular failure, liver dysfunction, renal failure, neutropenia and cellular apoptosis ensue, ultimately causing death(11).

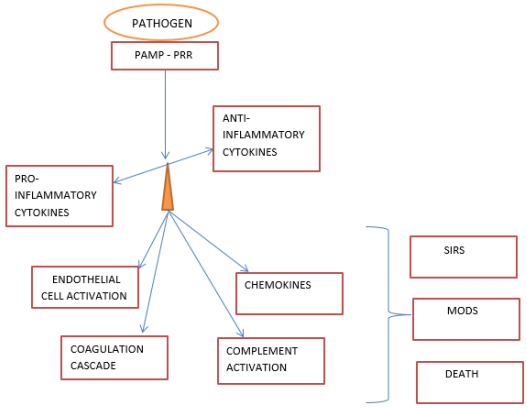

Figure 1: Pathogenesis of neonatal sepsis

PAMP – Pathogen Associated Molecular Pattern; PRR-Pattern Recognition Receptors; SIRS-Systemic inflammatory response syndrome; MODS- multi-organ dysfunction syndrome.

Conclusion

Understanding the pathophysiology of sepsis is extremely important to guide in management of neonatal sepsis. The prognosis depends on sickness status and management strategies. Maintaining balance of pro-inflammatory and anti-inflammatory cytokines forms the essential process in containment of infection. Cellular activation, expression of cytokines and chemokine, polymorphonuclear neutrophil recruitment and migration, complement activation and coagulation cascade propagation form important steps in pathogenesis of neonatal sepsis.

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