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Articles

Common Complications of Dysregulated Inflammation in the Neonate

Katherine Newnam, PhD, RN [a,*], Sheila M. Gephart, PhD, RN [b], Lori Wright, DNP, RN, NNP-BC [c]

[a] Children's Hospital of the King's Daughters, Norfolk, VA
[b] The University of Arizona, College of Nursing, Tucson, AZ
[c] Carilion Clinic Children's Hospital/Pediatrix Medical Group, Roanoke, VA

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ABSTRACT

Preterm infants are faced with a multitude of challenges related to immature systems at delivery placing them at risk for both acute and chronic health conditions. A major component of the human immune system is the inflammatory process and the primary controllers of inflammation are cytokines. Cytokine expression is tightly regulated in the normal host immune response, but in neonates, particularly those born prematurely, the dysregulation is more the norm than the exception. A state in which the inflammatory systems are persistently activated can lead to chronic inflammation affecting the neonate systemically rather than targeting a specific location of illness, injury, or both. Serious neonatal morbidities including white matter injury, chronic lung disease, retinopathy of prematurity and necrotizing enterocolitis have been linked to this chronic inflammatory state. Through the use of a systems approach this article will serve as a focused review of these common neonatal complications. First, an overview explaining the human immune system and the complex process of inflammation will be presented with a focus on systemic neonatal response following acute and/or chronic inflammation. This review is important to promote an understanding of one of the multifactorial influences, inflammation, contributing to long term neonatal health challenges. Empirically supported nursing implications and recommended care strategies are highlighted.

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Multiple efforts have been made over the last several decades to improve prenatal care and reduce the incidence of preterm birth. According to the National Center for Health Statistics, in 2011 the preterm birth rate within the United States (US) decreased for the fifth year in a row to 11.72%.[1] Although global improvements were reported, the largest decline in the US preterm birth rate occurred among infants born 34–36 weeks.[2] This work is critical because we clearly understand that preterm infants are faced with a multitude of challenges related to immature systems at delivery placing them at risk for both acute and chronic health conditions. One could argue that the infant's immature neurological or respiratory system places these infants at the greatest risk. However, recent empiric evidence supports the premise that it is the preterm infant's immune system that provides exquisite vulnerability which may contribute to common neonatal complications.

Although protective, neonatal inflammation is quickly up regulated (i.e. 'turned on') in response to infection or injury which mobilizes the infant's host defense and then is not well down regulated (i.e. 'turned off').[3] The primary controllers of inflammation are cytokines. Cytokines act as cell-to-cell communicators, altering gene expression and impacting cellular physiology.[4] One regulatory mechanism of the immune system is by the expression of pro-inflammatory and anti-inflammatory cytokines to maintain balance through a broad, systemic range of biologic activities. Cytokine expression is tightly regulated in the normal host immune response, but in neonates, particularly those born prematurely this dysregulation is more the norm than the exception. A state in which the inflammatory system remains turned on can lead to chronic inflammation affecting the neonate systemically rather than target the specific location of illness and/or injury. Serious neonatal morbidities including white matter injury, chronic lung disease, retinopathy of prematurity and necrotizing enterocolitis have been linked to this chronic inflammatory state.[5–7]

Through the use of a systems approach this article will serve as a focused review of four common neonatal complications directly affected by the neonatal inflammatory response. These complications include white matter injury (WMI), chronic lung disease (CLD), sepsis and necrotizing enterocolitis (NEC). First, an overview explaining the human immune system and the complex process of inflammation will be presented with a focus on systemic neonatal response following acute and/or chronic inflammation. This review is important to promote an understanding of how inflammation is one of the multifactorial influences contributing to long term neonatal health challenges. Empirically supported nursing implications and recommended care strategies will be highlighted.

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* Address correspondence to Katherine Newnam, PhD, RN, Children's Hospital of the King's Daughters, Chesapeake, VA 23322.
E-mail addresses: kathynewnam@cox.net (K. Newnam), gepharts@arizona.edu (S.M. Gephart), nnpbugs@cox.net (L. Wright).

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The Immune System

The human immune system provides a complex means of protection from injury and/or infection. Immune system defense mechanisms are typically classified into three types: 1) innate (also called natural) immunity, 2) acquired immunity and 3) the inflammatory response[8] (see Table 1 for definitions). In spite of an immature immune system, integral parts of all three of these defense mechanisms are functional prior to or at birth in the preterm infant.

The human immune system originates early in gestation with the development of the key components of cellular and humoral immunity, making up the fetal immune system. Humoral immunity is primarily made up of the complement system and immunoglobulins.[9] The complement system, consisting of approximately 40 plasma proteins is activated as part of both the inflammatory and acquired immunity. Detectable concentrations of measured complement proteins are present as early as 5 to 6 weeks gestation.[8] A second component of humoral immunity, immunoglobulins, is a heterogeneous group of proteins with diverse but overlapping functions. Each of the five immunoglobulins (IgG, IgM, IgA, IgE and IgD) are present in various amounts in the human fetus by 12 weeks of gestation.[9] IgG is the most abundant and accounts for greater than 75% of the circulating immunoglobulins in the term infant. It is actively and passively transported across placental membranes beginning at 20 weeks gestation.[9] Clearly, extremely preterm infants will receive less transfer of IgG from their mother when compared to late preterm or term infants, which will affect the immune response.[9]

Cellular immunity is the cell mediated immunologic response, playing a primary role in the infant during both the inflammatory response and acquired immune response. A primary actor in cellular immunity, lymphocytes develop from the hematopoietic stem cells in the fetal liver as early as 5 weeks gestation. These stem cells follow one of three lymphocytic lineages: 1) the thymus-dependent or T-cells, 2) bursa-derived or B-cells, or 3) the natural killer (NK) lymphocytes.[9]

In utero, the fetus is offered protection through innate immunity which provides barrier protection via the amniotic fluid and closed uterine wall. When this barrier is breached, bacteria ascend into the uterus vertically, can reach the fetus and cause injury by activating the fetal inflammatory process. In this same way, maternal infections (systemic or uterine) cross placental barriers and affect the fetus. In some cases, fetal infection from maternal origins leads to WMI, preterm labor or fetal loss.[10] (see Fig 1).

Table 1
Key Terms.

Acquired immunity: Considered the third line of defense. This process involves targeting particular invading microorganisms for which the system has acquired a memory. This process is slower and more specific in action than the first and second lines of human immune response.[8]

Antenatal infections: This term refers to maternal local or systemic infections (viral, bacterial or fungal) that occur during the pregnancy and can impact the mother, fetus or both.[10]

Anti-inflammatory cytokines: These cytokines include interlukin-4 (IL-4), IL-10 are critical for the down regulating the effects of the pro-inflammatory cytokines. The "turning off" of the inflammatory process maintains homeostasis for the proper function of organ systems.[15]

Chorioamnionitis: An infection of the uterus and its content during pregnancy usually demonstrated by maternal and/or fetal tachycardia, maternal fever, uterine tenderness, foul smelling amniotic fluid and/or maternal leucocytosis (elevated white blood cell count).[15]

Chronic lung disease (CLD): Characterized by the decreased alveolar septation and decreased microvascular development without significant fibrosis of the lung. Usually defined as the need for supplemental oxygen at 36 weeks post-conceptual age.[36,40]

Fetal inflammatory response (FIRS): The systemic independent fetal response marked by elevated levels of fetal inflammatory cytokine IL-6 usually in response to maternal infection. FIRS has been linked to preterm labor, preterm birth and WMI.[15]

Innate immunity: Also referred to as natural or native immunity. These are considered the first line of defense and are the natural barriers to infection that humans have including physical, mechanical and biochemical barriers. The second line of defense is the inflammatory process.[8]

Inflammatory cytokines: Proteins molecules released by the glial cells in response to a stressor (infection/injury) that bind to cell surfaces in order to alter cellular activity and functions.[25]

Inflammatory response: The first phase of the immune system is innate immunity (see above) and this is the second phase of the immune system. This is the rapid activation of biochemical and cellular mechanisms that are nonspecific with regard to particular organism or tissue damage.[8]

Innate immunity: Also referred to as natural or native immunity. These are considered the first line of defense and are the natural barriers to infection that humans have including physical, mechanical and biochemical barriers. The second line of defense is the inflammatory process.[8]

Pro-inflammatory cytokines: These cytokines include interlukin-1 (IL-1), IL-2, IL-6, IL-18, interferon-γ (IFN-γ), tumor necrosis factor α (TNF-α) and are primarily responsible for initiating an effective acute phase response against exogenous pathogens.[15]

Systemic inflammatory response syndrome (SIRS): The widespread progressive over-expression and dysregulation of inflammation at the endothelial level involving increasing vascular permeability, and perpetuated by infectious processes.[52]

White matter injury (WMI): These are focal, non-cystic lesions that are described as hyperintense areas, typically seen on magnetic resonance imaging (MRI).[17]

The Inflammatory Response

The inflammatory response is part of the human immune system and serves as protection from harmful pathogens and injury. Considered the third phase of the infant's immune system, inflammation is the rapid activation of biochemical and cellular mechanisms that are the body's response to a particular organism or tissue injury.[8] This targeted response sends required biochemical products to the site of cellular injury or infection through the following steps. First, the affected area is initially flooded with mast cells and granulocytes. The complement system, made up of over 40 serum proteins, is activated initially with release of pro-inflammatory cytokines. At the vascular level, blood vessel dilation brings needed blood and cellular products to the site of injury. Increased vascular permeability allows the flow of vital fluids outside of the vessel, causing secondary edema and inflammation at the site.[8] Secondly, leukocytes (white blood cells) and macrophages adhere to the walls of the vessels to offer protection from microbial invasion and clear debris from infectious process.[8,9] Next the biochemical mediators including histamine, bradykinin, leukotrienes and prostaglandins cause a constriction of the vasculature. This signals the need for plasma proteins (for clotting) and other cells (eosinophils) to protect the surrounding healthy tissues.

An interaction with the third part of the infant's immune system, the adaptative immune system is then involved to elicit a specific response to the type of organism or create memory for possible future invasion by the same microorganism, expediting later adaptive response.[11] It is imperative to remember that this adaptive system is immature and certainly less effective in the neonate, with only a small number of memory T-cells available. This memory T-cell shortage negatively influences the infant's ability to respond to foreign antigens, and may alter the production of cytokines.[12] Exposure to maternal antibodies through ingestion of human milk will aid the infant's response and maturation of this adaptive system through the transfer of antibiotics in the form of secretory IgA providing pathogen specific defense to those organisms that the mother was exposed to.[13,14]

Although these critical events are essential for the survival of the neonate, the inflammatory response has also been linked to secondary tissue loss. Tissue edema and increased vascular flow when injury occurs stimulate the effective release of inflammatory factors and result in stretch injury. This process can occur at any location. It is the free circulating inflammatory agents, stimulated by stress, infection or

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