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REVIEW ARTICLE

Immunometabolic approaches to prevent, detect, and treat neonatal sepsis

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The first days of postnatal life are energetically demanding as metabolic functions change dramatically to accommodate drastic environmental and physiologic transitions after birth. It is increasingly appreciated that metabolic pathways are not only crucial for nutrition but also play important roles in regulating inflammation and the host response to infection. Neonatal susceptibility to infection is increased due to a functionally distinct immune response characterized by high reliance on innate immune mechanisms. Interactions between metabolism and the immune response are increasingly recognized, as changes in metabolic pathways drive innate immune cell function and activation and consequently host response to pathogens. Moreover, metabolites, such as acetyl-coenzyme A (acetyl-CoA) and succinate have immunoregulatory properties and serve as cofactors for enzymes involved in epigenetic reprogramming or "training" of innate immune cells after an initial infectious exposure. Highly sensitive metabolomic approaches allow us to define alterations in metabolic signatures as they change during ontogeny and as perturbed by immunization or infection, thereby linking metabolic pathways to immune cell effector functions. Characterizing the ontogeny of immunometabolism will offer new opportunities to prevent, diagnose, and treat neonatal sepsis.

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INTRODUCTION

Sepsis, leading to life-threatening organ dysfunction due to a dysregulated host response to infection,[1] is a major contributor to global morbidity and mortality, particularly in early life.[2] In 2017, the World Health Organization estimated 5.4 million deaths in children aged <5 years, with newborns (those <28 days of life) accounting for nearly 50% of total deaths.[3] Those born preterm, comprising 11% of all births globally, are particularly susceptible to infection both early after birth and throughout childhood and at high risk for long-term complications.[4]

Defining neonatal sepsis remains challenging, without a clear consensus definition. Indeed, current pediatric definitions for sepsis are not validated in infants.[5] A better understanding of the pathophysiological basis and the molecular and biochemical processes involved in neonatal sepsis is crucial for early diagnosis and intervention.

In early life, response to infection is heavily reliant on innate immunity, including anatomical barriers such as skin, intestinal, and respiratory mucosae, as well as cellular (e.g., macrophages, monocytes, natural killer cells) and soluble (e.g., antimicrobial proteins and peptides and acute-phase reactants) components.[6,7] Patients with primary innate immunodeficiency (e.g., interleukin (IL)-1 receptor-associated kinase 4 deficiency, myeloid differentiation primary response 88 deficiency, etc.) have a high susceptibility to early life infection.[7] Of note, the innate immune system has adaptive features such that innate immune cells undergo epigenetic reprogramming after stimulation, leading to an altered, potentially enhanced, response after subsequent stimulation with unrelated pathogens, a property termed "innate immune memory."[8]

Key to the regulation of innate immunity is metabolism. Indeed, complex interactions between metabolism and the immune response are increasingly recognized, giving rise to the new field of "immunometabolism."[9] Metabolic pathways, such as glycolysis, the tricarboxylic acid (TCA) cycle (also known as Krebs Cycle), fatty acid oxidation (FAO), fatty acid synthesis (FAS), and amino acid pathways, play important roles in the generation of key products responsible for promoting innate immune cell survival or growth, function, and activation.[9] The energy cost required to fuel the immune response highlights the crucial role of metabolites and metabolic pathways in sepsis. In addition, certain metabolites such as acetyl-coenzyme A (acetyl-CoA), succinate, nicotinamide adenine dinucleotide (NAD^+), and α-ketoglutarate can serve as co-factors for epigenetic enzymes, thus potentiating innate immune memory.[10] In the era of systems biology, wherein the entire inventory of molecules of a given class can be measured, the unique dynamic changes of the newborn period can be studied at the molecular level and offer insights into the complex interactions between the host and the insulting pathogen.[11] Sepsis-induced alterations in the epigenome, transcriptome, proteome, and metabolome are reflected in changes in the concentration of the small molecules and chemicals in biological fluids and tissues,[12] thus opening opportunities for novel approaches to sepsis prevention, diagnosis, and treatment.

In this review, we focus on the current understanding of the neonatal energetic and metabolic response to sepsis. We identify

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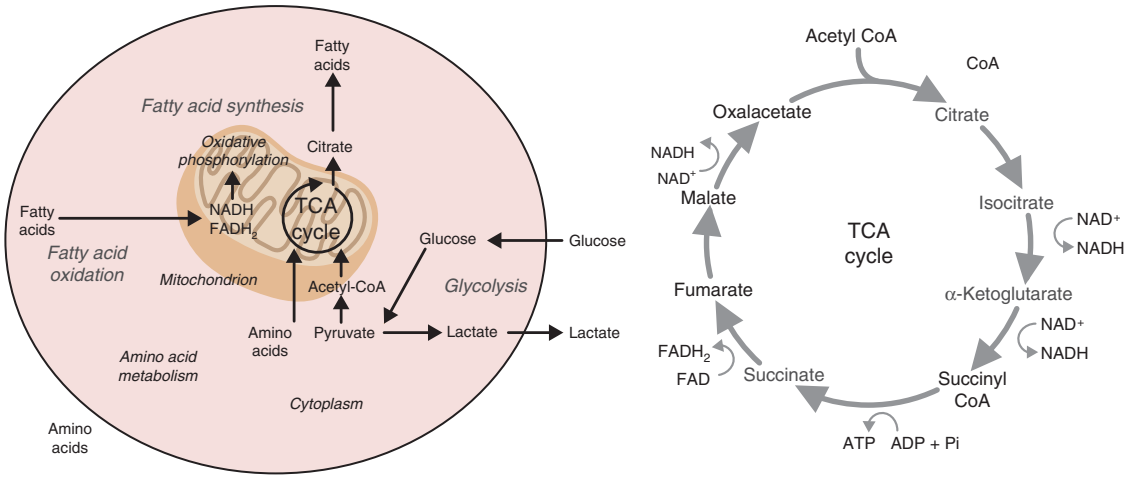

		Neonatal innate immune cell	Adult innate immune cell		
			Quiescent	Acute inflammation	Tolerance/ paralysis
Metabolic pathways	Glycolysis	↓	↓	↑↑	↓
	Oxidative phosphorylation	↓	↑	↓	↓
	Fatty acid synthesis	?	↓	↑	↓
	Fatty acid oxidation	↓	↑	↑	↓
	TCA cycle	?	↑	↓	↓
Metabolites	Lactate	?	↓	↑	↓
	Citrate	?	–	↑	↓
	Succinate	?	–	↑	↓
	α-Ketoglutarate	?	–	↓	↓
	Fumarate	?	–	↓	↓

Fig. 1 Overview of key immunometabolic pathways in quiescence and sepsis. Metabolic pathways upregulated and downregulated during quiescence, acute inflammation and tolerance/paralysis in adult monocytes. Distinct metabolic pathways in neonatal monocytes and macrophages demonstrate downregulation of glycolysis, oxidative phosphorylation, and fatty acid oxidation in quiescence. During sepsis, neonatal monocytes reveal upregulation of genes related to lipid metabolism but defective glycolysis.

certain metabolites as potential diagnostic markers, discuss the use of enhanced nutritional support as a tool to treat sepsis, and identify metabolically active medications as potential ways to manipulate immunometabolism with the goal of preventing and/or treating sepsis.

METABOLIC PATHOPHYSIOLOGY OF NEONATAL SEPSIS

Immunometabolism is thus far relatively underexplored with respect to neonatal health and disease. In sepsis, host defense to pathogen invasion is characterized by an early pro-inflammatory response, triggered mainly by innate immune system activation, leading to an exaggerated systemic release of cytokines. While aiming at pathogen elimination, this acute response can cause hypotension, cardiovascular dysfunction, tissue damage, and multi-organ failure.[13] During the later phases of sepsis, activation of modulatory pathways induces an anti-inflammatory state that contains inflammation and promotes tissue repair, while also limiting host defense; this regulatory mechanism is called innate immune tolerance (minimizing harm from immunopathology) or innate immune paralysis when this progresses toward a dysfunctional state, in which cells are unable to respond properly to stimulation, with consequent increased risk of opportunistic infections.[13] A shift in basic cellular energy metabolism from oxidative phosphorylation and FAO to glycolysis, known as the Warburg Effect, is required during early immune cell activation to provide the necessary rapid energy and metabolic intermediates, while in tolerance and paralysis all major metabolic pathways are impaired.[14,15]

The neonatal immune reaction to infection is markedly different from that of older infants, children, and adults[16]: (a) neonates demonstrate distinct polarized response to infections, and whole blood transcriptomics in neonates with septic shock demonstrated downregulation of genes related to innate and adaptive immunity compared to toddlers and older children[17]; (b) neonatal sepsis is accompanied by a heightened innate immune cellular response driven by monocytes/macrophages and neutrophils and counter-balanced by inhibitory pathways resulting in a dampened adaptive immune response[16]; (c) neonatal innate immunity is distinct: pattern recognition receptor (PRR)-mediated immune responses to most stimuli are generally polarized away from inflammatory/T helper type 1 (Th1)-polarizing cytokines.[18–20] Upregulation of specific inhibitory signaling genes has been described in neonatal sepsis, likely serving to avoid an excessive inflammatory response.[21] These unique features of the fetal/neonatal immune system serve to avoid energetically costly and potentially harmful immune responses during early life.[16,22]

In the following sections, we will discuss cellular metabolism in innate immune cells at quiescent and activated states (Fig. 1) and attempt to elucidate differences between newborns and adults.

GLYCOLYSIS AND THE ADENOSINE SYSTEM

Glycolysis is a relatively inefficient (producing only two molecules of ATP per unit of glucose) but rapidly initiated pathway for generation of cellular ATP. In acute inflammation, enhanced glycolysis enables immune cells to quickly generate (a) sufficient ATP, the main energy substrate to ensure cell functionality, and (b) biosynthetic intermediates (i.e., serine, glycine, alanine, acetyl-CoA for lipid synthesis) to carry out their specific effector functions.[13–15,23] ATP serves as a danger-associated molecular pattern for the immune system, which can initiate and prolong immune responses.[24] ATP levels increase significantly during inflammation, hypoxia, or ischemia, as seen in various disease states, including preeclampsia and sepsis.[25,26] To counteract ATP-induced immune effects, cells can hydrolyze ATP into adenosine diphosphate and adenosine monophosphate (AMP). AMP can subsequently be broken down into adenosine and phosphate. Adenosine levels rise rapidly in response to systemic inflammation to reduce pro-inflammatory/Th1-polarizing immune responses. Both ATP and adenosine bind to purinergic receptors, so the overall inflammatory effect of ATP on the biological system depends on the balance between ATP and adenosine.[27] Interestingly, levels of adenosine are significantly higher in neonatal compared to adult plasma, contributing to Th2 polarization of Toll-like receptor (TLR)-mediated responses.[28,29] Comparison of the glycolytic capacity of preterm, term, and adult monocytes at rest demonstrated a severe impairment of glycolysis in preterm monocytes compared to adults, while in monocytes of term newborns, glycolysis was variably affected, reflecting a transitional functional state.[23] Reduced glycolysis was also recently described in cord blood activated macrophages as a consequence of downregulation and lack of activity (reduced phosphorylation) of the mammalian target of rapamycin (mTOR).[30] The mTOR pathway promotes the metabolic switch toward glycolysis after PRR activation by pathogen-associated molecular patterns (i.e., TLR activation by lipopolysaccharide (LPS)) and is fundamental for robust cytokine production (i.e., tumor necrosis factor (TNF), IL-1β) and an effective host defense in the acute phase of infection and sepsis.[31,32] Downregulation of the mTOR pathway and shutdown of glycolysis is also mediated by alarmins (i.e., S100A8 and S100A9 proteins), which are secreted by neutrophils and activated macrophages and extremely abundant in neonatal serum, thus downregulating responses to microbes and thereby preventing harmful hyper-inflammatory responses.[30,33] Interestingly, in an in vitro model of immune paralysis, re-stimulation of immune-tolerant adult human monocytes with LPS revealed a defective ability to mount a Warburg effect with diminished production of lactate and enhanced production of NAD^+, and was not followed by production of pro-inflammatory cytokines.[15] The same study revealed that tolerant monocytes from adult septic patients have impaired metabolic pathways compared to healthy controls and septic patients with normal cytokine responsiveness (non-tolerant). Similar studies are needed to investigate the neonatal metabolic profile in immune tolerance and paralysis.

TCA CYCLE

The TCA cycle is based on the mitochondrial matrix and, together with oxidative phosphorylation, is the major metabolic pathway during the quiescent or non-proliferative cellular stage (e.g., M2 macrophages), efficiently generating ATP for cellular functions. On the other hand, activated innate immune cells (e.g., pro-inflammatory M1 macrophages, cells activated by LPS) experience TCA cycle interruptions to achieve accumulation of intermediary substrates, citrate and succinate, in order to promote their immune functions.[34] While citrate is necessary for FAS leading to production of inflammatory prostaglandins, succinate is involved in enzymatic activity controlling epigenetic modifications that might lead to a persistent inflammatory state. In a murine model of sepsis, LPS-induced succinate in bone marrow-derived macrophages stabilized hypoxia-inducible factor alpha interfering with the activity of the enzyme prolyl hydroxylase responsible for its degradation and leading to an increase of IL-1β, an important mediator in innate immune signaling during inflammation.[35] Studies are needed to elucidate the role of TCA cycle metabolites in neonatal sepsis.

LIPID METABOLISM

FAO and FAS have been thought to have opposing roles in immune system functions, i.e., FAO is required for anti-inflammatory cytokine production and thus linked with immune tolerance, while FAS seems to positively regulate the generation and function of pro-inflammatory innate immune cells.[36] However, recent literature highlights the role of FAO in macrophage activation, as it also supports inflammasome activation, a molecular complex that processes the secretion of pro-inflammatory cytokines IL-1β and IL-18 in innate immune cells.[37] Fatty acids serve as source of metabolic energy and biologically active components of cell membranes.[38] A gene ontogeny analysis comparing the transcriptome of unstimulated human preterm neonatal, term neonatal, and adult monocytes revealed markedly distinct metabolic profiles by age with an overall lower expression of genes related to oxidative phosphorylation and FAO metabolism in addition to lower glycolysis in preterm monocytes.[23] Studies of host–pathogen interactions using whole blood transcriptomics in culture-positive neonatal sepsis reveal upregulation of genes related to lipid metabolism.[21] Peroxisome proliferator-activated receptor gamma (PPARγ) is a nuclear receptor involved in lipid metabolism[39] and functionally linked to the inhibition of pro-inflammatory gene expression and to resolution of inflammation[40,41]. Of note, expression of PPARγ is increased in neonatal monocytes.[23] Enhanced lipid metabolism results in increased production of anti-inflammatory cytokines (IL-10, transforming growth factor (TGF)-β), as well as pro-resolving lipid mediators,[42] potent anti-inflammatory mediators that regulate the active resolution of inflammation and promotion of wound healing following tissue injury; studies on the role of these mediators in the newborns are still pending.

AMINO ACID METABOLISM

Amino acids are substrates for protein synthesis intimately linked to important anabolic cellular signaling pathways, most notably the mTOR pathway. Amino acid metabolism is important in immune function and sepsis.[43] Glutamine metabolism regulates the balance between effector T cells and regulatory T cells (T_{regs}); glutamine deficiency can impair generation and function of Th1 and Th17, whereas T_{regs} generation is not affected.[44] A role for glutamine in the cytotoxic and antimicrobial functions of macrophages has been described for (a) the generation of nitric oxide[45] and (b) induction of IL-1β by macrophages in response to LPS stimulation.[46] Little is known on the role of amino acid metabolism in the pathogenesis of neonatal sepsis; however; certain amino acids, such as glutamine[47] and arginine,[48] have been found to be depleted in neonates with sepsis compared to healthy newborns.

Overall, neonatal immunometabolism is apparently programmed to respond with immune tolerance, which can result in immune paralysis if not closely regulated.

METABOLOMICS IN NEONATAL SEPSIS: A TOOL TO IMPROVE DIAGNOSIS?

Early diagnosis and intervention remains a challenge for neonatal sepsis.[49] The diagnosis still relies on the clinician's experience due to lack of specificity of clinical signs and symptoms and poor predictive ability of routine laboratory tests, including the "gold standard" blood culture.[49–51] Combination of technology and biomarker

discovery can provide further insights and identify target pathways to improve diagnosis and outcome prediction. Systems biology approaches using technologies that comprehensively measure the inventory of molecules in a given biosample have been introduced to analyze complex datasets of signaling and response pathways to numerous diseases and interventions.[52]

Metabolomics comprehensively profiles, in a given biosample, small molecules that are downstream products of enzymatic processes. Metabolic profiling can employ either untargeted (global) approaches, which measure the broadest range of metabolites in a sample, or targeted approaches, which provide higher sensitivity and selectivity with known standards of a priori information, aiming to analyze and identify specific metabolites and metabolic pathways of interest.[53] At present, no analytical technology can adequately capture the entirety of a given metabolome. The current challenge for metabolomic studies is the lack of standardization of metabolomic data processing and analyses. One of the strengths of metabolomics is that data can be generated using a variety of biological matrices that are relevant for disease, including plasma,[54] serum,[55–57] saliva,[58] exhaled breath condensate,[59,60] urine,[47] and fecal samples.[61,62] Metabolomics has been successfully employed in newborns to identify alterations in plasma steroid and carbohydrate metabolites important for neurodevelopment, rapid cell proliferation, and nutrient uptake as well as to characterize molecular ontogeny of plasma across the first week of human life.[11]

Sepsis causes disruption in biochemical homeostasis and early detection of metabolite perturbations can predict severity.[52] A case–control study, involving both term and preterm septic human neonates and controls, recently employed urine metabolomics as a tool to identify biomarkers of late-onset neonatal sepsis using non-targeted nuclear magnetic resonance (NMR) spectroscopy and targeted liquid chromatography–tandem mass spectrometric analysis. Septic neonates demonstrated distinct metabolic profiles from non-septic age-matched controls, such as increased amounts of glucose, pyruvate, and lactate and lower levels of glutamine and vitamins of B complex, such as riboflavin (vitamin B2) and nicotinamide (vitamin B3).[47] A similar study on 25 human neonates (9 with diagnosis of sepsis and 16 healthy controls) using NMR and gas chromatography–mass spectrometry found increased urine levels of glucose, lactate, and acetate but decreased pentose phosphate pathway metabolites in septic neonates compared to non-septic controls.[63] Metabolomics has also been applied to sepsis-induced acute lung injury, finding differences in distinct plasma metabolites (glutathione, adenosine, phosphatidylserine, and sphingomyelin) between septic and healthy adult patients.[64] Changes in the levels of metabolites can also predict sepsis outcome and provide information on responsiveness to therapy. Mass spectrometry-based metabolomics strategies on the plasma metabolome of 21 adult septic shock patients suggest that lipidome alterations play an important role in an individual's response to infection.[65] In a plasma metabolomics and proteomics study involving 1000 adult sepsis patients, FAO was severely impaired in sepsis non-survivors, highlighting fatty acid metabolism as a promising metabolic predictor for survival in sepsis.[66]

Thus far, much remains to be learned regarding the neonatal metabolome at baseline, during early life ontogeny, and during sepsis. Future immunometabolic studies in early life will aid in defining biomarkers of those at high risk of sepsis and informing new approaches for prophylaxis, diagnosis, and treatment of neonatal sepsis.

POSSIBLE INTERVENTIONS AND NEW PERSPECTIVES

Trained immunity and metabolism

Neonates are heavily reliant on their innate immune system for mounting an acute response to infection.[7] Innate immune cells (e.g., macrophages, monocytes, dendritic cells (DCs)) were recently discovered to attain *antigen non-specific* memory capabilities through epigenetic and metabolic reprogramming after subsequent heterologous stimulation.[10] This phenomenon termed as innate immune memory or trained immunity may be manifested as a heightened (training) or attenuated (tolerance) immune response, enabling the host to efficiently and effectively adapt to environmental threats while ensuring cytoprotection.[8,67] Trained immunity can confer heterologous protection from a variety of subsequent pathogens[68] for a yet undetermined amount of time.

Several metabolites that accumulate in monocytes and macrophages seem to play a role in the induction of epigenetic modulators. The cholesterol synthesis pathway is essential to trained immunity, as statins, inhibitors of the cholesterol synthesis pathway, can prevent the induction of trained immunity.[69] Increased succinate and fumarate levels in activated innate immune cells antagonize histone demethylation and suppress anti-inflammatory genes, thereby promoting a pro-inflammatory phenotype.[35,70,71] Acetyl-CoA, increased in trained monocytes, is an essential substrate for acetylating processes. NAD^+ is important for epigenetic changes resulting in a switch from glucose to FAO during LPS-induced tolerance,[72] which represents a model of sepsis-induced immune paralysis. Understanding trained immunity and targeting cellular metabolic processes, for example, via nutritional intervention, may represent a novel approach to optimize immune responsiveness in vulnerable newborns.[73]

Impact of microbiome on metabolism in sepsis

The human microbiome, consisting of all microorganisms living in or on the human body, shares a symbiotic relationship with the host and shapes the innate and adaptive immune systems via maintaining gut-barrier functions and impacting host metabolism.

Although there is growing evidence that the early life microbiome has important effects on health and disease,[74,75] much remains to be learned regarding the impact of the microbiome in neonatal immune development and risk of neonatal sepsis. The neonatal microbiome undergoes dramatic changes during the first weeks of life influenced by diet, exposure to new microbes, antibiotics, and other environmental exposures.[76] Premature or low birth weight neonates often receive antibiotics during hospitalization, shaping the gut microbiome. Antibiotic treatment is associated with reduced gut bacteria diversity and may kill beneficial bacteria allowing multidrug-resistant pathogens to dominate the neonate's microbiome.[77] Antibiotic-suppressed gut microbiome affects whole-body metabolism (including urinary and plasma metabolomes) as demonstrated in antibiotic-treated pigs.[78] Of note, evidence is emerging that microbial metabolites may impact host immune function.[79] Short chain fatty acids (SCFAs), products of bacterial fermentation, have been linked to immune tolerance via (a) inhibition of nuclear factor-κB; (b) reduced expression of T cell-activating molecules on antigen-presenting cells[80]; and (c) increased number and function of T_{regs}, including their production of anti-inflammatory cytokines (TGF-β and IL-10).[81,82] The gene for free fatty acid receptor 2, a receptor for gut microbiota-derived SCFAs, was upregulated in human septic newborns,[21] suggesting that the metabolic activity of neonatal microbiota influences the innate and adaptive immune response to sepsis and may contribute to an anti-inflammatory state. Disruption of the intestinal microbiome during critical illness, resulting in a "pathobiome," could result in immune suppression and consequent higher risk of sepsis, altering the course and outcome of infection.[83,84] Further studies on the role of microbiome and related metabolites in neonatal sepsis are needed.

Nutritional support and the role of immunonutrients in preventing neonatal infection

Nutrition plays a key role in the development of multiple systems, including the immune system. In fact, undernutrition is the most

common cause of secondary immunodeficiency in the world,[85] with malnutrition in the critical early months of development having a profound and long-lasting impact on immunity. Nutrition, both enteral and parenteral, has an important role in the prevention of neonatal sepsis by minimizing nutrient loss and stimulating the maturation of the gastrointestinal tract, one of the largest immune organs of the body.[86] The use of human milk and early enteral nutrition are important for reducing the risk of infections. Indeed, the earlier an infant achieves full enteral nutrition, the lower the risk of late-onset sepsis.[87] Human milk is rich in multiple immune-active components, which optimize the intestinal microbiological and metabolic milieu of newborns and protect them from inflammation and infection. Those include immunoglobulins, cytokines, and growth factors, medium- and long-chain polyunsaturated free fatty acids, milk oligosaccharides, lactoferrin, and lysozyme. The immunomodulatory role of these components is reviewed elsewhere.[86] Human milk provides the gold standard for feeding term infants, while for preterm infants it is routinely supplemented with multi-nutrient fortifiers to provide recommended levels of protein, sodium, chloride, magnesium, and other micronutrients necessary to support the hypercatabolic state of prematurity. When exclusive human milk use is not possible, preterm formulas are the main alternative, though likely lacking the immunoprotective effects of human milk, based on observational studies. Harnessing the immunological benefits of maternal breast milk or its beneficial metabolic components might aid in prevention and treatment of neonatal sepsis, especially in vulnerable preterm infants.

Specific essential nutrients such as vitamins and trace minerals are also important to the immune response such that their deficiency can increase susceptibility to infection. Vitamin D (1,25OHD) deficiency has been associated with higher risk of developing sepsis in human neonatal,[88] adult, and murine[89] studies. Pretreatment of preterm (<32 weeks' gestational age) neonatal whole blood in vitro reversed endotoxin tolerance by enhancing reactive oxygen intermediate production from phagocytes.[90] Iron deficiency with or without anemia impairs cell-mediated immune response, intracellular killing of bacteria, and secretory IgA responses, increasing susceptibility of infants to infection.[91] Deficits in trace elements are common in both enterally and parenterally fed infants, with premature infants particularly susceptible to severe acute Zn-deficiency states. Zn deficiency causes atrophy of lymphoid tissue, impaired delayed cutaneous hypersensitivity reaction, decreased lymphocyte response to antigens, and impaired chemotaxis of monocytes and polymorphonuclear cells.[92] Serum Zn concentrations of septic adults and pediatric Intensive Care Unit patients are reduced relative to the normal physiological range in healthy age-matched controls.[93,94] Accordingly, several studies have examined whether Zn supplementation may be helpful in treating sepsis. In a mouse model of sepsis (intraperitoneal fecal-slurry injection with or without Zn supplementation), prophylactic Zn supplementation conferred a significant survival advantage by enhancing pathogen eradication, while simultaneously attenuating potentially detrimental excessive inflammation.[95] It is proposed that Zn redistributes from the blood compartment to the liver to meet the increased metabolic demands of sepsis.[96] Oral Zn supplementation reduced morbidity and mortality in hospitalized very low birth weight neonates in Italy,[97] as also demonstrated in a recent meta-analysis.[98] Selenium has a role in protecting against oxidative damage and preterm neonates are at risk of selenium deficiency. In a randomized clinical trial conducted in India including 90 preterm infants with <32 weeks of gestation and/or birth weight ≤1500 g, prophylactic selenium supplementation led to significant reductions in late-onset sepsis episodes compared to placebo, although it had no effect on overall mortality.[99,100]

Until such time as new recommendations regarding immunonutrient supplementation for at-risk, including preterm, newborns can be made, proven strategies to minimize infection prevention in young infants, such as exclusive use of human milk, standardized enteral feeding guidelines, avoidance of acid blockade, and appropriate minimization of antibiotic exposure should be incorporated in care bundles of term and preterm newborns.

Metabolically active drugs

Infection is associated with tissue infiltration by phagocytic cells such as neutrophils and macrophages and their production of reactive species that contribute to microbicidal activity. An excess of reactive oxygen species (ROS) and reactive nitrogen species is associated with microvascular dysfunction and organ failure. Accordingly, efforts to develop metabolically active agents to prevent or treat sepsis in early life have included development of antioxidants.

Melatonin, an endogenously produced indolamine principally synthesized in the pineal gland, acts as an antioxidant directly by neutralizing ROS and nitrogen oxygen species and indirectly by stimulating antioxidant enzyme activity, including that of superoxide dismutase, glutathione peroxidase, and glutathione reductase.[101] Supplementation of melatonin and its metabolites have shown effectiveness in human studies performed on several neonatal disorders characterized by massive inflammatory cascade and oxidative injury, including sepsis.[89,102]

Edaravone (3-methyl-1-phenyl-pyrazolin-5-one), a free radical scavenger, exerts multiple antioxidant effects, such as hydroxyl radical scavenging, suppression of hydroxyl-dependent lipid peroxidation, and electron donation to ROS.[103] In a piglet model of neonatal sepsis, edaravone reduced serum total hydroperoxide concentrations 1 h after cecal ligation and perforation and nitrite and nitrate levels at 3 and 6 h in comparison to septic untreated animals, paralleling clinical improvement of septic animals.[104] In the same study, edaravone delayed TNF surge in septic animals and prevented the increase of high mobility group box 1, a nuclear transcription factor involved in the systemic inflammatory response. These findings suggest possible beneficial effects of edaravone on sepsis clinical course in the newborns, but human trials are yet to be performed.

Pentoxifylline (PTX), a methylxanthine derivative with immunomodulating properties, has been used as an adjunct therapy for severe neonatal sepsis. PTX is a phosphodiesterase inhibitor that enhances intracellular cAMP concentrations, inhibits production of TLR-mediated inflammatory cytokines, including TNF-α, IL-6, and Interferon gamma, has beneficial effects on endothelial cell function and improves microcirculation and tissue perfusion.[105] PTX decreased LPS-induced hyperinflammation in monocytes of preterm infants in vitro.[106] Although a recent Cochrane review demonstrated a significant reduction in all-cause mortality of hospitalized septic neonates with adjunct use of PTX,[107] a subsequent randomized controlled trial of PTX for preterm infants with late-onset sepsis did not demonstrate a significant decrease in neonatal mortality and morbidity.[108]

CONCLUSIONS

Neonatal sepsis remains a major threat in early life, yet our tools to address it are limited. Growing evidence suggests that the distinct immunometabolism of early life contributes to susceptibility of infection and sepsis risk. On-going research is leveraging powerful new systems biology tools to define immunometabolic cellular and molecular signatures and trajectories associated with health and disease.[11] Metabolic agents such as Zn, edavarone, and PTX are currently being evaluated as prophylaxis or treatment for neonatal sepsis. Future studies on the ontogeny of early life immunometabolism in health and disease will provide new avenues to prevent, detect, and treat neonatal sepsis.

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AUTHOR CONTRIBUTIONS

M.G.C.: conception and design, drafting the article; A.A.: substantial contributions to conception and design, drafting the article, revising the article critically for important intellectual content; J.D.-A.: revising the article critically for important intellectual content; K.S.: revising the article critically for important intellectual content; J.L.-S.: drafting the article and revising it critically for important intellectual content; M.D.C. and O.L.: revising the article critically for important intellectual content, final approval of the version to be published.

ADDITIONAL INFORMATION

Competing interests: O.L. is a named inventor on several patents relating to vaccine adjuvants.

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