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REVIEW

Translational Physiology

Influence of innate immune activation on endocrine and metabolic pathways in infancy

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Abstract

Prematurity is the leading cause of neonatal morbidity and mortality worldwide. Premature infants often require extended hospital stays, with increased risk of developing infection compared with term infants. A picture is emerging of wide-ranging deleterious consequences resulting from innate immune system activation in the newborn infant. Those who survive infection have been exposed to a stimulus that can impose long-lasting alterations into later life. In this review, we discuss sepsis-driven alterations in integrated neuroendocrine and metabolic pathways and highlight current knowledge gaps in respect of neonatal sepsis. We review established biomarkers for sepsis and extend the discussion to examine emerging findings from human and animal models of neonatal sepsis that propose novel biomarkers for early identification of sepsis. Future research in this area is required to establish a greater understanding of the distinct neonatal signature of early and late-stage infection, to improve diagnosis, curtail inappropriate antibiotic use, and promote precision medicine through a biomarker-guided empirical and adjunctive treatment approach for neonatal sepsis. There is an unmet clinical need to decrease sepsis-induced morbidity in neonates, to limit and prevent adverse consequences in later life and decrease mortality.

biomarker; immune system; neonate; precision; sex

PRETERM INFANTS

Preterm birth is defined as delivery before 37 wk of gestation, which can be further subcategorized to include extremely preterm (<28 wk), very preterm (28–32 wk), and moderate-to-late preterm (32–37 wk) infants. Global data suggest that >1 in 10 infants are born too soon, resulting in an estimated 15 million preterm births annually (1). Prematurity is the leading cause of neonatal mortality and morbidity. More than 35% of infant deaths worldwide can be attributed directly to prematurity (2, 3). As a significant amount of development occurs during the third trimester of gestation, birth before full term disrupts the temporal physiological and anatomical development, resulting in immature endocrine and metabolic pathways, underdeveloped neuronal networks, as well as limited energy stores (4–7). Furthermore, preterm infants are separated from maternal hormone supplies, such as melatonin (8, 9). In recent years, survival of preterm infants has risen dramatically because of significant improvements in neonatal and obstetric care, including delivery in tertiary neonatal centers, increased use of antenatal steroids, targeted oxygen saturation limits, and vigorous handwashing (10–12). However, reported outcome measures such as death and all-cause mortality do not capture the wide range of short- and long-term morbidity caused by preterm birth and early-life interventions (3, 13, 14). Infants born preterm often require intensive care and extended hospital stays, resulting in further challenges for the infant (15). Complications associated with preterm birth include necrotizing enterocolitis and sepsis and longer-term challenges such as cerebral palsy and visual, hearing, and cognitive problems (1, 15–17). The unifying sequelae of many preterm complications are poor oxygenation, oxidative stress, and inflammation that alter the body's normal developmental trajectories. More research on newborn care as well as interventions to prevent and manage adverse consequences are needed to reduce neonatal morbidity and mortality (1).

NEONATAL SEPSIS

Neonatal sepsis is caused by bacteria, viruses, or fungi that impinge on normal development of newborn infants (18). Sepsis is a significant cause of morbidity and mortality

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worldwide and is now recognized as one of the most common illnesses that patients, hospitals, and public health agencies encounter (19, 20). Over the past two decades, epidemiological research and policies concerning infection control have intensified in an attempt to address this ongoing challenge. In 2018, a systematic review of studies from high- to middle-income countries estimated that there are 3 million cases of neonatal sepsis annually, with a mortality rate of 11–19%. Few studies are available from low-income countries, and the lack of standardized diagnostic criteria is an obstacle in the estimation of neonatal sepsis as a global burden (21).

Depending on the infant's age, neonatal sepsis can be subdivided into early-onset infection (EOI) and late-onset infection (LOI), which are defined as infections occurring in the first 48–72 h and after 48–72 h of life, respectively (22). EOI is typically caused by organisms transmitted from the mother to the infant in utero or at the time of birth (23). LOI is commonly caused by pathogens acquired from interaction with the hospital/community environment including mechanical ventilation, vascular catheters, indwelling lines, or nosocomial infection during extended hospital stays (24). Premature newborns have 3–10 times increased risk of developing sepsis compared with term infants (15, 25). Recent evidence highlights that preterm birth after hypertensive disorders and/or fetal growth restriction is associated with an increased risk of late-onset sepsis in the infant (26). In the neonatal intensive care unit (NICU), the majority of infection cases occur in premature infants (14, 27), with 70% of LOIs occurring in extremely premature infants (28). Moreover, males are more vulnerable to neonatal infection compared with females (29, 30).

LOI poses challenges for homeostatic control systems of major body functions (18), and a number of physiological signs and clinical symptoms are evident in neonates with LOI. These are used in clinical settings to instigate treatment for suspected infection (31–33). It has been suggested by the World Health Organization (WHO) that neonatal sepsis should be confirmed by evidence from at least two laboratory tests and at least two clinical symptoms in the case of suspected or proven infection (34). There is worldwide consensus that clinical disturbances associated with LOI include hypotension, temperature instability, apnea, respiratory distress, tachy/bradycardia, and gastrointestinal problems (18, 33). Laboratory criteria include high immature-to-total neutrophil ratio, low platelet count, high/low white blood cell counts, hypoglycemia/hyperglycemia, metabolic acidosis [base excess (less than −10 mEq/L) or an elevated serum lactate (>2 mmol/L)] (32, 35). Furthermore, acute-phase proteins such as C-reactive protein (CRP) and procalcitonin can be elevated in response to neonatal infection and are often used to corroborate LOI (32, 36, 37). After infection, proinflammatory cytokines, specifically interleukin (IL)-6, enhance hepatic synthesis of CRP in the late stages of neonatal sepsis, i.e., serum CRP is usually increased 6–8 h after the onset of symptoms (38). In infants with nosocomial infection, procalcitonin concentrations usually begin to rise 2 h after infection (39, 40). It is important to note that these acute-phase proteins are nonspecific biomarkers and can be influenced by any inflammatory condition, such as surgery or tissue injury (32). More reliable and specific biomarkers for identification of LOI in term and preterm infants would improve our knowledge of the infectious epidemiology and advance precision medicine for empirical and adjunctive treatment of neonatal sepsis within the NICU, which may in turn lead to a reduction in antibiotic administration, with an associated decrease in morbidity and mortality associated with LOI.

Currently, there are a number of international guidelines for empirical treatment of suspected or proven LOI (32). *The Lancet Child & Adolescent Health* published additional guidelines for managing pediatric sepsis early in 2020, which were devised by 49 international experts as a part of the Surviving Sepsis Campaign (41). These guidelines are a combined initiative from the European Society of Intensive Care Medicine and the Society of Critical Care Medicine. Although significant advances have been made, these suggestions are only recommended for infants >37 wk of age to young adults of 18 yr (41). The use of intravenous and oral antibiotics, such as vancomycin, ampicillin, and gentamicin, is routine in clinical settings to treat neonatal sepsis (34, 42, 43). There is a general consensus that an antibiotic regimen should begin once neonatal sepsis is suspected, but substantial debate exists as to when the treatment should be stopped (44, 45). Widespread and prolonged use of antibiotic administration, including the use of antibiotic regimens in suspected but not confirmed cases of neonatal sepsis, is associated with the emergence of antibiotic-resistant bacteria, which is detrimental for treatment success of neonatal sepsis (18, 45). For example, a multidrug-resistant *Staphylococcus captitis* clone has recently emerged as a major pathogen among infants in the NICU (46). These worrisome developments call for an urgent improvement in global standards for antibiotic treatment to prevent the emergence of other multidrug-resistant clones and highlight the importance of antibiotic stewardship programs. Reliable and accurate biomarkers may have potential to determine antibiotic initiation and duration, i.e., biomarker-guided therapy, which in turn may decrease rates of morbidity and mortality associated with sepsis (45). Supportive and adjunctive therapies are also mainstream treatments for neonatal sepsis and can be implemented as necessary. These include, but are not limited to, mechanical ventilation, administration of vasoactive or inotropic agents, as well as methods of glucose control (47).

INNATE IMMUNE SYSTEM

Pathogen-host protection occurs through highly coordinated actions of the innate and adaptive arms of the immune system (48, 49). At birth, the innate and adaptive components of the immune system are not fully mature (50, 51). The memory and specificity of the adaptive immune system develops in the infant's early years (51). Newborns rely heavily on the innate immune system as the first line of defense against foreign invaders (50). Activation of cell surface receptors called pattern recognition receptors (PRRs) by pattern-associated molecular patterns [PAMPs; e.g., peptidoglycan (PGN), lipoteichoic acid (LTA), and lipopolysaccharides (LPS)] or damage-associated molecular patterns (DAMPs; e.g., heat shock proteins) increases immune surveillance for antigens (52–54). The common structural patterns of PGN/LTA and LPS activate Toll-like receptor (TLR)-2 and TLR-4, respectively (55). TLR activation initiates a complex series of

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intracellular cascades that result in a variety of cellular responses including production of proinflammatory cytokines (56). The immaturity of the preterm infant's immune system is more pronounced compared with term infants. Functional deficits of the preterm infant's innate immune system are evident: reduced cytokine production, impaired bacterial clearance, and decreased phagocytosis, increasing the susceptibility of the infant to infection (48). Activation of the immune system in neonates and adults alters bidirectional communication between intrinsic physiological systems including neuroendocrine and metabolic pathways in order to protect the host by different strategies as discussed by Harbeson et al. (57), either enhancing host health or actively fighting the infection. We review emerging findings in human infants and animal studies on how immune system activation alters multiple endocrine and metabolic pathways. Figure 1 summarizes some of the major alterations reported in preterm and term infants with infection. We also examine proposed biomarkers for sepsis in the NICU, which may serve as viable targets for precision medicine healthcare for the treatment of neonatal sepsis.

IMMUNE-NEUROENDOCRINE CROSS TALK

Interactions between the neuroendocrine and immune systems were discovered in the 1930s (58). It is now well accepted that cross talk between these systems plays a vital role in controlling the duration and magnitude of the inflammatory response, as well as homeostatic physiological functions of the body during infection (59). Bidirectional communication occurs between the immune and neuroendocrine systems systemically at the level of the hypothalamic-pituitary-adrenal (HPA) axis, the hypothalamic-pituitary-gonadal (HPG) axis, and the hypothalamic-pituitary-thyroidal (HPT) axis. In addition to these classical pathways, hormones that regulate feeding behavior and the renin-angiotensin-aldosterone system, among others, are modulated by immune activation and play a part in immunological function.

Hypothalamic-Pituitary-Adrenal Axis

It is now apparent that when TLRs and other PRRs recognize bacterial or viral molecular patterns early activation of the HPA axis occurs, which is proposed to be related to prostaglandin E_2 signaling; proinflammatory cytokines in turn maintain the prolonged enhancement of the HPA axis (60, 61). Corticotropin-releasing hormone (CRH) is secreted from neurons within the paraventricular nucleus of the hypothalamus into the hypophysial portal blood supply, which stimulates adrenocorticotropic hormone (ACTH) release from the anterior pituitary gland. The adrenal gland in turn produces glucocorticoids in response to ACTH stimulation. CRH secretion is upregulated by serotonin, norepinephrine, histamine, and dopamine and downregulated by γ-aminobutyric acid and opiates as well as downstream hormones such as glucocorticoids and ACTH, via negative feedback (62, 63). The HPA axis plays a critical role in regulating inflammation in response to infection. Endogenous glucocorticoids and catecholamines attenuate the production of proinflammatory [tumor necrosis factor-α (TNF-α), interleukin (IL)-1, IL-6] and TH1-related (IL-2, IL-12, granulocyte macrophage colony-stimulating factor, interferon-γ) cytokines, as well as inflammatory mediators such as nitric oxide and prostaglandin. In addition, they also enhance the synthesis of anti-inflammatory cytokines (IL-4, IL-10) (63, 64).

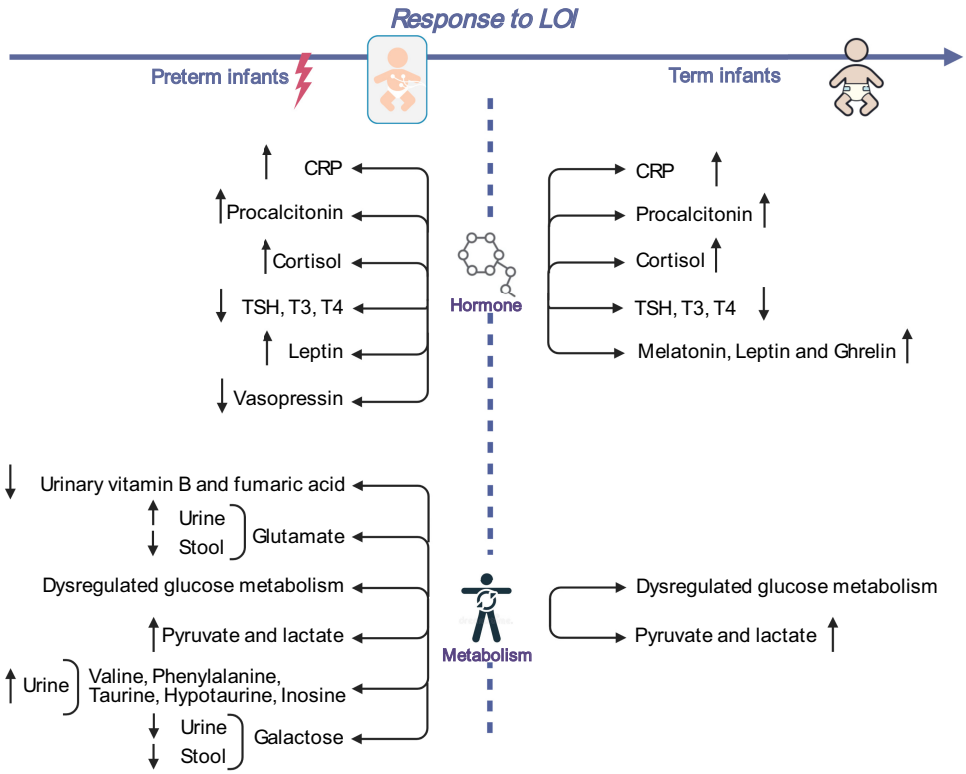


Figure 1. Reported endocrine and metabolic changes in term and preterm infants with sepsis. Novel biosignatures validated in term and preterm infants would guide improved diagnosis, prognosis, and therapeutic intervention. CRP, C-reactive protein; LOI, late-onset infection; TSH, thyroid-stimulating hormone; T_3, triiodothyronine; T_4, thyroxine. Figure created with BioRender.com. (Refs. 32, 36, 38, 45, 57, 78–80, 100, 146–148, 173, 183, 192, 205, 218–226, 269.)

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Cortisol in preterm infants.

In term neonates, a surge in cortisol concentration is normally observed during labor; however, during preterm birth this cortisol response is blunted (5). Under basal conditions, serum cortisol, which is a glucocorticoid hormone, is usually bound to cortisol-binding globulin or albumin, and only ~5–10% is in its free form. Studies of preterm infants reveal that both total and free cortisol concentrations are decreased in plasma and saliva, respectively (65, 66). Although the extra-adrenal chromaffin tissue undergoes maturation at 9–11 wk of gestation (67), the human adrenal cortex does not synthesize cortisol de novo until ~30 wk of gestation; thus it is widely suggested that low free cortisol is related to adrenal insufficiency in preterm infants (68). Others postulate that reduced cortisol in premature infants is due to blunted CRH production in the hypothalamus (69). Although the precise clinical consequences of reduced cortisol are currently unknown, it has been suggested that low cortisol is associated with hypotension; hydrocortisone therapy is sometimes used for the treatment of refractory hypotension or hemodynamic failure (65, 68, 70). Additionally, low cortisol in preterm infants might reflect insufficient stress response, which may be, in part, protective against catabolic cortisol levels (71). On the other hand, HPA activity is associated with reductions in proinflammatory cytokines and inflammatory mediators, as well as increased anti-inflammatory cytokines (63, 64). It is interesting to speculate that low cortisol concentrations in preterm infants have the potential to lead to uncontrolled inflammation, which might create a host environment optimal for pathogen colonization (72). Trials that have evaluated administration of steroids in preterm infants report variable effects on inflammation. Large doses above the physiological range provoke significant adverse side effects in the infant. Low-dose steroid administration displays anti-inflammatory properties; however, some infants appear to suffer adverse effects even with low doses, such as increased infection, poor weight gain, and hyperglycemia (73–77).

Neonatal sepsis and the HPA axis.

Preterm and term infants with sepsis, including LOI, display increased serum cortisol production compared with infants without laboratory signs or clinical symptoms of infection (Fig. 1) (78–80). At term birth, rodents are of developmental stage similar to that of preterm human infants and are common models in neurodevelopmental research (81). Similar to findings in preterm infants, endotoxin administration to rats on postnatal day (PND) 3 and PND 5 resulted in elevated circulating corticosterone (82–85), which persisted for 24 and 4 h after injection on PND 3 and PND 5, respectively (83). Together these findings illustrate immune-associated increases in stress hormone, cortisol/corticosterone, in both humans and rodent models, providing evidence of immune-mediated alterations of this neuroendocrine system in early life (Fig. 2). It is noteworthy that hypercortisolemia promotes significant disruptions to metabolism (Fig. 2), affecting the gluconeogenesis and glycogenolysis pathways as well as amino acid metabolism, and it also plays a regulatory role in other neuroendocrine axes (86, 87). There is some further discussion of these topics below in this review. Currently, there is no consensus regarding testing methods or interpretation of cortisol concentrations in neonates (68). However, more recently, researchers have established that free cortisol is a better indicator, and assessment of plasma

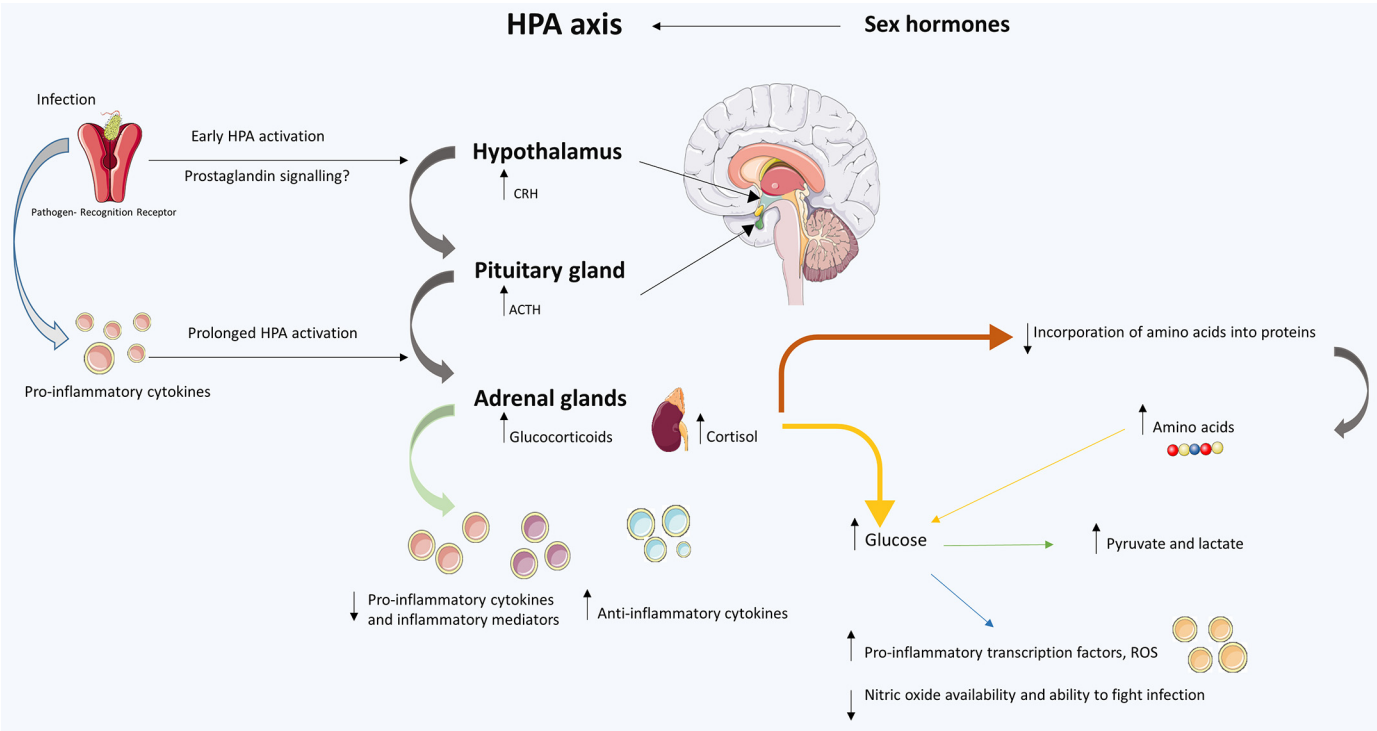


Figure 2. A summary schematic of evidence-based metabolic and neuroendocrine shifts that occur as a result of neonatal infection and inflammation. ACTH, adrenocorticotropic hormone; CRH, corticotropin-releasing hormone; HPA, hypothalamus-pituitary-adrenal; ROS, reactive oxygen species.

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total cortisol and corticosteroid binding globulin may prevent unnecessary use of glucocorticoid therapy in neonates (88). Furthermore, cortisol can easily be quantified from hair follicles and saliva, which are samples that can be obtained without the use of invasive methods. In preterm infants, it has been reported that salivary (free) and plasma (total) cortisol concentrations correlate (89). Although cortisol assessment is not routinely used in the identification of neonatal sepsis, it should be explored as a potential clinical biomarker of chronic stress and indeed neonatal sepsis. Alongside various other routinely used biomarkers, it may lead to better prognosis and result in biomarker-guided therapy for the treatment of neonatal sepsis.

Neonatal sepsis and the HPA axis in later life.

Immunological challenges during critical windows of development can produce persistent changes in HPA axis function. Shanks and colleagues (90) were the first to provide evidence of long-term adverse consequences in HPA axis activity in an animal model of neonatal LOI. Several independent studies have reported that rats administered endotoxin (*Salmonella enteritidis*) at PND 3 and PND 5 had greater corticosterone and ACTH concentrations at baseline and in response to stress as juveniles and adults compared with control animals (84, 85, 90). Adult male rats exposed to *S. enteritidis* as neonates had increased plasma CRH and hypothalamic paraventricular nucleus CRH mRNA concentrations (90). Furthermore, adult rats treated with LPS as neonates exhibited elevated plasma corticosterone and ACTH in response to a second LPS immunological challenge in adulthood (91, 92). Glucocorticoid receptor density was decreased in the forebrain in both sexes (90). Glucocorticoid receptors have been shown to mediate inhibitory effects of glucocorticoids on CRH synthesis in the hypothalamic paraventricular nucleus and ACTH release in response to stress. It has been suggested that reduction of glucocorticoid receptors and thus glucocorticoid sensitivity, due to neonatal endotoxin, in brain regions known to govern HPA activity could decrease inhibition of CRH synthesis, which would result in elevated ACTH release in response to stress (90).

Rats administered LPS (*Escherichia coli*/*S. enteritidis*) on PND 14 displayed attenuated febrile response and reduced hypothalamic cyclooxygenase-2 after LPS administration in adulthood (93). Intriguingly, these adult central nervous system immune responses were only evident in rats exposed to LPS after PND 7 and before PND 28 (94). Additionally, rats exposed to LPS on PND 14 and subsequently in adulthood had elevated corticosterone concentrations associated with decreased cytokine concentrations and blunted febrile response (95). Experimental evidence shows that animals exposed to neonatal immune activation on PND 14 had elevated hypothalamic CRH and pituitary proopiomelanocortin mRNA. Furthermore, in these animals, plasma ACTH concentrations were also increased after exposure to LPS as adults (61). As described above, decreased expression of glucocorticoid receptors is evident in neonatal rodents exposed to postnatal infection, which is proposed to be associated with reduced negative feedback on CRH production (90). In contrast to studies performed by Shanks and colleagues, hippocampal, pituitary, and hypothalamic glucocorticoid receptor RNA and protein concentrations were not different in adult rats exposed to LPS on PND 14. Therefore, altered negative feedback is unlikely to account for increased HPA axis activity in adult rats neonatally exposed to LPS on PND 14 (61). Furthermore, no difference in glucocorticoid receptor expression was evident in the liver, spleen, or adrenal gland (61). These observations suggest that distinct mechanisms appear to be responsible for increased HPA axis activity in adult rats when exposed to LPS on PND 14 compared with endotoxin exposure on PND 3 and PND 5 (61, 90).

There is a paucity of studies investigating the effects of neonatal sepsis on acute and long-term HPA activity in humans. However, studies in rodents provide convincing evidence that endotoxin exposure during a critical stage of physiological development leads to increased HPA responsiveness in neonates and in response to stress, by whatever means, in adulthood (61, 90, 93). Furthermore, a narrow critical early-life period may exist in which innate immune system activation results in profound alterations to HPA axis regulation in later life (94).

Vasopressin

Vasopressin is a neurohypophysial hormone synthesized in the hypothalamus and released from the posterior pituitary gland into the circulation. Vasopressin is an agonist of V_{1A}, V_{1B}, and V_2 receptors. The role of vasopressin in regulating the HPA axis remains a subject of debate, but it is suggested that vasopressin activates the release of ACTH (96). Vasopressin is important for maintaining osmotic gradients as well as many more divergent physiological actions including cardiovascular homeostasis, where it acts as an endogenous vasoconstrictor agent (97), and its role as an antipyretic, whereby it suppresses the febrile response (59, 98, 99).

A recent study in humans reported low plasma vasopressin concentrations in preterm infants with sepsis; infants who progressed to septic shock had significantly lower concentrations of vasopressin at the onset of the sepsis cascade (before laboratory/clinical evidence of organ dysfunction) compared with those infants who did not deteriorate to septic shock (100). Interestingly, subjects with plasma vasopressin levels $<$ 43.8 pg/mL had significantly higher risk of progression to septic shock. Furthermore, the authors continued this analysis to develop an in-depth equation that had an 89.5% predictive capacity for the development of septic shock, i.e., higher risk of mortality. Based on this equation, every 100 pg/mL elevation in plasma vasopressin levels resulted in a greater than twofold reduction in the likelihood of progression to septic shock (100). This study suggests that vasopressin concentrations, in line with other criteria, may form the basis for prediction of chances of severity of infection in infants and an opportunity for therapeutic intervention.

It is interesting to speculate that low vasopressin levels in preterm infants with sepsis may be one of multiple contributors to hypotension (101, 102), although this must be posited with considerable caution, as there is a scarcity of studies investigating vasopressin levels in preterm and term infants with sepsis. Dopamine is the most common antihypotensive medication used in preterm infants; however, the use of

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vasopressin is increasing (103). Case studies and small trials in both neonates and adults showed that vasopressin elevated arterial blood pressure in patients with sepsis (97, 104). The largest of these studies showed that vasopressin administration significantly increases blood pressure, cardiac index, left ventricular stroke work index, and systemic vascular resistance index in catecholamine-resistant vasodilator shock in adults (105). Although its use in neonatology is somewhat restricted (102, 106, 107), with only 0.8% of hypotensive infants being prescribed exogenous vasopressin (107), a recent pilot study in very low-birth-weight infants reported that vasopressin was as efficacious as dopamine for the treatment of hypotension (108). Vasopressin is an immune modulator, and it is also stimulated by cytokines such as IL-1a, IL-1b, and IL-6, in addition to prostaglandins and leukotrienes, potentially mediated by the Fos-Jun-AP1 pathway (109–113). The complex role of vasopressin in sepsis has been reviewed elsewhere, with actions on both innate and adaptive immunity (114). Interestingly, V_{1A} receptors are expressed on astrocytes, and stimulation of these receptors attenuates the release of inflammatory mediators via a protein kinase C (PKC) pathway (115). Anti-inflammatory actions of vasopressin would offer protection during infection. Although vasopressin administration has potential benefits as evidenced by the small pilot study data, exogenous vasopressin usage is not without side effects. Adverse effects of vasopressin administration in neonates with and without sepsis include transient thrombocytopenia, liver necrosis, and hyponatremia (106, 116–118). In animal models, myocardial ischemia and varied splanchnic blood flow occur at high doses (119, 120). Dosage and timing of the use of vasopressin as a therapeutic strategy to treat sepsis-induced hypotension are currently under investigation (121).

Hypothalamic-Pituitary-Gonadal Axis

Gonadotrophin-releasing hormone (GnRH) secretion from the hypothalamus stimulates release of the gonadotropins follicle-stimulating hormone (FSH) and luteinizing hormone (LH) in the anterior pituitary gland. Gonadotropins subsequently stimulate release of estrogen and progesterone from ovary glands in females and testosterone from Leydig cells in the male testes (63, 122). It is well known that progesterone and estrogen play a neuroprotective role in postnatal development (123–125), and males are more vulnerable to neonatal infection than females, a trend observed across many neonatal conditions (29, 30).

Neonatal sepsis and the HPG axis.

In recent years, studies have emerged suggesting that neonatal infection reprograms the HPG axis in a sex-specific manner (Fig. 3) (82, 84, 126). Administration of LPS (*Salmonella enterica*) to rats on PND 3 and PND 5 results in reduced testosterone in males and decreased LH in both sexes immediately after neonatal LPS exposure (82). Morphological assessment of neonatal rat testes revealed decreased gonocyte genesis following LPS administration. However, there was no difference in seminiferous tubule number per square millimeter, suggesting that the number of interstitial Leydig cells was unchanged (82). In female rats, LPS (*S. enterica*) administration on PND 3 and PND 5 had direct effects on 712 genes in the ovaries, which are implicated in inflammatory responses, reproductive system development, and immune cell signaling. Further analysis revealed that several canonical pathways involved in immune regulation and inflammation were activated in the ovaries in response to neonatal infection, including nuclear factor-κB (NF-κB) and mitogen-activated stimulating protein kinase (MAPK) signaling. Protein expression analysis of multiple components of the MAPK pathway revealed that TLR4 expression was increased in neonatal ovaries of LPS-treated rats (127). Elevated ovarian TLR4 expression has been associated with blunted follicular growth and function in cows (128). Collectively, these findings indicate that innate immune system activation with LPS in neonatal rodents results in decreased steroid hormone and glycoprotein concentrations, as well as impairments in ovarian and testicular development during a critical period of follicular formation and gonocyte proliferation, respectively. These alterations indicate mechanistic changes that could lead to decreased reproductive success in later life (82, 128).

Interestingly, cross talk between the HPG and HPA axes influences the sex-specific physiological response to infection (Fig. 3). Shanks et al. (126) examined the influence of gonadectomy on endotoxin (*S. enteritidis*)-induced rise in plasma ACTH and corticosterone at PND 3 in females compared with males. They found sex-specific outcomes such that removal of gonads in male rats elevated plasma corticosterone, whereas ovariectomy in female rats decreased plasma corticosterone. Interestingly, ACTH response to endotoxin administration in female ovariectomized pups was reduced compared with endotoxin-treated intact control pups. This effect was not evident in males (126). It appears that the gonadal secretions exert their influence at different levels of the HPA axis, which was also apparent in response to LPS administration. The effect of gonadal hormones on HPA regulation in males appears to occur only at the level of the adrenal gland or corticosterone metabolism in response to LPS (126). As males are more vulnerable to infection and general morbidity/mortality associated with infection, these HPA axis-related sex differences in response to infection may in part contribute to increased risk of males developing an infection. To our knowledge, this hypothesis has not been fully examined, and further research is required to tease apart the apparent sex-specific HPA axis effects in response to infection.

Neonatal sepsis and the HPG axis in later life.

NEONATAL SEPSIS, PERIPHERAL GONADOTROPHINS, AND STEROID HORMONES IN LATER LIFE. Early-life infection not only suppresses the HPG axis activity in the short term but also causes persistent long-term changes in homeostasis depending on the timing of early-life exposure (Fig. 3). LH and FSH concentrations were depressed in female adolescent rats after LPS administration on PND 3 and PND 5 (82, 84). The surge in LH concentrations during mating was significantly diminished in rats of both sexes that had been injected with LPS on PND 3 and PND 5 (82). After an immunological challenge in female adult rats, the suppression of the LH pulse interval was greater in those treated with LPS as neonates (PND 3 and 5) compared with those treated with saline (129).

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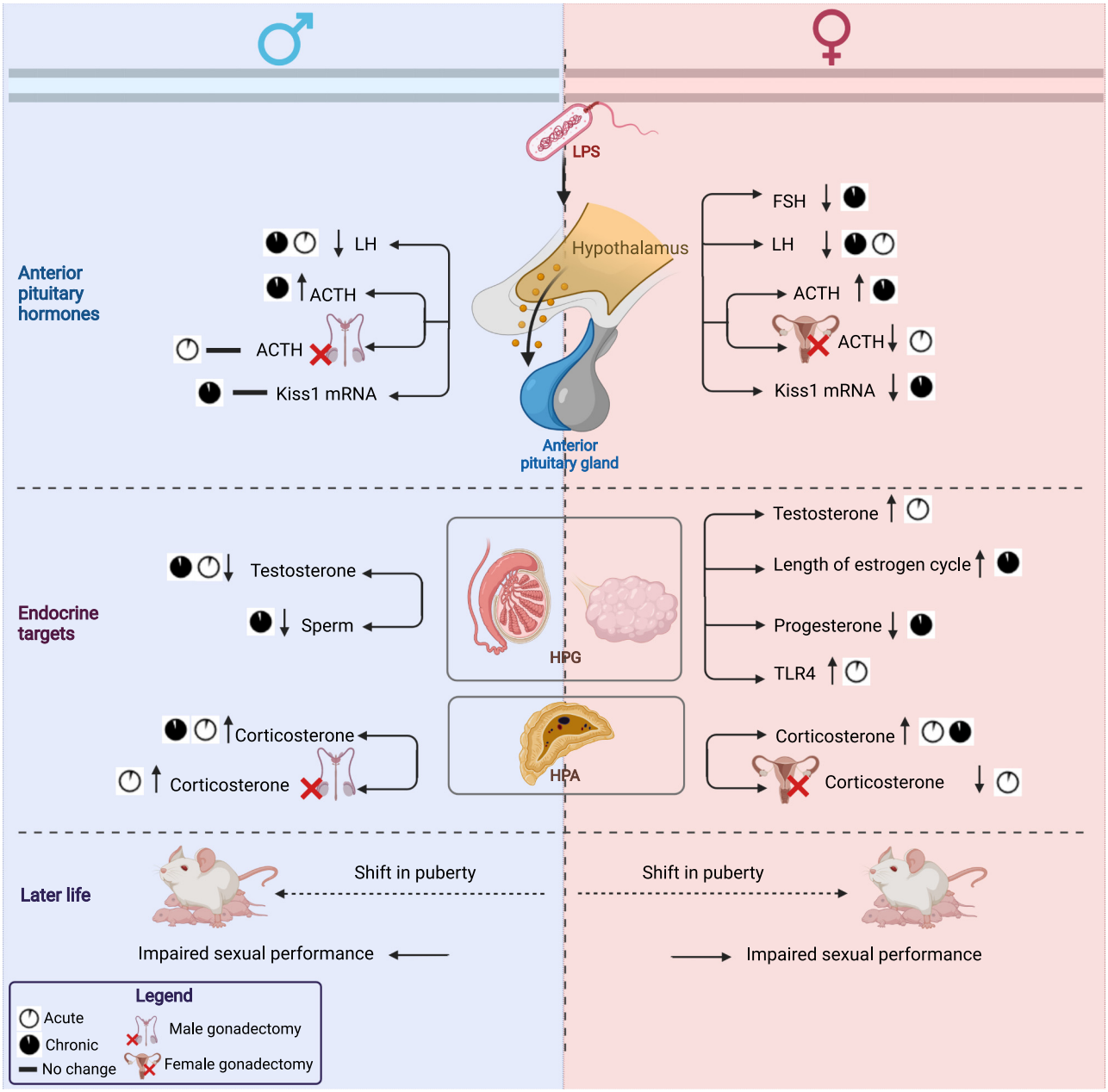


Figure 3. Major effects of neonatal lipopolysaccharide (LPS)-induced infection on the hypothalamus-pituitary-gonadal axis (HPG) and hypothalamus-pituitary-adrenal axis (HPA) in male and female rats. Neonatal LPS was administered between postnatal days 3 and 10. ACTH, adrenocorticotropic hormone; FSH, follicle-stimulating hormone; LH, luteinizing hormone; TLR, Toll-like receptor. Figure created with BioRender.com. (Refs. 82, 84, 85, 126, 127, 129, 130, 134–136.)

Intriguingly, LPS administration on PND 10 protected male rats from LH suppression in response to a second immunological challenge as adults. In contrast, a decrease in LH was observed in LPS-exposed adult male rats that were only treated with saline in early life (130). Male neonatal LPS-treated rats had significantly blunted testosterone surge during mating and in response to a second LPS exposure as adults, despite conserved circulating LH (82, 130). Female rats injected with *S. enteritidis* on PND 3 and PND 5 exhibited reduced circulating progesterone and had higher circulating testosterone as adults (85). These studies indicate that neonatal immune activation can greatly alter peripheral gonadotrophins and steroid hormones during adolescence and later when mating, which may be detrimental to puberty as well as sexual behavior and function (82, 84). Adult rats also display substantial changes in peripheral hormone concentrations in response to single and dual immunological challenges (82, 130). Accumulating evidence reveals that low progesterone concentrations evident in female adult rats after exposure to LPS on PND 3 and PND 5 (85) is associated with homeostatic imbalance, including decreased leptin secretion, insulin sensitivity, and altered lipid and glucose metabolism, resulting in reduced energy expenditure. The role of progesterone in metabolism, fused with its established neuroprotective

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and anti-inflammatory properties, further highlights the hormone's beneficial function beyond sexual behavior (131). Furthermore, high testosterone evident in female adult rats after LPS exposure during the neonatal period (85) increases risk of obesity and insulin sensitivity in females (132, 133). In contrast, low testosterone concentration evident in male adult rats exposed to neonatal LPS predisposes males to metabolic syndrome, increased insulin sensitivity, systemic inflammation, and obesity (132). Long-term shifts in peripheral gonadotrophins and steroid hormone concentrations as a result of an early-life immune challenge will disturb other integrated physiological homeostatic systems, resulting in adverse consequences for whole body health.

Neonatal sepsis, puberty, and reproductive function in later life.

Immune activation early in life potentially alters the control of gonadotrophic hormone release and therefore the onset of puberty and reproductive function (Fig. 3). LPS administration on PND 3 and PND 5 led to a shift in the first day of puberty in male and female rats, which was either earlier or delayed (82, 84, 134, 135). Additionally, mature female rats displayed longer estrogen cycles in response to repeated LPS administration, first on PND 10 and again in adulthood (136). These changes were not evident when neonatal rats received LPS injection on PND 7–9 and PND 14–16, indicating that a critical period during early life may exist in which an immune challenge may cause persistent dysfunction in the reproductive system (136). Kisspeptin (Kiss1) has been identified as a fundamental signaling protein that modulates the timing of reproductive development and gonadotropin secretion (137). LPS administration on PND 3 and PND 5 resulted in reduced Kiss1 mRNA expression in the medial preoptic area of female rats at the time of puberty (134), which may be associated with the alteration in puberty timing and gonadotrophin secretion. LPS-induced Kiss1 suppression is potentially mediated by TNF-α (138). Male rats exposed to LPS at PND 10 and in adulthood did not develop changes in Kiss1 mRNA expression in the hypothalamus, which may offer a mechanism for sex disparity observed in adult LH concentrations (130). In addition to delayed onset of maturation, neonatal LPS exposure on PND 3 and PND 5 resulted in impaired sexual performance in male and female adult rats (82). Furthermore, in adult female rats the follicle reserve was reduced and the thickness of the theca interna and expression of p75NGFR increased as a result of neonatal (PND 3 and 5) LPS injection (135). Sperm presence was significantly decreased, and disorganized seminiferous epithelium was evident within the testes in adult rats that were challenged as neonates with LPS on PND 3 and PND 5 (82). In summary, neonatal exposure to LPS in rats disrupts long-term HPG axis regulation, resulting in structural deficits to reproductive organs and disturbed maturation. Neonatal infection therefore results in profound and long-lasting implications for puberty as well as sexual performance, which may lead to reduced fertility in rodents. Although infection is more common in males, long-lasting disruptions to HPG regulation are evident regardless of sex.

Despite the significant research advances in rodents, to our knowledge there are no human studies investigating the effects of innate immune system activation on sexual development and reproductive success. Recent literature describes that in preterm infants an energy-conserving hypometabolic state is implemented to achieve a balance between disease tolerance and resistance that increases the chance of survival in the face of infection (57, 139, 140). This method of immunity leads to energy restrictions or competition of energy between homeostatic physiological systems. Impaired HPG axis regulation may in part be a result of shift in energy supply (8, 139), associated with elevated cortisol evident in rodent models and preterm infants with LOI (78–80), which may disturb integrated whole body systems.

Hypothalamic-Pituitary-Thyroidal Axis

Thyrotropin-releasing hormone (TRH) produced in the hypothalamus stimulates the anterior pituitary to release thyroid-stimulating hormone (TSH). Thyroxine (T_4) and triiodothyronine (T_3) are subsequently released from the thyroid gland in response to TSH. T_4 and T_3 complete a negative feedback loop, acting on both hypothalamus and pituitary to limit further secretion of TRH and TSH. After birth, the infant's thyroid gland is responsible for providing a sufficient supply of thyroid hormones to promote nervous, reproductive, and cardiovascular system development, immune system regulation, as well as energy metabolism, growth, and thermogenesis (141). Maturation of the HPT axis begins around 20 wk of gestation but is only completely mature close to full-term gestation (142). As such, preterm infants have an immature HPT axis and limited capacity to generate thyroid hormones (143). Pharmacological intervention with dopamine in the treatment of hypotension can further suppress T_4 concentrations in preterm infants (144). A recent study suggests that thyroid hypofunction is indicative of an at-risk baby who may be susceptible to development of LOI (145). Thyroid hormone concentrations are significantly lower in sick babies as described below (79, 80, 146–148).

Multiple studies report a reduction of serum T_3, T_4, and TSH concentrations in preterm and term newborn infants with LOI compared with healthy control subjects (79, 80, 146–148). Treating the primary infection with antibiotics normalizes serum thyroid hormone concentrations, and, as such, the infant experiences only a transient suppression in thyroid hormone concentrations in most cases (80, 146). Lower levels of T_3, T_4, and TSH were evident in nonsurvivors of sepsis, predicting an adverse outcome in these newborns (146, 147, 149), and a significant negative correlation was apparent between CRP and T_3/T_4 (80, 147).

Studies examining infection-induced changes in HPT axis are limited in animals. An immune challenge in young pigs (1–28 days old) decreased serum TSH concentrations 3 h after exposure (150). Lower T_3 and T_4 concentrations were also evident in full-term nonsurviving newborn foals with naturally occurring sepsis compared with foals that survived (151). In rats, the proinflammatory cytokine TNF-α rapidly reduces TSH secretion from cultured rat pituitary cells (152). These observations in human and animal studies suggest that LOI has the capacity to further exacerbate decreased thyroid hormone concentrations and impair HPT axis regulation in infants.

To our knowledge, thyroid hormone concentrations are not routinely used in the assessment of sepsis in neonates within the NICU, although thyroid function assessment has been suggested in critically ill newborns (153). Newborn

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thyroid hormone screening is conducted with heel-prick blood sampling and filter paper cards. Infants presenting with abnormal blood thyroid hormone concentrations are treated and monitored weekly/monthly thereafter. Levothyroxine is one of the standard treatments for reduced thyroid hormones in neonates (154). Low levels of thyroid hormones and high risk of neurodevelopment abnormalities in preterm infants support the hypothesis that neurodevelopmental problems in preterm infants are, at least in part, caused by low thyroid hormones (155, 156). However, continuous debate exists regarding the effects of transient low thyroid hormone concentrations on development. Other longitudinal studies display no long-term adverse neurodevelopment outcomes in children or adults who suffered from transient low thyroid hormones as newborns (157, 158).

Thyroid hormone deficiency results in reduced heart rate, prolonged systolic and diastolic times, and weakened inotropic function (159). Moreover, in adults with obstructive sleep apnea, mean apnea duration significantly correlated with TSH; subjects with lower T_3 showed longer mean apnea duration compared with those with higher T_3 (160). Similarly, an older study reported that severe hypothyroidism is associated with depressed ventilatory drive during hypoxic and hypercapnic respiration (161). Adults with hypothyroidism often suffer from disordered breathing (162). However, in patients with obstructive sleep apnea, low thyroid hormones is not a common comorbidity (162, 163). To our knowledge, there are no studies assessing associations between thyroid hormones and cardiorespiratory parameters in preterm or term infants with LOI. It would seem prudent to further extend these investigations. Thyroid hormone concentrations may have the capacity to function as biomarkers for neonatal sepsis diagnosis or at least stratify the patients at high risk. Large-scale clinical studies assessing thyroid hormone concentrations in preterm and term infants with sepsis could open avenues for diagnosis and lead to biomarker-guided adjunctive therapy and precision medicine for treatment of clinical consequences of sepsis such as pathophysiological cardiovascular control.

Sickness Behavior and Melatonin, Leptin, and Ghrelin

Neonatal sepsis and melatonin.

Melatonin is an endogenous anti-inflammatory and antioxidant indolamine produced in the pineal gland during darkness following acetylation and then methylation of serotonin (164). It has many physiological functions, including a fundamental role in sleep, reproduction, and circadian rhythm (165). Preterm infants are melatonin deficient compared with full-term infants (166, 167). Maternal melatonin concentrations progressively increase after 32 wk of gestation, and babies' levels likely rise in line with this (168, 169). Full-term infants usually begin to produce melatonin around 3 mo of age, resulting in a more regulated sleep pattern. However, preterm babies may not produce melatonin until around 5–6 mo, depending on how early the infant was born (170–172). Although there is a paucity of studies investigating the effects of LOI on endogenous melatonin concentrations in preterm infants, one study reports that melatonin was increased in full-term infants with LOI compared with healthy control neonates (173). In septic and sedated adults in intensive care melatonin is suppressed (174, 175).

Interestingly, the magnitude of LPS-induced cachexia, lethargy, fever, and anorexia (sickness behaviors) is decreased in Siberian hamsters exposed to short daylight compared with long daylight, presumably to conserve energy (176). LPS-induced fever was attenuated in Siberian hamsters in response to 6 wk of exogenous melatonin administration, which also decreased body mass, exhibited gonadal regression, and increased cortisol (177). It has been suggested that melatonin influences components of sickness behavior via complex interactions with other endocrine hormones, such as glucocorticoids or sex steroid hormones (177). Elevated melatonin during infection may be linked to energy conservation in infants. Furthermore, increased melatonin in infants with sepsis may protect the host against oxidative stress-induced cell dysfunction. Melatonin scavenges reactive oxygen and nitrogen species, enhances mitochondrial physiology, and restores glutathione homeostasis. It indirectly stimulates enzymes involved in glutathione production (178, 179). In addition to its important role as an antioxidant, a recent study has illustrated the importance of melatonin in glucose regulation, improving sepsis-induced hyperglycemia in an animal model (180). Exogenous melatonin as adjunctive therapy for sepsis in preterm and term infants has been associated with improvements in laboratory and clinical outcomes, due to the leading role of oxidative stress in pathogenesis of preterm morbidity and sepsis (181–187). In support of its amelioration in sepsis, a recent clinical trial has demonstrated improved patient outcomes when melatonin was used as an adjunctive therapy in adult sepsis (188).

Neonatal sepsis and leptin.

Leptin is an adipocyte-derived hormone that has long been recognized to have a vital role in metabolism, the neuroendocrine system, and other physiological functions. Premature delivery results in early separation from the placental and maternal leptin supplies, predisposing preterm infants to postnatal leptin deficiency up to 36 wk of postmenstrual age (189, 190). This prolonged period of low leptin concentrations may preclude sufficient adipose tissue or functional maturity (190). Circulating leptin concentrations are modulated by infection; an increase in serum leptin was apparent in a mixed cohort of preterm and term neonates with sepsis compared with age-matched control subjects (191, 192). To our knowledge there are no studies specifically investigating the effects of LOI on leptin concentrations in preterm infants. Neonatal sepsis in term infants treated with antimicrobial therapy for 2 wk returned leptin concentrations to values similar to those of control infants (192). Normalization of leptin with antimicrobial treatment suggests a short-term surge in leptin concentrations in response to infection. Specifically, the elevated leptin state may be associated with sickness behavior evident in sepsis. In adults, an increased leptin concentration has been observed in patients with severe sepsis. Leptin was, however, positively correlated with survival, which could indicate the beneficial role of leptin in the host defense mechanism against bacterial infection (193–195). In rodents, leptin antiserum treatment attenuated LPS-induced fever and anorexia (196, 197). Additionally, leptin administration to rats results in

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increased body temperature, which can be abolished by an IL-1 receptor antagonist (198), suggesting that proinflammatory cytokines released in response to leptin mediate its actions on the hypothalamus.

Neonatal sepsis and ghrelin.

Ghrelin is well known as a "hunger hormone" and plays a role in insulin resistance, energy homeostasis, and heart disease (199). Furthermore, ghrelin also displays antibacterial and anti-inflammatory activity and suppresses proinflammatory cytokine production (200, 201). Ghrelin is decreased in plasma but increased in cord blood in preterm newborns compared with term infants (189, 202). Ghrelin is suggested to originate from the maternal compartments, secreted by the placenta or produced by fetal tissue, but the source of ghrelin during fetal life is not well defined. As such, the underlying cause for difference in ghrelin concentrations in preterm compared with term infants is unknown (203, 204). However, it is plausible that disruption to synthesis and/or the clearance rate of ghrelin occurs in preterm infants (4).

Plasma ghrelin was significantly increased in full-term neonates with sepsis compared with healthy control subjects. In this population, ghrelin values higher than 1.4 ng/mL on admission accurately indicated infection, with sensitivity and specificity between 70% and 75% (205). Similarly, elevated ghrelin concentrations are also evident in adults with septic shock (206). Interestingly, a significant association was evident between ghrelin concentrations and the duration of fever in neonates, i.e., ghrelin levels decreased in infants whose fever improved within 36 h and increased in infants who were febrile for >36 h (205). This association may be related to fever mediators such as cytokines, as it has been previously reported in adults that ghrelin peaks 30 min after the peak in TNF-α (207). Additionally, an antipyretic role of ghrelin cannot be discounted. In adult rats, LPS administration combined with intraperitoneal injection of ghrelin reduced fever (208). Furthermore, ghrelin was significantly higher in adult rats with septic shock, who were hypotensive and displayed hypoglycemia and elevated lactate concentrations compared with control animals. Interestingly, exogenous administration of ghrelin in these rats resulted in elevated blood pressure and plasma glucose, as well as a reduction in plasma lactate compared with septic shock rats that did not receive treatment (209). To our knowledge there are no studies investigating the effects of sepsis on ghrelin concentrations in preterm infants. Currently the precise role of elevated ghrelin during sepsis is unknown, but with further research ghrelin has potential to serve as a diagnostic marker for the identification of infection. Although this area of research is in its infancy, melatonin, ghrelin, and leptin concentrations in infants with sepsis may offer therapeutic value for treatment of sickness behavior in sepsis.

IMMUNOMETABOLISM

Dramatic shifts in metabolism occur in response to immune activation (210). In turn, precise changes in metabolic pathways alter the immune response (211) (Fig. 4). Intracellular metabolic processes are vital for homeostatic function in whole body health and disease. Interconnected metabolic pathways, such as fatty acid synthesis and oxidation, glycolysis, amino acid pathways, and the Krebs cycle, play a fundamental role in the production of energy and multiple biosynthetic intermediates essential for the promotion of innate immune cell survival, proliferation, function, and sustained activation. Typically, activation of immune cells through PRRs upregulates hypoxia-inducible factor 1α, resulting in a shift of cellular energy metabolism from fatty acid oxidation and oxidative phosphorylation to glycolysis, known as the "Warburg effect" (aerobic glycolysis) (212). This redistribution of supply/demand is required to provide a rapid burst in energy (i.e., ATP) (211, 213). Furthermore,

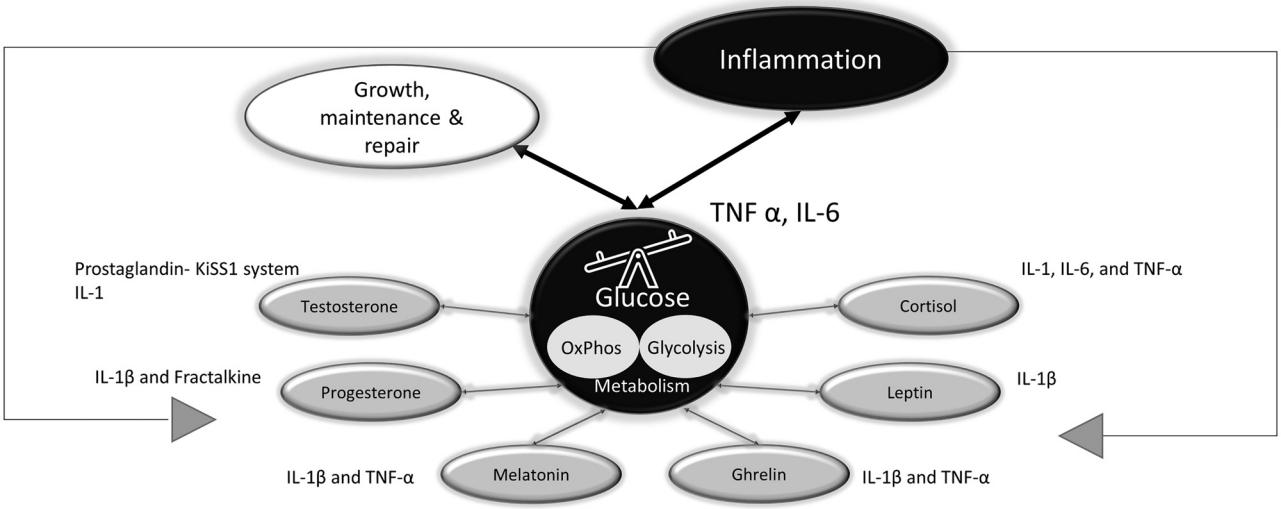


Figure 4. There is a complex interplay between the immune, endocrine, and metabolic systems during infection. Hormones regulate energy homeostasis in the body and are modulated during infection. Reported inflammatory mediators that modulate respective hormones are detailed above (115, 305–312), but their roles need to be further tested in neonatal animal models of infection. Energy is required for growth, maintenance, and repair particularly in the infant, but significant energy is also required to mount an inflammatory response; ultimately both the survival strategy and the subsequent outcome will be influenced by energy balance. IL, interleukin; OxPhos, oxidative phosphorylation; TNF-α, tumor necrosis factor-α. (Refs. 85, 115, 180, 209, 211, 216, 229, 230, 305–312.)

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glycolytic metabolism plays an essential role in providing metabolic intermediates (e.g., glucose-6-phosphate) for interconnected pathways (e.g., pentose phosphate pathway) to promote inflammatory responses (211). This shift to glycolytic activity is an essential step of immune-metabolic cross talk to minimize harm from pathogens (8).

Energy Reserves in Preterm Infants

Energy availability is paramount for preterm infants, as the basal energy requirements for growth and development are significant. Metabolic pathways regulate the inflammatory status, with important implications for survival (57). Although sustaining an adequate immune response requires high glycolytic activity, substantial fatty acid metabolic flux is necessary to regulate inflammatory responses and provide sufficient energy to host tissues (210, 212). Adults rely on protein and lipid stores to provide energy to protect the host without diverting supplies necessary for critical physiological processes, at least until late-stage infection. A 150% increase in resting energy is evident in adults during bacterial infection, allowing the adult immune system to execute efficient infection resistance mechanisms (8, 9). Energy reserves are significantly lower in neonates compared with adults. Many of these energy stores, i.e., liver glycogen and lipid reserves, develop only within the third trimester of gestation; therefore, preterm infants have very limited storage (9, 57, 214). Ideally, the ability to maintain homeostasis during infection is a balance between inflammation and aerobic glycolysis (disease resistance) and fatty acid metabolism and immunosuppression (disease tolerance) (Fig. 4). When less excess energy exists, by varied etiology, e.g., limited energy reserves or prolonged energy expenditure due to infection, the host relies more on disease tolerance in an effort to increase chance of survival (57). The concept of integrated metabolic strategies utilized in a changing environment of supply and demand is reviewed by eloquently by Ye and Medzhitov (215). Evidence exists that in preterm and term infants, as well as neonatal rodent models, distinct metabolic shifts occur in response to infection. In this context, we discuss immune-mediated changes in glucose, lactate, and a selection of amino acids in the following subsections of the review.

Glucose

Glucose is a vital nutrient for physiological homeostasis and brain function. Twenty percent of glucose-derived energy is consumed by the brain, because of neuronal and nonneuronal cellular maintenance requirements as well as production of neurotransmitters (216). Tight regulation of glucose is crucial for whole body homeostasis. In premature infants, hypoglycemia (low blood glucose) and hyperglycemia (elevated blood glucose) often occur because of various developmental or mechanistic deficits (e.g., diminished energy stores, increased energy requirements of newborns, inability to utilize glucose, altered insulin resistance, and stressful situations) (6, 217, 218). The risk of dysregulated glucose metabolism increases in response to infection (218).

Associations between blood hyperglycemia and LOI are evident in very low-body-weight infants of mean gestational age of 30 wk (219, 220). Similarly, late preterm infants (32–37 wk) with LOI have elevated urine glucose concentrations (glycosuria) and hyperglycemia compared with age-matched preterm control subjects (221, 222). Elevated glucose levels are also evident in serum samples collected from term infants with sepsis compared with healthy term infants (223). Although low blood glucose can also occur in preterm babies with LOI (224), longitudinal studies reveal that hyperglycemia is more common than hypoglycemia in preterm and very low-body-weight infants with LOI (225, 226). In rats, reduced plasma glucose concentrations are evident at PND 10, 7.5 h after injection with endotoxin (*S. enteritidis*) (227). Rats challenged with endotoxin (*S. enteritidis*) on PND 3 and PND 5 display reduced glucose concentrations by 8 h after injection, which remains significantly reduced until 8 h after injection on PND 5 (83). LPS and LTA in combination with hypoxic ischemic injury to rats at PND 7 resulted in an initial increase in glucose at 2 h followed by hypoglycemia, which lasted for 24 h (228). These studies in rodents demonstrate a biphasic glucose response to LOI. Discrepancies between rodent and human studies may be a result of timing of glucose assessment after the onset of sepsis. Glucose supplementation after LPS-induced infection in the rat was associated with decreased survival (229). Additional studies are required to determine whether a biphasic glucose response occurs in preterm infants with LOI and to understand the neonatal survival strategies underlying altered glucose.

Stress-induced hyperglycemia is a common clinical entity that occurs alongside an acute illness (230). Elevated cortisol, which occurs in preterm infants with LOI, promotes hepatic gluconeogenesis and glycogenolysis (86). These pathways utilize a variety of nonglucose precursors such as lactate, glycerol, and amino acids (alanine and glutamine) to form glucose (86, 231). Thus, it is plausible that elevations in blood glucose levels of preterm infants with LOI develop because of increased production of stress hormones, in particular cortisol (230). In the adult system, a feedback cycle occurs: high glucose levels induce a proinflammatory state, including both cellular oxidative stress and inflammation (232). Glucose increases proinflammatory transcription factors (early growth response, intranuclear NF-κB binding, and activator protein-1) and reactive oxygen species abundance and reduces nitric oxide availability. Furthermore, hyperglycemia alters the innate immune system, causing decreased neutrophil activity, which results in reduced chemotaxis, phagocytosis, and bacterial killing (232–234), reducing the efficacy of the host immune system in fighting the infection (Fig. 2). Heightened glucose utilization (i.e., glycolysis) and/or reduced glucose production alongside diminished energy reserves in preterm infants is likely responsible for LOI-induced hypoglycemia in preterm infants (57). Of note, some studies in adults suggest that either insulin therapy or lower glucose levels are anti-inflammatory (235). Others report that in human adults acute hypoglycemia promotes platelet-monocyte interactions, increases platelet reactivity and proinflammatory cytokines, and potentiates responses to endotoxins (236, 237). It is likely that shifts in glucose homeostasis due to sepsis further exacerbate the inflammatory status of the infant; treating glucose disturbances to maintain adequate availability may be all-important for the host in order to improve the ability to successfully recover from infection.

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Hyperglycemia and hypoglycemia are independent risk factors for early mortality. Infants with hypoglycemia and hyperglycemia are often subjected to extended hospital stays (238–241). Untreated and/or persistent hyperglycemia is associated with intraventricular hemorrhage, retinopathy of prematurity, as well as neurological and behavioral development abnormalities (238, 239, 242, 243). Complications of neonatal hypoglycemia include visual impairment, cerebral palsy, and other cognitive dysfunctions (238, 244–246).

As untreated hypoglycemia and hyperglycemia have significant pathological implications, routine glucose testing is necessary in preterm babies. Glucose screening is also recommended in infants with sepsis or clinical signs of altered glucose concentrations (247). Blood glucose is often measured very frequently (every 4 h) when an infant has hypoglycemia/hyperglycemia. The implementation of continuous glucose monitoring systems, which measure glucose concentration in interstitial fluid, is currently being piloted in some NICUs (248, 249). However, this technique is not widely used, and several technical issues need to be resolved before routine use in neonatal care (250). Implementation of continuous glucose monitoring would offer the possibility of adjusting glucose concentrations in real time while decreasing the number of blood tests required (251). Although shifts in glucose concentrations appear detrimental to the infant, precise blood glucose control in the NICU does not occur without significant challenges. Intravenous insulin therapy is the best approach to control hyperglycemia in infants (230), but the absence of evidence-based guidelines for safe insulin therapy leads to ongoing uncertainty (7). There are many pharmacological agents used to treat neonatal hypoglycemia, including continuous dextrose infusion and oral diazoxide administration (252), but further research is required to investigate the optimal treatment approach.

Lactate and Vitamin B Complex

Like glucose, lactate is a ubiquitously produced and utilized metabolite critical to many energy-related metabolic pathways (253). It is the normal end product of glycolysis and can be formed from pyruvate. In late preterm infants (32–37 wk of gestational age) with LOI, increased pyruvate (urine) and lactate (urine and blood) concentrations are reported (221). Similarly, term infants with sepsis have elevated serum and urinary lactate concentrations compared with control groups (222, 223). In rats at PND 7, LTA and LPS in combination with hypoxic injury resulted in elevated serum lactate concentrations from 6 to 10 h after LPS administration (228). Elevated serum lactate concentrations indicative of metabolic acidosis is a laboratory sign of sepsis in neonates and adults (34, 254–256). Hyperlactatemia is associated with poor prognosis for survival (257). Traditionally, hyperlactatemia is related to anaerobic glycolysis induced by tissue hypoxia (258). More recently, it has been proposed that increased lactate production is associated with metabolic shifts, i.e., decreased mitochondrial oxidative metabolism (oxidative phosphorylation) or increased protein breakdown (253).

Interestingly, preterm infants with LOI had decreased urinary concentrations of vitamin B complex including nicotinamide, thiamine, and riboflavin compared with healthy control subjects. These vitamins are precursors and coenzymes of several metabolic pathways (221). Thiamine plays an important role in multiple enzymatic pathways involved in brain function as well as myelin synthesis, nerve signal modulation, and tissue repair. Thiamine is also suggested to have anti-inflammatory effects, reducing activation of NF-κB (259). It functions as a cofactor for the multienzyme pyruvate dehydrogenase complex that converts pyruvate to fuel oxidative phosphorylation. Therefore, reductions in thiamine coincide with elevations in lactate concentrations; thiamine deficiency results in the conversion of pyruvate to lactate and is a known cause of lactic acidosis (260). To our knowledge, vitamin B complex levels are not routinely assessed in neonatal care. Nevertheless, recently several human clinical studies have explored the effects of thiamine administration as an adjunctive therapeutic agent in septic shock (261–263). Small pilot studies revealed that thiamine administration to adults and neonates with septic shock was associated with more rapid lactate clearance and reduced mortality compared with control subjects (261, 262). Furthermore, a randomized crossover trial in adults revealed that thiamine administration reduced blood pressure in hyperglycemic patients (264, 265). Additional investigators proposed that glucocorticoids, vitamin C, and thiamine have overlapping anti-inflammatory properties that would restore dysregulated immune system activity, which may occur in prolonged adult sepsis (266). Although investigations assessing the role of thiamine administration in lactate clearance are at an early stage, this area of research may open future avenues for adjunctive therapy, as even high doses of thiamine administration are considered safe (263).

Amino Acids

Glutamate, the most abundant amino acid in the human body, plays an important role in protein metabolism and lies at the crossroads of multiple metabolic pathways. Glutamate functions as a powerful excitatory neurotransmitter, playing a prominent role in neural circuits. Glutamine deamidation produces glutamate, which can be converted into GABA, 2-oxoglutarate, ornithine, glutathione, or glucose (267). Functions of glutamate products are well established, including antioxidant defense (glutathione) and inhibitory neurotransmission (GABA). Glutathione metabolism was markedly altered in preterm infants with early-onset sepsis (268). Glutamate concentrations are increased and decreased in urine and stool samples, respectively, in preterm infants with LOI (221, 269). Discrepancies between studies may relate to the gut microbiota configuration, as glutamate is produced by several bacterial species. Colonization of the gut with pathogens associated with sepsis may create a host environment, which shifts the competitive determinants deployed by a particular bacterial species (270). This may have potential to induce changes in the metabolomic profile. Additionally, antibiotic regimens/dosage administered to infants with LOI can deplete the gut microbiota and shift overall metabolic function. Furthermore, shifts in glutamate concentrations may be related to direct effects of glutamate dietary intake in preterm babies, which may not be uniform across NICUs (271). It is noteworthy that oral glutamine supplementation (enteral including oral or nasogastric administration in formula/breast milk and parenteral such as central venous catheter delivery) during sepsis did not have any significant benefit in preterm infants with and without

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sepsis (272). However, in the latter systematic review, the authors provided some limited evidence that enteral glutamine supplementation decreases the time to reach full enteral nutrition and rate of late-onset invasive infection in preterm infants (272).

The amino acids valine and phenylalanine are significantly elevated in urine samples of late preterm infants with LOI (221), implying disturbed protein metabolism or protein catabolism in LOI, which is closely related to activities of cytokines and inflammatory mediators (273). Although changes in valine and phenylalanine along with many other amino acids are also evident in adult patients with sepsis (274), this shift may be more detrimental to preterm infants given their limited protein reserves. Elevated cortisol, if prolonged, can reduce the incorporation of amino acids into proteins resulting from cortisol-induced inhibition of protein synthesis or increased protein breakdown (275, 276). In preterm infants with LOI, elevated cortisol may cause an increase in urinary amino acid concentrations. Furthermore, amino acids are precursors of gluconeogenesis (86); increased amino acid concentration may in part contribute to stress-induced hyperglycemia evident in preterm infants with LOI (221, 222) (Fig. 2).

Taurine and hypotaurine are significantly elevated in urine samples of late preterm infants with LOI (221). Taurine can be synthesized endogenously from methionine and cysteine in the presence of vitamin B complex, specifically pyridoxine, and/or can be obtained from the diet. It is now well established that taurine and its precursor hypotaurine have multiple diverse physiological functions (277). Taurine has long been recognized to play a role in energy metabolism, gene expression, neuromodulation, and osmoregulation (277). In addition, taurine and its analogs have been observed to exert antioxidant and anti-inflammatory properties, involving taurochloramine formation in neutrophils or reduction of prostaglandin E_2 (278, 279). Although taurine is not routinely monitored in neonatal or adult sepsis, clinical studies in adults report that taurine administration results in decreased blood pressure and left ventricular end-diastolic volume along with improved cardiac function (280–282). The precise mechanism of taurine inducing antihypertensive effects is unknown, but studies in animals suggest that it may be related to decreased oxidative stress, elevated hydrogen sulfide content, suppression of the sympathetic nervous system, and increased nitric oxide production (283, 284). Furthermore, taurine has been shown to protect cardiomyocytes by activating the ubiquitin-proteasome system (285). Further studies are required in this area to investigate the role of increased hypotaurine and taurine concentrations in preterm infants.

Fumaric Acid, Galactose Metabolism, and Inosine

Other metabolites such as fumaric acid, galactose, and inosine are also altered in preterm and term infants in response to LOI, but studies assessing these metabolites are limited. Fumaric acid is a naturally occurring metabolite of the Krebs cycle. Fumaric acid esters (fumarate) are proposed to have immunomodulating, antioxidative, and anti-inflammatory effects (286). In urine samples of late preterm infants with LOI, metabolomic analysis revealed that fumaric acid is significantly reduced (221), which may indicate defective operation of the Krebs cycle. Galactose is derived from dietary sources and enters glycolysis by converting to glucose 1-phosphate (287). Galactose metabolism was the most frequently reduced pathway in stool samples of preterm infants with LOI; sucrose and raffinose were the most frequent metabolites affected (269). Galactose metabolism was also altered in urine samples as a result of LOI in preterm infants (221). Inosine is a naturally occurring purine formed from adenosine breakdown by adenosine deaminase. It has been shown that inosine inhibits the release of proinflammatory cytokines and chemokines and has anti-inflammatory effects (288). Urinary inosine was increased in premature babies with LOI compounds (221). Interestingly, exogenous inosine administration reduced inflammation, vascular dysfunction, and organ damage, increasing survival in mice exposed to septic shock (289, 290). Although it should be postulated with caution, elevated inosine concentrations may offer protection during LOI in premature babies (291). However, further research is required in infants to identify and quantify changes of these specific metabolites and others. This may be achieved by using recent advances in high-throughput sequencing and multiomic approaches.

MULTIOMIC APPROACHES FOR IDENTIFICATION OF NEONATAL SEPSIS

Significant advances have been made to develop both laboratory and clinical diagnostic criteria for identification of neonatal sepsis. However, the ability to promptly and accurately diagnose neonatal sepsis with current laboratory and clinical criteria remains challenging. Currently, there is no single diagnostic test that satisfies the criteria of an ideal biomarker. Advances in high-throughput molecular technologies, including metabolomics, proteomics, and transcriptomics, seem promising methods to determine distinct metabolic and proteomic biomarkers as well as transcriptional signatures that occur at on the onset of, or during, sepsis (292–295). Metabolomics, a relatively new bioanalytical approach, studies the complete set of low- to intermediate-molecular-weight amino acids, lipids, carbohydrates, and other metabolites generated by interactions between the environment, the gut microbiome, and the host genome. This allows for the immediate identification of endogenous and exogenous metabolites, which is useful to establish metabolic perturbations that may occur during infection (292). A recent case-control study revealed a distinct metabolic profile in infants at birth who were subsequently diagnosed with early-onset sepsis (268), highlighting its potential impact in early therapeutic intervention. There are challenges with establishing consistent metabolomic profiles; however, by using large data sets it is possible to improve the application of metabolomic technology to generate reliable tools for diagnosis, prognosis, and treatment (296). Although proteins such as CRP are currently used clinically to identify neonatal sepsis, this biomarker is not sufficiently sensitive or specific for accurate diagnosis. Identification of additional proteins that are altered because of sepsis may improve accuracy. Mass spectrometry proteomics has the ability to screen thousands of proteins to establish abundance and post-translational modifications. Identification of specific changes

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in proteomics may lead to the development of optimized and validated assays for bench-top mass spectrometers that can be used in the clinical setting, including the NICU (297). Currently, there are several problems and challenges that will need to be overcome before the introduction of mass spectrometry proteomics to clinical settings. These include volume of data, testing and validation of computational methods, as well as the complexity of algorithms rendering unbiased comparisons (298). The induction of powerful transcriptome tools including microarrays and next-generation sequencing, in particular RNA sequencing such as single-cell and microRNA sequencing, has increased the ability to examine gene expression during infection. Although there have been no studies using RNA sequencing to identify transcriptional signatures for diagnosis of neonatal infection, it has shown potential in adults (299). Transcriptional profiling allows measurements of thousands of genes simultaneously, which could lead to the identification of a cell-specific gene signature(s) for diagnosis of neonatal sepsis (294). However, there are substantial challenges relating to downstream and upstream processes of translating next-generation sequencing into a bedside clinical tool. These challenges include extensive sample processing for nucleic acid extraction and library preparation for sequencing, as well as large data storage requirements. Furthermore, RNA sequencing is limited by high cost and time: 16–48 h is required for sample collection to quantification compared with 2 h with qRT-PCR. Future studies are required to address challenges of integrating multiomic data with current clinical and laboratory markers to translate the knowledge used for diagnostics to precision medicine for treatment of neonatal sepsis (293). A study by Langley et al. (300) integrated both clinical features with seven metabolites into an algorithm that predicted survival in adults. This combined approach may improve accuracy of potential algorithms employed. Employing machine learning to available neonatal clinical data has the potential to reveal novel biosignatures and distinct populations as already explored with adult patient data (301). Precision medicine would provide tailored treatment and therapy to patients based on measurements obtained at an individual level, using data retrieved from the population. This will allow for accurate and personalized therapeutic interventions that would improve outcomes. For precision medicine to be implemented, it relies heavily on biomarker-driver approaches for diagnosis. Fortunately, multiomics appears to be leading in the race to clinical application in pediatric health (302–304), which is a key driver in efforts to achieve precision medicine healthcare, derived from personal data, contributing to the future of medical practice (Fig. 5).

SUMMARY AND CONCLUSIONS

Several lines of inquiry converge to confirm that sepsis in preterm and term babies and animal models of similar development stages induces significant disturbances to intertwined neuroendocrine and metabolic pathways. The precise clinical consequences of these changes are not fully elucidated. Furthermore, it appears that sepsis during critical early-life periods, perhaps distinct in males and females, leads to an inescapable cycle that results in long-lasting impairments in later life. Emerging findings of neonatal

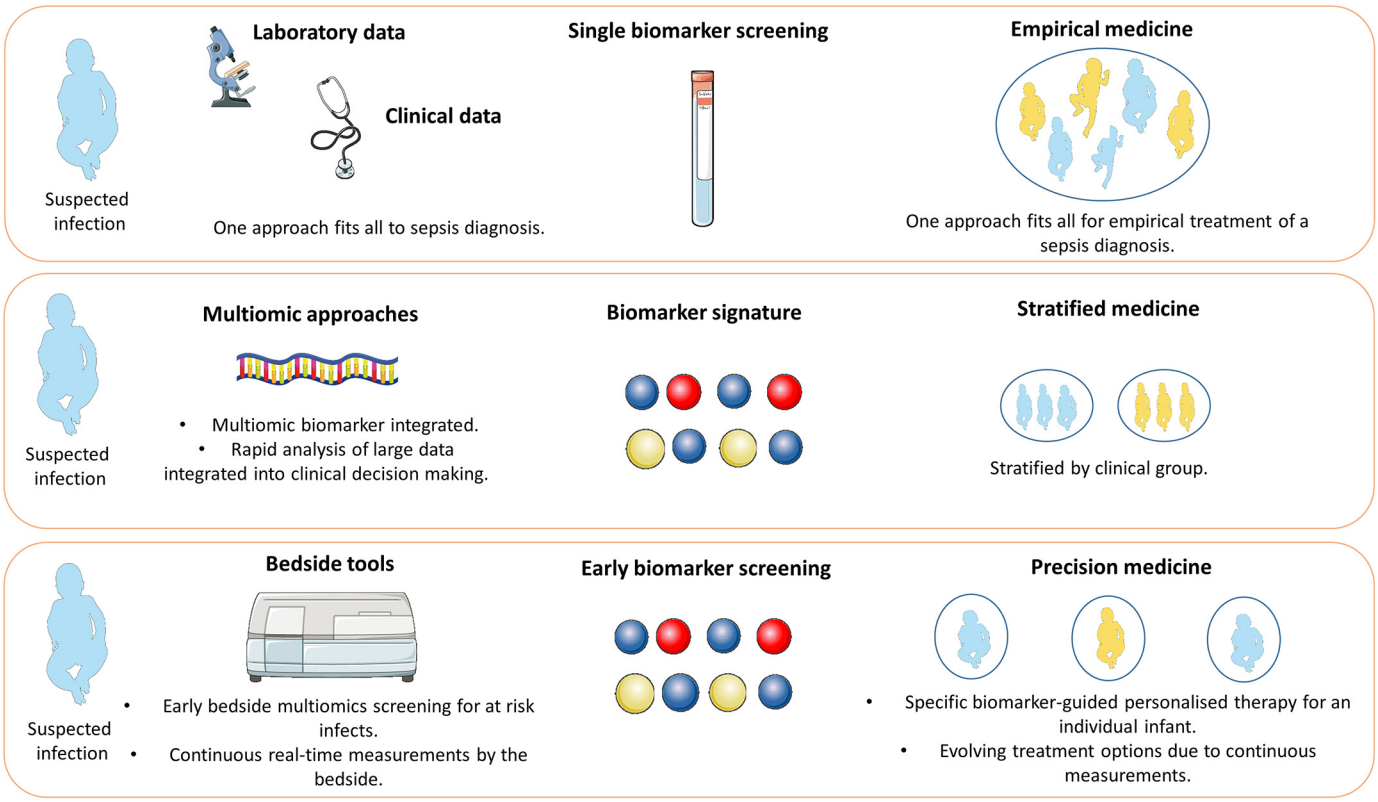


Figure 5. Summary of current and potential future approaches for diagnosis and treatment of neonatal sepsis.

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sepsis-associated changes in metabolites and hormones described in this review may serve as biomarkers and have potential to be instrumental in improving early diagnosis of sepsis in neonates. Biomarker-guided therapy may offer a reduction in antibiotic use and present increased opportunities for targeted empirical and adjunctive therapies to treat infection-induced physiological derangements in infants or indeed provide an opportunity for early stratification of infants at risk, which may reduce both morbidity and mortality within the NICU. Furthermore, early diagnosis and biomarker-guided therapy may help reduce long-lasting deficits that are apparent in later life. Much work, including large-scale controlled clinical trials, is required to provide an evidence-based platform for the study of infectious epidemiology and sex-specific initiation and progression of neonatal sepsis. The development of acute-phase biomarkers would result in significant implications for development and application of empirical and supportive management of neonatal sepsis within the NICU. Recent advances in high-throughput sequencing have significant potential to provide major advances in the treatment of neonatal sepsis. Multiomic technologies are essential to efforts toward effectively translating underlying biological knowledge into clinical action tools, aiming for precision medicine as the future of medical practice within the NICU.

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DISCLOSURES

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AUTHOR CONTRIBUTIONS

K.M.O., M.L.D., E.M.D., K.D.O., and F.B.M. conceived and designed research; K.M.O. and M.A. prepared figures; K.M.O., M.L.D., and F.B.M. drafted manuscript; K.M.O., M.A., M.L.D., E.M.D., K.D.O., and F.B.M. edited and revised manuscript; K.M.O., M.A., M.L.D., E.M.D., K.D.O., and F.B.M. approved final version of manuscript.

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