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.

1. Preterm infants

Preterm birth is defined as delivery prior to 37 weeks of gestation, which can be further sub-categorized to include extremely preterm (< 28 weeks), very preterm (28-32 weeks) and moderate-to-late preterm (32-37 weeks) infants. Global data suggests more than one in ten infants are born too soon resulting in an estimated 15 million preterm births annually (41). Prematurity is the leading cause of neonatal mortality and morbidity. More than 35% of infant deaths worldwide can be attributed directly to prematurity (30, 159). As a significant amount of development occurs during the 3rd 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 (46, 202, 237, 250). Furthermore, preterm infants are separated from maternal hormone supplies, such as melatonin (174, 282). In recent years, survival of preterm infants has risen dramatically due to significant improvements in neonatal and obstetric care including delivery in tertiary neonatal centres, increased use of antenatal steroids, targeted oxygen saturation limits and vigorous hand washing (8, 34, 234). However, reported outcome measures such as death and all-cause mortality does not capture the wide range of short- and long-term morbidity caused by preterm birth and early life interventions (30, 154, 155). Infants born preterm often require intensive care and extended hospital stays, resulting in further challenges for the infant (175). Complications associated with preterm birth include necrotising enterocolitis and sepsis and longer-term challenges such as cerebral palsy, and visual, hearing and cognitive problems (31, 41, 175, 219). 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 (41).

2. Neonatal sepsis

Neonatal sepsis is caused by bacteria, viruses or fungi that impinge on normal development of newborn infants (245). Sepsis is a significant cause of morbidity and mortality worldwide and is now recognized as one of the most common illnesses that patients, hospitals and public health agencies encounter (139, 230). Over the past two decades, epidemiological research and policies concerning infection control have intensified in an attempt to address this on-going 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 (87).

Depending on the infant's age, neonatal sepsis can be sub-divided into early-onset infection (EOI) and late-onset infection (LOI), which are defined as infections occurring in the first 48-72 hours, and after 48-72 hours of life, respectively (246). Early onset infection is typically caused by organisms transmitted from the mother to the infant *in utero* or at the time of birth (266). Late onset infection 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 (265). Premature newborns have 3-10 times increased risk of developing sepsis compared with term infants (116, 175). Recent evidence highlights that preterm birth after hypertensive disorders and/or fetal growth restriction are associated with an increased risk

of late onset sepsis in the infant (156). In the neonatal intensive care unit (NICU), the majority of infection cases occur in premature infants (32, 154) with 70 % of LOIs occurring in extremely premature infants (285). Moreover, males are more vulnerable to neonatal infection compared with females (253, 267).

Late onset infection poses challenges for homeostatic control systems of major body functions (245) 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 (98, 162, 218). It has been suggested by the World Health Organisation (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 (88). There is worldwide consensus that clinical disturbances associated with LOI include hypotension, temperature instability, apnea, respiratory distress, tachy/bradycardia and gastrointestinal problems (218, 245). Laboratory criteria include high immature-to-total neutrophil ratio, low platelet count, high/low white blood cell counts, hypoglycemia/hyperglycemia, metabolic acidosis (base excess (< -10 mEq/L) or an elevated serum lactate (> 2mMol/L)) (162, 229). 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 (36, 162, 264). After infection, pro-inflammatory cytokines, specifically IL-6, enhance hepatic synthesis of CRP in the late stages of neonatal sepsis i.e. serum CRP is usually increased 6-8 hours after the onset of symptoms (211). In infants with nosocomial infection, procalcitonin concentrations usually begin to rise 2 hours after infection (84, 287). It is important to note that these acute phase proteins are non-specific biomarkers and can be influenced by any inflammatory condition, such as surgery or tissue injury (162). 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 (162). Lancet Adolescent 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. 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 be made, these suggestions are only recommended for infants >37 weeks of age to young adults of 18 years old (276). The use of intravenous and oral antibiotics, such as vancomycin, ampicillin and gentamicin, are routine in clinical settings to treat neonatal sepsis (88, 89, 147). 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 (109, 189). 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 (189, 245). For example, a multidrug resistant *Staphylococcus captitis* clone has recently emerged as a major pathogen among infants in the NICU (300). 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 (189). 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 (68).

3. Innate immune system

Pathogen-host protection occurs through highly coordinated actions of the innate and adaptive arms of the immune system (52, 177). At birth, the innate and adaptive components of the immune system are not fully mature (104, 168). The memory and specificity of the adaptive immune system develops in the infant's early years (104). Newborns rely heavily on the innate immune system as the first line of defence against foreign invaders (168). 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) increase immune surveillance for antigens (2, 82, 143). The common structural patterns of PGN/LTA and LPS activate Toll-Like receptors (TLR) -2 and -4, respectively (241). TLR activation initiates a complex series of intracellular cascades that result in a variety of cellular responses including production of pro-inflammatory cytokines (173). 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 (177). Activation of the immune system in neonates and adults alters bidirectional communication between intrinsic physiological systems including neuroendocrine and

158 metabolic pathways in order to protect the host by different strategies as discussed by
159 Haberson et al., either enhancing host health or actively fighting the infection (105). We
160 review emerging findings in human infants and animal studies on how immune system
161 activation alters multiple endocrine and metabolic pathways. Figure 1. summarizes some of
162 the major alterations reported in preterm and term infants with infection in We also
163 examine proposed biomarkers for sepsis in the NICU, which may serve as viable targets for
164 precision medicine healthcare for the treatment of neonatal sepsis.

165 4. Immune-neuroendocrine crosstalk

166 Interactions between the neuroendocrine and immune systems were discovered in the
167 1930s (272). It is now well accepted that crosstalk between these systems plays a vital role
168 in controlling the duration and magnitude of the inflammatory response, as well as
169 homeostatic physiological functions of the body during infection (214). Bidirectional
170 communication occurs between the immune-neuroendocrine systems systemically at the
171 level of the hypothalamic-pituitary-adrenal (HPA) axis, hypothalamic-pituitary-gonadal
172 (HPG) axis and the hypothalamic-pituitary-thyroidal (HPT) axis. In addition to these classical
173 pathways, hormones that regulate feeding behaviour and the renin-angiotensin-aldosterone
174 system, amongst others, are modulated by immune activation and play a part in
175 immunological function.

176 4.1 Hypothalamic-pituitary-adrenal axis

177 It is now apparent that when TLRs and other PRRs recognize bacterial or viral molecular
178 patterns, early activation of the HPA axis occurs, which is proposed to be related to
179 prostaglandin E_2 signalling; pro-inflammatory cytokines in turn maintain the prolonged

enhancement of the HPA axis (188, 310). Corticotropin-releasing hormone (CRH) is secreted from neurons within the paraventricular nucleus of the hypothalamus into the hypophyseal 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, noradrenaline, histamine and dopamine and downregulated by γ-aminobutyric acid and opiates as well as downstream hormones such as glucocorticoids and ACTH, via negative feedback (39, 185). The HPA axis plays a critical role in regulating inflammation in response to infection. Endogenous glucocorticoids and catecholamines attenuate the production of pro-inflammatory (tumour necrosis factor-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) (185, 296).

4.1.1 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 (46). Under basal conditions, serum cortisol, which is a glucocorticoid hormone, is usually bound to cortisol-binding globulin or albumin and only about 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 (24, 196). Although the extra-adrenal chromaffin tissue undergoes maturation at 9-11 weeks of gestation (212), the human adrenal cortex does not synthesize cortisol de novo until about 30 weeks of gestation; thus it is widely suggested that low free cortisol is related to adrenal insufficiency in preterm infants (85). Others postulate that reduced

cortisol in premature infants is due to blunted CRH production in the hypothalamus (103). 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 (24, 85, 220). Additionally, low cortisol in preterm infants might reflect insufficient stress response which may be, in part, protective against catabolic cortisol levels (111). On the other hand, HPA activity is associated with reductions in pro-inflammatory cytokines and inflammatory mediators, as well as increased anti-inflammatory cytokines (185, 296). It is interesting to speculate that low cortisol concentrations in preterm infants has the potential to lead to uncontrolled inflammation, which might create a host environment optimal for pathogen colonisation (209). 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 (23, 66, 67, 101, 203).

4.1.2 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 (Figure 1) (58, 102, 277). At term birth, rodents are of similar developmental stage to that of preterm human infants and are common models in neurodevelopmental research (47). Similar to findings in preterm infants, endotoxin administration to rats on post-natal day (PND) 3 and 5 resulted in elevated circulating corticosterone (200, 257, 290, 292), which

persisted for 24 and 4 hours post-injection on PND 3 and 5, respectively (292). 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 (Figure 2). Noteworthy, hypercortisolemia promotes significant disruptions to metabolism (Figure 2), affecting the gluconeogenesis and glycogenolysis pathways as well as amino acid metabolism, and it also plays a regulatory role in other neuroendocrine axes (134, 249). There is some further discussion of these topics later in the review. Currently, there is no consensus regarding testing methods or interpretation of cortisol concentrations in neonates (85). However, more recently, researchers have established that free cortisol is a better indicator, and assessment of plasma total cortisol and corticosteroid binding globulin may prevent unnecessary use of glucocorticoid therapy in neonates (284). 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 (38). 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.

4.1.3 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 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 5, had greater corticosterone and ACTH concentrations at baseline and in response to stress as juveniles and adults compared with controls (200, 247, 257). Adult male rats exposed to *Salmonella enteritidis* as neonates had increased plasma CRH and hypothalamic paraventricular nucleus CRH mRNA concentrations (247). Furthermore, adult rats treated with LPS as neonates exhibited elevated plasma corticosterone and ACTH in response to a second LPS immunological challenge in adulthood (119, 291). Glucocorticoid receptor density was decreased in the forebrain in both sexes (247). 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 (247).

Rats administered LPS (*Escherichia coli/Salmonella enteritidis*) on PND 14, displayed attenuated febrile response and reduced hypothalamic cyclooxygenase-2 after LPS administration in adulthood (33). Intriguingly, these adult central nervous system immune responses were only evident in rats exposed to LPS after PND 7 and before PND 28 (260). 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 (77). 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 (188). 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 (247). In contrast to studies performed by Shank 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 (188). Furthermore, no difference in glucocorticoid receptor expression was evident in the liver, spleen or adrenal gland (188). 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 5 (188, 247).

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 (33, 188, 247). Furthermore, a narrow critical early-life period may exist wherein innate immune system activation results in profound alterations to HPA axis regulation in later life (260).

4.2 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 (99). Vasopressin is important for maintaining osmotic gradients as well as many more divergent physiological

297 actions including cardiovascular homeostasis, where it acts as an endogenous
298 vasoconstrictor agent (207), and its role as an antipyretic, whereby it suppresses the febrile
299 response (193, 214, 288).

300

301 A recent study in humans reported low plasma vasopressin concentrations in preterm
302 infants with sepsis; infants that progressed to septic shock had significantly lower
303 concentrations of vasopressin at the onset of the sepsis cascade (before laboratory/clinical
304 evidence of organ dysfunction) compared with those infants that did not deteriorate to
305 septic shock (9). Interestingly, subjects with plasma vasopressin levels <43.8 pg/ml had
306 significantly higher risk of progression to septic shock. Furthermore, the authors continued
307 this analysis to develop an in-depth equation that had an 89.5% predictive capacity for the
308 development of septic shock i.e. higher risk of mortality. Based on this equation every
309 100pm/ml elevation in plasma vasopressin levels resulted in a greater than two-fold
310 reduction in the likelihood of progression to septic shock (9). This study suggests that
311 vasopressin concentrations, in line with other criteria, may form the basis to predict chances
312 of severity of infection in infants and an opportunity for therapeutic intervention.

313 It is interesting to speculate that low vasopressin levels in preterm infants with sepsis may
314 be one of multiple contributors to hypotension (171, 228), although this must be posited
315 with considerable caution, as there is a scarcity of studies investigating vasopressin levels in
316 preterm and term infants with sepsis. Dopamine is the most common anti-hypotensive
317 medication used in preterm infants, however, the use of vasopressin is increasing (133).
318 Case studies and small trials both in neonates and adults showed that vasopressin elevated
319 arterial blood pressure in patients with sepsis (121, 207). 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 (69). Although its use in neonatology is somewhat restricted (180, 222, 228), with only 0.8% of hypotensive infants being prescribed exogenous vasopressin (222), a recent pilot study in very low birth weight infants reported that vasopressin was as efficacious as dopamine for the treatment of hypotension (221). Vasopressin is an immune-modulator and it is also stimulated by cytokines such as IL-1a, IL-1b, IL-6, in addition to prostaglandins and leukotrienes, potentially mediated by the Fos-Jun-AP1 pathway (124, 169, 289, 306, 309). The complex role of vasopressin in sepsis has been reviewed elsewhere, with actions on both innate and adaptive immunity (231). Interestingly, V_{1A} receptors are expressed on astrocytes and stimulation of these receptors attenuates the release of inflammatory mediators via a PKC pathway (311). Anti-inflammatory actions of vasopressin would offer protection during infection. Although vasopressin administration has potential benefits as evident 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 (1, 7, 123, 180). In animal models, myocardial ischemia and varied splanchnic blood flow occur at high doses (252, 299). Dosage and timing of the use of vasopressin as a therapeutic strategy to treat sepsis-induced hypotension is currently under investigation (239).

4.3 Hypothalamic-pituitary-gonadal axis

342 Gonadotrophin releasing hormone (GnRH) secretion from the hypothalamus stimulates
343 release of the gonadotropins, follicle stimulating hormone (FSH) and luteinizing hormone
344 (LH), in the anterior pituitary gland. Gonadotropins subsequently stimulate release of
345 estrogen and progesterone from ovary glands in females and testosterone from Leydig cells
346 in the male testes (49, 185). It is well known that progesterone and estrogen play a
347 neuroprotective role in postnatal development (19, 132, 153) and males are more
348 vulnerable to neonatal infection than females, a trend observed across many neonatal
349 conditions (253, 267).

350 **4.3.1 Neonatal sepsis and the HPG axis**

351 In recent years, studies have emerged suggesting neonatal infection reprograms the HPG
352 axis in a sex-specific manner (Figure 3) (248, 257, 290). Administration of LPS (*Salmonella*
353 *enterica*) to rats on PND 3 and 5 results in reduced testosterone in males and decreased LH
354 in both sexes immediately following neonatal LPS exposure (290). Morphological
355 assessment of neonatal rat testes revealed decreased gonocyte genesis following LPS
356 administration. However, there was no difference in seminiferous tubule number per mm^2
357 suggesting that the number of interstitial Leydig cells was unchanged (290). In female rats,
358 LPS (*Salmonella enterica*) administration on PND 3 and 5 had direct effects on 712 genes in
359 the ovaries, which are implicated in inflammatory responses, reproductive system
360 development, and immune cell-signalling. Further analysis revealed that several canonical
361 pathways involved in immune regulation and inflammation were activated in the ovaries in
362 response to neonatal infection, including nuclear factor kappa B (NFκB) and mitogen-
363 activated stimulating protein kinase (MAPK) signalling. Protein expression analysis of
364 multiple components of the MAPK pathway revealed that TLR4 expression was increased in

neonatal ovaries of LPS-treated rats (258). Elevated ovarian TLR4 expression has been associated with blunted follicular growth and function in cows (113). Collectively, these findings indicate that innate immune system activation, using 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 (113, 290).

Interestingly, cross talk between the HPG and the HPA axis influences the sex-specific physiological response to infection (Figure 3). Shanks *et al*., (248) examined the influence of gonadectomy on endotoxin (*Salmonella 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 controls. This effect was not evident in males (248). 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 (248). 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.

4.3.2 Neonatal sepsis and the HPG axis in later life

4.3.2.1 Neonatal sepsis, peripheral gonadotrophins and steroid hormones in later life

Early life infection not only supresses 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 (Figure 3). LH and FSH concentrations were depressed in female adolescent rats following LPS administration on PND 3 and 5 (257, 290). The surge in LH concentrations during mating, was significantly diminished in rats of both sexes, which had been injected with LPS on PND 3 and 5 (290). Following 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 (157). 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, which were only treated with saline in early life (127). 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 (127, 290). Female rats injected with *Salmonella enteritidis* on PND 3 and 5 exhibited reduced circulating progesterone and had higher circulating testosterone as adults (200). 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 (257, 290). Adult rats also display substantial changes in peripheral hormone concentrations in response to single and dual immunological challenges (127, 290). Accumulating evidence reveals that low progesterone concentrations evident in

412 female adult rats following exposure to LPS on PND 3 and 5 (200), is associated with
413 homeostatic imbalance, including decreased leptin secretion, insulin sensitivity and altered
414 lipid and glucose metabolism, resulting in reduced energy expenditure. The role of
415 progesterone in metabolism, fused with its established neuroprotective and anti-
416 inflammatory properties, further highlights the hormone's beneficial function beyond sexual
417 behavior (35). Furthermore, high testosterone, evident in female adult rats following LPS
418 exposure during the neonatal period (200), increases risk of obesity and insulin sensitivity in
419 females (192, 233). In contrast, low testosterone concentrations, evident in male adult rats
420 exposed to neonatal LPS, predisposes males to metabolic syndrome, increased insulin
421 sensitivity, systemic inflammation and obesity (192). Long-term shifts in peripheral
422 gonadotrophins and steroid hormone concentrations as a result of an early life immune
423 challenge will disturb other integrated physiological homeostatic systems, resulting in
424 adverse consequences for whole-body health.

425 **4.3.2.2 Neonatal sepsis, puberty and reproductive function in later**
426 **life**

427 Immune activation early in life potentially alters the control of gonadotrophic hormone
428 release and therefore the onset of puberty and reproductive function (Figure 3). LPS
429 administration on PND 3 and 5 led to a shift in the first day of puberty in male and female
430 rats, which was either earlier or delayed (145, 257, 290, 304). Additionally, mature female
431 rats displayed longer estrogen cycles in response to repeated LPS administration, firstly on
432 PND 10 and again in adulthood (128). These changes were not evident when neonatal rats
433 received LPS injection on PND 7-9 and 14-16, indicating that a critical period during early life
434 may exist in which an immune challenge may cause persistent dysfunction in the

435 reproductive system (128). Kisspeptin (Kiss1) has been identified as a fundamental signalling
436 protein that modulates the timing of reproductive development and gonadotropin secretion
437 (17). LPS administration on PND 3 and 5 resulted in reduced Kiss1 mRNA expression in the
438 medial preoptic area of female rats at the time of puberty (145), which may be associated
439 with the alteration in puberty timing and gonadotrophin secretion. LPS-induced Kiss1
440 suppression is potentially mediated by TNF-α (236). Male rats exposed to LPS, at PND 10 and
441 in adulthood, did not develop changes in Kiss1 mRNA expression in the hypothalamus,
442 which may offer a mechanism for sex disparity observed in adult LH concentrations (127). In
443 addition to delayed onset of maturation, neonatal LPS exposure, on PND 3 and 5 resulted in
444 impaired sexual performance in male and female adult rats (290). Furthermore, in adult
445 female rats, the follicle reserve was reduced and the thickness of the theca interna and
446 expression of p75NGFR increased as a result of neonatal (PND 3 and 5) LPS-injection (304).
447 Sperm presence was significantly decreased, and disorganized seminiferous epithelium was
448 evident within the testes in adult rats, which were challenged as neonates with LPS on PND
449 3 and 5 (290). In summary, neonatal exposure to LPS in rats disrupts long-term HPG axis
450 regulation, resulting in structural deficits to reproductive organs and disturbed maturation.
451 Neonatal infection therefore results in profound and long-lasting implications for puberty as
452 well as sexual performance, which may lead to reduced fertility in rodents. Although
453 infection is more common in males, long-lasting disruptions to HPG regulation are evident
454 regardless of sex.

455 Despite the significant research advances in rodents, to our knowledge there are no human
456 studies investigating the effects of innate immune system activation on sexual development
457 and reproductive success. Recent literature describe that in preterm infants, an energy
458 conserving hypometabolic state is implemented to achieve a balance between disease

459 tolerance and resistance that increases the chance of survival in the face of infection (93,
460 105, 242). This method of immunity leads to energy restrictions or competition of energy
461 between homeostatic physiological systems. Impaired HPG axis regulation may in part be a
462 result of shift in energy supply (93, 174), associated with elevated cortisol evident in rodent
463 models and preterm infants with LOI (58, 102, 277), which may disturb integrated whole-
464 body systems.

465 **4.4. Hypothalamic-pituitary-thyroidal axis**

466 Thyrotropin-releasing hormone (TRH) produced in the hypothalamus, stimulates the
467 anterior pituitary to release thyroid stimulating hormone (TSH). Thyroxine (T4) and
468 triiodothyronine (T3) are subsequently released from the thyroid gland in response to TSH.
469 T4 and T3 complete a negative feedback loop, acting on both hypothalamus and pituitary to
470 limit further secretion of TRH and TSH. After birth, the infant's thyroid gland is responsible
471 for providing a sufficient supply of thyroid hormones to promote nervous, reproductive and
472 cardiovascular system development, immune system regulation as well as energy
473 metabolism, growth and thermogenesis (205). Maturations of the HPT axis begins around
474 20 weeks of gestation, but is only completely mature close to full-term gestation (216). As
475 such, preterm infants have an immature HPT axis and limited capacity to generate thyroid
476 hormones (178). Pharmacological intervention with dopamine in the treatment of
477 hypotension can further suppress T4 concentrations in preterm infants (198). A recent study
478 suggests that thyroid hypofunction is indicative of an at-risk baby, that may be susceptible
479 to development of LOI (122). Thyroid hormone concentrations are significantly lower in sick
480 babies as described below (58, 102, 149, 227, 251).

Multiple studies report a reduction of serum T3, T4 and TSH concentrations in preterm and term newborn infants with LOI compared with healthy controls (58, 102, 149, 227, 251). Treating the primary infection with antibiotics normalizes serum thyroid hormone concentrations and as such, the infant experiences only a transient suppression in thyroid hormones concentrations in most cases (102, 149). Lower levels of T3, T4 and TSH were evident in non-survivors of sepsis, predicting an adverse outcome in these newborns (149, 251, 308) and a significant negative correlation was apparent between CRP and T3/T4 (102, 251).

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 hours post-exposure (172). Lower T3 and T4 concentrations were also evident in full-term non-surviving newborn foals with naturally occurring sepsis compared with foals that survived (117). In rats, the pro-inflammatory cytokine, TNF-α, rapidly reduces TSH secretion from cultured rat pituitary cells (295). 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 (135). Newborn thyroid hormone screening is conducted using 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 (151). Low levels of thyroid hormones and high risk of

504 neurodevelopment abnormalities in preterm infants supports the hypothesis that
505 neurodevelopmental problems in preterm infants are, at least in part, caused by low thyroid
506 hormones (11, 62). However, continuous debate exists regarding the effects of transient low
507 thyroid hormone concentrations on development. Other longitudinal studies display no
508 long-term adverse neurodevelopment outcomes in children or adults that suffered from
509 transient low thyroid hormones as newborns (65, 120).

510 Thyroid hormone deficiency results in reduced heart rate, prolonged systolic and diastolic
511 times and weakened inotropic function (283). Moreover, in adults with obstructive sleep
512 apnea, mean apnea duration significantly correlated with TSH; subjects with lower T3
513 showed longer mean apnea duration compared with those with higher T3 (273). Similarly,
514 an older study reported that severe hypothyroidism is associated with depressed ventilatory
515 drive during hypoxic and hypercapnic respiration (150). Adults with hypothyroidism often
516 suffer from disordered breathing (148). However, in patients with obstructive sleep apnea,
517 low thyroid hormones is not a common co-morbidity (137, 148). To our knowledge, there
518 are no studies assessing associations between thyroid hormones and cardiorespiratory
519 parameters in preterm or term infants with LOI. It would seem prudent to further extend
520 these investigations. Thyroid hormone concentrations may have the capacity to function as
521 biomarkers for neonatal sepsis diagnosis or at least stratify the patients at high risk. Large-
522 scale clinical studies assessing thyroid hormone concentrations in preterm and term infants
523 with sepsis could open avenues for diagnosis and lead to biomarker-guided adjunctive
524 therapy and precision medicine for treatment of clinical consequences of sepsis such as
525 pathophysiological cardiovascular control.

526 **4.5 Sickness behavior and melatonin, leptin and ghrelin**

527 **4.5.1 Neonatal sepsis and melatonin**

528 Melatonin is an endogenous anti-inflammatory and antioxidant indolamine, produced in the
529 pineal gland during darkness following acetylation and then methylation of serotonin (91). It
530 has many physiological functions including a fundamental role in sleep, reproduction and
531 circadian rhythm (48). Preterm infants are melatonin deficient compared with full-term
532 infants (28, 179). Maternal melatonin concentrations progressively increase after 32 weeks
533 of gestation and babies' levels likely rise in line with this (191, 274). Full-term infants usually
534 begin to produce melatonin around 3 months of age, resulting in a more regulated sleep
535 pattern. However, preterm babies may not produce melatonin until around 5-6 months,
536 depending on how early the infant was born (131, 140, 224). Although there is a paucity of
537 studies investigating the effects of LOI on endogenous melatonin concentrations in preterm
538 infants, one study reports melatonin was increased in full-term infants with LOI compared
539 with healthy control neonates (73). In septic and sedated adults in intensive care melatonin
540 is supressed (190, 206).

541 Interestingly, the magnitude of LPS-induced cachexia, lethargy, fever and anorexia (sickness
542 behaviours) are decreased in Siberian hamsters exposed to short-daylight compared with
543 long-daylight, presumably to conserve energy (298). LPS-induced fever was attenuated in
544 Siberian hamsters in response to 6 weeks of exogenous melatonin administration, which
545 also decreased body mass, exhibited gonadal regression and increased cortisol (27). It has
546 been suggested that melatonin influences components of sickness behaviour *via* complex
547 interactions with other endocrine hormones, such as glucocorticoids or sex steroid
548 hormones (27). Elevated melatonin during infection may be linked to energy conservation
549 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 (106, 226). In addition to its important role as an anti-oxidant, a recent study has illustrated the importance of melatonin in glucose regulation, improving sepsis-induced hyperglycemia in an animal model (43). 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 (71, 72, 76, 79, 96, 112, 215). In support of its amelioration in sepsis, a recent clinical trial has demonstrated improved patient outcomes when used as an adjunctive therapy in adult sepsis (3).

4.5.2 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 weeks of postmenstrual age (195, 261). This prolonged period of low leptin concentrations may preclude sufficient adipose tissue or functional maturity (261). 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 (74, 204). 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 two weeks, returned leptin concentrations to values similar to that of control infants (204).

573 Normalization of leptin with antimicrobial treatment, suggests a short-term surge in leptin
574 concentrations in response to infection. Specifically, the elevated leptin state may be
575 associated with sickness behavior evident in sepsis. In adults, an increased leptin
576 concentration has been observed in patients with severe sepsis. Leptin was however
577 positively correlated with survival which could indicate the beneficial role of leptin in the
578 host defence mechanism against bacterial infection (13, 25, 129). In rodents, leptin anti-
579 serum treatment attenuated LPS-induced fever and anorexia (107, 232). Additionally, leptin
580 administration to rats results in increased body temperature, which can be abolished by an
581 IL-1 receptor antagonist (161), suggesting that pro-inflammatory cytokines released in
582 response to leptin mediate its actions on the hypothalamus.

583 **4.5.3 Neonatal sepsis and ghrelin**

584 Ghrelin is well known as a 'hunger hormone' and plays a role in insulin resistance, energy
585 homeostasis and heart disease (217). Furthermore, ghrelin also displays anti-bacterial and
586 anti-inflammatory activity and suppresses pro-inflammatory cytokine production (44, 303).
587 Ghrelin is decreased in plasma, but increased in cord blood in preterm newborns, compared
588 with term infants (26, 195). Ghrelin is suggested to originate from the maternal
589 compartments, secreted by the placenta or produced by fetal tissue, but the source of
590 ghrelin during fetal life is not well defined. As such, the underlying cause for difference in
591 ghrelin concentrations in preterm compared with term infants is unknown (54, 144).
592 However, it is plausible that disruption to synthesis or/and the clearance rate of ghrelin
593 occurs in preterm infants (237).

594 Plasma ghrelin was significantly increased in full-term neonates with sepsis compared with
595 healthy controls. In this population, ghrelin values higher than 1.4ng/ml on admission

596 accurately indicated infection with sensitivity and specificity between 70-75% (255).
597 Similarly, elevated ghrelin concentrations are also evident in adults with septic shock (199).
598 Interestingly, a significant association was evident between ghrelin concentrations and the
599 duration of fever in neonates i.e. ghrelin levels decreased in infants whose fever improved
600 within 36 hours and increased in infants who were febrile for more than 36 hours (255). This
601 association may be related to fever mediators such as cytokines, as it has been previously
602 reported in adults that ghrelin peaks 30 minutes after the peak in TNF-α (286). Additionally,
603 an anti-pyretic role of ghrelin cannot be discounted. In adult rats, LPS administration
604 combined with intraperitoneal injection of ghrelin reduced fever (259). Furthermore, ghrelin
605 was significantly higher in adult rats with septic shock, who were hypotensive and displayed
606 hypoglycemia and elevated lactate concentrations compared with control animals.
607 Interestingly exogenous administration of ghrelin in these rats resulted in elevated blood
608 pressure and plasma glucose, as well as a reduction in plasma lactate compared with septic
609 shock rats that did not receive treatment (40). To our knowledge there are no studies
610 investigating the effects of sepsis on ghrelin concentrations in preterm infants. Currently the
611 precise role of elevated ghrelin during sepsis is unknown, but with further research, ghrelin
612 has potential to serve as a diagnostic marker for the identification of infection. Although this
613 area of research is in its infancy melatonin, ghrelin and leptin concentrations in infants with
614 sepsis may offer therapeutic value for treatment of sickness behavior in sepsis.

615

616 5. Immunometabolism

617 Dramatic shifts in metabolism occur in response to immune activation (201). In turn, precise
618 changes in metabolic pathways alter the immune response (53) (Figure 4). Intracellular

619 metabolic processes are vital for homeostatic function in whole-body health and disease.
620 Interconnected metabolic pathways, such as fatty acid synthesis and oxidation, glycolysis,
621 amino acid pathways and the Krebs cycle play a fundamental role in the production of
622 energy and multiple biosynthetic intermediates essential for the promotion of innate
623 immune cell survival, proliferation, function and sustained activation. Typically, activation of
624 immune cells through PRRs upregulates hypoxia-inducible factor 1α, resulting in a shift of
625 cellular energy metabolism from fatty acid oxidation and oxidative phosphorylation to
626 glycolysis, known as the 'Warburg Effect' (aerobic glycolysis)(208). This redistribution of
627 supply/demand is required to provide a rapid burst in energy (i.e. ATP) (53, 146).
628 Furthermore, glycolytic metabolism plays an essential role in providing metabolic
629 intermediates (e.g. glucose-6-phosphate) for interconnected pathways (e.g. pentose
630 phosphate pathway) to promote inflammatory responses (53). This shift to glycolytic activity
631 is an essential step of immune-metabolic crosstalk to minimize harm from pathogens (174).

632 **5.1 Energy reserves in preterm infants**

633 Energy availability is paramount for preterm infants as the basal energy requirements for
634 growth and development are significant. Metabolic pathways regulate the inflammatory
635 status with important implications for survival (105). Although sustaining an adequate
636 immune response requires high glycolytic activity, substantial fatty acid metabolic flux is
637 necessary in order to regulate inflammatory responses and provide sufficient energy to host
638 tissues (201, 208). Adults rely on protein and lipid stores to provide energy to protect the
639 host without diverting supplies necessary for critical physiological processes, at least until
640 late-stage infection. A 150% increase in resting energy is evident in adults during bacterial
641 infection, allowing the adult immune system to execute efficient infection resistance

mechanisms (174, 282). 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 3rd trimester of gestation, therefore preterm infants have very limited storage (105, 254, 282). Ideally, the ability to maintain homeostasis during infection is a balance between inflammation and aerobic glycolysis (disease resistance) with fatty acid metabolism and immunosuppression (disease tolerance) (Figure 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 (105). The concept of integrated metabolic strategies utilized in a changing environment of supply and demand, is reviewed by eloquently by Ye and Medzhitov (307). 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 will discuss immune-mediated changes in glucose, lactate and a selection of amino acids in the following subsections of the review.

5.2 Glucose

Glucose is a vital nutrient for physiological homeostasis and brain function. 20% of glucose-derived energy is consumed by the brain, due to neuronal and non-neuronal cellular maintenance requirements as well as production of neurotransmitters (78). Tight regulation of glucose is crucial for whole-body homeostasis. In premature infants, hypoglycemia (low blood glucose) and hyperglycemia (elevated blood glucose) often occur due to 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) (61, 114, 250). The risk of dysregulated glucose metabolism increases in response to infection (61).

665 Associations between blood hyperglycemia and LOI are evident in very low body weight
666 infants of mean gestational age of 30 weeks (4, 136). Similarly, late preterm infants (32-37
667 weeks) with LOI have elevated urine glucose concentrations (glycosuria) and hyperglycemia
668 compared with age-matched preterm controls (83, 235). Elevated glucose levels are also
669 evident in serum samples collected from term infants with sepsis compared with healthy
670 term infants (182). Although, low blood glucose can also occur in preterm babies with LOI
671 (75), longitudinal studies reveal that hyperglycemia is more common than hypoglycemia in
672 preterm and very low body weight infants with LOI (29, 42). In rats, reduced plasma glucose
673 concentrations are evident at PND 10, 7.5 hours after injection with endotoxin (*Salmonella*
674 *enteritidis*) (86). Rats challenged with endotoxin (*Salmonella enteritidis*) on PND 3 and 5
675 display reduced glucose concentrations by 8 hours post-injection, which remains
676 significantly reduced until 8 hours post-injection on PND 5 (292). LPS and LTA in
677 combination with hypoxic ischemic injury to rats at PND 7 resulted in an initial increase in
678 glucose at 2 hours followed by hypoglycemia, which lasted for 24 hours (70). These studies
679 in rodents demonstrate a biphasic glucose response to LOI. Discrepancies between rodent
680 and human studies may be a result of timing of glucose assessment after the onset of sepsis.
681 Glucose supplementation after LPS-induced infection in the rat was associated with
682 decreased survival (293). Additional studies are required to determine if a biphasic glucose
683 response occurs in preterm infants with LOI and understand the neonatal survival strategies
684 underlying altered glucose.

685 Stress-induced hyperglycemia is a common clinical entity that occurs alongside an acute
686 illness (183). Elevated cortisol, which occurs in preterm infants with LOI, promotes hepatic
687 gluconeogenesis and glycogenolysis (134). These pathways utilize a variety of non-glucose
688 precursors such as lactate, glycerol and amino acids (alanine and glutamine) to form glucose

689 (134, 142). Thus, it is plausible that elevations in blood glucose levels of preterm infants with
690 LOI develops due to increased production of stress hormones, in particular cortisol (183). In
691 the adult system, a feedback cycle occurs – high glucose levels induce a pro-inflammatory
692 state, including both cellular oxidative stress and inflammation (57). Glucose increases pro-
693 inflammatory transcription factors (early growth response, intranuclear NFκB binding and
694 activator protein-1) and reactive oxygen species abundance and reduces nitric oxide
695 availability. Furthermore, hyperglycemia alters the innate immune system causing
696 decreased neutrophil activity, which results in reduced chemotaxis, phagocytosis and
697 bacterial killing (18, 57, 279), reducing the efficacy of the host immune system in fighting
698 the infection (Figure 2). Heightened glucose utilisation (i.e. glycolysis) and/or reduced
699 glucose production alongside diminished energy reserves in preterm infants is likely
700 responsible for LOI-induced hypoglycemia in preterm infants (105). Of note, some studies in
701 adults suggest that either insulin therapy or lower glucose levels are anti-inflammatory (51).
702 Others report that in human adults acute hypoglycemia promotes platelet-monocyte
703 interactions, increases platelet reactivity and pro-inflammatory cytokines, and potentiates
704 responses to endotoxins (97, 125). It is likely that shifts in glucose homeostasis due to sepsis
705 further exacerbate the inflammatory status of the infant; treating glucose disturbances to
706 maintain adequate availability may be all-important for the host in order to improve the
707 ability to successfully recover from infection.

708 Hyperglycemia and hypoglycemia are independent risk factors for early mortality. Infants
709 will hypoglycemia and hyperglycemia are often subjected to extended hospital stays (6, 110,
710 243, 281). Untreated and/or persistent hyperglycemia is associated with intraventricular
711 haemorrhage, retinopathy of prematurity, as well as neurological and behavioural
712 development abnormalities (15, 95, 110, 281). Complications of neonatal hypoglycemia

include visual impairment, cerebral palsy and other cognitive dysfunctions (12, 37, 110, 141).

As untreated hypoglycemia and hyperglycaemia 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 (301). Blood glucose is often measured very frequently (every 4hrs) when an infant has hypoglycemia/hyperglycaemia. The implementation of continuous glucose monitoring systems, which measure glucose concentration in interstitial fluid is currently being piloted in some NICUs (55, 244). However, this technique is not widely used and several technical issues need to be resolved before routine use in neonatal care (225). Implementation of continuous glucose monitoring would offer the possibility of adjusting glucose concentrations in real time while decreasing the number of blood tests required (92). 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 (183), but the absence of evidence-based guidelines for safe insulin therapy leads to ongoing uncertainty (202). There are many pharmacological agents used to treat neonatal hypoglycemia, including continuous dextrose infusion and oral diazoxide administration (271), but further research is required to investigate the optimal treatment approach.

5.3 Lactate and vitamin B complex

Like glucose, lactate is a ubiquitously produced and utilized metabolite, critical to many energy-related metabolic pathways (94). It is the normal end-product of glycolysis and can be formed from pyruvate. In late preterm infants (32-37 weeks of gestational age) with LOI,

736 increased pyruvate (urine) and lactate (urine and blood) concentrations are reported (235).
737 Similarly, term infants with sepsis have elevated serum and urinary lactate concentrations
738 compared with control groups (83, 182). In rats at PND 7, LTA and LPS in combination with
739 hypoxic injury resulted in elevated serum lactate concentrations from 6 to 10 hours after
740 LPS administration (70). Elevated serum lactate concentrations, indicative of metabolic
741 acidosis is a laboratory sign of sepsis in neonates and adults (10, 60, 88, 269).
742 Hyperlactatemia is associated with poor prognosis for survival (213). Traditionally,
743 hyperlactatemia is related to anaerobic glycolysis induced by tissue hypoxia (90). More
744 recently, it has been proposed that increased lactate production is associated with
745 metabolic shifts i.e. decreased mitochondrial oxidative metabolism (oxidative
746 phosphorylation) or increased protein breakdown (94).

747 Interestingly, preterm infants with LOI had decreased urinary concentrations of vitamin B
748 complex including nicotinamide, thiamine and riboflavin compared with healthy controls.
749 These vitamins are precursors and coenzymes of several metabolic pathways (235).
750 Thiamine plays an important role in multiple enzymatic pathways involved in brain function
751 as well as myelin synthesis, nerve signal modulation and tissue repair. Thiamine is also
752 suggested to have anti-inflammatory effects, reducing activation of NFκB (165). It functions
753 as a cofactor for the multi-enzyme pyruvate dehydrogenase complex that converts pyruvate
754 to fuel oxidative phosphorylation. Therefore, reductions in thiamine coincide with
755 elevations in lactate concentrations; thiamine deficiency results in the conversion of
756 pyruvate to lactate and is a known cause of lactic acidosis (63). To our knowledge, vitamin B
757 complex levels are not routinely assessed in neonatal care. Nevertheless, recently several
758 human clinical studies have explored the effects of thiamine administration as an adjunctive
759 therapeutic agent in septic shock (187, 297, 302). 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 controls (297, 302). Furthermore, a randomized cross-over trial in adults revealed that thiamine administration reduced blood pressure in hyperglycemic patients (5, 108). 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 (167). Although, investigations assessing the role 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 (187).

5.4 Amino acids

Glutamate, the most abundant amino acid in the human body, plays an important role in protein metabolism and lies at the crossroad 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 (194). Functions of glutamate products are well established, including antioxidant defence (glutathione) and inhibitory neurotransmission (GABA). Glutathione metabolism was markedly altered in preterm infants with early onset sepsis (166). Glutamate concentrations are increased and decreased in urine and stool samples, respectively, in preterm infants with LOI (235, 263). Discrepancies between studies may relate to the gut microbiota configuration as glutamate is produced by several bacterial species. Colonisation of the gut with pathogens associated with sepsis may create a host environment, which shifts the competitive determinants deployed by a particular bacterial species (115). This may have potential to induce changes

783 in the metabolomic profile. Additionally, antibiotic regimens/dosage administered to infants
784 with LOI can deplete the gut microbiota and shift overall metabolic function. Furthermore,
785 shifts in glutamate concentrations may be related to direct effects of glutamate dietary
786 intake in preterm babies, which may not be uniform across NICUs (20). Noteworthy, oral
787 glutamine supplementation (enteral including oral or nasogastric administration in
788 formula/breast milk and parenteral such as central venous catheter delivery) during sepsis
789 did not have any significant benefit in preterm infants with and without sepsis (186).
790 However, in the latter systematic review, the authors provided some limited evidence that
791 enteral glutamine supplementation decreases the time to reach full enteral nutrition and
792 rate of late-onset invasive infection in preterm infants (186).

793 The amino acids valine and phenylalanine are significantly elevated in urine samples of late
794 preterm infants with LOI (235), implying disturbed protein metabolism or protein catabolism
795 in LOI, which is closely related to activities of cytokines and inflammatory mediators (268).
796 Although changes in valine and phenylalanine along with many other amino acids are also
797 evident in adult patients with sepsis (118), this shift may be more detrimental to the
798 preterm infant given their limited protein reserves. Elevated cortisol, if prolonged, can
799 reduce the incorporation of amino acids into proteins resulting from cortisol-induced
800 inhibition of protein synthesis or increased protein breakdown (80, 256). In preterm infants
801 with LOI, elevated cortisol may cause an increase in urinary amino acid concentrations.
802 Furthermore, amino acids are precursors of gluconeogenesis (134); increased amino acid
803 concentration may in part contribute to stress-induced hyperglycemia evident in preterm
804 infants with LOI (83, 235) (Figure 2).

Taurine and hypotaurine are significantly elevated in urine samples of late preterm infants with LOI (235). 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 (Schaffer and Kim 2018). Taurine has long been recognized to play a role in energy metabolism, gene expression, neuromodulation and osmoregulation (238). In addition, taurine and its analogues have been observed to exert antioxidant and anti-inflammatory properties, involving taurochloramine formation in neutrophils or reduction of prostaglandin E2 (14, 223). Although taurine is not routinely monitored in neonatal or adult sepsis, clinical studies in adults report taurine administration results in decreased blood pressure and left ventricular end-diastolic volume along with improved cardiac function (16, 130, 184). The precise mechanism of taurine inducing anti-hypertensive effects is unknown, but studies in animals suggest that it may be related to decreased oxidative stress, elevated hydrogen sulphide content, suppression of the sympathetic nervous system and increased nitric oxide production (138, 270). Furthermore, taurine has been shown to protect cardiomyocytes by activating ubiquitin-proteasome system (305). Further studies are required in this area to investigate the role of increased hypotaurine and taurine concentrations in preterm infants.

5.5 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, anti-oxidative and anti-inflammatory

828 effects (176). In urine samples of late preterm infants with LOI, metabolomic analysis
829 revealed that fumaric acid is significantly reduced (235), which may indicate defective
830 operation of the Krebs cycle. Galactose is derived from dietary sources and enters glycolysis
831 by converting to glucose-1 phosphate (50). Galactose metabolism was the most frequently
832 reduced pathway in stool samples of preterm infants with LOI; sucrose and raffinose were
833 the most frequent metabolites affected (263). Galactose metabolism was also altered in
834 urine samples as a result of LOI in preterm infants (235). Inosine is a naturally occurring
835 purine, formed from adenosine breakdown by adenosine deaminase. It has been shown
836 that inosine inhibits the release of pro-inflammatory cytokines and chemokines and has
837 anti-inflammatory effects (170). Urinary inosine was increased in premature babies with LOI
838 compounds (235). Interestingly, exogenous inosine administration reduced inflammation,
839 vascular dysfunction and organ damage, increasing survival in mice exposed to septic shock
840 (163, 164). Although, it should be postulated with caution, elevated inosine concentrations
841 may offer protection during LOI in premature babies (158). However, further research is
842 required in infants to identify and quantify changes of these specific metabolites and others.
843 This may be achieved using recent advances in high-throughput sequencing and multi-omic
844 approaches.

845

846 6. Multiomic approaches for identification of neonatal sepsis

847 Significant advances have been made to develop both laboratory and clinical diagnostic
848 criteria for identification of neonatal sepsis. However, the ability to promptly and accurately
849 diagnose neonatal sepsis using current laboratory and clinical criteria remains challenging.
850 Currently, there is no single diagnostic test that satisfies the criteria of an ideal biomarker.

851 Advances in high-throughput molecular technologies, including metabolomics, proteomics
852 and transcriptomics seem promising methods to determine distinct metabolic and
853 proteomic biomarkers as well as transcriptional signatures that occur at on the onset of, or
854 during sepsis (64, 100, 197, 275). Metabolomics, a relatively new bioanalytical approach,
855 studies the complete set of low-to-intermediate molecular weight amino acids, lipids,
856 carbohydrates and other metabolites generated by interactions between the environment,
857 the gut microbiome and the host genome. This allows for the immediate identification of
858 endogenous and exogenous metabolites, which is useful to establish metabolic
859 perturbations that may occur during infection (64). A recent case-control study revealed a
860 distinct metabolic profile in infants at birth that were subsequently diagnosed with early
861 onset sepsis (166) highlighting its potential impact in early therapeutic intervention. There
862 are challenges with establishing consistent metabolomic profiles, however using large data
863 sets it is possible to improve the application of metabolomic technology to generate reliable
864 tools for diagnosis, prognosis and treatment (294). Although, proteins such as CRP are
865 currently used clinically to identify neonatal sepsis, this biomarker is not sufficiently
866 sensitive or specific for accurate diagnosis. Identification of additional proteins that are
867 altered due to sepsis may improve accuracy. Mass spectrometry proteomics has the ability
868 to screen thousands of proteins to establish abundance and post-translational
869 modifications. Identification of specific changes in proteomics may lead to the development
870 of optimized and validated assays for bench-top mass spectrometers that can be used in the
871 clinical setting, including the NICU (160). Currently, there are several problems and
872 challenges that will need to be overcome before the introduction of mass spectrometry
873 proteomics to clinical settings. These include volume of data, testing and validation of
874 computational methods, as well as the complexity of algorithms rendering unbiased

875 comparisons (240). The induction of powerful transcriptome tools including microarrays and
876 next-generation sequencing, in particular RNA-sequencing such as single-cell and micro
877 RNA-sequencing, has increased the ability to examine gene-expression during infection.
878 Although, there have been no studies using RNA-sequencing to identify transcriptional
879 signatures for diagnosis of neonatal infection, it has shown potential in adults (210).
880 Transcriptional profiling allows measurements of thousands of genes simultaneously, which
881 could lead to the identification of a cell-specific gene signature(s) for diagnosis of neonatal
882 sepsis (197). However, there are substantial challenges relating to downstream and
883 upstream processes of translating next-generation sequencing into a bedside clinical tool.
884 These challenges include extensive sample processing for nucleic acid extraction and library
885 preparation for sequencing, as well as large data storage requirements. Furthermore, RNA-
886 sequencing is limited by high cost and time, 16-48 hours are required for sample collection-
887 to-quantification compared with 2 hours using qRT-PCR. Future studies are required to
888 address challenges of integrating multi-omic data with current clinical and laboratory
889 markers to translate the knowledge used for diagnostics to precision medicine for treatment
890 of neonatal sepsis (275). A study by Langley et al. (152) integrated both clinical features with
891 seven metabolites into an algorithm that predicted survival in adults. This combined
892 approach may improve accuracy of potential algorithms employed. Employing machine
893 learning to available neonatal clinical data has the potential to reveal novel biosignatures
894 and distinct populations as already explored with adult patient data (312). Precision
895 medicine would provide tailored treatment and therapy to patients based on measurements
896 obtained at an individual level, using data retrieved from the population. This will allow for
897 accurate and personalized therapeutic interventions that would improve outcomes. For
898 precision medicine to be implemented it relies heavily on biomarker-driver approaches for

899 diagnosis. Fortunately, multi-omics appears to be leading in the race to clinical application in
900 paediatric health (22, 59, 262), which is a key driver in efforts to achieve precision medicine
901 healthcare, derived from personal data, contributing to the future of medical practice
902 (Figure 5).

903

904 7. Summary and conclusion

905 Several lines of enquiry converge to confirm that sepsis in preterm and term babies and
906 animal models of similar development stages induce significant disturbances to intertwined
907 neuroendocrine and metabolic pathways. The precise clinical consequences of these
908 changes are not fully elucidated. Furthermore, it appears that sepsis during critical early-life
909 periods, perhaps distinct in male and females, leads to an inescapable cycle that results in
910 long-lasting impairments in later life. Emerging findings of neonatal sepsis-associated
911 changes in metabolites and hormones described in this review may serve as biomarkers and
912 have potential to be instrumental in improving early diagnosis of sepsis in neonates.
913 Biomarker-guided therapy may offer a reduction in antibiotic use and present increased
914 opportunities for targeted empirical and adjunctive therapies to treat infection-induced
915 physiological derangements in infants or indeed provide an opportunity for early
916 stratification of infants at risk, which may reduce both morbidity and mortality within the
917 NICU. Furthermore, early diagnosis and biomarker-guided therapy may help reduce long-
918 lasting deficits that are apparent in later life. Much work, including large-scale controlled
919 clinical trials are required, to provide an evidenced-based platform for the study of
920 infectious epidemiology and sex-specific initiation and progression of neonatal sepsis. The
921 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. Multi-omic technologies are essential to efforts of 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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Figure 1. Reported endocrine and metabolic changes in term and preterm infants with sepsis. Novel bio-signatures, validated in term and preterm infants would guide improved diagnosis, prognosis and therapeutic intervention. CRP- C Reactive Protein; TSH, Thyroid Stimulating Hormone; T3, Triiodothyronine; T4, Thyroxine. Figure created with BioRender.com

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 axis, hypothalamus-pituitary adrenal axis; PRR, pattern recognition receptor.

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 three and ten. FSH, Follicle Stimulating Hormone; LH, Luteinising Hormone; ACTH, Adrenocorticotropic hormone; TLR, Toll-Like Receptor. Figure created with BioRender.com

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 (21, 45, 56, 81, 126, 181, 278, 280, 311), 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.

1764 **Figure 5.** Summary of current and potential future approaches for diagnosis and treatment

1765 of neonatal sepsis.

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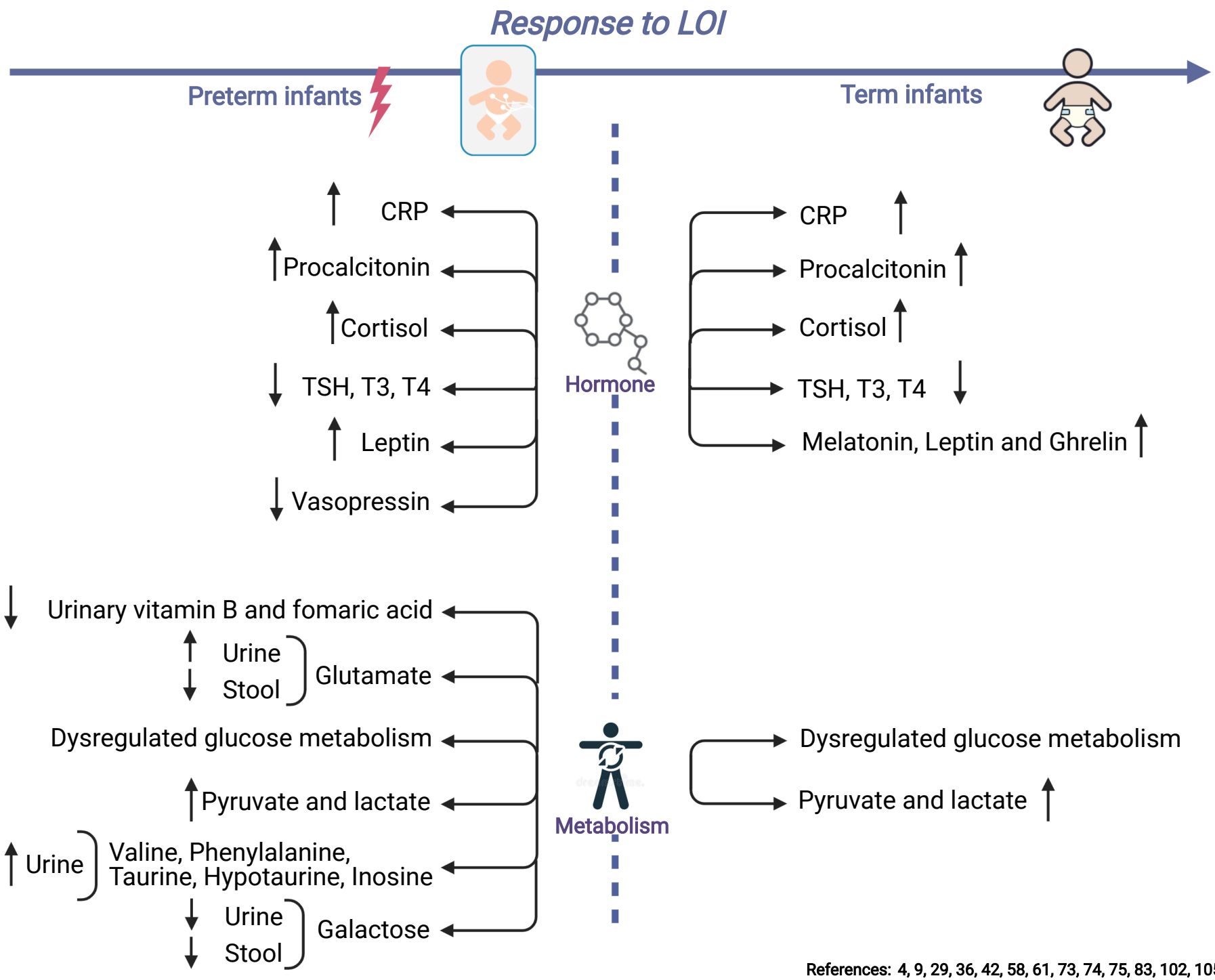
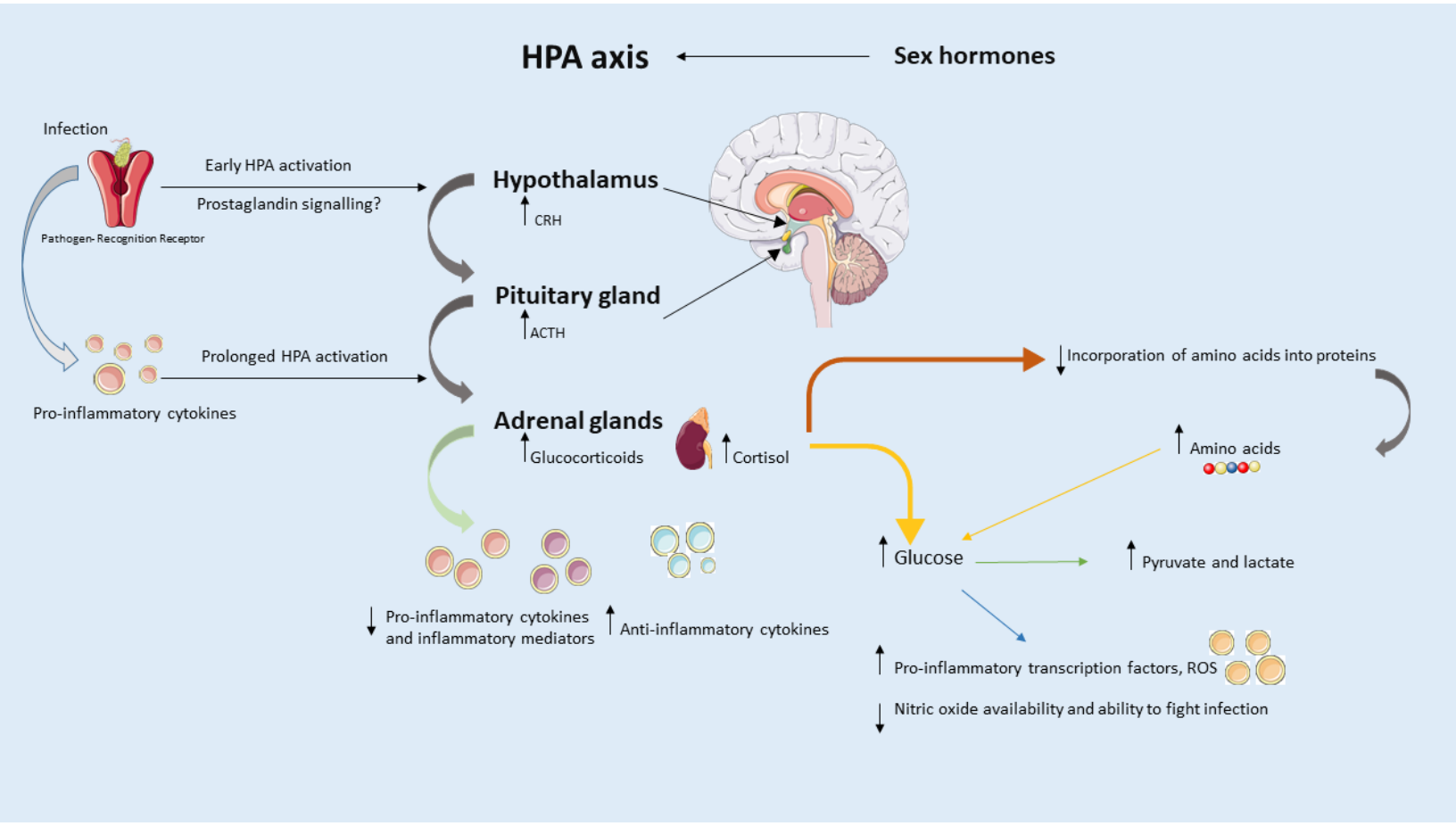
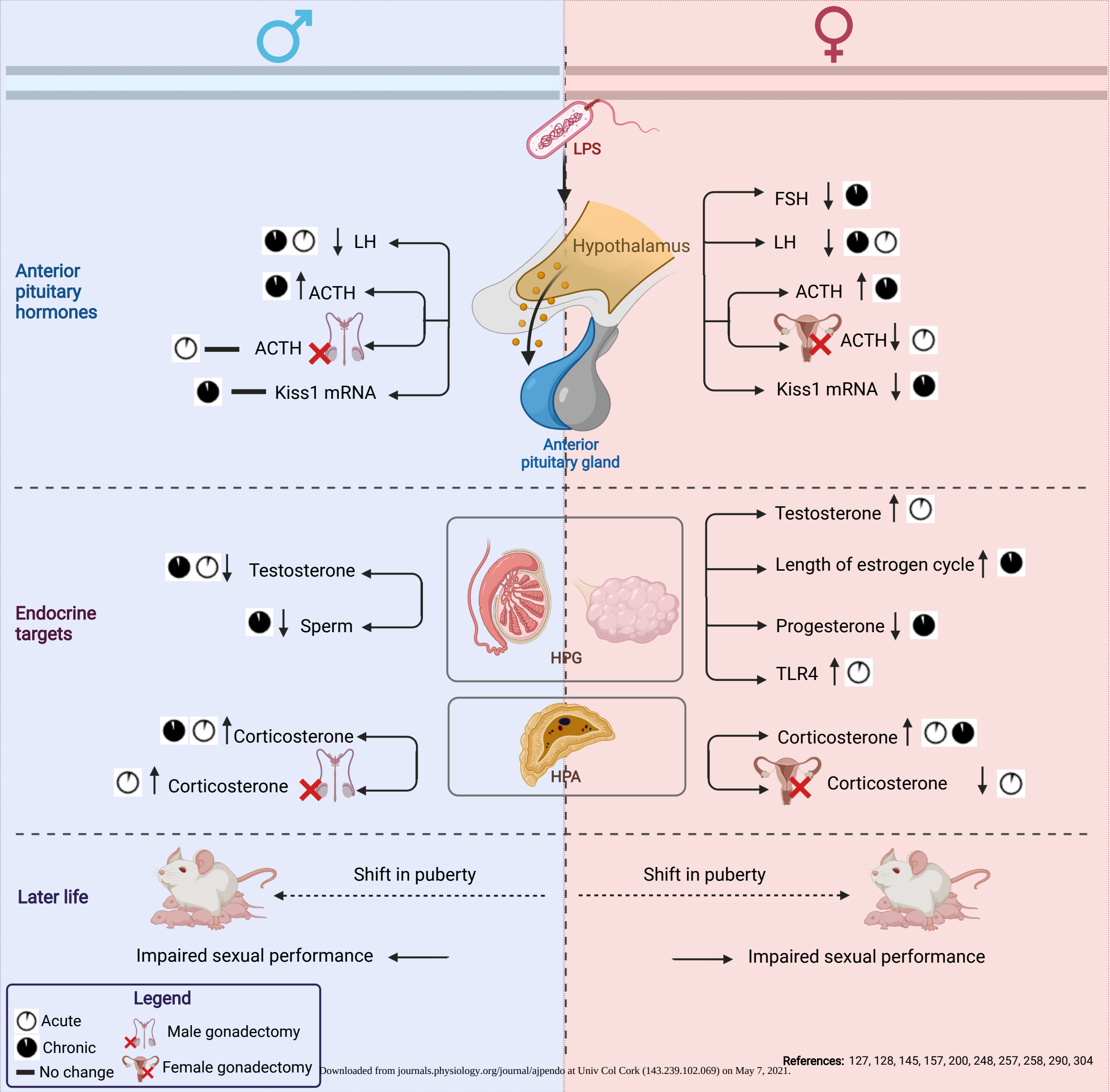


References: 4, 9, 29, 36, 42, 58, 61, 73, 74, 75, 83, 102, 105, 136, 149, 162, 182, 189, 204, 211, 227, 235, 251, 255, 263, 277





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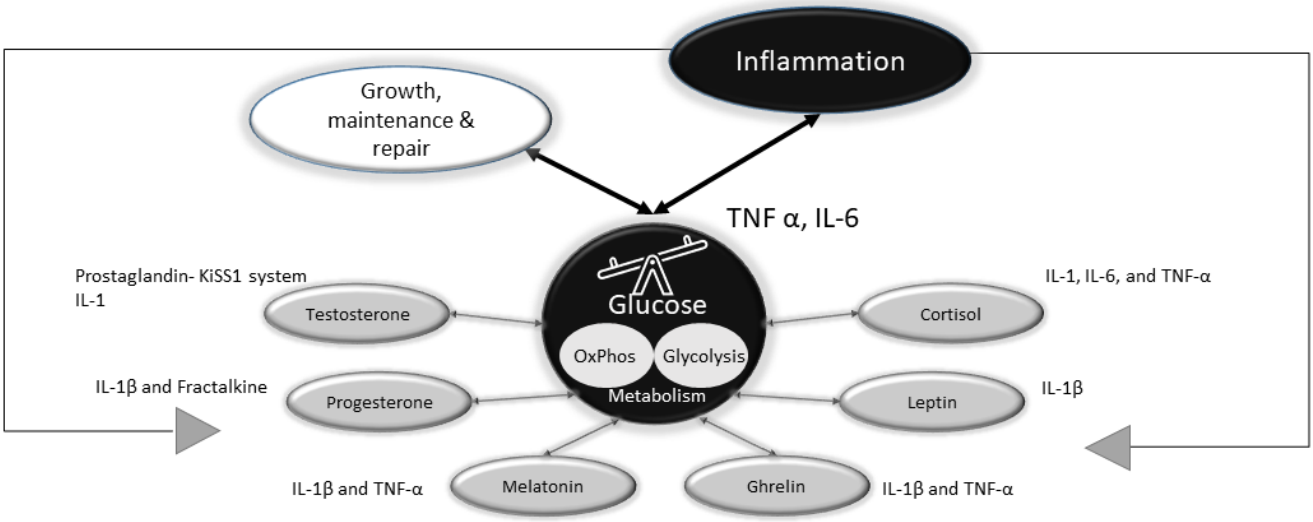


References: 21, 45, 56, 81, 126, 181, 278, 280, 311, 200,43, 40, 53, 78, 293, 183

Suspected infection

Laboratory data

Clinical data

One approach fits all to sepsis diagnosis.

Single biomarker screening

Empirical medicine

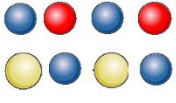
One approach fits all for empirical treatment of a sepsis diagnosis.

Suspected infection

Multiomic approaches

- Multiomic biomarker integrated.
- Rapid analysis of large data integrated into clinical decision making.

Biomarker signature



Stratified medicine

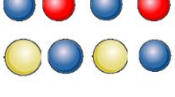
Stratified by clinical group.

Suspected infection

Bedside tools

- Early bedside multiomics screening for at risk infants.
- Continuous real-time measurements by the bedside.

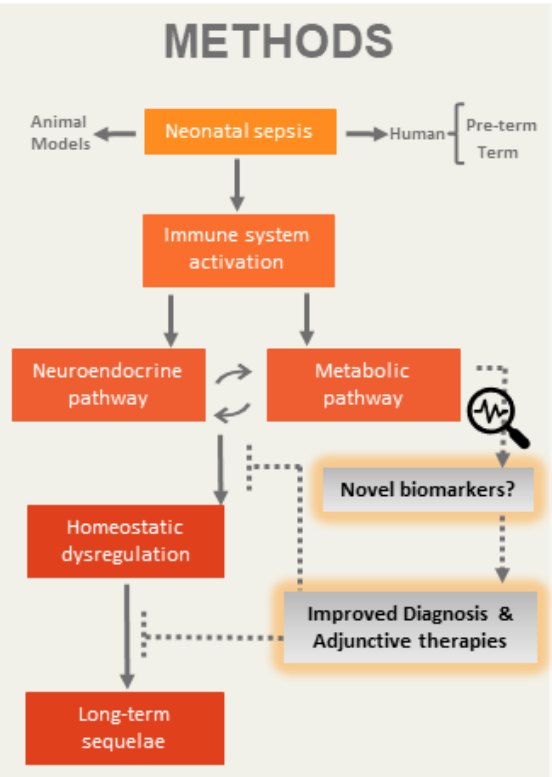
Early biomarker screening

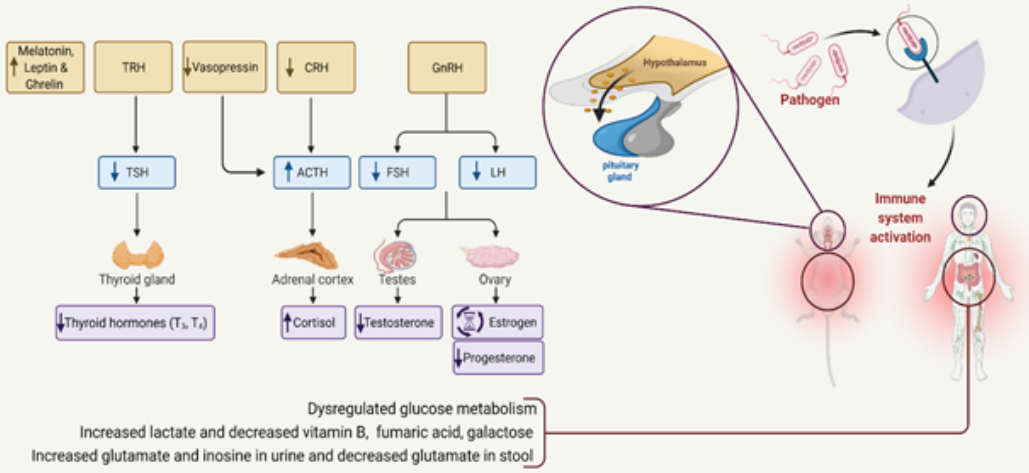


Precision medicine

- Specific biomarker-guided personalised therapy for an individual infant.
- Evolving treatment options due to continuous

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





CONCLUSION Sepsis in the neonatal period leads to short- and long-term disturbances in neuroendocrine and metabolic pathways. Novel biomarker-guided treatment approaches are required to improve diagnosis and use of adjunctive therapies.