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Authors

Underwood, Mark

Lakshminrusimha, Satyanarayana

Steinhorn, Robin

et al.

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Malnutrition, poor post-natal growth, intestinal dysbiosis and the developing lung

Mark A. Underwood[1], **Satyan Lakshminrusimha**[1], **Robin H. Steinhorn**[2], **Stephen Wedgwood**[1]

[1]Department of Pediatrics, UC Davis School of Medicine, Sacramento, CA, USA

[2]Department of Pediatrics, UC San Diego School of Medicine, La Jolla, CA, USA

Abstract

In extremely preterm infants, poor post-natal growth, intestinal dysbiosis and bronchopulmonary dysplasia are common, and each is associated with long-term complications. The central hypothesis that this review will address is that these three common conditions are interrelated. Challenges to studying this hypothesis include the understanding that malnutrition and poor post-natal growth are not synonymous and that there is not agreement on what constitutes a normal intestinal microbiota in this evolutionarily new population. If this hypothesis is supported, further study of whether "correcting" intestinal dysbiosis in extremely preterm infants reduces postnatal growth restriction and/or bronchopulmonary dysplasia is indicated.

Introduction

Malnutrition is not a designation often used in the care of preterm infants in developed countries, however poor growth after extremely preterm birth (often referred to as growth failure or extrauterine growth restriction or postnatal growth restriction, PNGR) is indeed common. A recent review noted that growth failure is "almost universal" among very preterm infants [1]; even when excluding very preterm infants who are small for gestational age at birth, the incidence of "true-PNGR" in a cohort of 411 infants born at less than 32 weeks was 43% at 36 weeks post-menstrual age and 15% at age 2–2.5 years [2]. Attempts to minimize PNGR in extremely preterm infants with early initiation of parenteral nutrition and trophic feeds, increased calorie intake and minimization of withholding of feeding have been marginally successful [3]. Cohort studies have demonstrated improved outcomes in very preterm infants with increased caloric intake in the first weeks of life [4, 5]. Deficient nutrient absorption in the immature intestine and the complications of parenteral nutrition combine to make optimum growth in the very preterm infant an ongoing clinical challenge and an area of active research.

For reasons that are not yet clear, PNGR in very preterm infants is associated with increased risk of lung disease, including bronchopulmonary dysplasia (BPD) and pulmonary

✉Mark A. Underwood, munderwood@ucdavis.edu.

Compliance with ethical standards

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hypertension (PH) [6, 7]. In a recent cohort, 79% of infants born at less than 28 weeks with severe BPD had a weight below the 10th percentile by 48 weeks post-menstrual age [8]. Whether poor growth causes or is the result of lung disease (or both) is challenging to determine from human studies and so preclinical models are valuable. We and others have utilized a rodent model of postnatal malnutrition, achieved by manipulating the number of pups cared for by a single dam [9, 10]. This model is useful as pre-weaning rat pups have an immature intestinal tract and immature lungs that are both comparable to those of premature infants born at 24–28 weeks gestation. We have shown in this model that malnutrition causes right ventricular hypertrophy (RVH), decreased numbers of pulmonary arterioles, increased medial wall thickness of pulmonary arterioles, and increased ratio of pulmonary artery acceleration time to ejection time (PAT/ET) - all of which are hallmarks of PH [10]. Moreover, exposure of pups to hyperoxia in this postnatal malnutrition model causes a more severe BPD and PH phenotype.

This rodent model has also allowed us to study the novel hypothesis that intestinal microbes influence lung development. We have shown that malnutrition causes intestinal dysbiosis (characterized by increased Enterobacteriaceae and decreased Lactobacillaceae) and that administration of probiotic *Lactobacillus reuteri* attenuates PH but does not improve weight gain [11]. Whether intestinal dysbiosis influences lung development in premature infants remains uncertain. In clinical trials and cohort studies of preterm infants, administration of probiotic microbes is beneficial, resulting in decreased mortality, decreased risk of necrotizing enterocolitis (NEC), improved feeding tolerance and decreased length of hospital stay, but no consistent impact on weight gain and no improvement in incidence of BPD have been demonstrated [12, 13]. In this review, we present the available evidence that there is an association between PNGR, intestinal development, intestinal dysbiosis and lung disease in very preterm infants with emphasis on new developments since a previous review by our group [14]. We also highlight gaps in current knowledge and areas of needed additional research.

Fetal growth restriction differs from postnatal growth restriction

Poor growth *in utero* (fetal growth restriction, FGR) and after birth (PNGR) are fundamentally different. In utero, nutrient accretion, gas exchange, and thermoregulation are guided by the mother and placenta; consequently FGR is typically the result of either maternal, placental or fetal disease. Pre-clinical FGR models utilizing either decreased maternal nutrition or decreased placental perfusion have demonstrated altered development of the gastrointestinal, pulmonary and cardiovascular systems. For instance, in a non-human primate model, maternal nutrient restriction during pregnancy and lactation resulted in right ventricular dysfunction in offspring including hypertrophy, decreased ejection fraction and decreased cardiac index [15].

There remains significant disagreement regarding whether the fetal intestinal tract becomes colonized with microbes in utero [16]. Examination of mid-gestation fetal small intestinal meconium demonstrated extremely low bacterial load near the limits of detection, however some of the identified bacteria appear to have immunomodulatory capacity [17]. While no compelling evidence suggests a role for fetal intestinal microbes in the development of the

lung parenchyma or vasculature, it is likely that maternal microbial metabolites cross the placenta and influence the developing fetal innate immune system and intestinal epithelium [18]. In a piglet model of FGR, the intestinal microbiota did not differ at birth between FGR piglets and normally grown siblings, however by 12 h of age there were differences in the composition of the fecal microbes with higher relative abundance of *Escherichia-Shigella* (family Enterobacteriaceae) and lower relative abundance of *Clostridium* (family Clostridiaceae) in FGR piglets suggesting differences in initial colonization [19]. In this study, the authors hypothesize that these differences are due to the observed altered intestinal morphology present at birth in FGR and lead to the observed higher expression of proinflammatory cytokines and lower expression of anti-inflammatory cytokines.

In PNGR, there is no placenta, the maternal role becomes provision of milk, microbes and non-nutritive nurturing, and microbes play an active role in nutrition both through assistance with digestion and provision of vitamins. Germ-free mice have poor growth after birth with altered development of many aspects of intestinal physiology, however they are protected from the negative effects of hyperoxia on the development of alveoli and the pulmonary vasculature, suggesting a role for airway microbes and/or gut microbes in BPD and PH [20]. Furthermore, clinical studies suggest that nutrient intake in the first days of life impacts long-term development. For instance, in a recent retrospective study of 130 premature infants, delayed initiation of enteral feedings until after the third day of life was associated with intestinal inflammation and an increased risk of BPD and retinopathy of prematurity [21]. In this study the infants fed later were sicker, smaller and more preterm, raising the possibility that in spite of the demonstration of significance in a logistic regression model, confounding effects may explain some of the association seen (and of course causality cannot be concluded from a retrospective cohort).

Although different in etiology, the consequences of both FGR and PNGR are amplified by preterm birth. The short-term consequences of either FGR or PNGR in preterm infants include increased risk for PH [22, 23], BPD [24], NEC, sepsis, retinopathy of prematurity [25], and neurodevelopmental delays [26]. In a rodent model of FGR followed by either catch-up growth or PNGR, the former group demonstrated PH and pulmonary artery remodeling at 14 weeks of life while the PNGR group demonstrated cognitive delays but not PH, suggesting that postnatal nutrition following FGR impacts the lung and brain differently [27]. The observed protective effect against PH of PNGR following FGR differs from the PH triggered by PNGR in our model underscoring the importance of the differences between FGR and PNGR and the potential importance of discovering optimal nutritional approaches for preterm infants with and without FGR.

Poor growth and chronic lung disease are both common in very preterm infants, and appear to be associated

There is disagreement as to how best to define malnutrition in the preterm infant. A recent statement by a large group of experts in the field of neonatal nutrition noted that any definition of PNGR in the very preterm infant that relies solely upon a weight that is less than the 10th centile at a specific time point is problematic in that it is by nature arbitrary,

not predictive of adverse outcome, does not consider head or length growth, proportionality, body composition, or genetic potential, ignores normal postnatal weight loss, and does not account for the normal growth slowing of the fetus that occurs around 36–40 weeks [28]. Overdiagnosis of postnatal malnutrition increases risk of excessive provision of nutrients. A comparison of a cross-sectional approach (single time points, e.g., 28 days of age, 36 or 40 weeks postmenstrual age, or day of discharge) to a longitudinal approach (changes over time) found the latter to be more predictive of head growth at age 24–30 months [29]. A definition of normal growth that accounts for a physiologic transition to a weight trajectory that is 0.8 z scores below the birth weight z score has been proposed based on a large international cohort [30] and an on-line calculator has been developed based on these data: https://www.growthcalculator.org/. In a recent cohort of 168 very preterm infants each decrease in weight by 1 z score from birth to 36 weeks correlated with a decrease of 5.6 points in the mental developmental index at 2 years of age [31]. While much of the clinical literature about PNGR in preterm infants relies on a definition that includes only a weight percentile at a given time point, it is clear that changes over time in weight, length and head circumference are of greater value in predicting outcomes and should be the gold standard for future studies [32].

Many very preterm infants progress to BPD, the devastating chronic lung disease of prematurity which is characterized by arrested development resulting in alveolar simplification [33]. The development of the pulmonary vasculature can also be impacted by prematurity resulting in decreased numbers of pulmonary arterioles with thickened medial walls resulting in pulmonary hypertension (PH) and right ventricular hypertrophy. Among U.S. infants born at less than 29 weeks the incidence of BPD is 42–68% [34]. The incidence of PH among extremely premature infants is as high as 18%, and rises to 25–40% in premature infants with BPD [35]. Among infants with BPD and PH, mortality rates by age 2 approach 50% [36]. Both BPD and BPD-PH are associated with poor growth [14].

Two studies mentioned in the introduction are noteworthy in demonstrating an association between poor growth and lung disease. First, in a retrospective review of 375 infants with severe BPD born at less than 28 weeks, 20% were below the 10^{th} percentile for weight at birth (FGR), while 79% had dropped below the 10^{th} percentile for weight by 48 weeks post-menstrual age [8]. Second, a retrospective case-control study found significantly decreased daily caloric and total fluid intake in the first four weeks of life among very preterm infants who went on to develop BPD compared to matched controls [5]. In addition, in a cohort of 296 infants born prior to 27 weeks, every 10 kcal/kg/d increase in energy intake between days of life 7 and 27 was associated with a reduced risk of BPD of 9% [37]. Clearly these are observational studies and can only address association not causality and are limited in their analysis of the impact of common confounders (sicker babies often receive fewer calories). We are aware of no study using propensity score analysis or randomization that has shown that increasing protein or calories early in very preterm infants decreases BPD.

Undernutrition as a major contributing factor to the pathogenesis of BPD was first proposed more than 30 years ago [38], and leaders in nutrition continue to note that growth failure in infants with BPD is predominantly due to malnutrition [39]. Improvement in post-natal weight gain over the past two decades has been demonstrated. For instance, among 362,833

infants with birth weight 510–1500 g at 736 hospitals in the US, the percentage of surviving infants below the 10th percentile at discharge was 64.5 in 2000 and 50.3 in 2013 and the percentage of surviving infants below the 3rd percentile dropped from 39.8% to 27.5% [40]. Concurrently, the incidence of BPD has decreased. A serial cross-section study demonstrated a decrease in BPD incidence among preterm infants born prior to 34 weeks gestation from 14% to 12.5% from 2003 to 2014 [41]. While several factors have contributed to this improvement (e.g., increases in non-invasive mechanical ventilation, more antenatal steroids, more surfactant, less NEC, less late-onset sepsis, and less postnatal steroids), it is likely that improved nutrition also plays a role.

Intestinal dysbiosis is common in very preterm infants and associated with poor growth, necrotizing enterocolitis and sepsis

Dysbiosis is defined as an alteration of the microbiota in a given anatomic niche that is associated with disease. Disease processes associated with neonatal intestinal dysbiosis are explored in the accompanying review article. The unique challenge in considering the intestinal microbiota of the very preterm infant is that this is an evolutionarily new population that was not able to survive prior to the late 20th century. Evolution has shaped the composition of human milk and the neonatal intestinal microbiota over millions of years to optimize survival of term infants, but this is not true of very preterm infants. The developing intestinal tract of the fetus at 22–28 weeks gestation was not designed or did not evolve under the influence of trillions of intestinal microbes, consequently, the normal or optimal intestinal microbiota of the very preterm infant is unknown and best approximated by comparing preterm infants with good growth and low morbidity to their smaller and sicker colleagues. Given the prolonged hospitalization necessary for the survival of extremely preterm infants, intestinal dysbiosis is almost universal in this population. In a cohort of 58 preterm infants with birth weight less than 1500 g (922 fecal samples), gestational age was the primary determinant of the composition of the microbiota at the class level with an early predominance of Bacilli followed by a predominance of γ-Proteobacteria from 28 to 34 weeks post-menstrual age followed by a predominance of Clostridia. This patterned progression was only marginally affected by mode of birth, antibiotics and feeding regimen (though there were only two exclusively formula-fed infants in this cohort) [42]. A similar pattern has been noted by others at the family level (early Staphylococcaceae replaced by Enterobacteriaceae replaced by Bifidobacteriaceae in term infants or Clostridiaceae in preterm infants) [43–45]. In a cohort of 95 preterm and 25 term infants, a delay in transition from Enterobacteriaceae to Clostridiaceae was seen in infants with poor growth; in this cohort there were significant effects of feeding type and antibiotics [44].

“Disrupted” maturation of the fecal microbiota was also seen in growth failure in a cohort of 58 very preterm infants with increased abundance of several genera of Enterobacteriaceae including *Citrobacter, Enterobacter, Serratia* and *Klebsiella* [45]. In a cohort of 83 very low birth weight infants, weight gain from birth to discharge was significantly negatively correlated with the relative abundance of two bacterial taxa, *Klebsiella* (family Enterobacteriaceae) and *Staphylococcus* (family Staphylococcaceae) [46].

Just prior to the onset of NEC, an expansion of γ-Proteobacteria/Enterobacteriaceae was observed in a meta-analysis of 8 observational studies [47], and may represent a microbial signature of epithelial dysfunction [48]. This is relevant in that both human milk feeding and probiotic administration have been shown to both alter the intestinal microbiota and decrease the risk of NEC without improving growth. Preclinical models of NEC have demonstrated the protective effects of several components of human milk including epidermal growth factor [49], lactoferrin [50], human milk oligosaccharides [51], and exosomes [52] as well as probiotic microbes [53] and the potentially harmful effects of triacylglycerols in infant formula [54].

Studies of late-onset sepsis in very preterm infants have demonstrated decreased microbial diversity and an abundance of Bacilli (particularly coagulase-negative staphylococci) prior to the onset of infection with the identical organisms responsible for sepsis often found in the feces [55]. Preclinical models have established causality with the demonstration of exacerbation and prevention of late-onset sepsis with eradication and enrichment of commensal *Lactobacillus* species respectively [56].

Severe acute malnutrition and intestinal dysbiosis

Severe acute malnutrition (SAM) is the most common cause of death in young children. It is mentioned here as a second example of a biological link between intestinal dysbiosis and disease with some similarities to the hypothesized link between malnutrition, dysbiosis and lung disease in preterm infants. Current treatment regimens for SAM in developing countries that focus primarily on nutrient supplementation are modestly successful at improving weight gain, but do not correct stunting or the associated neurodevelopmental delays [57]. Recent investigations in gnotobiotic mouse and piglet models (gnotobiotic means “known biota” and commonly refers to germ-free animals colonized with a defined community of microbes), as well as clinical trials in infants and children have demonstrated that intestinal dysbiosis is important in the pathogenesis of SAM in infancy and childhood. These landmark studies have identified specific bacterial strains that are associated with poor growth, defined metabolic pathways that are altered by these microbes, and demonstrated improved growth with provision of foods that preferentially stimulate the growth of desirable bacteria [58, 59]. Antibiotic administration is recommended as part of initial treatment of uncomplicated SAM with limited evidence suggesting improved outcomes [60]. SAM during the period of alveolarization (first two years of life) has been postulated to increase risk of adult lung disease, however survivors of SAM have similar lung function to matched controls at age 9 [61].

Table 1 summarizes similarities and differences between postnatal malnutrition (from our rodent model) [10, 11, 62–64] and SAM in clinical studies of infants and children and in animal models [58, 59, 65–70]. While profound intestinal dysbiosis is common in very preterm infants [42], it is unknown whether these alterations in the intestinal microbiota play a role in PNGR, as has been demonstrated in SAM of infancy and childhood in developing countries. The association between intestinal dysbiosis and an intestinal disease like NEC is well established as is the association between FGR and lung disease, however the possibility that intestinal dysbiosis is associated with growth and influences development at a distant

site like the pulmonary vasculature and parenchyma in the premature infant represents a paradigm shift in thinking about the pathogenesis of PH and BPD.

Causation, association, or just overlap?

Given that intestinal dysbiosis, poor postnatal growth, and lung disease are all common in extremely preterm infants, it is possible that there is no causal relationship and that the associations seen are simply a reflection of common complications (Fig. 1). However, the reported associations between NEC and pulmonary vein stenosis further suggest a link between the gut and the developing lung [71, 72]. The cohort studies noted above [5, 8, 37] suggest a true association rather than random overlap (dysbiosis and lung disease are more common in extremely preterm infants with poor growth), but causality could be bidirectional. It seems as likely that severe lung disease causes dysbiosis and poor growth as that malnutrition and dysbiosis alter lung development leading to lung disease. A recent review of nutrition and lung growth found stronger evidence of a causal relationship for poor nutrition and abnormal lung development in utero and in the neonate than in the child [73].

If there is a causal link between poor nutrition, intestinal dysbiosis and lung disease, one would expect that interventions to attenuate intestinal dysbiosis would be helpful in decreasing the incidence of BPD and PH and that interventions that worsen intestinal dysbiosis would have the opposite effect. Probiotics have been shown to attenuate dysbiosis and decrease NEC and death in this population but studies to date have not shown a decrease in BPD with probiotic administration and their effect on PH has not been studied [13, 74]. Human milk has been shown to attenuate intestinal dysbiosis in term infants, but the effect in very preterm infants on the intestinal microbiota is less profound. Human milk decreases risk of both NEC and BPD without enhancing growth [75–77]. Empiric antibiotic administration causes intestinal dysbiosis and in some studies increases risk of NEC though this has not been universal [78, 79]. In a large retrospective study of more than 14,000 very low birth weight babies, administration of empiric antibiotics for 4–7 days increased the risk of BPD compared to 1–3 days (adjusted OR 1.37, 95% CI 1.25, 1.51) [80]. In the subset of infants at low risk for early onset sepsis, 31% of infants were treated with 4–7 days of antibiotics and this was associated with an increased risk of BPD compared to infants that did not receive antibiotics (adjusted OR 1.39 95% CI 1.11, 1.75). Medications that suppress gastric acid production increase intestinal dysbiosis in preterm infants [81] and increase risk of NEC [82]. The recent demonstration of worsening of BPD in a rodent model with administration of omeprazole suggests the possibility of a role for intestinal dysbiosis [83].

These clinical studies leave significant gaps in the links between nutrition, intestinal dysbiosis and lung disease and certainly do not establish causality. As a randomized controlled trial of poor vs adequate nutrition is not ethically acceptable, preclinical models are useful in establishing causality and determining possible mechanisms. In newborn mice, disrupting postnatal colonization with antibiotics decreased numbers of IL22-producing innate lymphoid cells in the lung increasing susceptibility to pneumonia, and this process was reversed with restoration of the intestinal microbiota with fecal transplant [84]. Alteration of the traditional hyperoxia-BPD mouse model with the addition of either antibiotic exposure or germ-free conditions have yielded mixed results. Perinatal antibiotic

exposure resulted in exacerbation of hyperoxia-induced lung disease in some models [85] but not others [86], suggesting the possibility that choice/dose of antibiotic and baseline composition of the microbiota may be important [87]. As noted above germ-free mice pups appear to be protected from hyperoxia-induced lung disease [20]. Many FGR models of lung injury have shed considerable light on the link between nutrition in utero and lung development [88, 89], but models of post-natal malnutrition and lung development are few.

A rodent model of early life malnutrition

When the rat dam provides nutrition to 16–17 pups instead of the usual 10, the milk provided by the dam decreases in fat content [90]. The pups in larger litters demonstrate poor growth (body weight 22% lower at 10 days of life), altered body composition (25% decrease in body fat at 22 days of life), marked decreases in IGF-1 and leptin, and poor neurodevelopment [63, 64]. The decreased growth in this model is not purely related to decreased nutrient and energy intake, but likely includes factors such as poor thermoregulation and increased energy expenditure [90] that have particular relevance to premature infants. Others using a similar model recently found that PNGR causes PH in male rats at 9 weeks of age [9]. With further modification of this model, we demonstrated that PNGR causes PH in both male and female rats as early as 14 days of life [10], exacerbates the severity of hyperoxia-induced PH, alters the composition of the intestinal microbiota, and alters a variety of metabolites [62].

In our model, timed-pregnant Sprague Dawley dams were maintained in room air and allowed to deliver at term (a time at which lung development is in the saccular phase, similar to premature infants). After birth, pups were pooled and randomly assigned to litter sizes of 10 pups (control) or 17 pups (PNGR). Additionally, pups were randomly assigned to cages maintained in room air or continuously exposed to 75% oxygen in a plexiglass chamber (dams were rotated with the appropriate control or PNGR groups every 24 h to avoid hyperoxic injury to the dams). At postnatal day 14, the pups in the PNGR-room air group had poor growth and PH as evidenced by decreased numbers of pulmonary vessels, increased medial wall thickness of pulmonary arterioles and right ventricular hypertrophy (RVH) [10]. Transthoracic echocardiography prior to euthanasia at 14 days of age demonstrated a decrease in the ratio of pulmonary artery acceleration time to pulmonary ejection time (PAT/ET), a marker of increased pulmonary arterial pressure in rodents [91]. The combination of PNGR and hyperoxia causes a more severe PH phenotype [10].

Potential Mechanisms by which postnatal malnutrition and intestinal dysbiosis lead to BPD and PH (Fig. 2)

Epigenetics

The large amount of data supporting the theory of the fetal origin of many adult diseases includes strong correlations between low birth weight and hypertension and other cardiovascular diseases [92]. These studies suggest that fetal and neonatal nutritional deprivation leads to epigenetic programming that in the short term is life-saving, but in

the long term is detrimental. In a rodent model, nine-week-old rats exposed to postnatal malnutrition (20 pups per dam) developed PH and analysis of isolated pulmonary vascular endothelial cells revealed alterations in histone modification of the endothelial nitric oxide synthase gene resulting in decreased expression at the protein level plus altered cytosine methylation in 500 loci compared to control pups (10 pups per dam), including hypermethylation of genes important in vascular development and hypomethylation of genes important in signal transduction [9]. The same group has also demonstrated epigenetic modifications in the promoter regions of the Notch1 gene and decreased Notch1 expression in pulmonary vascular endothelial cells at 3 and 9 weeks of age following postnatal malnutrition [93]. Notch1 plays an important role in angiogenesis. Combined these studies suggest that the decreased numbers and increased medial wall thickness of pulmonary blood vessels seen in PNGR-associated PH are related to epigenetic changes with long-term consequences. Whether similar epigenetic changes occur in other organs and cell types remains unclear.

Local and systemic inflammation

Toll-like receptors (TLR) recognize pathogen-associated molecular patterns and trigger innate immune responses. TLR4 recognizes lipopolysaccharide that is abundant in the outer membrane of Gram negative organisms such as Enterobacteriaceae, and this receptor has been implicated in the pathogenesis of inflammatory disease processes including NEC, acute lung injury, and PH [94, 95]. As noted above, the intestinal microbiota of premature infants is characterized by high numbers of pro-inflammatory Gram negative Enterobacteriaceae particularly during the highly vulnerable period from 28 to 34 weeks postmenstrual age [42, 96]. The TLR4/MyD88/NFκB pathway is upregulated in the fetus where it plays a role in development of the intestinal tract [97, 98]. TLR4 signaling is also important in lung injury and inflammation [94], PH [99], and chronic obstructive pulmonary disease [100]. The increase in intestinal Enterobacteriaceae in PNGR (with or without hyperoxia) in our rodent model [11] and in cohorts of preterm infants with poor postnatal growth [45, 46] suggests a potential role for TLR4 activation in PNGR-associated PH. Treatment with an inhibitor of TLR4 in our rodent model attenuated the right ventricular hypertrophy, the altered PAT/ET ratio, and markers of inflammation in both plasma and lung tissue in animals exposed to PNGR and hyperoxia [101]. It remains to be determined whether TLR4 activation in the gut or lung or both is important in PNGR-associated PH and whether there is a developmental window during which TLR4 activation is of particular importance.

The key role of the intestinal microbiota in the development and activation of both the innate and adaptive immune systems has been extensively reviewed [102]. The compelling example of genetic and environmental factors causing intestinal dysbiosis leading to increased expression of TH1, TH2 and TH17 cells, decreased expression of regulatory T cells and decreased production of secretory IgA by gut B cells leading to chronic inflammation in inflammatory bowel disease underscores the importance of local host-microbe interactions at the intestinal mucosa [102]. Similarly, infants with NEC have been shown to have increased circulating TH17 cells and decreased regulatory T cells compared to matched controls without NEC [103].

The gut-lung axis refers to the impact of gut microbes on immune responses in the lung and suggests a systemic response to intestinal dysbiosis [104]. In preterm infants, chorioamnionitis and sepsis both increase the risk of development of BPD. Postnatal treatment of mouse pups with lipopolysaccharide during the saccular stage of lung development decreased somatic growth, arrested lung development, increased pulmonary macrophages, decreased regulatory T cells and increased markers of lung inflammation [105]. Whether similar patterns of systemic and lung inflammation are triggered by malnutrition and/or intestinal dysbiosis in preterm infants remains to be determined.

Oxidative stress

Markers of oxidative stress are increased in rodent and piglet models of both malnutrition and induced colitis with some markers showing additive effects [106–108]. Malnutrition and chronic lung disease are hallmarks of cystic fibrosis and chronic obstructive pulmonary disease with both of these diseases manifesting oxidative stress and improvement with anti-oxidant therapies [109, 110]. SAM causes both increased production of reactive oxygen species and decreased anti-oxidant activity [111]. Microbiomic, proteomic and metabolomic studies demonstrate a role for oxidative stress in BPD and yet a microbiomic or metabolomic fingerprint predictive of increased risk of BPD remains elusive [112].

Glutathione (GSH) is an important anti-oxidant involved in maintenance of oxidative status. In our rat malnutrition model we found increased reactive oxygen species and decreased GSH in lung tissue at 14 days with more severe changes in pups exposed to PNGR + hyperoxia [62].

Recent studies of dietary polyphenols and anthocyanins have demonstrated attenuation of high-fat diet-induced dysbiosis and increased intestinal permeability through redox-regulated mechanisms [113, 114]. A recent meta-analysis demonstrated increased anti-oxidant capacity and decreased markers of oxidative stress in diabetic adults receiving probiotics [115]. Human milk feeding reduced markers of oxidative stress in preterm infants compared to formula feeding [116]. Further study of mechanisms by which malnutrition and dysbiosis in very preterm impact oxidative stress in the developing gut, liver or lung would be valuable.

Short-chain fatty acids and lactate

In term breast-fed infants, *Bifidobacterium* and *Bacteroides* species ferment the abundant human milk oligosaccharides to produce lactate and acetate in large quantities lowering the luminal pH and facilitating further growth of lactic acid bacteria and inhibiting growth of facultative anaerobes [117]. In adult models a similar process occurs, with commensal *Clostridium* species fermenting plant glycans producing the short-chain fatty acids acetate, propionate and butyrate. Butyrate is utilized by human colonocytes as an energy source maintaining a hypoxic environment within the lumen of the colon [118] and increasing production of mucins by colonocytes to decrease intestinal permeability [119]. Administration of butyrate enemas increased expression of the mucin MUC2 in uninfected adult mice and decreased inflammation and weight loss in *C. rodentium* infected adult mice [120]. The roles of short-chain fatty acids in fortifying tight junctions, increasing goblet cell

differentiation and production of mucus, promoting synthesis of IgA by B cells, influencing differentiation of T cells and modulating production of pro-inflammatory cytokines by leukocytes have recently been reviewed [104, 121]. Whether increased lumenal short chain fatty acids impact intestinal mucin production, intestinal permeability or inflammation in the developing gut is unknown.

Lactate has historically been viewed as simply a waste product of anaerobic glycolysis, however recent studies suggest that lactate is produced even in aerobic conditions and is an important energy source serving as substrate for both hepatic gluconeogenesis and for aerobic oxidation through the citric acid cycle in many tissues [122]. The recent observation that small volume feeding of human milk to very preterm infants caused an increase in serum lactate levels that was not seen in matched infants receiving small volume formula feeding suggests that metabolic responses differ in this population based on feeding type and that lactate may play an important role in either nutrition or metabolism [123]. Study of the cellular metabolism of lactate has focused predominantly on skeletal muscle [124], however recent in vitro work demonstrated that vascular smooth muscle cells grown in a lactate rich medium upregulate genes important in repair, migration and proliferation [125]. Whether an increase in production of lactate by gut microbes has any effect outside the intestinal lumen in preterm infants is unknown.

Altered intestinal permeability

Very preterm infants have immature tight junctions between enterocytes and a thin mucus layer resulting in increased intestinal permeability [126]. As a result, translocation of bacteria from the intestinal lumen to the lamina propria is common in this population resulting in sepsis and NEC. A rodent model of late-onset sepsis demonstrated that manipulation of the intestinal microbiota prevented sepsis [56]. Bacteria that exit the intestinal lumen and enter the lamina propria trigger both a local and a systemic inflammatory response [127]. In a small cohort of preterm infants, increased fecal Clostridiales was associated with decreased permeability suggesting that “maturation” of the microbiota is associated with maturation of intestinal permeability [128]. Multiple animal studies have demonstrated decreased permeability of the immature intestine with administration of probiotic microbes [129]. Increased intestinal permeability plays an important role in SAM in infants and children in developing countries, but whether there is an association between intestinal permeability and growth in very preterm infants remains uncertain. Probiotic microbes attenuate increased intestinal permeability in a variety of mucosal injury animal models including NEC [130], antibiotic treatment [131], high-fat diet [132], chemotherapy [133], aging [134], and even hypertension [135]. The two most studied mechanisms are alteration of the mucus layer and alteration of tight junction proteins. Associations between the intestinal microbiota and altered intestinal permeability have been demonstrated using both the Ussing chamber [136] and tissue occludin expression [137].

Whether increased intestinal permeability (triggered by either malnutrition or dysbiosis) plays a role in BPD or PH in preterm infants remains unknown. In a calf model, hypoxia induces both increased intestinal permeability and PH, but a causal relationship between the two outcomes has not been established [138].

Altered vascular and lymphatic development

Altered expression of vascular endothelial growth factor (VEGF) plays a central role in the development of BPD, PH, pulmonary vein stenosis, retinopathy of prematurity and NEC and has been proposed as an explanation for the observed association between NEC and pulmonary vein stenosis [139]. In the gut, VEGF regulates development of both blood vessels and the lacteals (open-ended lymphatic vessels in the center of the villi responsible for conducting absorbed lipids to larger lymphatic vessels). The recent observations that antibiotic-induced dysbiosis and germ-free conditions both delay lacteal development and lipid absorption in the immature rodent gut, that colonization of the germ-free pup with conventional microbiota leads to maturation of lacteals, and that microbiota-induced expression of VEGF by intestinal macrophages plays an essential role in this process present compelling evidence linking nutrition, dysbiosis and VEGF expression [140]. The observation that *Clostridium difficile* toxin stimulates VEGF expression in *C. difficile* colitis further supports a local interaction between gut microbes and host growth factor response [141]. In our rodent model, poor nutrition led to significant decreases in both VEGF and VEGF receptor in lung tissue. We also found decreased expression of upstream regulators of VEGF expression in lung tissue including the hypoxia-inducible factors and the mammalian target of rapamycin [10].

Micronutrients

The roles of vitamins A, C, D and E, zinc, iron and flavonoids in lung development and risk for lung disease in preterm infants have been extensively reviewed [142–145]. Intestinal microbes either compete for or influence absorption of many of these micronutrients, so it is reasonable to conclude that deficiency of a given micronutrient alters the intestinal microbiota. For instance, both vitamins A and D influence intestinal permeability, intestinal inflammation and the intestinal microbiota [146]. Enterobacteriaceae are aggressive consumers of luminal iron, and in a rodent model iron administration and luminal iron depletion were both associated with changes in the intestinal microbiota [147]. Indeed, iron supplementation in the absence of iron deficiency has been associated with decreased growth, intestinal dysbiosis, increased inflammatory markers, and impaired neurodevelopment [148]. In a preclinical model, zinc deficiency during pregnancy alters the intestinal microbiota, increases both intestinal permeability and markers of inflammation in the brain of the dam [149]. Exposure to moderate zinc deficiency in utero and during lactation in rodents decreased nitric oxide synthase activity at day of life 6 and this persisted into adulthood in males [150]. In extremely preterm infants with BPD and poor growth, zinc supplementation improved weight gain [151]. Clearly more research is needed into the importance of micronutrient malnutrition and its consequences in very preterm infants.

Conclusion: Is there a gut-lung axis?

Intestinal dysbiosis has been demonstrated in infants, children and adults with a variety of chronic lung diseases including BPD, asthma, chronic obstructive pulmonary disease, and cystic fibrosis. Furthermore, the recent observations that half of preterm infants with pulmonary vein stenosis had a history of NEC and that a history of NEC increases the risk of PH for preterm infants with or without BPD suggest a link between gut inflammation

and injury and the pulmonary vasculature [71, 152]. These observations have prompted the hypothesis that nutrition, intestinal microbes, intestinal permeability, lung microbes, and systemic and local inflammation are interrelated in a gut-lung axis and that changes in the gut impact pathology in the lung [153].

The following observations suggest the hypothesis that malnutrition, intestinal dysbiosis and altered lung development in the very preterm infant are related: (1) clinical and translational data that intestinal dysbiosis is important in SAM in developing countries, (2) associations between malnutrition and PH, BPD and other adverse outcomes in extremely premature infants, (3) evidence that marked dysbiosis, with a predominance of Enterobacteriaceae, is common in very premature infants, (4) clinical and translational research evidence that correction of dysbiosis improves outcomes in malnourished children in developing countries and premature infants in developed countries, (5) preclinical data demonstrating an association of intestinal dysbiosis with PH and attenuation of malnutrition-associated PH with probiotic administration, (6) associations between malnutrition, inflammation and oxidative stress and (7) preclinical evidence of a role for TLR4 in malnutrition/dysbiosis-associated PH. The clinical relevance of these observations are underscored by evidence that (1) most extremely premature infants have poor post-natal growth and profound intestinal dysbiosis and (2) all premature infants undergo a shift from physiologic hypoxia in utero to relative hyperoxia after birth, even infants not exposed to high levels of oxygen (i.e., at the gestational age of premature infants, the intestinal tract normally develops in a relatively hypoxic environment). The lack of evidence from clinical trials that probiotic administration improves growth or decreases BPD suggests that either current probiotic formulations do not contain the optimal probiotic strain(s), that administered doses are sub-optimal, or that alteration of the intestinal microbiota is not sufficient to affect growth or lung development. Preclinical models to determine mechanisms important in the interplay between nutrition, the intestinal microbiota, and development of the lung parenchyma and vasculature are needed to inform large clinical trials of interventions combining optimized nutrition, correction of intestinal dysbiosis and lung protective ventilation strategies to decrease BPD and PH.

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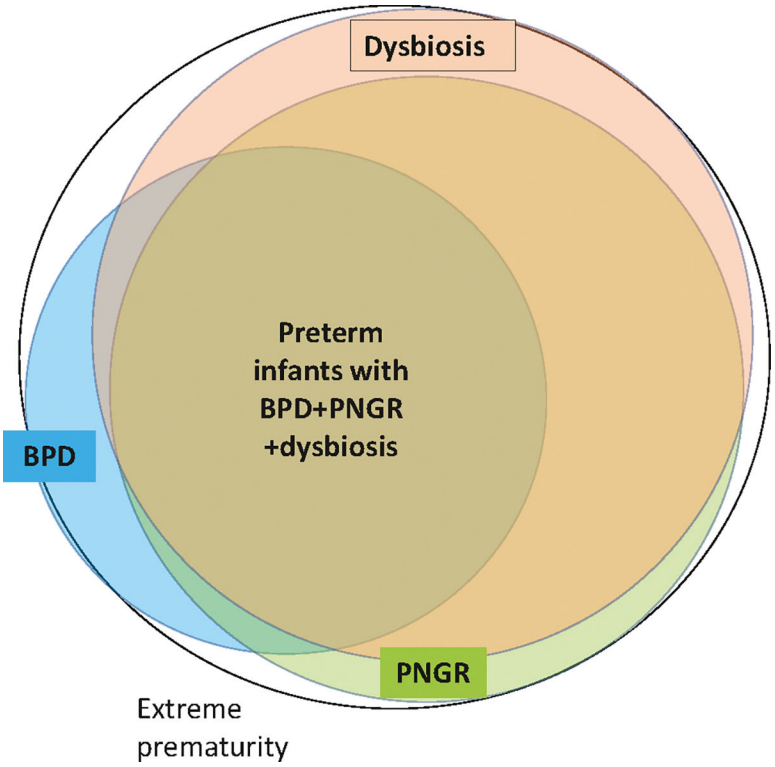

Fig. 1. Representation of common overalapping conditions in extremely preterm infants.
Intestinal dysbiosis, BPD and poor postnatal growth are all common in extremely preterm infants with significant overlap.

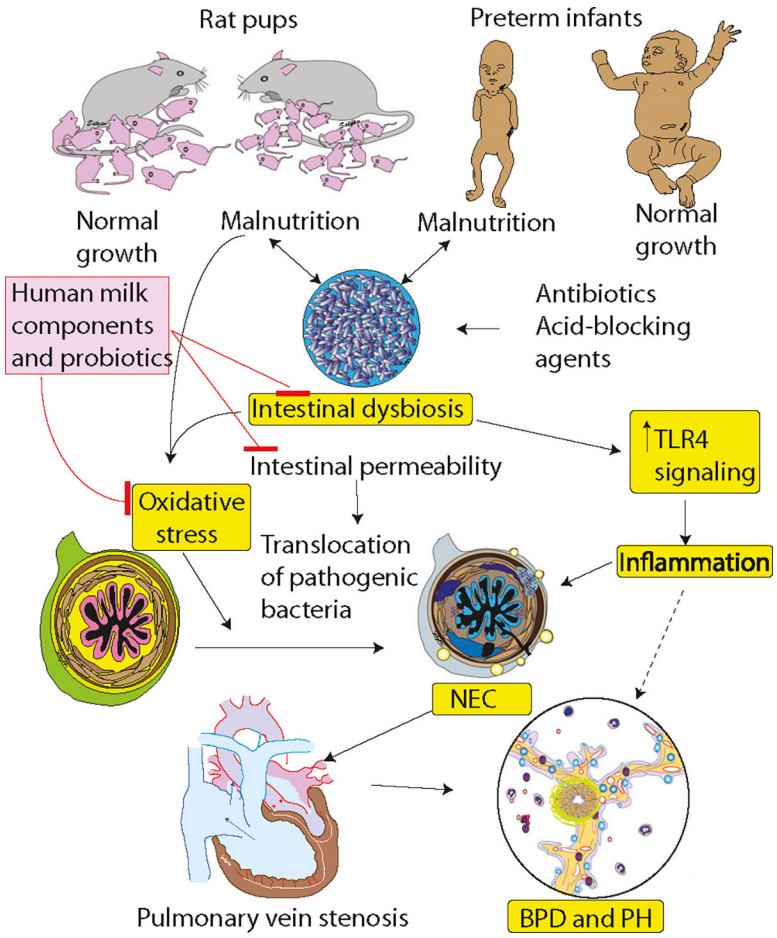

Fig. 2. Potential mechanisms by which poor postnatal growth and intestinal dysbiosis lead to pulmonary parenchymal and vascular disease.

Solid lines indicate good evidence of causality and the dotted line presents the primary hypothesis. Copyright Satyan Lakshminrusimha and Mark A. Underwood.

Table 1

Similarities and differences between PNGR and SAM.

	PNGR (animal model of malnutrition and poor growth)	SAM (human studies and animal models)
Provision of increased calories only partially helpful	x	x
Evidence of intestinal dysbiosis	x	x
Differences in relative abundance of specific groups of microbes	x	x
Antibiotics improve weight gain	??	x
Specific groups of metabolites differentially expressed	x	x
Decreased expression of IGF-1[a], leptin[b] and mTOR[c]	x	x
Decreased branched chain amino acids[d]	x	x
Altered lipid metabolism	x	x
Increased TLR4 expression	x	??
Altering the microbiota improves bone density	??	x
Altering the microbiota decreases osteoclastic activity	??	x
Altering the microbiota attenuates lung disease	x	??

[a]Serum insulin-like growth factor (IGF-1) at day 22 decreased in PNGR [20]. IGF-1 is a mediator of the effects of growth hormone. Circulating IGF-1 is low in both kwashiorkor and marasmus and improves only partially with treatment [68].

[b]Serum leptin decreased at days 10 and 60 in PNGR [64]. Leptin is a hormone that regulates energy balance and hunger. Serum leptin is decreased in SAM and a marker of increased risk of mortality [69, 70].

[c]Decreased phosphorylated 4E-BP1 (a marker of mechanistic target of rapamycin (mTOR) activity) in lung tissue at 14 days in PNGR; [62] mTOR is a central regulator of a variety of cellular processes (growth, proliferation, survival). mTOR activity is decreased during fasting and increases with feeding [67].

[d]Plasma valine and leucine decreased at day 14 in PNGR pups exposed to hyperoxia; [62] branched-chain amino acids are decreased in SAM [70].