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REVIEW

Preterm birth and sustained inflammation: consequences for the neonate

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Abstract

Almost half of all preterm births are caused or triggered by an inflammatory process at the feto-maternal interface resulting in preterm labor or rupture of membranes with or without chorioamnionitis ("first inflammatory hit"). Preterm babies have highly vulnerable body surfaces and immature organ systems. They are postnatally confronted with a drastically altered antigen exposure including hospital-specific microbes, artificial devices, drugs, nutritional antigens, and hypoxia or hyperoxia ("second inflammatory hit"). This is of particular importance to extremely preterm infants born before 28 weeks, as they have not experienced important "third-trimester" adaptation processes to tolerate maternal and self-antigens. Instead of a balanced adaptation to extrauterine life, the delicate co-regulation between immune defense mechanisms and immunosuppression (tolerance) to allow microbiome establishment is therefore often disturbed. Hence, preterm infants are predisposed to sepsis but also to several injurious conditions that can contribute to the onset or perpetuation of sustained inflammation (SI). This is a continuing challenge to clinicians involved in the care of preterm infants, as SI is regarded as a crucial mediator for mortality and the development of morbidities in preterm infants. This review will outline the (i) role of inflammation for short-term consequences of preterm birth and (ii) the effect of SI on organ development and long-term outcome.

Keywords Preterm infants · Sustained inflammation · Sepsis · Microbiome · Neurocognitive outcome · Chronic pulmonary insufficiency of prematurity

Determinants of outcome after preterm birth

The main driver for the success of modern neonatology was the overarching aim to reduce preterm infant mortality rates. In the last decades, this goal has been achieved in many high-income countries mainly due to the significant progress in the perinatal management of high-risk pregnancies and the recent advances in neonatal intensive care. Current international network data indicate that preterm babies even at the margin of viability of 24 weeks of gestation survive in more than > 70% Fig. 1. Increasing survival of highly vulnerable babies underscores the need to assess and implement care that prevents adverse short-term complications and optimizes long-term outcomes. In Table 1, the incidences of typical adverse short-term outcomes after preterm birth are summarized. It should be noted that the current scientific evidence is primarily related to extremely preterm infants < 28 weeks of gestation (EPI; 0.3–0.6% of births in high-income countries) and to a lesser extent to very preterm infants (VPI; 28–32 weeks of gestation, 0.5–1.5% of births). The numerical majority of preterm babies—the cohort of moderate-to-late preterm infants (MLPI; 33–36 6/7 weeks of gestation; 5.5–7% of births)—has not been studied in great detail yet [5, 6].

The etiology of adverse outcomes is multifactorial with inflammatory processes being a crucial driving force.

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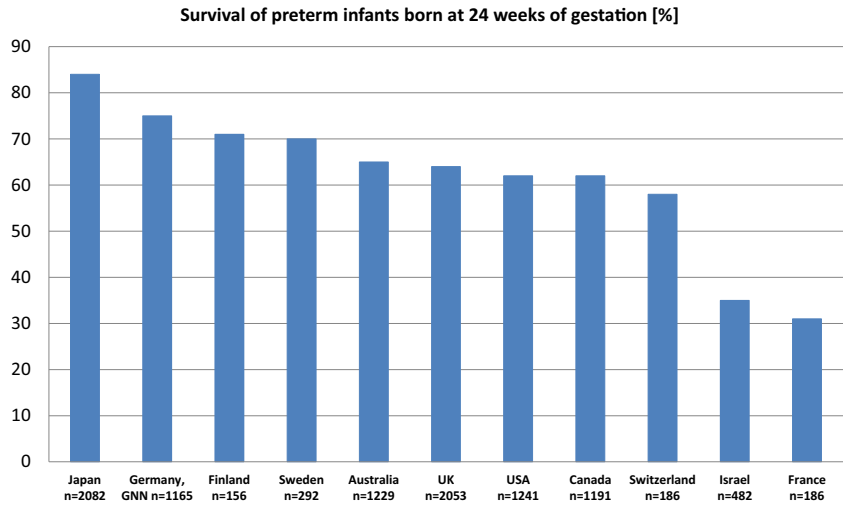

Fig. 1 Survival rates of preterm infants born at 24 weeks of gestation in different high-income countries [1–4]; GNN German Neonatal Network

Inflammation is particularly important for the development of bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC), and retinopathy of prematurity (ROP) but also for intracerebral hemorrhage (ICH) and periventricular leukomalacia (PVL). Classical "inflammatory phenotypes" are seen in preterm infants with sepsis or NEC which are still the second most common causes of death in preterm infants after respiratory failure [4]. Acute inflammatory processes, specifically in survivors from sepsis or NEC, may not be well resolved and therefore result in SI. As outlined in Fig. 2, the main endogenous risk factors for SI are gestational age, birth weight, and gender. Genetic background is proposed to play a role for SI; however, in the specific situation of preterm infants, no single candidate variant has yet been confirmed as risk factor [17]. Thus, SI risk might represent a mixture of individual predispositions, which are the cause of preterm birth or its consequence. Due to the care under highly controlled conditions, the distinct cohort of preterm infants can serve as a model to disentangle the impact of (epi-)genetic factors from environmental influences on the development of SI. Longitudinal studies could therefore pioneer the investigation of entities in adulthood that are mediated by prolonged inflammation (e.g., chronic lung disease, coronary heart disease, neurodegenerative disease, metabolic syndrome) [18].

Table 1 Incidences of major short-term complications of preterm birth

Outcome	EPI < 28 weeks	VPI 28–32 weeks	MPI/LPI 33–< 37 weeks	References
Intracerebral hemorrhage				
All	15–25%	1–4%	1–2%	[5–13]
Grade III–IV (Papile)	3–6%	1–2%	< 1%	
PVL	2–8%	1–6%	?	
Sepsis				
Clinical	25–60%	10–30%	5–9%	[5, 6, 8, 9, 13–15]
Blood culture confirmed	15–50%	2–6%	1–3%	[7, 8, 13, 14]
EOS	1–1.5%	0.1–0.3%	0.1–0.2%	[13, 14]
LOS	15–50%	1.5–6%	1–3%	[13–15]
NEC requiring surgery	4–10%	0.5–3%	< 1%	[6–13, 16]
SIP requiring surgery	3–8%	< 1%	< 1%	[6, 13]
Pneumothorax	4–7%	1–4%	1–2%	[5–8, 13]
BPD	15–50%	5–25%	?	[13]
ROP	2–5%	1–3%	?	[13]
Death in hospital	10–20%	2–5%	1%	[5, 6, 9–13]

PVL periventricular leukomalacia, *EOS* early-onset sepsis (≤ 72 h of age), *LOS* late-onset sepsis (> 72 h of age), *NEC* necrotizing enterocolitis, *SIP* spontaneous intestinal perforation, *ROP* retinopathy of prematurity, *BPD* bronchopulmonary dysplasia

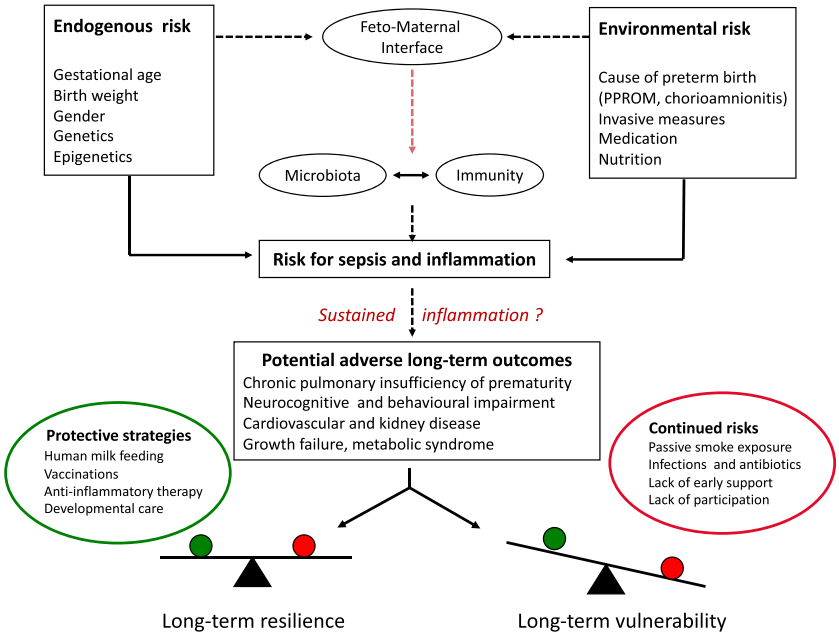

Fig. 2 Complex risk profile of preterm infants for sustained inflammation and long-term vulnerability. This simplified model depicts that preterm infants are at risk for sustained inflammation by the virtue of their immaturity and several environmental exposures ("inflammatory" hits). The neonatal immunity is primed by the feto-maternal interface and interacts with the yet unstable microbiome. A delicate balance is needed between tolerating microbiological colonization and adequate immune responses to invasive pathogens. The neonatal "inflammatory phenotype" may result from a disturbed immune-microbiome development. The acute inflammatory process often fails to be properly resolved after clinical recovery with the consequence of sustained inflammation. The cross talk between immunity and microbiota continues and is proposed to affect developmental trajectories and long-term outcomes. Longitudinal studies are needed to account for protective modulators and continued risks for dysregulatory influences. PPROM, preterm premature rupture of membranes

It is an overarching hypothesis of this narrative review that SI contributes to long-term complications of several organ systems including central nervous system (CNS) (e.g., cerebral palsy, neurobehavioral impairment), lung (chronic pulmonary insufficiency of prematurity, CPIP) [19, 20], and gut [21–24] (Fig. 2). A clear relationship has not yet been demonstrated, while indirect evidence comes from observational data. For example, the follow-up examination of GNN infants at 5 years of age ($n = 1552$) noted that neonatal sepsis ($n = 538$) is associated with a twofold risk to have a Wechsler Preschool and Primary Scale of Intelligence (WPPSI) score < 85 as compared with unaffected preterm infants (28.1 vs 12.7%, $p < 0.001$; adjusted for gestational age, intracerebral hemorrhage, and maternal educational level: OR 1.92 (95% CI: 1.40–2.64)). Hence, there is an urgent need to prevent sepsis but also to evaluate new resolution strategies of SI in order to promote long-term health in preterm infants. The major challenge, however, is the time lag between "a window of opportunity" (usually within the first 4 weeks of life when most postnatal inflammatory episodes occur) [25] and the time-point at which relevant determinants of outcome can be properly assessed (i.e., lung function, intelligence tests at school age).

Sustained inflammation in the context of preterm birth

Preterm infants have a remarkably different system of immune regulation as compared with term infants and adults. For the immune defense, the preterm infant relies on the non-specific innate immunity, while T cell responses including those T helper cells counter-regulating inflammation, e.g., regulatory T cells (T_{reg}), might be less functional. Hence, pro-inflammatory cytokine responses (e.g., interleukin (IL)-1, IL-6, IL-8, tumor necrosis factor (TNF)-a) and other inflammation-related proteins (e.g., C-reactive protein (CRP), intercellular cellular adhesion molecule (ICAM)-1, erythropoietin, ferritin) are overexpressed and insufficiently balanced by immunosuppressive elements (e.g., IL-10, S100 A8/9, myeloid-derived suppressor cells, T_{reg}, CD71+ cells). In inflammation-related protein measurements in blood spots, serum and plasma are therefore used as surrogate markers to define SI in preterm babies, as outlined in several reports of the multicenter Extremely Low Gestational Age Newborn Study (ELGAN, infants < 28 weeks of gestation) group [26–29]. There is, however, a certain ambiguity in the definition of SI. Elevated concentrations of inflammation markers on two time-points within an interval of 1 week may reflect an ongoing process with failure of inflammation resolution (as

we define SI in this review). Alternatively, flare-ups of a recent acute inflammatory process or two separate episodes of inflammation may be associated with elevated concentrations of inflammatory markers and cannot be discriminated from SI [30]. Hence, follow-up examinations are needed to ascertain SI in a clinical context. Notably, inflammatory processes cannot only be sustained over a long time in preterm infants but also in term infants who survived neonatal encephalopathy [31].

Recent developments in the molecular analysis of complex biomaterials suggest that there are multiple dimensions to SI in preterm infants, i.e., a disturbed interaction between the immune system and the microbiota (see also Fig. 2). The "healthy" microbiome implies a symbiotic life of the host with "friendly" microbes which provides homeostasis and protection from adverse short-term outcome. In preterm infants, however, there is evidence that (i) systemic inflammation (sepsis) often originates from the gut, (ii) the microbiota of preterm infants develops in a highly dynamic fashion and is therefore prone to dysbiosis, an imbalance with reduced microbial diversity and deficient metabolic capacity to control potential pathogens ("enemies"), and (iii) most circulating metabolic compounds (with potential to perpetuate inflammation) are actually derived from gut bacteria [32–35]. Specific diseases, such as sepsis and NEC, are preceded by gut dysbiosis and immunological dysbalance [36, 37].

Microorganisms perform essential functions mechanistically linked to the immune system of the preterm infant. Metabolites (e.g., short-chain fatty acids, SCFAs) and microbe-associated molecular patterns (MAMPs, e.g., lipopolysaccharide (LPS), peptidoglycan, flagellin) are supposed to play an important role as mediators. SCFAs such as butyrate are able to generate and enhance the pool of regulatory T cells which are capable to suppress inflammation [38]. Butyrate can also restore anti-inflammatory cytokine expression IL-10 levels by inhibiting the histone deacetylase in myeloid-derived suppressor cells (MDSCs) which limits inflammation in a *K. pneumoniae* murine sepsis model [39]. Translational studies with adult cohorts demonstrate that the composition of the gut microbiome is a crucial determinant for ex vivo cytokine production capacity and that the abundance of SCFA-producing bacteria in the gut is associated with a decreased infection risk following allogenic stem cell transplantation [40, 41]. In preterm infants, the potential link between dysbiosis-sustained inflammation and long-term outcome has not been evaluated yet [42]. A recent study in preterm babies < 32 weeks suggested that a subgroup of infants is capable of rapidly acquiring adequate immune functionality, independently of the developing heterogeneous microbiome. Preterm infants who had an inflammatory insult, however, have reduced percentages of CXCL8 but comparable levels of TNF-producing T cells, as precursors of adverse outcome. Hence, distinct identifiable differences in functionality may predict subsequent infection-mediated outcomes [43]. Intriguingly, there is evidence that the developing organ systems at risk for long-term sequelae have a significant cross talk via the microbiome-immune interaction (gut-brain axis, gut-lung axis, gut-heart axis) [44]. This emerging field of research offers new targets for microbiota stabilization in order to strengthen the ability to downregulate or resolve immune responses.

Sustained inflammation and long-term outcome of developing organ systems

There are strong arguments for SI contributing to systemic alterations on the immune system itself but also on the tissue-/organ-specific development of organ systems. The experimental evidence for a causal relationship are often lacking, while observational studies provide indirect evidence. With regard to long-term immunological vulnerability, the risk of rehospitalization due to infections during childhood is inversely correlated with gestational age [53, 54]. Other association studies suggest a potential role of accelerated immunological aging in ex-preterm infants as indicated by telomere length differences in comparison with term-born infants [55]. On the other hand, preterm infants have a reduced risk of developing immune-mediated atopic dermatitis [56]. As potential mechanisms have currently been discussed a reduced exposure to environmental antigens, the early weaning from human milk and the premature development of a skin microbiome which can trigger specific local immune reactions to prevent dermatitis. Most of these data are case-control designs. A careful interpretation is needed, and the potential effect size of SI requires adjustment for other confounding factors for immunological susceptibility later in life including small anatomy and organ-specific predispositions which are outlined below.

Inflammation and the preterm brain

In recent years, it has been demonstrated that the brain of preterm infants responds differently to injurious exposures than the brain of term neonates or children [57–63].

This explains the high susceptibility of extremely preterm infants to neurodevelopmental impairment and cerebral palsy [64]. Other studies indicate that also moderate and late preterm children exhibit a risk for developmental delay, most marked in the language domain, at 2 years, and behavioral problems at 7 years [65–67]. The CNS is an immune-privileged organ. However, inflammatory hits such as maternal immune activation (MIA) during pregnancy or other exposures during vulnerable periods of development (Fig. 3) can severely affect the development of the CNS [68, 69]. Three main cell types account for neuroinflammation in the human brain: microglia,

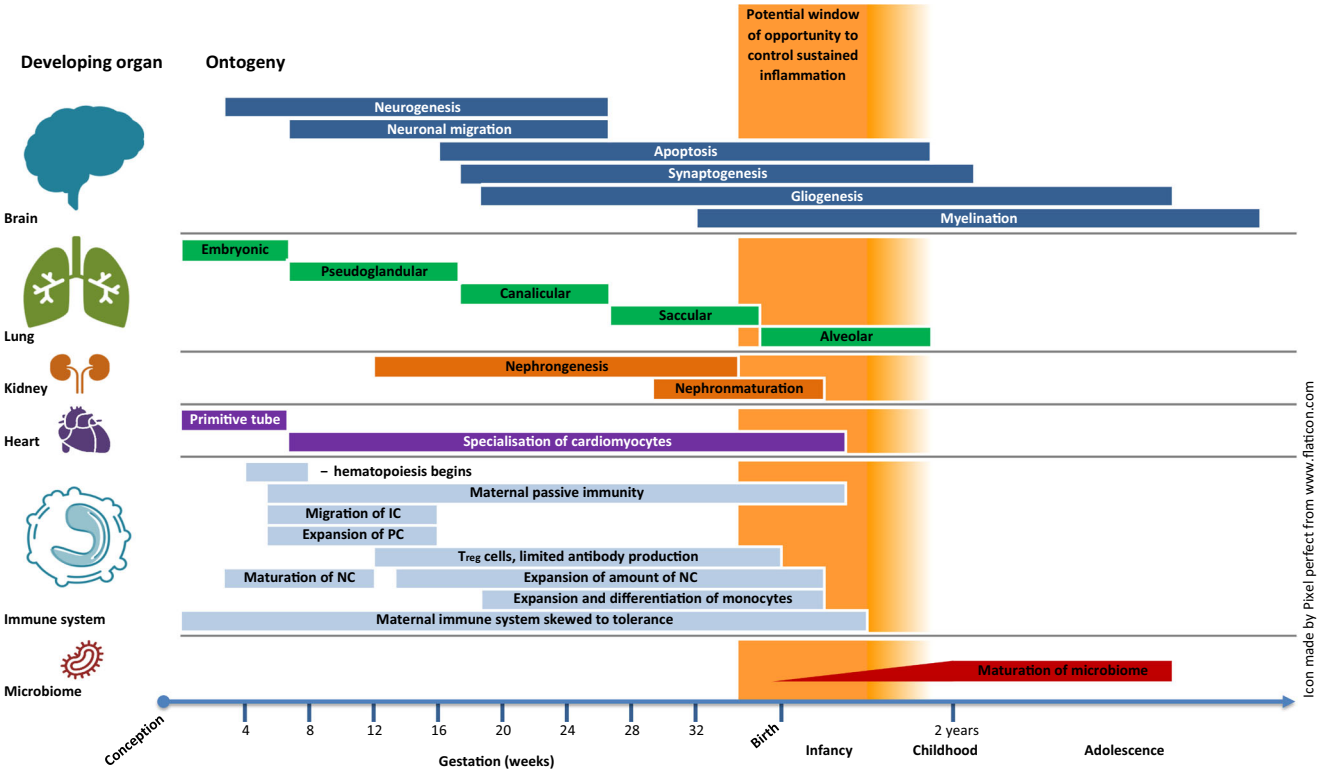

Fig. 3 Ontogeny and potential impact of sustained inflammation on the development of the brain, lungs, kidneys, and immune system. IC, immune cells; PC, progenitor cells; NC, neutrophil cells; adapted from [45–52]

astrocytes, and immune cells from the peripheral system migrating into the brain tissue after blood-brain barrier dysfunction. Pro-inflammatory cytokines are produced which further induce the activation, migration, and proliferation of cytotoxic T cells and natural killer cells. As a consequence, tissue damage occurs, particularly in the white matter [70]. The extent of damage apparently depends on the developmental stage as inflammatory stimulants (e.g., IL-1ß) lead to more pronounced neutrophil migration, chemokine production, and more disrupted blood-brain barrier in neonatal mice than in adult mice [71–73]. Microglial cells have an important physiological role for the regulation of neuronal apoptosis and neurogenesis and promote synaptic formation, pruning, and maturation [69, 74–79]. They also support axon fasciculation and myelinisation [80] and are important for the synaptogenesis and degradation of weak synapses. In terms of inflammatory function, the microglial cells display a plentitude of receptors for cytokines, chemokines, as well as for damage-associated molecular patterns (DAMPs), pathogen-associated molecular patterns (PAMPs), and factors of extracellular matrix [81]. Long cellular processes scan the environment for changes in brain tissue and are able to switch the cell into an activated stage [82–84]. Activated microglia transforms into macrophage-like cells which have the ability for phagocytosis [84], proliferation, and migration into the areas of injury. In preterm postmortem brains, the concentration of microglia was shown to be increased around cystic lesions indicating that an inflammatory process has not been properly resolved [85–87]. In the cerebrospinal fluid (CSF) of newborns with perinatal hypoxic-ischemic encephalopathy, significantly elevated levels of inflammatory markers derived from microglia were found and causally linked to neonatal white matter damage leading to spastic cerebral palsy [88–93].

Astrocytes display multiple functions on synapses, metabolite transfer, production of extracellular matrix, myelination, and blood-brain barrier formation. Proliferation of astrocytes starts around gestational age of 24 weeks with a peak around 26–28 weeks [84]. Astrocytes are usually important for anti-inflammatory homeostasis and microglia modulation [94]. However, after specific microglial stimuli, astrocytes may turn into inflammation triggering cells by releasing pro-inflammatory cytokines inducing brain damage [95–97]. A cytokine storm further supports the plasticity of astrocytes which remarkably contributes to SI in the brain [97].

Preterm infants with SI have adverse neurodevelopmental outcomes at 18–22 months including cerebral palsy, reduced Bayley Scales of Infant Development II testing scores, reduced mental and psychomotor development indices, and vision impairment [24]. The ELGAN study group [29] reported that sustained elevations of acute inflammatory proteins during the first 4 weeks of life were associated with a 2- to 5-fold increased risk for various impairments of intelligence quotient (IQ) and executive function. There was a measurable "dose effect" of early vs late elevations indicating that the

consequent implementation of prevention strategies of infections such as breast milk feeding, less invasive care, hand hygiene, and antibiotic stewardship programs is needed to improve neurodevelopmental outcome [98–100].

Postmortem studies of preterm brains and animal sepsis studies suggested that γδ T cells were also linked with injury of the developing brain. Depletion of these cells protected mice against brain injury after induction of inflammatory cascades [101, 102]. Specialized B cells with innate-like functions, maternal antibodies (especially when blood-brain barrier is disrupted), and the complement system may play a further role in detrimental effects on brain tissue [103–106] which is reviewed elsewhere [45, 107]. A causal relationship between maternal infection and inflammation during pregnancy and adverse neonatal brain development has recently been demonstrated for Zika virus infection and microcephaly [108] but also exists for *Toxoplasma gondii*, herpes viruses, and several bacterial infections [109–122]. Animal models have suggested that maternal immune activation induces sustained inflammation in the offspring at a much higher likelihood when the offspring was additionally exposed to stress or drug use [123–125]. In the human context, infants that undergo early (prenatal) and subsequent inflammation have a higher risk for adverse neurocognitive and behavioral outcome [126–130]. Several clinical studies imply that a distortion of the gut-immune axis has an impact on neurocognitive outcome. Similar to the central nervous system, the enteric nervous system is able to release distinct signaling molecules which are key regulators in local (and systemic) inflammatory processes of the gut [131–135]. The complex gut-CNS interplay via neural, endocrine, metabolic, and immune factors is referred to as the "gut-brain axis," but the pathways remain to be fully elucidated. However, several diseases of the gastrointestinal tract with inflammatory characteristics impact neurodevelopment and behavioral outcome [23, 135]. In preterm infants, NEC is a good example for the potential clinical relevance of a "gut-brain axis." NEC is a devastating disease characterized by inflammation of the mucosa with subsequent necrosis of the intestinum. A multifactorial pathogenesis with immune response to non-physiologic intestinal microbiota ("dysbiosis"), immature intestinal anatomy, and increased expression of pro-inflammatory mediators is involved in the pathogenesis. Several studies have shown significant higher incidences of neurodevelopmental dysfunction [23, 136–140], and brain injury in magnetic resonance imaging [141], especially when infants were longer exposed to the inflammatory process [139, 140]. Given the major instability of the microbiome in the first months of life (Fig. 3), a multifactorial therapeutic approach by modulation of early dysbiosis via probiotics, controlled administration of antibiotics in accordance with antibiotic stewardship, and early termination of inflammation through early surgery may improve neurocognitive outcome [142, 143]. More research is needed to address the critical need for the early determination (at best pre-symptomatic) of adverse neurological outcome by potent biomarkers such as brain imaging and sensitive testing batteries.

Inflammation and the preterm gut

The gastrointestinal tract (GI) underlies a vast transition through pregnancy and the period of preterm birth which makes it susceptible to inflammatory damage [144]. Major risk factors include immature mucosal barriers, dysfunctions of immune cells, reduced motility of the GI tract, decreased concentrations of secretory IgA and antimicrobial peptides, and an increased risk of dysbiosis and bacterial overgrowth as outlined above [145]. Several exogenic factors (e.g., chronic ischemia during pregnancy, chorioamnionitis, antibiotic exposure, parenteral nutrition) trigger dysbiosis and seem relevant for the risk of inflammation-mediated acute gut complications (e.g., NEC). In pregnancy mouse models, maternal inflammation leads to subsequent GI injury in the mucosal and submucosal layers of the gut [146] and alteration of GI epithelial cells in the offspring, which play a key role in innate immunity [147, 148]. In a human study of preterm infants, chorioamnionitis was shown to higher the incidence of late-onset sepsis and death among preterm infants and shifted the fecal microbiome of preterm infants [149]. The gut microbiota and its metabolites can influence immune functions and immune homeostasis both within the gut and systematically. Beyond the role of microbial-derived short-chain fatty acid (SCFA) and biotransformed bile acid (BA) potential immune ligands, inflammation can be mediated via epigenetic processes or by specific cell signaling receptors like GPRCs, TGR5, and FXR [150]. Intestinal permeability and bacterial translocation are important contributors of SI and, without repair of the intestinal barrier, might represent a continuous inflammatory stimulus leading to growth failure, short bowel syndrome, and a higher risk for autoimmunity (e.g., inflammatory bowel disease) after preterm birth [56, 151]. Growth failure is the main cause of rehospitalization of highly preterm infants during infancy [53]. Mechanistic models, e.g., short bowel syndrome zebrafish, show that the short bowel syndrome results in an increased expression of genes involved in inflammation, proliferation, and bile acid synthesis. Vice versa, genes in folate synthesis, gluconeogenesis, glycogenolysis, and fatty acid oxidation as well as activation in drug and steroid metabolism are downregulated [152]. These significant and complex alterations in pathways suggest that short bowel syndrome is provoked by SI and aggravated by long-term exposure to potential inflammatory compounds such as parenteral nutrition. Hence, anti-inflammatory strategies including human milk and pre-, pro-, and synbiotics are attractive interventions to target gut-mediated SI which are discussed in detail elsewhere (e.g., [153]).

Inflammation and the preterm lung

The continuous antenatal process of lung tissue development makes survival of preterm infants possible when differentiation of the lung structures enables gas exchange. Lung development has been traditionally characterized in different stages [48], as outlined in Fig. 3, but goes far beyond birth. Especially at early developmental steps, interruptions can disturb lung maturation, leading to impairments in lung function and structure [47]. Therefore, extremely preterm infants are at high risk to develop chronic lung disease (CLD), which may be characterized as the BPD "phenotype," i.e., oxygen need > 36 weeks, corrected age, or a CPIP which has clinical overlaps with the early childhood "asthma phenotype" [19]. A meta-analysis of 31 birth cohorts showed that preterm birth is associated with an increased risk of wheezing (OR 1.34 (95% CI: 1.25–1.43)) and school-age asthma (OR 1.40 (95% CI: 1.18–1.67)) [154]. A potential explanation is that preterm infants are more likely to be exposed to multiple risk factors for the development of the "asthma phenotype" (cesarean delivery, infections, and antibiotic use) as compared with term infants. All these risk factors are associated with a higher risk to SI [155].

Recent animal and human studies have also demonstrated cross talks between different mucosal sites, e.g., gut-lung axis [156]. Hence, microbiome-immunity interactions might be important for the development of BPD/CPIP which is indirectly supported by epidemiological data. In particular, multivariate logistic regression analysis from the GNN cohort (n = 2527 BPD-diagnosed infants, n = 12,826 unaffected controls) indicate that neonatal sepsis is an independent risk factor for BPD (odds ratio, OR 2.2, 95% CI: 1.9–2.4, $p < 0.001$). Sepsis also increases the risk for oxygen need at discharge (n = 432 affected infants/n = 11,634 controls; OR 1.68 (1.35–2.08), $p = 0.001$). In contrast, potential "stabilizer" of the immune-microbiome interaction such as nutrition with human milk and probiotic supplementation is associated with a reduced risk for BPD and respiratory infections [151]. Infants with BPD were shown to have a decreased airway microbiome diversity and higher concentrations of *Ureaplasma spp.* as compared with non-BPD infants. However, clinical and methodological heterogeneity make these data difficult to interpret [157, 158]. Furthermore, changes in the composition of the airway microbiome do not necessarily impact on inflammatory cytokine levels and might be heavily confounded by the clinical practice (e.g., exposure to antibiotic therapy, ventilation, nutrition, surrounding) [157, 159, 160].

The histological picture of CLD includes alterations of the lung structure with reduced septation, vascularization, number of alveoli, and simplified alveolar structures leading to a reduced capability of gas exchange and relevant lung function restrictions persisting into adulthood [47, 161, 162]. SI in the lung is triggered by mechanical ventilation, oxygen use, and infection. Tracheal aspirates of infants mechanically ventilated had higher concentrations of pro-inflammatory cytokines (IL-1β, IL-6, IL-8, TNF-α) [163, 164] (for review, see [47]). In a myriad of animal studies, a clear link between intrauterine inflammation and impaired fetal lung development is described [165–169]. Intra-amniotic injection of LPS resulted in changes of vascular markers and structural alterations of the preterm lung [167, 170]. In particular, intra-amniotic inflammation induced smooth muscle hypertrophy [167], decrease of alveoli number, and increase of alveolar volume [170]. Studies in fetal lambs with intra-amniotic administration of LPS prior to delivery showed effects on pulmonary hemodynamics [171], especially when time to delivery after injection of LPS was long enough for vascular remodeling [172], suggesting a link between maternal immune activation and pulmonary hypertension. Models of in utero infection further revealed decreased expression of vascular endothelial growth factor (VEGF) in lung tissue (important for alveologenesis), increased synthesis of extracellular matrix (collagen), and higher levels of inflammatory markers (IL-1β, IL-6, IL-17A) in lung tissue samples leading to inflammatory damage of the lungs [173–180]. Other authors demonstrated that intrauterine infection enhanced Th17 expression resulting in an immune modification of the lungs leading to uncontrolled inflammatory responses [181, 182]. This is in line with the finding that extremely preterm neonates with BPD had increased levels of Th17 and IL-17+ T_{reg} lymphocytes in cord blood samples as compared with unaffected controls [180].

Postnatal inflammation also plays an important role in the pathogenesis of CLD. Several postnatal factors are known to have an effect on the expression of pro-inflammatory cascades. One of the most important triggers in the pathogenesis of CLD is mechanical stretch injury via the use of invasive ventilation [183]. In a multitude of animal models, increased levels of pro-inflammatory cytokines [184–186] and inflammatory cells in the bronchoalveolar lavage fluid were found secondary to invasive ventilation [183, 184]. Cytokine levels are dependent on the duration of invasive ventilation [187], tidal volume strategy [188, 189], and the type of ventilatory support. Decreased inflammation was associated with non-invasive ventilation models [190, 191]. In the pathogenesis of CLD, early onset of inflammation processes seem to play an important role as an early cytokine storm was shown to impact the progress of chronic lung disease. In a longitudinal analysis of human serum cytokine profiles in preterm infants, infants with later diagnosis of BPD were shown to have elevated levels of IL-6, IL-8, and granulocyte-colony stimulating factor (G-CSF) at first weeks of life [192]. Using a murine BPD model, Rudloff et al. could demonstrate that early anti-inflammatory intervention on day one after birth via administration of IL-1 receptor antagonists was beneficial to protect from murine BPD as treatment initiated at day 6 [193]. In the clinical setting, studies on the administration of steroids to reduce the incidence of BPD argue for an effect of early

administration (</= 7 days), but potential drug-related adverse outcomes need to be considered [194]. A major challenge is the assessment of early lung function parameters in preterm infants. The lung clearance index (LCI) measured by multiple breath washout (cumulative expired volume (CEV) divided by the functional residual capacity (FRC) at 1/40 of the starting gas SF6 concentration) might become a useful physiological test to detect obstructive lung disease, air trapping, or ventilation inhomogeneities. Future research needs to evaluate the significance of respiratory rate, lung MRI, or lung impedance tomography as functional biomarkers.

Inflammation and the preterm heart

Cardiac dysfunction in adults is well described in the setting of sepsis and inflammation and is linked to the release of cytokines and tissue hypoxia [195, 196] (see for review [197]).

Little is known about the effects of intrauterine or early postnatal inflammation on the morphogenesis of the heart and its consequences for the preterm infant. Growth, formation, and development of the cardiomyocytes continue until birth [198] and may be potentially disrupted through inflammation as changes in the transcriptome of fetal cardiac tissue after inflammation were found [199]. Since the first description of David Barker [200], growing evidence suggests an association of preterm birth and high blood pressure, type 2 diabetes, and stroke in adulthood [201–203], but pathophysiological mechanisms remain to be determined. The fetal environment seems to play an important role in morphogenesis of the heart during pregnancy, as infants born after preeclampsia have a higher risk to develop high blood pressure and stroke in later years [204–206]. Exposure of the immature heart and vessels to a pro-inflammatory milieu [207, 208] may lead to epigenetic modifications [209, 210], perturbation in cardiac development-related genes, and changes of the activity of transcription factors linked to chronic inflammation and later atherosclerosis [211]. Furthermore, direct effects of bacterial toxins were shown to injure cardiomyocytes in vitro and reduce the number of cardiomyocytes [212–214] with subsequent loss of cardiac function [215]. Further hits during the neonatal period (infections, oxygen delivery) may potentially increase the risk for a chronic inflammatory response which may predispose for cardiovascular diseases in later life [216, 217]. In adults, toll-like receptors (TLR) play a role in septic myocardial dysfunction [218], demonstrated by a reduced dysfunction after administration of TLR4 inhibitors in experimental models [218–220]. In fetal sheep endotoxin models, an increase of TLR2 and 4 mRNA levels was also detectable, suggesting identical mechanisms in the fetus [214]. Other clinical studies of chorioamnionitis suggest effects of intra-amniotic inflammation on cardiac dysfunction [221, 222].

The heart of preterm infants is functionally and structurally immature and susceptible to the preterm environment [216]. Ex-preterm infants have increased left and right ventricular mass and altered systolic and diastolic function [204, 223]. Inflammatory processes are known to play an important role in the pathogenesis of pulmonary hypertension and therefore have an indirect effect on cardiac outcome. However, inflammation has direct effects on myocardial structure and function in preterm infants. Velten et al. could demonstrate an effect of systemic maternal inflammation followed by neonatal hyperoxia on left ventricular structure and systolic and diastolic dysfunction [224]. Therefore, inflammation in early life might play a significant role in remodeling of the cardiac structures with consecutive loss of function in later life. Associations between infection-related hospitalization in infancy and cardiovascular disease in adulthood were reported [225]. Ex-preterm infants often have restricted activities of daily living which might be associated with cardiorespiratory insufficiency and increased energy requirements (due to SI). Hence, growth failure is a critical issue. In the GNN follow-up investigation at 5 years of age, we noted that a significant proportion of preterm infants has a growth disadvantage as compared with term infants examined in the "German Health Interview and Examination Survey for Children and Adolescents" (KiGGS) study (mean ~2.5 kg less body weight, ~4 cm less body length). The administration of *Lactobacillus acidophilus/Bifidobacterium* spp. probiotics—as proposed "stabilizer of the microbiome"—during primary stay in hospital resulted in improved growth, particularly in infants who were early exposed to antibiotics [151].

Inflammation and the preterm kidney

Little information exists on the effects of inflammation on preterm kidney function. Term newborns present usually with an amount of over 300,000 nephrons [226]. Theoretically, nephrogenesis is sensitive for inflammatory events, as it continues until 34–36 weeks of gestation [46] (Fig. 3). Susceptibility of the nephrogenesis to exogenous noxious substances was proven in experimental models with postnatal exposure to hyperoxia and a 25% reduction of nephron numbers that persisted into adulthood [227]. In adults with septicemia, oliguria is interpreted as manifestation of renal inflammation [228, 229]. Oliguria is often a hallmark of the "inflammatory phenotype" in preterm infants. Clinical data of infants born after chorioamnionitis and treated with indomethacin suggest a harming effect on renal development [230]. In preterm fetal sheep exposed to LPS-induced intrauterine inflammation, a reduction of nephron numbers, but not of kidney or birth weight, was demonstrated [231]. This might be a risk factor for impaired renal function or a predisposition for second hits (indomethacin) during the neonatal period and for hypertension in later life [232]. How these observations occur

if these are the result of renal hypoperfusion or renal inflammation during chorioamnionitis and which molecular pathways lead to such damages is largely unknown and remains speculative.

Inflammation and preterm sex differences

The personalized approach to maximize results and minimize risks particularly of new targeted treatments against SI requires genotypic and phenotypic fine-tuning of the single preterm baby including information beyond gestational age as the main contributor to adverse SI-related outcome. The significance of gender (including the role of sex hormones, sex chromosomes) has been well established for inflammation processes and microbiome development in animal models and observed in a variety of human studies [233]. The gender difference is particularly marked among preterm infants, where females have a distinct survival and outcome advantage at similar birth weights and gestational ages [4, 234]. Female preterm infants have a decreased risk for severe courses of infectious diseases as compared with males (bacterial, viral, fungal) [234–241]. Gender differences have also been reported in several responses of inflammatory signaling processes, with a tendency towards a more anti-inflammatory environment in female infants. For example, reduced oxidative stress biomarkers and concentrations of myeloperoxidase were found in female preterms [242, 243]. In umbilical cord blood, females were shown to have increased CD4+/CD8+ T cell ratios and reduced numbers of NK cells [233]. After stimulation with LPS, female cord blood cells showed reduced concentrations of pro-inflammatory cytokines (IL-1ß and IL-6) than male cells [244]. Animal models reveal a gender-specific response to inflammatory stimuli with an advantage for female rodents. In female newborn rats, for example, the increased production of IL-2, IFN-γ, and TNF-α is thought to promote the Th-1 response in better defending against infection [245]. Reasons for the mmunological advantage of female infants are mainly unknown, while multidirectional cross talk between host immunity, microbiota, and the endocrine system is anticipated. Bacteria are able to produce hormones (e.g., serotonin, dopamine, and somatostatine), to interact with host hormones (e.g., estrogens), and to regulate the host hormones' homeostasis (e.g., by inhibiting gene prolactin transcription or converting glucocorticoids to androgens) which can lead to context-dependent immunosuppression or activation. Differences in the gut microbiome profiles in newborn infants have been described with higher abundance of *Enterobacteriales* and lower abundance of *Clostridiales* in males shortly after birth [246].

Some light is shed on the important role of sex chromosomes, signaling genes and single nucleotide polymorphisms, microRNAs, methylation alterations, and hormonal concentrations which are discussed elsewhere [247]. The role of these findings on clinical effects is unknown and requires further studies.

Conclusions and future outlook

The concept that sustained inflammation contributes to short- and long-term complications after preterm birth has been largely accepted. Numerous observational studies demonstrate a risk association between unfavorable immune adaptation and long-term vulnerability for infections [248], CPIP and asthma [56, 249], neurodevelopmental impairment, and stress incontinence [250, 251]. The underlying mechanisms, in particular the host factors determining resilience or long-term vulnerability, remain to be elucidated. To improve outcome in preterm babies, clinicians hope for the successful identification of distinct "immune-microbiome signatures" in preterm babies as biomarkers for the development of new SI-targeted therapies. The main challenges and potential approaches are described in Table 2. At this stage, non-specific preventive measures of acute inflammatory episodes and SI have the highest priority in clinical practice, including the following:

(i) Hygiene and surveillance: the key to reduce sepsis rates is hand hygiene, training of staff and parents, surveillance and network participation, and the avoidance of understaffing and overcrowding.
(ii) Less invasive care approach: preterm infants may benefit from less invasive respiratory management [13, 252] and rapid feeding advancement [253].
(iii) Human milk feeding: human milk is beneficial in terms of sepsis rates and reduces the risk for ROP and BPD and asthma. It contains S100 A8/9, growth factors, and human milk oligosaccharides (HMOs) which cannot be digested by humans that facilitate the growth of "beneficial" bifidobacteria and support the production of SFCAs.
(iv) Antibiotic stewardship programs: the implementation of antibiotic stewardship programs increases awareness and reduces the rates of drug-resistant organisms.
(v) Strengthening the immune system: vaccinations to mothers and infants are important modes of infection prevention and immunological maturation, and the continuum of parental care from birth even in an intensive care setting is highly immune promoting.
(vi) Avoidance of adverse exposures: extensive counseling of parents is needed to avoid passive smoking and stressful experiences.

Table 2 Targeting sustained inflammation to improve outcome in preterm infants: challenges and outcomes

Challenge	Approach
Inflammatory episodes (sepsis, NEC) remain predominant causes of mortality and long-term morbidity	Implementation of inflammation prevention bundles (hygiene, antibiotic stewardship programs, restrictive use of invasive measures, promotion of human milk feeding)
Large center-specific variations	Continuous establishment of quality improvement networks
Understanding of underlying pathophysiological mechanisms	Well-phenotyped large-scale longitudinal studies, systems biology approaches
	Mechanistic neonatal mouse or rhesus monkey models, in silico modeling
Availability of animal models for preterm infants	Organoid models to investigate organ-specific mechanisms of SI
Limited opportunity to study tissue-specific aspects	
Disentangle the impact of prenatal and postnatal factors	Linking perinatal, neonatal datasets to follow-up data from cohort studies; target "neonatal window of opportunity"
Establishment of a physiological immune-microbiome adaptation despite postnatal intensive care	Basic research addressing long-term effects of perinatal exposures (e.g., antibiotics), postnatal biomarkers (e.g., S100 A8/9, T_{reg}), and interventions (pre-/pro-/synbiotics; anti-inflammatory compounds; stem cells)
	Phase I–III clinical trials and randomized, placebo controlled trials with long-term follow-up
Lack of valid outcome measures of important organ functions (e.g., cognition, lung function)	Development of new tools for early short-term assessment; childhood follow-up with detailed determination of beneficial factors (human milk feeding, vaccinations) and harmful exposures (passive smoke, lack of participation)
	Define further "windows of opportunity" during infancy and childhood; study interventions to promote long-term health in controlled trials (e.g., music, sport, nutrition)
Targeted personalized therapies of preterm infants	Use of polygenic risk scores from adult cohorts for preterm infants and establishment of valuable trajectory-specific biomarkers (e.g., S100 A8/9)

(vii) Provision of developmental care: early neurodevelopmental support and continued case management are needed to promote long-term health.

Hence, a more personalized precision medicine approach is needed. The neonatal period has lifelong imprinting effects and remains the primary window of opportunity for prevention or intervention [254]. It could be promising to extrapolate the set trajectory of immune development in term infants [255] into the context of preterm birth. A proportion of preterm babies is capable of rapid neonatal progression to "catch up" immune function with immune profiles converging in a similar time frame to term babies [256]. Infants with postnatal inflammation, however, may have distinct immune signatures and microbiome patterns before the "inflammatory" event and thereafter. Polygenic risk profiling can identify several stages of vulnerability, and standardized observational times can target gene-environment interactions. Systems biology approaches and large sample sizes are needed to account for the different factors which challenge the transcriptional and epigenetic reprogramming of systemic and mucosal immunity, e.g., colonizing microbes and their metabolites, nutritional antigens, drugs, and vaccines [257, 258]. Multinational network approaches are needed to align definitions for sepsis and sustained inflammation and to study interventions in prespecified subgroups.

Authors' contributions AH and CH had the idea of the review; AH, MF, BS, and CH performed the literature research; AH, EH, MK, WG, and CH performed the data analysis; AH and CH drafted the first version of the manuscript; and all authors critically revised the work.

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Compliance with ethical standards

Conflicts of interest Christoph Härtel is a lead principal investigator of the PRIMAL clinical study investigating the effect of probiotics to prevent gut dysbiosis and inflammation in preterm infants born at 28–32 weeks of gestation. All other authors have no conflicts of interest relevant to this article to disclose.

Abbreviations BA, Bile acid; BPD, Bronchopulmonary dysplasia; CI, Confidence interval; CNS, Central nervous system; CPIP, Chronic pulmonary insufficiency of prematurity; CRP , C-reactive protein; CSF , Cerebrospinal fluid; DAMP , Damage-associated molecular patterns; ELGAN, Extremely Low Gestational Age Newborn Study; EOS, Early-onset sepsis; EPI, Extremely preterm infants; FXR, Farnesol X receptor; G-CSF , Granulocyte-colony stimulating factor; GI, Gastrointestinal tract; GNN, German Neonatal Network; GPRC, G protein-coupled receptor; ICAM , Intercellular cellular adhesion molecule; ICH, Intracerebral hemorrhage; IL, Interleukin; IQ, Intelligence quotient; KiGGS, German Health Interview and Examination Survey for Children and Adolescents; LOS, Late-onset sepsis; LPI, Late preterm infants; LPS, Lipopolysaccharide; MAMP, Microbe-associated molecular patterns;

MDSCs, Myeloid-derived suppressor cells; MIA, Maternal immune activation; MLPI, Moderate and late preterm infants; MPI, Moderate preterm infants; NEC, Necrotizing enterocolitis; OR, Odds ratio; PAMP, Pathogen-associated molecular patterns; PPROM, Preterm premature rupture of membranes; PVL, Periventricular leukomalacia; ROP, Retinopathy of prematurity; SCFA, Short-chain fatty acids; SI, Sustained inflammation; TLR, Toll-like receptors; TNF, Tumor necrosis factor; T_{reg}, Regulatory T cells; VEGF, Vascular endothelial growth factor; VPI, Very preterm infants; WPPSI, Wechsler Preschool and Primary Scale of Intelligence

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