Review Article

A narrative review of precision medicine in neonatal sepsis: genetic and epigenetic factors associated with disease susceptibility

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Background and Objective: Neonatal sepsis is a dysregulated host response to an infectious agent that results in severe morbidity and mortality among neonates worldwide. Given the complex and heterogenous nature of neonatal sepsis, early diagnosis and individualized treatment remain challenges for clinicians despite clinical advance. Epidemiological studies on twins suggest that hereditary factors act in conjunction with environmental factors to affect neonatal sepsis susceptibility. However, little is known about hereditary risks at present. This review aims to elucidate neonatal hereditary predisposition to sepsis and outline thoroughly the genomic landscape underlying neonatal sepsis, which may, to a large extent, facilitate precision medicine in this area.

Methods: PubMed was searched for all published literature relating to neonatal sepsis using Medical Subject Headings (MeSH) terms, with a focus on hereditary factors. Without any restriction on article type, articles published in English prior to June 1, 2022, were retrieved. Additionally, pediatric, adult, and animal- and laboratory-based studies were reviewed wherever possible.

Key Content and Findings: This review provides a detailed introduction regarding the hereditary risk of neonatal sepsis in terms of genetics and epigenetics. Its findings demonstrate the potential for translation to precision medicine, where risk stratification, early diagnosis, and individualized interventions might be matched to the certain population.

Conclusions: This review delineates the comprehensive genomic landscape underpinning inherent susceptibility to neonatal sepsis, allowing future studies to integrate hereditary information into a routine protocol and drive precision medicine from the bench to the bedside.

Keywords: Neonatal sepsis; hereditary susceptibility; genetics; epigenetics; precision medicine

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Introduction

Background

Neonatal sepsis is generally defined as a systematic condition caused by dysregulated host responses to infection, with pathogens ranging from bacteria to viruses and fungi (1-3). Based on the timing of onset, neonatal sepsis can be divided into either early-onset sepsis (EOS) or late-onset sepsis (LOS), with the classical cut-off point being the first 72 h after birth (4). In most cases, EOS results from vertical mother-to-infant transmission before and during delivery, whereas LOS is attributed to postnatal exposure to environmental organisms. Although overlap exists, the microorganisms isolated in EOS are typically different to those isolated in LOS. For example, Group B streptococcus and Escherichia coli are the top two causes of EOS, with infection rates of 43% and 29%, respectively (2), whereas coagulase-negative staphylococci and staphylococcus aureus are frequently detected in patients with LOS (5). Of note, considering the inherent vulnerability of neonates, opportunistic bacteria and fungi cannot be ignored. Neonatal sepsis may present asymptomatically or non-specifically with multiple systems involved. These symptoms can include temperature instability, poor feeding, respiratory distress, oliguria, diarrhea, jaundice, and purpura, which might mimic other diseases (3). The clinical usage of blood culture, the gold standard in diagnostics, is constrained by its low positive detection rate, long turnaround time and the influence of antibiotic administration (5). Due to its high negative predictive value and time- and sample-saving capabilities, quantitative real-time polymerase chain reaction (qPCR) of bacterial DNA is increasingly being used, but it is unable to conduct susceptibility tests or distinguish between active and resolved infections (6). Moreover, other culture-independent diagnostic tests, including complete blood count, C reactive protein, and procalcitonin, are regarded as being less than ideal indicators due to their lack of specificity (7).

Rationale and knowledge gap

Given the predicaments mentioned above, early diagnosis of neonatal sepsis is difficult; as a consequence, morbidity and mortality remain high despite advances in treatments. A more efficient prophylactic and diagnostic procedure is therefore urgently needed. The epidemiological study on twins suggests that hereditary factors act in conjunction with environmental factors to affect neonatal sepsis susceptibility (8). However, at present, little is known about the hereditary risks. Previous research has demonstrated that genomic polymorphisms change gene functions by altering transcription or translation, which is possibly involved in the pathophysiology of certain diseases including sepsis (9,10). Therefore, the identification of genetic components would potentially aid early risk stratification and individualized treatment and would provide the theoretical foundation for the clinical translation of precision medicine, which is a burgeoning paradigm intended to match the right interventions to the right population. To our knowledge, most existing papers are devoted to metabolomics, proteomics, or a subset of genomics (11-13), and no study to date has comprehensively summarized the hereditary risks of neonatal sepsis.

Objective

In this review, we will elaborate on the genetic and epigenetic factors of neonatal susceptibility to sepsis and endeavor to thoroughly define the genomic landscape underlying neonatal sepsis (*Figure 1*). We hope that integrating specific genomic makeup with other omics data will promote optimal precision medicine, where risk stratification, early diagnosis and personalized management are no longer dreams. We present the following article in accordance with the Narrative Review reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-22-369/rc).

Methods

A comprehensive search of PubMed was conducted using appropriate MeSH terms and keywords (*Table 1*). Without any restriction on the study type, articles published in English prior to June 1, 2022, were retrieved. Relevant pediatric, adult, and animal- and laboratory-based studies were reviewed wherever possible.

Genetic factors related to neonatal sepsis susceptibility

In sepsis, the immune and endothelium interact closely with the coagulation and fibrinolysis systems (1,9). Research indicates that functional changes of genes involved in these three systems, including substitutions, insertions, or deletions of base pairs, and copy number variants, are

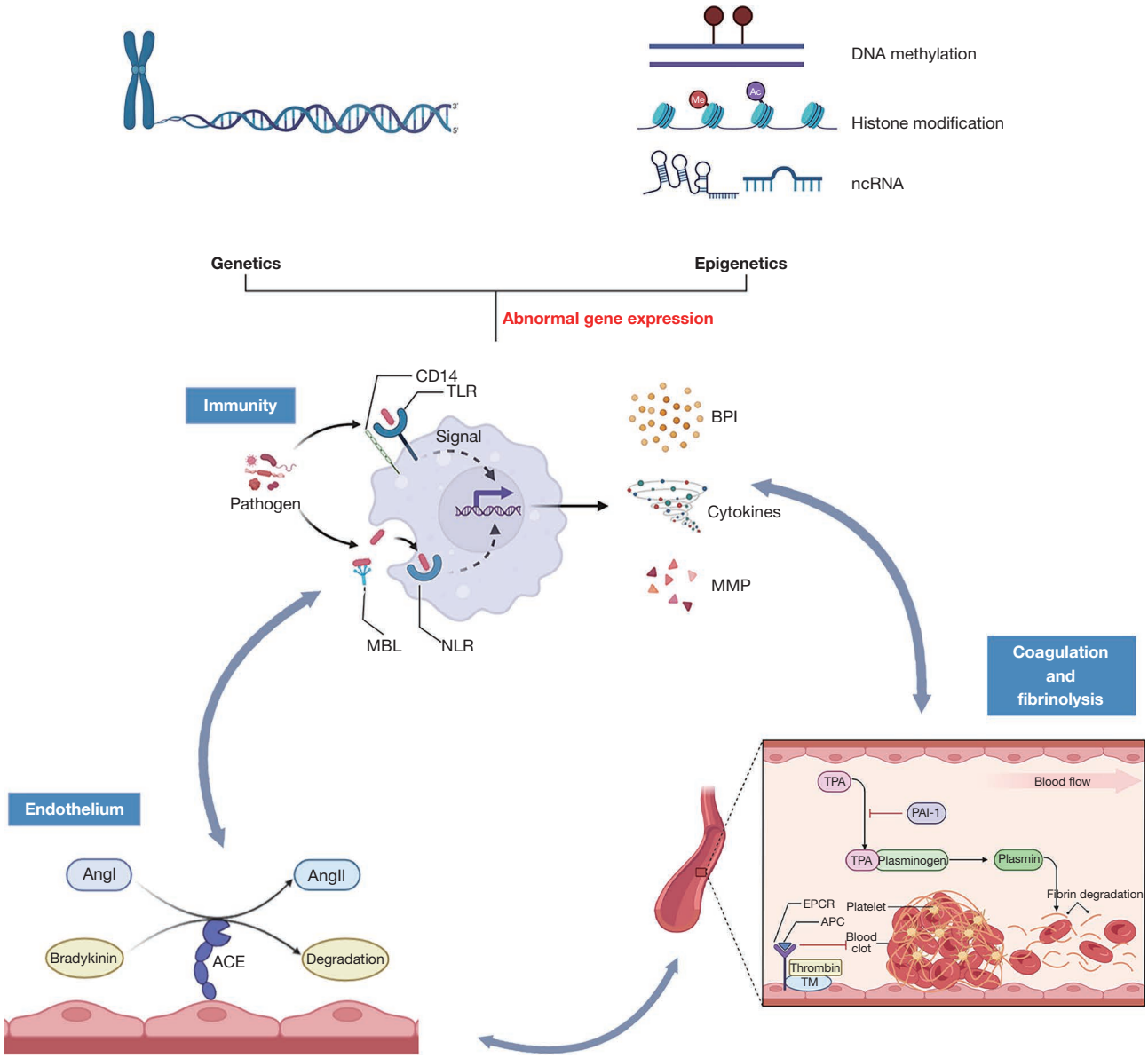

Figure 1 Potential mechanisms of hereditary susceptibility to neonatal sepsis. Both genetically and epigenetically aberrant gene expression involved in three closely interacted systems, immunity, epithelium together with coagulation and fibrinolysis, play a critical role in inherent tendency to sepsis. In newborns with above-mentioned risk determinants, once recognized by PRRs like TLRs and NLRs, the pathogen triggers a cascade of host responses, where underpowered clearance, 'cytokine storm', epithelial injury and unbalanced coagulation occur more frequently. Ultimately, these abnormal events give rise to sepsis development and even worse, multiple organ failure. ncRNA, non-coding RNA; TLR, Toll-like receptor; NLR, NOD-like receptor; MBL, mannose-binding lectin; BPI, bactericidal permeability increasing protein; MMP, matrix metalloproteinase; ACE, angiotensin converting enzyme; Ang, angiotensin; TPA, tissue plasminogen activator; PAI-1, plasminogen activator inhibitor-1; EPCR, endothelial protein C receptor; APC, activated protein C; TM, thrombomodulin; PRRs, pattern recognition receptors.

Table 1 The search strategy summary

Items	Specification
Date of search	June 1, 2022
Databases and other sources searched	PubMed
Search terms used	neonatal sepsis, pediatric sepsis, sepsis, genetics, epigenetics, polymorphism, variation, risk, susceptibility, precision medicine
Timeframe	Published before June 1, 2022
Inclusion and exclusion criteria	There was no restriction to the study type but only articles in English were included
Selection process	The search was conducted by the first author using methods discussed and approved by both authors

responsible for an individual's predisposition to neonatal sepsis (14). The putative loci are discussed below and summarized in *Table 2*.

Genes involved in the immune system

Recognition of pathogenic components

Toll-like receptors (TLRs) and relevant signaling molecules

TLRs, which comprise dozens of members, are a battery of receptors expressed in immune cells. They participate in a critical mechanism in recognizing various patterns of invading pathogens and subsequently inducing signaling transduction pathways (15,16). In recent decades, increasing evidence has shown whether polymorphisms in genes coding for or in the regulation of these pleiotropic receptors can affect the neonates' hereditary propensity to sepsis (17,18).

For *TLR2*, rs5743708G/A Arg753Gln has been investigated with mixed findings. In 2007, a case-control study of 143 Turkish children indicated a close relationship between the Arg753Gln polymorphism and a tendency for recurrent febrile bacteremia (19). Intriguingly, a recently published meta-analysis implied that unlike adults, children were marginally protected from sepsis by this genetic alteration (20). Another two polymorphisms, rs3804099T/C and rs3804100T/C, were found to be characterized by a potent correlation with neonatal sepsis in a retrospective study (21); however, a later investigation failed to produce similar results (18).

Regarding *TLR4* rs4986790A/G Asp299Gly and rs4986791C/T Thr399Ile, two of the most frequent hotspots, Sampath *et al.* carried out a prospective nested case-control study of 408 neonates with very low birth weight (VLBW, birth weight <1,500 g) and reported that both rendered neonates susceptible to gram-negative infections even in regression models with control for confounders (P=0.004) (22), which is consistent with the findings from Yuan *et al.* (23). Conversely, several other relevant investigations found that neither rs4986790 nor rs4986791 was linked with neonatal susceptibility to sepsis (18,20,24-26).

Molecules that interact with TLRs and then modulate downstream signals, such as interleukin-1 receptor-associated protein kinase 1 (IRAK1) and toll-interacting protein (TOLLIP), are also of clinical relevance. Sampath *et al.* reported that female infants with VLBW who had the *IRAK1* rs1059703C/T genotype tended to experience fewer gram-negative infections (22), and *TOLLIP* rs5743867T/C was found to decrease the sepsis risk in patients undergoing complex open-heart surgery who were under 1 year of age (27). Furthermore, additional variants have been topics of interest and studied in adults (28). Given that age is considered to be a confounder, more confirmatory research is needed to clarify whether these candidate variations play a pivotal role in neonates.

Nucleotide-binding oligomerization domains (NOD)-like receptors (NLRs)

NLRs serve as the receptors to diverse components derived from invasive microorganisms and induce autophagy for antigen presentation (29,30). NOD1 and NOD2, two members of the NLR superfamily, have attracted considerable attention. In an international cohort, Sampath *et al.* verified that the C allele of *NOD1* rs6958571 significantly increased the prevalence of gram-positive bacterial bloodstream infection in extremely low birth weight (birth weight <1,000 g) and Caucasian preterm neonates (31). In a study of 356 infants, Härtel *et al.* noted that those with VLBW and *NOD2*-3020insC mutation were more likely to suffer from blood culture-

Table 2 Genetic factors of neonatal sepsis discussed in our review

Gene name	Polymorphisms	Authors and publication year
TLR2	rs5743708+2477G/A Arg753Gln	Kutukculer *et al.*, 2007; Lu *et al.*, 2019
	rs3804099+19216T/C Asn199Asn	Abu-Maziad *et al.*, 2010; Martin *et al.*, 2018
	rs3804100T/C	Abu-Maziad *et al.*, 2010; Martin *et al.*, 2018
TLR4	rs4986790+896A/G Asp299Gly	Ahrens *et al.*, 2004; Härtel *et al.*, 2007; Yuan *et al.*, 2008; Sampath *et al.*, 2013; Swierzko *et al.*, 2016; Martin *et al.*, 2018; Lu *et al.*, 2019
	rs4986791+1196C/T Thr399Ile	Ahrens *et al.*, 2004; Härtel *et al.*, 2007; Yuan *et al.*, 2008; Sampath *et al.*, 2013; Swierzko *et al.*, 2016; Martin *et al.*, 2018; Lu *et al.*, 2019
IRAK1	rs1059703+1595T/C Leu532Ser	Sampath *et al.*, 2013
TOLLIP	rs5743867T/C	Fakhri *et al.*, 2016
NOD1(CARD4)	rs6958571 indel T/GG	Sampath *et al.*, 2017
NOD2(CARD15)	rs2066847+3020-/C Leu1007Pro	Ahrens *et al.*, 2004; Härtel *et al.*, 2007; Tekin *et al.*, 2012
	rs2066844C/T Arg702Trp	Tekin *et al.*, 2012
	rs2066845G/C Gly908Arg	Tekin *et al.*, 2012
CD14	rs2569190-159G/A (-260C/T)	Ahrens *et al.*, 2004; Baier *et al.*, 2006; Abu-Maziad *et al.*, 2010; Zhang *et al.*, 2013; Esposito *et al.*, 2014; Martin *et al.*, 2018; Mustarium *et al.*, 2019
MBL2	A/O haplotype (rs5030737+154C/T Asp52Cys, rs1800450+161G/A Gly54Asp, rs1800451+170G/A Gly57Glu	Ahrens *et al.*, 2004; Frakking *et al.*, 2007; Härtel *et al.*, 2007; Dzwonek *et al.*, 2008; van *et al.*, 2008; Abu-Maziad *et al.*, 2010; Koroglu *et al.*, 2010; Cinzia *et al.*, 2010; Ozkan *et al.*, 2012; Luo *et al.*, 2014; Swierzko *et al.*, 2016; Badawy *et al.*, 2018; Martin *et al.*, 2018; Lu *et al.*, 2019
TNFα	rs1800629-308G/A	Hedberg *et al.*, 2004; Sipahi *et al.*, 2006; Härtel *et al.*, 2011; Srinivasan *et al.*, 2017
IL-1B	rs16944-511G/A	Abu-Maziad *et al.*, 2010; Esposito *et al.*, 2014; Allam *et al.*, 2015; Mustarium *et al.*, 2019; Varljen *et al.*, 2020
	rs143634+3954C/T	Balding *et al.*, 2003; Treszl *et al.*, 2003; Abu-Maziad *et al.*, 2010; Zhang *et al.*, 2014; Lu *et al.*, 2019
IL-6	rs1800795-174G/C	Kilpinen *et al.*, 2001; Balding *et al.*, 2003; Treszl *et al.*, 2003; Harding *et al.*, 2003; Ahrens *et al.*, 2004; Gopel *et al.*, 2006; Sipahi *et al.*, 2006; Michalek *et al.*, 2007; Reiman *et al.*, 2008; Abu-Maziad *et al.*, 2010; Zidan *et al.*, 2014; Allam *et al.*, 2015; Gao *et al.*, 2015; Srinivasan *et al.*, 2017
IL-8(CXCL8)	rs4073-251T/A	Abu-Maziad *et al.*, 2010; Esposito *et al.*, 2014; Hu *et al.*, 2016; Fu *et al.*, 2019; Lu *et al.*, 2019
IL-10	rs1800896-1082A/G	Balding *et al.*, 2003; Treszl *et al.*, 2003; Baier *et al.*, 2006; Abu-Maziad *et al.*, 2010; Emonts *et al.*, 2010; Esposito *et al.*, 2014; Pan *et al.*, 2015; Srinivasan *et al.*, 2017
BPI	rs4358188+645A/G Lys216Glu	Michalek *et al.*, 2007; Abu-Maziad *et al.*, 2010; Esposito *et al.*, 2014; Martin *et al.*, 2018; Mustarium *et al.*, 2019
	rs5743507+545G/C Val182Val	Michalek *et al.*, 2007
MMP16	rs2664349+39811 A/G	Esposito *et al.*, 2014; Mustarium *et al.*, 2019
ACE	rs4646994/rs4340 intron16 289bp Alu ins/del	John *et al.*, 2005; Cogulu *et al.*, 2008; Spiegler *et al.*, 2010; Hou *et al.*, 2015; Dou *et al.*, 2017; Lu *et al.*, 2019; Jarahzadeh *et al.*, 2022
Factor V	rs6025+1691G/A Arg506Gln	Härtel *et al.*, 2006
Factor II	20210G/A	Härtel *et al.*, 2006

Table 2 (*continued*)

Table 2 (*continued*)

Gene name	Polymorphisms	Authors and publication year
Factor VII	323del/ins	Härtel *et al.*, 2006
Factor XIII	rs5985C/A Val34Leu	Härtel *et al.*, 2006
PAI-1	rs1799768-675 5G/4G	Li *et al.*, 2013; Shi C *et al.*, 2015; Shi Q *et al.*, 2015; Lu *et al.*, 2019; Jarahzadeh *et al.*, 2022
EPCR	exon3 23bp del/ins	Taylor *et al.*, 2000; Esmon *et al.*, 2003; Sipahi *et al.*, 2006
VDR	rs2228570T/C (FokI)	Das *et al.*, 2016; Zeljic *et al.*, 2017; Tayel *et al.*, 2018
	rs731236C/T (TaqI)	Das *et al.*, 2016; Zeljic *et al.*, 2017; Tayel *et al.*, 2018
	rs2107301	He *et al.*, 2021
	rs2189480	He *et al.*, 2021
	rs9729	He *et al.*, 2021
	rs2239815	He *et al.*, 2021
	rs3782905	He *et al.*, 2021
	rs4516035T/C	He *et al.*, 2021
	rs7139166	He *et al.*, 2021
	rs11168266	He *et al.*, 2021
	rs11168293	He *et al.*, 2021
	rs739837	Xiao *et al.*, 2022
TREM1	rs2234246G/A	Xiao *et al.*, 2022

TLR, Toll-like receptor; IRAK1, interleukin-1R-associated protein kinase 1; TOLLIP, Toll-interacting protein; NOD, nucleotide-binding oligomerization domains; CD14, cluster of differentiation 14; MBL, mannose-binding lectin; TNFα, tumor necrosis factor alpha; IL, interleukin; BPI, bactericidal permeability increasing protein; MMP, matrix metalloproteinase; ACE, angiotensin converting enzyme; PAI-1, plasminogen activator inhibitor 1; EPCR, endothelial protein C receptor; VDR, vitamin D receptor; TREM1, triggering receptor expressed on myeloid cells 1.

proven sepsis (25); however, Ahrens *et al.* drew a different conclusion (24). Additionally, Tekin *et al.* evaluated three common mutations within the *NOD2* gene (Arg702Trp, Gly908Arg, and Leu1007Pro) and illustrated their contributions to septic susceptibility, which highlighted the role of *NOD2* (32).

Cluster of differentiation 14 (CD14)

CD14 is an adjuvant co-receptor with a constitutive expression in a large variety of cells, which aids better recognition of pathogenic components by TLRs (33,34). *CD14* rs2569190-159G/A, which is identical to -260C/T, has been explored in newborns with conflicting results. A retrospective study recruiting 293 mechanically ventilated infants with VLBW showed effects of the T allele on multiple episodes of blood stream infection, of which the strongest was in African-American infants (CC: 15%, CT: 11%, TT: 39%, P=0.003) (35). Another survey seems appeared to verify this tendency, where Esposito *et al.* considered this polymorphic site to be a risk factor for severe sepsis (36). Nonetheless, Martin *et al.* argued a protective effect of the T/T genotype on neonatal sepsis (18), but several other meta-analyses were unable to demonstrate any association (21,24,37,38). Inherent differences, such as ethnicity and comorbidities, may in part explain these divergent results.

Mannose-binding lectin (MBL)

MBL, a type of opsonin, plays a part in the binding of pathogenic components, boosting of lectin-dependent complement activation, and mediation of phagocytic clearance of pathogens (39-41). *MBL2* rs5030737, rs1800450, and rs1800451 form three distinct alleles, named B, C, and D, respectively, and are collectively known as O, with A being the wild type. Cumulative evidence confirmed that a low serum MBL concentration resulting from O was

associated with a higher incidence of sepsis in all age groups (20,26,42-46). Unfortunately, this theory did not hold in observations focused on neonatal sepsis, in which no such correlation was found (18,21,24,25,47-49). The mixed data mentioned above raise the question as to the exact role of *MBL2* in neonatal sepsis.

Cytokine responses

Tumor necrosis factor alpha (TNFα)

Soon after an infectious stimulus, a host with normal immune function is flooded with a crucial cytokine TNFα, triggering a succession of primitive responses to invasion (50). In this regard, aberrance in the quality or quantity of TNFα secretion caused by polymorphic variations might remodel the susceptibility to, or prognosis of, sepsis. Among several candidate mutations, *TNFα* rs1800629-308G/A stands out as having high potential. Through *in vitro* experiments, the rarer A allele was delineated to increase the transcriptional and translational activities of *TNFα* compared with the G allele (51). Sipahi *et al.* evaluated 53 children with severe sepsis aged 0 to 15 years and found that allele A-carrying status was related to the prevalence but not the outcome (52). In a retrospective cohort with 173 mechanically ventilated infants with VLBW, the allele A was reported to be a genetic modulator of mortality once sepsis had developed (53). However, these findings could not be replicated in the following research (54,55). Moreover, a pattern of predisposition conferred by the G allele was observed in a group of Saudi term neonates (56), which concurred with the findings of an updated meta-analysis on the pediatric subgroup (57). Even though these discoveries have linked -308G/A with the predisposition to and the severity of sepsis, an explicit conclusion cannot be drawn due to the lack of studies in larger cohorts and with more stringent control for confounders.

Interleukin (IL)-1

IL-1 is a potent member of the chemokine superfamily and is generally accepted as an integral mediator in the pathogenesis of sepsis. Three disparate polypeptides—IL-1α, IL-1β, and IL-1Ra (IL-1 receptor antagonist) constitute the whole IL-1 family (58). As early as 1993, elevated IL-1β was detected in neonates with EOS compared with controls (59), which provided a rationale for speculation that genetic variability fluctuating IL-1β level might modulate the course of neonatal sepsis.

Regarding *IL-1B*, the coding gene of IL-1β, Varljen *et al.* discovered an enrichment of the rs16944-511AA genotype in preterm infants suffering from and succumbing to EOS (60). Although no positive association was reported by Abu-Maziad *et al.* (21), Esposito *et al.* ascertained a notable increase in the overall risk of sepsis development in preterm infants with the rs1143643 TT or CT genotype, which supported the latter observation (36). However, in a Saudi Arabian neonatal cohort, CC genotype carriers presented with a higher concentration of circulating IL-1β and an increased risk of EOS. *IL-1B* rs143634+3954C/T is a synonymous variant with no amino acid changes, and its TT genotype was linked with increased IL-1β but decreased susceptibility to sepsis in adults (20,61); however, similar conclusions have not been drawn in younger individuals so far (21,62,63). It is worth pointing out that such discernable age gap awaits to be addressed, and these results will add evidence to the notion that the balance of the ratio of IL-1 to IL-1Ra plays a role in sepsis progression, rather than IL-1 or IL-1Ra alone.

IL-6

IL-6 is a proinflammatory cytokine that activates lymphocytes, induces pyrogen, and accelerates acute-phase reactants and antibody synthesis (64). These pleiotropic properties make IL-6 an integrative index and a biologically plausible candidate gene of sepsis. A pilot study involving neonates illustrated that lipopolysaccharide induced higher IL-6 expression in monocytes isolated from carriers of the C allele of rs1800795 (65), and this finding was supported by several subsequent articles in which the C allele was concluded to be a sepsis-predisposing and/or -modifying variant (35,66,67). Discrepant results are unsurprising considering of the diversity in research methods and the general characteristics of samples. Harding *et al.* put forward that the G allele might impair the defense against bacteria (68), and Zidan *et al.* verified an association of the G allele with community-acquired pneumonia (69). Similarly, increased EOS frequency, repeated septicemia episodes, and decreased survival rate were reported in GG homozygotes (24,56,62). Beyond that, several studies failed to obtain any correlation (21,52,55,63,70,71). Excessive systemic release of IL-6 is thought to be a core in the pathophysiology of sepsis, but which allele is responsible has yet to be determined.

IL-8

IL-8, also termed CXCL8, possesses the ability to motivate neutrophil recruitment, adjust inflammatory reactions, and promote angiogenesis (64). Studies have observed that *IL-8* rs4073-251T/A boosted IL-8 production under lipopolysaccharide stimulation and, thus, exerted an

influence on various pathological conditions to a certain degree (72-75). Hu *et al.* found that males carrying the T allele or TT genotype were more susceptible to sepsis (76), which was diametrically opposite to Lu *et al.* and Fu *et al.* (20,77). Interestingly, focusing on premature infants, Esposito *et al.* concluded that the AT genotype aggravated the development of sepsis (36), whereas Abu-Maziad *et al.* dismissed any effect caused by this mutation (21). Admixture of ethnicity and sex, combined with the distinct definitions used, might partially explain why such notable conflicts have emerged.

IL-10

Under normal circumstances, to maintain homeostasis, overwhelming proinflammatory responses are under tight regulation by anti-inflammatory mediators, of which IL-10 works best. *IL-10* rs1800896-1082A/G is positioned in the 5'-flanking region with higher IL-10 inducibility (78). Similar to Baier *et al.* and Balding *et al.* (35,62), Srinivasan *et al.* clarified a defensive function of the GG genotype (odds ratio =0.51) (55). However, not all studies have obtained statistically significant results (36,63,79). Abu-Maziad *et al.* illustrated an inverse relationship between the GG genotype and gram-negative infection risk in a large preterm cohort (21), which corresponded with results from a meta-analysis confirmed in an Asian population (80). The insufficient reproducibility may be explained by developmental differences; that is to say, the propensity or progression of sepsis is influenced by the degree of immune system maturation.

Other immunological genes

Bactericidal permeability increasing protein (BPI)

With high potency and affinity to lipopolysaccharide, BPI acts as a key effector in antibacterial defense. The increased risk of gram-negative bacterial infection can be partially attributed to selective BPI deficiency in neonates (81), and a randomized controlled trial proposed that recombinant BPI held promise as an adjunctive treatment for children with severe meningococcal sepsis (82). According to Esposito *et al.*, the rs4358188 AG genotype protected premature neonates from sepsis (36), and Abu-Maziad *et al.*, Martin *et al.*, and Mustarim *et al.* did not detect any genetic risk profile of *BPI* alleles (18,21,37). Moreover, Michalek *et al.* noted that children carrying rs4358188 GG combined with rs5743507 AG or GG haplotypes were more likely to suffer from gram-negative sepsis and resultant complications (83).

Matrix metalloproteinases (MMPs)

Several lines of evidence have made it clear that zinc-relevant MMPs are not only matrix-degrading enzymes but also function as a mechanism in immune modulation (84,85). While appropriate MMP secretion accelerates infection eradication, excess MMP production becomes a tissue destroyer, which favors microorganism dissemination and persistence. This lays the foundation for MMP genetic polymorphisms being a logical candidate (85). *MMP-16* is a new player in bronchopulmonary dysplasia (86), whose rs2664349+39811 GG genotype was described as being closely correlated with bacteriologically proven sepsis (36). Findings from a cross-sectional study suggested that this G to A mutation might eventually pose a danger, as most preterm infants in both the proven and unproven neonatal sepsis groups exhibited variations, albeit with inadequate statistical significance (37). As a corollary, preparations targeting aberrant MMP have been evaluated for the adjunctive treatment of patients with sepsis and septic shock including retinoids and glucocorticoids (2).

Genes involved in endothelial factors

Chiefly distributed on epithelial cells, the carboxypeptidase angiotensin converting enzyme (ACE) functions as a crucial regulator of hemodynamic stasis by converting angiotensin (Ang) I to Ang II and participating in bradykinin catabolism (87). In both *in vivo* and *in vitro* studies, ACE deficiency has been widely characterized in patients suffering from sepsis, indicating a potential role of ACE in sepsis (87,88). The variation consisting of either the presence (insertion, I) or the absence (deletion, D) of a 287 bp Alu repeat fragment has been assessed and is believed to be a leading contributor in determining serum ACE concentration (89). Findings on the predictive value of allele D in the propensity to and the outcome of sepsis are extremely inconsistent in different studies (20,90,91). In keeping with Spiegler *et al.* (92), John Baier *et al.* discovered comparable rates of sepsis mortality and morbidity independent of *ACE* I/D genotype in mechanically ventilated infants with VLBW (93). On the other hand, a retrospective study demonstrated an adverse effect of I allele on pediatric sepsis development (94), providing favorable evidence for a subsequent meta-analysis (91). However, this was conclusively proven to be incorrect by a more recent one (95). Selection bias should be taken into consideration since mechanical ventilation and low birth weight can predispose newborns to sepsis (2).

As a mandatory participant of the renin-angiotensin-aldosterone system (RAAS), there is not only an ongoing

debate regarding the influence of *ACE* I/D on sepsis risk and outcomes but also in relation to the therapeutic value of RAAS derivatives (96-99). Despite the current lack of an unequivocal answer, in no way can we exclude the possibility of other variations or haplotypes of the ACE coding gene or linkage disequilibrium with functional genetic determinants.

Genes involved in the coagulation and fibrinolysis system

Homeostasis is badly disrupted during sepsis and a vicious circle occurs. Fulminant inflammation elicited by cytokines or other proinflammatory elements concurrently exacerbates the coagulation cascade, which in turn amplifies inflammation (100). This mutual independence underlines the notion that malfunction in any part of the coagulation pathway may modify the onset and evolution of sepsis and, consequently, offer novel insights into biomarkers and therapeutic implications for clinical exploration, especially in naturally hypercoagulable newborns (101,102).

Coagulation factors

Culminating in thrombin generation, the intrinsic and extrinsic coagulation pathways are regulated by 13 coagulation factors (Factor I to XIII). Härtel *et al.* removed *Factor V* rs6025G/A Arg506Gln (Factor V Leidon or FVL), *Factor II* 20210G/A, and *Factor VII* 323del/ins from the list of candidate inherited risk predictors, and simultaneously illustrated that the rs5985C/A Val34Leu mutation of *Factor XIII*—a transglutaminase that enhances the stability of cross-linked fibrin polymers through bridging bonds between monomers—predisposed carriers to neonatal sepsis (103). It is tempting to postulate that transformation of the fibrin meshwork to premature structures with thinner fibers and smaller pores as well as the resultant less vigorous response prompted by Val34Leu may contribute to risk alterations (104,105), but a tenable interpretation is currently lacking due to shortcomings in reproducibility.

Plasminogen activator inhibitor-1 (PAI-1)

Fibrin is viewed as a double-edged sword in that moderate generation prevents bleeding while overzealous deposition gives rise to vessel occlusion and, in severe cases, organ dysfunction. Degradation of fibrin is mostly performed by plasmin, a ubiquitous proteinase existing in the form of deactivated plasminogen. Plasminogen activator converts the precursor to its active form, whose proteolytic contributions can be rapidly diminished by specific blocker PAI-1. The *PAI-1* gene possesses an insertion/deletion of G residue polymorphism (either the 4G or 5G allele), of which the 5G allele accounts for profoundly decreased plasma PAI-1 concentration secondary to repressed transcription (106). Shi *et al.* suggested no association between *PAI-1* 4G/5G with sepsis (107), which was dramatically overturned in the same year (108). Recently, Jarahzadeh *et al.* published literature restricted to pediatric cases, and they stated that children with the 4G allele showed higher incidence of sepsis than their peers (95), which was identical to the conclusions of Lu *et al.* and Li *et al.* (20,109). Case-control reports involving neonates leave much to be desired, and caution is warranted until rigorous experimental verification becomes available.

Endothelial protein C receptor (EPCR)

EPCR is a receptor that indirectly facilitates PC activation by presenting PC to the membrane-bound thrombin-thrombomodulin complex, and exhibits an anti-inflammatory function in animal experiments (110,111). Sipahi *et al.* once explored a 23 bp insertion mutation within exon 3 of the *EPCR* gene and found a significantly higher odds ratio in children with sepsis (52). Together with other supporting evidence (112,113), these emerging findings pave the way to a better understanding of neonatal sepsis.

The demise of recombinant human activated PC marks the last chapter of the story and addresses a conundrum about the real role of coagulation in sepsis (114). As Fiusa *et al.* discussed from an evolutionary medicine perspective, a threshold might exist, above which coagulation activation is harmful and below which it enhances pathogen clearance (115). This again emphasizes the extreme complexity of the sepsis triad of inflammation, coagulation, and fibrinolysis, and more importantly, provides a unique insight into sepsis pathophysiology and tailored interventions.

Other potential genes

Vitamin D receptor (VDR)

In addition to being a classical modulator of calcium and phosphorus homeostasis, vitamin D exhibits antimicrobial and anti-inflammatory properties in a VDR-binding method (116,117). Emerging evidence has revealed a trend of alteration in vitamin D production and stability driven by several *VDR* gene polymorphic differences (118). For example, assessing rs2228570T/C (FokI) and rs731236C/T (TaqI) in a small Indian cohort, Das *et al.* discovered vitamin D insufficiency in participants with sepsis, but

the distributions of both FokI and TaqI deviated from the Hardy-Weinberg equilibrium (119). TaqI has not been indicated to have any association in subsequent reports (120,121). Regarding the silent mutation FokI, the TT genotype and T allele were delineated as a hazard to vitamin D expression and EOS development (121), which was the exact opposite of findings in Serbian adults (120). Recent efforts involving other allelic loci have further underscored the association between the *VDR* gene and sepsis (122). Of note, other than the G allele of *VDR* rs739837, Xiao *et al.* stated that the rs2234246 T allele of triggering receptor expressed on myeloid cells 1 (*TREM-1*), an immunoglobulin activated transmembrane receptor, could predict neonatal sepsis (123). One can easily posit that vitamin D supplements can have a favorable effect in sepsis prevention and alleviation, but whether *VDR* polymorphisms and haplotypes are eligible to be included in the expanding array of genetic markers remains to be established.

On balance, whether and how genetic alterations of this "restless warrior" contribute to individuals' variability in sepsis have yet to be explored. The current evidence represents only a small step in the assessment of the contribution of genetics to sepsis, and studies with high homogeneity are needed to correlate existing single nucleotide polymorphisms with specific products and other separate causative polymorphisms based on linkage disequilibrium.

Epigenetic factors related to neonatal sepsis susceptibility

Epigenetic traits emerge as a new layer of reshaping genomic topology without alterations in the DNA sequence. This fine-tuned heritable phenomenon, by and large, encompasses DNA methylation, non-coding RNAs (ncRNAs), and post-transcriptional modifications of histones, and functions as a gene-specific 'volume control' to activate or silence gene transcription (124,125). Evidence has shown that epigenetic changes participate in short- and long-term events of sepsis (126,127). Below, we outline a framework of recently proposed epigenetic signatures concerning sepsis.

Histones, a group of proteins responsible for packaging lengthy DNA strands into highly organized chromatin and post-transcriptional modifications, have a share in modifying chromatin dynamics and gene transcription. Underscoring the finding of sepsis-induced alterations in histone post-transcriptional modifications (128), Bermick *et al.* delineated a unique H3K4me3 pattern in neonatal monocytes exposed to chorioamnionitis (129). In synergy with changes in several known immune genes, this H3K4me3 pattern resulted in an insufficient defense against secondary microbial challenge, predisposing neonates to sepsis attack (129). Structural maintenance of chromosome (Smc) 4, a core subunit of condensin, was found to promote NF-κB essential modulator transcription to augment TLR- and virus-triggered proinflammatory responses by recruiting H4K5 acetylation (130). Furthermore, Smc4 knockdown protected mice from sepsis and sepsis-related mortality (130). These observations provided a basis for future explorations in risk prediction and even gene-editing therapy for neonatal sepsis.

DNA methylation is a chemical process where human DNA methyltransferases add a methyl group to cytosine, predominantly at CpG dinucleotides (131). In line with assessments in adults (132,133), differential methylation profiles were disclosed in neonates with and without sepsis, suggesting a potential use of DNA methylation as an indicator for neonatal sepsis prediction and subtype distinction (134). A similar result was yielded by a small epigenome-wide association study in which up to 81 differentially methylated CpGs mapped in 64 genes emerged with biological and clinical relevance (135). For example, protocadherin beta (*PCDHB*) genes, a panel of genes involved in calcium-dependent cell adhesion and antigen presentation, were hypermethylated in neonates with sepsis compared with healthy controls (135). According to Tendl *et al.*, pathogen-specific DNA methylation changes were only detected in the promoter region of the procalcitonin-relevant calcitonin-related polypeptide α (*CALCA*) gene and not in other simultaneously activated genes (*TLR4*, *MyD88*, and *CRP*) during neonatal sepsis (136). These findings mean that PCDHBm and CALCAm, along with other rarely studied sites, should be included into the list of epigenomic biomarkers of neonatal sepsis.

ncRNAs comprise a different set of molecules which are not translated to functional proteins (137). Aberrant expression profiles of ncRNAs have been consistently detected in various cell types and tissues from individuals with sepsis (138-140). Additionally, using samples from 87 neonates with sepsis or respiratory infection, Wang *et al.* evaluated the levels of miRNAs, which were considered to be indicators of adult sepsis (141). Up-regulation of miR-15a/16 was observed in cases with sepsis, the molecular mechanism of which pointed to the suppression of

lipopolysaccharide-promoted TLR4/IRAK1 signaling (141). Another study of neonatal sepsis identified 59 differentially expressed miRNAs between the case and control groups (including miR-181a, miR-141, and miR-143), and miR-16 was found to be down-regulated in gram-negative sepsis (142). Although these data suggest that some ncRNAs hold potential as potent fingerprints in neonatal sepsis, no consensus has been reached as to which single ncRNA or ncRNA panel bears maximal sensitivity and specificity while being translated into clinical use.

Overall, the data mentioned above theoretically reinforce the developmental programming hypothesis that, as an interface between the genome and the environment, epigenetic marks are rewritten in response to the early environmental input, maintaining a perpetual memory of alteration and holding the potential to provoke susceptibility to specific diseases in later life (143). There are promising signs that the development of reliable epigenetic biomarkers based on personal profiles for sepsis risk prediction, proper management, and prognostic assessment is on the horizon.

Precision medicine in neonatal sepsis

Timely and accurate diagnosis based solely on clinical and laboratory parameters has achieved only partial success. As a result, there is a relatively low threshold for clinical suspicion of infection and extensive empirical antibiotics usage due to concerns about catastrophic collapse secondary to delayed management. Furthermore, from the latter arises another concern about drug resistance. Undertreatment or overtreatment poses a profound threat to neonatal health, and continuous efforts have been dedicated to the search for an appropriate solution. The evidence mentioned above lays a theoretical foundation for the clinical translation of precision medicine, which is a burgeoning paradigm proposed to match the right interventions to the right population.

Polygenic risk scores (PRSs) have recently made strides in providing risk discrimination in several heterogenous clinical entities, including breast cancer and type 2 diabetes (144,145). This quantitative metric summarizes individual hereditary liability to a disease or a trait by calculating the cumulative impact of a range of genetic polymorphisms according to their respective weighed effect sizes (146). For sepsis, a single variant inadequately reflects the overall risk, but partial susceptibility may be captured when pooling a suite of genetic alleles, rendering the application of PRSs possible. Lu *et al.* extracted 17 variants from 64 candidate loci to construct a weighted genetic risk score, which was confirmed to be positively correlated with traumatic sepsis morbidity and fitted better when the injury severity score was added (147). Similarly, another PRSs program showed a good performance in screening out high-risk individuals (148). The PRSs of patients with septic shock reflected clinically relevant traits at genomic level, with the PRSs for a higher level of CRP being related to a higher septic shock risk (149). These interesting findings inform the translation from the percentile of PRSs to a quantitative estimation of an individual's predisposition to sepsis, which not only allows for timely prophylactic methods such as pathogen exposure attenuation and antibiotic interventions direct for those at-risk, but avoids unnecessary waste of resources. Despite the existing pioneering work, the PRSs have only just started to be translated from the bench to the bedside, and trials specific to neonates have yet to be conducted.

Evidence is accumulating that some of the abovementioned genetic variants are involved at different points of the disease trajectory. For instance, *TNFα* rs1800629-308G/A was designated as a popular genetic biomarker of susceptibility to and severity of sepsis in newborns (53,56), a probabilistic explanation of which might be the resultant excessive TNFα production and consequent uncontrolled tissue damage. An innovative macrophage-targeted RNA-interference system achieved the goal of down-regulation of TNFα, indicating a fundamental therapy for sepsis free of side effects, and analogous indications could be extrapolated to other polymorphisms (150). Moreover, emerging themes such as gene therapy and genetic editing systems hold promise to be included as adjunctive approaches once an in-depth complete genomic map has been drawn (151).

With the advent of the omics-data-driven era, identifying a genetic background at birth has become a feasible tool for prognostic and predictive enrichment and stratify neonates into cohorts with more homogeneity (12). Such precise stratification based on interrogation of genome will evolve to provide the basis for tailored managements, which is derived from the underpinning molecular mechanisms rather than common phenotypic signs. Nonetheless, given the unique predicaments in neonatology, there is still a long way to go before precision medicine can be fully embraced in the field of neonatal sepsis.

Discussion

Despite the progress in multidisciplinary treatment, a growing number of neonates are confronted with the potentially fatal challenge of sepsis after birth, which remains difficult to detect in its early stage. The epidemiological study on twins suggests that hereditary factors together with environmental factors modify the risk of neonatal sepsis (8). Understanding hereditary susceptibility comprehensively is therefore a cornerstone in further optimizing the risk assessment, continuous monitoring, accurate diagnosis, and personalized management of this vulnerable population.

In this review, the pathophysiological process of neonatal sepsis was divided into the following three parts and the genetic factors were summarized: the immune, endothelium, and coagulation and fibrinolysis systems. A single locus is unlikely to account fully for susceptibility to sepsis. Instead, it is the synthetic action of multiple causal loci, each of which has a slight effect, combined with other environmental risk factors, that determines the ultimate sepsis phenotype. Inconsistent results point to a flip-flop phenomenon, which describes opposite contributions made by the same allelic variant within the same disease based on different studies (152). Such discrepancies regarding the impact of a certain genetic polymorphism on susceptibility to neonatal sepsis may be explained by the following reasons to some extent. Firstly, the conspicuous heterogeneity of study population covers gestational age, birthweight, and comorbidities, which may mask the slight effect conferred by risk alleles. Secondly, some studies show methodological weaknesses in the selection of participants, where the controls might not have exposed to similar pathogens as cases. Therefore, more appropriate inclusion criteria are warranted, such as enrolling well-matched infectious individuals without deteriorating into sepsis. Thirdly, false positives or false negatives could be attributed to the relatively small sample sizes of studies. Fourthly, as allele frequencies, linkage disequilibrium patterns, and effect sizes of common polymorphisms vary with ancestry, caution should be exercised when extrapolating results to populations with different ancestral backgrounds. The fifth explanation relates to discrepancies in clinical phenotypes. It is problematic to include both EOS and LOS in terms of pathogenic microorganisms and immune maturation. Moreover, a consensus on neonatal sepsis definition is essential for the interpretation of blended findings. Finally, a polymorphism which has been demonstrated to be correlated with the risk or severity of sepsis, may, in reality, not be directly but rather indirectly involved through linkage with the actual genetic variation. Given that genes are not isolated, linkage disequilibrium, extended haplotype of a set of allelic mutations, and gene-environment interplay are issues that are too crucial to be dismissed without closer consideration.

Potential epigenetic mechanisms are discussed in the light of histone modifications, DNA methylation, and ncRNAs. The causal relationship between the two elements—that is, whether the pathogen exposure drives changes in epigenetics, or epigenetic signatures initiate development of sepsis—remains to be clarified. However, as James Watson said that "*You can inherit something beyond the DNA sequence. That's where the real excitement of genetics is now*." (153), epigenetics is still a frontier in biology in terms of understanding the possible mechanisms underpinning neonatal sepsis and delineating the new paradigm of precision medicine.

Finally, we introduce the prospect of applying precision medicine philosophy to neonatal sepsis. The inherent nature of neonatal medicine that constant vigilance and monitoring posed on babies are usually over protracted periods from birth, renders it an ideal setting for moving precision medicine to the clinical arena. The drawbacks of our current approach appear to be offset by the superiority of PRSs in remaining stable throughout life and enabling predictions to be made before noticeable symptoms. Moreover, gene therapy and immunomodulators based on individual genomic architecture might offer adjunctive resolutions to the emergence of antimicrobial-resistant bacteria. However, there remain some obstacles to transforming genomic data into practical paradigms, such as the cost-effect ratio, the training of clinicians, access to ancestry-matched gene banks, and, most importantly, negative public attitudes toward gene testing. Although skepticism regarding the adoption of precision medicine remains, a wealth of omics data and bioinformatics tools will assist with the implementation of precision medicine.

Strengths and limitations

To best of our knowledge, this is the first review to summarize the genetic and epigenetic risks of neonatal sepsis in detail and to outline promising opportunities for precision medicine. However, we must acknowledge, as a limitation of our review, that only published English language sources were retrieved. Furthermore, the drawing

of stronger conclusions warrants studies with improved methodology.

Conclusions

To conclude, inherited susceptibility to neonatal sepsis has been reviewed in detail in terms of genetics and epigenetics, which has shown that the candidate factors, together with pathways they participate in, play key roles in modifying host-pathogen interaction. Although controversies exist, it is time to integrate genomic sequencing into routine protocols for neonatal sepsis. In the future, precision medicine will make risk stratification, early diagnosis, and personalized management achievable. Future efforts are warranted to capture the full spectrum of inherited susceptibility to neonatal sepsis, focusing on the collection of additional sources of evidence such as gene knockout experiments, the development of functional machine-learning approaches, and the construction of global-wide biobanks. Furthermore, the requirements for legal and ethical frameworks regarding patient privacy should always be kept in mind to protect against genetic discrimination.

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