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Review

Gut bacteria and late-onset neonatal bloodstream infections in preterm infants

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SUMMARY

Late-onset neonatal bloodstream infections remain challenges in neonatology. Hand hygiene, line care, and judicious use of indwelling lines are welcome interventions, but might not reduce the incidence of late-onset neonatal bloodstream infections from bacteria originating in the gut. Accumulating data suggest that many pathogens causing late-onset neonatal bloodstream infections are of gut origin, including Gram-positive cocci. In addition to the host-canonical paradigm (i.e., all bacteria have equal risk of invasion and bloodstream infections are functions of variable infant susceptibility), we should now consider bacteria-canonical paradigms, whereby late-onset neonatal bloodstream infection is a function of colonization with a specific subset of bacteria with exceptional invasive potential. In either event, we can no longer be content to reactively approach late-onset neonatal bloodstream infections; instead we need to reduce the occurrences of these infections by broadening our scope of effort beyond line care, and determine the pre-invasive habitat of these pathogens.

1. Introduction

Late-onset neonatal bloodstream infections in preterm infants are illnesses (i) in which a credible pathogen is recovered from the blood, and (ii) that occur after the first 72 h of age [1–5]. The Gram-negative bacilli, Gram-positive cocci, and fungi that represent the majority of infections have differing pre-invasion habitats in the body, control strategies, treatments, and prognoses when they cause extraintestinal infections.

Infants who have had culture-proven late-onset neonatal bloodstream infections have higher mortality than those who have not had these infections [1,6]. Late-onset neonatal bloodstream infections in very low birth weight infants bestow independent risks to long-term child development, in addition to the well-recognized risks bestowed by brain injury, bronchopulmonary dysplasia, and retinopathy of prematurity [2]. Indeed, it has been calculated that a single late-onset neonatal bloodstream infection in a preterm infant approximately quadruples the likelihood of cerebral palsy, independent of intracranial structural abnormalities [7]. Neonatal infections are also associated with lower Bayley Scale of Infant Development II scores, worse psychomotor development, abnormal vision, and lesser occipital frontal circumferences, among those infants who survive their episode of late-onset neonatal bloodstream infections and who are discharged to home [3].

Our understanding of late-onset neonatal bloodstream infections is severely limited by their unpredictable onset in infants at risk. In this review, we emphasize data from human cohorts, and cite animal data only if they might illuminate human biology relevant to late-onset neonatal bloodstream infections.

2. Prospects for preventing late-onset neonatal bloodstream infections beyond line care and hand hygiene

Lessons can be learned from attempts to control early-onset (occurring <72 h after birth) infection with *Streptococcus agalactiae* (Group B streptococcus (GBS)). Screening for maternal colonization with GBS, and the treatment of mothers and their newborns with parenteral antibiotics (usually β-lactam agents), have reduced the incidence of early-onset bloodstream infections with GBS [8,9]. In contrast, the incidence of late-onset neonatal bloodstream infections caused by GBS is increasing [10,11], and can

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exceed the incidence of early-onset GBS bloodstream infections [12]. It is logical, therefore, to extend successful strategies to reduce early-onset GBS infections to late-onset neonatal bloodstream infections, caused by GBS as well as by other pathogens. However, it is important to note that prevention strategies focused on early-onset GBS rely on one critical assumption: the mother at risk, by virtue of gut or birth canal colonization with GBS, may be identified. Once this risk is identified, it can be managed (perinatal and usually parenteral antibiotics). We do not yet know if this strategy can be extended to late-onset neonatal bloodstream infections, but data are emerging that might inform the discussion.

Late-onset neonatal bloodstream infections are generally caused by species whose members are well represented in the gut and elsewhere in and on the body in health. There are, therefore, two distinct paradigms for the pathobiology that underlies the occurrence of a late-onset neonatal bloodstream infection (Box 1). The first paradigm, and one that is highly ingrained among neonatologists, assumes that risk for a late-onset neonatal bloodstream infection is a function of specific host factors that increase susceptibility. Such variably at-risk hosts are then exposed to a population of microbes that have constant pathogenic potential. In this "host-canonical" situation, invasion of the bloodstream is considered to be driven by physical breaches in the integrity of the mucosa or the integument, or by impaired or poorly developed innate or acquired host defense mechanisms. According to this first model, late-onset neonatal bloodstream infections would be best prevented by attention to host biology (though recognizing that beyond line care and hand hygiene, protection interventions are not well validated). The second paradigm assumes that among preterm infants, there is a fairly constant level of impairment of host defense against bacteria that can invade the bloodstream. In this "bacteria-canonical" situation, late-onset neonatal bloodstream infections result when a specific member (i.e., a species, serotype, pathotype, or clade) of a genus that is widely found in or on infants in the healthy state, colonizes a host and then invades the bloodstream, because that specific member has exceptional invasive potential.

It is quite plausible that all very preterm infants are at high risk for late-onset neonatal bloodstream infections, by virtue of their poorly developed immune systems, increased gut permeability, and the near-universal use of indwelling lines (at least temporarily), and that this risk is further stratified according to gestational age at birth, day of life, and certain co-morbidities. Such a non-dissimilar high risk background would tend to support the bacteria-canonical paradigm, within defined subgroups (e.g., gestational age at birth, age, etc.). That is to say, late-onset neonatal bloodstream infections occur only if a rare member of a common bacterial taxon colonizes the infant and if that colonizer has pathogenic potential. Additional data support this concept. For example, even though there are many genera of bacteria in and on the bodies of preterm infants, the number of identified genera in blood cultures is highly circumscribed. Specifically, Gram-negative bacilli (largely *Escherichia coli*, *Klebsiella*, *Serratia*, *Enterobacter*, and *Pseudomonas* spp.), GBS, enterococci, *Staphylococcus aureus*, and coagulase-negative *Staphylococci* account for almost all late-onset neonatal bloodstream infections [14,15]. Interestingly, with few modifications, these pathogens account for the bulk of bloodstream infections at all ages, and in diverse settings, even though they are not the most prevalent members of the gut bacterial communities.

If the bacterial canonical paradigm explains even a subset of late-onset neonatal bloodstream infections, it would be logical that by reducing the rate, duration, and consequences of colonization by highly virulent bacteria, there will be great benefit to very low birth weight infants. If the host-canonical paradigm is more appropriate,

Box 1
Host-canonical vs bacteria-canonical paradigms for late-onset neonatal bloodstream infections.

Host-canonical risk for late-onset neonatal bloodstream infections

There are major inter-individual variations in host risk. There are minor variations in bacterial populations to which the hosts are exposed, at least at taxonomic levels of genus and higher. Therefore, specific host risks ordain late-onset neonatal bloodstream infections in infants exposed to a set of bacteria with similar pathogenic potential.

Observations in support of a host-canonical paradigm for late-onset neonatal bloodstream infections:

1 Line care checklists and protocols, and augmented hand hygiene reduce late-onset neonatal bloodstream infection incidence. This is a host-specific intervention.
2 Children "age-out" of a period of high risk for late-onset neonatal bloodstream infections. This suggests maturation of a host-defense process.

Bacteria-canonical risk for late-onset neonatal bloodstream infections

There are inter-individual variations in host risk, but most differences are based on gestational age and illness severity. Hence, among infants of the same gestational age, day of life, and with a similar set of general co-morbidities, there is a fairly consistent inter-child risk from mucosal and integumentary barrier defects, and from poorly developed immune systems. However, there may be major variations in bacterial populations that hosts encounter. If a preterm infant is colonized with an organism with highly virulent potential, even though it might belong to a taxon that is often regarded as "commensal" or harmless, bloodstream infections occur. In this scenario, the specific organism ordains most of the risk.

Observations in support of a bacteria-canonical paradigm for late-onset neonatal bloodstream infections:

1 The number of taxa that inhabit the gut is large, whereas the number of species that cause late-onset neonatal bloodstream infections (and, indeed, bloodstream infections at all ages) is much more circumscribed. This demonstrates, at least at the species level, variant pathogenic potential.
2 Considerable molecular epidemiologic data suggest that species causing many episodes of late-onset neonatal bloodstream infections, namely *E. coli* and Group B streptococcus, belong to phylogenetic subsets that are associated with extra-intestinal pathogenicity.
3 One technique to interdict outbreaks of late-onset neonatal bloodstream infections is to isolate infected infants, even though the pathogens in question may belong to organisms that, at a genus and species level, are frequently found in the gut.
4 Bacteria that invaded the bloodstream of patients in the study by Carl et al. [13] were rarely found in "overlap" or random controls. The inferred relative risk for invasion by these specific organisms is high.

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