What's In?

Pediatric Infectious Disease (2020): 10.5005/jp-journals-10081-1278

Source: Sinnar SA, Schiff SJ. The problem of microbial dark matter in neonatal sepsis. Emerging Infectious Diseases 2020 Nov;26(11):2543.

Neonatal sepsis (NS) kills 750,000 infants every year. Effectively treating, NS requires timely diagnosis and antimicrobial therapy matched to the causative pathogens, but most blood cultures for suspected NS do not recover a causative pathogen. The authors refer to these suspected but unidentified pathogens as "microbial dark matter." Given these low-culture recovery rates, *many non-culture-based technologies are being explored to diagnose NS, including PCR, 16S amplicon sequencing, and whole metagenomic sequencing*. However, few of these newer technologies are scalable or sustainable globally. To reduce worldwide deaths from NS, one possibility may be *performing population-wide pathogen discovery*. Because pathogen transmission patterns can vary across space and time, computational models can be built to predict the pathogens responsible for NS by region and season. This approach could help to optimally treat patients, decreasing deaths from NS and increasing antimicrobial stewardship until effective diagnostics that are scalable become available globally.

Source: Ochoa TJ, Zegarra J, Bellomo S, Carcamo CP, Cam L, Castañeda A, Villavicencio A, Gonzales J, Rueda MS, Turin CG, Zea-Vera A. Randomized controlled trial of bovine lactoferrin for prevention of sepsis and neurodevelopment impairment in infants weighing less than 2000 grams. The Journal of pediatrics 2020 Feb 6.

The authors report an RCT to determine the effect of bovine lactoferrin on prevention of late-onset sepsis (LOS) and neurodevelopment delay in neonates with a birth weight of 500–2000 g in three neonatal units in Lima, Peru, comparing bovine lactoferrin 200 mg/kg/day with placebo administered for 8 weeks with a primary outcome objective of its effect on first episode of culture-proven LOS or sepsis-associated death. Late-onset sepsis or sepsis-associated death occurred in 22 infants (10.5%) in the bovine lactoferrin group vs 30 (14.6%) in the placebo group; there was no difference after adjusting for hospital and birth weight; hazard ratio 0.73 (95% CI, 0.42–1.26). For infants with birth weights of <1500 g, the hazard ratio was 0.69 (95% CI, 0.39–1.25). Growth outcomes and rehospitalization rates during the 2-year follow-up were similar in both groups, except for significantly less bronchiolitis in the bovine lactoferrin group (rate ratio, 0.34; 95% CI, 0.14–0.86). The authors conclude that supplementation with bovine lactoferrin *did not decrease* the incidence of sepsis in infants with birth weights of <2000 g. Growth and neurodevelopment outcomes at 24 months of age were similar. Neonatal bovine lactoferrin supplementation had no adverse effects.

Source: Brook B, Harbeson DJ, Shannon CP, Cai B, He D, Ben-Othman R, Francis F, Huang J, Varankovich N, Liu A, Bao W. BCG vaccination-induced emergency granulopoiesis provides rapid protection from neonatal sepsis. Science Translational Medicine 2020 May 6;12(542).

Death from sepsis in the neonatal period remains a serious threat for millions. The authors describe the effects of bacille Calmette-Guérin (BCG) administration in mouse models and also in human neonates; within 3 days of administration, BCG vaccination can reduce mortality from neonatal sepsis in human newborns, but the underlying mechanism for this rapid protection is unknown. The authors found that BCG was also protective in a mouse model of neonatal polymicrobial sepsis, where it induced granulocyte colony-stimulating factor (G-CSF) within hours of administration. This was necessary and sufficient to drive emergency granulopoiesis (EG), resulting in a marked increase in neutrophils. This increase in neutrophils was directly and quantitatively responsible for protection from sepsis. Rapid induction of EG after BCG administration also occurred in three independent cohorts of human neonates.

Source: Carbone F, Montecucco F, Sahebkar A. Current and emerging treatments for neonatal sepsis. Expert Opinion on Pharmacotherapy 2020 Mar 23;21(5):549–556.

Despite many efforts, the peculiarity of the infant immune system has limited further advances in its treatment. Indeed, neonates experience a dramatic physiological transition from immune tolerance to the maternal antigens to functional maturity. Such a transition is extremely dynamic, as is the pathophysiology of infant sepsis, which is dependent on many infant, maternal, and environmental factors. *In this review, the authors critically update and summarize the current paradigm of immunomodulation in infant sepsis*. They confirm how exogenous stimulation of the immune system through intravenous immunoglobulin, colony-stimulating factors, and granulocyte transfusion have failed to impact on the prognosis of infant sepsis. They also strongly support the beneficial effects of supplementation/replacement therapies with products naturally contained within maternal milk as well as antioxidant compounds. The consensus and undisputable opinion is that breastfeeding is beneficial against sepsis. The authors finally comment that knowledge of the neonatal immune system is indeed too limited to effectively strengthen immune response by exogenous interventions, especially in preterm and low-birth-weight infants. Awareness of this limitation should pave the way for future studies (e.g., gender- and omics-based) aimed at better characterizing the infant immune system and promoting a more tailored approach.

Source: Rudd KE, Johnson SC, Agesa KM, et al. Global, regional, and national sepsis incidence and mortality, 1990–2017: analysis for the global burden of disease study. Lancet 2020;395:200–221.

Neonatal sepsis is considered a major cause of health loss, but data for the global burden of sepsis are limited. As a syndrome caused by underlying infection, sepsis is not part of standard Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) estimates. Accurate estimates are important to inform and monitor health policy interventions, allocation of resources, and clinical treatment initiatives. *The authors estimate the global, regional, and national incidence of sepsis and mortality from this disorder using data from GBD 2017.* The authors use multiple cause-of-death data from 109 million individual death records to calculate mortality related to sepsis among each of the 282 underlying causes of death in GBD 2017. Sepsis-related mortality for each age group, sex, location, GBD cause, and year (1990–2017) was estimated by applying modeled cause-specific fractions to GBD 2017 cause-of-death estimates. The authors have used data for 8.7 million individual hospital records to calculate in-hospital sepsis-associated case fatality, stratified by underlying GBD cause. In 2017, an estimated 48.9 million (95% uncertainty interval [UI] 38.9–62.9) incident cases of sepsis were recorded worldwide and 11.0 million (10·1–12·0) sepsis-related deaths were reported, representing 19.7% (18.2–21.4) of all global deaths. Age-standardized sepsis incidence fell by 37.0% (95% UI 11.8–54.5) and mortality decreased by 52.8% (47.7–57.5) from 1990 to 2017. Sepsis incidence and mortality varied substantially across regions, with the highest burden in sub-Saharan Africa, Oceania, South Asia, East Asia, and Southeast Asia. The authors observe that despite declining age-standardized incidence and mortality, sepsis remains a major cause of health loss worldwide and has an especially high health-related burden in sub-Saharan Africa.

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