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Reducing Antibiotic Exposure at the Beginning of Life

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The transition of the fetus from a usually sterile intrauterine environment to postnatal life is accompanied by rapid colonization with bacteria. Despite the developmental immaturity of the neonatal immune system, the vast majority of newborns adapt well to the extrauterine environment. Not surprisingly, the lifetime risk of infection is highest during the first days of life, as a result of infections acquired shortly before, during, or after birth.[1] As this transitional period is characterized by dramatic physiologic adaptations, the timely recognition of infection has remained a challenge. Concerns centered around the particular vulnerability of the newborn to infections led to a range of programs targeting early-onset sepsis (EOS), usually applying a low threshold to treat. In high-income countries, the mortality associated with EOS in term and near-term newborns is low,[2] and powering trials to prevent and treat EOS for such outcomes is becoming almost impossible. Conversely, available evidence indicates that overtreatment with antibiotics remains highly common, exposing large numbers of neonates to antibiotics with unwanted effects, such as drug-related toxic effects, alteration of the neonatal microbiome, unnecessary hospitalizations, and increasing antimicrobial resistance. The largest randomized trial[3] conducted in this field to date reported that only 27 of 1710 (1.6%) neonates treated for suspected EOS had confirmed infection.

Informed by this discrepancy, Giannoni et al[4] investigated a unique data set of 757 979 neonates born at a gestational age of equal to or greater than 34 weeks. The Antibiotic Exposure for Suspected Neonatal Early-Onset Sepsis (AENEAS) study represents the largest study to date exploring early antibiotic exposure in relation to the burden of EOS and was performed across 11 high-income countries in Europe and North America and Australia. Although the study design does not allow us to draw firm conclusions on population-based estimates, the report demonstrates that approximately 1 in 35 (2.86%) late preterm and term newborns were started on antibiotics, which contrasts with the observed incidence of proven EOS (0.49 cases per 1000 live births) and with the low sepsis-related mortality (12 potential EOS-associated deaths in 21 703 newborns treated for EOS).[4] The strikingly wide range of antimicrobial usage across networks was not sufficiently explained by local EOS incidence, indicating that variability in practices to screen and treat neonates for EOS remains a key contributor to unrestrained antimicrobial usage in this age group. Intriguingly, although the authors[4] unfortunately do not provide a quantitative analysis of this aspect, this discrepancy seems not to relate to the types of protocols and strategies officially used in each of the networks. Furthermore, the median duration of treatment even in those without EOS was 4 days,[4] which is substantially longer than the time required to assess microbiological cultures and clinical response, implying that there were ample opportunities to shorten not only antibiotic duration, but also length of stay, with sizeable cost-saving potential.

This study[4] highlights important considerations that can improve our understanding of both antibiotic exposure and EOS burden in early life and can stipulate future benchmarking and quality improvement initiatives. The findings indicate a large potential for antimicrobial stewardship in this area and should pave the way toward incentives designed to safely shift the balance toward more judicious use of antibiotics. There is, thus, an urgent need to define a roadmap for antimicrobial stewardship research in EOS, including more effective approaches to implement antimicrobial stewardship in this population. At present, we lack solid understanding of the individual variance underlying antimicrobial overuse in this setting, and the performance characteristics of available tools may be insufficiently accurate to enable a sufficient safety net on its own.[5,6] A systematic review and meta-analysis reporting the sensitivity of the Kaiser Permanente EOS calculator including

more than 180 000 neonates demonstrated that, compared with the National Institute for Health and Care Excellence guidelines, the probability of the calculator missing a case of EOS was approximately 20% to 30%.[7] Another promising initiative to support antimicrobial stewardship is the use of biomarker-guided antibiotic discontinuation algorithms, which should include embedded cost-effectiveness analyses.[3,8] Implementation studies are warranted to explore clinicians' beliefs and practices in relation to guideline compliance. Importantly, the findings of Giannoni et al[4] raise the question of whether antimicrobial stewardship initiatives, commonly focused on tertiary centers with in-house pediatric infectious disease specialists and pharmacists, fail to reach smaller clinics where the majority of newborns with suspected EOS are born and treated. Finally, careful titration of measures to reduce antimicrobial usage against the background incidence of EOS as proposed by Giannoni et al[4] should be specific to the resource level of the respective health care setting and need to evaluate robust safety measures because of the low incidence of mortality.

Giannoni et al[4] conclude that in view of contemporary epidemiology, the exposure of neonates to antibiotics for suspected EOS is disproportionate. The proposed minimal set of indicators to benchmark antimicrobial usage against EOS incidence should serve as the basis for prospective studies designed to tackle the excessive use of antibiotics early in life.

ARTICLE INFORMATION

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REFERENCES

1. Giannoni E, Agyeman PKA, Stocker M, et al; Swiss Pediatric Sepsis Study. Neonatal sepsis of early onset, and hospital-acquired and community-acquired late onset: a prospective population-based cohort study. *J Pediatr*. 2018;201:106-114.e4. doi:10.1016/j.jpeds.2018.05.048

2. Gan MY, Lee WL, Yap BJ, et al. Contemporary trends in global mortality of sepsis among young infants less than 90 days: a systematic review and meta-analysis. *Front Pediatr*. Published online June 3, 2022. doi:10.3389/fped.2022.890767

3. Stocker M, van Herk W, El Helou S, et al; NeoPInS Study Group. Procalcitonin-guided decision making for duration of antibiotic therapy in neonates with suspected early-onset sepsis: a multicentre, randomised controlled trial (NeoPIns). *Lancet*. 2017;390(10097):871-881. doi:10.1016/S0140-6736(17)31444-7

4. Giannoni E, Dimopoulou V, Klingenberg C, et al; AENEAS Study Group. Analysis of antibiotic exposure and early-onset neonatal sepsis in Europe, North America, and Australia. *JAMA Netw Open*. 2022;5(11):e2243691. doi:10.1001/jamanetworkopen.2022.43691

5. Achten NB, Klingenberg C, Benitz WE, et al. Association of use of the neonatal early-onset sepsis calculator with reduction in antibiotic therapy and safety: a systematic review and meta-analysis. *JAMA Pediatr*. 2019;173(11):1032-1040. doi:10.1001/jamapediatrics.2019.2825

6. Achten NB, Dorigo-Zetsma JW, van der Linden PD, van Brakel M, Plötz FB. Sepsis calculator implementation reduces empiric antibiotics for suspected early-onset sepsis. *Eur J Pediatr*. 2018;177(5):741-746. doi:10.1007/s00431-018-3113-2

7. Pettinger KJ, Mayers K, McKechnie L, Phillips B. Sensitivity of the Kaiser Permanente early-onset sepsis calculator: a systematic review and meta-analysis. *EClinicalMedicine*. 2019;19:100227. doi:10.1016/j.eclinm.2019.11.020

8. Geraerds AJLM, van Herk W, Stocker M, et al. Cost impact of procalcitonin-guided decision making on duration of antibiotic therapy for suspected early-onset sepsis in neonates. *Crit Care*. 2021;25(1):367. doi:10.1186/s13054-021-03789-x