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Review article

Early detection of neonatal sepsis and reduction of overall antibiotic exposure: Towards precision medicine☆

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ABSTRACT

Infections claim the lives of over half a million newborns annually and expose survivors to the risk of lifelong disability. The challenge to clinicians is to identify newborns with invasive infections rapidly, promptly initiate antimicrobial treatment, and take measures to prevent and treat organ dysfunction. Moreover, excessive antibiotic use is a global public health problem. Despite considerable research on clinical and laboratory markers of neonatal sepsis, the effective translation into clinical practice remains limited. There is no single clinical or laboratory marker, nor any combination of markers that definitively confirms or rules out neonatal sepsis. The interpretation of these markers should take into account their diagnostic value for a given patient, along with their added value to the clinical decision-making process. The digitalization of health care systems, combined with increased computational power and advances in machine learning, offers the possibility of developing accurate predictive algorithms for early detection of neonatal sepsis.

1. Introduction

Neonatal bacterial infections present with nonspecific signs and are often difficult to distinguish from noninfectious diseases. These infections can rapidly progress toward dysfunction of vital organs, with a risk of death or permanent disability. Clinicians thus have a low threshold for starting empirical antibiotic therapy. Suspected neonatal infection is one of the most common diagnoses in neonatal units, and antibiotics are among the drugs most frequently prescribed [1]. Nonetheless, in the great majority of cases, blood cultures remain negative and bacterial infections can be ruled out. The current approach leads to substantial antibiotic overtreatment and exposes newborns to colonization by antibiotic-resistant bacteria. Antibiotic treatments also induce disruption of the microbiota, which can have a durable negative impact on the infant's health. There is a need for accurate diagnostic tools and machine learning algorithms that can accelerate the diagnosis of neonatal sepsis while simultaneously minimizing overtreatment.

2. Clinical decision-making in suspected infection

Marked variations in antibiotic use have been described between neonatal units [2]. To some extent, this can be explained by differences between the guidelines, patient populations, level of implementation of antimicrobial stewardship programs, and management in each institution. The effects of seniority, the interactions between junior physicians and those who have been in practice for several years, habit, and negative experiences with decision-making are more difficult to assess. A systematic review of qualitative studies on physicians' antibiotic prescription behaviors has revealed that complacency and fear are the most influential intrinsic factors [3]. Moreover, clinicians facing similar scenarios do not always make the same decisions. Decision-making about antibiotic prescription is affected simultaneously by bias, a systematic tendency to overtreat, and by "noise", a random dispersion [4,5].

The key aspects of the decision-making process are the determination of the probability of a bacterial infection and an evaluation of the risk-benefit ratio of initiating, not initiating or stopping antibiotic therapy in a given patient. The probability of a bacterial infection in a given patient can be assessed by applying a structured approach including the

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following stages: 1) determination of the baseline incidence of sepsis, 2) assessment of risk factors and clinical and laboratory markers, and consideration of potential alternative diagnoses to estimate the specific probability of sepsis for a given patient, 3) assessment of the course of the clinical and laboratory markers to adapt the assessment of the probability of sepsis, 4) definitive confirmation or exclusion of sepsis with the aid of the microbiology results [6].

3. Guidelines and training

Guidelines aimed at standardizing the diagnostic work-up and treatment strategies have been published in many countries. In general, guidelines contribute to reducing variability in clinical care. Nonetheless, data from several European countries indicate poor adherence with national guidelines on neonatal sepsis [7–9]. It is important to note that guidelines do not cover all clinical scenarios and do not replace clinical judgment. Adequate physician education is essential for translating scientific data into clinical decisions at the patient's bedside, for the implementation of guidelines and antimicrobial stewardship programs, and for decision-making in general.

4. Determination of the baseline incidence

An important but often neglected stage in assessing the probability of infection is the determination of its baseline incidence in a particular clinical scenario. The patients' baseline characteristics and data from epidemiologic studies, as well as local epidemiologic data, constitute important sources of information. Neonatal sepsis mainly presents as three different scenarios, with distinct risk factors, clinical presentations, and outcomes [10]. Early-onset sepsis (EOS) results from the transmission of pathogenic agents by the mother, either *in utero* or at birth, in the context of chorioamnionitis or vaginal colonization by these microorganisms. The great majority of newborns with EOS develop symptoms within the 48–72 hours after birth. Hospital-acquired late-onset sepsis (LOS) accounts for more than 60% of all cases of neonatal sepsis. It generally presents after the third postnatal day as a nosocomial infection in preterm newborns or infants treated with invasive devices. LOS of community-acquired origin mainly occurs in term newborns discharged home after an uncomplicated delivery.. Like most diseases affecting newborns, gestational age has an important impact on the incidence of neonatal sepsis. Considering the two extremes, the incidence of hospital-acquired LOS ranges from 10% to 40% in extremely preterm infants, while the incidence of EOS ranges from 0.2 to 0.8 per 1000 births in term newborns.

5. Risk-benefit ratio of antibiotics

Neonatal sepsis is a major cause of death and permanent disability. Early detection of an invasive infection, followed by the rapid administration of antibiotics and the introduction of life support measures, is essential for reducing mortality and morbidity. Antibiotics constitute our principal response to bacterial infections and prevent millions of deaths each year worldwide. There is nonetheless irrefutable evidence that antibiotics can be harmful. Antibiotic treatment is associated with increased antimicrobial resistance, risks related to drug toxicity, longer hospitalizations, mother-child separation, a reduction in breast-feeding rates, and higher health-care costs [5]. Exposure to antibiotics at the start of life disrupts microbiota development, modifies host immune responses, affects growth, and contributes to the development of numerous diseases, including asthma, obesity, and inflammatory diseases of the gut [5]. In very low birthweight preterm infants, prolonged antibiotic exposure is associated with an increased risk of death, necrotizing enterocolitis, nosocomial infections, retinopathy of prematurity, and chronic lung disease [11]. Antibiotic treatments have disproportionate consequences at the beginning of life, when the evolving neonatal microbiota and immune system are particularly sensitive to disruption.

6. Additional risk factors

Once the baseline incidence according to gestational age and clinical scenario has been determined, the next step is to take into account potential additional risk factors in order to estimate the probability of sepsis with greater precision. The main risk factors are well known. Nonetheless, the impact of each individual risk factor and each possible combination of them on the probability of developing sepsis can be difficult to grasp for clinicians. The "neonatal early-onset sepsis calculator" is a multivariate assessment tool designed to predict the risk of EOS in children born at or close to term; it uses the baseline incidence of EOS, together with an objective assessment of the risk factors and clinical signs [12]. Although such an approach has the advantage of increasing physicians' ability to assess a given patient's risk of developing EOS, the recommendation provided by the calculator — to administer antibiotics at an estimated EOS risk $\geq 3/1000$ — is extremely controversial.

7. Clinical signs of neonatal sepsis

Sepsis is a heterogeneous syndrome defined in adults and children as life-threatening organ dysfunction, resulting from a deregulated host response to an infection [13,14]. The initial manifestations are often subtle, and their evolution toward multiorgan dysfunction is an important predictive factor of mortality. The optimal approach for reducing mortality and morbidity should allow clinicians to identify patients before the onset of organ dysfunction. Clinical manifestations can arise from any organ or system, reflecting local and systemic invasion by pathogenic agents, host response, and progressive organ dysfunction. This explains the diverse, nonspecific, and dynamic nature of clinical signs. Because of the complex and rapid changes in the function of organs and systems that occur as part of normal physiology early in life, it is difficult to define thresholds that distinguish physiology from disease. Moreover, many newborns present abnormal physiological signs before the onset of sepsis due prematurity and comorbidities such as congenital malformations. It is therefore particularly difficult for clinicians to diagnose neonatal sepsis at an early stage and distinguish it from noninfectious disease.

8. Algorithms based on clinical signs

Given the dynamic changes that occur during sepsis, and the increasing availability of high-resolution data in the electronic health records of digitalized hospitals, analysis of continuous vital signs is a promising approach for developing patient-specific algorithms for the early detection of neonatal sepsis.

Reduced heart rate variability and transient decelerations have been identified in preterm newborns during the hours or days before the LOS diagnosis. Analysis of these abnormal heart rate characteristics with mathematical modeling has led to the development of the heart rate characteristics (HRC) index, which represents fold-increases in the risk of sepsis during the next 48 hours. HRC monitoring can be used as an early, noninvasive alert tool that warns physicians before clinical deterioration appears. A randomized controlled trial including 3003 preterm infants with birthweights below 1500 g showed a reduction in mortality when real-time continuous monitoring of the HRC index was displayed [15]. Subsequent studies have shown that the HRC index has modest accuracy for the diagnosis of LOS (area under the curve of the receiving operating characteristic curve, AUROC 0.66–0.70), with gestational age strongly influencing its performance [16,17].

Models using several clinical markers showed a greater diagnostic accuracy. Studies analyzing high resolution clinical data from continuous monitoring of thoracic impedance, electrocardiography waveforms, and pulse oximetry waveforms in preterm infants have shown the

doubling of apnea, bradycardia, and desaturation in 43% of newborns, and extreme periodic respiration in 12% of the newborns on the day before the diagnosis of LOS [18,19]. Algorithms based on clinical signs such as heart rate, respiratory rate, temperature, desaturations, and bradycardia predicted LOS earlier than conventional management with an AUROC between 0.86 and 0.90[20,21].To the best of our knowledge, the clinical benefit of none of these algorithms was assessed in a randomized clinical trial.

9. Biomarkers of neonatal sepsis

More than 250 biomarkers of sepsis have been evaluated in more than 8000 clinical studies [22]. For neonatal sepsis, many studies have investigated leukocyte counts, platelets, C-reactive protein (CRP), procalcitonin (PCT), and proinflammatory cytokines (IL-1, IL-6, IL-8, and TNF), as well as leukocyte surface proteins (CD64, presepsin) [23]. Most of these studies have at least one important design limitation, e.g., observational study, inadequate sample size, and missing or inadequate definition and documentation of sepsis. Diagnostic performance is limited by the many noninfectious conditions that influence biomarker values in newborns with suspected sepsis [24]. These limitations thus reduce the benefit of biomarkers for guiding decisions concerning the initiation, continuation, or stopping of antibiotic treatment. No robust evidence demonstrates the superiority of a panel of biomarkers compared with a single biomarker.

Currently, the greatest problem probably lies in how the biomarkers are used. Several studies have shown negative effects of their use [24,25]. One of the problems is dichotomous thinking, the tendency to consider a result as positive if it is not negative. Nature is rarely dichotomized as strictly negative and positive but is instead a continuum with a large gray area between these extremes. We must rethink how to use these molecular markers for neonatal sepsis. Large studies show that CRP and PCT can be used to shorten the duration of antibiotic therapy in newborns with suspected EOS [26,27]. A leukocyte count less than $5 \times 10^3/\mu L$ signals an increased probability of neonatal sepsis [28]. Most important, molecular markers must be studied and analyzed as part of an algorithm or management strategy for neonatal sepsis and not as isolated markers.

10. Multimodal approaches

To overcome the limitations associated with the use of clinical and laboratory markers and with their modest diagnostic accuracy, multimodal approaches have been applied to develop scores or algorithms intended to diagnose neonatal sepsis. Globally, the performance of these algorithms for the early detection of neonatal sepsis is low to moderate [29]. The existing studies have several limitations, including a relatively low number of patients, a single-center design, a small number of variables, and an absence of clearly defined clinical phenotypes (as they include both suspected and confirmed cases). The dynamic nature of sepsis implies that a limited temporal resolution of clinical data is an important limitation.

The modest performance of the existing algorithms has created concern about their potential impact on clinical decisions. Nonetheless, given the limitations of the current approaches, use of algorithms with low to moderate diagnostic accuracy can still have a positive effect on the clinical results, at least in some contexts. This has been demonstrated for the "neonatal early-onset sepsis calculator" and for the NeoPInS algorithm, both of which have been associated with a reduction in antibiotic exposure in term and late preterm newborns with suspected EOS [12,27], as well as for real-time display of the HRC index, which has been associated with a reduction in mortality in preterm infants [15].

11. Future prospects

Analysis of clinical and laboratory markers of infection requires a holistic approach. It is difficult for clinicians to estimate the value of all the available information to predict the risk of infection and adverse outcomes of infection and to use these predictions to optimize decision-making at the bedside. Future work must include a consensus definition of neonatal sepsis, the development and updating of guidelines and management bundles as well as the discovery and validation of new clinical and laboratory markers. International guidelines based on sound data are necessary to define the diagnostic work-up and strategies for early treatment. They should be supported by professional organizations to promote practitioners' adherence. While blood cultures remain the reference standard, new diagnostic methods are necessary to compensate for traditional microbiology's limited sensitivity and slow speed. Research on biomarkers must not concentrate only on inflammation, but also target other early signals, taking into account the heterogeneous nature of sepsis, with the aim of developing tests with high sensitivity and rapid turnaround times.

New approaches investigating RNA signatures are more forward-looking and provide a more global view of the host response [30]. Changes in the intestinal microbiota are associated with the onset of LOS in preterm infants. The analysis of the volatile organic compounds contained in these infants' stool has identified a distinct signature in the days preceding the diagnosis of Gram-negative LOS [31]. Technological advances have led to the development of new monitoring methods. Motion quantification based on analysis of electrocardiogram waveforms has made it possible to observe a reduction in newborns' spontaneous activity that precedes clinical suspicion of LOS [32]. The study of microcirculatory dysfunction by spectroscopy or by video-microscopy can also contribute to early detection of sepsis [33].

The term "precision medicine" describes a model in which medical decisions and treatments are adapted to patients' needs with the aid of information collected at different levels, especially clinical data and "omics" data (genomic, transcriptomic, proteomic, and metabolomic) [34].

Machine learning (ML) makes it possible to analyze a very large quantity of data on multiple clinical and laboratory markers and their interactions and can identify patterns in variables that might otherwise pass unnoticed. Identifying a combination of markers with high diagnostic accuracy requires not only consideration of the heterogeneity and dynamic nature of sepsis, but also a multimodal approach based on ML that assesses the patient's demographic data, risk factors, high-resolution vitals and clinical markers, laboratory test results as well as new biomarkers in large cohorts of newborns with well-defined, microbiologically documented phenotypes. There is no doubt that in the future, algorithms will make predictions more precise than humans can, but the performance of these algorithms depends on the quality of the data used to develop them.

12. Conclusion

The current approaches based on the assessment of risk factors and clinical signs, with or without the use of biomarkers, simultaneously lack sensitivity and specificity and thus lead to delays in the initiation of antibiotic treatment for some newborns and unnecessary antibiotic exposure for others. Although our diagnostic tools are imperfect, a structured decision framework integrating all available relevant information is likely to optimize clinical decisions. Algorithms based on ML will play an important role in guiding medical decisions in the future.

Declaration of competing interest

None.

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