NEONATAL SEPSIS UPDATES ON ETHIOLOGY, PATHOGENESIS, DIAGNOSIS AND TREATMENT.

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Introduction: Sepsis is a leading cause of pediatric mortality(1) . Defined as systemic inflammatory response syndrome in the presence of a suspected or confirmed infection, it is a clinical syndrome principally characterized by dysregulation of the host innate immune response and may result in an immune phenotype of coexistent systemic inflammation and immunosuppression(2). Sepsis affects over 25 million children every year, causing an estimated 3 million deaths in neonates, children and adolescents globally (1). The life-time incidence of sepsis is strongly age-dependent, with highest rates observed in preterm neonates, followed by neonates, infants, and children(2).

НЕОНАТАЛЬНЫЙ СЕПСИС: ОБНОВЛЕНИЕ В ЭТИОЛОГИИ, ПАТОГЕНЕЗ, ДИАГНОЗ И ЛЕЧЕНИЕ.

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Введение: Сепсис является основной причиной детской смертности (1). Определяемый как синдром системного воспалительного ответа в присутствии подозреваемой или подтвержденной инфекции, это клинический синдром, в основном характеризующийся нарушением регуляции врожденного иммунного ответа организма и может привести к иммунному фенотипу сосуществующего системного воспаления и иммуносупрессии (2). Ежегодно сепсис поражает более 25 миллионов детей, вызывая, по оценкам, 3 миллиона смертей новорожденных, детей и подростков во всем мире (1). Заболеваемость сепсисом в течение жизни сильно зависит от возраста, причем самые высокие показатели наблюдаются у недоношенных новорожденных, за которыми следуют новорожденные, младенцы и дети.

Epidemiology: Despite a decline in child mortality during the last decades, close to 6 million children died before the age of 5 years in 2015 with almost half of

these patients dying during the neonatal period.(1) In 2015, infectious diseases were responsible for 9.5% of neonatal deaths worldwide, mainly focusing on lower and middle income countries where healthcare and appropriate antibiotics may be difficult to access.(1)

Pathogenesis: The autonomic nervous system (ANS) regulates the functions of many organ systems, responding to stressors such as infection. Badke and his colleagues evidence supporting the key role of the ANS response to infection, and the importance of ANS dysfunction in the pathophysiology of sepsis. The ANS is activated early on during infection by afferent fibers which sense pathogens and tissue damage. Such activation can be assessed by changes in heart rate variability which has been shown to be associated with organ dysfunction and death in adults and children.(3) Hence, non-invasive monitoring of heart rate characteristics represents a promising early warning tool to detect sepsis, and is associated with reduced mortality in preterm newborns.

Sensing of pathogens and tissue damage leads to rapid alterations of innate and adaptive immune responses, complement and coagulation, vascular, neuronal, metabolic, and endocrine systems.

Neonates are immunologically immature, have reduced skin barrier, reduced humoral response and a diminished microbial diversity in gut microbiota, all contributing to a higher risk of life-threatening bacterial infection, often presenting as sepsis. The initiation of the pro-inflammatory cascade may cause wide spread tissue injury It should be noted that sepsis continues to impact not only neonates, but also affects a considerable proportion of young and older infants receiving intensive care. A recent study showed that global prevalence of severe sepsis in pediatric intensive care units is 8.2%.

Pathological cross-talk between inflammatory and coagulation cascades, complement activation, and neuro-endocrine signals wreak havoc on homeostatic controls. This hyperinflammatory response has untoward effects on the cardiopulmonary system, vascular endothelium, and gut, precipitating progressive organ dysfunction until the host succumbs. The morbidity, mortality, and costs associated with pediatric sepsis

impose a significant burden on the healthcare community and global economy.

Ethiology: The distribution of pathogens causing invasive infection evolves over time and is influenced by the practices used to prevent and treat infections. Epidemiological studies are important for bench marking and quality improvement, to update policies and practices based on the most prevalent pathogens and their susceptibility to antibiotics, and to identify patients at the highest risk of developing infection and infection-related complications. Conjugated meningococcal vaccines have had a tremendous impact on reducing the incidence meningococcal sepsis and meningitis. Yet, *Neisseria meningitides* remains a major agent causing sepsis and meningitis worldwide, and is associated with significant mortality, and long-term disability in many survivors. Nadel and Ninis reviewed the preventive strategies, clinical features, and management of invasive meningococcal disease in the area of vaccination, highlighting the importance of detection and early management of the disease to improve patient outcome.(4) Xuetal. reported on a cohort of term newborns with meningitis in Shanghai. Group B *Streptococcus* and *Escherichia coli* were the predominant pathogens. The high proportion of patients with abnormal neurological examination at discharge, abnormal magnetic resonance imaging and/or withdrawal of treatment underscores the considerable burden of disease.(5) Furthermore, particular patient groups are muchmore susceptible to sepsis, as illustrated by patients with sickle cell disease. Increased blood viscosity and vascular occlusion result in functional asplenia and immune deficiency, thereby increasing susceptibility to bacterial infections. Ochocinski et al. reviewed the life-threatening infectious complications of sicklecell disease, and identified priorities for prevention and treatment of infections in high-and low-income countries(6).

Toxic Shock Syndrome (TSS) is a severe acute illness caused by toxin-producing strains of *Staphylococcus aureus*or *Streptococcus pyogenes*. The study by Javouhey et al. shows that *Staphylococcus* and *Streptococcus* TSS in children differ by their source of infection, clinical presentation, disease severity and outcome. *Staphylococcus* TSS predominantly originated from the female genital tract, while *Streptococcus* TSS was associated with pulmonary infection and bacteremia, a more

frequent occurrence of respiratory failure and a longer duration of mechanical ventilation and stay in PICU(7).

Bacterial and fungal infections are most commonly attributed as the cause of sepsis. However, viruses can trigger dysregulated host responses, leading to life-threatening organ dysfunction as illustrated by the current COVID-19 pandemic. Guptaetal. summarized the epidemiology, pathophysiology and diagnosticand therapeutic aspects of the management of viral sepsis. The importance of early recognition and pathogen identification in viral sepsis has important implications for AMS, infection control measures, risk stratification, and in some cases antiviral therapies(8).

Types: Sepsis in very preterm neonates exposed to multiple iatrogenic risks likely represents a very distinct disease from vertically transmitted early-onset-sepsis in a term newborn, pneumococcal sepsis in a young infant, hospital-acquired sepsis in a neutropenic child, or staphylococcal toxic shock in an adolescent patient. Neonatal sepsis can be divided into early and late onset neonatal sepsis (EONS and LONS), which reflects the timing of onset of symptoms, type and virulence of organism and associated pathogenesis. Among VLBW neonates, Gram-positive organisms are most commonly associated with LONS, although it has been shown that the mortality rate is 2–3 times higher in neonates with Gram-negative infections. Prolonged indwelling catheter use and other invasive procedures are potential risk factors.

Viral sepsis in children is typically presumed to be bacterial in origin until proven otherwise, but frequently bacterial cultures ultimately return negative. Viral sepsis can be defined as a severe inflammatory response to a suspected or confirmed viral infection. However, making the definitive diagnosis of viral sepsis in a child is particularly challenging for clinicians. The astute clinician must incorporate the patient’s history of present illness, physical exam, laboratory and radiographic data to determine the likelihood of a viral etiology for sepsis. Even with a positive viral test, limitations of the testing result should be considered. Despite these challenges, timely diagnosis of viral sepsis has significant implications on clinical management, including guiding the use of appropriate antiviral therapy and informing isolation and containment strategies. Although viruses may be important causative agents of

culture-negative sepsis worldwide, the incidence, disease burden and mortality of viral-induced sepsis is poorly elucidated. Consideration of viral sepsis is critical as its recognition carries implications on appropriate use of antibacterial agents, infection control measures, and, in some cases, specific, time-sensitive antiviral therapies. This review outlines our current understanding of viral sepsis in children and addresses its epidemiology and pathophysiology, including pathogen-host interaction during active infection. Clinical manifestation, diagnostic testing, and management options unique to viral infections will be outlined.

Diagnosing in adults, Sepsis differentiates sepsis from uncomplicated infection by the presence of organ dysfunction (15). The Sequential Organ Failure Assessment (SOFA) score has better prognostic accuracy in adults compared to former sepsis criteria. Age adapted pediatric (pSOFA) and neonatal (nSOFA) scores have shown promising results in pediatric intensive care units (PICUs) and neonatal intensive care units (NICUs) from high-income countries.

The diagnosis of viral sepsis is typically one of exclusion. Bacterial sepsis, whether primary or secondary, is usually of higher initial concern because failure to recognize this diagnosis and promptly administer systemic antibiotics has lethal consequences. Unfortunately, in our current state of limited antiviral therapies, even the prompt recognition and treatment of viral sepsis may not quickly improve a patient’s clinical course. Nonetheless, early, definitive diagnosis of a primary viral septic process may inform treatment decision-making and help limit unnecessary systemic antibiotic administration.

Innovative Cell Population Data (CPD) have been used as early biomarkers for diagnosing sepsis in adults. We assessed the usefulness of CPD in pediatric patients with sepsis/septic shock, in terms of early recognition and outcome prediction. We revised 54 patients (0–15 y) admitted to our Pediatric Intensive Care Unit (PICU) for sepsis/septic shock during a 4-year period. Twenty-eight patients were excluded, 26 septic patients were enrolled (G1). Forty children admitted for elective surgery served as controls (G2). Data on five selected CPD parameters, namely neutrophils fluorescence intensity (NE-SFL), monocytes cells complexity (MO-X), monocytes

fluorescence intensity (MO-Y), monocytes complexity and width of dispersion of events measured (MO-WX), and monocytes cells size and width dispersion (MO-WZ), were obtained at time of PICU admission (*t0*) by a hematological analyzer (Sysmex XN9000®). As the primary outcome we evaluated the relevance of CPD for diagnosing sepsis/septicshock on PICU admission. Furthermore, we investigated if CPD at *t0* were correlated with C-reactive protein (CRP), patient survival, or complicated sepsis course. We found higher values of NE-SFL, MO-WX, and MO-Y in children with sepsis/septic shock upon PICU admission. These parameters may be a promising adjunct for early sepsis diagnosis in pediatric populations. Larger, prospective studies are needed to confirm our preliminary observations.

Treatment: In a clinical setting, there is generally no time to wait for the result from microbiologic samples when there is suspected sepsis. Antibiotic treatment can therefore be viewed as having two phases, namely an initial, empirical treatment phase followed by a targeted treatment phase once a causative pathogen is confirmed. Both phases are time-related, and antibiotic dose optimization may focus on either efficacy or safety, respectively.

Empirical Treatment Phase: In the first hours of treatment, the primary focus is to deliver effective treatment. During this earliest stage mortality is directly related to the effects of the life-threatening infection and managing toxicity is less central. As the causative organism generally remains unknown, selection of the antibiotic regimen needs to take into account the overall epidemiology of sepsis in the age group of the patient.

A key parameter describing susceptibility to antibiotics and used in dose-finding is the minimal inhibitory concentration, or MIC, which reflects the lowest antibiotic concentration needed to inhibit visible growth of the pathogen. MIC breakpoints for pathogens are established based on various *in vitro* tests and are applied to an entire population. Initial antibiotic doses should be targeting the “worst-case” minimal inhibitory concentrations, captured by the phrase “go hard and go home”. During the empirical treatment phase, the benefits (e.g., high probability that causative pathogens are killed) outweigh the risks (e.g., development of renal toxicity) and

therefore a certain trade-off in dosing regimen to achieve relatively high exposures in relation to non-pathogen specific MIC may be acceptable.

Targeted Treatment Phase: After an initial empirical treatment there are two possible outcomes. Treatment may be discontinued because the clinical picture of sepsis cannot be microbiologically confirmed and an alternative diagnosis emerges. On the other hand, the microbiological cause confirming the diagnosis of sepsis may be identified. In the latter case treatment will be continued and toxicity issues become more important. During this targeted treatment phase, antibiotic dose optimization will be individualized to achieve an optimal efficacy-safety balance. When patients experience or are at high risk of toxicity (for example because of renal failure), three options are available: if susceptibility testing suggests a less toxic alternative, antibiotic treatment may be switched; depending on the exact infection and treatment response, only a short course is necessary and treatment may be stopped; or the antibiotic is question is considered the optimal therapeutic choice, in which case dose adjustments will be needed, possibly combined with therapeutic drug monitoring(TDM).

It has been explored the complex relationship between antibiotic regimen, exposure and response. Selecting the best antibiotic regimen is particularity challenging for neonates, due to rapid changes in drug metabolism and renal function during the first days and weeks of life which altogether alter drug distribution and elimination. Tauzin et al. presented a study on exposure to vancomycin in neonates receiving continuous drug infusion, and compared their results to those obtained using simulations with different models. This study highlights the challenges of prescribing a drug with a narrow therapeutic margin, the need for therapeutic drug monitoring and the importance of conducting pharmacokinetic studies.

The relationship between antibiotic dose and exposure is subject to high levels of inter- and intra-individual variability and to achieve effective antibiotic exposure, antibiotic drug monitoring is becoming crucial. This variability is known to be increased in patients with life-threatening infection; when rapid pathophysiological fluctuations even over the course of a few hours can impact the pharmacokinetics,

and therefore the relationship between dose and antibiotic exposure. Reliable measurements area prerequisite for effective TDM, accordingly turn-around times >24 h should be disregarded for critically illpatients. TDM is used to personalize the dosing strategies to ensure antimicrobial exposures which have therapeutic success and low probabilities of toxicity and generation of antimicrobial resistance. The percentage of patients with sub-therapeutic concentrations decreased from 58 to 40% after applying TDM for vancomycin in preterm and term neonates (24). Adequate antibiotic drug monitoring requires expertise in different fields and calls for the collaboration of physicians together with the lab-technicians and clinical pharmacologists. While the above is likely to be applicable to any antibiotic treatment, different antibiotics have different characteristics.

Recombinant human activated protein C (rhAPC) possesses a broad spectrum of activity including modulation of coagulation, inflammation, and apoptosis(9). However, results among adults and children demonstrated lack of efficacy and an increased risk of bleeding associated with higher mortality rates(10,11). Consequently, rhAPC was withdrawn from the market before any randomized trials were performed in preterm neonates, and in 2012 a clear recommendation against the treatment with rhAPC for neonatal sepsis was proclaimed(12).

Mostβ-lactams have a wide therapeutic window, meaning that even high exposure is unlikely to be associated with toxicity. In contrast, aminoglycosides and glycopeptides have an arrow therapeutic window and require more attention to avoid toxicity.

Complication: In adults, sepsis-induced immune suppression (SII) is characterized by alterations of innate and adaptive immune responses, including, but not limited to, a prominent bias toward anti-inflammatory cytokine secretion, diminished antigen presentation to T cells, and reduced activation and proliferation of T cells. Itis unclear if sepsis-immunosuppression also plays a role in the adverse outcomes associated with neonatal sepsis. This review will focus on exploring if key characteristics associated with SII in adults are observed in neonates with sepsis.

The early peak mortality in sepsis is associated with overwhelming inflammation and

organ dysfunction seen across all age groups. At the same time, sepsis-induced immune suppression, a state characterized by exhaustion of innate and adaptive immune responses has been described in adults, leading to impaired pathogen clearance, reactivation of latent viral infections, nosocomial infections and late mortality. A limited capacity to mount efficient immune response mediates the increased susceptibility to infection observed in newborns and is likely affected by suppression by immune cells, erythroid cells, and placental mediators. Contrary to the traditional belief that the neonatal immune system is primarily characterized by energy or low function, newborns can in fact display dysregulated immune responses associated with excessive inflammation and early death. Hibbert et al. reviewed the evidence suggesting that sepsis may induce immune suppression in neonates or aggravate a pre existing state of developmental immune suppression. A better understanding of the biological pheno-or endo types of newborns and children with sepsis will open avenues for future immune modulating strategies(13).

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