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Clinical Pearl: Do You Still Believe in the Existence of Culture Negative Sepsis in Neonates?

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"About 45 years ago, when I was the senior pediatric resident on the Pediatric Infectious Disease floor and in the Neonatal Intensive Care Unit (NICU), and Mike Schreiber was one of our interns, we believed in a clinical concept, which was called culture negative sepsis (CNS) in our neonates (1)."

About 45 years ago, when I was the senior pediatric resident on the Pediatric Infectious Disease floor and in the Neonatal Intensive Care Unit (NICU), and Mike Schreiber was one of our interns, we believed in a clinical concept, which was called culture negative sepsis (CNS) in our neonates (1). The baby had signs of sepsis or a systemic inflammatory response syndrome (SIRS) which could include at least 2 of the following four criteria in Table 1, one of which would be an abnormal temperature or leukocyte count (1-2). However, when a blood culture was drawn, ideally 1 ml in volume peripherally, the culture returned negative after 48 hours. Because of our heightened clinical suspicion of sepsis in this infant, we decided to continue antibiotic therapy for 5 to 7 days despite the negative culture. More recently, there has been more discussion about whether neonatologists still believe in CNS (1-2). A commentary by Cantey and Prusakov provides a "proposed framework for the clinical management of neonatal CNS (3)". These authors consider two facts (1) neonatal CNS exists; (2) it should be rare 3). Here are several excellent practice considerations to optimize sepsis diagnostics and avoid unnecessary antibiotic use for CNS.

1. Consider noninfectious mimics of sepsis and localized infections that may not be associated with bacteremia.
2. Optimize blood volume for blood culture (1 ml) to maximize yield and minimize antibiotic use.
3. Do not waste blood on ancillary non-culture biomarkers.
4. Microbiological diagnostics are critical. Anaerobic blood cultures may be helpful when gastrointestinal pathology like spontaneous intestinal perforation or necrotizing enterocolitis is considered.
5. Consider respiratory viral panel in the context of viral late-onset sepsis.
6. Parasitic and fungal cultures can be done if the clinical situation dictates.
7. Treatment of suspected CNS can be considered if the index of suspicion is high but should be short (3).

One must consider that in adult and larger pediatric patients, it is

Table 1. Definitions of SIRS, Infection and Sepsis Modified for Pediatric Patients Including Neonates

Systemic inflammatory response syndrome (SIRS): The presence of the findings listed under at least two of the following four criteria, one of which must be abnormal temperature or leukocyte count.

Temperature

- Core temperature of >38.5°C or <36°C

HR

- Tachycardia, defined as a mean HR >2 SD above normal for age
  - in the absence of external stimulus, chronic drugs, or painful stimuli
- Otherwise unexplained persistent elevation over a 0.5- to a 4-h time period
- Bradycardia, defined as a mean HR <10th percentile for age
  - in the absence of external vagal stimulus, b-blocker drugs, or congenital heart disease
- Otherwise unexplained persistent depression over a 0.5-h time period

Respiratory rate

- Mean respiratory rate >2 SD above normal for age
- Mechanical ventilation for an acute process not related to underlying neuromuscular disease or the receipt of general anesthesia

Leukocyte count

- Leukocyte count elevated or depressed for age
- >10% immature neutrophils

Infection:

A suspected or proven (by a positive culture, tissue stain, or PCR test) infection caused by any pathogen or a clinical syndrome associated with a high probability of infection. Evidence of infection includes positive findings on clinical examination, imaging, or laboratory tests (e.g., white blood cells in normally sterile body fluid, perforated viscus, chest radiograph consistent with pneumonia, petechial or purpuric rash, or purpura fulminans).

Sepsis:

SIRS in the presence of or as a result of suspected or proven infection.

HR.heart rate; PCR.polymerase chain reaction; SIRS.systemic inflammatory response syndrome (1).

not unusual for at least 10 – 15 mL of blood to be utilized to obtain not one but two or three culture bottles. While 1 mL may be sufficient, evolving sepsis is more likely to give a positive result with a higher sample volume. The positive culture is sufficient but not necessary in the neonate to demonstrate the need for a 5-7 day course of antibiotics. The value of a physical exam and vital signs in this context cannot be emphasized enough. Furthermore, although biomarkers may appear to direct therapy, they too are subject to interpretation and missense due to overemphasizing their importance when the clinical picture does not match the result.

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In our antibiotic stewardship initiative working with Illinois Perinatal Quality Collaborative (ILPQC), thus far, we have reviewed 660 babies with blood cultures and complete blood counts along with their clinical histories beginning in October 2020- July 2022. We have found that 51/414 or 12.3% of babies born at ≥ 35 weeks gestation received antibiotic therapy for 5-7 days for CNS (j.Hageman, personal communication, July 14, 2022). For those babies born at < 35 weeks gestation treated for CNS, our review demonstrated that 38 of 246, or 15.4%, were treated for CNS for 5-7 days (j Hageman, personal communication, July 14, 2022).

References:

1. *Piantino JH, Schreiber MD, Alexander K, Hageman JR. Culture negative sepsis and systemic inflammatory response syndrome in neonates. NeoReviews 2013; 14 (6): e294-e305.*
2. *Cantey J, Prusakov P. A proposed framework for the clinical management of neonatal "Culture Negative" Sepsis. J Pediatr. https://doi.org/10.1016/jpeds.2022.01.006.*

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