PEDIATRICS PERSPECTIVES

Ending the Culture of Culture-Negative Sepsis in the Neonatal ICU

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Sepsis is a major cause of morbidity and mortality among infants in the NICU. Because septic infants present with nonspecific clinical findings, providers are justifiably concerned about missing sepsis. Blood cultures are the gold standard for diagnosis of sepsis, and when adequate volumes are obtained, cultures have excellent sensitivity even when the infant has very low levels of bacteremia.[1] However, many providers view sterile culture results with skepticism, especially when the infant appears ill or received antibiotics before cultures were obtained. Therefore, we have developed a culture (no pun intended) of acceptance in treating "culture-negative" sepsis. Recent reports suggest that up to 10 times as much antibiotic is used for culture-negative sepsis as for culture-proven sepsis.[2,3] This practice must stop. The evidence for unintended harm caused by prolonged or unnecessary antibiotic exposure continues to mount and includes increased risk for obesity, atopy, and, for preterm infants, necrotizing enterocolitis, sepsis, bronchopulmonary dysplasia, and death.[4] Why then do providers view sterile cultures with such skepticism?

The first reason is that providers have all-too-frequent experiences with cultures that are obtained incorrectly. Blood cultures collected inappropriately cannot be trusted, but such cultures, unfortunately, are a common problem. The recommendation is that a minimum of 1 mL of blood, either in 1 culture or divided into 2 0.5 mL cultures, be obtained from infants with suspected sepsis before initiation of antimicrobial therapy.[5] However, sampling is limited by blood volume, particularly among extremely low birth weight infants, who are at the highest risk for sepsis but have the lowest total blood volume. Providers may prioritize blood gas analysis or other laboratory studies, using whatever volume remains to inoculate blood cultures. However, blood culture sensitivity decreases by 10% to 40% when 0.5 mL is inoculated compared with 1 mL.[1] Therefore, blood cultures need to be prioritized to ensure that an adequate volume is cultured. Additionally, cultures obtained after antibiotics are initiated are difficult to interpret and frequently lead to prolonged therapy. Finally, contaminated blood cultures require additional blood draws and continued treatment while the repeat cultures are processing. These inappropriate cultures can be minimized through education and quality improvement initiatives with a focus

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on ensuring that adequate volume is collected.[6] Drawing cultures appropriately the first time will lead to decreased blood sampling and reduced antibiotic exposure. To quote hall-of-fame basketball coach John Wooden, "If you don't have time to do it right, when will you have time to do it over?"

More difficult to address is the properly obtained blood culture that providers refuse to believe. Some argue that the sensitivity of blood culture is suboptimal at low bacterial concentrations. However, Schelonka et al[1] demonstrated that the sensitivity of blood cultures approaches 100% when 1 mL is inoculated and the infant has a bacteremia concentration of at least 4 colony-forming units (CFU) per milliliter. The detection threshold is even lower with current blood culture techniques, which have excellent sensitivity even at low levels of organism (1–4 CFU/mL); considerably less than the median concentration of bacteria in neonatal sepsis (>100 CFU/mL).[7] Admittedly, the sensitivity of blood cultures decreases at ultralow (<1 CFU/mL) bacteremia. The question then becomes whether 36 to 48 hours of empirical therapy is sufficient for the treatment of ultralow bacteremia. If the purpose of antimicrobial therapy is to reduce the bacterial burden to a level that the infant's innate immune system can overcome, then 36 hours may be adequate when pathogen concentration is already several logs lower than usual sepsis. This theory is reinforced by clinical experience, which shows that infants with sterile blood cultures who receive 36 to 48 hours of empirical therapy virtually never require retreatment.[2] It is our opinion that ultralow bacteremia is not clinically significant, particularly when infants are empirically treated for 36 to 48 hours.

Another argument is that blood cultures obtained from infants whose mothers received adequate intrapartum antibiotic prophylaxis (IAP) should be discounted. After all, because the purpose of IAP is to achieve bactericidal levels of antibiotic in the fetus, shouldn't we consider those infants pretreated? However, to those who say blood cultures may be sterile after adequate IAP, we answer, "Yes, that is the whole point!" Infants whose mothers received IAP, either because of group B streptococcal colonization or chorioamnionitis, are at a lower risk for early onset sepsis than infants whose mothers did not receive adequate IAP. Yet providers consistently view these infants as being at greater risk instead of lower. Indeed, an infant treated for culture-negative sepsis receives more total therapy (ampicillin and gentamicin) than an infant with a blood culture positive for group B *Streptococcus* (ampicillin monotherapy).[2,3] Paradoxically, the result of an adequate maternal IAP and sterile blood cultures is often more treatment. Our view is that when cultures are sterile after adequate IAP, bacterial concentrations in the infant either have been reduced to ultralow concentrations or sterilized, neither of which require additional antibiotic therapy.

Finally, some providers are hesitant to discontinue therapy because they are convinced that the infant has sepsis despite a sterile culture. However, the idea that providers can differentiate sepsis from other conditions in the ill neonate has been disproven.[8] Clinical signs such as respiratory distress, hypotension, and temperature instability are nonspecific for sepsis and occur at much higher rates among preterm infants than sepsis does. Unsurprisingly, the majority of ill-appearing infants who are evaluated for sepsis are uninfected.[2] Even among infected infants, a meaningful number have viral rather than bacterial infection.[9] The pretest probability of sepsis, even among critical infants, is low. Models that attempt to better define the likelihood of sepsis have been effective in reducing the number of blood cultures and empirical antibiotic courses among term and late preterm infants.[10] However, such models have not been validated in more premature infants. It is perfectly appropriate to obtain proper cultures and treat these infants empirically when sepsis is part of the differential, but we must train ourselves to trust our cultures and discontinue empirical therapy if they remain sterile at 36 to 48 hours of incubation. Additionally, ancillary laboratory tests such as complete blood counts or C-reactive protein have poor positive predictive value, lack specificity, and cannot be used to screen for or diagnose neonatal sepsis. In short, there are no substitutes for properly obtained blood cultures.

CONCLUSIONS

Blood cultures are an excellent resource for providers caring for neonates. When drawn properly, they have excellent sensitivity. However, providers justify treating sterile blood cultures on the basis of 3 incorrect assumptions: that they are insensitive, unreliable after maternal IAP, or inferior to the clinician's own judgement. In reality, blood cultures are the gold standard for diagnosing neonatal sepsis. Put simply, if the bacteria cannot grow in the blood culture bottle (an ideal medium at an ideal temperature, free of antibiotics, complement, or phagocytes), then why would they grow effectively in the infant's bloodstream? As we learn more about the adverse effects of antibiotic exposure on short- and long-term neonatal outcomes, it becomes increasingly clear that prolonged antibiotic therapy for suspected sepsis is a luxury our infants cannot afford. To end the culture of culture-negative sepsis,

providers must systematically obtain appropriate blood cultures . . . and then trust them.

ABBREVIATIONS

CFU: colony-forming unit
IAP: intrapartum antibiotic prophylaxis

REFERENCES

1. Schelonka RL, Chai MK, Yoder BA, Hensley D, Brockett RM, Ascher DP. Volume of blood required to detect common neonatal pathogens. *J Pediatr*. 1996;129(2):275–278
2. Cantey JB, Wozniak PS, Pruszynski JE, Sánchez PJ. Reducing unnecessary antibiotic use in the neonatal intensive care unit (SCOUT): a prospective interrupted time-series study. *Lancet Infect Dis*. 2016;16(10):1178–1184
3. Fjalstad JW, Stensvold HJ, Bergseng H, et al. Early-onset sepsis and antibiotic exposure in term infants: a nationwide population-based study in Norway. *Pediatr Infect Dis J*. 2016;35(1):1–6
4. Ting JY, Synnes A, Roberts A, et al; Canadian Neonatal Network Investigators. Association between antibiotic use and neonatal mortality and morbidities in very low-birth-weight infants without culture-proven sepsis or necrotizing enterocolitis. *JAMA Pediatr*. 2016;170(12):1181–1187
5. Polin RA; Committee on Fetus and Newborn. Management of neonates with suspected or proven early-onset bacterial sepsis. *Pediatrics*. 2012;129(5):1006–1015
6. Connell TG, Rele M, Cowley D, Buttery JP, Curtis N. How reliable is a negative blood culture result? Volume of blood submitted for culture in routine practice in a children's hospital. *Pediatrics*. 2007;119(5):891–896
7. Sabui T, Tudehope DI, Tilse M. Clinical significance of quantitative blood cultures in newborn infants. *J Paediatr Child Health*. 1999;35(6):578–581
8. Fischer JE. Physicians' ability to diagnose sepsis in newborns and critically ill children. *Pediatr Crit Care Med*. 2005;6(suppl 3):S120–S125
9. Ronchi A, Michelow IC, Chapin KC, et al. Viral respiratory tract infections in the neonatal intensive care unit: the VIRIoN-I study. *J Pediatr*. 2014;165(4):690–696
10. Kuzniewicz MW, Puopolo KM, Fischer A, et al. A quantitative, risk-based approach to the management of neonatal early-onset sepsis. *JAMA Pediatr*. 2017;171(4):365–371

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