How Long Do You Treat Clinically Diagnosed Neonatal Sepsis With Negative Cultures?

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As a Pediatric Infectious Diseases specialist it is very common for me to be asked to comment on how long a child with a particular illness should be treated with antibiotics. While I do have some opinions based upon experience, it is usually very difficult to apply Evidenced-Based Medicine to this situation. Once an infection is defined, one can look up the opinions of experts in textbooks and medical reviews for guidance but often it is either difficult to categorize the infection status of a particular patient with complex or unique findings, or the recommendations are vague. Why is this?

It is necessary to know what duration of treatment is unacceptably short, in order to really know the optimal amount of time to treat a certain infection. Consider the possibility of conducting a prospective study to treat a specific infection in which a suitable number of patients are randomized to treatment groups with a duration of antibiotics of 5, 7, 10, 12, or 14 days. If the outcome is satisfactory for 5% of those treated for 5 days, 15% for those treated for 7 days, and 95% for those treated for 10, 12 or 14 days it would be easy to judge that treatment for 10 days is recommended. Fewer than 10 days may cause the patient unacceptable risk and longer than 10 days is associated with an excess of exposure to antibiotics. If the only published clinical study used treatment for 14 days, we might never know that a shorter duration is acceptable. Indeed there may be some concern about the ethics of putting patients to unacceptable risk by performing a study to shorten the duration of treatment.

Saini, *et al*. [1], in this issue, recognized that the recommendations for treatment of neonates who are suspected of having sepsis but who have negative cultures are not based on strong evidence. Indeed there is a lack of information regarding whether such infants actually have infection. In all the studies of neonatal sepsis in which I have participated, we require culture of a pathogen from blood, an organ, or pus from a closed space [2-4]. This requires exclusion of patients diagnosed as having "clinical sepsis" with negative cultures.

Saini, *et al*. [1] have shown equivalent outcomes for infants with negative cultures and whose symptoms have remitted whether they are treated for 48-96 hours or 7 days. This is gratifying as I have recommended 2-3 days of antibiotics for infants suspected of having sepsis but whose cultures were all sterile [5,6]. It is necessary to note some limitations of how this study was conducted and any conclusions must take into consideration that the sample size was small. First, the infants were all over 30 weeks gestation age and over 1000 grams birth weight. Since the rate of sepsis is highest for infants <1000 grams birthweight, the infants in this study were not at maximum risk for sepsis. Second, there were only a small number of infants whose mothers received antibiotics before delivery (10 in all). Since one of the most vexing areas for management of infants with suspected sepsis is whether negative cultures can be trusted if the infant has already been exposed to antibiotics by mother's treatment, this study does not provide guidance for such infants. Finally, it is doubtful that I could persuade neonatologists who routinely treat

for 7 days to shorten to 2-3 days based on a study with only 26 infants in each arm. However, it might allow such neonatologists to participate in a much larger study aimed at reducing the length of treatment for infants with negative cultures. Our own data suggest the decision to start antibiotic treatment in low birth weight infants is most frequently made on the day of birth [2,3]. If a sufficiently-sized study confirms that antibiotics can be discontinued after 2-3 days it would save unnecessary treatment in a considerable number of infants.

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