Research Roundtable Summary

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Neonatal "Sepsis Work-Up": A Population Study

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About This Series

The Research Roundtable Series, sponsored by the Maternal and Child Health Bureau (MCHB), disseminates the results of MCHB-funded research to policymakers, researchers, and practitioners in the public and private sectors. The results of these projects influence future service, research, and policy development. The Research Roundtable sessions provide an opportunity for researchers to discuss their findings with policymakers, MCH program directors, service providers, and other health professionals.

The MCHB Research Program is directed by Dr. Gontran Lamberty and administered through the Division of Systems, Education and Analysis, MCHB, Health Resources and Services Administration (HRSA), U.S. Department of Health and Human Services. The purpose of the research program is to support applied research relating to maternal and child health services that shows promise of substantial contribution to the advancement of these services.

Presentation of Research and Relevant Findings

Statement of the Problem

Although the frequency of sepsis, meningitis, and other confirmed bacterial infections has remained constant for years, the number of infants evaluated and treated is much higher. "Rule out sepsis" may be the second most common neonatal discharge diagnosis in the United States (after "well baby"). Newborn infections have a frequency of 1/1,000 to 5/1,000 live births, but each year as many as 600,000 U.S. infants are evaluated for suspected bacterial infection at least once during the birth hospitalization. The number treated is estimated at 130,000 to 400,000 per year. Despite massive overtreatment, delayed diagnosis still occurs.

The management of infants with proven infection is generally agreed upon. Controversy exists with respect to newborns whose presentations are considered equivocal, high-risk newborns who are asymptomatic, and newborns whose mothers received intrapartum antibiotics.

Despite calls for randomized clinical trials in this area, the existing literature is still insufficient. Studies should address five key methodologic issues: (1) use of proper denominators, (2) use of proper numerators, (3) stratification by initial severity of illness, (4) consideration of maternal treatment status, and (5) postdischarge outcomes, particularly of infants who were not treated during the birth hospitalization.

Research Questions

This study had two aims: to characterize the neonatal "sepsis work-up" during the birth hospitalization, and to clearly define which predictors should be employed in evidence-based

guidelines suitable for use by clinicians. To our knowledge, this is the first population-based study to provide maternal and neonatal data on all babies ever evaluated and to provide information on postdischarge follow-up.

Population Description and Sampling Plan

We employed the proper denominator: all babies ever evaluated for sepsis (with a complete blood count, a blood culture, or both). Babies were included if they (1) weighed 2,000 grams at birth; (2) were born in selected Kaiser Permanente hospitals in California from October 1995 through November 1996; (3) were evaluated for bacterial infection during the birth hospitalization; and (4) did not meet exclusion criteria. Babies were excluded if (1) a major congenital anomaly was present; (2) the first evaluation was for suspected nosocomial infection; (3) the baby was born outside the hospital; (4) the first evaluation occurred after discharge; (5) a complete blood count was performed for other reasons (e.g., jaundice); or (6) the complete blood count was obtained to evaluate for syphilis, gonorrhea, or HIV infection.

On-site research assistants prospectively reviewed nursery logs, laboratory results, and patient records. We recorded demographic factors; risk factors such as length of rupture of membranes; objective signs (e.g., highest/lowest temperature or heart rate in a given time frame); subjective findings (e.g., feeding difficulty, chorioamnionitis); roentgenogram results; use of antibiotics, supplemental oxygen, or assisted ventilation; and clinical status at various time points. We downloaded and manually reviewed the electronic results of (1) all maternal genital cultures for Streptococcus agalactiae (group B streptococcus) obtained during pregnancy; (2) the first three neonatal complete blood counts; (3) the first three arterial blood gas results; and (4) the first two cerebral spinal fluid cell counts.

Babies born to members of Kaiser Foundation Health Plan, Inc., are automatically covered for the first month of life, which permits very high follow-up rates during the neonatal period. We scanned all available Kaiser Foundation Health Plan databases, including those tracking out-of-plan use, to determine whether, during the first week after discharge, study subjects (1) left the Kaiser Plan; (2) were rehospitalized (i.e., admitted within 7 days of discharge); or (3) died. We also tried to contact the families of all study subjects by mail or phone to inquire about the infant's outcome during the first week after the birth hospitalization. We then reviewed electronic hospitalization records, laboratory data, and paper records of all babies rehospitalized.

The primary outcome of interest was whether a newborn had a vertically transmitted bacterial infection. Outcome assignment was based on culture results or clinical factors (e.g., results of physical examinations or chest roentgenograms).

Results

A total of 19,043 birth hospitalizations occurred at the six sites; of these, 2,785 (14.6% of live births) met study criteria. We were able to track all but 10 (0.4%) of these infants to 1 week postdischarge.

Of the 2,785 infants, 2,539 (91.2%) were identified as being at risk for sepsis by 12 hours of age; 853 (30.6%) received systemic antibiotics; 206 (7.4%) were ventilated; 22 (0.8%) had a positive culture (15 group B streptococcus, 5 E. coli, 2 other; 1 death occurred in this group); 15 (0.5%) had a probable infection (2 deaths occurred in this group); 25 (0.9%) had a possible infection (1 death occurred in this group); and 67 (2.4%) were rehospitalized (2 with group B streptococcus bacteremia). The most common reasons for rehospitalization were jaundice and dehydration/feeding difficulties.

By 12 hours of age, the required therapy was initiated for 93.1% of the 679 babies who needed supplemental oxygen and 89.8% of the 206 babies who needed assisted ventilation. Maternal fever, chorioamnionitis, low neonatal absolute neutrophil count (ANC) for age, and presence of neonatal clinical signs were associated with infection. There were 1,217 infants whose mothers received intrapartum antibiotics and 1,568 whose mothers did not. Infants of mothers who were treated were more likely to be asymptomatic (71.5% vs. 50.9%, p = 0.001) and less likely to be critically ill within 6 hours of birth (5.4% vs. 7.5%, p = 0.038).

We stratified infants according to maternal treatment status and conducted multivariate analyses. Among infants whose mothers were not treated, maternal chorioamnionitis (adjusted odds ratio [OR] = 2.40; 95% confidence interval [CI] = 1.15. 5.00); low ANC for age (adjusted OR = 2.84; 95% CI = 1.50. 5.38); and presence of meconium in the amniotic fluid (adjusted OR = 2.23; 95% CI = 1.18. 4.21) were associated with an increased risk of infection, while initial asymptomatic status was associated with a decreased risk (adjusted OR = 0.26; 95% CI = 0.11. 0.63). Results were similar for infants whose mothers were treated, except that chorioamnionitis was not a significant predictor for infection.

We also found that (1) use of epidural anesthesia is associated with a 0.5˚F increase in maternal temperature, even after controlling for chorioamnionitis; (2) published ANC norms misclassify almost half of babies with infections; (3) increased risk of infection is seen when time of rupture of membranes exceeds 12 hours; and (4) practice varies widely with respect to maternal and neonatal antibiotic treatment.

Findings

Current guidelines need to be revised in light of these data, which highlight the protective effect of maternal intrapartum antibiotics. Evidence-based approaches should emphasize (1) careful assessment in the first 24 hours after birth; (2) close attention to maternal risk factors; and (3) modification of ANC norms used to categorize infants as being at high risk for sepsis.

Four Kaiser Permanente regions have used data to define a formal guideline that will be implemented throughout the Kaiser Permanente Medical Care Program. A key component in the development of this guideline was the use of the data set from this study to simulate various treatment strategies.

Reactor Response

Infection-related deaths have declined by about 30 percent since 1979 among U.S. infants. Between 1979 and 1997 the rate of postneonatal deaths that occurred as a result of septicemia declined by 32 percent. Although the rate of death from infant sepsis has leveled off in recent years, establishing guidelines for how to diagnose and treat septicemia in the best and most cost-effective manner remains an important step that has yet to be taken. Dr. Escobar and his colleagues have risen to the challenge of making recommendations for an evidence-based approach to managing infant sepsis. Their data and their recommendations for future research may be useful to both the research and the practice community.

Dr. Escobar notes that even within the Kaiser system, where he conducted his study, practice varies widely with respect to maternal and neonatal antibiotic treatment. Elsewhere, practice may vary even more. Community physicians may be less aggressive than academic physicians in treating infants suspected to have sepsis. Their respective styles may be related to the amount and type of patient data at their disposal, and to risk issues. Larger academic centers with more distant relationships with patients, and less personal knowledge of them, may feel pressure to avoid underdiagnosis, whereas smaller community practices in which health professionals know their patients better may tend to

factor this personal knowledge into their decisions about patient management, and may therefore be more prone to underdiagnose. Dr. Escobar suggests that the establishment of practice guidelines for managing infant sepsis may lead to more uniform and effective practice styles.

Most of the work done on the topic of infant sepsis appears to be in the area of group b streptococcal disease, which remains the predominant organism recovered from culture. Thus, the literature has not set forth as clear a management path for nonstreptococcal disease as it has for streptococcal disease. This lack is especially evident in cases of infants who become ill but do not have the expected risk profile (i.e., the mother's membranes were ruptured for more than 18 hours before the infant's birth, the mother had a fever during labor, or the gestation period was less than 37 weeks). Dr. Escobar's work points to unanticipated risks that need to be better defined, including absolute neutrophil count and the presence of chorioamnionitis in the mother.

Questions that remain include the following: How do we define and manage probable infection, possible infection, and risk reduction of post-discharge infection? What guidelines can be recommended for nonstreptococcal infection risk to minimize adverse outcomes in infants? What are some strategies to further disseminate the scientific data and guidelines to the broader health professional audience so that standard, proven treatment regimens are used more consistently?

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