Neonatal Sepsis Workups in Infants ≥2000 Grams at Birth: A Population-Based Study

Gabriel J. Escobar, MD*‡; De-kun Li, MD, PhD*; Mary Anne Armstrong, MA*; Marla N. Gardner, BA*; Bruce F. Folck*; Joan E. Verdi, MBA*; Blong Xiong, MPH*; and Randy Bergen, MD‡, for the Neonatal Infection Study Group

ABSTRACT. *Background.* **Few data are available on the outcome of neonatal sepsis evaluations in an era when intrapartum antibiotic therapy is common.**

Methods. **We identified all newborns weighing ≥2000 g at birth who were ever evaluated for suspected bacterial infection at 6 Kaiser Permanente hospitals between October 1995 and November 1996, reviewed their records and laboratory data, and tracked them to 1 week after discharge. We analyzed the relationship between key predictors and the presence of neonatal bacterial infection.**

Results. **Among 18 299 newborns ≥2000 g without major congenital anomalies, 2785 (15.2%) were evaluated for sepsis with a complete blood count and/or blood culture. A total of 62 (2.2%) met criteria for proven, probable, or possible bacterial infection: 22 (.8%) had positive cultures and 40 (1.4%) had clinical evidence of bacterial infection. We tracked all but 10 infants (.4%) to 7 days postdischarge. There were 67 rehospitalizations (2.4%; 2 for group B streptococcus bacteremia). Among 1568 infants who did not receive intrapartum antibiotics, initial asymptomatic status was associated with decreased risk of infection (adjusted odds ratio [AOR]: .26; 95% confidence interval [CI]: .11–.63), while chorioamnionitis (AOR: 2.40; 95% CI: 1.15–5.00), low absolute neutrophil count (AOR: 2.84; 95% CI: 1.50–5.38), and meconium-stained amniotic fluid (AOR: 2.23; 95% CI: 1.18–4.21) were associated with increased risk. Results were similar among 1217 infants who were treated, except that maternal chorioamnionitis was not significantly associated with neonatal infection.**

Conclusions. **The risk of bacterial infection in asymptomatic newborns is low. Evidence-based observation and treatment protocols could be defined based on a limited set of predictors: maternal fever, chorioamnionitis, initial neonatal examination, and absolute neutrophil count. Many missed opportunities for treating mothers and infants exist.** *Pediatrics* **2000;106:256–263;** ***neonatal sepsis, neonatal meningitis, neonatal intensive care, group B streptococcus, streptococcus agalactiae, antibiotic therapy, sepsis evaluations, neonatal infections.***

From *Kaiser Permanente Medical Care Program, Division of Research, Perinatal Research Unit, Oakland, California; and the ‡Department of Pediatrics, Kaiser Permanente Medical Center, 1425 S Main St, Walnut Creek, California.

Received for publication Apr 12, 1999; accepted Oct 5, 1999.

Reprint requests to (G.J.E.) Kaiser Permanente Medical Care Program, Division of Research, Perinatal Research Unit, 3505 Broadway, Room 718, Oakland, CA 94611. E-mail: gabriel.escobar@ncal.kaiperm.org

ABBREVIATIONS. KPMCP, Kaiser Permanente Medical Care Program; CBC, complete blood count; GBS, group B streptococcus(al); CSF, cerebrospinal fluid; I:T ratio, ratio of immature to total neutrophils; ANC, absolute neutrophil count; ROM, rupture of membranes; SD, standard deviation; AOR, adjusted odds ratio; CI, confidence interval; OR, odds ratio; CRP, C-reactive protein.

The frequency of neonatal bacterial infections ranges from 1 to 5 per 1000 live births.[1,2] However, between 4.4% and 10.5% of all infants born in the United States (130 000–400 000/year) receive systemic antibiotics.[3–6] General agreement seems to exist with respect to management of infants with proven infection.[7,8] Controversy exists with respect to newborns whose presentations are considered equivocal, high-risk newborns who are asymptomatic, and newborns whose mothers received intrapartum antibiotics.[9–12]

This article reports on the outcome of neonatal sepsis work-ups in infants ≥2000 g at birth in an era of widespread intrapartum antibiotic treatment. We focused on the first evaluation performed for perinatally acquired non-nosocomial bacterial sepsis shortly after birth. Our setting was the Kaiser Permanente Medical Care Program (KPMCP), a mature managed care organization with integrated information systems.

METHODS

This project was approved by the KPMCP Institutional Review Board for the Protection of Human Subjects. An expert panel, the Neonatal Infection Study Group, defined predictors and outcomes and reviewed study data. The panel consisted of a pediatric infectious disease specialist, a pediatric pathologist, and 9 neonatologists.

Infants were included if they: 1) weighed ≥2000 g at birth; 2) were born in the hospital at the KPMCP Hayward, Oakland, Sacramento, San Francisco, Santa Clara, and Walnut Creek facilities between October 1995 and November 1996; 3) were ever evaluated for bacterial infection during the birth hospitalization; and 4) did not meet exclusion criteria. An infant was considered to have been evaluated if a complete blood count (CBC) and/or a blood culture was obtained. Infants were excluded if: 1) a major congenital anomaly was present; 2) the first evaluation was for suspected nosocomial infection; 3) the infant was born outside the hospital; 4) the first evaluation occurred after discharge home; 5) a CBC was performed for other reasons (eg, jaundice); or 6) the CBC was obtained to evaluate for syphilis, gonorrhea, or human immunodeficiency virus infection.

Study subjects were identified prospectively. Paper and electronic records were reviewed retrospectively. On-site research assistants reviewed nursery logs, laboratory results, and patient records. A complete chart review of maternal and neonatal

records was performed for all newborns who ever had a CBC and/or blood culture obtained.

The information systems of KPMCP use a common medical record number and clinical data repository. These information systems permit multiple linkages (eg, downloading all neonatal CBCs and linking their results to hospitalization records). The methods used for subject identification, data abstraction, and electronic linkage have been described in this journal[13–16] and elsewhere.[17–20]

We downloaded and manually reviewed the electronic results of: 1) all maternal genital cultures for *Streptococcus agalactiae* (group B streptococcus [GBS]) obtained during pregnancy; and 2) all neonatal urine, blood, and cerebrospinal fluid (CSF) cultures obtained on members of the study cohort. We also downloaded and manually reviewed the following neonatal results: the first 3 CBCs; the first 3 arterial blood gas results; and the first 2 CSF cell counts.

Infants born to women who are Kaiser Foundation Health Plan, Inc members are automatically covered for the first month of life, which permits very high follow-up rates during the immediate neonatal period.[16] We scanned all available KPMCP electronic databases, including those tracking out-of-plan use, to define whether study subjects: 1) left the health plan after discharge from the birth hospitalization; 2) were rehospitalized during the first week after discharge from the birth hospitalization; or 3) died during the first week after discharge from the birth hospitalization. We also contacted the families of all study subjects by mail at 14 to 60 days postdischarge to enquire whether their infant was hospitalized or died during the first week after the birth hospitalization. If an infant's outcome during the first week after the birth hospitalization could not be ascertained using the above methods, we attempted to contact the infant's family by phone. We then reviewed electronic hospitalization records, laboratory data, and paper charts of all rehospitalized infants.

The ratio of immature to total neutrophils (I:T ratio) was calculated in the same manner as described by Manroe et al[21] and Schelonka et al.[22,23] Because neonatal leukocyte indices change over time, we did not assess the predictive ability of a single absolute neutrophil count (ANC) value. Rather, the ANC was categorized as being abnormally high or low if it fell outside the upper and lower 10th percentiles for chronological age. We used results from recent studies,[22–30] rather than the more commonly cited study by Manroe et al,[21] to define these percentile ranges, which are provided in the "Appendix" (available to readers on request).

We categorized chorioamnionitis as definite if an obstetrician documented it, supporting evidence was provided (eg, uterine tenderness or foul smelling amniotic fluid was present), and the highest antepartum temperature exceeded 101.9°F. The definition of probable chorioamnionitis was similar, except that the temperature threshold used was >100.4°F. The definition of possible chorioamnionitis only required an obstetrician's note.

We considered an infant to be asymptomatic if no abnormalities were recorded in the chart. An infant was defined as critically ill if any of the following occurred: 1) assisted ventilation (nasal continuous positive airway pressure or intermittent mandatory ventilation), 2) chest compressions, 3) needling of the chest or thoracostomy tube placement, 4) continuous infusion of vasoactive drugs, and/or 5) transport to a higher level of care (eg, for refractory persistent pulmonary hypertension).

Screening for GBS

Screening for GBS is not routinely performed in the KPMCP, whose obstetricians endorsed a risk factor-based strategy in 1994.[31,32] Screening is performed based on the discretion of individual clinicians. Intrapartum therapy uses either ampicillin or a cephalosporin.

Outcome Assignment

Outcome assignment was based on culture results or clinical factors (eg, results of physical examinations or chest roentgenograms). To avoid circular reasoning, we did not use CBC results or treatment decisions to define outcome. A culture-proven infection is defined as an infection confirmed by a positive culture from a normally sterile site. A probable infection is one in which the clinical course strongly suggested that infection was present, although culture results were negative. An example of a probable infection (meningitis) is an infant with clinical signs and CSF pleocytosis (defined as having >30 white blood cells and <45 000 red blood cells in the CSF[33]). A possible infection is one in which an infant had negative cultures and equivocal clinical findings but infection could not be excluded. An example of this category is an infant who required assisted ventilation and had only a single chest radiograph showing lung infiltrates. An infection was considered nosocomial if it could be ascribed to care processes (eg, *Staphylococcus epidermidis* sepsis after prolonged intubation). Rehospitalization was defined as admission within 7 days after an infant first went home.

Statistical Methods

Statistical analyses were performed using SAS (SAS, Cary, NC).[34] χ^2 or Fischer's exact tests were used to compare categorical predictors and Student's t tests were used to compare mean differences of continuous predictors. Least-square adjusted means were produced using analysis of variance. Multivariate analyses were performed using logistic regression after stratification by maternal treatment. The area under the receiver operator characteristic curve was calculated using the method of Hanley and McNeil.[35]

RESULTS

A total of 19 043 birth hospitalizations occurred at the 6 study sites. We excluded 744 infants for the following reasons: 589 weighed <2000 g at birth and 155 had major anomalies. Of the remaining 18 299 infants, 15 391 never had a CBC or blood culture obtained during the birth hospitalization. Among the 2908 infants who had a CBC during the birth hospitalization, medical record review showed that the CBC was obtained for reasons other than to rule out sepsis in 123 cases: 5 were born out of asepsis; 78 had a CBC as part of a jaundice evaluation; 4 had a CBC and blood culture obtained as part of a syphilis and/or human immunodeficiency virus evaluation; and 36 had a CBC performed for some other reason. Table 1 summarizes characteristics of the remaining 2785 infants, who constitute the study cohort.

A total of 67 infants met our criteria for infection. Table 2 summarizes these infections and shows that 62 were non-nosocomial, 2 were nosocomial, and 3 were not under a caregiver's control. The 62 infants with non-nosocomial infections, thus, constitute the numerator for this study. Of these 62 infants, 12 were either asymptomatic or had transient clinical signs (ie, they seemed to have bacteremia rather than sepsis) and 2 of these 12 infants were sent home before confirmation of the diagnosis. Both of these infants were rehospitalized and treated with systemic antibiotics.

Deaths and Postdischarge Outcomes

There were a total of 8 deaths in the cohort, including 4 with infections mentioned above. We were unable to track 10 infants to 1 week postdischarge. These 10 infants were healthy at discharge, and 2 had received antibiotic therapy.

The rehospitalization rate in the first week after discharge was 2.4% (67/2785). Infants were rehospitalized for the following reasons: jaundice and/or feeding difficulties, 52; confirmed infections (included in Table 1), 4; rule out sepsis with negative cultures, 4; and miscellaneous diagnoses, 7.

TABLE 1. Description of Study Cohort

	<37 Weeks	≥37 Weeks	All
n	492	2293	2785
Maternal age (y)			
Median	30	29	29
Range	15–46	15–47	15–47
Mean ± SD	29.6 ± 6.3	28.6 ± 6.1	28.8 ± 6.2
Maternal race			
% white	42.8	42.9	42.9
% black	16.0	14.8	15.0
% Asian	21.3	20.3	20.5
% Hispanic	18.5	20.4	20.0
% other	1.4	1.6	1.6
% born by cesarean section	26.6	30.6	29.9
% who received any intrapartum antibiotic treatment	58.4	40.5	43.7
% who received intrapartum antibiotic treatment ≥4 h before delivery	46.3	23.8	27.8
Birth weight			
Median	2460	3549	3398
Range	2000–4133	2003–6130	2000–6130
Mean ± SD	2515 ± 360	3550 ± 556	3367 ± 658
Product of multiple gestation (%)	13.0	1.5	3.5
Sex (% male)	61.7	55.1	56.3
% of infants treated with	41.2	28.4	30.7
Systemic antibiotics			
Supplemental oxygen	30.6	23.0	24.4
Assisted Ventilation	19.7	4.8	7.4

TABLE 2. Infants With Infections

	No. of Infants*	Asymptomatic†	Pneumonia	Sepsis	Meningitis	Other‡
Culture-positive infection	26	11	3	22	0	4
Probable infection	16	0	7	3	5	1
Possible infection	25	1	16	6	5	0
Total	67	12	26	31	10	5

* Infants can be categorized more than once.
† Asymptomatic includes infants who either had no clinical signs in first 12 hours of age or whose signs were transient.
‡ Other infections include 2 nosocomial infections and 3 infections that could not be anticipated (enterovirus, postdischarge urinary infection, postdischarge herpes simplex with no known maternal risk factors).

Other Cases of Vertically Transmitted Sepsis or Meningitis

We scanned the electronic records of the 15 391 infants who did not have a sepsis evaluation and of the 123 infants who had a CBC obtained for other reasons. Searches in KPMCP clinical, administrative, and research databases showed that none of these infants had sepsis or meningitis during the week after discharge from the birth hospitalization.

Descriptions of deaths, infants with infections, and infants lost to follow-up are provided in the "Appendix."

Neonatal Evaluation and Treatment

The majority of infants (75.8%) were first noted to be at risk for sepsis before or at the moment of birth and 91.2% were identified by 12 hours of age. The same occurred with the 205 infants who experienced assisted ventilation. Among these infants, 89.8% had such therapy initiated by 12 hours of age. All 62 of the infants with infections were identified by 10 hours of age.

A total of 1510 infants had clinical signs consistent with infection. Among the remaining 1275 infants who were initially asymptomatic, evaluations were performed because of risk factors for sepsis. These included maternal chorioamnionitis (425 infants or 33.3% of the asymptomatic infants); rupture of membranes (ROM) >18 hours (432; 33.9%); fever >100.4°F (315; 24.7%); GBS carriage (60; 4.7%); 188 prematurity; and foul smelling amniotic fluid (37; 2.9%)

Maternal Treatment

There were 1217 infants whose 1206 mothers were treated with intrapartum antibiotics. Among these 1206 mothers, 435 had chorioamnionitis documented by a physician's note; 589 had ROM >18 hours; 487 had other clinical signs consistent with infection (eg, temperature >100.9°F, ROM before delivery, and foul smelling amniotic fluid); 279 delivered at <37 weeks' gestation; and 81 were GBS carriers. The reason for intrapartum antibiotic therapy could not be determined in 125 women. There were 1568 infants

whose 1541 mothers did not receive intrapartum antibiotics. Among these 1541 mothers, 121 had chorioamnionitis documented by a physician's note; 148 had ROM >18 hours; 154 had other clinical signs consistent with infection (eg, temperature >100.9°F, ROM before delivery, and foul smelling amniotic fluid); 194 delivered at <37 weeks' gestation; and 48 were GBS carriers.

Infection Rates in Specific Subgroups

Infection rates among specific infant subgroups are shown in Table 3 (stratified by maternal characteristics) and in Table 4 (stratified by neonatal characteristics). Among treated infants, the highest infection rates observed were in those who were critically ill (where the rate was 9.7%) and those whose mothers' highest antepartum temperature was ≥102°F (6.1%). The infection rate was lowest among asymptomatic infants (.9%). Among untreated infants, the highest infection rates were among those whose mothers' highest antepartum temperature was ≥101.5°F (12.0%) and those who were critically ill (10.3%). The infection rate was lowest among asymptomatic infants (1.0%). Likelihood of infection increased with increasing temperature, more rigorous documentation of chorioamnionitis, and increased clinical signs. More detailed data are provided in the "Appendix."

Among the 853 infants who received antibiotic therapy during the birth hospitalization, the first CBC was obtained before antibiotics were given in 669 cases (78%), within 2 hours after treatment in 173 (20%), and >2 hours in 11 (2%). The median difference between the time of the first CBC and the initiation of antibiotic therapy was 4 hours. All but 5 of these infants had a blood culture obtained.

Among the 1932 infants who were not treated with antibiotics during the birth hospitalization, 1492 (77.2%) had the first CBC obtained between 0 and 11.9 hours of age, 242 (12.5%) between 12.0 and 23.9 hours of age, and 194 (10.0%) at ≥24 hours of age. Only 61.2% of these infants had a blood culture obtained. There were 4 infants who only had a blood culture result recorded, because CBC results were lost.

A total of 68 asymptomatic infants experienced at least 1 lumbar puncture. None had meningitis. There were 10 cases of meningitis among the 153 symptomatic infants who experienced lumbar puncture.

Among the 1275 initially asymptomatic infants, where the infection rate was 1.0%, the treatment rate was 10.9%. If an infant had clinical signs but was not initially critically ill, where the infection rate was 2.3%, the treatment rate was 38.2%. Among the 182 infants who were critically ill, the infection rate was 10.9%. Only 144 of these 182 infants (79.1%) were treated with antibiotics. All 38 infants who were initially critically ill and who did not receive systemic antibiotics during the birth hospitalization were discharged from the hospital in good condition. We could not determine why physicians elected not to treat these infants.

TABLE 3. Relationship Between Infection Rates and Maternal Characteristics

Predictor	Infection Rate* Among Infants of		
	Treated Mothers	Untreated Mothers	All
Maternal chorioamnionitis			
None documented	1.2%	2.3%	2.0%
Possible	.6%	4.5%	2.4%
Probably	1.7%	5.5%	2.5%
Definite	8.6%	0†	8.1%
Any mention	.8%	4.9%	2.9%
Length of ROM (h)			
Not documented	0†	0†	0†
≤12	2.3%	2.4%	2.4%
12–17.9	3.5%	4.6%	4.1%
≥18	.8%	2.9%	1.3%
Highest antepartum temperature			
Not documented	0†	0†	0†
<99.5°F	1.0%	2.3%	1.9%
99.5°F–100.4°F	1.3%	3.6%	2.5%
100.5°F–101.4°F	1.0%	4.1%	1.8%
101.5°F–101.9°F	3.9%	15.4%	5.5%
≥102°F	6.1%	8.3%	6.4%

*Infection rate refers to the presence of any infection (n = 62 in cohort) in the subgroup. See text for definition of infection, chorioamnionitis, and highest antepartum temperature.
† Number of infants in each cell is small (<150).

TABLE 4. Relationship Between Infection Rates and Neonatal Characteristics

Predictor	Infection Rate* Among Infants of		
	Treated Mothers	Untreated Mothers	All
Birth weight <2500 g	2.3%	1.3%	1.8%
Gestational age <37 wk	1.7%	1.5%	1.6%
Initial clinical examination			
Asymptomatic	.9%	1.0%	.9%
Some clinical signs	1.8%	2.8%	2.4%
Critically ill	9.0%	10.2%	10.0%
Initial ANC <10th percentile	3.3%	4.7%	4.0%

* Infection rate refers to the presence of any infection (n = 62 in cohort) in the subgroup. See text for definition of infection, clinical examination categories, and ANC percentile ranges.

Overall Effect of Maternal Antibiotic Treatment

Compared with infants who did not receive intrapartum antibiotics, infants whose mothers were so treated were more likely to be asymptomatic (694/1217 vs 781/1568; P = .001) and were less likely to be critically ill (65/1217 vs 718/1568; P = .021). They were also less likely to be infected (20/1217 vs 72/1568; P = .066).

Infections Among Infants of Confirmed GBS Carriers

The neonatal infection rate among confirmed GBS carriers was 11.5% (15/131). Among these women, 59/131 received antibiotic prophylaxis ≥4 hours before delivery. There were 5 infants with infections in this group, but only 1 with a positive blood culture. All 5 infants showed clinical signs of infection by 8 hours of age. There were 10 infections (6 with positive cultures) among the infants of the 72/131 GBS carriers who did not receive antibiotic prophylaxis ≥4 hours before delivery. All 10 infants showed clinical signs of infection by 12 hours of age.

Neutrophil Kinetics

The 62 infants with infections had significantly lower ANCs than those without infections, even after controlling for age of the infant at the time the test was obtained, whether the mother received intrapartum antibiotics, cesarean section status, prematurity, and presence of preeclampsia. The adjusted mean ± standard deviation (SD) for the ANC in infected infants was 6290 ± 710, whereas that for noninfected infants was 9610 ± 230. Having a high ANC was not associated with the presence of infection in multivariate analyses.

Figure 1 shows the ANCs of the 62 infants with infections superimposed on the 90th and 10th percentile bands. Figure 2 shows the ANCs of the 62 infants with infections superimposed on the 90th and 10th percentile bands according to Manroe et al.[21] Nearly one half of the infants with infections would not have been considered to have a low ANC using these commonly used criteria. Table 5 compares the sensitivity, specificity, positive predictive value, and negative predictive value for the ANC, I:T ratio, and clinical examination. The area under the receiver operator characteristic curve for the I:T ratio was .74 ± .03.

Multivariate Analyses (Table 6)

Evaluation of predictors for infection was performed separately for infants who did and who did not receive intrapartum antibiotics. The dependent variable was the presence of any infection ($n = 42$ for the untreated group; $n = 20$ for the treated group). Logistic models included the following potential predictors: race (white, black, Hispanic, and all other), maternal age (≤20, 21–30, and ≥31 years); presence of maternal chorioamnionitis; ROM length (≤11, 12–17, and ≥18 hours); infant asymptomatic status; use of epidural anesthesia; history of diabetes; history of illegal drug use in this pregnancy; preeclampsia; whether the ANC was in the lowest 10th percentile for age (both criteria); gestation (<37 vs ≥37 weeks); birth weight (<2500 g vs ≥2500 g); and parity (primigravidas vs all others). We added the following predictors to models for the treated group: whether antibiotic therapy occurred ≥4 hours before delivery; meconium-stained amniotic fluid; and placental problems (oligohydramnios or polyhydramnios). In light of the results of bivariate analyses (provided in the "Appendix"), we added the following predictors to models for the untreated group: obstetric catastrophe (placenta previa, placental abruption, uterine rupture, and/or prolapsed umbilical cord); cesarean section; and oligohydramnios.

Stepwise models showed that the following variables were significantly associated with an increased risk of infection: ANC in lowest 10th percentile for chronological age and presence of meconium in the amniotic fluid. Initial asymptomatic status was protective. Maternal chorioamnionitis was significantly associated with neonatal infection in the untreated group but not in the treated group.

We tested 2 additional models, substituting 2 objective variables for chorioamnionitis: ROM length and highest maternal antepartum temperature. The first model included highest antepartum temperature ≥101.5°F; ROM ≥12 hours; ANC in lowest 10th

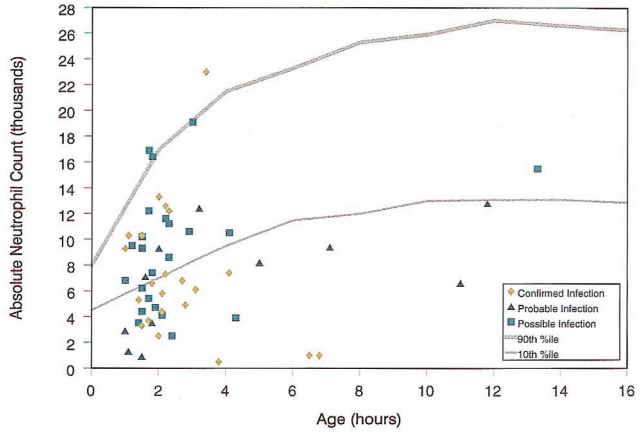

Fig 1. ANCs of infants with culture-proven (yellow diamonds), probable (green triangles), and possible (teal squares) bacterial infections as a function of infant age. Percentile bands are based on the work of Schelonka et al[22,23] and others.[26–30,33] No infant with an infection had a first CBC obtained after 16 hours of age.

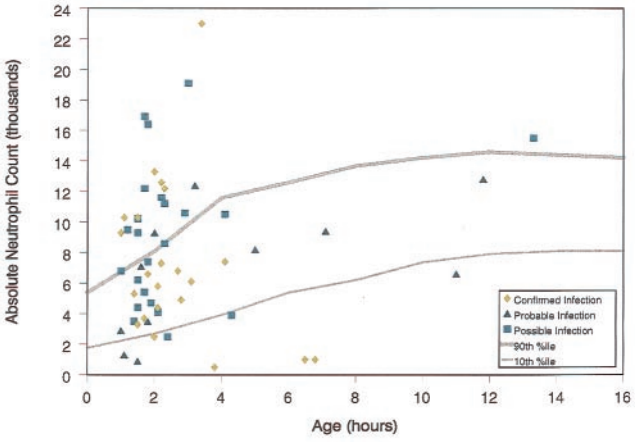

Fig 2. ANCs of infants with culture-proven (yellow diamonds), probable (green triangles), and possible (teal squares) bacterial infections as a function of infant age. Percentile bands are those defined by Manroe et al.[21] No infant with an infection had a first CBC obtained after 16 hours of age.

TABLE 5. Predictive Values of ANC, I:T Ratio, and Clinical Examination

	Sensitivity	Specificity	+PV*	−PV†
Presence of clinical signs‡	92%	53%	4%	99%
Baby critically ill§	31%	6%	10%	98%
ANC <10th percentile‖	48%	73%	4%	98%
ANC <10th percentile¶ Manroe et al[21]	16%	96%	8%	98%
I:T ratio, ≥.25 cutoff	45%	84%	6%	98%
I:T ratio, ≥.30 cutoff	35%	89%	7%	98%

* Positive predictive value.
† Negative predictive value.
‡ See text for exact definition; 1610/2785 infants had some clinical signs on presentation.
§ See text for exact definition: 182/2785 infants were critically ill on presentation.
‖See text and references 22, 23, 26–30, and 33 for exact definition.
¶ See text and reference 21 for exact definition.

TABLE 6. Results of Multivariate Analyses

Infants of Mothers Who Did Not Receive Intrapartum Antibiotics Denominator: 1568 Numerator: 42 Chorioamnionitis model	
Predictor	OR (95% CI)
Chorioamnionitis*	2.40 (1.15–5.00)
Low ANC for age†	2.84 (1.50–5.38)
Infant initially asymptomatic	.26 (.11–.63)
Meconium in amniotic fluid‡	2.23 (1.18–4.21)
Temperature + length of ROM model§	
Predictor	OR (95% CI)
Highest antepartum temperature ≥101.5°F‖	5.78 (1.57–21.29)
ROM ≥12 hours¶	2.05 (1.06–3.96)
Low ANC for age†	2.82 (1.50–5.34)
Baby initially asymptomatic	.27 (.11–.65)
Meconium in amniotic fluid‡	2.24 (1.19–4.22)
Infants of Mothers Who Did Receive Intrapartum Antibiotics **Denominator: 1217 Numerator: 20** **Chorioamnionitis model**	
Predictor	OR (95% CI)
Low ANC for age†	3.55 (1.43–8.84)
Infant initially asymptomatic	.36 (.14–.96)
Meconium in amniotic fluid‡	2.73 (1.08–6.94)
Temperature + length of ROM model§	
Predictor	OR (95% CI)
Highest antepartum temperature ≥101.5°F‖	3.50 (1.30–9.42)
Low ANC for age†	3.60 (1.45–8.96)

* Compared with mothers who did not have any documentation of chorioamnionitis.
†Compared with infants whose ANCs were above the 10th percentile using our revised criteria (see text). Having an ANC above the 90th percentile was not significant. This predictor was also significant using the norms defined by Manroe et al,[21] although CIs were much wider.
‡ Compared with infants whose amniotic fluid did not have meconium present.
§ Model substitutes highest temperature in 12 hours before delivery and length of ROM for the chorioamnionitis variable in the previous model.
‖ Compared with women whose temperature was <101.5°F.
¶ Compared with women whose length of ROM was <12 hours.

percentile for chronological age; asymptomatic status; and presence of meconium in the amniotic fluid. Among infants of untreated mothers, all of these predictors remained significant. Among infants of treated mothers, only fever and low ANC remained significant, although asymptomatic status approached significance (adjusted odds ratio [AOR]: .42; 95% confidence interval [CI]: .16–1.11). The second model used ROM ≥18 hours; this predictor was not significant in either group.

We also forced race (white vs non-white), maternal age (≤20, 21–30, and ≥31 years), and parity (primigravidas vs all others) into the models shown on Table 4. The same variables remained predictive without major changes in odds ratios (ORs). To assess possible treatment bias in our infection definition, we tested the above models using modified criteria (infants who received systemic antibiotics and experienced assisted ventilation or received pressors were considered to have an infection). Chorioamnionitis, initial asymptomatic status, and low ANC for age remained predictive.

We did not find significant associations between time of maternal treatment and infection in bivariate or multivariate analyses.

DISCUSSION

Rule out sepsis is one of the most common discharge diagnoses in neonatology. We are not aware of other population-based studies that provide maternal and neonatal data on all infants ever evaluated or of any similar studies with postdischarge follow-up.

We must stress certain limitations. Our study population is one of relatively low risk. However, less controversy exists about treating high-risk infants, so this limitation is not significant, and our findings can be generalized to other insured populations. A second limitation inherent in our study design is that we cannot fully assess the effect of certain risk factors (eg, prematurity) because women with such risk factors receive special treatment (eg, intrapartum antibiotics) in the KPMCP. Our retrospective methodology may underestimate the true frequency of infection attributable to false-negative culture results and prompt resolution of clinical signs in some infants. Because only 221/2785 newborns had one, our study can only have a limited role in addressing another controversial issue, whether all infants suspected of sepsis should have a lumbar punc-

ture.[5,9,10,12] Finally, we did not use a test recommended by some authors, C-reactive protein (CRP).[36–38] Use of CRP is not widespread in the KPMCP because the existing literature does not permit full assessment of its utility (eg, no data are available comparing the predictive ability of CRP with that of the clinical examination).

The risk of sepsis among asymptomatic infants is very low.[9,11,12] In our cohort, asymptomatic infants had an infection rate of 1.0%. This low rate is still 10 times as high as the population rate (~1/1000 live births in this birth weight range).[1,2] This finding supports the notion that screening, treatment, and observation protocols cannot be based on asymptomatic status alone.

We found that outcomes among infants whose mothers received intrapartum antibiotics are better than among those whose mothers did not. Infants whose mothers were treated were less likely to be symptomatic, need assisted ventilation, or have bacterial infection. The rationale for intrapartum treatment is based on randomized clinical trials.[39,40] However, adoption of this strategy by obstetricians is not uniform, and many pediatricians remain unconvinced that maternal treatment obviates the need for neonatal treatment.[39–43] One key concern is that such treatment may partly suppress bacterial growth leading to false-negative culture results.[39,40,42]

We did not find differences in outcome associated with the timing of maternal treatment. This should be interpreted carefully. Strong biologic reasons for supporting early maternal antibiotic treatment exist.[44–46] Similar caution should be exercised with respect to conditions (eg, diabetes) associated with perinatal morbidity, which, although predictive, failed to reach statistical significance in our analyses because of limited numbers.

Our findings with respect to the CBC suggest that use of this test needs reassessment. Current recommendations are vague and are based on small studies. They emphasize using CBC results obtained at 12 to 24 hours of age and the use of the I:T ratio, an extremely subjective and statistically unreliable[47] test which Schelonka et al[22,23] have shown to classify large numbers of normal newborns as being at risk for sepsis. A better way to use the CBC as a screening tool would be to define likelihood ratios for ANC percentile ranges based on an infant's chronological age.[48] Our finding that the sensitivity of the physical examination is greater than that of the I:T ratio or ANC supports this approach.

Our finding that only 144/182 of initially critically ill infants received systemic antibiotics suggests that more variation exists in this area than has been previously suspected. Our data provide a hint as to what may account for some of this variation. First, some infants may be misclassified by existing approaches used to interpret CBC results. Second, given limited data, clinicians are both overestimating and underestimating infants' risk for infection. Other reasons may have played a role, but determining these is outside the scope of this article. A recent study suggests that what we are describing may not be so uncommon. Baker et al[49] developed and implemented an evidence-based protocol and recently reported that 28/422 febrile infants were not managed according to a defined standard of care, including 21/321 high-risk infants who did not receive antibiotics.[50] Clearly, more research is needed in the areas of clinician compliance as well as clinician perception of risk.

We were also surprised that many women with clear indications for systemic antibiotics (eg, presence of chorioamnionitis) did not receive them. These findings point out how clinician behavior deviates from what is considered appropriate in the literature, and that nominal adherence to a given strategy (such as the risk factor-based strategy proposed by the Centers for Disease Control and Prevention[39]) may be insufficient to change clinician behavior. Screening for GBS is not universal in the KPMCP. The fact that only 15% of women who were screened tested positive suggests that current KPMCP strategies may not be that effective. This phenomenon has been documented in other settings.[39–41,43]

A detailed assessment of how findings from this study could help define strategies for evaluating newborns at risk for sepsis is outside the scope of this article. Such strategies should be based on combinations of predictors, 4 of which are critical: chorioamnionitis; elevated maternal temperature; initial neonatal examination; and whether the mother received intrapartum treatment. Coupled with judicious, empirically defined time frames, it should be possible to define rational recommendations for appropriate neonatal antibiotic treatment and/or observation. Such recommendations would undoubtedly lead to increased treatment in some infants (eg, those experiencing respiratory failure) and less treatment in a larger group of infants (those with few or no clinical signs).

ACKNOWLEDGMENTS

This study was supported by the Kaiser Foundation Health Plan, Inc and the Permanente Medical Group, Inc (Innovation Program Grant 115-6030); by the Sidney Garfield Memorial Fund (Grant 115-9025); and by Grant MCJ-060803 from the Maternal and Child Health Program (Title V, Social Security Act), Health Resources and Services Administration, Department of Health and Human Services.

Neonatal Infection Study Group includes the following members: Dr Randy Bergen, KPMC Walnut Creek; Dr Lawrence Dong, KPMC Santa Clara; Dr Allen Fischer, KPMC Sacramento; Dr Michael Jennis, KPMC Oakland; Dr James Kantor, KPMC San Francisco; Dr Alma Martinez, San Francisco General Hospital; Dr Stephen McMurtry, KPMC Vallejo; Dr Brian Saunders, KPMC San Diego; Dr Cindy Wikler, KPMC Hayward; and Dr Ted Zukin, KPMC Walnut Creek.

We extend special thanks to Drs Marc Usatin, Albert Kahane, W. Harry Caulfield, Steve Black, Henry Shinefield, William Likosky, and Francis J. Crosson, whose enthusiastic administrative support made completion of this study possible.

We also thank Randy Watson, Wesley Hawkins, Ana Macedo, Vernal Mason, Marlena Jacobs, and Jodi Cupp for their assistance during the course of the study, and Dr Janet Mohle-Boetani for her help in the review of group B streptococcal data.

We also thank Drs Joseph V. Selby, Tracy A. Lieu, Thomas B. Newman, and Douglas K. Richardson for reviewing the manuscript.

REFERENCES

1. Wientzen RL Jr, McCracken GH Jr. Pathogenesis and management of neonatal sepsis and meningitis. *Curr Probl Pediatr*. 1977;8:1–61
2. Siegel JD, McCracken GH Jr. Sepsis neonatorum. *N Engl J Med*. 1981; 304:642–647
3. Hammerschlag MR, Klein JO, Herschel M, Chen FC, Fermin R. Patterns of use of antibiotics in two newborn nurseries. *N Engl J Med*. 1977;296: 1268–1269
4. Townsend TR, Shapiro M, Rosner B, Kass EH. Use of antimicrobial drugs in general hospitals. IV. Infants and children. *Pediatrics*. 1979;64: 573–578
5. Schwersenski J, McIntyre L, Bauer CR. Lumbar puncture frequency and cerebrospinal fluid analysis in the neonate. *Am J Dis Child*. 1991;145: 54–58
6. Guyer B, Martin JA, MacDorman MF, Anderson RN, Strobino DM. Annual summary of vital statistics—1996. *Pediatrics*. 1997;100:905–918
7. Avery GB, Fletcher MA, MacDonald MG. *Neonatology: Pathophysiology and Management of the Newborn*. 4th ed. Philadelphia, PA: Lippincott; 1994:1082–1116
8. Remington JS, Klein JO. *Infectious Diseases of the Fetus and Newborn Infant*. 3rd ed. Philadelphia, PA: WB Saunders; 1990:601–656, 742–811
9. Wiswell TE, Stoll BJ, Tuggle JM. Management of asymptomatic, term gestation neonates born to mothers treated with intrapartum antibiotics. *Pediatr Infect Dis J*. 1990;9:826–831
10. Wiswell TE, Baumgart S, Gannon CM, Spitzer AR. No lumbar puncture in the evaluation for early neonatal sepsis: will meningitis be missed? *Pediatrics*. 1995;95:803–806. See comments
11. Mecredy RL, Wiswell TE, Hume RF. Outcome of term gestation neonates whose mothers received intrapartum antibiotics for suspected chorioamnionitis. *Am J Perinatol*. 1993;10:365–368
12. Johnson CE, Whitwell JK, Pethe K, Saxena K, Super DM. Term newborns who are at risk for sepsis: are lumbar punctures necessary? *Pediatrics*. 1997;99(4). URL: http://www.pediatrics.org/cgi/content/full/99/4/e10
13. Escobar GJ. The neonatal "sepsis work-up": personal reflections on the development of an evidence-based approach toward newborn infections in a managed care organization. *Pediatrics*. 1999;103:360–373
14. Escobar GJ, Fischer A, Li DK, Kremers R, Armstrong MA. Score for neonatal acute physiology: validation in three Kaiser Permanente neonatal intensive care units. *Pediatrics*. 1995;96:918–922
15. Cavalier S, Escobar GJ, Fernbach SA, Quesenberry CP Jr, Chellino M. Postdischarge utilization of medical services by high-risk infants: experience in a large managed care organization. *Pediatrics*. 1996;97:693–699
16. Escobar GJ, Joffe S, Gardner M, Armstrong MA, Folck BF, Carpenter DM. Rehospitalization in the first two weeks after discharge from the neonatal intensive care unit. *Pediatrics*. 1999;104:(1). URL: http://www.pediatrics.org/cgi/content/full/104/1/e2
17. Escobar GJ, Fischer A, Kremers R, Usatin MS, Macedo AM, Gardner MN. Rapid retrieval of neonatal outcomes data: the Kaiser Permanente Neonatal Minimum Data Set. *Qual Manag Health Care*. 1997;5:19–33
18. Escobar GJ, Gardner MN, Chellino M, Fireman B, Verdi J, Yanover M. Identification of neonatal deaths in a large managed care organisation. *Paediatr Perinat Epidemiol*. 1997;11:93–104
19. Escobar GJ, Yanover M, Gardner MN, et al. Structured review of neonatal deaths in a managed care organisation. *Paediatr Perinat Epidemiol*. 1998;12:422–436
20. Selby JV. Linking automated databases for research in managed care settings. *Ann Intern Med*. 1997;127:719–724
21. Manroe BL, Weinberg AG, Rosenfeld CR, Browne R. The neonatal blood count in health and disease. I. Reference values for neutrophilic cells. *J Pediatr*. 1979;95:89–98
22. Schelonka RL, Yoder BA, des Jardins SE, Hall RB, Butler J. Peripheral leukocyte count and leukocyte indexes in healthy newborn term infants. *J Pediatr*. 1994;125:603–606
23. Schelonka RL, Yoder BA, Bradley A. The WBC count and differential: Its uses and misuses. *Contemp Obstet Gynecol*. 1996;13:124–166
24. Escobar GJ, Zukin T, Usatin MS, et al. Early discontinuation of antibiotic treatment in newborns admitted to rule out sepsis: a decision rule. *Pediatr Infect Dis J*. 1994;13:860–866
25. De Waele M, Foulon W, Renmans W, et al. Hematologic values and lymphocyte subsets in fetal blood. *Am J Clin Pathol*. 1988;89:742–746
26. Forestier F, Daffos F, Catherine N, Renard M, Andreux JP. Developmental hematopoiesis in normal human fetal blood. *Blood*. 1991;77: 2360–2363
27. Carballo C, Foucar K, Swanson P, Papile LA, Watterberg KL. Effect of high altitude on neutrophil counts in newborn infants. *J Pediatr*. 1991; 119:464–466
28. Christensen RD, Rothstein G. Pitfalls in the interpretation of leukocyte counts of newborn infants. *Am J Clin Pathol*. 1979;72:608–611
29. Christensen RD, Rothstein G, Hill HR, Hall RT. Fatal early onset group B streptococcal sepsis with normal leukocyte counts. *Pediatr Infect Dis*. 1985;4:242–245
30. Krause JR. The automated white blood cell differential: a current perspective. *Hematol Oncol Clin North Am*. 1994;8:605–616
31. Lieu TA, Mohle-Boetani JC, Ray GT, Ackerson LM, Walton DL. Neonatal group B streptococcal infection in a managed care population. Perinatal Group B Streptococcal Infection Study Group. *Obstet Gynecol*. 1998;92:21–27
32. Mohle-Boetani JC, Lieu TA, Ray GT, Escobar G. Preventing neonatal group B streptococcal disease: cost-effectiveness in a health maintenance organization and the impact of delayed hospital discharge for newborns who received intrapartum antibiotics. *Pediatrics*. 1999;103: 703–710
33. Sarff LD, Platt LH, McCracken GH Jr. Cerebrospinal fluid evaluation in neonates: comparison of high-risk infants with and without meningitis. *J Pediatr*. 1976;88:473–477
34. SAS. *Statistical Analysis Software*. 6th ed. Carey, NC: SAS Institute; 1989
35. Hanley J, McNeil B. The meaning and use of the area under a receiver operating characteristic (ROC) curve. *Radiology*. 1982;143:29–36
36. Pourcyrous M, Bada HS, Korones SB, Baselski V, Wong SP. Significance of serial C-reactive protein responses in neonatal infection and other disorders. *Pediatrics*. 1993;92:431–435
37. Ehl S, Gering B, Bartmann P, Hogel J, Pohlandt F. C-reactive protein is a useful marker for guiding duration of antibiotic therapy in suspected neonatal bacterial infection. *Pediatrics*. 1997;99:216–221
38. Benitz WE, Han MY, Madan A, Ramachandra P. Serial serum C-reactive protein levels in the diagnosis of neonatal infection. *Pediatrics*. 1998; 102(4). URL: http://www.pediatrics.org/cgi/content/full/102/4/e41
39. Centers for Disease Control and Prevention. Prevention of perinatal group B streptococcal disease: a public health perspective [published erratum appears in *MMWR Morb Mortal Wkly Rep*. 1996;45:679]. *MMWR Morb Mortal Wkly Rep*. 1996;45:1–24
40. American Academy of Pediatrics, Committee on Infectious Diseases and Committee on Fetus and Newborn. Revised guidelines for prevention of early-onset group B streptococcal (GBS) infection. *Pediatrics*. 1997;99:489–496
41. Gibbs RS, McGregor JA, Mead PB, Eschenbach DA, Hager WD, Sweet RL. A survey of practices in infectious diseases by obstetrician-gynecologists. *Obstet Gynecol*. 1994;83:631–636
42. Pylipow M, Gaddis M, Kinney JS. Selective intrapartum prophylaxis for group B streptococcus colonization: management and outcome of newborns. *Pediatrics*. 1994;93:631–635
43. Gibbs RS, McDuffie RS Jr, McNabb F, Fryer GE, Miyoshi T, Merenstein G. Neonatal group B streptococcal sepsis during 2 years of a universal screening program. *Obstet Gynecol*. 1994;84:496–500
44. Bray RE, Boe RW, Johnson WL. Transfer of ampicillin into fetus and amniotic fluid from maternal plasma in late pregnancy. *Am J Obstet Gynecol*. 1966;96:938–942
45. de Cueto M, Sanchez MJ, Sampedro A, Miranda JA, Herruzo AJ, Rosa-Fraile M. Timing of intrapartum ampicillin and prevention of vertical transmission of group B streptococcus. *Obstet Gynecol*. 1998;91:112–114
46. Tyler CW Jr, Albers WH. Obstetric factors related to bacteremia in the newborn infant. *Am J Obstet Gynecol*. 1966;94:970–976
47. Rumke C. The statistically expected variability in differential leukocyte counting. In: Koepke J, ed. *Differential Leukocyte Counting*. Skokie, IL: College of American Pathologists; 1977:39–45
48. Sackett DL. *Clinical Epidemiology: A Basic Science for Clinical Medicine*. 2nd ed. Boston, MA: Little Brown; 1991:69–152
49. Baker MD, Bell LM, Avner JR. Outpatient management without antibiotics of fever in selected infants. *N Engl J Med*. 1993;329:1437–1441
50. Baker MD, Bell LM, Avner JR. The efficacy of routine outpatient management without antibiotics of fever in selected infants. *Pediatrics*. 1999; 103:627–631

Neonatal Sepsis Workups in Infants ≥2000 Grams at Birth: A Population-Based Study

Gabriel J. Escobar, De-kun Li, Mary Anne Armstrong, Marla N. Gardner, Bruce F. Folck, Joan E. Verdi, Blong Xiong, Randy Bergen and for the Neonatal Infection Study Group

Pediatrics 2000;106;256

PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Neonatal Sepsis Workups in Infants ≥2000 Grams at Birth: A Population-Based Study

Gabriel J. Escobar, De-kun Li, Mary Anne Armstrong, Marla N. Gardner, Bruce F. Folck, Joan E. Verdi, Blong Xiong, Randy Bergen and for the Neonatal Infection Study Group

Pediatrics 2000;106;256