Neonatal Early-Onset Escherichia coli Disease

The Effect of Intrapartum Ampicillin

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Background: Maternal intrapartum ampicillin has been recommended for the prevention of neonatal group B streptococcal disease.

Objectives: To assess the effect of this practice, if any, on neonatal early-onset Escherichia coli infection and to delineate the clinical characteristics of infected neonates.

Patients and Methods: All neonates with early-onset E coli infection who were born at Cook County Children’s Hospital, Chicago, Ill, from January 1, 1982, through December 31, 1993, were identified from a microbiological register of all neonatal bacteremias and infections. Because intrapartum ampicillin use increased in our hospital since 1988, infection and case fatality rates from 1982 through 1987 (period 1) were compared with data from 1988 through 1993 (period 2). We studied maternal risk factors, clinical characteristics of infected neonates, and microbiological sensitivities of E coli isolates.

Results: Early-onset E coli infection was diagnosed in 30 of 61 498 live births. The overall infection rate (0.49 per 1000 live births) did not change significantly during the 2 time periods (0.37 per 1000 live births during period 1 vs 0.62 per 1000 live births during period 2, P = .21; $\chi^2$ test); however, there was an increase in the infection rate in neonates weighing between 1501 and 2500 g. Infected neonates had a clinical syndrome that was indistinguishable from early-onset group B streptococcal infection; respiratory distress was the single most frequent finding in 73% (22/30) infected neonates. An increase in the proportion of infections caused by ampicillin-resistant E coli was observed during period 2 (12/18) compared with period 1 (3/12, P = .03; Fisher exact test). During period 2, 61% (11/18) of mothers of infected neonates received intrapartum ampicillin compared with 17% (2/12; P = .02) during period 1. Overall, a higher proportion of neonates born to ampicillin-treated women had ampicillin-resistant infection (12/13 vs 3/17; P < .001). Mothers of 10 of 15 neonates with ampicillin-resistant infection had received more than 2 doses of intrapartum ampicillin. The difference between the prevalence of intrapartum fever in mothers with sensitive organisms (40%, or 6/15) and resistant organisms (93%, or 14/15) was also significant (P = .003). All 6 early-onset E coli–related deaths were due to ampicillin-resistant organisms; 4 of the 6 mothers received intrapartum ampicillin.

Conclusions: We have shown a shift of early-onset E coli infection from a less fulminant disease caused by ampicillin-sensitive organisms to a more fulminant disease caused by ampicillin-resistant organisms. Increased use of maternal intrapartum ampicillin therapy may account for these changes. In the absence of evidence for group B streptococcal disease, clinicians should consider the possibility of ampicillin-resistant E coli infection in critically ill neonates born to women with a history of intrapartum fever and treatment with intrapartum ampicillin.


Editor’s Note: Here we have more fuel to fire the concern over the use (and abuse) of antibiotics. Are we trading headaches for upset stomachs, or far worse?  

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Escherichia coli has been recognized as 1 of the common organisms responsible for sepsis in the newborn period, and yet information about the incidence, distribution, and clinical manifestations of neonatal early-onset E coli disease is limited. After the initial controlled clinical trial demonstrating the efficacy of intrapartum ampicillin in prevention of neonatal early-onset group B streptococcal (GBS) disease, chemoprophylaxis for GBS has been increasingly used by obstetricians. Guidelines for the use of intrapartum chemoprophylaxis for all GBS carriers with risk factors or for all women with risk factors were subsequently published. However, the consequences of widespread use of intrapartum ampicillin, if any, on the incidence, distribution, and clinical manifestations of neonatal early-onset E coli disease are unknown. We observed an increase in early-onset E coli disease among low birth weight neonates delivered in our hospital during the years after implementation of GBS prophylaxis; hence, we hy-
PATIENTS AND METHODS

Neonates with early-onset E. coli infection who were born at Cook County Children’s Hospital, Chicago, Ill, from January 1, 1982, through December 31, 1993, were selected from a microbiological register of all neonatal bacteremias and infections. All infected neonates had an onset of symptoms during the first 7 days of life. In each case, a pure culture of E. coli was isolated from samples of peripheral blood; blood samples for culture were not obtained from indwelling central lines.

Cultures were routinely obtained from preterm neonates who were born at less than 35 weeks’ gestation, neonates suspected of having sepsis, and all neonates who had high risk factors for infection. The latter included neonates born to women with clinical evidence of chorioamnionitis, women treated with intrapartum antibiotics, and women with a history of rupture of membranes for more than 24 hours. Samples of cerebrospinal fluid were obtained from neonates with a blood culture positive for the presence of E. coli who remained asymptomatic were considered to have transient bacteremia; those with 1 or more of the following symptoms were given a diagnosis of sepsis: fever, hypothermia, apnea, lethargy, irritability, poor feeding, unexplained hyperbilirubinemia, vomiting, or abdominal distention. Respiratory distress was defined as the presence of 1 or more of the following: respiratory rate of more than 60 breaths per minute, grunting, or retractions. Respiratory distress syndrome was diagnosed in neonates with respiratory distress and characteristic roentgenograms.

Microbiological identification of E. coli and determination of antimicrobial susceptibilities were accomplished by standard laboratory methods. Postmortem examinations were performed on neonates if parental consent was available. For this study, lung sections of infected neonates were reexamined microscopically using Gram and Geimsa stains.

At the initial examination of all symptomatic neonates and of neonates at high risk for sepsis, blood samples were routinely obtained for a complete white blood cell count and differential count. Neutropenia was defined as an absolute neutrophil count of 1500 per microliter or less. Initial chest roentgenograms were taken within 24 hours of birth for all neonates, and the roentgenograms were reviewed by a pediatric radiologist. Blood pH measurements were obtained from arterial samples or arterialized capillary samples. Urine was routinely obtained for a latex agglutination test to detect the GBS antigen by the Directigen method (Wellcogen Strep B, Murex Diagnostics, Dartford, England).

The clinical records of mothers of infected neonates were studied for the identification of intrapartum risk factors. These factors included the following: (1) maternal intrapartum fever of 38.4°C or more, (2) positive maternal blood culture for E. coli, (3) rupture of the membranes for 24 hours or more, (4) evidence of fetal distress as noted by the obstetrician, (5) presence of meconium in the amniotic fluid, and (6) documentation of intravenous, intrapartum ampicillin administration (2 g initially; 1 to 2 g every 4 to 6 hours) to the mother before delivery. In addition to the demographic data, the following neonatal data were recorded on a standardized form: (1) age at onset of symptoms, (2) presenting clinical findings, (3) clinical course, (4) laboratory data, (5) interpretation of chest roentgenogram findings, and (6) postmortem findings.

Intrapartum ampicillin chemoprophylaxis of high-risk women was implemented at Cook County Children’s Hospital after the initial report that such therapy effectively prevents GBS disease. Hence, data from 1982 through 1987 were pooled (period 1) and compared with data from 1988 through 1993 (period 2). The incidence or disease rate was defined as the number of neonates with early-onset E. coli infection per 1000 live births in the weight category studied. The case-fatality rate was the percentage of infected neonates who died; an E. coli–associated death was defined as a death occurring in a neonate who died during the acute E. coli infection. The Student t test was used to compare continuous variables, and the Fischer exact test was used to compare groups for categorical variables.

RESULTS

POPULATION RATES

During the 12-year study period, 61,498 live-born neonates were delivered at Cook County Hospital; early-onset E. coli infection was diagnosed in 30 of these neonates. Overall infection rate was 0.49 per 1000 live births. Table 1 summarizes the early-onset E. coli infection rate and the case-fatality rate for the 2 periods; the overall infection rate was 0.37 per 1000 during period 1 and 0.62 per 1000 during period 2. This difference was not statistically different and was due to a difference in the group of neonates weighing between 1501 and 2500 g. Likewise, the case-fatality rates in the 2 periods were not different, 17% and 22%, respectively.

CLINICAL CHARACTERISTICS OF NEONATES

Of the 30 neonates with early-onset infection, 16 were boys and 23 were black, a distribution similar to the rest of the patient population at this institution. Only 2 neonates had an Apgar score of less than 5 at 5 minutes; however, the initial pH was less than 7.2 in 30% (9/30). Respiratory distress was the predominant symptom at or shortly after birth in 73% (22/30) of the neonates (Table 2); 6 had other signs suggesting sepsis, and 2 were asymptomatic. Symptoms occurred within 4 hours of birth in 23 neonates: 92% (11/12) of the neonates who weighed less than 2500 g and 67% (12/18) of the larger neonates. The 5 remaining symptomatic neonates mani-
fested symptoms between 5 and 24 hours of birth. The initial chest roentgenograms were abnormal in 19 neonates and were interpreted as compatible with meconium aspiration, respiratory distress syndrome, wet lung, or pneumonia. All cases of meconium aspiration were found in the neonates larger than 2500 g, and all but 1 of the cases of respiratory distress syndrome were found in the smaller neonates. Neutropenia was detected in the

### Table 1. Summary of Early-Onset Escherichia coli Infection Rate and Case-Fatality Rates: 1982 Through 1993*

<table>
<thead>
<tr>
<th>Birth Weight, g</th>
<th>1000-1500</th>
<th>1501-2500</th>
<th>≥2501</th>
</tr>
</thead>
<tbody>
<tr>
<td>Live births</td>
<td>1012</td>
<td>893</td>
<td>3124</td>
</tr>
<tr>
<td>No. of infected neonates</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Infection rate</td>
<td>0.99</td>
<td>1.1</td>
<td>0.64</td>
</tr>
<tr>
<td>Positive cerebrospinal fluid culture</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>No. of neonates who died</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Case-fatality rate</td>
<td>100</td>
<td>100</td>
<td>25</td>
</tr>
</tbody>
</table>

*Period 1, 1982 to 1987; period 2, 1988 to 1993.
†P=.05.

### Table 2. Characteristics of the Patients with Early-Onset Escherichia coli Infection*

<table>
<thead>
<tr>
<th>Birth Weight, g</th>
<th>Intrapartum</th>
<th>Neonatal</th>
<th>Radiographic Findings</th>
<th>E. coli</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Infection</td>
<td>Duration†</td>
<td>Presenting Symptoms</td>
<td>Neutropenia</td>
</tr>
<tr>
<td></td>
<td>ROM, h</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>500-1500</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2211</td>
<td>10</td>
<td>+</td>
<td>Respiratory distress</td>
<td>+</td>
</tr>
<tr>
<td>2440</td>
<td>−10</td>
<td>+</td>
<td>Sepsis</td>
<td>−</td>
</tr>
<tr>
<td>2830</td>
<td>26</td>
<td>+</td>
<td>Respiratory distress, PPHN</td>
<td>−</td>
</tr>
<tr>
<td>3430</td>
<td>25</td>
<td>+</td>
<td>Respiratory distress</td>
<td>+</td>
</tr>
<tr>
<td>3629</td>
<td>12</td>
<td>+</td>
<td>Respiratory distress</td>
<td>−</td>
</tr>
<tr>
<td>4010</td>
<td>14</td>
<td>+</td>
<td>Respiratory distress</td>
<td>−</td>
</tr>
<tr>
<td>4111</td>
<td>18</td>
<td>−</td>
<td>Sepsis</td>
<td>−</td>
</tr>
<tr>
<td>1010h§</td>
<td>+166</td>
<td>+</td>
<td>Respiratory distress</td>
<td>+</td>
</tr>
<tr>
<td>3147</td>
<td>+12</td>
<td>−</td>
<td>7 d</td>
<td>Respiratory distress</td>
</tr>
<tr>
<td>4131†</td>
<td>+19</td>
<td>+</td>
<td>12 h</td>
<td>Respiratory distress</td>
</tr>
</tbody>
</table>

*ROM indicates rupture of membranes; PPHN, persistent pulmonary hypertension; MAS, meconium aspiration syndrome; RDS, respiratory distress syndrome; DIC, disseminated intravascular coagulation; plus sign, yes; and minus sign, no. Neutropenia was defined as an absolute neutrophil count of 1500 per microliter or less.
†Duration of therapy before delivery.
§Death associated with E. coli infection.
Positive findings on maternal blood culture.
Positive findings on cerebrospinal fluid culture.
Ampicillin was administered; duration unknown.
first white blood cell count in 9 neonates: 7 of these weighed less than 2500 g, and 2 weighed more than 2500 g (P < .05). None of the neonates had congenital malformations, diarrhea, evidence of necrotizing enterocolitis, or GBS antigenuria. Twenty-eight neonates were treated with ampicillin and gentamicin sulfate at birth, and the 2 asymptomatic neonates were treated after the initial blood culture reports became available.

**INTRAPARTUM RISK FACTORS**

Intrapartum complications occurred in the mothers of all but 1 of the 30 neonates with early-onset *E.coli* infection (Table 2). Maternal fever was recognized in 67% (20/30) of the women; prolonged rupture of membranes (>24 hours) occurred in 37% (11/30); meconium staining of amniotic fluid was present in 53% (16/30); and meconium staining of amniotic fluid was present in 47% (14/30). *Escherichia coli* was isolated from the blood of 2 of the mothers. During period 2, 61% (11/18) of the mothers received intrapartum intravenous ampicillin as prophylaxis against neonatal GBS infection; 4 of these mothers received clindamycin phosphate and gentamicin in addition to ampicillin. This proportion was significantly greater (P < .05) than the 17% (2/12) of women who received intrapartum ampicillin during period 1.

**AMPICILLIN RESISTANCE**

Ampicillin-resistant *E.coli* were isolated from a total of 15 neonates: 25% (3/12) born during period 1 and 67% (12/18) born during period 2 (P < .05). This correlates with the increased use of intrapartum ampicillin during period 2. Ampicillin-resistant *E.coli* were isolated from 92% (12/13) of infected neonates whose mothers received intrapartum ampicillin and from only 18% (3/17) of infected neonates whose mothers were not treated (P < .001). Ten treated mothers had received more than 2 doses of intrapartum ampicillin; 7 of these received treatment for more than 24 hours. Intrapartum fever, suggestive of intra-amniotic infection, occurred more often (P < .01) in mothers of neonates infected with ampicillin-resistant *E.coli* (93%, or 14/15) than in those infected with ampicillin-sensitive *E.coli* (40%, or 6/15). Clinical characteristics of the neonates with ampicillin-sensitive and of the neonates with ampicillin-resistant infection are given in Table 3.

**CLINICAL OUTCOME**

Fulminant death occurred in 6 of the 30 neonates with sepsis despite aggressive treatment with gentamicin and ampicillin at birth; 4 of these neonates died within the first 24 hours of life. All deaths occurred in neonates with ampicillin-resistant *E.coli* disease (Figure). Features that occurred more often in the 6 nonsurvivors than in the 24 survivors included the following: history of rupture of the membranes for 36 hours or more (67% vs 13%, or 4/24; P < .01); maternal intrapartum ampicillin therapy (67% vs 38%, or 4/6 vs 9/24); birth weight of 2500 g or less (67% vs 33%, or 4/6 vs 8/24); metabolic acidosis at birth (83% vs 17%, or 5/6 vs 4/24; P < .01); features of respiratory distress syndrome (83% vs 4%, or 5/6 vs 1/24; P < .001); neutropenia (83% vs 17%; or 5/6 vs 0; P < .001); and cerebrospinal fluid cultures positive for the presence of *E.coli* (67% vs 4/6 vs 0; P < .001).

A consent for autopsy was available for 4 of 6 neonates who died. Microscopic examination of the lung sections of all 4 neonates showed hyaline membranes within the respiratory bronchioles and alveolar ducts. Gram-negative bacilli were observed in the lung sections in 1 neonate who died within 24 hours of birth.

**COMMENT**

Our findings demonstrate that infection caused by *E.coli* produces a neonatal syndrome similar to that caused by GBS infection of the early-onset type. In most cases, infection was established before delivery as evidenced by the onset of symptoms at or within hours following birth. Respiratory distress was the predominant clinical finding in neonates with early-onset *E.coli* disease; this is similar to the manifestation of early-onset GBS disease in the nursery of Cook County Children’s Hospital. The clini-
cal, roentgenographic, and pathologic manifestation in these neonates was indistinguishable from other causes of respiratory distress in newly born neonates. The features that distinguished survivors from nonsurvivors in this study were similar to those seen in neonates with early-onset GBS disease.

Although the overall incidence of early-onset E coli infection did not significantly increase during period 2 compared with period 1, there was an increase in the infection rate in neonates weighing between 1501 and 2500 g. The overall incidence of early-onset GBS infection was not significantly different during the same periods in the nursery (2.2 per 1000 live births vs 1.7 per 1000 live births, period 2 vs period 1). However, there was a decrease in early-onset GBS infection rate in neonates weighing less than 1500 g at birth (19.8 per 1000 live births vs 4.5 per 1000 live births, period 2 vs period 1; P<.01); this was attributable to GBS chemoprophylaxis. There was no difference in early-onset E coli case-fatality rates between the 2 periods; this is in contrast to improvement in early-onset GBS survival rates during period 2 (26.8% vs 8%, period 2 vs period 1; P<.05) in the nursery.13 We observed a steady shift of early-onset GBS infections from small neonates with high fatality rates to larger neonates with lower fatality rates. Other tertiary care centers have also reported improvements in early-onset GBS disease survival rates.14,15

The proportion of ampicillin-resistant isolates among infected neonates was significantly greater during period 2 than during period 1. Our data support the concept that this rise occurred concomitantly with the increase in the use of intrapartum ampicillin for GBS prophylaxis. Most of the mothers of neonates with ampicillin-resistant E coli infection had received intrapartum ampicillin, indicating that perhaps such treatment may have selected for or permitted overgrowth of resistant organisms. Although intrapartum antibiotic therapy has been recommended and is widely used, researchers have expressed concern that increased use of such therapy can cause morbidity because of allergic reactions, antibiotic-associated colitis, and overgrowth of resistant organisms.16 However, the associated increase in incidence of ampicillin-resistant E coli has not been previously described. McDuffie et al16 have reported 3 cases wherein resistant E coli was cultured from a maternal or neonatal source following oral ampicillin therapy for prolonged rupture of the membranes; in 1 of these cases, the neonate had clinical sepsis. Because the number of pregnancies from which these cases were derived was not available, McDuffie et al were unable to determine the incidence of ampicillin-resistant E coli cases. In another report,17 1 case of neonatal E coli sepsis was observed among 34 patients who received prophylaxis for GBS.

Our observations indicate that ampicillin resistance is associated with intrapartum fever. Of the women with ampicillin-resistant E coli, 93% (14/15) had intrapartum fever compared with only 40% (6/15) of women with ampicillin-sensitive E coli. Fever in these mothers was perhaps due to intra-amniotic infection. Four mothers with ampicillin-resistant E coli and fever were treated with intrapartum broad-spectrum antibiotics; yet, fulminating disease developed in their neonates. In 2 mothers, fever developed late in the course of labor, and they delivered their neonate before broad-spectrum antibiotic therapy could be initiated. Ampicillin monotherapy for the remaining 8 mothers with fever may have contributed to the adverse outcome in their neonates. Aggressive intrapartum management of intra-amniotic infections with a broad-spectrum regimen18 may prevent neonatal morbidity and mortality associated with neonatal E coli infections.

Although ampicillin-resistant E coli infections occur in many nurseries, neonatal morbidity associated with these infections has not been described or compared with infections caused by ampicillin-sensitive isolates. During the 12-year study, there were 6 deaths attributable to fulminating E coli infection. All of these deaths occurred in neonates with ampicillin-resistant E coli strains, despite early and aggressive treatment with gentamicin and ampicillin. Five of the deaths occurred in neutropenic neonates; results of the measured peripheral white blood cell count were not available for the sixth neonate. Three of the 4 surviving neonates with neutropenia had ampicillin-susceptible E coli infections. All 30 neonates were infected with E coli sensitive to gentamicin. However, gentamicin monotherapy may be inadequate for E coli infections in neutropenic neonates. In neutropenic mice with Pseudomonas aeruginosa infections, gentamicin monotherapy selects for gentamicin-resistant variants.19 We identified gentamicin-resistant E coli in the postmortem blood cultures in 1 neonate who was severely neutropenic.
We have shown a shift of neonatal early-onset *E coli* infections from less fulminant disease associated with ampicillin-sensitive strains to more fulminant disease associated with ampicillin-resistant strains. Increased use of intrapartum ampicillin may account for some of these changes. Our findings support the recent guideline proposing that penicillin G potassium or sodium is preferable to ampicillin for intrapartum prophylaxis, because penicillin has a narrow spectrum of activity and is therefore less likely to select for antibiotic-resistant organisms. Women with intrapartum fever should be carefully assessed for clinical intra-amniotic infection and be treated with an appropriate broad-spectrum regimen. Physicians should be aware of the possibility of ampicillin-resistant *E coli* infection in critically ill neonates who are born to women with a history of having received intrapartum ampicillin therapy, especially if the mothers show evidence of intra-amniotic infection.

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REFERENCES