Bacterial Infections in Infants 60 Days and Younger

Epidemiology, Resistance, and Implications for Treatment

Karin Berger Sadow, MD; Robert Derr, MD; Stephen J. Teach, MD, MPH

Objective: To establish what might be more optimal initial antibiotic therapy for suspected invasive bacterial infections in infants 60 days or younger who are evaluated in the emergency department (ED).

Setting: Urban university-affiliated pediatric referral center with an average yearly ED census of 52,000 visits during the study period.

Design and Methods: We assembled a retrospective case series of all positive blood, urine, and cerebrospinal fluid cultures in children 60 days or younger from January 1, 1994, through December 31, 1997, obtained from both inpatients and patients initially evaluated in the ED. From this case series we determined the frequency of bacterial pathogens responsible for such infections in this age group. Pathogens were defined as group B streptococcus, various enteric gram-negative rods (GNRs), Listeria monocytogenes, enterococcus, Streptococcus pneumoniae, Neisseria meningitidis, Haemophilus influenzae type B, and Staphylococcus aureus. A subgroup analysis was performed to determine resistance patterns among the GNRs isolated from patients evaluated in the ED.

Results: A total of 367 pathogens were isolated: 187 (51.0%) in the neonatal intensive care unit, 153 (41.7%) in the ED, 20 (5.4%) in the inpatient wards, and 7 (1.9%) in the pediatric intensive care unit. Of the 121 pathogens isolated from 120 ED patients that were eligible for review, 94 (77.7%) were in the urine only, 16 (13.2%) in blood only, 4 (3.3%) in cerebrospinal fluid only, 3 (2.5%) in blood and cerebrospinal fluid, and 4 (3.3%) in blood and urine. Organisms isolated included GNRs (n = 96, 79.3%), group B streptococcus (n = 14, 11.6%), enterococcus (n = 7, 5.8%), S pneumoniae (n = 3, 2.5%), and N meningitidis (n = 1, 0.8%). No Listeria were isolated. Of the 96 GNRs isolated, 60 (62.5%; 95% confidence interval, 52.8%-72.1%) were ampicillin resistant. All were sensitive to gentamicin sulfate and cefotaxime sodium.

Conclusions: Our results reveal 2 important facts: (1) during a 4-year period, no isolates of Listeria were identified from any patients 60 days or younger; and (2) of the 96 GNRs isolated from patients in the ED, more than 60% were ampicillin resistant. These data suggest that in similar centers with a low incidence of infection with Listeria and high levels of ampicillin resistance among GNRs, empiric use of ampicillin as part of a combination for presumed bacterial infections in patients 60 days or younger initially evaluated in the ED may be neither necessary nor beneficial. Consideration should be given to empiric initial antibiotic therapy using a third-generation cephalosporin with or without gentamicin.


Editor’s Note: The take-home message from this study is that expensive coverage for Listeria beyond the perinatal period is not warranted unless meningitis is present. How long do you think it will take for physicians to believe it and act accordingly? Catherine D. DeAngelis, MD

Although practice varies regionally, infants 60 days or younger with fever who are initially evaluated in the emergency department (ED) are frequently given intravenous antibiotics as inpatients after a comprehensive examination for a focal bacterial infection that includes evaluation of the blood, urine, and cerebrospinal fluid (CSF). In patients with normal CSF cell counts and no evidence of focal infection, initial empiric antibiotic therapy for suspected but undetected invasive bacterial infections typically includes ampicillin (to cover Listeria monocytogenes and group B streptococcus) and either gentamicin sulfate or a third-generation cephalosporin to enhance coverage of gram-negative rods (GNRs).1-4,8,20-22 Because of the decreasing incidence of infections with Listeria1 in the United States and the increasing incidence of ampicillin resistance among GNRs8 this combination may not be optimal. Therapy with a third-generation cephalosporin with or without gentamicin may be superior.

To examine these recommendations for empiric antibiotic therapy in light of these clinical observations, the present...
PATIENTS AND METHODS

We assembled a retrospective case series of patients aged 60 days or younger with invasive bacterial infections seen at Children’s National Medical Center, Washington, DC. All positive blood, urine, and CSF cultures were identified from the database of the microbiology laboratory for the 4-year period from January 1, 1994, to December 31, 1997. During this period, the average yearly ED census was 52,000 visits. Pathogens were defined as Group B streptococcus, various enteric GNRs, L monocytogenes, enterococcus, Streptococcus pneumoniae, Neisseria meningitidis, Haemophilus influenzae type B, and Staphylococcus aureus. We then reviewed the records of all patients from the ED with positive cultures to determine the resistance patterns for GNRs isolated from this population. All patients evaluated in the ED were admitted and treated as inpatients. In addition, the age, sex, and initial antibiotic regimen were recorded. Patients were excluded if they had a central venous catheter or other indwelling medical device, if they had a documented humoral or cellular immunodeficiency, if their only positive culture was a urine culture with less than 10^3 colony-forming units per milliliter, or if the medical record was unavailable. Urine specimens were obtained for culture by urethral catheterization according to established hospital protocol.

Statistical analysis was performed using the binomial test on Epistat statistical software (Epistat Services, Richardson, Tex). Descriptive statistics are reported as means (SDs) with ranges. Significance was defined as P < .05.

This study was approved by the institutional review board at the Children’s National Medical Center. The study was performed (1) to describe the incidence of various invasive bacterial pathogens in all patients 60 days and younger in an urban pediatric medical center; and (2) to describe the resistance patterns in GNRs isolated among patients initially evaluated in the ED.

RESULTS

From January 1994 through December 1997, a total of 367 pathogens were isolated at Children’s National Medical Center. There were 187 pathogens isolated from patients in the neonatal intensive care unit (51.0%), 153 isolated from patients in the ED (41.7%), 20 isolated from patients in the inpatient wards (5.4%), and 7 isolated from patients in the pediatric intensive care unit (1.9%). Organisms isolated included enteric GNRs (n = 245, 66.8%), enterococcus (n = 49, 13.4%), S aureus (n = 38, 10.4%), group B streptococcus (n = 31, 8.4%), S pneumoniae (n = 3, 0.8%), and N meningitidis (n = 1, 0.3%).

The 153 ED pathogens were isolated from 150 patients. Of these 150 patients, 30 were excluded for the following reasons: 14 patients had unavailable medical records, 10 patients had a total of 12 pathogens isolated only in the urine with less than 10^3 colony-forming units per milliliter, and 6 patients were considered to be immunocompromised. The remaining 120 ED patients were analyzed. All were admitted to the hospital after their initial ED encounter. There were significantly more males (n = 84, 70.0%) than females (n = 36, 30.0%) (P < .001). The mean age of all patients was 3315 days (range, 5-60 days). Nineteen (15.8%) were aged 0 to 15 days; 34 (28.3%) were aged 16 to 30 days; 34 (28.3%) were aged 31 to 45 days; and 33 (27.5%) were aged 46 to 60 days.

A total of 121 pathogens were isolated from 1 or more body sites in these 120 patients: 94 (77.7%) were in the urine only, 16 (13.2%) in blood only, 4 (3.3%) in CSF only, 3 (2.5%) in blood and CSF, and 4 (3.3%) in blood and urine. One patient’s culture yielded Escherichia coli and Klebsiella pneumoniae simultaneously in the blood. All 7 patients with positive CSF cultures also had CSF pleocytosis. Organisms isolated included GNRs (n = 96, 79.3%), group B streptococcus (n = 14, 11.6%), enterococcus (n = 7, 5.8%), S pneumoniae (n = 3, 2.5%), and N meningitidis (n = 1, 0.8%). Isolation by body site is described in the Table. The GNRs isolated included E (n = 68, 70.8%), Klebsiella species (n = 11, 11.5%), Entrobacter aerogenes (n = 4, 4.2%), lactose-fermenting GNRs, not otherwise specified (n = 4, 4.2%), Enterobacter cloacae (n = 3, 3.1%), Citrobacter koseri (n = 2, 2.1%), Pseudomonas species (n = 2, 2.1%), Escherichia fergusonii (n = 1, 1.0%), and Serratia marcescens (n = 1, 1.0%).

Of the 96 GNRs isolated, 60 were resistant to ampicillin (62.5%; 95% confidence interval, 52.8%-72.1%). Fifty-two (60%) of the 86 nonbacteremic urinary tract infections with GNRs were ampicillin resistant, 6 (75%) of the 8 cases of GNR bacteremia were ampicillin resistant, and both cases of meningitis with GNRs were ampicillin resistant. All GNRs isolated were sensitive to gentamicin and cefotaxime sodium. Initial antibiotic regimens are listed in the tabulation below.

### Antibiotic Regimen

<table>
<thead>
<tr>
<th>Antibiotic Regimen</th>
<th>No. (%) of Patients</th>
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<tbody>
<tr>
<td>Ampicillin and cefotaxime</td>
<td>43 (35.8)</td>
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<tr>
<td>Ampicillin and gentamicin</td>
<td>39 (32.5)</td>
</tr>
<tr>
<td>Cephalosporin alone</td>
<td>17 (14.2)</td>
</tr>
<tr>
<td>None</td>
<td>13 (10.8)</td>
</tr>
<tr>
<td>Ampicillin alone</td>
<td>2 (1.7)</td>
</tr>
<tr>
<td>Ampicillin, gentamicin, and acyclovir</td>
<td>2 (1.7)</td>
</tr>
<tr>
<td>Ampicillin, cefotaxime, and vancomycin</td>
<td>2 (1.7)</td>
</tr>
<tr>
<td>Vancomycin and cefotaxime</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td>Cefazidime and gentamicin</td>
<td>1 (0.8)</td>
</tr>
</tbody>
</table>

Despite the high resistance to ampicillin among GNRs, more than 70% of the initial antibiotic regimens included ampicillin, either alone or in combination. None of the patients evaluated in the ED had a recorded history of antibiotic therapy within 72 hours of the attainment of cultures.

COMMENT

Our analysis reveals 2 important facts: (1) no isolates of Listeria were identified in patients aged 60 days or younger over a 4-year period at a major urban pediatric referral center; and (2) more than 60% of the GNRs isolated from these patients evaluated in the ED were ampicillin resistant. These data may have important implications for future decisions about initial empiric antibiotic therapy for...
suspected invasive bacterial infections in patients initially evaluated in the ED.

At our institution, we have reconsidered our choices of empiric therapy. The importance of ampicillin therapy has clearly diminished, while that of third-generation cephalosporins has increased. One possible alternative regimen would use a third-generation cephalosporin with or without gentamicin in all cases of suspected invasive bacterial infections in all patients 60 days or younger initially evaluated in the ED.

This regimen would have different implications depending on the organism and specific infection under consideration. In the case of all infections with GNRs, by far the most common set of organisms isolated from our population, such a regimen would be beneficial. In our own center, the incidence of ampicillin resistance among GNRs has been steadily increasing. Resistance among isolates of *E. coli*, for example, rose from 46.5% in 1991 to 55.0% in 1997. In addition, none of the *Citrobacter*, *Enterobacter*, or *Klebsiella* isolates from 1997 were susceptible to ampicillin. Other centers have reported similar increases in ampicillin-resistant GNRs. Joseph et al. observed a rise in the proportion of neonatal infections with ampicillin-resistant *E. coli* from 23% during the period 1982-1987 to 67% during the period 1988-1993. The authors correlate this finding with an increase in the administration of intrapartum ampicillin. Given these trends, we conclude that ampicillin can no longer be considered an effective agent against GNR infections in infants 60 days or younger initially evaluated in the outpatient setting. Cefotaxime, on the other hand, covered 89.7% of the GNRs isolated at our institution in 1997, and, when used with gentamicin, may offer synergy against GNRs that the combination of ampicillin and a third-generation cephalosporin does not.

In the case of infection with *Listeria*, the proposed regimen of a third-generation cephalosporin with or without gentamicin would be problematic because cephalosporins have no activity against the organism, and gentamicin is recommended only as an adjunct to ampicillin. We isolated no cases of *Listeria* during a 4-year observation period, but data collected by the Centers for Disease Control and Prevention and the Food and Drug Administration from surveillance areas around the United States with a historically high prevalence of *Listeria* have documented a 51% decrease in perinatal listeriosis between 1989 and 1993. The organism is clearly diminishing in importance as a pathogen in the newborn period.

In addition, when it does occur, listeriosis has a bimodal age distribution. Similar to infections with group B streptococcus, it is clinically recognized as “early-onset” (7 days) and “late-onset” (>7 days) disease. The mean age for onset of late-onset disease is 15 days (range, 9-33 days), and between 84% and 90% of these patients will have meningitis at presentation. In the present study, 101 (84.2%) of 120 ED patients presented at 15 days of age or older. Since most late-onset disease presents as meningitis, it is reasonable to conclude that in centers with a documented low incidence of infections with *Listeria*, potentially septic infants with negative CSF findings, particularly those 15 days or older, have an exceedingly low risk of infection with the organism. Empiric antibiotic therapy should not be designed to account for it.

Although published experience with the use of third-generation cephalosporins with group B streptococcus is limited, we nonetheless believe that the proposed regimen of a third-generation cephalosporin with or without gentamicin therapy is adequate. In vitro data show 100% sensitivity to the third-generation cephalosporins, and there have been in vivo studies demonstrating the clinical efficacy of third-generation cephalosporins with group B streptococcus sepsis and meningitis. To further confirm the clinical efficacy of the third-generation cephalosporins, a large-scale prospective clinical trial would be necessary. Once group B streptococcus has been isolated from the blood, urine, or CSF, penicillin or ampicillin can be used.

Another possible weakness of this proposed strategy lies in the management of infections with the enterococci. These infections are usually confined to the urine, but bacteremia and meningitis do occur. Ampicillin with or without gentamicin is the recommended antibiotic regimen for enterococcal infection. The organism is not susceptible to cephalosporins, nor is it susceptible to gentamicin alone. An initial empiric regimen using a third-generation cephalosporin with gentamicin would therefore be suboptimal. In our study, only 7 isolates of enterococcus were identified during a 4-year period (5.8% of all isolates), all of which were confined to the urinary tract. This problem could be overcome with the early use of a urine Gram stain to identify gram-positive cocci. In such cases, ampicillin could be used initially. If a Gram stain is not immediately available, an alternative approach would be to use ampicillin initially in all children with urinalyses highly suggestive of a urinary tract infection. Overall, we believe that the benefits of enhanced coverage of GNRs with a third-generation cephalosporin and gentamicin may outweigh the risks of suboptimal coverage for enterococcus.

Increased empiric use of the cephalosporins in infants 60 days or younger may carry the risk of an increase in cephalosporin-resistance amongst GNRs. In fact, routine use of the cephalosporins is not recommended in neonatal nurseries unless gram-negative bacterial meningitis is strongly suspected, due to the emergence of cephalosporin resistance.

Two additional points argue for restricted use of ampicillin in the first 60 days of life. The first is the risk of encouraging further ampicillin resistance. Increased use

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<tr>
<th>Isolation of Pathogens by Body Site</th>
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<tbody>
<tr>
<td>Cerebrospinal</td>
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<tr>
<td>Urine Blood</td>
</tr>
<tr>
<td>Blood Fluid (CSF)</td>
</tr>
<tr>
<td>Blood + Urine</td>
</tr>
<tr>
<td>Blood + CSF</td>
</tr>
<tr>
<td>Gram-negative rods</td>
</tr>
<tr>
<td>Group B streptococci</td>
</tr>
<tr>
<td>Enterococcus</td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
</tr>
<tr>
<td><em>Neisseria meningitidis</em></td>
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<tr>
<td>Total</td>
</tr>
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of ampicillin in the immediate peripartum period has been correlated with increased ampicillin resistance among GNRs isolated in the neonatal period. Others have raised the concern that it may lead to penicillin resistance among group B streptococcus, as it has for the pneumococcus. Restricting its use in the first 60 days of life among infants initially evaluated as outpatients may slow the increase in ampicillin resistance in these groups. The second point has to do with cost. The pharmacy charge in our hospital for a 5-kg infant more than 7 days of age receiving ampicillin and cefotaxime for 2 days is $330.20 (including drug, administration, and infusion costs), and that for ampicillin and gentamicin therapy is $318.80. If cefotaxime is used alone, the cost is reduced to $147.

In summary, our observations suggest that in similar centers with a low incidence of infection with Listeria and a high incidence of ampicillin resistance among GNRs, strong consideration should be given to empiric initial antibiotic therapy with a third-generation cephalosporin with or without gentamicin for patients 60 days or younger with suspected invasive bacterial infections initially evaluated in the outpatient setting. These patients should have normal CSF findings and no other evidence of a focal infection such as omphalitis, mastitis, or pneumonia. Patients with a suspected urinary tract infection should have a urine Gram stain that does not demonstrate gram-positive cocci. The addition of gentamicin may be indicated in toxic-appearing children because of the synergy possibly afforded by the combination of a β-lactam antibiotic and an aminoglycoside. Patients with abnormal CSF examination results should receive a regimen that includes ampicillin because of the increased risk of infection with Listeria. Patients with evidence of focal infection such as omphalitis, mastitis, or pneumonia should be treated with antibiotics specifically chosen for those infections.

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Reprints: Karin Berger Sadow, MD, Children’s National Medical Center, 111 Michigan Ave NW, Suite 1450, Washington, DC.

REFERENCES